**Report on the Deliberation Results**

June 1, 2016
Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Lumicef Subcutaneous Injection 210 mg Syringe |
| **Non-proprietary Name** | Brodalumab (Genetical Recombination) (JAN) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 30, 2015 |

**Results of Deliberation**

In its meeting held on May 30, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

**Condition of Approval**

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

**Japanese Accepted Name (modified INN)*

**Review Report**

May 19, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

| | |
|---|---|
| **Brand Name** | Lumicef Subcutaneous Injection 210 mg Syringe |
| **Non-proprietary Name** | Brodalumab (Genetical Recombination) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 30, 2015 |
| **Dosage Form/Strength** | Solution for injection: Each syringe (1.5 mL) contains 210 mg of Brodalumab (Genetical Recombination). |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |
| **Definition** | Brodalumab is a recombinant human IgG2 monoclonal antibody against human interleukin-17 receptor A. Brodalumab is produced in Chinese hamster ovary cells. Brodalumab is a glycoprotein (molecular weight, ca. 147,000) composed of 2 H-chains (γ2-chains) consisting of 442 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each. |

**Structure**

Amino acid sequence

L-chain

EIVMTQSPAT LSVSPGERAT LSCRASQSVS SNLAWFQQKP GQAPRPLIYD
ASTRATGVPA RFSGSGSGTD FTLTISSLQS EDFAVYYCQQ YDNWPLTFGG
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC

H-chain

QVQLVQSGAE VKKPGASVKV SCKASGYTFT RYGISWVRQA PGQGLEWMGW
ISTYSGNTNY AQKLQGRVTM TTDTSTSTAY MELRSLRSDD TAVYYCARRQ
LYFDYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN
VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR
TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV
LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF
LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK

Four isomers exist for brodalumab (IgG2-A, 34.7%; IgG2-A/B, 34.7%; IgG2-B1 or IgG2-B2, 30.2%). All isomers have equivalent biological activity.

IgG2-A

Intra-chain disulfide bonds: L-chain C23-L-chain C88, L-chain C134-L-chain C194, H-chain C22-H-chain C96, H-chain C143-H-chain C199, H-chain C256-H-chain C316, H-chain C362-H-chain C420

Inter-chain disulfide bonds: L-chain C214-H-chain C130, H-chain C218-H-chain C218, H-chain C219-H-chain C219, H-chain C222-H-chain C222, H-chain C225-H-chain C225

IgG2-A/B

Intra-chain disulfide bonds: L-chain C23-L-chain C88, L-chain C134-L-chain C194, H-chain C22-H-chain C96, H-chain C143-H-chain C199, H-chain C256-H-chain C316, H-chain C362-H-chain C420

Inter-chain disulfide bonds: L-chain C214-H-chain C130, L-chain C214-H-chain C218, H-chain C130-H-chain C218, H-chain C219-H-chain C219, H-chain C222-H-chain C222, H-chain C225-H-chain C225

IgG2-B1

Intra-chain disulfide bonds: L-chain C23-L-chain C88, L-chain C134-L-chain C194, H-chain C22-H-chain C96, H-chain C143-H-chain C199, H-chain C256-H-chain C316, H-chain C362-H-chain C420

Inter-chain disulfide bonds: L-chain C214-H-chain C218, H-chain C130-H-chain C219, H-chain C222-H-chain C222, H-chain C225-H-chain C225

IgG2-B2

Intra-chain disulfide bonds: L-chain C23-L-chain C88, L-chain C134-L-chain C194, H-chain C22-H-chain C96, H-chain C143-H-chain C199, H-chain C222-H-chain C225, H-chain C256-H-chain C316, H-chain C362-H-chain C420

Inter-chain disulfide bonds: L-chain C214-H-chain C218, H-chain C130-H-chain C219

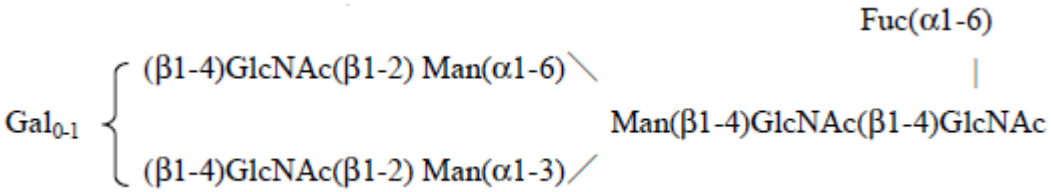
H-chain

Pyroglutamic acid (partial): Q1

Glycosylation site: N292

Partial processing: K442

Main proposed carbohydrate structure




Gal, Galactose; GlcNAc, N-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula: L-chain, $C_{1020}H_{1585}N_{277}O_{333}S_6$

H-chain, $C_{2160}H_{3338}N_{576}O_{665}S_{20}$

Molecular weight: 143,773.56 (protein moiety, 4 chains)

**Items Warranting Special Mention** None

**Reviewing Office** Office of New Drug IV

**Results of Review**

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have had an inadequate response to conventional therapies, and show acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. 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. Post-marketing surveillance should be conducted to collect information on serious infections, malignant tumors, etc. occurring in patients receiving the product. Information gathered from the surveillance should be provided to physicians, patients, etc.

**Indications**

Treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have had an inadequate response to conventional therapies

**Dosage and Administration**

The usual adult dosage is 210 mg of Brodalumab (Genetical Recombination) administered subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

**Condition of Approval**

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

**Attachment**

# Review Report (1)

April 15, 2016

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

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Lumicef Subcutaneous Injection 210 mg Syringe |
| **Non-proprietary Name** | Brodalumab (Genetical Recombination) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 30, 2015 |
| **Dosage Form/Strength** | Solution for injection: Each syringe (1.5 mL) contains 210 mg of Brodalumab (Genetical Recombination). |

**Proposed Indications**

Treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have had an inadequate response to conventional therapies

**Proposed Dosage and Administration**

The usual adult dosage is 210 mg of Brodalumab (Genetical Recombination) administered subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

**Table of Contents**



**List of Abbreviations**

| | |
|---|---|
| ACR20, ACR50, and ACR70 response rates | American College of Rheumatology 20, 50, 70 responder index |
| AUC | Area under the concentration-time curve |

| | |
|---|---|
| ACR20, ACR50, and ACR70 response rates | American College of Rheumatology 20, 50, 70 responder index |
| BVCF | Baseline value carried forward |
| CI | Confidence interval |
| $C_{max}$ | Maximum concentration |
| C-SSRS | Columbia-suicide severity rating scale |
| CYP | Cytochrome P450 |
| ELISA | Enzyme-linked immunosorbent assay |
| FAS | Full analysis set |
| GROα | Growth-related oncogene-α |
| $IC_{50}$ | 50% inhibitory concentration |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| MACE | Major Adverse Cardiovascular Events |
| MCB | Master cell bank |
| NAPSI score | Nail psoriasis severity index score |
| NRI | Non-responder imputation |
| PASI score | Psoriasis area and severity index score |
| Percent improvement in PASI score | Percent reduction from baseline in PASI score |
| PASI 75, PASI 90, and PASI 100 response rates | The proportions of subjects achieving ≥75%, ≥90%, and 100% reduction from baseline in PASI score |
| PHQ-8 | Patient health questionnaire-8 depression scale |
| PMDA | The Pharmaceuticals and Medical Devices Agency |
| PSSI score | Psoriasis scalp severity index score |
| Q2W | Every 2 weeks |
| Q4W | Every 4 weeks |
| Q8W | Every 8 weeks |
| RT-PCR | Reverse transcription polymerase chain reaction |
| SE-HPLC | Size exclusion chromatography |
| SMQ | Standardised MedDRA queries |
| SOC | System organ class |
| sPGA | Static physician global assessment |
| $t_{max}$ | Time of maximum concentration |
| TNF-α | Tumor necrosis factor alpha |
| UV spectrophotometry | Ultraviolet-visible spectrophotometry |
| $V_{max}$ | Maximum velocity |
| WCB | Working cell bank |

**1. Origin or history of discovery, use in foreign countries, and other information**

The active ingredient of “Lumicef Subcutaneous Injection 210 mg Syringe” is Brodalumab (Genetical Recombination) (hereinafter referred to as brodalumab). Brodalumab is a human IgG2 monoclonal antibody against human IL-17 receptor A discovered by Amgen Inc. (US).

Psoriasis is a chronic inflammatory skin disorder, and is categorized, according to clinical symptoms, into psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, erythrodermic psoriasis, and guttate psoriasis. Psoriasis vulgaris is characterized by erythematous plaques with scales, affecting approximately 90% of all patients with psoriasis. Psoriatic arthritis is an inflammatory arthritis accompanied by skin plaques. Pustular psoriasis manifests as localized or generalized sterile pustules. Erythrodermic psoriasis is characterized by generalized rash and diffuse erythema. Patients with pustular psoriasis or erythrodermic psoriasis may have systemic symptoms that can be fatal.

Patients with mild to moderate symptoms are treated with topical agents, such as corticosteroids and vitamin $D_3$ derivatives. Patients with moderate to severe symptoms undergo systemic therapies (e.g., cyclosporine and etretinate) and phototherapy or photochemotherapy, in addition to topical therapy. In Japan, anti-TNFα agents Infliximab (Genetical Recombination) and Adalimumab (Genetical Recombination), an anti-IL-12/23 agent Ustekinumab (Genetical Recombination), and an anti-IL-17A agent Secukinumab (Genetical Recombination) have been approved to treat patients who have had an inadequate response to these conventional therapies.

IL-17 family members (e.g. IL-17A, IL-17F, IL-17C) (pro-inflammatory cytokines) have been shown to contribute to the pathogenesis of psoriasis and the retention and amplification of inflammation (*J Immunol.* 2010; 185: 5453-62, *Mol Cell Biochem.* 2012; 359: 419-29, etc.). IL-17A, IL-17F, and IL-17A/F transduce signals via the IL-17 receptor A/IL-17 receptor C complex. IL-17C transduces signals via the IL-17 receptor A/IL-17 receptor E complex. IL-25 (IL-17E) transduces signals via the IL-17 receptor A/IL-17 receptor B complex. Brodalumab binds with high affinity to the human IL-17 receptor A and inhibits ligand binding to the receptor, thereby blocking signaling. Thus, brodalumab was developed as a treatment for psoriasis.

In Japan, the clinical development of brodalumab for the treatment of psoriasis began in November 2011. The marketing application for brodalumab has been filed based on data including foreign clinical study results, in accordance with the International Conference on Harmonisation (ICH) E5 guideline ("Ethnic Factors in the Acceptability of Foreign Clinical Data" PMSB/ELD Notification No. 672 dated August 11, 1998). US and European applications for brodalumab were submitted in November 2015 and are currently under review.

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

### 2.1 Drug substance

#### 2.1.1 Generation and control of the cell substrate

Transgenic mice producing human IgG were immunized with human IL-17 receptor A. The splenocytes obtained from the mice were fused with murine myeloma cells to generate a hybridoma cell line. A hybridoma clone was selected from the cell line, and gene fragments encoding the variable domains on the heavy chain and light chain of the human IgG were prepared from the base sequence of the hybridoma clone. The expression constructs for heavy and light chains were generated by using the gene fragments and a plasmid containing the constant domains of human IgG2. These 2 expression constructs were transfected into a Chinese hamster ovary (CHO) cell line adapted to serum-free medium. A clone most suitable for the manufacture of brodalumab was selected from the CHO cell line and was used to prepare the master cell bank (MCB) and working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age were characterized by isoenzyme analysis, Southern blot analysis, Northern blot analysis, gene copy number analysis, and DNA sequence analysis to confirm genetic stability during the production of brodalumab.

The MCB, WCB, and cells at the limit of *in vitro* cell age were subjected to purity tests: sterility testing, mycoplasma testing, co-cultivation assay (mink lung cells), transmission electron microscopy, *in vitro* viral assay, *in vivo* viral assay, mouse antibody production test, hamster antibody production test, and porcine or bovine virus test. As a result, neither adventitious viruses nor non-viral infectious agents were detected in any of the tests conducted.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. There is no plan for creating a new MCB for the life of the product, but a new WCB will be created as necessary.

**2.1.2 Manufacturing process**

The manufacturing process for the drug substance consists of preculture, production culture, harvest, [redacted] chromatography, virus inactivation at low pH, [redacted] chromatography, [redacted] chromatography, virus removal filtration, concentration and buffer replacement, [redacted]/filling, and testing and storage steps. The obtained drug substance is dispensed into [redacted] and stored at ≤ -30°C.

Quality by Design (QbD) approaches were used to develop the manufacturing process. A quality control strategy was established based on the following considerations, etc.

- Identification of critical quality attributes (CQAs) of the drug substance and the drug product (COAs: [redacted], host cell proteins, [redacted], bioburden, endotoxin, and [redacted]).
- Identification of process steps that impact CQAs and critical process parameters and critical process controls for these steps
- Establishment of procedures to control CQAs ([redacted]).

The important processes include [redacted] chromatography, [redacted] chromatography, [redacted] chromatography, [redacted], and [redacted].

Process validation of the manufacturing process for the drug substance was carried out at commercial scale.

**2.1.3 Safety evaluation of adventitious agents**

Except for the host CHO cell line, no animal- or human-derived raw materials are used in the manufacturing process of the drug substance.

Purity tests were performed on the MCB, WCB, and cells at the limit of *in vitro* cell age [see 2.1.1 Generation and control of the cell substrate]. Pre-harvest unprocessed bulk at commercial scale was subjected to tests for bioburden, mycoplasma, and adventitious viruses. None of the tests revealed contamination with viral or nonviral

adventitious agents. Tests for bioburden, mycoplasma, and adventitious viruses are included as in-process controls for unprocessed bulk.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process, as shown in Table 1.

Table 1. Results of viral clearance studies

| Process step | Virus reduction factor ($log_{10}$) | | | |
|---|---|---|---|---|
| | Xenotropic murine leukemia virus | Pseudorabies virus | Reovirus type 3 | Minute virus of mice |
| Virus inactivation at low pH | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] | [redacted] |
| Virus removal filtration | [redacted] a) | [redacted] a) | [redacted] a) | [redacted] |
| Overall reduction factor | ≥14.66 a) | ≥15.11 a) | ≥6.79 a) | ≥7.39 |

a) A study of the virus removal filtration step was performed with [redacted] only. The applicant explained that when estimates of log reduction value for [redacted] are added, the overall reduction factors are ≥19.96 for xenotropic murine leukemia virus, ≥20.41 for pseudorabies virus, and ≥12.09 for reovirus type 3.

### 2.1.4 Manufacturing process development (comparability)

The following are major changes made to the drug substance manufacturing process during development (Process 1, Process 2, the proposed commercial process). For all process changes, comparability between pre-change and post-change drug substances has been demonstrated. The drug products produced from the drug substances manufactured by Process 2 and the proposed commercial process were used in the pivotal phase III studies.

- Process 1 → Process 2: [redacted], etc.
- Process 2 → Proposed commercial process: Manufacturing site and scale changes, [redacted], etc.

### 2.1.5 Characterization

#### 2.1.5.1 Structure

- The primary structure was determined by reduced Lys-C and Asp-N peptide mapping with mass spectrometry and tandem mass spectrometry.
- The higher order structure was determined by non-reduced and reduced Lys-C peptide mapping with mass spectrometry, analysis of free sulfhydryl groups, near-ultraviolet circular dichroism spectroscopy, Fourier-transform infrared absorption spectrometry, and differential scanning calorimetry.
- The glycosylation site and carbohydrate structure were determined by peptide mapping of peptide-N-glycanase F-treated and untreated trypsin digests and ion exchange chromatography, hydrophilic interaction chromatography-mass spectrometry after peptide-N-glycanase F treatment, hydrophilic

interaction chromatography of peptide-N-glycanase F-treated, sialidase-digested and undigested samples, hydrophilic interaction chromatography of peptide-N-glycanase F-treated, α-(1-3, 6) galactosidase-digested and undigested samples, tryptic peptide mapping, and ion exchange chromatography.

**2.1.5.2 Physicochemical properties**

- The molecular weight was determined by electrospray ionization/time-of-flight mass spectrometry (non-reduced, non-reduced deglycosylation, reduced deglycosylation).
- Charge variants were identified by capillary isoelectric focusing, capillary isoelectric focusing of carboxypeptidase B-digested or undigested samples, and Lys-C peptide mapping with mass spectrometry.
- Size variants were identified by SE-HPLC, non-reduced and reduced capillary SDS gel electrophoresis, SE-HPLC coupled with multi-angle light scattering, and sedimentation velocity analytical centrifugation.

**2.1.5.3 Biological properties**

- Flow cytometry using [redacted] expressing the IL-17 receptor A or IL-17 receptor C showed the specific binding of brodalumab to the IL-17 receptor A.
- The IL-17A- or [redacted]-dependent [redacted] production in [redacted] was assessed by ELISA. As a result, brodalumab inhibited the IL-17A-induced [redacted] production only.
- A receptor-ligand binding assay ([redacted]) showed that brodalumab inhibits the binding of IL-17A to the IL-17 receptor A.
- IL-17A-, IL-17F-, and IL-17A/F-stimulated [redacted] production in [redacted] was evaluated by a receptor-ligand binding assay ([redacted]). The results showed that brodalumab inhibits [redacted] production stimulated by each ligand.
- [redacted] showed that brodalumab binds to Fcγ Receptor IIα.
- [redacted] showed that brodalumab binds to Fcγ Receptor IIIα.
- The antibody-dependent cellular cytotoxicity (ADCC) activity of brodalumab was evaluated using [redacted] as target cells and [redacted] as effector cells. As a result, brodalumab exhibited almost no ADCC activity.
- [redacted] cells expressing the neonatal Fc receptor were added with fluorescent-labeled [redacted] and incubated with brodalumab. As a result, brodalumab was shown to bind to the neonatal Fc receptor and inhibit [redacted] binding to the neonatal Fc receptor.

**2.1.5.4 Product-related substances/Product-related impurities**

Based on the analysis results presented in 2.1.2.1 to 2.1.5.3, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were considered product-related substances. High molecular weight (HMW) species, fragments, partially reduced species, and methionine oxidation variants were considered product-related impurities. Among the product-related impurities, fragments and HMW species are controlled by the drug substance and drug production specifications (Test B, [redacted]), respectively. However, neither partially reduced species nor methionine oxidation variants are controlled by any specifications because they are present at low levels that do not impact the efficacy or safety of brodalumab.

**2.1.5.5 Process-related impurities**

Host cell proteins, host cell DNA, and [redacted] were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed in the manufacturing process.

**2.1.6 Control of drug substance**

The proposed specifications for the drug substance consist of content, description, identification (ELISA), purity ([redacted], Test A, Test B), bacterial endotoxins, microbial limits, biological activity (cell-based bioassay), and assay (UV spectrophotometry).

Purity (Test A, Test B) and assay (UV spectrophotometry) were included in the specifications in the course of regulatory review [see 2.R.1 Specifications for drug substance and drug product].

**2.1.7 Stability of drug substance**

The primary stability studies on the drug substance are shown in Table 2.

Table 2. Overview of primary stability studies on drug substance

| | Manufacturing process | No. of batches | Storage conditions | Testing period | Storage package |
|---|---|---|---|---|---|
| Long-term testing | Process 2 | 3 | -30 ± [redacted]°C | 48 months[a)] | [redacted] |
| | Proposed commercial process | 3 | | [redacted] months[a)] | |
| Accelerated testing | | 3 | 5 ± [redacted]°C | 6 months | |
| Stress testing | | 3 | 25 ± [redacted]°C | 3 months | |

a) The stability studies are ongoing for up to [redacted] months.

The long-term testing showed no significant changes in quality attributes throughout the testing period.

In the accelerated testing, Test A showed increase of [redacted] and [redacted] showed increase of HMW species.

In the stress testing, Test A showed increases of [redacted] and [redacted] and [redacted] showed increase of HMW species.

Based on the above stability data, a shelf life of 48 months has been proposed for the drug substance when stored in [redacted] containers at -30°C.

**2.2 Drug product**

**2.2.1 Description and composition of drug product and formulation development**

The drug product is a solution for injection containing 210 mg of brodalumab in a 1.5-mL glass syringe. It contains L-glutamate, L-proline, polysorbate 20, and water for injection as excipients. Lumicef is a combination product (a pre-filled syringe). The primary container consists of a glass syringe with a needle and a butyl rubber plunger stopper, packaged in a blister pack and a carton. A glass syringe with a needle, a butyl rubber plunger, and other constituent parts have been certified as the designated controlled medical device, “pre-filled syringe with a needle” (Certification No. 224AFBZX00097000).

### 2.2.2 Manufacturing process

The manufacturing process of the drug product consists of thawing of the drug substance, drug solution preparation, sterile filtration, filling, packaging, and testing and storage. [redacted] and [redacted] have been defined as critical steps.

The commercial-scale manufacturing process of the drug product was subjected to process validation.

### 2.2.3 Manufacturing process development

The following are major changes made to the drug product manufacturing process during development (Process 1, Process 2, the proposed commercial process). For all process changes, comparability between pre-change and post-change drug products has been demonstrated.

- Process 1 → Process 2: [redacted], [redacted], [redacted], [redacted] changes, etc.
- Process 2 → Proposed commercial process: Manufacturing site, scale changes, etc.

### 2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (ELISA, peptide map), osmotic pressure, pH, purity ([redacted], Test A, Test B), extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, biological activity, and assay (UV spectrophotometry).

Identification (peptide map), [redacted], purity (Test A, Test B), and biological activity were included in the specifications in the course of regulatory review [see 2.R.1 Specifications for drug substance and drug product].

### 2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 3. The stability studies used the drug products produced from the drug substances manufactured by Process 2 and the proposed commercial process.

Table 3. Overview of primary stability studies on drug product

| | No. of batches | Manufacturing process | Storage conditions | Testing period | Storage package |
|---|---|---|---|---|---|
| Long-term testing | 3 | Process 2 | 5 ± [redacted]°C | 18 months[a)] | A glass syringe with a butyl rubber plunger |
| Accelerated testing | 3 | Proposed commercial process | 25 ± [redacted]°C | 6 months | |
| Stress testing | 3 | Process 2 | 40 ± [redacted]°C | 3 months | |
| Photostability testing | 1 | | Cool white fluorescent lamp (an overall illumination of 1.2 million lux·h) and near ultraviolet fluorescent lamp (an integrated near ultraviolet energy of 200 W·h/m$^2$), 5 ± [redacted]°C | | A glass syringe with a butyl rubber plunger (not packaged or packaged in a carton) |

a) [redacted]-month data for 3 batches produced by the proposed commercial process have been submitted. The stability study is ongoing for up to [redacted] months.

The long-term testing showed no significant changes in quality attributes throughout the testing period.

The accelerated testing showed a trend towards an increase in the HMW peak on [redacted], an increase in [redacted] on Test A, and a trend towards an increase in fragments in Test B.

The stress testing showed an increase in the HMW peak on [redacted], increases in [redacted] and [redacted] on Test A, and an increase in fragments in Test B, and an increase in partially reduced species in Test C.

Photostability testing showed that the drug product is photolabile.

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

**2.3 Reference materials**

A reference material is prepared from the drug substance and stored at ≤ [redacted]°C. The stability of the reference material is tested every [redacted] months. The proposed specifications for the reference material consist of description, identification (ELISA), purity (Test A, [redacted], Test B, Test C). When a new reference material is prepared, characterization analyses including [redacted] and [redacted], in addition to the specification tests, are performed.

**2.R Outline of the review conducted by PMDA**

Based on the data submitted and the following considerations, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

**2.R.1 Specifications for drug substance and drug product**

At the time of regulatory submission, the drug substance and drug product specifications did not include purity (Test A and Test B) for the drug substance and the drug product, assay (UV spectrophotometry) for the drug substance, or biological activity assay for the drug product, because there was a certain history of commercial-scale manufacturing, and because long-term testing showed no significant changes in quality attributes.

For the following reasons, PMDA concluded that the specifications should include purity (Test A and Test B) for the drug substance and the drug product, assay (UV spectrophotometry for the drug substance only), and biological activity assay (for the drug product only). PMDA asked the applicant to take action accordingly.

- Critical quality attributes should be controlled consistently throughout the product lifecycle.
- Test A and Test B showed changes at the accelerated and stress conditions.
- The biological activity of the drug product should be controlled to assure the efficacy of the product.

The applicant responded that all of these tests and assays would be added to the specifications. PMDA accepted the applicant's response and confirmed that the application data were handled appropriately.

At the time of regulatory submission, ELISA only was proposed for identification of the drug substance and the drug product. PMDA instructed the applicant to also include peptide mapping in identification testing, because peptide mapping can detect changes in the primary structure and post-translational modifications, etc., and is considered useful also for verifying the consistency of the primary structure.

The applicant responded that peptide mapping would be added to the drug product specifications. PMDA accepted the applicant's response.

**2.R.2 Novel excipient**

The drug product contains L-glutamate, a novel excipient, in an amount higher than the amounts present in existing subcutaneous formulations.

**2.R.2.1 Specification and stability**

L-glutamate conforms to the Japanese Pharmacopoeia. PMDA concluded that there were no problems with the specification and stability.

**2.R.2.2 Safety**

As a result of reviewing the data submitted, PMDA concluded that L-glutamate is unlikely to raise a safety concern.

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

The applicant submitted the results from primary pharmacodynamic studies, namely studies to determine the binding affinity to human IL-17 receptor A extracellular domain, inhibition of human IL-17A binding to human IL-17 receptor A, and the effect of anti-mouse IL-17 receptor A antibody in mouse models of psoriasis and inflammatory arthritis, etc. Secondary pharmacodynamic studies were conducted to determine the binding affinity to human IL-17 receptor B and human IL-17 receptor C, the activation of human IL-17 receptor A, and the effect in inflammatory bowel disease models, etc.

Although no safety pharmacology studies have been performed, the effects of brodalumab on the functions listed in the safety pharmacology core battery were assessed in 1-month, 3-month, and 6-month subcutaneous toxicity studies in cynomolgus monkeys. Unless otherwise specified, the pharmacodynamic parameters are expressed as the mean.

**3.1 Primary pharmacodynamics**

**3.1.1 Binding affinity to human IL-17 receptor A (CTD4.2.1.1-1)**

Surface plasmon resonance was used to determine the binding affinity of brodalumab to the extracellular domain peptides (0.46-1000 nmol/L) of human IL-17 receptor A. The dissociation constant of brodalumab was 239 pmol/L.

**3.1.2 Effect on IL-17A binding to IL-17 receptor A (CTD4.2.1.1-2)**

The effect of brodalumab on the specific binding of $^{125}$I-labeled human IL-17A to human IL-17 receptor A on human foreskin fibroblasts was investigated. The inhibition constants of brodalumab and unlabeled human IL-17A were 157 and 1601 pmol/L, respectively.

### 3.1.3 Binding to human peripheral blood cells (CTD4.2.1.1-3)

The binding of phycoerythrin-labeled brodalumab or biotin-labeled human IL-17A to peripheral blood cells in human whole blood was examined by flow cytometry. Biotin-labeled human IL-17A and phycoerythrin-labeled brodalumab showed binding affinity for lymphocytes, monocytes, and granulocytes.

### 3.1.4 Effect on IL-17A-induced IL-6 mRNA expression (CTD4.2.1.1-4)

Brodalumab at 16 ng/mL to 50 μg/mL showed a concentration-dependent inhibition of human IL-17A-induced IL-6 mRNA expression in the presence of TNF-α (3 ng/mL) in human whole blood.

### 3.1.5 Effect on human IL-17A, etc.-induced GROα production from human dermal fibroblasts (CTD4.2.1.1-5)

ELISA was used to assess the effect of brodalumab on human IL-17A-, human IL-17F-, or human IL-17A/F-induced GROα production by human dermal fibroblasts in the presence of TNF-α. Brodalumab inhibited GROα production in a concentration-dependent manner. The $IC_{50}$ values for inhibition of IL-17A-, IL-17F-, and IL-17A/F-induced GROα production were 42, 21, and 55 pmol/L, respectively.

### 3.1.6 Effect on human IL-17C-induced *Defensin β4* mRNA expression in human epidermal keratinocytes (CTD4.2.1.1-8)

RT-PCR was used to assess the effect of brodalumab on human IL-17C-induced *Defensin β4*[1] mRNA expression in human epidermal keratinocytes in the presence of TNF-α. Brodalumab at 1000 nmol/L inhibited mRNA expression by approximately 40%.

### 3.1.7 Effect on human IL-25-induced IL-5 production by human peripheral blood mononuclear cells (CTD4.2.1.1-9)

ELISA was used to assess the effect of brodalumab on human IL-25-induced IL-5 production, in the presence of human IL-2, by human peripheral blood mononuclear cells that had been stimulated by human thymic stromal lymphopoietin. Brodalumab at 0.1 to 10 μg/mL inhibited IL-5 production in a concentration-dependent manner.

### 3.1.8 Binding to IL-17 receptor A from different species or inhibition of biological activity (CTD4.2.1.1-10 to 4.2.1.1-12)

Flow cytometry was used to assess the binding ability of brodalumab to the IL-17 receptor A on peripheral blood mononuclear cells from mice, rats, rabbits, and dogs. Brodalumab bound to rabbit peripheral blood mononuclear cells, but did not bind to mouse or rat peripheral blood mononuclear cells.

ELISA was used to assess the effect of brodalumab on cynomolgus monkey IL-17A- or IL-17F-induced IL-6 production by cynomolgus dermal fibroblasts. Brodalumab at 0.002 to 100 μg/mL inhibited IL-6 production in a concentration-dependent manner.

[1] An antimicrobial peptide that plays a role in inflammation.

RT-PCR was used to examine the effect of brodalumab on rabbit IL-17A-induced IL-6 mRNA expression in rabbit dermal fibroblasts and the effect of brodalumab on human IL-17A-induced IL-6 mRNA expression in human dermal fibroblasts. Brodalumab at 0.001 to 300 µg/mL inhibited IL-6 mRNA expression in a concentration-dependent manner. The $IC_{50}$ values were 18,514 pmol/L for rabbit dermal fibroblasts and 221 pmol/L for human dermal fibroblasts.

**3.1.9 Effect in a mouse model of psoriasis-like dermatitis (CTD4.2.1.1-17)**

Since brodalumab does not cross-react with mouse IL-17 receptor A, the following surrogate antibodies were used: a rat anti-mouse IL-17 receptor A monoclonal IgG2b antibody (M750); and a chimeric antibody with mouse IgG1 constant regions and the variable regions of rat anti-mouse IL-17 receptor A monoclonal antibody (M751).

Dermal application of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) to K14/mIL-1F6 transgenic mice induces cutaneous inflammation, parakeratosis, and epidermal thickness, which are pathological features of psoriasis (*J Exp Med*. 2007; 204: 2603-14). M751 500 µg, rat anti-mouse IL-17A antibody (M210) 500 µg, or control antibody (mouse IgG or rat IgG) 500 µg was intraperitoneally administered to this psoriasis-like dermatitis model 1 day before and 3 days after TPA application, to assess pathological findings (e.g., epidermal hyperplasia, intra-epidermal neutrophilic pustules, parakeratotic scaling, and inflammatory cell infiltration into the dermis) and measure the mRNA expression levels of various pro-inflammatory chemokines and cytokines in skin tissue. Treatment with M751 tended to improve skin lesions and reduce the mRNA expression levels of pro-inflammatory substances, compared with control IgG antibody or M210.

**3.1.10 Effects in mouse models of inflammatory arthritis (CTD4.2.1.1-19 to 4.2.1.1-20)**

Arthritis was induced in mice by intradermal injection of type II collagen and complete or incomplete Freund's adjuvant (2 injections at a 3-week interval). The effect of a surrogate antibody on the symptoms of arthritis was assessed in this mouse model of collagen-induced arthritis. The mice received intraperitoneal administration of M750 10 to 300 µg, negative control antibody 300 µg, or phosphate-buffered saline on the day of arthritis induction (Day 0); or M750 150 µg, negative control antibody 150 µg, or phosphate-buffered saline 3 times weekly beginning on Day 5. M750 reduced the symptoms of arthritis (i.e., redness and swelling of extremities, bone destruction, and articular cartilage erosion) compared with negative control antibody or phosphate-buffered saline.

M750 reduced the symptoms of arthritis also in a tumor necrosis factor receptor *p55/p75* knockout mouse model of arthritis induced by intradermal injection of type II collagen and complete or incomplete Freund's adjuvant.

**3.2 Secondary pharmacodynamics**

**3.2.1 Binding activities to human IL-17 receptor B and human IL-17 receptor C (CTD4.2.1.2-1 to 4.2.1.2-2)**

The binding activities of brodalumab to human IL-17 receptor B and human IL-17 receptor C were determined by ELISA or flow cytometry. Brodalumab did not bind to human IL-17 receptor B or human IL-17 receptor C.

**3.2.2 Activation of IL-17 receptor A (CTD4.2.1.2-3)**

The activation of IL-17 receptor A by brodalumab was measured by GROα production in human foreskin fibroblasts as assessed by ELISA. Brodalumab did not induce GROα production.

**3.2.3 Effects in mouse models of inflammatory bowel disease (CTD4.2.1.2-5 to 4.2.1.2-7)**

M751 was administered intraperitoneally to a mouse model of dextran sulfate sodium-induced colitis and a model of colitis induced by the adoptive transfer of CD45 $RB^{high}$ CD4-positive T cells into immunodeficient CB-17 $Prkdc^{scid}$ mice. M751 did not tend to improve colitis, compared with negative control. Intraperitoneal injection of M751 exacerbated colitis in another mouse model of colitis (*Mdr1a*-deficient mice infected with *Helicobacter bilis*).

**3.3 Safety pharmacology (CTD4.2.3.2-1 to 4.2.3.2-3)**

The effects of brodalumab on clinical signs and behavior, ECG, heart rate, blood pressure, respiratory rate, and body temperature were assessed in cynomolgus monkeys in a 1-month subcutaneous or intravenous injection study (up to 350 mg/kg/week), a 3-month subcutaneous injection study (up to 350 mg/kg/week), and a 6-month subcutaneous injection study (up to 90 mg/kg/week). As a result, no brodalumab-related findings were observed.

**3.R Outline of the review conducted by PMDA**

The applicant's explanation on the mechanism of action of brodalumab in the treatment of psoriasis:

IL-17 receptor A is a type I transmembrane receptor expressed on fibroblasts, epithelial cells, monocytes, etc.

(*Cytokine* 1997; 9: 794-800). IL-17A, IL-17F, and IL-17A/F transduce signals into cells via the IL-17 receptor A/IL-17 receptor C complex. IL-17C transduces signals into cells via the IL-17 receptor A/IL-17 receptor E complex. IL-25 transduces signals into cells via the IL-17 receptor A/IL-17 receptor B complex (*Nat Immunol.* 2011; 12: 1151-8, *Nat Rev Immunol.* 2009; 9: 556-67, etc.).

Increased expression of IL-17 family cytokines is observed in skin lesions of patients with psoriasis. IL-17A, IL-17A/F, IL-17F, and IL-17C are considered to be involved in the pathogenesis and maintenance of psoriasis by promoting the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides, etc. through signaling after receptor activation in epidermal keratinocytes and dermal fibroblasts (*Nat Rev Immunol.* 2010; 10: 479-90, *Immunity*. 2008; 28: 454-67, etc.), thereby inducing the mobilization of neutrophils and Th17 cells to skin lesions and the initiation, retention, and amplification of skin inflammation. IL-17 levels in the synovial fluid have been reported to be approximately 10-fold higher in patients with psoriatic arthritis than in patients with osteoarthritis (*Mol Cell Biochem*. 2012; 359: 419-29). Reports have suggested that IL-17 and macrophage colony-stimulating factor induce osteoclastogenesis from monocytes in the joints (*J Cell Biochem*. 2009; 108; 947-55) and that IL-17 induces bone resorption by enhancing the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in osteoblasts (*J Bone Miner Metab*. 2012; 30: 125-35, etc.). Brodalumab is considered to show efficacy in psoriasis by selectively binding to the IL-17 receptor A and blocking signaling by IL-17A, IL-17A/F, IL-17F, IL-17C, etc. Since mouse surrogate anti-IL-17 receptor A antibody has shown efficacy in mouse models of psoriasis-like dermatitis and arthritis, brodalumab is expected to be effective in treating skin plaques and joint symptoms of psoriasis.

PMDA's conclusion:
The data submitted show that brodalumab blocks the IL-17 receptor A. Brodalumab is expected to be effective in treating psoriasis because IL-17 family cytokines are assumed to contribute to the pathogenesis of psoriasis.

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

The applicant submitted absorption and distribution data, namely the results from subcutaneous and intravenous injection studies in cynomolgus monkeys. Serum brodalumab concentrations were determined by ELISA using horseradish peroxidase-labeled anti-brodalumab antibodies (quantification range, 50-2500 ng/mL). Anti-brodalumab binding antibodies were detected by an electrochemiluminescence immunoassay. Anti-brodalumab neutralizing antibodies were detected by a bioassay using human foreskin fibroblasts expressing the IL-17 receptor A (lower limit of detection, 5 μg/mL). Since brodalumab was expected to be degraded into amino acids through the same pathway for endogenous IgG, no metabolism or elimination studies were performed. Since a single intravenous dose study in cynomolgus monkeys indicated that brodalumab is distributed largely in serum, no brodalumab tissue distribution study was performed. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean (± standard deviation [SD]).

**4.1 Absorption**

**4.1.1 Single-dose study (CTD4.2.2.2-1)**

Table 4 shows the pharmacokinetic parameters of brodalumab in male cynomolgus monkeys (3/group) receiving

a single subcutaneous or intravenous administration of brodalumab. A 2-compartment model with first-order elimination and Michaelis-Menten elimination was constructed, taking account of the non-linear pharmacokinetics of brodalumab. The absolute bioavailability of brodalumab administered subcutaneously was estimated at 97.7% based on the pharmacokinetic parameters estimated using the 2-compartment model. Anti-brodalumab binding antibodies were detected in 10 of 15 animals, and anti-brodalumab neutralizing antibodies in 2 of 15 animals.

Table 4. Pharmacokinetic parameters following a single dose of brodalumab

| Route of administration | Dose (mg/kg) | Number of animals | $C_{max}$ [a)] (μg/mL) | $t_{max}$ [b)] (h) | $AUC_{0-\infty}$ (μg·h/mL) | Total body clearance or apparent total body clearance (mL/h) | Volume of distribution or apparent volume of distribution (mL) |
|---|---|---|---|---|---|---|---|
| Intravenous (i.v.) | 0.5 | 3 | 9.8 ± 1.0 | – | 168 ± 46.0 | 8.3 ± 2.6 | 142 ± 14.0 |
| | 50 | 3 | 673 ± 66.5 | – | 57,000 ± 18,600 | 2.3 ± 0.6 | 75.2 ± 23.6 |
| Subcutaneous (s.c.) | 0.5 | 3 | 1.3 ± 0.8 | 24 (8.0 - 48) | 74.2 ± 41.0 | 22.2 ± 11.2 | 681 ± 522 |
| | 5 | 3 | 20.7 ± 4.8 | 72 (72 - 72) | 3120 ± 1160 | 4.7 ± 1.6 | 98.7 ± 7.0 |
| | 50 | 3 | 166 ± 33.4 | 72 (72 - 72) | 33,700 ± 10,400 | 4.0 ± 1.2 | 72.2 ± 9.2 |

a) $C_0$ for intravenous administration, b) Median (range)

**4.1.2 Repeat-dose studies (Toxicokinetics, CTD4.2.3.2-1 to 4.2.3.2-3)**

Table 5 shows the pharmacokinetic parameters of brodalumab in male and female cynomolgus monkeys (4-6/sex/group) receiving once-weekly subcutaneous or intravenous administration of brodalumab.

In a 4-week repeat-dose study (CTD4.2.3.2-1), anti-brodalumab binding antibodies were detected in 6 of 10 animals in the 25 mg/kg s.c. group, 5 of 10 animals in the 90 mg/kg s.c. group, 4 of 10 animals in the 350 mg/kg s.c. group, and 3 of 10 animals in the 350 mg/kg i.v. group. Anti-brodalumab neutralizing antibodies were detected in 4 of 10 animals in the 25 mg/kg s.c. group, 3 of 10 animals in the 90 mg/kg s.c. group, 2 of 10 animals in the 350 mg/kg s.c. group, and 0 of 10 animals in the 350 mg/kg i.v. group. A decrease in brodalumab exposure was observed in 2 animals given brodalumab 25 mg/kg s.c. and 1 animal given brodalumab 90 mg/kg s.c. among these antibody-positive animals.

In a 13-week repeat-dose study (CTD4.2.3.2-2), anti-brodalumab binding antibodies were detected in 6 of 12 animals in the 25 mg/kg s.c. group, 4 of 12 animals in the 90 mg/kg s.c. group, and 4 of 12 animals in the 350 mg/kg s.c. group. Anti-brodalumab neutralizing antibodies were detected in 4 of 12 animals in the 25 mg/kg s.c. group, 0 of 12 animals in the 90 mg/kg s.c. group, and 1 of 12 animals in the 350 mg/kg s.c. group. A decrease in brodalumab exposure was observed in 4 animals given brodalumab 25 mg/kg among these antibody-positive animals.

In a 26-week repeat-dose study (CTD4.2.3.2-3), anti-brodalumab binding antibodies were detected in 4 of 8 animals in the 10 mg/kg s.c. group, 2 of 8 animals in the 25 mg/kg s.c. group, and 6 of 12 animals in the 90 mg/kg s.c. group. Anti-brodalumab neutralizing antibodies were detected in 3 of 8 animals in the 10 mg/kg s.c. group, 1 of 8 animals in the 25 mg/kg s.c. group, and 5 of 12 animals in the 90 mg/kg s.c. group. A decrease in brodalumab exposure was observed in 4 animals given brodalumab 10 mg/kg, 2 animals given brodalumab 25 mg/kg, and 1 animal given brodalumab 90 mg/kg among these antibody-positive animals.

Table 5. Pharmacokinetic parameters following once-weekly administration of brodalumab

| Duration of dosing | Route of administration | Dose (mg/kg) | Number of animals | Time point | $C_{max}$ (μg/mL) | $t_{max}$ a) (h) | $AUC_{0-\tau}$ (μg·h/mL) |
|---|---|---|---|---|---|---|---|
| 4 weeks | Intravenous | 350 | 10 | Day 1 | 7270 ± 1860 | — | 569,000 ± 141,000 |
| | | | | Day 22 | 10,100 ± 2200 | — | 782,000 ± 199,000 |
| | Subcutaneous | 25 | 10 | Day 1 | 155 ± 32.9 | 84 (24 - 120) | 20,700 ± 4140 |
| | | | | Day 22 | 225 ± 102 | 24 (24 - 72) | 31,900 ± 16,700 |
| | | 90 | 10 | Day 1 | 522 ± 112 | 72 (24 - 96) | 70,200 ± 11,600 |
| | | | | Day 22 | 762 ± 206 | 24 (24 - 120) | 103,000 ± 36,600 |
| | | 350 | 10 | Day 1 | 1680 ± 404 | 48 (24 - 96) | 212,000 ± 59,900 |
| | | | | Day 22 | 2400 ± 780 | 24 (24 - 72) | 325,000 ± 126,000 |
| 13 weeks | Subcutaneous | 25 | 12 | Day 1 | 174 ± 30.3 | 72 (72 - 120) | 23,400 ± 3990 |
| | | | | Day 78 | 233 ± 169 | 48(24 - 120) | 34,000 ± 26,000 |
| | | 90 | 12 | Day 1 | 613 ± 117 | 72 (72 - 72) | 81,600 ± 17,700 |
| | | | | Day 78 | 1180 ± 315 | 24 (24 - 96) | 159,000 ± 47,300 |
| | | 350 | 12 | Day 1 | 2480 ± 530 | 72 (24 - 72) | 322,000 ± 63,800 |
| | | | | Day 78 | 4100 ± 844 | 24 (24 - 96) | 529,000 ± 108,000 |
| 26 weeks | Subcutaneous | 10 | 8 | Day 1 | 52.6 ± 12.7 | 72 (24 - 96) | 6820 ± 1630 |
| | | | | Day 92 | 60.1 ± 65.1 | 24 (24 - 72) | 8400 ± 9430 |
| | | | | Day 176 | 76.4 ± 89.4 | 24 (24 - 72) | 11,000 ± 12,800 |
| | | 25 | 8 | Day 1 | 153 ± 25.9 | 48 (24 - 72) | 21,000 ± 3850 |
| | | | | Day 92 | 252 ± 103 | 24 (24 - 24) | 31,700 ± 16,600 |
| | | | | Day 176 | 310 ± 175 | 24 (24 - 24) | 38,700 ± 21,400 |
| | | 90 | 12 | Day 1 | 437 ± 80.4 | 72 (24 - 96) | 57,400 ± 10,400 |
| | | | | Day 92 | 814 ± 307 | 24 (24 - 120) | 108,000 ± 43,300 |
| | | | | Day 176 | 1090 ± 450 | 24 (24 - 72) | 137,000 ± 63,900 |

a) Median (range)

**4.2 Fetal transfer and excretion in milk (CTD4.2.3.5.3-1)**

Pregnant cynomolgus monkeys (16-18/group) received 19 to 22 doses of subcutaneous brodalumab 25 or 90 mg/kg at weekly intervals from gestation day 20-22 to the end of pregnancy. Brodalumab fetal transfer and excretion in milk were studied. The serum brodalumab concentrations on post-partum day 14 were 6.7 ± 11.8 μg/mL (25 mg/kg) and 95.2 ± 81.0 μg/mL (90 mg/kg) in maternal animals; and 14.1 ± 43.1 μg/mL (25 mg/kg) and 108 ± 50.2 μg/mL (90 mg/kg) in infants. These findings suggest that brodalumab was detected in infant serum because of placental transfer in the fetal period.

Trace amounts of brodalumab (0.081 ± 0.084 μg/mL) were detected in milk in the 90 mg/kg group only. The milk concentration amounted to 0.098% of the serum concentration.

**4.R Outline of the review conducted by PMDA**

PMDA considers that the body's handling of brodalumab can be understood to a certain extent, based on the non-clinical pharmacokinetic data submitted.

**5. Toxicity and Outline of the Review Conducted by PMDA**

The following toxicity studies of brodalumab were conducted: repeat-dose toxicity, reproductive and developmental toxicity, local tolerance, and other toxicity (a tissue cross-reactivity study) studies. The cynomolgus monkey was selected as a relevant species for evaluation of toxicity since brodalumab cross-reacts with cynomolgus monkey IL-17 receptor A, but not with mouse or rat IL-17 receptor A [see 3.1.8 Binding to IL-17 receptor A from different species or inhibition of biological activity]. Only a small number of animals tested positive for anti-brodalumab antibodies or showed a decrease in serum brodalumab levels suggestive of

the presence of anti-brodalumab antibodies [see 4.1.2 Repeat-dose studies]. In all *in vivo* studies, brodalumab exposure during the dosing period was considered adequate to evaluate toxicity. Unless otherwise specified, a solution containing [redacted] was used as vehicle in *in vivo* studies.

**5.1 Single-dose toxicity**

No single-dose toxicity studies of brodalumab were conducted. Brodalumab was subcutaneously or intravenously administered at doses up to 350 mg/kg in 1-, 3-, and 6-month repeat-dose toxicity studies in cynomolgus monkeys (CTD4.2.3.2-1, 4.2.3.2-2, 4.2.3.2-3). Since the first dose of brodalumab was well-tolerated and no acute toxicity was observed, the approximate lethal dose by subcutaneous or intravenous route was determined to be >350 mg/kg.

**5.2 Repeat-dose toxicity**

A 1-month subcutaneous or intravenous toxicity study and 3- and 6-month subcutaneous toxicity studies in monkeys were conducted. In the 6-month subcutaneous toxicity study, the no-observed-adverse-effect level (NOAEL) was determined to be 90 mg/kg. The estimated AUC over 2 weeks at the NOAEL (11,417 μg·day/mL) was 36 times the $AUC_{0\text{-}\tau}$ (319 μg·day/mL)[2] following biweekly subcutaneous administration of brodalumab 210 mg to patients with psoriasis.

**5.2.1 One-month subcutaneous and intravenous toxicity study in monkeys (CTD4.2.3.2-1)**

Male and female cynomolgus monkeys received 4 doses of 0 (vehicle control), 25, 90, or 350 mg/kg subcutaneous brodalumab or 350 mg/kg intravenous brodalumab at weekly intervals. Some animals were given a 13-week recovery period following a 1-month dosing period.

Crusts on the skin of the limbs, chronic inflammation, and ulcer were observed in the 350 mg/kg s.c. and i.v. groups. Periorbital scabs or scabs on the head were noted in the 350 mg/kg i.v. group, and bacteria were detected in the scabs. All findings were reversible during the dosing period or after a 13-week recovery period.

The skin lesions observed were localized and slight, did not affect clinical observations, and were reversible. These findings were therefore considered of no toxicological significance. The NOAEL was thus determined to be 350 mg/kg for both subcutaneous and intravenous administration.

**5.2.2 Three-month subcutaneous toxicity study in monkeys (CTD4.2.3.2-2)**

Male and female cynomolgus monkeys received 14 doses of 0 (vehicle control), 25, 90, or 350 mg/kg subcutaneous brodalumab at weekly intervals. Some animals were given a 17-week recovery period following a 3-month dosing period.

The ≥90 mg/kg groups showed histiocytic inflammation at the injection site. The 350 mg/kg group

[2] A clinical study in which Japanese patients with psoriasis received multiple subcutaneous doses of brodalumab 210 mg (CTD5.3.5.1-1, 4827-002).

showed swelling, scabs, thickening, abscess, and discoloration (red, dark red, tan) at the injection site. In the 350 mg/kg group, scars developed at the injection site during the 17-week recovery period. All findings including the scars were reversible.

The findings at the injection site observed in the 350 mg/kg group were considered to be adverse because of their seriousness. The findings at the injection site observed in the 90 mg/kg group were considered of no toxicological significance, because they were trivial findings with no impact on the systemic condition. The NOAEL was thus determined to be 90 mg/kg.

**5.2.3 Six-month subcutaneous toxicity study in monkeys (CTD4.2.3.2-3)**

Sexually mature male and female cynomolgus monkeys received 27 doses of 0 (vehicle control), 10, 25, or 90 mg/kg subcutaneous brodalumab at weekly intervals. Some animals were given a 6-month recovery period following a 6-month dosing period. This study included measurement of T-cell dependent antibody responses to keyhole-limpet hemocyanin, semen analysis, and histopathological examination including special staining (periodic acid-Schiff stain, Gram stain, Grocott stain).

The ≥10 mg/kg groups showed superficial glossitis primarily involving lymphocytic infiltration accompanied by macrophage or neutrophil infiltration. The ≥25 mg/kg groups showed scaly skin; red skin and dry skin around the mouth and nose and in the abdomen, inguinal region, hindlimb, chest, axilla, forelimb, etc.; acanthosis/hyperkeratosis in the chest and axilla; superficial dermatitis characterized by abnormal growth of indigenous microbes (yeast and bacteria)[3] and lymphocytic infiltration; intracorneal mycelia[4] in the tongue; and chronic inflammation at the injection site. The 90 mg/kg group showed crusted skin, red skin, increased neutrophils, increased cell count in the sternal bone marrow (probably secondary to inflammation in the skin, etc.). Brodalumab had no effect on T-cell dependent antibody response or semen analysis. All findings were reversible after a 6-month recovery period.

The applicant's explanation on skin and tongue inflammation observed in 3- and 6-month subcutaneous toxicity studies:

IL-17 induces the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides in epithelial cells, etc. [see 3.R Outline of the review conducted by PMDA]. *IL-17 receptor A*-, *IL-17A*-, and *IL-17F*-deficient mouse models of bacterial infection showed delayed neutrophil mobilization, decreased clearance of bacteria, increased mortality, etc. (*Immunity*. 2009; 30:108-19, *J Immunol*. 2011; 186: 1666-74, etc.). *IL-17 receptor A*-deficient and *IL-17A*-deficient mice are susceptible to disseminated *Candida albicans* infection, resulting in severe mucocutaneous candidiasis (*J Immunol*. 2010; 185: 5453-62, *J Infect Dis*. 2004; 190: 624-31). A report suggested that impaired neutrophil mobilization or reduced antimicrobial peptide production is involved in the mechanism of development of severe mucocutaneous candidiasis (*J Exp Med*. 2009; 206: 299-311). Thus, skin and tongue inflammation was considered attributable to brodalumab-induced inhibition of

[3] Based on the results of special staining (periodic acid-Schiff stain, Gram stain, Grocott stain).
[4] Based on the results of special staining (periodic acid-Schiff stain, Grocott stain).

the IL-17 signaling pathway-mediated host immune regulation against indigenous microbiota. However, the changes considered related to brodalumab were trivial skin findings with no impact on the systemic condition of the animals. These findings were therefore considered of little toxicological significance and the NOAEL was determined to be 90 mg/kg.

**5.3 Genotoxicity**

Since brodalumab, an antibody drug, would not interact directly with DNA or other chromosomal material, no genotoxicity studies of brodalumab have been conducted.

**5.4 Carcinogenicity**

Brodalumab does not cross-react with mouse or rat IL-17 receptor A [see 3.1.8 Binding to IL-17 receptor A from different species or inhibition of biological activity] with no pharmacological activity. Thus, no carcinogenicity studies in rodent species have been performed.

According to reports, the IL-17 signaling pathway is involved in promoting tumorigenesis by inducing neovascularization (*Blood*. 2003; 101: 2620-7, etc.) and increasing pro-inflammatory cytokine secretion (*Cancer Res*. 1999; 59: 3698-704, etc.), and is also involved in inhibiting tumorigenesis (*Blood*. 2002; 99: 2114-21, etc.). These reports thus suggest that carcinogenicity modulation by IL-17 is involved in both promoting and inhibiting tumorigenesis. However, brodalumab was considered to have a low risk of carcinogenesis because of the following findings:

- No findings suggestive of carcinogenicity or effects on the immune system were observed in a 6-month repeat-dose toxicity study of brodalumab [see 5.2.3 Six-month subcutaneous injection study in monkeys].
- The incidences of malignant tumors in clinical studies were similar to that in the general population [see 7.R.3.5 Malignant tumors].

**5.5 Reproductive and developmental toxicity**

A dose range-finding developmental embryo-fetal toxicity study was conducted in rabbits. An enhanced pre- and postnatal development study was conducted in monkeys. In the enhanced pre- and postnatal development study, the NOAEL for maternal animals and offspring was determined to be 90 mg/kg. The estimated AUC over 2 weeks at the NOAEL (6458 μg·day/mL) was approximately 20 times the $AUC_{0-\tau}$ (319 μg·day/mL)[2] following biweekly subcutaneous administration of brodalumab 210 mg to patients with psoriasis.

### 5.5.1 Male and female reproductive assessment in monkeys (CTD4.2.3.2-3)

Histopathologic examination of the male and female reproductive organs, semen analysis (motility, density, morphology) etc. were performed in a 6-month subcutaneous toxicity study in sexually mature male and female cynomolgus monkeys. No brodalumab-related effects were observed even in animals given 90 mg/kg, the highest dose. The NOAEL for male and female reproductive toxicity was thus determined to be 90 mg/kg.

### 5.5.2 Dose range-finding developmental embryo-fetal toxicity study in rabbits (CTD4.2.3.5.2-1)

Brodalumab was administered subcutaneously at 0 (vehicle control), 25, 90, or 350 mg/kg to pregnant rabbits on gestation days 7 and 14.

Dams given ≥25 mg/kg showed glomerular immune complex deposition in the kidneys and other findings. Dams given ≥90 mg/kg showed reduced food consumption, body weight loss, and thickened glomerular basement membrane in the kidneys. One of 7 dams given 350 mg/kg died. As for embryos and fetuses, abortion occurred in 1 of 7 dams given 25 mg/kg and 1 of 7 dams given 90 mg/kg. Reduced fetal body weights were observed in the ≥90 mg/kg groups.

The maternal death and abortions were considered attributable to nephrotoxicity associated with renal immune complex deposition induced by anti-brodalumab antibody production. The rabbits showed reduced brodalumab exposure and renal immune complex deposition, both due to anti-brodalumab antibody production. Rabbits were therefore considered an inappropriate species for evaluation of reproductive and developmental toxicity of brodalumab. The clinical studies of brodalumab showed a low incidence of anti-brodalumab antibodies and no renal effects. Renal effects due to immunogenicity are therefore considered specific to rabbits and unlikely to be relevant to humans.

### 5.5.3 Enhanced pre- and postnatal development study in monkeys (CTD4.2.3.5.3-1)

Pregnant cynomolgus monkeys received 19 to 22 doses of 0 (vehicle control), 25, or 90 mg/kg subcutaneous brodalumab at weekly intervals from gestation day 20-22 to parturition. In this study, lymphocyte subset analysis was performed, T-cell dependent antibody responses to keyhole-limpet hemocyanin were measured, and behavioral observations, etc. were performed for infants. The infants were necropsied on birth day 180, and external and visceral examinations were performed and organ weights were measured.

Maternal animals showed no brodalumab-related effects.

One of 12 neonates in the 25 mg/kg group and 3 of 13 neonates in the 90 mg/kg group died by birth day 28. The neonatal deaths were all attributed to maternal rejection, umbilical septicemia, etc., and were considered unrelated to the effects of brodalumab on dams or neonates. The incidence of neonatal deaths on birth day 28 was similar to that in cynomolgus macaques (*Lab Anim Sci*. 1989; 39: 205-12, *J Med Primatol.* 1975; 4: 8-22) and to the historical control data from enhanced pre- and postnatal development studies performed at the test facility. Surviving neonates/infants showed no brodalumab-related effects.

Based on the above, the NOAEL for maternal animals, fetuses, and offspring was determined to be 90 mg/kg.

**5.6 Local tolerance (CTD4.2.3.6-1)**

Local tolerance was evaluated in rabbits that received single subcutaneous injections of Test Article 1 (a 70 mg/mL solution of brodalumab in Formulation 1 used in non-clinical studies), Test Article 2 (a 140 mg/mL solution of brodalumab in Formulation 2[5] [vehicle, 10 mmol/L L-glutamate, 3% L-proline, 0.01% polysorbate 20]), and Test Article 3 (a 70 mg/mL solution of brodalumab prepared by diluting Test Article 2 [vehicle, 10 mmol/L L-glutamate, 3% L-proline, 0.01% polysorbate 20]). Test Articles were injected into the back of the rabbits.

Macroscopic examination of the injection site revealed no local injection site irritation in rabbits given Test Article 1 or 3 (a 70 mg/mL solution of brodalumab). Rabbits given Test Article 2 (a 140 mg/mL solution of brodalumab) showed edema and erythema at the injection site within 24 hours post-dose, with reversibility confirmed at 72 hour postdose. Histopathological examination of the injection site revealed bleeding, fibrosis, myofiber degeneration and regeneration, and macrophage infiltration of similar severity for all Test Articles. These changes were probably due to subcutaneous injection procedure.

Injection site reactions reported in clinical studies of brodalumab were reversible. The local irritant effects of brodalumab are therefore considered unlikely to pose a safety issue for its clinical use.

**5.7 Other toxicity studies**

**Tissue cross-reactivity study with human, cynomolgus monkey, and rabbit tissues (CTD4.2.3.7.7-1)**

The potential cross-reactivity of brodalumab with normal human, cynomolgus monkey, and rabbit tissues was evaluated. Brodalumab cross-reacted with mononuclear and dendritic cells (cells morphologically consistent with lymphocytes, macrophages including Kupffer cells, histiocytes, and dendritic cells), the epidermis, the mucosal epithelium, and hair follicle epithelial cells in various tissues from all the species. The cross-reactivity observed in this study was generally consistent with the IL-17 receptor-expression sites reported (*N Engl J Med*. 2009; 361: 888-98).

**5.R Outline of the review conducted by PMDA**

Based on the data submitted, PMDA considers that there are no obstacles to the clinical use of brodalumab from a toxicological perspective.

[5] The same formulation as proposed for marketing.

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

The applicant submitted evaluation data: the results from foreign clinical studies in healthy adults (Studies 20130307, 20120337), Japanese and foreign clinical studies in healthy adults and patients with psoriasis (Studies 4827-001, 20060279), and Japanese and foreign clinical studies in patients with psoriasis (Studies 20110184, 4827-002, 20090062, 20101227, 4827-004); and the results of a population pharmacokinetic analysis, and other data.

Serum brodalumab concentrations were determined by ELISA using horseradish peroxidase-labeled anti-brodalumab antibody (quantification range, 50-2000 ng/mL). Anti-brodalumab binding antibodies were detected by an electrochemiluminescence immunoassay (lower limit of quantification, 5-15 ng/mL). Anti-brodalumab neutralizing antibodies were detected by a bioassay using human foreskin fibroblasts expressing the IL-17 receptor A (lower limit of quantification, 2.5 μg/mL). IL-17 receptor occupancy was calculated by measuring the binding of fluorescence-labeled anti-IL-17 receptor A antibody to the IL-17 receptor A on leukocytes in human peripheral blood using flow cytometry. Doses are expressed in terms of brodalumab.

### 6.1 Bioequivalence study (CTD5.3.1.2-1, Study 20130307 [September 2014 to November 2014])

A randomized, open-label, 2-treatment, 2-period crossover study was conducted in healthy adults (N = 145) to evaluate the bioequivalence between (a) a single subcutaneous injection of a pre-filled syringe of brodalumab 210 mg (the proposed commercial formulation)[6] and (b) 2 subcutaneous injections of prefilled syringes of brodalumab 140 and 70 mg. The $C_{max}$ was 13.8 ± 7.9μg/mL following (a) 210 mg and 14.8 ± 7.7 μg/mL following (b) 140 mg + 70 mg. The $AUC_t$ was 125 ± 69.0 μg·day/mL following (a) 210 mg and 149 ± 81.5 μg·day/mL following (b) 140 mg+70 mg. The geometric least-squares mean ratios of (a) to (b) were 0.98 (90% confidence interval [CI]: 0.91, 1.05) for $C_{max}$ and 0.89 (90% CI: 0.82, 0.98) for $AUC_t$; this demonstrates the bioequivalence between (a) and (b).

### 6.2 Single-dose studies

#### 6.2.1 Japanese intravenous and subcutaneous dose study (CTD5.3.3.2-1, Study 4827-001 [November 2011 to June 2012])

The pharmacokinetics of brodalumab were evaluated in a single-blind, ascending dose study in healthy adults and patients with psoriasis. Table 6 shows the pharmacokinetic parameters in healthy adults receiving a single dose of 210 mg intravenous brodalumab or 70, 140, 210, or 420 mg subcutaneous brodalumab and in patients with psoriasis who received a single dose of 140 or 350 mg subcutaneous brodalumab. The applicant explained that brodalumab exhibited non-linear pharmacokinetics because at high serum concentrations of brodalumab, target-mediated clearance became saturated, resulting in a higher contribution of slow clearance by the reticuloendothelial system.

None of the subjects tested positive for anti-brodalumab antibodies.

[6] In Japanese clinical studies, 70 mg and 140 mg pre-filled syringes were used, which are different from 210 mg pre-filled syringe with regard to fill volume only.

Table 6. Pharmacokinetic parameters following a single intravenous or subcutaneous administration of brodalumab

| | Route of administration | Dose | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_t$ (μg·day/mL) |
|---|---|---|---|---|---|---|
| Healthy adults | Intravenous | 210 mg | 6 | 64.3 ± 10.2 | 4.1 (0.5 - 7.9) [a] | 396 ± 57 |
| | Subcutaneous | 70 mg | 6 | 1.3 ± 1.1 | 1.0 (1.0 - 3.0) | 5.4 ± 6.2 |
| | | 140 mg | 6 | 4.5 ± 4.0 | 2.0 (1.0 - 4.0) [b] | 53.2 ± 47.6 [b] |
| | | 210 mg | 6 | 10.0 ± 4.7 | 4.0 (4.0 - 7.0) | 119 ± 58 |
| | | 420 mg | 6 | 21.6 ± 5.2 | 7.0 (4.0 - 11.0) | 349 ± 80 |
| Patients with psoriasis | Subcutaneous | 140 mg | 6 | 4.5 ± 3.8 | 2.0 (2.0 - 7.0) | 35.2 ± 35.0 |
| | | 350 mg | 7 | 14.5 ± 4.6 | 7.0 (2.0 - 7.0) | 194 ± 90 |

Mean ± SD; Median (range) for $t_{max}$; $AUC_t$, area under the serum drug concentration-time curve up to the last measured time point
a) Unit, hour; b) n = 5

### 6.2.2 Foreign intravenous and subcutaneous dose study (CTD5.3.3.2-2, Study 20060279 [December 2007 to September 2009])

The pharmacokinetics of brodalumab were evaluated in a placebo-controlled, randomized, double-blind, ascending dose study in healthy adults and patients with psoriasis. Table 7 shows the pharmacokinetic parameters[7] in healthy adults receiving a single dose of 21, 210, or 700 mg intravenous brodalumab or 7, 21, 70, 210, or 420 mg subcutaneous brodalumab and in patients with psoriasis who received a single dose of 700 mg intravenous brodalumab or 140 or 350 mg subcutaneous brodalumab.

Anti-brodalumab binding antibodies were detected in 1 healthy adult receiving 21 mg intravenous brodalumab, 1 healthy adult receiving 210 mg subcutaneous brodalumab, 1 healthy adult receiving 420 mg subcutaneous brodalumab, 1 patient with psoriasis who received 700 mg intravenous brodalumab, and 1 patient with psoriasis who received 350 mg subcutaneous brodalumab. None of the subjects had neutralizing antibodies.

Table 7. Pharmacokinetic parameters following a single intravenous or subcutaneous administration of brodalumab

| | Route of administration | Dose | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_t$ (μg·day/mL) |
|---|---|---|---|---|---|---|
| Healthy adults | Intravenous | 21 mg | 3 | 6.7 ± 2.1 | 0.63 (0.63 - 4.0) [a] | 9.9 ± 3.3 |
| | | 210 mg | 4 | 63.9 ± 12.6 | 0.65 (0.63 - 0.65) [a] | 345 ± 60.1 |
| | | 700 mg | 6 | 159 ± 29.5 | 0.67 (0.67 - 0.75) [a] | 1500 ± 369 |
| | Subcutaneous | 70 mg | 6 | 2.5 ± 1.4 | 2.0 (2.0 - 4.0) | 13.0 ± 8.9 |
| | | 210 mg | 6 | 10.6 ± 8.9 | 4.0 (3.0 - 4.0) | 116 ± 114 |
| | | 420 mg | 6 | 23.6 ± 5.4 | 7.0 (4.0 - 7.0) | 390 ± 106 |
| Patients with psoriasis | Intravenous | 700 mg | 8 | 198 ± 39.6 | 2.0 (0.68 - 4.9) [a] | 1660 ± 352 |
| | Subcutaneous | 140 mg | 4 | 5.5 ± 3.0 | 2.0 (1.8 - 2.2) | 26.3 ± 14.5 |
| | | 350 mg | 8 | 12.3 ± 5.8 | 7.0 (1.9 - 7.0) | 151 ± 104 |

Mean ± SD, Median (range) for $t_{max}$
a) Unit: hours

[7] Pharmacokinetic parameters in subjects receiving 7 or 21 mg brodalumab were not evaluated because all pharmacokinetic samples from subjects receiving 7 mg and most pharmacokinetic samples from subjects receiving 21 mg were below the lower limit of quantification.

### 6.2.3 Foreign subcutaneous dose study (CTD5.3.3.1-2, Study 20120337 [March 2013 to May 2013])

Healthy adults received 2 subcutaneous doses of 140 mg brodalumab, with an adequate interval between the doses. The pharmacokinetic parameters following the first and second doses are shown in Table 8. The pharmacokinetic parameters following the first and second doses were compared by an analysis of variance including treatment timing and subject as factors. The estimated inter-subject and intra-subject variability for $C_{max}$ were 87.8% and 46.6%, respectively, and those for $AUC_t$ were 108.9% and 56.3%, respectively.

Table 8. Pharmacokinetic parameters following subcutaneous administration of brodalumab

| Dose | Dose | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_t$ (μg·day/mL) |
|---|---|---|---|---|---|
| First | 140 mg | 26 | 7.8 ± 4.5 | 3.0 (1.0 - 4.0) | 57.9 ± 38.3 |
| Second | 140 mg | 24 | 7.5 ± 4.3 | 3.0 (2.0 - 4.0) | 56.8 ± 36.1 |

Mean ± SD, Median (range) for $t_{max}$

## 6.3 Multiple-dose studies

### 6.3.1 Japanese phase II study in patients with psoriasis (CTD5.3.5.1-1, Study 4827-002 [November 2012 to July 2013])

The pharmacokinetics of brodalumab were evaluated in a placebo-controlled, randomized, double-blind, parallel-group study in patients with psoriasis vulgaris or psoriatic arthritis. Brodalumab 70, 140, or 210 mg was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter. The pharmacokinetic parameters following multiple doses of brodalumab are shown in Table 9.

None of the subjects tested positive for anti-brodalumab antibodies.

Table 9. Pharmacokinetic parameters following multiple doses of brodalumab in Japanese patients with psoriasis

| Dose | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_{0-\tau}$ (μg·day/mL) |
|---|---|---|---|---|
| 70 mg | 15 | 2.3 ± 1.7 | 2.9 (2.0 - 4.2) | 14.3 ± 12.9 |
| 140 mg | 15 | 6.0 ± 3.6 | 3.2 (1.8 - 7.0) | 56.1 ± 49.6 |
| 210 mg | 11 | 27.3 ± 11.1 | 2.9 (1.9 - 6.9) | 319 ± 136 |

Mean ± SD, Median (range) for $t_{max}$

### 6.3.2 Japanese phase III study in patients with psoriasis (CTD5.3.5.2-4, Study 4827-004 [January 2013 to May 2014])

The pharmacokinetics of brodalumab were evaluated in an open-label, uncontrolled study in patients with pustular psoriasis or erythrodermic psoriasis. Brodalumab 140 mg was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter.[8] The pharmacokinetic parameters following multiple doses of brodalumab are shown in Table 10. Serum concentrations tended to be higher in Study 4827-004 than in Study 4827-002. The applicant explained that this was probably due to a trend towards lower body weight in Study 4827-004 (Study 4827-002, 73.8 ± 9.7 kg; Study 4827-004, 64.7 ± 18.5 kg).

One patient with pustular psoriasis tested positive for anti-brodalumab binding antibodies, but had no neutralizing antibodies.

[8] A dose increase to 210 mg was allowed in subjects with an inadequate response after Week 4.

Table 10. Pharmacokinetic parameters following multiple doses of brodalumab in Japanese patients with pustular psoriasis or erythrodermic psoriasis

| Type of psoriasis | Dose | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_{0-\tau}$ (μg·day/mL) |
|---|---|---|---|---|---|
| Pustular | 140 mg | 4 | 10.1 ± 9.1 | 3.0 (2.0 - 3.1) | 92.0 ± 89.9 |
| Erythrodermic | 140 mg | 4 | 11.8 ± 8.6 | 2.0 (1.9 - 6.9) | 125 ± 108 |
| | 210 mg | 1 | 31.3 | 6.9 | 364 |

Mean ± SD, Median (range) for $t_{max}$

### 6.3.3 Foreign phase II study in patients with psoriasis (CTD5.3.5.1-2, Study 20090062 [December 2009 to September 2010])

The pharmacokinetics of brodalumab were evaluated in a placebo-controlled, randomized, double-blind, parallel-group study in patients with psoriasis vulgaris or psoriatic arthritis. Brodalumab 70, 140, or 210 mg was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter, or brodalumab 280 mg was administered subcutaneously every 4 weeks. The pharmacokinetic parameters following multiple doses of brodalumab are shown in Table 11.

Anti-brodalumab binding antibodies were detected in 7.6% (12 of 158) of subjects, but none of the subjects had neutralizing antibodies.

Table 11. Pharmacokinetic parameters following multiple doses of brodalumab in non-Japanese patients with psoriasis

| Dosing regimen | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_{0-\tau}$ (μg·day/mL) |
|---|---|---|---|---|
| 70 mg Q2W | 9 | 1.3 ± 1.4 | 2.0 (0.0 - 6.9) | 9.5 ± 11.1 |
| 140 mg Q2W | 11 | 9.6 ± 7.5 | 2.8 (1.9 - 11.8) | 87.7 ± 86.0 |
| 210 mg Q2W | 9 | 23.3 ± 13.6 | 2.0 (0.0 - 7.9) | 237 ± 186 |
| 280 mg Q4W | 7 | 11.4 ± 9.02 | 2.9 (1.9 - 6.8) | 119 ± 102 |

Mean ± SD, Median (range) for $t_{max}$

### 6.3.4 Foreign phase II study in patients with psoriasis (CTD5.3.5.1-6, Study 20101227 [December 2009 to September 2010])

The pharmacokinetics of brodalumab were evaluated in a placebo-controlled, randomized, double-blind, parallel-group study in patients with psoriatic arthritis. Brodalumab 140 or 280 mg was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter. The pharmacokinetic parameters following multiple doses of brodalumab are shown in Table 12.

One subject in the brodalumab 280 mg group tested positive for anti-brodalumab binding antibodies, but had no neutralizing antibodies.

Table 12. Pharmacokinetic parameters following multiple doses of brodalumab in non-Japanese patients with psoriatic arthritis

| Dose | N | $C_{max}$ (μg/mL) | $t_{max}$ (day) | $AUC_{0-\tau}$ (μg·day/mL) |
|---|---|---|---|---|
| 140 mg | 14 | 7.4 ± 5.4 | 3.0 (2.0 - 7.9) | 71.2 ± 72.6 |
| 280 mg | 21 | 18.5 ± 17.8 | 5.0 (0.0 - 7.9) | 214 ± 229 |

Mean ± SD, Median (range) for $t_{max}$

### 6.4 Drug-drug interactions (CTD5.3.3.4-1, Study 20110184 [September 2013 to July 2014])

Pro-inflammatory cytokines have been reported to affect the clearance of drugs metabolized by

drug-metabolizing enzymes such as CYP enzymes (*Clin Pharmacokinet*. 2010; 49: 295-310, *Crit Care Med*. 2003; 31: 1338-46). Potential drug interactions between midazolam (a CYP3A4 substrate) and brodalumab were therefore assessed in a clinical pharmacology study in patients with psoriasis (N = 31). The $C_{max}$ and $AUC_t$ of midazolam were 9.9 ± 3.6 ng/mL and 30.5 ± 11.5 ng·h/mL, respectively, in patients receiving midazolam 2 mg alone; and 11.5 ± 4.6 ng/mL and 39.0 ± 19.2 ng·h/mL, respectively, in patients receiving midazolam and brodalumab 210 mg. The geometric mean ratios of $C_{max}$ and $AUC_t$ (midazolam + brodalumab vs. midazolam alone) were 1.16 [90% CI: 1.00, 1.36] and 1.23 [90% CI: 1.12, 1.37], respectively. The applicant explained that the degree of the observed effect by this drug interaction does not warrant adjustment of the midazolam dose.

**6.5 Population pharmacokinetic analysis (CTD5.3.3.5-1)**

A population pharmacokinetic analysis was performed with NONMEM (version 7.2) using the serum brodalumab concentration data obtained from Japanese clinical studies (Studies 4827-001, 4827-002) and foreign clinical studies (Studies 20060279, 20090062) in healthy adults and patients with psoriasis (2703 sampling points from 340 subjects).

A 2-compartment model with first-order absorption and first-order elimination with body weight as a covariate was developed as a base model. Additionally, ethnicity (Japanese or non-Japanese) was tested as a covariate on CL (clearance), $V_1$ (volume of distribution for the central compartment), and $V_{max}$, and disease (healthy adults, patients with psoriasis) was tested as a covariate on CL and $V_{max}$. As a result, the base model was used as the final model.

The population pharmacokinetic parameters (inter-subject variability, %CV) estimated from the final model were 0.26 L/day (43.7%) for CL, 4.1 L (29.6%) for $V_1$, 2.4 L (35.0%) for $V_2$ (volume of distribution for the peripheral compartment), 0.27 $d^{-1}$ (59.3%) for $K_a$ (absorption rate constant), and 4.6 mg/day (29.3%) for $V_{max}$.

**6.6 Population pharmacokinetic/pharmacodynamic analysis (CTD5.3.3.5-3)**

A population pharmacokinetic/pharmacodynamic analysis was performed using the serum brodalumab concentration data, PASI scores, and sPGA response rates obtained from foreign clinical studies in healthy adults and patients with psoriasis (Studies 20060279, 20090062, 20120102, 20120104).

The pharmacokinetics of brodalumab were estimated using a population pharmacokinetic model developed with NONMEM (version 7.2) based on the serum brodalumab concentration data from foreign clinical studies (Studies 20060279, 20110106, 20110184, 20090062, 20120102, 20120103, 20120104). The base model was a 2-compartment model with first-order absorption and first-order elimination. Body weight was selected as a significant covariate on CL, $V_{max}$, Q (inter-compartmental clearance), $V_1$, and $V_2$. Baseline PASI score was selected as a significant covariate on $V_{max}$ in the final model. An indirect response model (*J Pharmacokinet Biopharm*. 1996; 24: 611-35) was used to estimate the pharmacodynamics of brodalumab. $IC_{50}$ and $IC_{90}$ were estimated to be 0.58 μg/mL and 1.51 μg/mL, respectively, based on the model. Body weight was selected as a significant covariate on the $IC_{50}$; heavier subjects were expected to have higher $IC_{50}$ values.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Ethnic differences in pharmacokinetics/pharmacodynamics

The applicant's explanation:

The following findings indicate that the pharmacokinetics/pharmacodynamics of brodalumab did not differ between Japanese and non-Japanese subjects.

- In Japanese and foreign phase I studies in healthy adults (Japanese Study 4827-001, Foreign Studies 20060279 and 20120337) and Japanese and foreign phase II studies (Japanese Study 4827-002, Foreign Study 20090062), the pharmacokinetic parameters following intravenous or subcutaneous administration of brodalumab were largely similar in both Japanese and non-Japanese subjects [see 6.2 Single-dose studies and 6.3 Multiple-dose studies].
- The population pharmacokinetic model was used to simulate the steady-state serum exposure in 1000 Japanese and 1000 non-Japanese patients who received 70, 140, and 210 mg brodalumab at Weeks 0, 1, and 2 and every 2 weeks thereafter.[9] As shown in Figure 1, serum brodalumab concentrations tended to be slightly higher in Japanese patients than in non-Japanese patients, but the distribution of estimated serum brodalumab concentrations was largely similar in both Japanese and non-Japanese patients.
- As shown in Table 13, the IL-17 receptor occupancy by brodalumab was largely similar in both Japanese and non-Japanese subjects.
- The relationship between the average serum brodalumab concentration $C_{ss}$ and percent improvement in PASI score was similar in both the bridging study (Study 4827-002) and the study to be bridged (Study 20090062) (Figure 2).

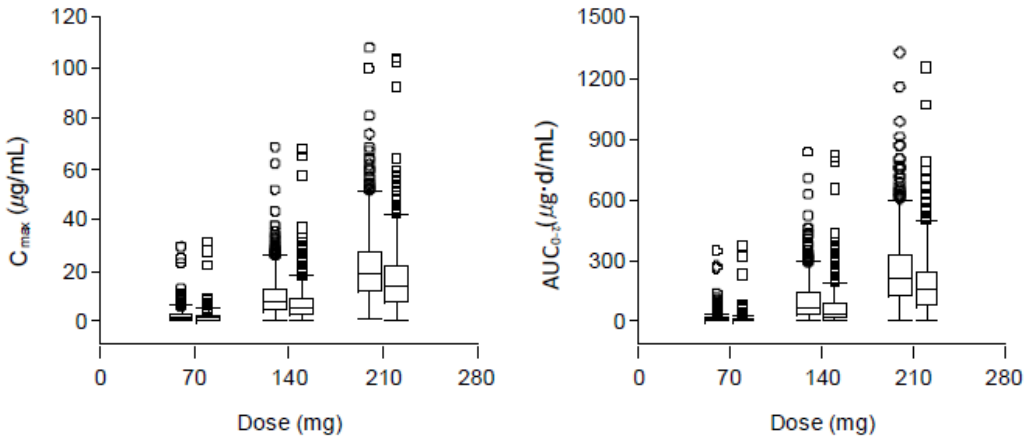



Figure 1. Estimated steady-state serum exposure following multiple subcutaneous doses of brodalumab in Japanese and non-Japanese patients with psoriasis
(Left, Japanese patients [mean body weight, 74.2 kg]; Right, non-Japanese patients [mean body weight, 90.0 kg])

[9] Steady-state serum exposure was simulated separately for Japanese and non-Japanese patients by dose group (sample size, 1000 patients) based on body weights of Japanese and non-Japanese patients generated as normal random numbers with the subjects' body weight (74.2 ± 17.1 kg) in Study 4827-002 and the subjects' body weight (90.0 ± 21.8 kg) in Study 20090062.

Table 13. IL-17 receptor occupancy over time following subcutaneous administration of brodalumab to Japanese and non-Japanese subjects

| | | | IL-17 receptor occupancy (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose | Study ID | N | Predose | Day 3 | Day 5 | Day 8 | Day 15 | Day 29 | Day 64 |
| 70 mg | 4827-001 | 6 | 0.4 | 86.4 | — | 75.8 | 36.6 | — | 3.6 |
| | 20060279 | 6 | 5.7 | 94.6 | 92.7 | 88.6 | — | −4.4 | 9.4[a)] |
| 140 mg | 4827-001 | 6 | 0.2 | 86.8 | — | 85.2 | 70.9 | 9.7 | −6.0 |
| | 20060279 | 4 | 3.4 | — | — | 97.2 | 81.7 | −0.5 | −6.3 |
| 210 mg | 4827-001 | 6 | 0.4 | 93.1 | — | 94.7 | 92.2 | 14.8 | 3.1 |
| | 20060279 | 6 | −7.6 | — | 95.5 | 96.1 | — | 31.8 | −5.6 |
| 350 mg | 4827-001 | 7 | 0.03 | 94.7 | — | 96.4 | 94.1 | 54.4 | 4.7 |
| | 20060279 | 8 | −2.8 | — | — | 98.0 | 95.7 | 69.7 | −9.0 |
| 420 mg | 4827-001 | 6 | 2.2 | 94.4 | — | 95.4 | 95.4 | 89.7 | 3.2 |
| | 20060279 | 6 | 0.6 | — | 97.8 | — | 96.3 | 91.1 | 10.1 |

—: not available
a) Day 43

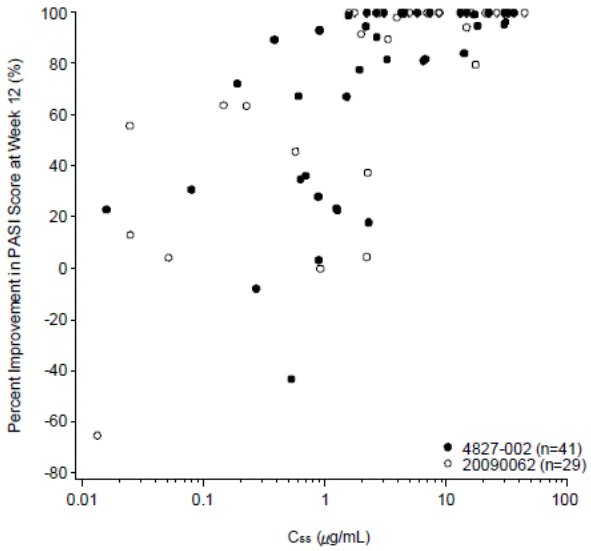



Figure 2. Relationship between serum brodalumab concentration and percent improvement in PASI score in Japanese and non-Japanese patients with psoriasis (at Week 12)

PMDA accepted the applicant's explanation and considers that there is no particular problem with the use of foreign clinical data from a pharmacokinetic point of view.

### 6.R.2 Relationship between the efficacy of brodalumab and serum brodalumab concentration, and dosage regimen

The applicant explained the relationship between serum brodalumab concentration and efficacy, and provided justification for the brodalumab 210 mg dose from a clinical pharmacological standpoint.

The applicant's explanation:

Table 14 shows the relationship between the $C_{ss}$ and percent improvement in PASI score at Week 8 to 10 or at Week 10 to 12 in phase II studies (Studies 4827-002, 20090062) and foreign phase III studies (Studies 20120102, 20120103, 20120104). The percent improvement in PASI score tended to increase in a $C_{ss}$-dependent manner. The median $C_{ss}$ in subjects achieving ≥75% and <90% improvement in PASI score suggest that brodalumab is expected to show efficacy by maintaining $C_{ss}$ at approximately 5.0 μg/mL.

Table 14. Serum brodalumab concentrations in subgroups according to percent improvement in PASI score in clinical studies

| | Serum brodalumab concentration (μg/mL) | | | |
|---|---|---|---|---|
| | PASI ≥50 and <75 | PASI ≥75 and <90 | PASI ≥90 and <100 | PASI 100 |
| N | 6 | 8 | 12 | 26 |
| Phase II studies (Studies 4827-002 and 20090062) | 0.21 (0.025 - 1.5) | 4.9 (0.39 - 17.5) | 3.3 (0.90 - 30.9) | 8.8 (1.6 - 44.2) |
| N | 13 | 41 | 79 | 91 |
| Phase III studies (Studies20120102, 20120103, 20120104) | 3.2 (0.16 - 8.7) | 5.0 (0.32 - 45.9) | 7.5 (0.16 - 44.9) | 10.7 (1.7 - 64.6) |

Median (range)

The relationship between the $C_{ss}$ and body weight in a Japanese phase II study (Study 4827-002) is presented in Table 15. Although the $C_{ss}$ tended to decrease as body weight increased, the mean $C_{ss}$ was >5.0 μg/mL in the brodalumab 210 mg group across all body weight categories. Thus, the 210 mg dose of brodalumab is justified to achieve serum brodalumab concentrations associated with efficacy.

Table 15. Serum brodalumab concentrations by body weight in subjects receiving brodalumab in Japanese phase II study (Study 4827-002)

| | Serum brodalumab concentration (μg/mL) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ≥40 kg and <50 kg | ≥50 kg and <60 kg | ≥60 kg and <70 kg | ≥70 kg and <80 kg | ≥80 kg and <90 kg | ≥90 kg and <100 kg | ≥100 kg and <110 kg | ≥120 kg and <130 kg |
| N | 1 | 2 | 1 | 4 | 1 | 3 | 2 | 1 |
| 70 mg | 1.5 | 2.4 ± 1.2 | 0.39 | 1.5 ± 0.71 | 0.53 | 0.39 ± 0.44 | 0.36 ± 0.48 | 0.27 |
| N | 0 | 2 | 2 | 8 | 2 | 1 | 0 | 0 |
| 140 mg | — | 6.0 ± 2.0 | 4.5 ± 3.2 | 3.6 ± 4.4 | 3.9 ± 3.7 | 2.7 | — | — |
| N | 0 | 1 | 4 | 5 | 1 | 0 | 0 | 0 |
| 210 mg | — | 17.1 | 30.5 ± 5.9 | 19.7 ± 10.4 | 13.1 | — | — | — |

Mean or Mean ± SD

$C_{ss}$ was not calculated for subjects weighing ≥110 kg and <120 kg.

PMDA's view:

The applicant explained that serum brodalumab concentration is correlated with percent improvement in PASI score from a clinical pharmacological standpoint, and that a 210 mg dose should be recommended to achieve adequate efficacy in patients with high body weight as well. This explanation is acceptable. PMDA has no objection to the applicant's conclusion that the recommended dose of brodalumab should be 210 mg.

**6.R.3 Anti-brodalumab antibodies**

The applicant explained that the development of anti-brodalumab antibodies would pose no problems with the clinical use of brodalumab.

The applicant's explanation:

Anti-brodalumab binding antibodies were detected in 2 subjects in Japanese Study 4827-003, 1 subject in Japanese Study 4827-004, and 2.7% (122 of 4461) of all subjects in foreign clinical studies (pooled data from Studies 20090062, 20090403, 20120102, 20120103, and 20120104). None of the subjects had neutralizing antibodies.

The effects of anti-brodalumab binding antibodies on the pharmacokinetics of brodalumab were investigated in subjects from foreign phase III studies (Studies 20120102, 20120103, 20120104). The results are shown in Table 16. Serum brodalumab concentrations tended to be slightly lower in subjects positive for anti-brodalumab binding antibodies than in subjects negative for the antibodies. However, no major differences were observed in

the interquartile range; this suggests that the development of anti-brodalumab binding antibodies have no major impact on the pharmacokinetics of brodalumab.

Table 16. Serum brodalumab concentrations by anti-brodalumab binding antibody status

| Dose | Time point | Antibodies (N) | Serum brodalumab concentration (μg/mL) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean ± SD | Min | 25th percentile | Median | 75th percentile | Max |
| 140 mg | Week 24 | Absent (188) | 2.5 ± 3.7 | BLQ | BLQ | 0.46 | 3.94 | 21.7 |
| | | Present (3) | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ |
| | Week 48 | Absent (176) | 3.3 ± 4.4 | BLQ | BLQ | 1.6 | 5.2 | 22.1 |
| | | Present (5) | 3.5 ± 3.2 | BLQ | 0.96 | 3.3 | 6.0 | 7.4 |
| 210 mg | Week 24 | Absent (344) | 9.7 ± 11.4 | BLQ | 0.86 | 6.3 | 15.4 | 61.1 |
| | | Present (4) | 5.3 ± 6.8 | BLQ | 0.65 | 3.0 | 9.9 | 15.1 |
| | Week 48 | Absent (316) | 10.4 ± 11.3 | BLQ | 1.4 | 7.9 | 15.3 | 68.4 |
| | | Present (6) | 8.0 ± 6.9 | 0.052 | 0.42 | 9.5 | 9.9 | 18.5 |

BLQ: Below the lower limit of quantification (0.05 μg/mL)

Table 17 shows the sPGA success (0 or 1) rates by anti-brodalumab binding antibody status in subjects treated with brodalumab 140 or 210 mg until the end of the maintenance phase in Studies 20120103 and 20120104. Antibody formation had no effects on efficacy.

Table 17. sPGA success (0 or 1) rate at Week 52 by anti-brodalumab binding antibody status (NRI)

| Anti-brodalumab binding antibodies (N) | 140 mg Q2W | 210 mg Q2W |
|---|---|---|
| Present (35) | 23.8 (5/21) | 50.0 (7/14) |
| Absent (1314) | 44.4 (292/657) | 62.3 (409/657) |

% (n/N)

Table 18 lists adverse events by anti-brodalumab binding antibody status based on the pooled data from foreign clinical studies. Anti-brodalumab binding antibodies had no effects on safety.

Table 18. Adverse events reported by ≥5% of subjects by anti-brodalumab binding antibody status (Safety analysis set)

| | Anti-brodalumab antibody | |
|---|---|---|
| | Present (N = 107) | Absent (N = 4354) |
| All adverse events | 93 (86.9) | 3551 (81.6) |
| Nasopharyngitis | 24 (22.4) | 724 (16.6) |
| Upper respiratory tract infection | 21 (19.6) | 600 (13.8) |
| Arthralgia | 18 (16.8) | 462 (40.6) |
| Pain in extremity | 14 (13.1) | 155 (3.6) |
| Hypertension | 9 (8.4) | 219 (5.0) |
| Cough | 8 (7.5) | 184 (4.2) |
| Headache | 7 (6.5) | 349 (8.0) |
| Back pain | 7 (6.5) | 236 (5.4) |
| Influenza | 7 (6.5) | 156 (3.6) |
| Pharyngitis | 6 (5.6) | 151 (3.5) |
| Gastroenteritis | 6 (5.6) | 124 (2.8) |
| Musculoskeletal pain | 6 (5.6) | 107 (2.5) |

n (%)

PMDA's view:

Although the number of patients studied was limited, no particular clinical problems have so far been found in subjects positive for anti-brodalumab antibodies. Information on the effects of anti-brodalumab antibodies should continue to be collected.

### 6.R.4 Effect of injection site

The applicant's explanation on the effect of injection site on the pharmacokinetics, efficacy, and safety of brodalumab:

Table 19 shows serum brodalumab concentrations by site of the first injection in foreign phase III studies (Studies 20120102, 20120103, 20120104). There were no major differences in serum brodalumab concentrations according to injection site.

Table 19. Serum brodalumab concentrations at 1 week post-dose by injection site

| Dose | Injection site (N) | Serum brodalumab concentration (μg/mL) |
|---|---|---|
| 210 mg | Upper arm (774) | 7.3 ± 5.3 |
| | Abdomen (399) | 7.9 ± 5.2 |
| | Thigh (78) | 11.9 ± 6.6 |

In foreign phase III studies (Studies 20120102, 20120103, 20120104), subjects received up to 8 injections through Week 12. Table 20 shows efficacy results at Week 12 by injection site in subjects receiving ≥6 injections at the same site that accounted for ≥80% of all injections. Differences in injection site did not affect the efficacy of brodalumab. The exposure-adjusted rates of adverse events were 298.4 events per 100 subject-years for the upper arm, 370.9 events per 100 subject-years for the abdomen, and 349.7 events per 100 subject-years for the thigh. There was no trend towards differences in safety according to injection site.[10]

Table 20. Efficacy results at Week 12 by injection site (NRI)

| Dose | Injection site (N) | PASI 75 response rate | PASI 100 response rate | sPGA success (0 or 1) rate |
|---|---|---|---|---|
| 210 mg | Upper arm (531) | 84.6 (449/531) | 40.7 (216/531) | 76.6 (407/531) |
| | Abdomen (271) | 88.2 (239/271) | 38.0 (103/271) | 83.0 (225/271) |
| | Thigh (32) | 96.9 (31/32) | 40.6 (13/32) | 90.6 (29/32) |

% (n/N)

PMDA's view:

Serum brodalumab concentrations tended to be higher after injections in the thigh compared with the upper arm or the abdomen. The efficacy and safety results by injection site, however, indicate no clinically relevant differences between injection in the thigh and the other sites. Thus any of these injection sites can be used without problems.

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

The applicant submitted the main evaluation data: the results from a Japanese phase II study in patients with psoriasis vulgaris or psoriatic arthritis (Study 4827-002), a Japanese study in patients with pustular psoriasis or erythrodermic psoriasis (Study 4827-004), Japanese long-term treatment studies (Studies 4827-003, 4827-005), a foreign phase II study in patients with psoriasis vulgaris or psoriatic arthritis (Study 20090062), a foreign long-term treatment study (Study 20090403), foreign phase III studies (Studies 20120102, 20120103, 20120104), and a foreign phase II study in patients with psoriatic arthritis (Study 20101227), etc.

### 7.1 Phase II studies

[10] Comparisons were made among subjects who received ≥22 injections at the same site that accounted for ≥80% of all injections through Week 52.

### 7.1.1 Japanese phase II study (CTD5.3.5.1-1, Study 4827-002 [November 2012 to July 2013]) (A bridging study)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis, including psoriatic arthritis [11] (target sample size, 140 subjects).

Brodalumab 70, 140, or 210 mg or placebo was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter for 12 weeks.

The full analysis set (FAS) included all of 151 subjects randomized (39 in the brodalumab 70 mg group, 37 in the brodalumab 140 mg group, 37 in the brodalumab 210 mg group, 38 in the placebo group). The safety analysis set included the 151 subjects in the FAS who received study drug (39 in the brodalumab 70 mg group, 37 in the brodalumab 140 mg group, 37 in the brodalumab 210 mg group, and 38 in the placebo group). The FAS was used for efficacy analyses.

The discontinuation rates were 5.1% (2 of 39 subjects) in the brodalumab 70 mg group and 10.5% (4 of 38 subjects) in the placebo group. The reasons for discontinuation were adverse event (2.6% [1 of 39 subjects] in the brodalumab 70 mg group, 2.6% [1 of 38 subjects] in the placebo group), consent withdrawal (2.6% [1 of 39 subjects] in the brodalumab 70 mg group, 2.6% [1 of 38 subjects] in the placebo group), and the investigator's decision (5.3% [2 of 38 subjects] in the placebo group).

The primary efficacy endpoint was the percent improvement in PASI score[12] from baseline to Week 12 (for results, see Table 21). Pairwise comparisons showed statistically significant differences between each brodalumab dose (70, 140, 210 mg) and placebo. The secondary efficacy endpoints were the PASI 50, 75, 90, and 100 response rates and the sPGA[13] success (0 or 1) and sPGA 0 rates (for results, see Table 22).

Table 21. Percent improvement in PASI score at Week 12 (FAS, BVCF)

| | Brodalumab 70 mg (N = 39) | Brodalumab 140 mg (N = 37) | Brodalumab 210 mg (N = 37) | Placebo (N = 38) |
|---|---|---|---|---|
| Percent improvement in PASI score | 37.7 ± 46.8 | 82.2 ± 28.1 | 96.8 ± 7.4 | 9.4 ± 45.4 |
| Difference from placebo [95% CI] a) | 28.3 [12.05, 44.5] | 72.8 [56.4, 89.2] | 87.3 [70.9, 103.8] | |
| *P*-value b) | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | |

Mean ± SD
a) ANOVA model with treatment as an explanatory variable
b) Adjusted for multiplicity by Williams test (One-sided significance level of 2.5%)

[11] Patients with (a) ≥10% body surface area (BSA) affected by psoriasis and (b) PASI score ≥12.

[12] The body is divided into 4 parts: the head, trunk, upper limbs, and lower limbs. For each body part, the severity of erythema, thickening (plaque elevation, induration), and scaling (desquamation) is scored separately on a 5-point scale (0 [none] to 4 [very severe]). The scores are summed to produce a body part score. Each body part score is multiplied by the percentage of affected area and the percentage of body surface area (10% for head, 20% for upper limbs, 30% for trunk, and 40% for lower limbs). The resulting scores are summed to yield the PASI score (maximum, 72.0).

[13] A physician's global assessment of a patient's psoriasis lesions overall based on the severity of infiltration/thickening, erythema, and scaling/desquamation (a score ranging from 0 to 5).

Table 22. PASI 50, 75, 90, and 100 response rates and sPGA success and sPGA 0 rates at Week 12 (FAS, NRI)

| | Brodalumab 70 mg | Brodalumab 140 mg | Brodalumab 210 mg | Placebo |
|---|---|---|---|---|
| PASI 50 | 35.9 (14/39) | 83.8 (31/37) | 100.0 (37/37) | 18.4 (7/38) |
| PASI 75 | 25.6 (10/39) | 78.4 (29/37) | 94.6 (35/37) | 7.9 (3/38) |
| PASI 90 | 15.4 (6/39) | 64.9 (24/37) | 91.9 (34/37) | 2.6 (1/38) |
| PASI 100 | 2.6 (1/39) | 35.1 (13/37) | 59.5 (22/37) | 0 (0/38) |
| sPGA success (0 or 1) | 25.6 (10/39) | 78.4 (29/37) | 94.6 (35/37) | 5.3 (2/38) |
| sPGA 0 | 2.6 (1/39) | 43.2 (16/37) | 70.3 (26/37) | 0 (0/38) |

% (n/N)

Adverse events occurred in 53.8% (21 of 39 subjects) of the brodalumab 70 mg group, 56.8% (21 of 37 subjects) of the brodalumab 140 mg group, 73.0% (27 of 37 subjects) of the brodalumab 210 mg group, and 44.7% (17 of 38 subjects) of the placebo group. The main events are shown in Table 23. No deaths were reported.

Serious adverse events occurred in 5.1% (2 of 39 subjects [psoriasis and myocardial infarction in 1 subject each]) of the brodalumab 70 mg group, 2.7% (1 of 37 subjects, appendicitis perforated) of the brodalumab 210 mg group, and 2.6% (1 of 38 subjects, tibia fracture) of the placebo group. The causal relationship to study drug could not be ruled out for all events, except for tibia fracture. The outcomes of these serious adverse events were reported as “improved” or “resolved,” except for psoriasis.

Adverse events leading to discontinuation occurred in 2.6% (1 of 38 subjects, bronchopneumonia) of the placebo group, 2.6% (1 of 39 subjects, myocardial infarction) of the brodalumab 70 mg group, and 2.7% (1 of 37 subjects, appendicitis perforated) of the brodalumab 210 mg group. A causal relationship to study drug could not be ruled out for all events.

Adverse events for which a causal relationship to study drug could not be ruled out (adverse drug reactions) occurred in 28.2% (11 of 39 subjects) of the brodalumab 70 mg group, 35.1% (13 of 37 subjects) of the brodalumab 140 mg group, 40.5% (15 of 37 subjects) of the brodalumab 210 mg group, and 18.4% (7 of 38 subjects) of the placebo group.

Table 23. Adverse events reported by ≥2 subjects in any group (Safety analysis set)

| Event term | Brodalumab 70 mg (N = 39) | Brodalumab 140 mg (N = 37) | Brodalumab 210 mg (N = 37) | Placebo (N = 38) |
|---|---|---|---|---|
| Nasopharyngitis | 5 (12.8) | 5 (13.5) | 4 (10.8) | 3 (7.9) |
| Diarrhoea | 2 (5.1) | 1 (2.7) | 3 (8.1) | 0 |
| Upper respiratory tract inflammation | 2 (5.1) | 2 (5.4) | 0 | 0 |
| Blood bilirubin increased | 2 (5.1) | 1 (2.7) | 0 | 0 |
| Dental caries | 1 (2.6) | 0 | 2 (5.4) | 0 |
| Folliculitis | 0 | 2 (5.4) | 2 (5.4) | 0 |
| Eczema | 0 | 2 (5.4) | 1 (2.7) | 0 |
| Skin papilloma | 0 | 2 (5.4) | 0 | 0 |
| Solar dermatitis | 0 | 2 (5.4) | 0 | 0 |
| Contusion | 0 | 1 (2.7) | 0 | 2 (5.3) |
| Xeroderma | 0 | 0 | 3 (8.1) | 0 |
| Tinea pedis | 0 | 0 | 2 (5.4) | 1 (2.6) |
| Paraesthesia | 0 | 0 | 2 (5.4) | 0 |
| Blood triglycerides increased | 0 | 0 | 2 (5.4) | 0 |
| Seasonal allergy | 0 | 0 | 2 (5.4) | 0 |

n (%)

### 7.1.2 Foreign phase II study (CTD5.3.5.1-2, Study 20090062 [December 2009 to September 2010]) (A study to be bridged)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 5 countries including the US and Canada to evaluate the efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis, including psoriatic arthritis[14] (target sample size, 175 subjects).

Brodalumab 70, 140, or 210 mg or placebo was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter for 12 weeks (Q2W), or brodalumab 280 mg was administered subcutaneously every 4 weeks for a total of 3 doses (placebo was administered subcutaneously at Weeks 1, 2, 6, and 10) (Q4W).

The FAS included all of 198 subjects randomized to the brodalumab 70 mg Q2W, 140 mg Q2W, 210 mg Q2W, 280 mg Q4W, or placebo group, with stratification by drug concentration measurement[15] (yes vs. no) and BMI ($\leq$35 kg/m$^2$ vs. >35 kg/m$^2$) (39 in the brodalumab 70 mg Q2W group, 39 in the brodalumab 140 mg Q2W group, 40 in the brodalumab 210 mg Q2W group, 42 in the brodalumab 280 mg Q4W group, 38 in the placebo group). Of the 198 subjects (FAS), 195 who received study drug (38 in the brodalumab 70 mg Q2W group, 39 in the brodalumab 140 mg Q2W group, 40 in the brodalumab 210 mg Q2W group, 41 in the brodalumab 280 mg Q4W group, 37 in the placebo group) were included in the safety analysis set. The FAS was used for efficacy analyses. The discontinuation rates were 5.1% (2 of 39 subjects) in the brodalumab 70 mg Q2W group, 2.6% (1 of 39 subjects) in the brodalumab 140 mg Q2W group, 7.5% (3 of 40 subjects) in the brodalumab 210 mg Q2W group, 4.8% (2 of 42 subjects) in the brodalumab 280 mg Q4W group, and 15.8% (6 of 38 subjects) in the placebo group. The main reasons for discontinuation were consent withdrawal (2.5% [1 of 40 subjects] in the brodalumab 210 mg Q2W group, 7.9% [3 of 38 subjects] in the placebo group), etc.

The primary efficacy endpoint was the percent improvement in PASI score at Week 12 (for results, see Table 24). Pairwise comparisons showed statistically significant differences between each brodalumab dose (70, 140, 210, 280 mg) and placebo. The secondary efficacy endpoints were the PASI 50, 75, 90, and 100 response rates and sPGA success (0 or 1) and sPGA 0 rates (for results, see Table 25).

Table 24. Percent improvement in PASI score at Week 12 (FAS, BVCF)

| | Brodalumab 70 mg Q2W (N = 39) | Brodalumab 140 mg Q2W (N = 39) | Brodalumab 210 mg Q2W (N = 40) | Brodalumab 280 mg Q4W (N = 42) | Placebo (N = 38) |
|---|---|---|---|---|---|
| Percent improvement in PASI score | 45.0 ± 41.7 | 85.9 ± 22.5 | 86.3 ± 27.6 | 76.0 ± 32.7 | 16.0 ± 27.0 |
| Difference from placebo [95% CI] [b)] | 28.9 [15.8, 42.1] | 70.5 [57.4, 83.7] | 70.9 [57.8, 84.0] | 60.5 [47.6, 73.5] | |
| *P*-value [a), b)] | $P < 0.0001$ | $P < 0.0001$ | $P < 0.0001$ | $P < 0.0001$ | |

Mean ± SD

a) ANCOVA model with baseline value and BMI (≤35 vs. >35) as explanatory variables

b) For multiplicity adjustment, each pairwise comparison was done sequentially starting with 210 mg Q2W vs. placebo followed by 140 mg Q2W vs. placebo, 280 mg Q4W vs. placebo, and 70 mg Q2W vs. placebo.

Table 25. PASI 50, 75, 90, and 100 response rates and sPGA success and sPGA 0 rates at Week 12 (FAS, NRI)

| | Brodalumab 70 mg Q2W | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Brodalumab 280 mg Q4W | Placebo |
|---|---|---|---|---|---|
| PASI 50 | 51.3 (20/39) | 89.7 (35/39) | 90.0 (36/40) | 81.0 (34/42) | 15.8 (6/38) |

[14] Patients with (a) ≥10% BSA affected by psoriasis and (b) PASI score ≥12.

[15] Some subjects underwent frequent blood sampling for the determination of serum brodalumab concentrations.

| | | | | | |
|---|---|---|---|---|---|
| PASI 75 | 33.3 (13/39) | 76.9 (30/39) | 82.5 (33/40) | 66.7 (28/42) | 0 (0/38) |
| PASI 90 | 17.9 (7/39) | 71.8 (28/39) | 75.0 (30/40) | 57.1 (24/42) | 0 (0/38) |
| PASI 100 | 10.3 (4/39) | 38.5 (15/39) | 62.5 (25/40) | 28.6 (12/42) | 0 (0/38) |
| sPGA success (0 or 1) | 25.6 (10/39) | 84.6 (33/39) | 80.0 (32/40) | 69.0 (29/42) | 2.6 (1/38) |
| sPGA 0 | 10.3 (4/39) | 41.0 (16/39) | 62.5 (25/40) | 28.6 (12/42) | 0 (0/38) |

% (n/N)

Adverse events occurred in 68.4% (26 of 38 subjects) of the brodalumab 70 mg Q2W group, 69.2% (27 of 39 subjects) of the brodalumab 140 mg Q2W group, 82.5% (33 of 40 subjects) of the brodalumab 210 mg Q2W group, 73.2% (30 of 41 subjects) of the brodalumab 280 mg Q4W group, and 62.2% (23 of 37 subjects) of the placebo group. The main events are shown in Table 26. No deaths were reported.

Serious adverse events occurred in 2.6% (1 of 38 subjects, renal colic) of the brodalumab 70 mg Q2W group, 2.5% (1 of 40 subjects, neutropenia) of the brodalumab 210 mg Q2W group, and 2.7% (1 of 37 subjects, extrauterine pregnancy) of the placebo group. A causal relationship to study drug could not be ruled out for neutropenia. The outcomes of these serious adverse events were all reported as “resolved.”

Adverse events leading to discontinuation occurred in 5.0% (2 of 40 subjects, neutropenia [2 subjects]) of the brodalumab 210 mg Q2W group, 2.4% (1 of 41 subjects, urticaria) of the brodalumab 280 mg Q4W group, and 2.7% (1 of 37 subjects, sinusitis) of the placebo group. A causal relationship to study drug could not be ruled out for all events.

Adverse drug reactions occurred in 26.3% (10 of 38 subjects) of the brodalumab 70 mg Q2W group, 30.8% (12 of 39 subjects) of the brodalumab 140 mg Q2W group, 37.5% (15 of 40 subjects) of the brodalumab 210 mg Q2W group, 24.4% (10 of 41 subjects) of the brodalumab 280 mg Q4W group, and 18.9% (7 of 37 subjects) of the placebo group.

Table 26. Adverse events reported by ≥2 subjects in any group (Safety analysis set)

| Event term | Brodalumab 70 mg Q2W (N = 38) | Brodalumab 140 mg Q2W (N = 39) | Brodalumab 210 mg Q2W (N = 40) | Brodalumab 280 mg Q4W (N = 41) | Placebo (N = 37) |
|---|---|---|---|---|---|
| Nasopharyngitis | 6 (15.8) | 1 (2.6) | 4 (10.0) | 2 (4.9) | 3 (8.1) |
| Nausea | 4 (10.5) | 1 (2.6) | 1 (2.5) | 0 | 1 (2.7) |
| Upper respiratory tract infection | 3 (7.9) | 3 (7.7) | 2 (5.0) | 5 (12.2) | 2 (5.4) |
| Diarrhoea | 3 (7.9) | 2 (5.1) | 3 (7.5) | 0 | 1 (2.7) |
| Back pain | 3 (7.9) | 2 (5.1) | 0 | 1 (2.4) | 0 |
| Injection site pain | 3 (7.9) | 1 (2.6) | 1 (2.5) | 1 (2.4) | 0 |
| Fatigue | 2 (5.3) | 2 (5.1) | 2 (5.0) | 0 | 2 (5.4) |
| Headache | 2 (5.3) | 2 (5.1) | 1 (2.5) | 0 | 1 (2.7) |
| Procedural pain | 2 (5.3) | 1 (2.6) | 0 | 0 | 1 (2.7) |
| Oral herpes | 2 (5.3) | 0 | 0 | 0 | 0 |
| Pharyngitis | 1 (2.6) | 3 (7.7) | 3 (7.5) | 2 (4.9) | 1 (2.7) |
| Psoriatic arthropathy | 1 (2.6) | 3 (7.7) | 0 | 1 (2.4) | 0 |
| Arthralgia | 1 (2.6) | 2 (5.1) | 0 | 4 (9.8) | 1 (2.7) |
| Injection site erythema | 1 (2.6) | 1 (2.6) | 3 (7.5) | 4 (9.8) | 1 (2.7) |
| Pain in extremity | 1 (2.6) | 0 | 3 (7.5) | 4 (9.8) | 0 |
| Psoriasis | 1 (2.6) | 0 | 1 (2.5) | 2 (4.9) | 1 (2.7) |
| Gastroenteritis | 1 (2.6) | 0 | 1 (2.5) | 2 (4.9) | 2 (5.4) |
| Oropharyngeal pain | 0 | 2 (5.1) | 1 (2.5) | 2 (4.9) | 0 |
| Cough | 0 | 2 (5.1) | 0 | 3 (7.3) | 0 |
| Rhinitis allergic | 0 | 2 (5.1) | 0 | 0 | 1 (2.7) |
| Constipation | 0 | 2 (5.1) | 0 | 0 | 0 |
| Localised infection | 0 | 0 | 2 (5.0) | 0 | 0 |
| Pharyngitis streptococcal | 0 | 0 | 2 (5.0) | 0 | 0 |
| Pustular psoriasis | 0 | 0 | 2 (5.0) | 0 | 0 |
| Conjunctivitis | 0 | 0 | 2 (5.0) | 0 | 0 |
| Neutropenia | 0 | 0 | 2 (5.0) | 0 | 0 |
| Injection site induration | 0 | 0 | 1 (2.5) | 2 (4.9) | 0 |
| Musculoskeletal pain | 0 | 0 | 0 | 2 (4.9) | 0 |

n (%)

### 7.1.3 Foreign phase II study (CTD5.3.5.1-6, Study 20101227 [ongoing since October 2011 (data cutoff, July 2014)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in the US and Canada to evaluate the efficacy and safety of brodalumab in patients with psoriatic arthritis that had been diagnosed ≥6 months before (by the Classification Criteria for Psoriatic Arthritis [CASPAR]) who had ≥3 tender and ≥3 swollen joints (target sample size, 156 subjects).

Brodalumab 140 or 280 mg or placebo was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter for 12 weeks (the double-blind phase). After Week 12 (the open-label extension phase), all subjects were to receive brodalumab 280 mg[16] by subcutaneous injection every 2 weeks.

The FAS included all of 168 subjects randomized to the brodalumab 140 mg Q2W, 280 mg Q2W, or placebo group with stratification by body weight (≤100 kg vs. >100 kg) and previous biologic therapy (yes vs. no) (57 in the brodalumab 140 mg Q2W group, 56 in the brodalumab 280 mg Q2W group, 55 in the placebo group). Of the 168 subjects (FAS), 167 who received study drug (56 in the brodalumab 140 mg Q2W group, 56 in the brodalumab 280 mg Q2W group, 55 in the placebo group) were included in the safety analysis set. The FAS was used for efficacy analyses.

[16] In accordance with the protocol amendment (May 16, 2013), the dosage was changed from 280 mg to 210 mg s.c. Q2W.

The discontinuation rates during the double-blind phase were 5.3% (3 of 57 subjects) in the brodalumab 140 mg Q2W group, 7.1% (4 of 56 subjects) in the brodalumab 280 mg Q2W group, and 5.5% (3 of 55 subjects) in the placebo group. The main reasons for discontinuation were adverse event (3.5% [2 of 57 subjects] in the brodalumab 140 mg Q2W group, 3.6% [2 of 56 subjects] in the brodalumab 280 mg Q2W group, 3.6% [2 of 55 subjects] in the placebo group), etc. Among 157 subjects who completed the double-blind treatment phase (53 in the brodalumab 140 mg Q2W group, 52 in the brodalumab 280 mg Q2W group, 52 in the placebo group), 156 subjects entered the open-label extension phase, excluding 1 subject in the brodalumab 280 mg Q2W group.

The primary efficacy endpoint was the ACR20 response rate at Week 12 (for results, see Table 27). Pairwise comparisons showed statistically significant differences between each brodalumab dose (140 and 280 mg) and placebo. The secondary efficacy endpoints were the ACR50 and ACR70 response rates (for results, see Table 27).

Table 27. ACR20, ACR50, and ACR70 response rates at Week 12 (FAS, NRI)

| | Brodalumab 140 mg Q2W | Brodalumab 280 mg Q2W | Placebo | Difference from placebo [95% CI], *P*-value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 140 mg Q2W | 280 mg Q2W |
| ACR20 | 36.8 (21/57) | 39.3 (22/56) | 18.2 (10/55) | 18.7 [2.5, 34.8]<br>*P* = 0.0314 | 21.1 [4.7, 37.5]<br>*P* = 0.0156 |
| ACR50 | 14.0 (8/57) | 14.3 (8/56) | 3.6 (2/55) | 10.4 [0.1, 20.7] | 10.6 [0.2, 21.1] |
| ACR70 | 5.3 (3/57) | 5.4 (3/56) | 0 (0/55) | 5.3 [-0.5, 11.1] | 5.4 [-0.5, 11.3] |

% (n/N)
a) Cochran-Mantel-Haenszel test stratified by body weight (≤100 kg vs. >100 kg) and previous biologic therapy (yes vs. no)
b) For multiplicity adjustment, each pairwise comparison was done sequentially starting with 280 mg Q2W vs. placebo followed by 140 mg Q2W vs. placebo.

During the double-blind phase, adverse events occurred in 62.5% (35 of 56 subjects) of the brodalumab 140 mg Q2W group, 71.4% (40 of 56 subjects) of the brodalumab 280 mg Q2W group, and 65.5% (36 of 55 subjects) of the placebo group. The main events are shown in Table 28. No deaths were reported.

Serious adverse events occurred in 1.8% (1 of 56 subjects, abdominal pain) of the brodalumab 140 mg Q2W group, 3.6% (2 of 56 subjects, [cholecystitis and cellulitis in 1 subject each]) of the brodalumab 280 mg Q2W group, and 1.8% (1 of 55 subjects, cellulitis) of the placebo group. A causal relationship to study drug could not be ruled out for cellulitis observed in the brodalumab 280 mg Q2W group. The outcomes of these serious adverse events were all reported as “resolved.”

Adverse events leading to discontinuation occurred in 3.6% (2 of 56 subjects [mouth ulceration and psoriatic arthropathy in 1 subject each]) of the brodalumab 140 mg Q2W group, 3.6% (2 of 56 subjects [diarrhoea, nausea, vomiting, headache, and hot flush in 1 subject, and skin bacterial infection in 1 subject]) of the brodalumab 280 mg Q2W group, and 3.6% (2 of 55 subjects [nausea, duodenogastric reflux, lip swelling, fatigue, headache, pharynx irritated sensation of, and pruritus generalised in 1 subject, and cellulitis in 1 subject]) of the placebo group. A causal relationship to study drug could not be ruled out for these events, except for cellulitis and psoriatic arthropathy.

Adverse drug reactions occurred in 30.4% (17 of 56 subjects) of the brodalumab 140 mg Q2W group, 28.6% (16 of 56 subjects) of the brodalumab 280 mg Q2W group, and 18.2% (10 of 55 subjects) of the placebo group.

Table 28. Adverse events reported by ≥3 subjects in any group (Double-blind phase, Safety analysis set)

| Event term | Brodalumab 140 mg Q2W (N = 56) | Brodalumab 280 mg Q2W (N = 56) | Placebo (N = 55) |
|---|---|---|---|
| Upper respiratory tract infection | 5 (8.9) | 8 (14.3) | 4 (7.3) |
| Fatigue | 5 (8.9) | 3 (5.4) | 2 (3.6) |
| Nausea | 4 (7.1) | 1 (1.8) | 2 (3.6) |
| Psoriatic arthropathy | 4 (7.1) | 0 | 3 (5.5) |
| Arthralgia | 3 (5.4) | 1 (1.8) | 1 (1.8) |
| Dizziness | 3 (5.4) | 1 (1.8) | 0 |
| Headache | 2 (3.6) | 5 (8.9) | 4 (7.3) |
| Diarrhoea | 2 (3.6) | 5 (8.9) | 2 (3.6) |
| Injection site erythema | 2 (3.6) | 1 (1.8) | 3 (5.5) |
| Nasopharyngitis | 0 | 0 | 3 (5.5) |

n (%)

During the open-label extension phase (through Week 108), adverse events occurred in 92.5% (49 of 53) of subjects treated with brodalumab 140 mg/280 mg, 98.0% (50 of 51) of subjects treated with brodalumab 280 mg/280 mg, and 96.2% (50 of 52) of subjects treated with placebo/brodalumab 280 mg. The main events are shown in Table 29. No deaths were reported.

Serious adverse events occurred in 15.1% (8 of 53) of subjects treated with brodalumab 140 mg/280 mg, 19.6% (10 of 51) of subjects treated with brodalumab 280 mg/280 mg, and 9.6% (5 of 52) of subjects treated with placebo/brodalumab 280 mg. Events reported by ≥2 subjects in any cohort were coronary artery disease (2 subjects treated with brodalumab 140 mg/280 mg) and cholelithiasis (2 subjects treated with placebo/brodalumab 280 mg).

Adverse events leading to discontinuation occurred in 15.1% (8 of 53) of subjects treated with brodalumab 140 mg/280 mg, 9.8% (5 of 51) of subjects treated with brodalumab 280 mg/280 mg, and 9.6% (5 of 52) of subjects treated with placebo/brodalumab 280 mg. The event reported by ≥2 subjects in any cohort was psoriatic arthropathy (2 subjects treated with brodalumab 140 mg/280 mg, 2 subjects treated with brodalumab 280 mg/280 mg, 1 subject treated with placebo/brodalumab 280 mg).

Adverse drug reactions occurred in 50.9% (27 of 53) of subjects treated with brodalumab 140 mg/280 mg, 56.9% (29 of 51) of subjects treated with brodalumab 280 mg/280 mg, and 48.1% (25 of 52) of subjects treated with placebo/brodalumab 280 mg.

Table 29. Adverse events reported by ≥3 subjects in any cohort (Open-label extension phase, Safety analysis set)

| Event term | 140 mg/280 mg (N = 53) | 280 mg/280 mg (N = 51) | Placebo/280 mg (N = 52) |
|---|---|---|---|
| Upper respiratory tract infection | 11 (20.8) | 10 (19.6) | 5 (9.6) |
| Arthralgia | 11 (20.8) | 6 (11.8) | 4 (7.7) |
| Nasopharyngitis | 10 (18.9) | 9 (17.6) | 8 (15.4) |
| Diarrhoea | 10 (18.9) | 9 (17.6) | 1 (1.9) |
| Urinary tract infection | 9 (17.0) | 8 (15.7) | 4 (7.7) |
| Psoriatic arthropathy | 8 (15.1) | 11 (21.6) | 6 (11.5) |
| Sinusitis | 8 (15.1) | 7 (13.7) | 3 (5.8) |
| Psoriasis | 7 (13.2) | 3 (5.9) | 4 (7.7) |
| Bronchitis | 6 (11.3) | 7 (13.7) | 4 (7.7) |
| Nausea | 6 (11.3) | 5 (9.8) | 3 (5.8) |
| Pyrexia | 5 (9.4) | 3 (5.9) | 1 (1.9) |
| Bursitis | 5 (9.4) | 2 (3.9) | 1 (1.9) |
| Vomiting | 5 (9.4) | 2 (3.9) | 0 |
| Oropharyngeal pain | 4 (7.5) | 7 (13.7) | 3 (5.8) |
| Cough | 4 (7.5) | 6 (11.8) | 3 (5.8) |
| Cellulitis | 4 (7.5) | 3 (5.9) | 0 |
| Stomatitis | 4 (7.5) | 3 (5.9) | 0 |
| Back pain | 4 (7.5) | 2 (3.9) | 3 (5.8) |
| Sinus congestion | 4 (7.5) | 2 (3.9) | 2 (3.8) |
| Oral candidiasis | 4 (7.5) | 2 (3.9) | 2 (3.8) |
| Arthritis | 4 (7.5) | 1 (2.0) | 2 (3.8) |
| Insomnia | 4 (7.5) | 1 (2.0) | 1 (1.9) |
| Influenza | 4 (7.5) | 0 | 5 (9.6) |
| Fatigue | 3 (5.7) | 2 (3.9) | 2 (3.8) |
| Carpal tunnel syndrome | 3 (5.7) | 0 | 1 (1.9) |
| Haematuria | 3 (5.7) | 0 | 0 |
| Dyspnoea | 3 (5.7) | 0 | 0 |
| Myalgia | 3 (5.7) | 0 | 0 |
| Depression | 2 (3.8) | 6 (11.8) | 1 (1.9) |
| Pain in extremity | 2 (3.8) | 5 (9.8) | 3 (5.8) |
| Musculoskeletal pain | 2 (3.8) | 5 (9.8) | 2 (3.8) |
| Rash | 2 (3.8) | 4 (7.8) | 2 (3.8) |
| Hypertension | 2 (3.8) | 1 (2.0) | 3 (5.8) |
| Headache | 1 (1.9) | 4 (7.8) | 3 (5.8) |
| Muscle spasms | 1 (1.9) | 4 (7.8) | 3 (5.8) |
| Dizziness | 1 (1.9) | 4 (7.8) | 2 (3.8) |
| Sciatica | 1 (1.9) | 4 (7.8) | 2 (3.8) |
| Gastroenteritis | 1 (1.9) | 3 (5.9) | 5 (9.6) |
| Influenza like illness | 1 (1.9) | 3 (5.9) | 2 (3.8) |
| Paraesthesia | 1 (1.9) | 3 (5.9) | 1 (1.9) |
| Diabetes mellitus | 1 (1.9) | 3 (5.9) | 1 (1.9) |
| Injection site pain | 1 (1.9) | 2 (3.9) | 4 (7.7) |
| Injection site erythema | 1 (1.9) | 1 (2.0) | 4 (7.7) |
| Tinea pedis | 1 (1.9) | 1 (2.0) | 3 (5.8) |
| Gastrooesophageal reflux disease | 1 (1.9) | 1 (2.0) | 3 (5.8) |
| Procedural pain | 1 (1.9) | 0 | 4 (7.7) |
| Seasonal allergy | 1 (1.9) | 0 | 3 (5.8) |
| Anaemia | 0 | 4 (7.8) | 1 (1.9) |
| Oedema peripheral | 0 | 3 (5.9) | 2 (3.8) |
| Laceration | 0 | 3 (5.9) | 1 (1.9) |
| Anxiety | 0 | 3 (5.9) | 1 (1.9) |
| Mouth ulceration | 0 | 3 (5.9) | 0 |
| Haemorrhoids | 0 | 1 (2.0) | 3 (5.8) |

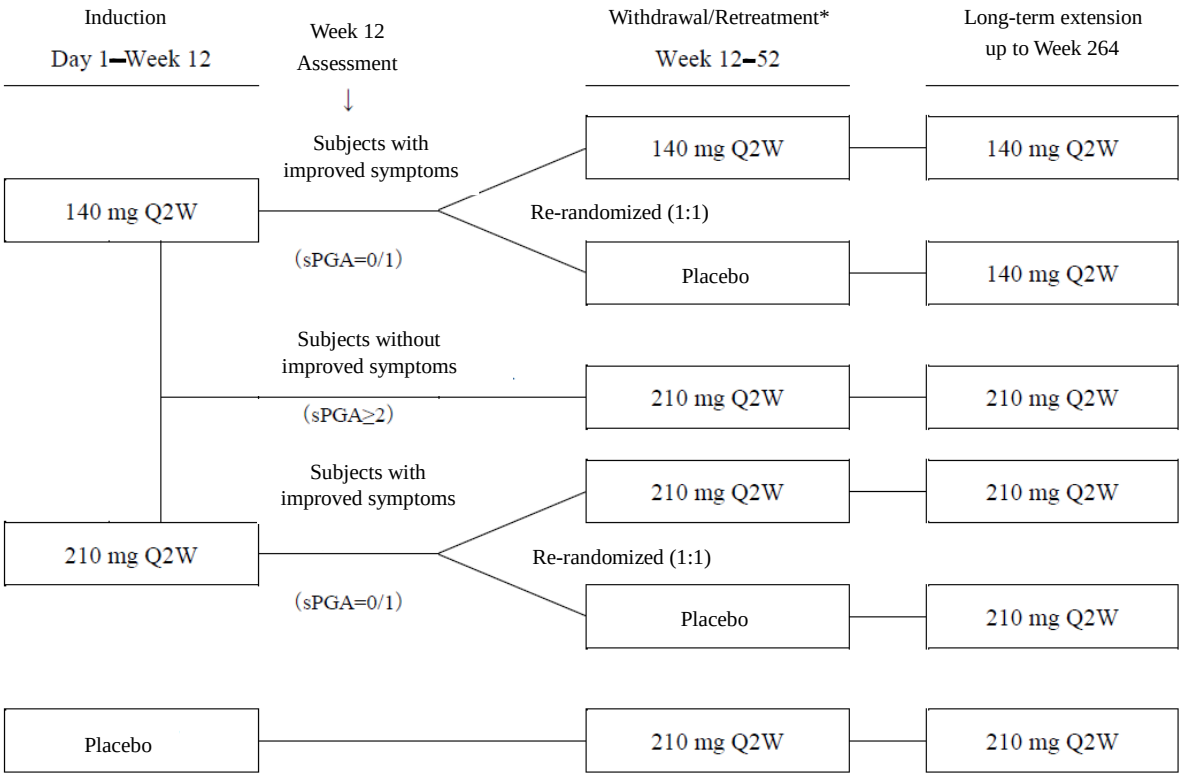
n (%)

## 7.2 Phase III studies

### 7.2.1 Foreign phase III study (CTD5.3.5.1-3, Study 20120102 [ongoing since August 2012]; data cutoff, March 2014)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in 6 countries including the US and Canada to evaluate the efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis, including psoriatic arthritis[17] (target sample size, 600 subjects).

The study consisted of 3 phases (induction phase, until Week 12; withdrawal/retreatment phase, from Week 12 to Week 52; long-term extension phase, from Week 52 up to Week 264). Brodalumab 140 or 210 mg or placebo was administered subcutaneously according to Figure 3.




* Subjects who experienced relapse of disease (sPGA ≥3) between Weeks 16 and 52 were retreated with their induction-phase dose of KHK4827 once weekly for 3 doses and every 2 weeks thereafter.

Figure 3. Assignment to treatment and dosing schedule for Study 20120102
Q2W = Administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter
Subjects with inadequate response to retreatment were allowed to receive rescue treatment with brodalumab 210 mg Q2W.

The FAS included all of 661 subjects randomized to the brodalumab 140 or 210 mg or placebo group with stratification by body weight (≤100 kg vs. >100 kg), prior biologic use (yes vs. no), and geographic region (219 in the brodalumab 140 mg group, 222 in the brodalumab 210 mg group, 220 in the placebo group). The 661 subjects who received study drug in the FAS (219 in the brodalumab 140 mg group, 222 in the brodalumab 210 mg group, and 220 in the placebo group) were included in the safety analysis set. The FAS was used for efficacy analyses.

[17] Patients with (a) ≥10% BSA affected by psoriasis, (b) PASI score ≥12, and (c) sPGA score ≥3.

The discontinuation rates during the induction phase were 5.0% (11 of 219 subjects) in the brodalumab 140 mg group, 4.5% (10 of 222 subjects) in the brodalumab 210 mg group, and 5.5% (12 of 220 subjects) in the placebo group. The main reasons for discontinuation were adverse event (1.4% [3 of 219 subjects] in the brodalumab 140 mg group, 0.9% [2 of 222 subjects] in the brodalumab 210 mg group, 1.4% [3 of 220 subjects] in the placebo group), etc. Among 633 subjects who completed the induction phase, 628 subjects (208 in the brodalumab 140 mg group, 212 in the brodalumab 210 mg group, and 208 in the placebo group) entered the withdrawal/retreatment phase. Of the 208 subjects in the brodalumab 140 mg group, 116 subjects achieving sPGA 0 or 1 were re-randomized to the 140 mg/140 mg (57 subjects) or 140 mg/placebo (59 subjects) group, and subjects with sPGA ≥2 (92 subjects) were switched to brodalumab 210 mg Q2W. Of the 212 subjects in the brodalumab 210 mg group, 167 achieving sPGA 0 or 1 were re-randomized to the 210 mg/210 mg (83 subjects) or 210 mg/placebo (84 subjects) group, and subjects with sPGA ≥2 (45 subjects) continued to receive brodalumab 210 mg Q2W. The 208 subjects in the placebo group were switched to brodalumab 210 mg Q2W.

The co-primary efficacy endpoints were the PASI 75 response and sPGA success (0 or 1) rates at Week 12 (for results, see Table 30). Pairwise comparisons showed statistically significant differences between each brodalumab dose (140 and 210 mg) and placebo, confirming the superiority of brodalumab 140 and 210 mg to placebo. The secondary efficacy endpoints were the PASI 100 response and sPGA 0 rates (for results, see Table 31).

Table 30. PASI 75 response and sPGA success (0 or 1) rates at Week 12 (FAS, NRI)

| | Brodalumab 140 mg | Brodalumab 210 mg | Placebo | Difference from placebo [95% CI], *P*-value[a), b)] | |
|---|---|---|---|---|---|
| | | | | Brodalumab 140 mg | Brodalumab 210 mg |
| PASI 75 | 60.3 (132/219) | 83.3 (185/222) | 2.7 (6/220) | 57.5 [49.4, 64.7]<br>*P* < 0.001 | 80.6 [74.7, 85.7]<br>*P* < 0.001 |
| sPGA success (0 or 1) | 53.9 (118/219) | 75.7 (168/222) | 1.4 (3/220) | 52.5 [44.1, 60.0]<br>*P* < 0.001 | 74.3 [67.7, 80.2]<br>*P* < 0.001 |

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by body weight (≤100 kg vs. >100 kg), prior biologic use (yes vs. no), geographic region, and baseline value of the endpoints (≤ median, >median for PASI; 3, 4, 5 for sPGA)

b) A sequential testing procedure was applied for multiplicity adjustment. The testing hierarchy was as follows: pairwise comparison between brodalumab 210 mg and placebo for PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary endpoints); pairwise comparison between brodalumab 140 mg and placebo for the co-primary endpoints; pairwise comparison between brodalumab 210 mg and placebo for PASI 100 response and sPGA (0) rates at Week 12 and sPGA success (0 or 1) rate at Week 52 (the secondary endpoints); and pairwise comparison between brodalumab 140 mg and placebo for the secondary endpoints. Both pairwise comparisons for the co-primary endpoints of PASI 75 response and sPGA success (0 or 1) rates at Week 12 were required to be statistically significant in order to move to the next pairwise comparison.

Table 31. PASI 100 response and sPGA 0 rates at Week 12 (FAS, NRI)

| | Brodalumab 140 mg | Brodalumab 210 mg | Placebo |
|---|---|---|---|
| PASI 100 | 23.3 (51/219) | 41.9 (93/222) | 0.5 (1/220) |
| sPGA 0 | 23.3 (51/219) | 41.9 (93/222) | 0.5 (1/220) |

% (n/N)

During the induction phase (until Week 12), adverse events occurred in 57.5% (126 of 219 subjects) of the brodalumab 140 mg group, 59.0% (131 of 222 subjects) of the brodalumab 210 mg group, and 50.9% (112 of 220 subjects) of the placebo group. The main events are shown in Table 32. No deaths were reported.

Serious adverse events occurred in 2.7% (6 of 219 subjects [cellulitis, diverticulitis, pancreatitis acute, volvulus of small bowel, intervertebral disc protrusion, and pyrexia in 1 subject each]) of the brodalumab 140 mg group, 1.8% (4 of 222 subjects [cellulitis, back pain, cholecystitis acute, and diabetes mellitus in 1 subject each]) of the brodalumab 210 mg group, and 1.4% (3 of 220 subjects [psoriasis in 2 subjects and chronic obstructive pulmonary disease in 1 subject]) of the placebo group. A causal relationship to study drug could not be ruled out for pyrexia and cellulitis observed in the brodalumab 210 mg group. (A causal relationship to study drug was ruled out for the other events.) The outcomes of these serious adverse events were reported as "resolved," except for cellulitis observed in the brodalumab 140 mg group and psoriasis reported by 2 subjects in the placebo group.

Adverse events leading to discontinuation[18] occurred in 1.8% (4 of 219 subjects [psoriatic arthropathy, arrhythmia, pancreatitis acute, and eosinophil count increased in 1 subject each]) of the brodalumab 140 mg group, 0.9% (2 of 222 subjects [psoriasis and dactylitis in 1 subject each]) of the brodalumab 210 mg group, and 1.4% (3 of 220 subjects [psoriasis in 2 subjects and pain in 1 subject]) of the placebo group. A causal relationship to study drug could not be ruled out for 3 cases (psoriatic arthropathy, arrhythmia, and eosinophil count increased in 1 subject each) in the brodalumab 140 mg group, 2 cases (psoriasis and dactylitis in 1 subject each) in the brodalumab 210 mg group, and 1 case (pain) in the placebo group.

Adverse drug reactions occurred in 20.1% (44 of 219 subjects) of the brodalumab 140 mg group, 18.0% (40 of 222 subjects) of the brodalumab 210 mg group, and 10.9% (24 of 220 subjects) of the placebo group.

Table 32. Adverse events reported by ≥3% of subjects in any group (Induction phase, Safety analysis set)

| Event term | Brodalumab 140 mg (N = 219) | Brodalumab 210 mg (N = 222) | Placebo (N = 220) |
|---|---|---|---|
| Nasopharyngitis | 20 (9.1) | 21 (9.5) | 22 (10.0) |
| Upper respiratory tract infection | 18 (8.2) | 18 (8.1) | 14 (6.4) |
| Headache | 12 (5.5) | 11 (5.0) | 7 (3.2) |
| Arthralgia | 10 (4.6) | 6 (2.7) | 6 (2.7) |
| Hypertension | 8 (3.7) | 2 (0.9) | 4 (1.8) |

n (%)

During the induction and withdrawal/retreatment phases, adverse events occurred in 75.4% (46 of 61 subjects) of the constant brodalumab 140 mg group,[19] 74.9% (259 of 346 subjects) of the constant brodalumab 210 mg group,[20] 83.8% (83 of 99 subjects) of the brodalumab 140 mg/210 mg group,[21] and 70.6% (101 of 143 subjects) of the brodalumab/placebo group.[22] The main events are shown in Table 33. Three subjects died (sudden death, intentional overdose, and oesophageal varices haemorrhage in 1 subject each) in the constant brodalumab 210 mg group. One subject died (cerebrovascular accident) in the brodalumab/placebo group. A causal relationship to study drug was ruled out for all deaths.

[18] While adverse events leading to study discontinuation were counted in other clinical studies, adverse events leading to study drug discontinuation only were counted in Study 20120102.
[19] Subjects who received brodalumab 140 mg during the induction and withdrawal/retreatment phases.
[20] Subjects who received brodalumab 210 mg during the induction and withdrawal/retreatment phases and subjects who received placebo during the induction phase and brodalumab 210 mg during the withdrawal/retreatment phase.
[21] Subjects who received brodalumab 140 mg during the induction phase and brodalumab 210 mg during the withdrawal/retreatment phase.
[22] Subjects who received brodalumab 140 or 210 mg during the induction phase and placebo during the withdrawal/retreatment phase.

Serious adverse events occurred in 6.6% (4 of 61 subjects) of the constant brodalumab 140 mg group, 6.1% (21 of 346 subjects) of the constant brodalumab 210 mg group, 10.1% (10 of 99 subjects) of the brodalumab 140 mg/210 mg group, and 4.2% (6 of 143 subjects) of the brodalumab/placebo group. The event reported by ≥2 subjects in any group was acute myocardial infarction (2 subjects in the constant brodalumab 210 mg group).

Adverse events leading to discontinuation[18] occurred in 6.6% (4 of 61 subjects) of the constant brodalumab 140 mg group, 2.6% (9 of 346 subjects) of the constant brodalumab 210 mg group, 1.0% (1 of 99 subjects) of the brodalumab 140 mg/210 mg group, and 0.7% (1 of 143 subjects) of the brodalumab/placebo group.

Adverse drug reactions occurred in 31.1% (19 of 61 subjects) of the constant brodalumab 140 mg group, 27.2% (94 of 346 subjects) of the constant brodalumab 210 mg group, 29.3% (29 of 99 subjects) of the brodalumab 140 mg/210 mg group, and 28.0% (40 of 143 subjects) of the brodalumab/placebo group.

Table 33. Adverse events reported by ≥3% of subjects in any group (Induction and withdrawal/retreatment phases, Safety analysis set)

| Event term | Constant brodalumab 140 mg (N = 61) | Constant brodalumab 210 mg (N = 346) | Brodalumab 140 mg/210 mg (N = 99) | Brodalumab/Placebo (N = 143) |
|---|---|---|---|---|
| Upper respiratory tract infection | 11 (18.0) | 47 (13.6) | 15 (15.2) | 13 (9.1) |
| Nasopharyngitis | 9 (14.8) | 45 (13.0) | 14 (14.1) | 28 (19.6) |
| Headache | 6 (9.8) | 21 (6.1) | 7 (7.1) | 10 (7.0) |
| Hypertension | 5 (8.2) | 12 (3.5) | 7 (7.1) | 1 (0.7) |
| Cough | 5 (8.2) | 11 (3.2) | 2 (2.0) | 3 (2.1) |
| Arthralgia | 4 (6.6) | 25 (7.2) | 14 (14.1) | 7 (4.9) |
| Nausea | 4 (6.6) | 12 (3.5) | 1 (1.0) | 2 (1.4) |
| Vomiting | 3 (4.9) | 3 (0.9) | 2 (2.0) | 2 (1.4) |
| Blood glucose increased | 3 (4.9) | 3 (0.9) | 1 (1.0) | 0 |
| Blood uric acid increased | 3 (4.9) | 2 (0.6) | 2 (2.0) | 1 (0.7) |
| Pyrexia | 3 (4.9) | 2 (0.6) | 2 (2.0) | 1 (0.7) |
| Back pain | 2 (3.3) | 19 (5.5) | 3 (3.0) | 5 (3.5) |
| Pruritus | 2 (3.3) | 12 (3.5) | 3 (3.0) | 4 (2.8) |
| Oropharyngeal pain | 2 (3.3) | 7 (2.0) | 4 (4.0) | 2 (1.4) |
| Pain in extremity | 2 (3.3) | 6 (1.7) | 2 (2.0) | 2 (1.4) |
| Tooth infection | 2 (3.3) | 4 (1.2) | 4 (4.0) | 2 (1.4) |
| Conjunctivitis | 2 (3.3) | 4 (1.2) | 2 (2.0) | 5 (3.5) |
| Seborrhoeic dermatitis | 2 (3.3) | 2 (0.6) | 1 (1.0) | 2 (1.4) |
| Epistaxis | 2 (3.3) | 2 (0.6) | 1 (1.0) | 0 |
| Intervertebral disc protrusion | 2 (3.3) | 2 (0.6) | 0 | 1 (0.7) |
| Anaemia | 2 (3.3) | 0 | 0 | 0 |
| Benign prostatic hyperplasia | 2 (3.3) | 0 | 0 | 0 |
| C-reactive protein increased | 2 (3.3) | 0 | 0 | 0 |
| Enterocolitis infectious | 2 (3.3) | 0 | 0 | 0 |
| Puncture site reaction | 2 (3.3) | 0 | 0 | 0 |
| Sinusitis | 1 (1.6) | 15 (4.3) | 2 (2.0) | 7 (4.9) |
| Diarrhoea | 1 (1.6) | 13 (3.8) | 4 (4.0) | 7 (4.9) |
| Bronchitis | 1 (1.6) | 12 (3.5) | 4 (4.0) | 7 (4.9) |
| Toothache | 1 (1.6) | 11 (3.2) | 2 (2.0) | 1 (0.7) |
| Psoriatic arthropathy | 1 (1.6) | 7 (2.0) | 3 (3.0) | 1 (0.7) |
| Muscle strain | 1 (1.6) | 7 (2.0) | 3 (3.0) | 1 (0.7) |
| Fall | 1 (1.6) | 1 (0.3) | 3 (3.0) | 2 (1.4) |
| Pharyngitis | 0 | 11 (3.2) | 2 (2.0) | 7 (4.9) |
| Urinary tract infection | 0 | 9 (2.6) | 4 (4.0) | 3 (2.1) |
| Rhinitis | 0 | 7 (2.0) | 1 (1.0) | 5 (3.5) |
| Musculoskeletal pain | 0 | 6 (1.7) | 3 (3.0) | 1 (0.7) |
| Viral upper respiratory tract infection | 0 | 5 (1.4) | 5 (5.1) | 2 (1.4) |
| Folliculitis | 0 | 5 (1.4) | 4 (4.0) | 1 (0.7) |
| Tinea pedis | 0 | 5 (1.4) | 3 (3.0) | 1 (0.7) |
| Gastroenteritis | 0 | 5 (1.4) | 2 (2.0) | 5 (3.5) |
| Arthritis | 0 | 5 (1.4) | 1 (1.0) | 5 (3.5) |
| Psoriasis | 0 | 4 (1.2) | 3 (3.0) | 2 (1.4) |
| Rhinitis allergic | 0 | 1 (0.3) | 3 (3.0) | 1 (0.7) |

n (%)

### 7.2.2 Foreign phase III study (CTD5.3.5.1-4, Study 20120103 [ongoing since August 2012]; data cutoff, September 2014)

A randomized, double-blind, parallel-group study was conducted in 11 countries including the US and Poland to evaluate the efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis, including psoriatic arthritis[23] (target sample size, 1800 subjects).

The study consisted of 3 phases (induction phase, until Week 12; maintenance phase, from Week 12 to Week 52; long-term extension phase, from Week 52 up to Week 264). Brodalumab 140 or 210 mg, Ustekinumab (Genetical Recombination) [24] (hereinafter referred to as ustekinumab), or placebo was administered subcutaneously according to Figure 4.

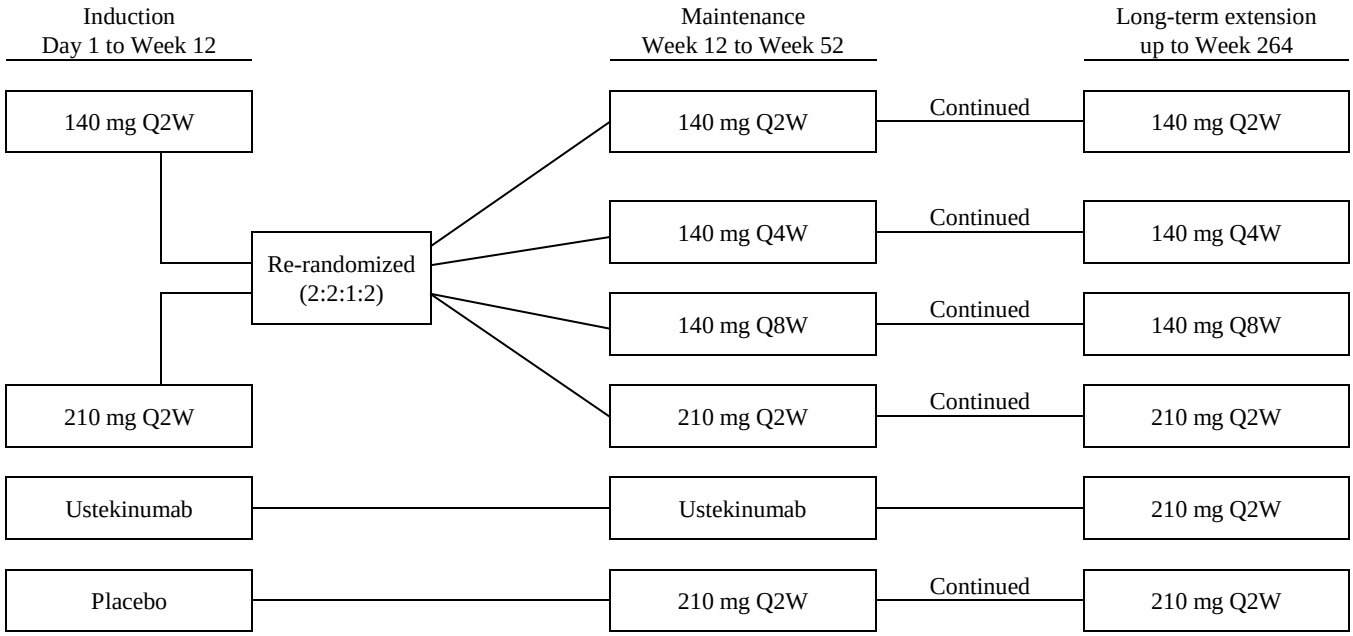



Figure 4. Assignment to treatment and dosing schedule for Study 20120103

Q2W: Administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter
Q4W: Administered subcutaneously every 4 weeks
Q8W: Administered subcutaneously every 8 weeks
Subjects who did not visit the study site at Week 12 were withdrawn from study treatment (i.e., not allowed to receive study drug after Week 12).
Subjects showing an inadequate response to brodalumab or ustekinumab at Week 16 (a single sPGA score of ≥3; or sPGA scores remaining at ≥2 for at least 4 weeks) were allowed to receive rescue treatment with brodalumab 210 mg Q2W. Between Weeks 16 and 52, subjects with an inadequate response to brodalumab were allowed to receive rescue treatment with brodalumab 210 mg Q2W, and subjects with an inadequate response to ustekinumab continued to receive ustekinumab.

During the induction phase, 1831 subjects were randomized in a 2:2:1:1 ratio to the brodalumab 140 mg, 210 mg, ustekinumab, or placebo group with stratification by baseline body weight (≤100 kg vs. >100 kg), previous biologic use (yes vs. no), and geographic region (610 in the brodalumab 140 mg group, 612 in the brodalumab 210 mg group, 300 in the ustekinumab group, 309 in the placebo group). The FAS included the 1831 subjects. Among them, 1828 subjects who received study drug (607 in the brodalumab 140 mg group, 612 in the

[23] Patients with (a) ≥10% BSA affected by psoriasis, (b) PASI score ≥12, and (c) sPGA score ≥3.
[24] Subjects weighing ≤100 kg at baseline received 45 mg Ustekinumab (Genetical Recombination) and subjects weighing >100 kg at baseline received 90 mg Ustekinumab (Genetical Recombination) at Weeks 0 and 4 and every 12 weeks thereafter.

brodalumab 210 mg group, 300 in the ustekinumab group, and 309 in the placebo group) were included in the safety analysis set. The FAS was used for efficacy analyses.

The discontinuation rates during the induction phase were 3.6% (22 of 610 subjects) in the brodalumab 140 mg group, 2.5% (15 of 612 subjects) in the brodalumab 210 mg group, 3.0% (9 of 300 subjects) in the ustekinumab group, and 2.9% (9 of 309 subjects) in the placebo group. The main reasons for discontinuation were consent withdrawal (1.8% [11 of 610 subjects] in the brodalumab 140 mg group, 0.3% [2 of 612 subjects] in the brodalumab 210 mg group, 1.0% [3 of 300 subjects] in the ustekinumab group, 1.6% [5 of 309 subjects] in the placebo group), etc. In total, 1776 subjects (588 in the brodalumab 140 mg group, 597 in the brodalumab 210 mg group, 291 in the ustekinumab group, 300 in the placebo group) completed the induction phase. Of the 1776 subjects, 1185 receiving brodalumab 140 or 210 mg during the induction phase were re-randomized to the brodalumab 140 mg Q2W (337 subjects), 140 mg Q4W (335 subjects), 140 mg Q8W (168 subjects), or 210 mg Q2W (334 subjects) group.

Table 34 shows the results of (a) pairwise comparisons between each brodalumab dose (140 and 210 mg) and placebo for the PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary efficacy endpoints); and (b) pairwise comparisons between brodalumab 210 mg and ustekinumab and between weight-based brodalumab (the weight-based analysis group[25]) and ustekinumab for the PASI 100 response rate at Week 12 (the primary efficacy endpoint). The pairwise comparisons showed statistically significant differences between each brodalumab dose (140 and 210 mg) and placebo, between brodalumab 210 mg and ustekinumab, and between weight-based brodalumab and ustekinumab. The results confirmed the superiority of brodalumab 140 and 210 mg to placebo and the superiority of brodalumab 210 mg and weight-based brodalumab to ustekinumab.

[25] This group consists of subjects receiving 140 mg Q2W with a body weight of ≤100 kg and subjects receiving 210 mg Q2W with a body weight of >100 kg.

Table 34. PASI 75 and 100 response rates and sPGA success (0 or 1) rate at Week 12 (FAS, NRI)

| | Brodalumab 140 mg | Brodalumab 210 mg | Weight-based brodalumab | Ustekinumab | Placebo |
|---|---|---|---|---|---|
| PASI 75 | 66.6 (406/610) | 86.3 (528/612) | 77.0 (470/610) | 70.0 (210/300) | 8.1 (25/309) |
| Difference from placebo [95% CI], *P*-value [a), b)] | 58.5 [52.6, 64.0] *P* < 0.001 | 78.2 [73.3, 82.6] *P* < 0.001 | | | |
| sPGA (0 or 1) | 58.0 (354/610) | 78.6 (481/612) | 68.9 (420/610) | 61.0 (183/300) | 3.9 (12/309) |
| Difference from placebo [95% CI], *P*-value [a), b)] | 54.1 [48.1, 59.9] *P* < 0.001 | 74.7 [69.5, 79.3] *P* < 0.001 | | | |
| PASI 100 | 25.7 (157/610) | 44.4 (272/612) | 33.6 (205/610) | 21.7 (65/300) | 0.6 (2/309) |
| Difference from ustekinumab [95% CI], *P*-value [a), b)] | | 22.8 [16.0, 29.5] *P* < 0.001 | 11.9 [5.0, 18.8] *P* < 0.001 | | |

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by body weight (≤100 kg vs. >100 kg), previous biologic use (yes vs. no), geographic region, and baseline value of the endpoints (≤ median, > median for PASI; 3, 4, 5 for sPGA)

b) The testing hierarchy was as follows: pairwise comparison between brodalumab 210 mg and placebo for PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary endpoints); pairwise comparison between brodalumab 140 mg and placebo for the co-primary endpoints; pairwise comparison between brodalumab 210 mg and placebo for PASI 100 response and sPGA (0) rates at Week 12 (the secondary endpoints); and pairwise comparison between brodalumab 140 mg and placebo for the secondary endpoints, etc. (two-sided significance level of 1%).

A sequential testing procedure was applied for multiplicity adjustment. The testing hierarchy was as follows: pairwise comparison between brodalumab 210 mg and ustekinumab for PASI 100 response rate at Week 12 (the primary endpoint); pairwise comparison between weight-based brodalumab and ustekinumab for PASI 100 response rate at Week 12 (the primary endpoint); pairwise comparison between brodalumab 140 mg and ustekinumab for PASI 100 response rate at Week 12 (the secondary endpoint); pairwise comparison between brodalumab 210 mg and ustekinumab for PASI 75 response rate at Week 12 (the secondary endpoint); and pairwise comparison between weight-based brodalumab and ustekinumab for PASI 75 response rate at Week 12 (the secondary endpoint) (two-sided significance level of 4%).

Both pairwise comparisons for PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary endpoints) were required to be statistically significant in order to move to the next pairwise comparison. In the efficacy analyses consisting of placebo and ustekinumab families, if the null hypotheses within 1 family were all rejected, the fraction of the overall alpha allocated to that family was to be recycled to the testing of the hypotheses in the other family (*Stat Med*. 2009; 28: 739-61).

During the induction phase (until Week 12), adverse events occurred in 60.1% (365 of 607 subjects) of the brodalumab 140 mg group, 57.8% (354 of 612 subjects) of the brodalumab 210 mg group, 59.0% (177 of 300 subjects) of the ustekinumab group, and 53.4% (165 of 309 subjects) of the placebo group. The main events are shown in Table 35. One death occurred (cerebral infarction) in the brodalumab 210 mg group, but its causal relationship to study drug was ruled out.

Serious adverse events occurred in 2.1% (13 of 607 subjects) of the brodalumab 140 mg group, 1.0% (6 of 612 subjects) of the brodalumab 210 mg group, 1.3% (4 of 300 subjects) of the ustekinumab group, and 2.6% (8 of 309 subjects) of the placebo group. A causal relationship to study drug could not be ruled out for 2 cases (cellulitis and angina unstable in 1 subject each) in the brodalumab 140 mg group, 1 case (cellulitis) in the brodalumab 210 mg group, and 1 case (Escherichia urinary tract infection) in the placebo group. None of the events were reported by ≥2 subjects in any group. The outcomes of these events were reported as “resolved” except for 2 cases (pancreatic carcinoma and pancreatic mass in 1 subject and angina pectoris in 1 subject) in the brodalumab 140 mg group, 1 case (subarachnoid haemorrhage) in the brodalumab 210 mg group, 1 case (prostate cancer) in the ustekinumab group, and 3 cases (blood glucose increased and diabetes mellitus inadequate control in 1 subject, hip fracture in 1 subject, and ligament rupture in 1 subject) in the placebo group.

Adverse events leading to discontinuation occurred in 1.2% (7 of 607 subjects [neutrophil count decreased, angina pectoris, gastroenteritis eosinophilic, pancreatic carcinoma, eczema, urticaria, and neutropenia in 1 subject each]) of the brodalumab 140 mg group, 1.0% (6 of 612 subjects [hepatic enzyme increased, appendicitis, oesophageal candidiasis, staphylococcal skin infection, upper gastrointestinal haemorrhage, cerebral infarction, and subarachnoid haemorrhage in 1 subject each]) of the brodalumab 210 mg group, 1.3% (4 of 300 subjects [acute coronary syndrome, asthenia, fatigue, and prostate cancer in 1 subject each]) of the ustekinumab group,

and 0.3% (1 of 309 subjects, liver function test abnormal) of the placebo group. A causal relationship to study drug could not be ruled out for 4 cases (eczema, neutrophil count decreased, neutropenia, and gastroenteritis eosinophilic) in the brodalumab 140 mg group, 1 case (staphylococcal skin infection) in the brodalumab 210 mg group, and 2 cases (asthenia and fatigue) in the ustekinumab group.

Adverse drug reactions occurred in 20.4% (124 of 607 subjects) of the brodalumab 140 mg group, 23.2% (142 of 612 subjects) of the brodalumab 210 mg group, 16.0% (48 of 300 subjects) of the ustekinumab group, and 13.3% (41 of 309 subjects) of the placebo group.

Table 35. Adverse events reported by ≥3% of subjects in any group (Induction phase, Safety analysis set)

| Event term | Brodalumab 140 mg (N = 607) | Brodalumab 210 mg (N = 612) | Ustekinumab (N = 300) | Placebo (N = 309) |
|---|---|---|---|---|
| Nasopharyngitis | 45 (7.4) | 45 (7.4) | 18 (6.0) | 14 (4.5) |
| Headache | 35 (5.8) | 31 (5.1) | 12 (4.0) | 9 (2.9) |
| Arthralgia | 33 (5.4) | 28 (4.6) | 9 (3.0) | 12 (3.9) |
| Upper respiratory tract infection | 30 (4.9) | 33 (5.4) | 20 (6.7) | 23 (7.4) |
| Pruritus | 19 (3.1) | 14 (2.3) | 6 (2.0) | 7 (2.3) |
| Fatigue | 11 (1.8) | 16 (2.6) | 12 (4.0) | 2 (0.6) |

n (%)

During the induction and maintenance phases, adverse events occurred in 76.0% (79 of 104 subjects) of the constant brodalumab 140 mg Q2W group,[26] 78.0% (379 of 486 subjects) of the constant brodalumab 210 mg Q2W group,[27] 82.7% (350 of 423 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group,[28] 86.7% (436 of 503 subjects) of the brodalumab 140 mg Q4W/Q8W group,[29] 68.6% (35 of 51 subjects) of the ustekinumab/brodalumab 210 mg Q2W group,[30] and 84.0% (252 of 300 subjects) of the ustekinumab group.[31] The main events are shown in Table 36. Four deaths occurred (1 subject in the constant brodalumab 210 mg Q2W group [death], 1 subject in the brodalumab 140 mg Q2W/210 mg Q2W group [abortion missed], 2 subjects in the ustekinumab group [death and pancreatic carcinoma in 1 subject each]) during the maintenance phase; a causal relationship to study drug could not be ruled out for the 1 case of pancreatic carcinoma only.

Serious adverse events occurred in 6.7% (7 of 104 subjects) of the constant brodalumab 140 mg Q2W group, 5.8% (28 of 486 subjects) of the constant brodalumab 210 mg Q2W group, 6.4% (27 of 423 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group, 5.0% (25 of 503 subjects) of the brodalumab 140 mg Q4W/Q8W group, 2.0% (1 of 51 subjects) of the ustekinumab/brodalumab 210 mg Q2W group, and 7.0% (21 of 300 subjects) of the ustekinumab group. Serious adverse events reported by ≥2 subjects in any group were cellulitis (3 subjects in the brodalumab 140 mg Q2W/210 mg Q2W group, 1 subject in the brodalumab 140 mg Q4W/Q8W group), angina unstable (2 subjects in the constant brodalumab 210 mg Q2W group, 1 subject in the constant brodalumab 140 mg Q2W group, 1 subject in the brodalumab 140 mg Q2W/210 mg Q2W group, and 1 subject in the ustekinumab group), cholelithiasis (2 subjects in the constant brodalumab 210 mg

[26] Subjects who received brodalumab 140 mg Q2W during the induction and maintenance phases.
[27] Subjects who received brodalumab 210 mg Q2W during the induction and maintenance phases and subjects who received placebo during the induction phase and brodalumab 210 mg Q2W during the maintenance phase.
[28] Subjects who received brodalumab 140 mg Q2W during the induction phase and brodalumab 210 mg Q2W during the maintenance phase and subjects who received brodalumab 210 mg Q2W during the induction phase and brodalumab 140 mg Q2W during the maintenance phase.
[29] Subjects who received brodalumab 140 mg Q4W or Q8W during the maintenance phase.
[30] Subjects who received ustekinumab during the induction phase and brodalumab 210 mg Q2W during the maintenance phase.
[31] Subjects who received ustekinumab during the induction and maintenance phases.

Q2W group, 1 subject in the brodalumab 140 mg Q2W/210 mg Q2W group), and syncope (2 subjects in the brodalumab 140 mg Q4W/Q8W group).

Adverse events leading to discontinuation occurred in 4.8% (5 of 104 subjects) of the constant brodalumab 140 mg Q2W group, 3.1% (15 of 486 subjects) of the constant brodalumab 210 mg Q2W group, 1.7% (7 of 423 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group, 3.0% (15 of 503 subjects) of the brodalumab 140 mg Q4W/Q8W group, 5.9% (3 of 51 subjects) of the ustekinumab/210 mg Q2W group, and 3.3% (10 of 300 subjects) of the ustekinumab group.

Adverse drug reactions occurred in 33.7% (35 of 104 subjects) of the constant brodalumab 140 mg Q2W group, 32.7% (159 of 486 subjects) of the constant brodalumab 210 mg Q2W group, 33.3% (141 of 423 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group, 38.4% (193 of 503 subjects) of the brodalumab 140 mg Q4W/Q8W group, 25.5% (13 of 51 subjects) of the ustekinumab/brodalumab 210 mg Q2W group, and 30.7% (92 of 300 subjects) of the ustekinumab group.

Table 36. Adverse events reported by ≥3% of subjects in any group (Induction and maintenance phases, Safety analysis set)

| Event term | Constant brodalumab 140 mg Q2W (N = 104) | Constant brodalumab 210 mg Q2W (N = 486) | Brodalumab 140 mg Q2W/210 mg Q2W (N = 423) | Brodalumab 140 mg Q4W/Q8W (N = 503) | Ustekinumab/ Brodalumab 210 mg Q2W (N = 51) | Ustekinumab (N = 300) |
|---|---|---|---|---|---|---|
| Nasopharyngitis | 17 (16.3) | 65 (13.4) | 83 (19.6) | 88 (17.5) | 7 (13.7) | 40 (13.3) |
| Arthralgia | 11 (10.6) | 32 (6.6) | 51 (12.1) | 53 (10.5) | 5 (9.8) | 22 (7.3) |
| Headache | 10 (9.6) | 31 (6.4) | 30 (7.1) | 57 (11.3) | 1 (2.0) | 23 (7.7) |
| Pruritus | 9 (8.7) | 18 (3.7) | 24 (5.7) | 34 (6.8) | 3 (5.9) | 12 (4.0) |
| Back pain | 7 (6.7) | 21 (4.3) | 15 (3.5) | 32 (6.4) | 0 | 13 (4.3) |
| Pain in extremity | 7 (6.7) | 17 (3.5) | 10 (2.4) | 19 (3.8) | 5 (9.8) | 3 (1.0) |
| Upper respiratory tract infection | 5 (4.8) | 66 (13.6) | 65 (15.4) | 75 (14.9) | 6 (11.8) | 46 (15.3) |
| Hypertension | 5 (4.8) | 17 (3.5) | 22 (5.2) | 34 (6.8) | 0 | 17 (5.7) |
| Oropharyngeal pain | 4 (3.8) | 14 (2.9) | 17 (4.0) | 23 (4.6) | 1 (2.0) | 7 (2.3) |
| Diarrhoea | 4 (3.8) | 10 (2.1) | 20 (4.7) | 26 (5.2) | 1 (2.0) | 14 (4.7) |
| Gout | 4 (3.8) | 9 (1.9) | 8 (1.9) | 6 (1.2) | 0 | 4 (1.3) |
| Dry skin | 4 (3.8) | 4 (0.8) | 3 (0.7) | 8 (1.6) | 0 | 2 (0.7) |
| Bronchitis | 3 (2.9) | 18 (3.7) | 11 (2.6) | 17 (3.4) | 1 (2.0) | 9 (3.0) |
| Myalgia | 3 (2.9) | 16 (3.3) | 9 (2.1) | 22 (4.4) | 0 | 7 (2.3) |
| Urinary tract infection | 3 (2.9) | 12 (2.5) | 16 (3.8) | 19 (3.8) | 0 | 8 (2.7) |
| Musculoskeletal pain | 3 (2.9) | 11 (2.3) | 10 (2.4) | 17 (3.4) | 2 (3.9) | 4 (1.3) |
| Pyrexia | 3 (2.9) | 9 (1.9) | 8 (1.9) | 15 (3.0) | 3 (5.9) | 6 (2.0) |
| Cough | 2 (1.9) | 22 (4.5) | 19 (4.5) | 20 (4.0) | 0 | 9 (3.0) |
| Fatigue | 2 (1.9) | 19 (3.9) | 8 (1.9) | 14 (2.8) | 2 (3.9) | 19 (6.3) |
| Influenza | 2 (1.9) | 14 (2.9) | 11 (2.6) | 17 (3.4) | 0 | 10 (3.3) |
| Nausea | 2 (1.9) | 12 (2.5) | 13 (3.1) | 11 (2.2) | 1 (2.0) | 12 (4.0) |
| Toothache | 2 (1.9) | 9 (1.9) | 14 (3.3) | 14 (2.8) | 0 | 11 (3.7) |
| Arthritis | 2 (1.9) | 8 (1.6) | 11 (2.6) | 7 (1.4) | 2 (3.9) | 2 (0.7) |
| Psoriatic arthropathy | 2 (1.9) | 8 (1.6) | 9 (2.1) | 23 (4.6) | 0 | 1 (0.3) |
| Vomiting | 2 (1.9) | 6 (1.2) | 11 (2.6) | 9 (1.8) | 0 | 11 (3.7) |
| Laceration | 2 (1.9) | 3 (0.6) | 6 (1.4) | 4 (0.8) | 2 (3.9) | 5 (1.7) |
| Sinusitis | 1 (1.0) | 17 (3.5) | 18 (4.3) | 16 (3.2) | 2 (3.9) | 14 (4.7) |
| Viral upper respiratory tract infection | 1 (1.0) | 11 (2.3) | 11 (2.6) | 11 (2.2) | 1 (2.0) | 9 (3.0) |
| Muscle strain | 1 (1.0) | 8 (1.6) | 11 (2.6) | 16 (3.2) | 0 | 5 (1.7) |
| Psoriasis | 0 | 11 (2.3) | 8 (1.9) | 16 (3.2) | 1 (2.0) | 2 (0.7) |
| Insomnia | 0 | 9 (1.9) | 6 (1.4) | 3 (0.6) | 2 (3.9) | 8 (2.7) |
| Hordeolum | 0 | 4 (0.8) | 6 (1.4) | 4 (0.8) | 2 (3.9) | 1 (0.3) |
| Injection site reaction | 0 | 2 (0.4) | 3 (0.7) | 1 (0.2) | 2 (3.9) | 4 (1.3) |

n (%)

### 7.2.3 Foreign phase III study (CTD5.3.5.1-5, Study 20120104 [ongoing since September 2012]; data cutoff, August 2014)

A randomized, double-blind, parallel-group study was conducted in 11 countries including the US and Poland to evaluate the efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis, including psoriatic arthritis[32] (target sample size, 1800). This study and Study 20120103 were identical in design [for study design, see 7.2.2 Foreign phase III study].

The FAS included all of 1881 subjects randomized in a 2:2:1:1 ratio to the brodalumab 140 mg, 210 mg, ustekinumab, or placebo group with stratification by baseline body weight (≤100 kg vs. >100 kg), previous

[32] Patients with (a) ≥10% BSA affected by psoriasis, (b) PASI score ≥12, and (c) sPGA score ≥3.

biologic use (yes vs. no), and geographic region (629 in the brodalumab 140 mg group, 624 in the brodalumab 210 mg group, 313 in the ustekinumab group, 315 in the placebo group).Of the 1881 subjects (FAS), 1874 who received study drug (626 in the brodalumab 140 mg group, 622 in the brodalumab 210 mg group, 313 in the ustekinumab group, 313 in the placebo group) were included in the safety analysis set. The FAS was used for efficacy analyses.

The discontinuation rates during the induction phase were 3.7% (23 of 629 subjects) in the brodalumab 140 mg group, 3.2% (20 of 624 subjects) in the brodalumab 210 mg group, 3.8% (12 of 313 subjects) in the ustekinumab group, and 4.1% (13 of 315 subjects) in the placebo group. The main reasons for discontinuation were consent withdrawal (1.1% [7 of 629 subjects] in the brodalumab 140 mg group, 0.8% [5 of 624 subjects] in the brodalumab 210 mg group, 1.0% [3 of 313 subjects] in the ustekinumab group, 2.2% [7 of 315 subjects] in the placebo group), etc. In total, 1816 subjects (604 in the brodalumab 140 mg group, 608 in the brodalumab 210 mg group, 303 in the ustekinumab group, 301 in the placebo group) completed the induction phase. Of the 1816 subjects, 1200 receiving brodalumab 140 or 210 mg during the induction phase were re-randomized to the brodalumab 140 mg Q2W (343 subjects), 140 mg Q4W (341 subjects), 140 mg Q8W (174 subjects), or 210 mg Q2W (342 subjects) group.

Table 37 shows the results of (a) pairwise comparisons between each brodalumab dose (140 and 210 mg) and placebo for the PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary efficacy endpoints); and (b) pairwise comparisons between brodalumab 210 mg and ustekinumab and between weight-based brodalumab (the weight-based analysis group) and ustekinumab for the PASI 100 response rate at Week 12 (the primary efficacy endpoint). The pairwise comparisons showed statistically significant differences between each brodalumab dose (140 and 210 mg) and placebo, between brodalumab 210 mg and ustekinumab, and between weight-based brodalumab and ustekinumab. These results confirmed the superiority of brodalumab 140 and 210 mg to placebo and the superiority of brodalumab 210 mg and weight-based brodalumab to ustekinumab.

Table 37. PASI 75 and 100 response rates and sPGA success (0 or 1) rate at Week 12 (FAS, NRI)

| | Brodalumab 140 mg | Brodalumab 210 mg | Weight-based brodalumab | Ustekinumab | Placebo |
|---|---|---|---|---|---|
| PASI 75 | 69.2 (435/629) | 85.1 (531/624) | 77.1 (484/628) | 69.3 (217/313) | 6.0 (19/315) |
| Difference from placebo [95% CI], *P*-value [a), b)] | 63.1 [57.5, 68.3] *P* < 0.001 | 79.1 [74.4, 83.4] *P* < 0.001 | | | |
| sPGA (0 or 1) | 59.9 (377/629) | 79.6 (497/624) | 68.5 (430/628) | 57.2 (179/313) | 4.1 (13/315) |
| Difference from placebo [95% CI], *P*-value [a), b)] | 55.8 [49.9, 61.4] *P* < 0.001 | 75.5 [70.4, 80.0] *P* < 0.001 | | | |
| PASI 100 | 27.0 (170/629) | 36.7 (229/624) | 30.4 (191/628) | 18.5 (58/313) | 0.3 (1/315) |
| Difference from ustekinumab [95% CI], *P*-value [a), b)] | | 18.2 [11.4, 24.8] *P* < 0.001 | 11.9 [5.1, 18.6] *P* < 0.001 | | |

% (n/N)

a) Cochran-Mantel-Haenszel test stratified by body weight (≤100 kg, >100 kg), previous biologic use (yes vs. no), geographic region, and baseline value of the endpoints (≤ median, > median for PASI; 3, 4, 5 for sPGA)

b) The testing hierarchy was as follows: pairwise comparison between brodalumab 210 mg and placebo for PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary endpoints); pairwise comparison between brodalumab 140 mg and placebo for the co-primary endpoints; pairwise comparison between brodalumab 210 mg and placebo for PASI 100 response and sPGA (0) rates at Week 12 (the secondary endpoints); and pairwise comparison between brodalumab 140 mg and placebo for the secondary endpoints, etc. (two-sided significance level of 1%).

A sequential testing procedure was applied for multiplicity adjustment. The testing hierarchy was as follows: pairwise comparison between brodalumab 210 mg and ustekinumab for PASI 100 response rate at Week 12 (the primary endpoint); pairwise comparison between weight-based brodalumab and ustekinumab for PASI 100 response rate at Week 12 (the primary endpoint); pairwise comparison between brodalumab 140 mg and ustekinumab for PASI 100 response rate at Week 12 (the secondary endpoint); pairwise comparison between brodalumab 210 mg and ustekinumab for PASI 75 response rate at Week 12 (the secondary endpoint); and pairwise comparison between weight-based brodalumab and ustekinumab for PASI 75 response rate at Week 12 (the secondary endpoint) (two-sided significance level of 4%).

Both pairwise comparisons for PASI 75 response and sPGA success (0 or 1) rates at Week 12 (the co-primary endpoints) were required to be statistically significant in order to move to the next pairwise comparison. In the efficacy analyses consisting of placebo and ustekinumab families, if the null hypotheses within 1 family were all rejected, the fraction of the overall alpha allocated to that family was to be recycled to the testing of the hypotheses in the other family (*Stat Med*. 2009; 28: 739-61).

During the induction phase, adverse events occurred in 52.6% (329 of 626 subjects) of the brodalumab 140 mg group, 56.8% (353 of 622 subjects) of the brodalumab 210 mg group, 53.7% (168 of 313 subjects) of the ustekinumab group, and 48.6% (152 of 313 subjects) of the placebo group. The main events are shown in Table 38. No deaths were reported.

Serious adverse events occurred in 1.6% (10 of 626 subjects) of the brodalumab 140 mg group, 1.4% (9 of 622 subjects) of the brodalumab 210 mg group, 0.6% (2 of 313 subjects) of the ustekinumab group, and 1.0% (3 of 313 subjects) of the placebo group. A causal relationship to study drug could not be ruled out for 2 cases (appendicitis and rash papular in 1 subject each) in the brodalumab 140 mg group and 1 case (meningitis cryptococcal) in the brodalumab 210 mg group. None of the events were reported by ≥2 subjects in any group, and the outcomes of these events were reported as “resolved” except for 1 case (bladder cancer) in the brodalumab 210 mg group.

Adverse events leading to discontinuation occurred in 0.8% (5 of 626 subjects [arthralgia in 2 subjects, leukopenia and neutropenia in 1 subject, psoriasis in 1 subject, and myocardial infarction in 1 subject]) of the brodalumab 140 mg group, 1.1% (7 of 622 subjects [glomerulonephritis, acute renal failure, arthralgia, meningitis cryptococcal, colitis ulcerative, gastritis, erythrodermic psoriasis, influenza like illness, arthropod bite, and bladder cancer in 1 subject each]) of the brodalumab 210 mg group, 0.6% (2 of 313 subjects [liver function test abnormal and neutrophil count abnormal in 1 subject each]) of the ustekinumab group, and 1.0% (3 of 313 subjects [renal failure, leukopenia, and localised infection in 1 subject each]) of the placebo group. A causal relationship to study drug could not be ruled out for 3 cases (arthralgia in 1 subject, psoriasis in 1 subject, and leukopenia and neutropenia in 1 subject) in the brodalumab 140 mg group, 2 cases (colitis ulcerative

and meningitis cryptococcal in 1 subject each) in the brodalumab 210 mg group, and 1 case (leukopenia) in the placebo group.

Adverse drug reactions occurred in 15.5% (97 of 626 subjects) of the brodalumab 140 mg group, 19.9% (124 of 622 subjects) of the brodalumab 210 mg group, 15.3% (48 of 313 subjects) of the ustekinumab group, and 12.5% (39 of 313 subjects) of the placebo group.

Table 38. Adverse events reported by ≥3% of subjects in any group (Induction phase, Safety analysis set)

| Event term | Brodalumab 140 mg (N = 626) | Brodalumab 210 mg (N = 622) | Ustekinumab (N = 313) | Placebo (N = 313) |
|---|---|---|---|---|
| Nasopharyngitis | 36 (5.8) | 31 (5.0) | 16 (5.1) | 22 (7.0) |
| Headache | 32 (5.1) | 21 (3.4) | 11 (3.5) | 14 (4.5) |
| Arthralgia | 25 (4.0) | 36 (5.8) | 6 (1.9) | 10 (3.2) |
| Fatigue | 20 (3.2) | 20 (3.2) | 4 (1.3) | 6 (1.9) |
| Upper respiratory tract infection | 19 (3.0) | 33 (5.3) | 16 (5.1) | 17 (5.4) |
| Pruritus | 17 (2.7) | 9 (1.4) | 6 (1.9) | 15 (4.8) |

n (%)

During the induction and maintenance phases, adverse events occurred in 71.7% (81 of 113 subjects) of the constant brodalumab 140 mg Q2W group,[26] 79.1% (387 of 489 subjects) of the constant brodalumab 210 mg Q2W group,[27] 80.6% (345 of 428 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group,[28] 81.6% (420 of 515 subjects) of the brodalumab 140 mg Q4W/Q8W group,[29] 69.1% (47 of 68 subjects) of the ustekinumab/brodalumab 210 mg Q2W group,[30] and 80.2% (251 of 313 subjects) of the ustekinumab group.[31] The main events are shown in Table 39. During the maintenance phase, 2 deaths occurred (cardiac arrest and accidental death in 1 subject each) in the brodalumab 140 mg Q2W/210 mg Q2W group, but a causal relationship to study drug was ruled out for both deaths.

Serious adverse events occurred in 4.4% (5 of 113 subjects) of the constant brodalumab 140 mg Q2W group, 4.7% (23 of 489 subjects) of the constant brodalumab 210 mg Q2W group, 5.8% (25 of 428 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group, 5.8% (30 of 515 subjects) of the brodalumab 140 mg Q4W/Q8W group, 4.4% (3 of 68 subjects) of the ustekinumab/brodalumab 210 mg Q2W group, and 2.9% (9 of 313 subjects) of the ustekinumab group. The events reported by ≥2 subjects in any group were myocardial infarction (3 subjects in the brodalumab 140 mg Q2W/210 mg Q2W group, 1 subject each in the constant brodalumab 140 mg Q2W, constant brodalumab 210 mg Q2W, and 140 mg Q4W/Q8W groups), cholelithiasis (2 subjects in the brodalumab 140 mg Q4W/Q8W group, 1 subject in the constant brodalumab 210 mg Q2W group), nephrolithiasis (2 subjects in the brodalumab 140 mg Q2W/210 mg Q2W group, 1 subject in the brodalumab 140 mg Q4W/Q8W group), cellulitis (2 subjects in the constant brodalumab 210 mg Q2W group, 1 subject in the ustekinumab group), fall (2 subjects in the brodalumab 140 mg Q2W/210 mg Q2W group), and thrombocytopenia (2 subjects in the brodalumab 140 mg Q4W/Q8W group).

Adverse events leading to discontinuation occurred in 3.5% (4 of 113 subjects) of the constant brodalumab 140 mg Q2W group, 2.5% (12 of 489 subjects) of the constant brodalumab 210 mg Q2W group,

2.1% (9 of 428 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group, 1.6% (8 of 515 subjects) of the brodalumab 140 mg Q4W/Q8W group, and 1.3% (4 of 313 subjects) of the ustekinumab group.

Adverse drug reactions occurred in 27.4% (31 of 113 subjects) of the constant brodalumab 140 mg Q2W group, 28.6% (140 of 489 subjects) of the constant brodalumab 210 mg Q2W group, 30.6% (131 of 428 subjects) of the brodalumab 140 mg Q2W/210 mg Q2W group, 33.4% (172 of 515 subjects) of the brodalumab 140 mg Q4W/Q8W group, 29.4% (20 of 68 subjects) of the ustekinumab/brodalumab 210 mg Q2W group, and 24.6% (77 of 313 subjects) of the ustekinumab group.

Table 39. Adverse events reported by ≥3% of subjects in any group (Induction and maintenance phases, Safety analysis set)

| Event term | Constant brodalumab 140 mg Q2W (N = 113) | Constant brodalumab 210 mg Q2W (N = 489) | Brodalumab 140 mg Q2W/ 210 mg Q2W (N = 428) | Brodalumab 140 mg Q4W/Q8W (N = 515) | Ustekinumab/ Brodalumab 210 mg Q2W (N = 68) | Ustekinumab (N = 313) |
|---|---|---|---|---|---|---|
| Nasopharyngitis | 15 (13.3) | 63 (12.9) | 70 (16.4) | 54 (10.5) | 6 (8.8) | 48 (15.3) |
| Arthralgia | 12 (10.6) | 49 (10.0) | 54 (12.6) | 50 (9.7) | 5 (7.4) | 19 (6.1) |
| Oropharyngeal pain | 10 (8.8) | 20 (4.1) | 18 (4.2) | 24 (4.7) | 0 | 13 (4.2) |
| Upper respiratory tract infection | 7 (6.2) | 51 (10.4) | 42 (9.8) | 68 (13.2) | 6 (8.8) | 47 (15.0) |
| Headache | 7 (6.2) | 34 (7.0) | 28 (6.5) | 36 (7.0) | 4 (5.9) | 18 (5.8) |
| Nausea | 7 (6.2) | 12 (2.5) | 14 (3.3) | 10 (1.9) | 1 (1.5) | 6 (1.9) |
| Back pain | 6 (5.3) | 24 (4.9) | 20 (4.7) | 11 (2.1) | 1 (1.5) | 16 (5.1) |
| Myalgia | 6 (5.3) | 9 (1.8) | 11 (2.6) | 9 (1.7) | 2 (2.9) | 6 (1.9) |
| Pain in extremity | 5 (4.4) | 10 (2.0) | 13 (3.0) | 21 (4.1) | 2 (2.9) | 8 (2.6) |
| Pruritus | 5 (4.4) | 8 (1.6) | 21 (4.9) | 27 (5.2) | 1 (1.5) | 9 (2.9) |
| Erythema | 5 (4.4) | 2 (0.4) | 2 (0.5) | 3 (0.6) | 0 | 0 |
| Fatigue | 4 (3.5) | 22 (4.5) | 19 (4.4) | 25 (4.9) | 1 (1.5) | 8 (2.6) |
| Urinary tract infection | 4 (3.5) | 22 (4.5) | 14 (3.3) | 13 (2.5) | 2 (2.9) | 15 (4.8) |
| Diarrhoea | 4 (3.5) | 17 (3.5) | 14 (3.3) | 19 (3.7) | 2 (2.9) | 6 (1.9) |
| Bronchitis | 4 (3.5) | 11 (2.2) | 11 (2.6) | 17 (3.3) | 1 (1.5) | 11 (3.5) |
| Psoriasis | 4 (3.5) | 6 (1.2) | 9 (2.1) | 20 (3.9) | 0 | 2 (0.6) |
| Pharyngitis | 3 (2.7) | 22 (4.5) | 6 (1.4) | 13 (2.5) | 0 | 7 (2.2) |
| Cough | 3 (2.7) | 16 (3.3) | 18 (4.2) | 26 (5.0) | 0 | 14 (4.5) |
| Oral herpes | 3 (2.7) | 10 (2.0) | 14 (3.3) | 7 (1.4) | 0 | 3 (1.0) |
| Influenza | 2 (1.8) | 14 (2.9) | 17 (4.0) | 10 (1.9) | 3 (4.4) | 13 (4.2) |
| Musculoskeletal pain | 2 (1.8) | 10 (2.0) | 12 (2.8) | 7 (1.4) | 3 (4.4) | 2 (0.6) |
| Influenza like illness | 2 (1.8) | 3 (0.6) | 10 (2.3) | 16 (3.1) | 0 | 2 (0.6) |
| Hypertension | 1 (0.9) | 21 (4.3) | 25 (5.8) | 22 (4.3) | 3 (4.4) | 16 (5.1) |
| Sinusitis | 1 (0.9) | 8 (1.6) | 14 (3.3) | 20 (3.9) | 3 (4.4) | 5 (1.6) |
| Psoriatic arthropathy | 1 (0.9) | 7 (1.4) | 14 (3.3) | 13 (2.5) | 1 (1.5) | 4 (1.3) |
| Gastroenteritis | 1 (0.9) | 5 (1.0) | 7 (1.6) | 18 (3.5) | 1 (1.5) | 6 (1.9) |
| Weight increased | 1 (0.9) | 6 (1.2) | 6 (1.4) | 3 (0.6) | 3 (4.4) | 4 (1.3) |

n (%)

### 7.2.4 Japanese long-term treatment study (CTD5.3.5.2-1, Study 4827-003 [February 2013 to July 2014])

An open-label, uncontrolled study was conducted to evaluate the long-term safety of brodalumab in patients with psoriasis vulgaris or psoriatic arthritis who completed the treatment period (12 weeks) of Study 4827-002 (target sample size, 140 subjects).

Brodalumab 140 or 210 mg was administered subcutaneously every 2 weeks for 52 weeks.[33]

[33] Subjects receiving brodalumab 140 or 210 mg in Study 4827-002 continued to receive the same dose of brodalumab. Subjects receiving brodalumab 70 mg or placebo in Study 4827-002 were randomly assigned to receive brodalumab 140 or 210 mg. The re-randomized subjects received brodalumab also at Week 1.

All of 145 subjects treated[34] (73 in the brodalumab 140 mg group, 72 in the brodalumab 210 mg group) were included in the FAS and in the safety analysis set. The discontinuation rates were 12.3% (9 of 73 subjects) in the brodalumab 140 mg group and 4.2% (3 of 72 subjects) in the brodalumab 210 mg group. The main reasons for discontinuation were consent withdrawal (2.7% [2 of 73 subjects] in the brodalumab 140 mg group, 1.4% [1 of 72 subjects] in the brodalumab 210 mg group), etc.

Adverse events occurred in 86.3% (63 of 73 subjects) of the brodalumab 140 mg group and 91.7% (66 of 72 subjects) of the brodalumab 210 mg group. The main events are shown in Table 40. No deaths were reported.

Serious adverse events occurred in 5.5% (4 of 73 subjects [allergy to arthropod sting, cellulitis, osteoarthritis, and varicose vein in 1 subject each]) of the brodalumab 140 mg group and 5.6% (4 of 72 subjects [myocardial ischaemia, cellulitis, infection, and contact dermatitis in 1 subject each]) of the brodalumab 210 mg group. A causal relationship to study drug could not be ruled out for 1 case (cellulitis) in the brodalumab 140 mg group and 2 cases (cellulitis and infection in 1 subject each) in the brodalumab 210 mg group, but the outcomes of these events were reported as “improved” or “resolved.”

Adverse events leading to discontinuation or interruption occurred in 8.2% (6 of 73 subjects [parotitis, pharyngitis, atrial fibrillation, staphylococcal impetigo, upper respiratory tract inflammation, and blood bilirubin increased in 1 subject each]) of the brodalumab 140 mg group and 16.7% (12 of 72 subjects [upper respiratory tract inflammation in 3 subjects; pyrexia in 2 subjects; and pharyngitis, cellulitis, gastroenteritis, oral candidiasis, enteritis infectious, blood bilirubin increased, eosinophil count increased, computerised tomogram thorax abnormal, hepatic enzyme increased, cell marker increased, and drug eruption in 1 subject each]) of the brodalumab 210 mg group. A causal relationship to study drug could not be ruled out for 4 cases (pharyngitis, parotitis, staphylococcal impetigo, and blood bilirubin increased in 1 subject each) in the brodalumab 140 mg group and the events reported by 6 subjects (upper respiratory tract inflammation in 2 subjects; and oral candidiasis, cell marker increased, hepatic enzyme increased, cellulitis, eosinophil count increased, and gastroenteritis in 1 subject each) in the brodalumab 210 mg group.

Adverse drug reactions occurred in 57.5% (42 of 73 subjects) of the brodalumab 140 mg group and 55.6% (40 of 72 subjects) of the brodalumab 210 mg group.

Table 40. Adverse events reported by ≥3 subjects in either group (Safety analysis set)

| Event term | Brodalumab 140 mg (N = 73) | Brodalumab 210 mg (N = 72) |
|---|---|---|
| Nasopharyngitis | 23 (31.5) | 28 (38.9) |
| Arthralgia | 9 (12.3) | 3 (4.2) |
| Upper respiratory tract inflammation | 7 (9.6) | 8 (11.1) |
| Contact dermatitis | 6 (8.2) | 8 (11.1) |
| Folliculitis | 5 (6.8) | 7 (9.7) |
| Back pain | 5 (6.8) | 5 (6.9) |
| Eczema | 4 (5.5) | 5 (6.9) |

[34] In Study 4827-002, 34 subjects receiving placebo, 37 subjects receiving 70 mg, 37 subjects receiving 140 mg, and 37 subjects receiving 210 mg completed the study. The 71 subjects receiving placebo or 70 mg were randomized to receive 140 mg (36 subjects) or 210 mg (35 subjects).

| | | |
|---|---|---|
| Dental caries | 4 (5.5) | 4 (5.6) |
| Headache | 4 (5.5) | 3 (4.2) |
| Tinea pedis | 3 (4.1) | 8 (11.1) |
| Pharyngitis | 3 (4.1) | 6 (8.3) |
| Skin papilloma | 3 (4.1) | 5 (6.9) |
| Hepatic function abnormal | 3 (4.1) | 2 (2.8) |
| Influenza | 3 (4.1) | 2 (2.8) |
| Arthropod sting | 3 (4.1) | 2 (2.8) |
| Musculoskeletal pain | 3 (4.1) | 2 (2.8) |
| Eczema asteatotic | 3 (4.1) | 2 (2.8) |
| Type 2 diabetes mellitus | 3 (4.1) | 1 (1.4) |
| Miliaria | 3 (4.1) | 1 (1.4) |
| Pruritus | 3 (4.1) | 1 (1.4) |
| Gastritis | 3 (4.1) | 0 |
| Seasonal allergy | 2 (2.7) | 5 (6.9) |
| Cellulitis | 2 (2.7) | 4 (5.6) |
| Pyrexia | 2 (2.7) | 3 (4.2) |
| Asteatosis | 2 (2.7) | 3 (4.2) |
| Xeroderma | 1 (1.4) | 7 (9.7) |
| Blood triglycerides increased | 1 (1.4) | 6 (8.3) |
| Periodontitis | 1 (1.4) | 5 (6.9) |
| Dry skin | 1 (1.4) | 4 (5.6) |
| Oral candidiasis | 0 | 6 (8.3) |
| Seborrhoeic dermatitis | 0 | 4 (5.6) |
| Dyshidrotic eczema | 0 | 3 (4.2) |

n (%)

**7.2.5 Japanese clinical study (CTD5.3.5.2-4, Study 4827-004 [January 2013 to May 2014])**

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of brodalumab in patients with pustular psoriasis or erythrodermic psoriasis (target sample size: ≥4 subjects with pustular psoriasis, ≥4 subjects with erythrodermic psoriasis).

Brodalumab 140 mg was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter until Week 52. If a subject was considered to have an inadequate response at Week ≥4,[35] brodalumab 210 mg was administered subcutaneously every 2 weeks.

All of 30 treated subjects (12 patients with pustular psoriasis, 18 patients with erythrodermic psoriasis) were included in the FAS and in the safety analysis set.[36] The FAS was used for efficacy analyses. The discontinuation rates were 17% (2 of 12) among patients with pustular psoriasis and 11% (2 of 18) among patients with erythrodermic psoriasis.

The primary efficacy endpoint was Clinical Global Impression[37] at different time points (for a summary of results, see Table 41). The proportion of subjects rated as “improved” or “remission” on the Clinical Global Impression scale at the end of the study was 91.7% (11 of 12) in patients with pustular psoriasis and 100% (18 of 18) in

[35] Patients with pustular psoriasis were allowed to increase their dose to 210 mg if their pustular score was moderate or severe at Week ≥4. Patients with erythrodermic psoriasis were allowed to increase their dose to 210 mg if they had a <50% reduction in PASI score at Week ≥4. A dose reduction to 140 mg after the dose increase was prohibited.

[36] The FAS was defined as subjects who received study drug with efficacy data available. The safety analysis set was defined as subjects who received study drug.

[37] Investigator’s or sub-investigator’s global assessment of outcome on a 4-point scale (1 Remission, 2 Improved, 3 No change, 4 Worsened) based on PASI score, psoriasis findings over time, joint symptoms for patients with psoriatic arthritis, nail and scalp symptoms if any, and a pustular score for patients with pustular psoriasis.

patients with erythrodermic psoriasis. Eight subjects (3 with pustular psoriasis, 5 with erythrodermic psoriasis) did not have an adequate response[38] to brodalumab 140 mg; the dose was therefore increased to 210 mg. All of the 8 subjects switched to 210 mg showed improved symptoms such as an improvement in PASI score.

Table 41. Clinical Global Impression over time in patients with pustular psoriasis or erythrodermic psoriasis (FAS)

| Time point | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 24 | Week 36 | Week 52 | End of study[a)] |
|---|---|---|---|---|---|---|---|---|---|
| Pustular psoriasis | | | | | | | | | |
| N | 12 | 11 | 12 | 12 | 12 | 11 | 11 | 10 | 12 |
| Clinical Global Impression (n [%]) | | | | | | | | | |
| Remission | 0 | 0 | 3 (25.0) | 3 (25.0) | 6 (50.0) | 3 (27.3) | 7 (63.6) | 6 (60.0) | 7 (58.3) |
| Improved | 9 (75.0) | 8 (72.7) | 6 (50.0) | 7 (58.3) | 5 (41.7) | 7 (63.6) | 3 (27.3) | 4 (40.0) | 4 (33.3) |
| No change | 3 (25.0) | 2 (18.2) | 2 (16.7) | 1 (8.3) | 1 (8.3) | 0 | 1 (9.1) | 0 | 0 |
| Worsened | 0 | 1 (9.1) | 1 (8.3) | 1 (8.3) | 0 | 1 (9.1) | 0 | 0 | 1 (8.3) |
| Erythrodermic psoriasis | | | | | | | | | |
| N | 18 | 18 | 18 | 18 | 18 | 16 | 15 | 16 | 18 |
| Clinical Global Impression (n [%]) | | | | | | | | | |
| Remission | 0 | 0 | 2 (11.1) | 3 (16.7) | 4 (22.2) | 7 (43.8) | 8 (53.3) | 11 (68.8) | 12 (66.7) |
| Improved | 17 (94.4) | 18 (100.0) | 16 (88.9) | 15 (83.3) | 14 (77.8) | 9 (56.3) | 7 (46.7) | 5 (31.3) | 6 (33.3) |
| No change | 1 (5.6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Worsened | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

a) At Week 52 or at discontinuation

The incidence of adverse events was 93.3% (28 of 30 subjects: 91.7% [11 of 12] in patients with pustular psoriasis and 94.4% [17 of 18] in patients with erythrodermic psoriasis). The main events are shown in Table 42. No deaths were reported.

The incidence of serious adverse events was 16.7% (5 of 30 subjects: 3 patients with pustular psoriasis [hepatocellular carcinoma, lumbar vertebral fracture, and pustular psoriasis in 1 patient each] and 2 patients with erythrodermic psoriasis [ectopic pregnancy and prostate cancer in 1 patient each]). A causal relationship to study drug was ruled out for all events. The outcomes were reported as “resolved” or “improved” except for 2 cases (hepatocellular carcinoma and prostate cancer).

The incidence of non-serious adverse events leading to discontinuation or interruption was 20.0% (6 of 30 subjects: 3 patients with pustular psoriasis [neutrophil count decreased, alopecia, and alopecia totalis in 1 patient each] and 3 patients with erythrodermic psoriasis [ventricular extrasystoles in 1 patient; nasopharyngitis, headache, and liver function test abnormal in 1 patient; and white blood cell count decreased, oesophageal candidiasis, and oropharyngeal pain in 1 patient]). A causal relationship to study drug could not be ruled out for all events except for the 3 events of ventricular extrasystoles, neutrophil count decreased, and headache.

The incidence of adverse drug reactions was 53.3% (16 of 30 subjects: 66.7% [8 of 12] in patients with pustular psoriasis and 44.4% [8 of 18] in patients with erythrodermic psoriasis).

[38] Pustular psoriasis: a pustular score of moderate or severe after Week 4, Erythrodermic psoriasis: a <50% reduction in PASI score after Week 4

Table 42. Adverse events reported by ≥2 subjects in the overall population (Safety analysis set)

| Event term | Pustular psoriasis (N = 12) | Erythrodermic psoriasis (N = 18) | Total (N = 30) |
|---|---|---|---|
| Nasopharyngitis | 4 (33.3) | 6 (33.3) | 10 (33.3) |
| Diarrhoea | 2 (16.7) | 1 (5.6) | 3 (10.0) |
| Folliculitis | 2 (16.7) | 1 (5.6) | 3 (10.0) |
| Skin papilloma | 2 (16.7) | 1 (5.6) | 3 (10.0) |
| Dry skin | 2 (16.7) | 1 (5.6) | 3 (10.0) |
| Periarthritis | 1 (8.3) | 2 (11.1) | 3 (10.0) |
| Arthralgia | 1 (8.3) | 1 (5.6) | 2 (6.7) |
| Neck pain | 1 (8.3) | 1 (5.6) | 2 (6.7) |
| Spinal osteoarthritis | 1 (8.3) | 1 (5.6) | 2 (6.7) |
| Contact dermatitis | 1 (8.3) | 1 (5.6) | 2 (6.7) |
| Urticaria | 1 (8.3) | 1 (5.6) | 2 (6.7) |
| Asteatosis | 1 (8.3) | 1 (5.6) | 2 (6.7) |
| Dental caries | 0 | 2 (11.1) | 2 (6.7) |
| Tooth fracture | 0 | 2 (11.1) | 2 (6.7) |

n (%)

### 7.2.6 Japanese long-term treatment study (CTD5.3.5.2-5, Study 4827-005 [ongoing since January 2014]; data cutoff, January 2015)

An open-label, uncontrolled study was conducted to evaluate the long-term safety of brodalumab in patients with psoriasis who completed Study 4827-003 or 4827-004.

Brodalumab 140 mg was administered subcutaneously every 4 weeks. Subjects treated with brodalumab 210 mg in Study 4827-004 were allowed to receive subcutaneous brodalumab 210 mg every 2 weeks. Between Weeks 2 and 28, patients who met the specified criteria[39] were allowed to receive brodalumab 140 or 210 mg every 2 weeks. After Week 28, all subjects were allowed to change their dosage regimen to brodalumab 140 mg Q2W, Q4W, or Q8W, or 210 mg Q2W[40] at the discretion of the investigator.

All of 155 subjects treated (148 in the brodalumab 140 mg group, 7 in the brodalumab 210 mg group) were included in the safety analysis set. Discontinuation occurred in 1.4% (2 of 148 subjects) of the brodalumab 140 mg group.

The incidence of adverse events was 80.0% (124 of 155 subjects). The main events are shown in Table 43. No deaths were reported. The incidence of serious adverse events was 3.9% (6 of 155 subjects [Wolff-Parkinson-White syndrome, retinal detachment, cellulitis, suicide attempt, benign prostatic hyperplasia, and psoriasis in 1 subject each]). A causal relationship to study drug was ruled out for all events; the outcomes of all events were reported as “resolved.”

The incidence of adverse events leading to discontinuation or interruption was 1.9% (3 of 155 subjects, cellulitis; pneumonia bacterial; and dysthymic disorder, 1 subject each). A causal relationship to study drug could not be ruled out for cellulitis and pneumonia bacterial. The incidence of adverse drug reactions was 31.6% (49 of 155 subjects).

[39] For subjects from Study 4827-003, a single sPGA score of ≥3 (moderate) or sPGA scores remaining at 2 (mild) for at least 4 weeks.
For subjects from Study 4827-004, a Clinical Global Impression score of “4 (worsened)” as compared with the score at Week 52 in Study 4827-004

[40] If the dose was reduced or the dosing interval was prolonged, the dosage regimen was changed in the following order: (1) 210 mg Q2W, (2) 140 mg Q2W, (3) 140 mg Q4W, and (4) 140 mg Q8W.

Table 43. Adverse events reported by ≥3% of subjects (Safety analysis set)

| Event term | Brodalumab-treated subjects (N = 155) |
|---|---|
| Nasopharyngitis | 26 (16.8) |
| Dental caries | 10 (6.5) |
| Tinea pedis | 8 (5.2) |
| Arthropod sting | 7 (4.5) |
| Back pain | 7 (4.5) |
| Diarrhoea | 5 (3.2) |
| Periodontitis | 5 (3.2) |

n (%)

### 7.2.7 Foreign long-term treatment study (CTD5.3.5.2-2, Study 20090403 [ongoing since April 2010]; data cutoff, June 2014 [Data up to Week 168])

An open-label, uncontrolled study was conducted in 5 countries including the US and Canada to evaluate the long-term safety of brodalumab in patients with psoriasis who completed Study 20090062 (target sample size, 155 subjects).

Brodalumab 210 mg was administered subcutaneously at Weeks 0, 1, 2, and 4 and every 2 weeks thereafter for up to 360 weeks. Subjects treated with brodalumab in Study 20090062 underwent a ≥6-week washout period. The protocol was amended (in January 2011) to change the brodalumab dose from 210 mg to 140 mg[41] in subjects weighing ≤100 kg. As a result, 65.2% (118 of 181) of subjects had their dose reduced. The protocol was amended again (in April 2012) to increase the brodalumab dose from 140 mg to 210 mg[42] in subjects with an inadequate response[43] to 140 mg. As a result, 16.6% (30 of 181) of subjects had their dose increased.

All of 181 subjects treated were included in the safety analysis set. The discontinuation rate was 25.4% (46 of 181 subjects); the main reasons for discontinuation were adverse event (7.7% [14 of 181 subjects]), consent withdrawal (7.2% [13 of 181 subjects]), etc.

The incidence of adverse events was 96.7% (175 of 181 subjects). The main events are shown in Table 44. One death occurred (aortic aneurysm rupture), but its causal relationship to study drug was ruled out.

The incidence of serious adverse events was 12.7% (23 of 181 subjects); the event reported by ≥2 subjects was myocardial infarction (1.7% [3 of 181 subjects]). The incidence of adverse events leading to discontinuation was 10.5% (19 of 181 subjects); the events reported by ≥2 subjects were psoriasis (2.8% [5 of 181 subjects]) and psoriatic arthropathy (1.1% [2 of 181 subjects]). The incidence of adverse drug reactions was 29.3% (53 of 181 subjects).

[41] The subgroup analysis of Study 20090062 showed that a sufficient PASI 75 response rate can be achieved with brodalumab 140 mg in subjects weighing ≤100 kg. The protocol was thus amended.
[42] The protocol was amended to evaluate the effect of an increased dose in subjects with an inadequate response to brodalumab 140 mg.
[43] Subjects with sPGA scores remaining at 3 or 2 for at least 4 weeks.

Table 44. Adverse events reported by ≥3% of subjects (Safety analysis set)

| Event term | Brodalumab-treated subjects (N = 181) |
|---|---|
| Nasopharyngitis | 49 (27.1) |
| Upper respiratory tract infection | 41 (22.7) |
| Arthralgia | 34 (18.8) |
| Influenza | 23 (12.7) |
| Gastroenteritis | 21 (11.6) |
| Sinusitis | 20 (11.0) |
| Back pain | 20 (11.0) |
| Oropharyngeal pain | 18 (9.9) |
| Psoriasis | 17 (9.4) |
| Bronchitis | 16 (8.8) |
| Psoriatic arthropathy | 16 (8.8) |
| Muscle strain | 15 (8.3) |
| Pain in extremity | 14 (7.7) |
| Headache | 14 (7.7) |
| Anxiety | 13 (7.2) |
| Hypertension | 13 (7.2) |
| Viral upper respiratory tract infection | 11 (6.1) |
| Pharyngitis | 10 (5.5) |
| Pharyngitis streptococcal | 10 (5.5) |
| Rhinitis | 10 (5.5) |
| Musculoskeletal pain | 10 (5.5) |
| Gastrooesophageal reflux disease | 10 (5.5) |
| Nausea | 10 (5.5) |
| Contusion | 10 (5.5) |
| Nephrolithiasis | 10 (5.5) |
| Tendonitis | 9 (5.0) |
| Diarrhoea | 9 (5.0) |
| Fatigue | 9 (5.0) |
| Carpal tunnel syndrome | 9 (5.0) |
| Conjunctivitis | 8 (4.4) |
| Osteoarthritis | 8 (4.4) |
| Abdominal pain | 8 (4.4) |
| Injection site pain | 8 (4.4) |
| Cough | 8 (4.4) |
| Insomnia | 8 (4.4) |
| Seasonal allergy | 8 (4.4) |
| Urinary tract infection | 7 (3.9) |
| Bursitis | 7 (3.9) |
| Neck pain | 7 (3.9) |
| Constipation | 7 (3.9) |
| Injection site erythema | 7 (3.9) |
| Folliculitis | 6 (3.3) |
| Hordeolum | 6 (3.3) |
| Oral candidiasis | 6 (3.3) |
| Vulvovaginal mycotic infection | 6 (3.3) |
| Myalgia | 6 (3.3) |
| Vomiting | 6 (3.3) |
| Procedural pain | 6 (3.3) |
| Contact dermatitis | 6 (3.3) |
| Pruritus | 6 (3.3) |
| Rhinitis allergic | 6 (3.3) |
| Migraine | 6 (3.3) |

n (%)

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Feasibility of extrapolating foreign clinical data

This application is based on a bridging strategy. The applicant conducted a Japanese phase II study (a placebo-controlled, randomized, parallel-group, double-blind study) (Study 4827-002) as a bridging study and a foreign phase II study (Study 20090062) as a study to be bridged. The applicant produced a clinical data package based on comparison of the results of the 2 studies. The clinical data package contains the pivotal efficacy and safety evaluation data, namely the results from Japanese clinical studies and 3 foreign phase III clinical studies in patients with plaque psoriasis (Studies 20120102, 20120103, 20120104) (Figure 5).

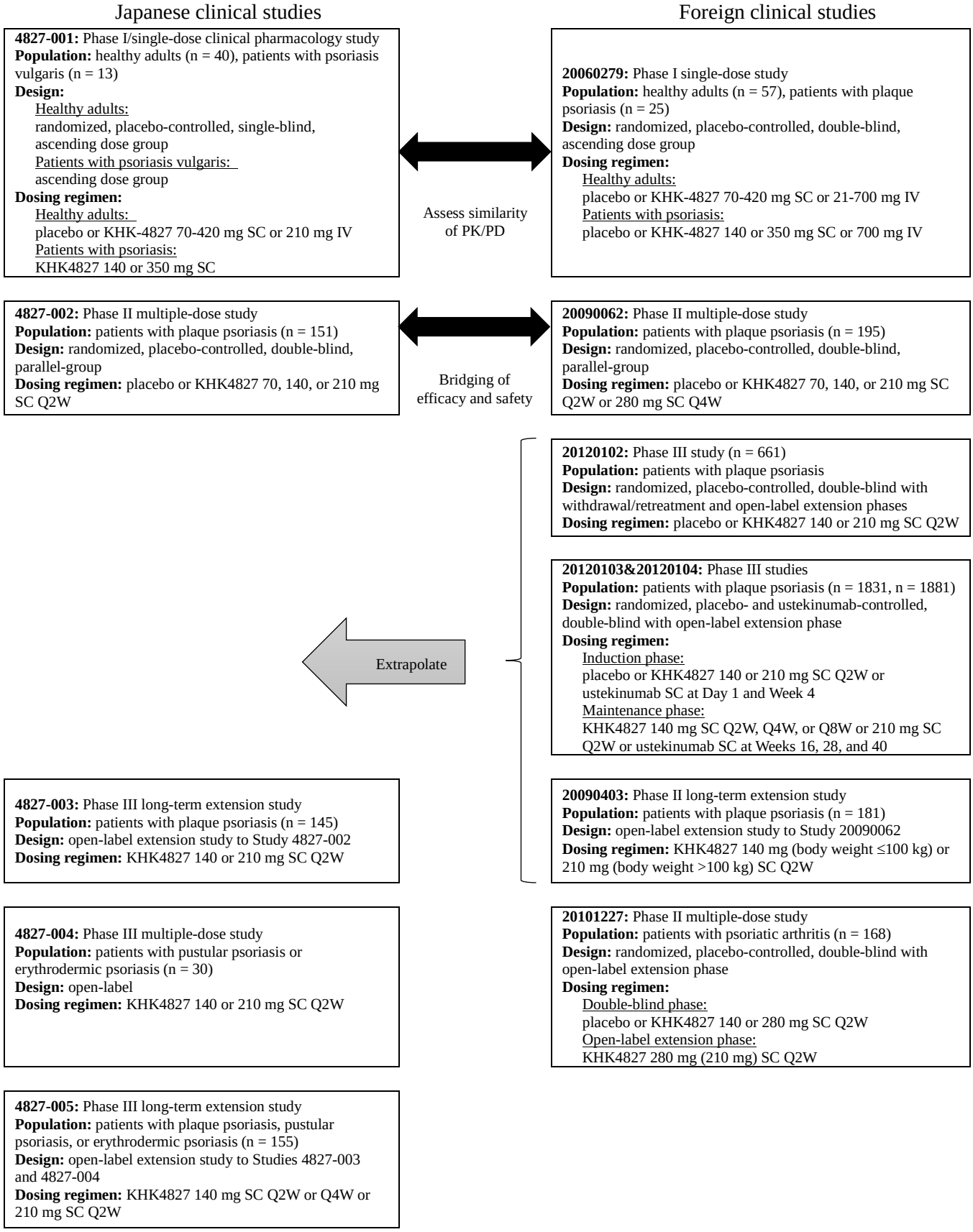



Figure 5. Clinical data package to support the application

The applicant explained the appropriateness of the clinical data package for the present application and the feasibility of extrapolating foreign clinical data.

The applicant's explanation:

Since there are no major differences in the definition of psoriasis, the diagnostic criteria, and treatment between Japan and overseas and there are no clinically relevant differences in the pharmacokinetics of brodalumab between Japanese and non-Japanese subjects [see 6.R.1 Ethnic differences in pharmacokinetics/pharmacodynamics] etc., it was considered possible to develop brodalumab in Japan based on a bridging strategy, in accordance with the International Conference on Harmonisation (ICH) E5 guideline ("Ethnic Factors in the Acceptability of Foreign Clinical Data" PMSB/ELD Notification No. 672 dated August 11, 1998). The following are the pre-defined criteria for allowing bridging (extrapolating) clinical data from overseas to Japan: (1) A Japanese phase II study (Study 4827-002) should show the superiority of brodalumab to placebo in the percent improvement in PASI score at Week 12, and the dose-response relationship in this study should be visually similar to that in a foreign phase II study (Study 20090062). (2) The safety profile should not differ between the Japanese and foreign phase II studies.

Table 45 and Figure 6 show the percent improvement in PASI score at Week 12 in the Japanese and foreign phase II studies. Both studies revealed statistically significant differences between placebo and each brodalumab dose (70, 140, and 210 mg) by pairwise comparisons. The dose-response relationship appeared largely similar in both studies.

Table 45. Percent improvement in PASI score at Week 12 in the bridging study and the study to be bridged (FAS, BVCF)

| | Brodalumab 70 mg | Brodalumab 140 mg | Brodalumab 210 mg | Placebo |
|---|---|---|---|---|
| Japanese phase II study (Bridging study) | 37.7 ± 46.8 (39) | 82.2 ± 28.1 (37) | 96.8 ± 7.4 (37) | 9.4 ± 45.4 (38) |
| Difference from placebo [95% CI], *P*-value | 28.3 [12.05, 44.5] *P* < 0.001 | 72.8 [56.4, 89.2] *P* < 0.001 | 87.3 [70.9, 103.8] *P* < 0.001 | |
| Foreign phase II study (Study to be bridged) | 45.0 ± 41.7 (39) | 85.9 ± 22.5 (39) | 86.3 ± 27.6 (40) | 16.0 ± 27.0 (38) |
| Difference from placebo [95% CI], *P*-value | 28.9 [15.8, 42.1] *P* < 0.0001 | 70.5 [57.4, 83.7] *P* < 0.0001 | 70.9 [57.8, 84.0] *P* < 0.0001 | |

Mean ± SD (N)

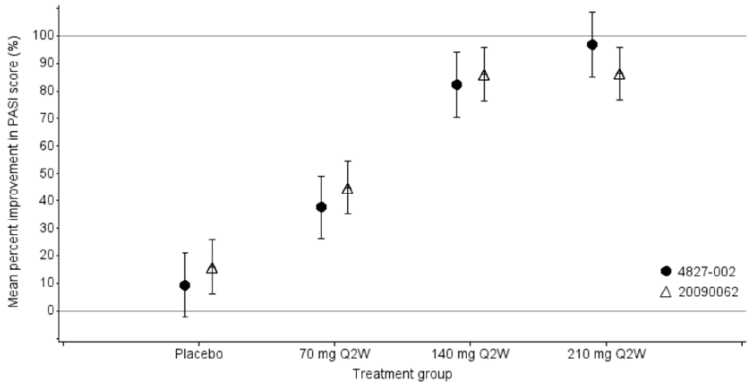



Figure 6. Percent improvement in PASI score at Week 12 in Japanese phase II study (Study 4827-002) and foreign phase II study (Study20090062) (Mean and 95% CI)

The patient characteristics were compared between the 2 studies. Compared with the foreign phase II study, the Japanese phase II study tended to have a lower proportion of female subjects (20.5% in the Japanese study, 37.8%

in the foreign study), a lower body weight (74.2 ± 17.1 kg in the Japanese study, 89.6 ± 21.6 kg in the foreign study), a lower BMI (26.6 ± 5.6 kg/m$^2$ in the Japanese study, 30.1 ± 6.9 kg/m$^2$ in the foreign study), a lower proportion of subjects with psoriatic arthritis (15.9% in the Japanese study, 24.4% in the foreign study), a lower proportion of subjects with previous biologic therapy (10.6% in the Japanese study, 32.7% in the foreign study), a higher baseline PASI score (27.0 ± 11.6 in the Japanese study, 19.4 ± 6.9 in the foreign study), and a higher BSA involvement (40.9% ± 22.4% in the Japanese study, 24.4% ± 14.5% in the foreign study). The results of subgroup analyses are presented in Table 46. Subjects with higher body weight and BMI tended to have lower percent improvement in PASI score in the brodalumab groups. These differences, however, did not affect the overall results of the Japanese phase II study. The applicant thus considered that the differences in these patient characteristics do not significantly affect efficacy evaluation of brodalumab.

Table 46. Results of subgroup analyses of percent improvement in PASI score at Week 12 in Japanese and foreign phase II studies (FAS, BVCF)

| Patient characteristics | | Japanese phase II study | | | | Foreign phase II study | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | 70 mg | 140 mg | 210 mg | Placebo | 70 mg | 140 mg | 210 mg |
| Sex | Male | 10.7 ± 53.0 (27) | 31.7 ± 47.1 (34) | 80.4 ± 30.5 (30) | 95.9 ± 8.1 (29) | 16.5 ± 25.6 (22) | 36.4 ± 46.3 (22) | 85.2 ± 22.7 (28) | 90.3 ± 17.9 (25) |
| | Female | 6.4 ± 18.2 (11) | 78.2 ± 13.0 (5) | 89.9 ± 12.7 (7) | 100.0 ± 0.0 (8) | 15.3 ± 29.6 (16) | 56.2 ± 33.0 (17) | 87.9 ± 22.9 (11) | 79.6 ± 38.7 (15) |
| Body weight (kg) | ≤75 kg | 3.4 ± 51.8 (21) | 55.7 ± 38.2 (20) | 86.9 ± 24.8 (21) | 98.6 ± 2.4 (24) | 25.2 ± 34.0 (11) | 84.7 ± 18.9 (13) | 99.9 ± 0.4 (8) | 98.8 ± 2.7 (11) |
| | >75 kg and ≤90 kg | 14.7 ± 24.5 (11) | 20.9 ± 43.2 (8) | 76.0 ± 31.7 (11) | 94.3 ± 9.2 (9) | 16.1 ± 25.9 (13) | 39.7 ± 32.8 (8) | 95.0 ± 10.6 (8) | 76.7 ± 39.6 (11) |
| | >90 kg and ≤100 kg | 20.0 ± 61.1 (5) | 41.8 ± 32.7 (5) | 88.4 ± 16.6 (3) | 99.5 ± 0.8 (3) | 7.2 ± 22.6 (7) | 49.4 ± 19.9 (5) | 96.7 ± 3.4 (9) | 99.1 ± 2.0 (5) |
| | >100 kg | 26.2 (1) | -3.4 ± 62.1 (6) | 58.4 ± 58.9 (2) | 65.3 (1) | 10.0 ± 20.2 (7) | 7.0 ± 33.0 (13) | 65.9 ± 26.9 (14) | 78.9 ± 28.4 (13) |
| BMI (kg/m$^2$) | <25 | 15.4 ± 35.1 (15) | 55.5 ± 43.9 (12) | 85.9 ± 27.3 (17) | 98.6 ± 2.4 (19) | 29.3 ± 32.0 (9) | 74.8 ± 30.7 (11) | 99.8 ± 0.5 (6) | 96.7 ± 10.7 (11) |
| | ≥25 and <30 | 0.79 ± 52.4 (16) | 41.8 ± 39.6 (17) | 83.0 ± 27.5 (14) | 94.4 ± 8.8 (10) | 10.8 ± 28.9 (16) | 69.9 ± 29.2 (10) | 96.7 ± 8.2 (14) | 88.7 ± 25.5 (15) |
| | ≥30 and <35 | 21.1 ± 54.6 (6) | 15.7 ± 13.8 (4) | 75.9 ± 24.3 (4) | 99.4 ± 0.8 (5) | 16.2 ± 18.8 (5) | 16.7 ± 38.6 (10) | 79.7 ± 29.8 (10) | 80.0 ± 44.7 (5) |
| | ≥35 | -11.9 (1) | 4.8 ± 69.1 (6) | 58.4 ± 58.9 (2) | 88.4 ± 20.0 (3) | 11.2 ± 19.0 (8) | 8.6 ± 12.4 (8) | 66.9 ± 21.9 (9) | 73.1 ± 32.4 (9) |
| Joint symptoms | Yes | -18.9 ± 20.8 (7) | -3.3 ± 61.3 (6) | 61.6 ± 41.0 (6) | 98.3 ± 1.7 (5) | 3.2 ± 33.4 (7) | 46.7 ± 39.4 (8) | 90.1 ± 19.7 (11) | 89.0 ± 28.4 (12) |
| | No | 15.8 ± 47.2 (31) | 45.1 ± 40.6 (33) | 86.2 ± 23.8 (31) | 96.5 ± 7.9 (32) | 18.9 ± 25.0 (31) | 44.6 ± 42.9 (31) | 84.3 ± 23.6 (28) | 85.1 ± 27.7 (28) |
| Previous biologic use | Yes | -67.6 ± 69.8 (3) | 26.1 ± 95.7 (5) | 95.4 ± 2.0 (3) | 99.3 ± 1.7 (5) | 17.9 ± 28.7 (12) | 30.4 ± 45.7 (13) | 81.6 ± 28.6 (10) | 89.2 ± 26.5 (16) |
| | No | 16.0 ± 37.3 (35) | 39.4 ± 37.3 (34) | 81.1 ± 29.1 (34) | 96.4 ± 7.9 (32) | 15.1 ± 26.7 (26) | 52.4 ± 38.4 (26) | 87.4 ± 20.3 (29) | 84.3 ± 28.7 (24) |
| PASI score | ≤20.4 | -3.7 ± 52.6 (15) | 53.1 ± 31.7 (12) | 89.9 ± 12.7 (8) | 98.7 ± 2.7 (15) | 13.1 ± 27.1 (24) | 51.7 ± 39.3 (28) | 88.0 ± 19.0 (29) | 89.7 ± 26.6 (24) |
| | >20.4 | 18.0 ± 39.0 (23) | 30.8 ± 51.2 (27) | 80.1 ± 30.9 (29) | 95.4 ± 9.2 (22) | 21.0 ± 26.9 (14) | 28.0 ± 44.8 (11) | 79.9 ± 30.9 (10) | 81.1 ± 29.2 (16) |
| BSA involvement | ≤25% | -8.6 ± 55.4 (14) | 49.7 ± 34.0 (12) | 89.7 ± 11.5 (11) | 98.8 ± 2.8 (12) | 11.6 ± 26.8 (26) | 50.5 ± 37.3 (26) | 84.7 ± 24.5 (30) | 83.8 ± 32.5 (24) |
| | >25% | 20.0 ± 35.7 (24) | 32.4 ± 51.2 (27) | 79.1 ± 32.4 (26) | 95.8 ± 8.7 (25) | 25.6 ± 25.7 (12) | 34.1 ± 49.2 (13) | 90.1 ± 14.2 (9) | 90.0 ± 18.5 (16) |

Mean ± SD (N)

The nature and incidence of adverse events were similar between the 2 studies [see 7.1.1 Japanese phase II study and 7.1.2 Foreign phase II study].

The applicant's conclusion:

Data presented above meet the criteria for allowing bridging the clinical data. Thus a clinical data package for a new drug application in Japan can be produced using the results from foreign phase II and III studies, etc.

PMDA accepted the applicant's explanation about the bridging strategy and concluded that the efficacy and safety of brodalumab in patients with psoriasis can be evaluated based on a clinical data package produced using the results from Japanese phase II and foreign phase II and III studies, etc.

**7.R.2 Efficacy**

**7.R.2.1 Efficacy in patients with plaque psoriasis**

PMDA concluded that brodalumab was shown to have efficacy in patients with plaque psoriasis, for the following reasons: (1) In a Japanese phase II study (Study 4827-002) and a foreign phase II study (Study 20090062) in patients with plaque psoriasis, including psoriatic arthritis, pairwise comparisons showed statistically significant differences between each brodalumab dose (70, 140, 210 mg) and placebo in the percent improvement in PASI score (assessment of the severity of skin symptoms) [see 7.1.1 Japanese phase II study and 7.1.2 Foreign phase II study]. (2) As shown in Table 46, the efficacy of brodalumab in improving skin symptoms was suggested also in subjects with joint symptoms. (3) Foreign phase III studies (Studies 20120102, 20120103, 20120104) confirmed the superiority of brodalumab 140 and 210 mg to placebo in the PASI 75 response rate and sPGA success (0 or 1) rate at Week 12 (the co-primary endpoints) [see 7.2.1 Foreign phase III study, 7.2.2 Foreign phase III study, and 7.2.3 Foreign phase III study].

**7.R.2.2 Efficacy in reducing joint symptoms of psoriatic arthritis**

The applicant's explanation on the efficacy of brodalumab in reducing joint symptoms of psoriatic arthritis:

A Japanese phase II study (Study 4827-002) and a Japanese long-term treatment study (Study 4827-003) evaluated the efficacy of brodalumab in the treatment of plaque psoriasis. Among the Japanese patients with psoriatic arthritis enrolled in these studies, those who had a diagnosis of psoriatic arthritis according to the CASPAR criteria, with ≥1 joint with pain (tenderness) and ≥1 swollen joint at enrollment were evaluated for joint symptoms based on the ACR core set, as well as for skin symptoms. In the Japanese phase II study, the ACR core set variables were assessed in 19 subjects. Among the 19 subjects, ACR20 response was achieved at Week 12 in 1 of 5 subjects receiving 70 mg, 2 of 5 subjects receiving 140 mg, 4 of 4 subjects receiving 210 mg, and 0 of 5 subjects receiving placebo. In the Japanese long-term treatment study, the ACR core set variables were assessed in 13 subjects. Among the 13 subjects, ACR20 response was achieved at Week 52 in 3 of 5 subjects receiving 140 mg and 6 of 8 subjects receiving 210 mg. These results suggest that brodalumab improves joint symptoms.

In a foreign phase II study in patients with psoriatic arthritis (Study 20101227), the ACR20 response rates at Week 12 were 36.8% (21 of 57 subjects) in the brodalumab 140 mg group, 39.3% (22 of 56 subjects) in the brodalumab 280 mg group, and 18.2% (10 of 55 subjects) in the placebo group. Pairwise comparisons showed statistically significant differences between placebo and each brodalumab dose (140 and 280 mg) [see 7.1.3 Foreign phase II study].

Brodalumab is thus expected to have efficacy in reducing joint symptoms in Japanese patients with psoriatic arthritis.

PMDA's view:

Given the limited number of patients with psoriatic arthritis in Japan, it is difficult to design and conduct a confirmatory study in Japanese patients with psoriatic arthritis. Therefore, there is no choice but to evaluate the efficacy and safety of brodalumab in patients with psoriatic arthritis based on the results from foreign and Japanese clinical studies in patients with psoriatic arthritis. Brodalumab is expected to have efficacy in reducing joint symptoms in Japanese patients with psoriatic arthritis, in view of (1) the statistically significant differences in the ACR20 response rate between placebo and each brodalumab dose (140 and 280 mg) by pairwise comparisons in the foreign phase II study (Study 20101227), and (2) the results in patients with psoriatic arthritis from the Japanese phase II study (Study 4827-002). However, as the clinical study data in Japanese patients with psoriatic arthritis are limited, the efficacy of brodalumab in reducing joint symptoms in patients with psoriatic arthritis should continue to be evaluated in the post-marketing surveillance.

**7.R.2.3 Efficacy in patients with pustular psoriasis or erythrodermic psoriasis**

The applicant's explanation on the efficacy of brodalumab in patients with pustular psoriasis or erythrodermic psoriasis:

An open-label, uncontrolled study was designed to evaluate the efficacy and safety of brodalumab in patients with pustular psoriasis or erythrodermic psoriasis, because patients with pustular psoriasis or erythrodermic psoriasis account for approximately 1% of all patients with psoriasis in Japan (Overview of Report on Public Health Administration and Services FY2013. MHLW. 2014; 1-31, etc.), and because a confirmatory study in this patient population was unfeasible. Table 47 shows the efficacy results in a Japanese clinical study in patients with pustular psoriasis or erythrodermic psoriasis (Study 4827-004). In total, 96.7% (29 of 30) of subjects were rated as "improved" or "remission" on the Clinical Global Impression scale at the end of the study. The patients showed a trend towards improvement in percent improvement in PASI score, severity score[44] (*Jpn J Dermatol*. 2010; 120: 815-39), BSA involvement, sPGA[45] success (0 or 1) rate, NAPSI score,[46] and PSSI score.[47] These improving effects were maintained until Week 52. These results suggest the efficacy of brodalumab in patients with pustular psoriasis or erythrodermic psoriasis.

[44] Total score (0-17) was calculated by assessing skin symptoms and systemic symptoms/test findings (fever, white blood cells, CRP, serum albumin).

[45] A physician's global assessment of a patient's psoriasis lesions overall on a 0-5 scale based on the severity of erythema, infiltration, and desquamation.

[46] The nail showing the most severe symptoms of nail psoriasis was divided into quadrants. Each quadrant was scored for nail matrix psoriasis and nail bed psoriasis. The scores of each quadrant were summed to yield a total score (0-32)

[47] Total score (0-72) was calculated by assessing the severity of erythema, infiltration, and scaling of the scalp and the area of affected scalp.

Table 47. Efficacy endpoints over time in patients with pustular psoriasis or erythrodermic psoriasis (FAS)

| | Baseline | Week 2 | Week 4 | Week 8 | Week 12 | Week 24 | Week 36 | Week 52 | End of study [a)] |
|---|---|---|---|---|---|---|---|---|---|
| **Pustular psoriasis** | | | | | | | | | |
| N | 12 | 12 | 11 | 12 | 12 | 11 | 11 | 10 | 12 |
| Clinical Global Impression Improved or Remission | – | 9 (75.0) | 8 (72.7) | 9 (75.0) | 10 (83.3) | 10 (90.9) | 10 (90.9) | 10 (100.0) | 11 (91.7) |
| Percent improvement in PASI score | – | 50.4 ± 36.2 | 57.1 ± 38.5 | 60.7 ± 46.1 | 64.0 ± 42.0 | 68.6 ± 44.0 | 85.1 ± 36.5 | 92.7 ± 18.8 | 78.5 ± 54.2 |
| Severity score | 4.4 ± 2.4 | 2.8 ± 1.7 | 2.5 ± 1.5 | 1.9 ± 1.8 | 1.9 ± 2.5 | 1.3 ± 1.0 | 1.0 ± 1.8 | 0.5 ± 0.5 | 0.8 ± 1.4 |
| NAPSI score[b)] | 10.8 ± 7.9 | – | – | – | 7.0 ± 6.8 | 5.5 ± 5.5 | 4.0 ± 3.7 | 2.5 ± 3.8 | 2.5 ± 3.8 |
| PSSI score[c)] | 16.7 ± 13.0 | – | – | – | 2.9 ± 3.5 | 3.3 ± 6.9 | 0.8 ± 1.5 | 0.4 ± 0.5 | 1.2 ± 2.6 |
| **Erythrodermic psoriasis** | | | | | | | | | |
| N | 18 | 18 | 18 | 18 | 18 | 16 | 15 | 16 | 18 |
| Clinical Global Impression Improved or Remission | – | 17 (94.4) | 18 (100.0) | 18 (100.0) | 18 (100.0) | 16 (100.0) | 15 (100.0) | 16 (100.0) | 18 (100.0) |
| Percent improvement in PASI score | – | 48.0 ± 27.3 | 67.6 ± 26.2 | 79.6 ± 24.8 | 85.1 ± 18.4 | 91.6 ± 14.9 | 95.5 ± 7.5 | 95.3 ± 14.5 | 93.4 ± 16.4 |
| BSA involvement (%) | 87.9 ± 4.6 | 65.5 ± 19.1 | 44.1 ± 23.6 | 24.0 ± 21.6 | 15.2 ± 17.3 | 9.0 ± 11.6 | 4.8 ± 7.2 | 2.2 ± 6.7 | 3.3 ± 8.3 |
| sPGA success (0 or 1) | 1 (5.6) | 5 (27.8) | 10 (55.6) | 10 (55.6) | 12 (66.7) | 15 (93.8) | 15 (100.0) | 15 (93.8) | 16 (88.9) |
| NAPSI score[b)] | 6.2 ± 3.3 | – | – | – | 3.9 ± 3.5 | 2.8 ± 3.6 | 1.5 ± 2.7 | 1.6 ± 3.2 | 1.5 ± 3.1 |
| PSSI score[c)] | 35.4 ± 18.2 | – | – | – | 3.0 ± 5.7 | 2.3 ± 3.8 | 0.8 ± 1.6 | 0.7 ± 2.5 | 1.1 ± 2.9 |

n (%) or Mean ± SD
a) At Week 52 or at discontinuation
b) Assessed by NAPSI in 4 patients with pustular psoriasis and 11 to 13 patients with erythrodermic psoriasis.
c) Assessed by PSSI in 7 to 9 patients with pustular psoriasis and 15 to 18 patients with erythrodermic psoriasis.

PMDA's view:

Although there are limitations to evaluation of the efficacy of brodalumab in patients with pustular psoriasis or erythrodermic psoriasis based on the data from Study 4827-004, brodalumab is expected to have efficacy in patients with pustular psoriasis or erythrodermic psoriasis, for the following reasons: (1) In Study 4827-004, 11 of 12 patients with pustular psoriasis and 18 of 18 patients with erythrodermic psoriasis were rated as "improved" or "remission" on the Clinical Global Impression scale at the end of the study.[48] (2) There was a trend towards improvement in other endpoints including percent improvement in PASI score as well. However, as the number of patients assessed in the Japanese clinical study was very limited, the efficacy of brodalumab in patients with pustular psoriasis or erythrodermic psoriasis should continue to be evaluated via post-marketing surveillance.

### 7.R.3 Safety

The applicant explained the safety of brodalumab, based on the pooled data from the induction phase (through Week 12) of foreign phase II and III studies (Studies 20090062, 20120102, 20120103, 20120104) (Pool A), the pooled data from Weeks 0 to 52 of 5 studies (the above 4 studies plus a foreign phase III study [Study 20090403]) (Pool B[49]), the pooled data from the entire treatment period (from the start of treatment to data cutoff [March to September 2014]) of the 5 studies in Pool B (Pool C[49]), the pooled data from a Japanese phase II study, Japanese long-term treatment studies, and a Japanese clinical study (Studies 4827-002, 4827-003, 4827-004, 4827-005) (Japanese Pool 1), and the pooled data from Japanese phase II and long-term treatment studies in patients with plaque psoriasis (Studies 4827-002, 4827-003) (Japanese Pool 2).

Adverse events in Pool A, Pool C, and Japanese Pool 2 are summarized in Table 48.

[48] The dose was increased from 140 mg to 210 mg after Week 4 in 8 patients (3 patients with pustular psoriasis, 5 patients with erythrodermic psoriasis).
[49] Events occurring during the exposure period (up to 14 days after the last dose for the Q2W group, up to 28 days after the last dose for the Q4W group up to 56 days after the last dose for the Q8W group) were collected.

Table 48. Adverse events in clinical studies in patients with psoriasis (Pool A, Pool C, Japanese Pool 2)

| | Pool A (Induction phase) | | | | Pool C (Entire treatment period) | | | | Japanese Pool 2 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Overall brodalumab 140 mg Q2W [a)] | Overall brodalumab 210 mg Q2W [b)] | Ustekinumab/ Brodalumab[c)] | Combined brodalumab group[d)] | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W |
| N | 1491 | 1496 | 879 | 613 | 279 | 1291 | 564 | 4461 | 73 | 72 |
| Deaths | 0 | 1 (0.1) | 0 | 0 | 0 | 3 (0.2) | 0 | 8 (0.2) | 0 | 0 |
| Adverse events | 845 (56.7) | 870 (58.2) | 451 (51.3) | 345 (56.3) | 222 (79.6) | 1072 (83.0) | 340 (60.3) | 3644 (81.7) | 66 (90.4) | 68 (94.4) |
| Serious adverse events | 29 (1.9) | 20 (1.3) | 15 (1.7) | 6 (1.0) | 15 (5.4) | 88 (6.8) | 15 (2.7) | 315 (7.1) | 5 (6.8) | 5 (6.9) |
| Adverse events leading to study drug discontinuation | 16 (1.1) | 17 (1.1) | 8 (0.9) | 6 (1.0) | 14 (5.0) | 37 (2.9) | 9 (1.6) | 141 (3.2) | 6 (8.2) | 12 (16.7) |
| Adverse drug reactions | 277 (18.6) | 320 (21.4) | 111 (12.6) | 96 (15.7) | 97 (34.8) | 446 (34.5) | 112 (19.9) | 1,505 (33.7) | 44 (60.3) | 45 (62.5) |
| Total exposure (subject-years) | 334.0 | 335.6 | 194.9 | 139.5 | 302.7 | 1471.5 | 310.0 | 5448.8 | 79.0 | 82.1 |

n (%)
a) ≥75% of doses were 140 mg only.
b) ≥75% of doses were 210 mg only.
c) Subjects who received ustekinumab and brodalumab 210 mg
d) All brodalumab-treated subjects

The applicant's explanation:

The main adverse events in Pool A and Pool C are shown in Table 49 and Table 50, respectively. In Pool A, no events showed a particularly higher incidence in the brodalumab group than in the placebo or ustekinumab group. In Pool A and Pool C, no events showed a particularly higher incidence in subjects receiving brodalumab 210 mg Q2W than in subjects receiving brodalumab 140 mg Q2W. The nature and incidence of adverse events did not differ between "Japanese Pools 1 and 2" and "the pooled data from foreign clinical studies."

Table 49. Adverse events reported by ≥3% of subjects in any group (Pool A)

| Event term | Brodalumab 140 mg Q2W (N = 1491) | Brodalumab 210 mg Q2W (N = 1496) | Placebo (N = 879) | Ustekinumab (N = 613) |
|---|---|---|---|---|
| Nasopharyngitis | 101 (6.8) | 101 (6.8) | 61 (6.9) | 34 (5.5) |
| Upper respiratory tract infection | 70 (4.7) | 86 (5.7) | 56 (6.4) | 36 (5.9) |
| Headache | 81 (5.4) | 64 (4.3) | 31 (3.5) | 23 (3.8) |
| Arthralgia | 71 (4.8) | 71 (4.7) | 29 (3.3) | 15 (2.4) |
| Pruritus | 41 (2.7) | 28 (1.9) | 27 (3.1) | 12 (2.0) |

n (%)

Table 50. Adverse events reported by ≥3% of all brodalumab-treated subjects (Pool C)

| Event term | Overall brodalumab 140 mg Q2W (N = 279) | Overall brodalumab 210 mg Q2W (N = 1291) | Ustekinumab/ Brodalumab (N = 564) | Combined brodalumab group (N = 4461) |
|---|---|---|---|---|
| Nasopharyngitis | 54 (19.4) | 214 (16.6) | 43 (7.6) | 748 (16.8) |
| Arthralgia | 29 (10.4) | 126 (9.8) | 22 (3.9) | 480 (10.8) |
| Headache | 27 (9.7) | 93 (7.2) | 18 (3.2) | 356 (8.0) |
| Upper respiratory tract infection | 26 (9.3) | 196 (15.2) | 40 (7.1) | 621 (13.9) |
| Oropharyngeal pain | 18 (6.5) | 42 (3.3) | 6 (1.1) | 189 (4.2) |
| Back pain | 17 (6.1) | 80 (6.2) | 14 (2.5) | 243 (5.4) |
| Pruritus | 17 (6.1) | 42 (3.3) | 4 (0.7) | 190 (4.3) |
| Nausea | 13 (4.7) | 39 (3.0) | 3 (0.5) | 137 (3.1) |
| Pain in extremity | 12 (4.3) | 38 (2.9) | 16 (2.8) | 169 (3.8) |
| Bronchitis | 11 (3.9) | 49 (3.8) | 10 (1.8) | 171 (3.8) |
| Hypertension | 11 (3.9) | 52 (4.0) | 13 (2.3) | 228 (5.1) |
| Diarrhoea | 11 (3.9) | 48 (3.7) | 15 (2.7) | 193 (4.3) |
| Cough | 10 (3.6) | 52 (4.0) | 10 (1.8) | 192 (4.3) |
| Pharyngitis | 9 (3.2) | 61 (4.7) | 8 (1.4) | 157 (3.5) |
| Influenza | 8 (2.9) | 46 (3.6) | 12 (2.1) | 163 (3.7) |
| Urinary tract infection | 8 (2.9) | 46 (3.6) | 11 (2.0) | 159 (3.6) |
| Fatigue | 7 (2.5) | 49 (3.8) | 7 (1.2) | 161 (3.6) |
| Sinusitis | 6 (2.2) | 53 (4.1) | 13 (2.3) | 188 (4.2) |
| Psoriatic arthropathy | 6 (2.2) | 27 (2.1) | 7 (1.2) | 140 (3.1) |

n (%)

In Pool C (including the follow-up period), 16 deaths were reported. The causes of the deaths were completed suicide in 2 subjects; and death, cardiac arrest, cerebrovascular accident, aortic aneurysm rupture, cardiomyopathy, traumatic lung injury, haematophagic histiocytosis, accidental death, intentional overdose, oesophageal varices haemorrhage, cerebral infarction, abortion missed, cardiopulmonary failure, and sudden death in 1 subject each. A causal relationship to study drug was ruled out for all events except for 1 patient with haematophagic histiocytosis. No deaths were reported in Japanese Pool 1.

In Pool C, the serious adverse events reported were myocardial infarction (17 subjects) (0.4%, 0.3 events per 100 subject-years), cellulitis (11 subjects) (0.2%, 0.2 events per 100 subject-years), and cholelithiasis (8 subjects) (0.2%, 0.1 events per 100 subject-years), etc. In Japanese Pool 1, the most common serious adverse event was cellulitis (3 subjects) (1.7%).

Considering the pharmacological actions, etc. of brodalumab, PMDA focused its safety review on the events discussed in Sections 7.R.3.1 to 7.R.3.8.

**7.R.3.1 Infections**

The applicant's explanation on the occurrence of serious injections in patients treated with brodalumab:

A report has suggested that the IL-17 signaling pathway is important to host defense against infections (*Curr Allergy Asthma Rep*. 2013; 13: 587-95). In addition, toxicity studies revealed dermatitis with abnormal growth of indigenous microbes (yeast and bacteria) and glossitis with intracorneal mycelia. The risk of infections associated with brodalumab was thus assessed.

Table 51 shows the main adverse events in the "Infections and infestations SOC" reported in clinical studies. In

Pool A and Pool B, no events showed a particularly higher incidence in brodalumab-treated subjects than in placebo- or ustekinumab-treated subjects. The occurrence of adverse events in the "Infections and infestations SOC" in Pool C was largely similar to that in Pool B.

Table 51. Adverse events in the Infections and infestations SOC reported by ≥1% of all brodalumab-treated subjects (Pool A and Pool B)

| | Pool A (Induction phase) | | | | Pool B (through Week 52) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Constant brodalumab 140 mg Q2W [a)] | Constant brodalumab 210 mg Q2W [b)] | Ustekinumab [c)] | All subjects receiving brodalumab [d)] |
| N | 1491 | 1496 | 879 | 613 | 280 | 1335 | 613 | 4019 |
| Infections and infestations (SOC) | 340 (22.8) | 412 (27.5) | 206 (23.4) | 156 (25.4) | 116 (41.4) | 672 (50.3) | 331 (54.0) | 2092 (52.1) |
| Nasopharyngitis | 101 (6.8) | 101 (6.8) | 61 (6.9) | 34 (5.5) | 40 (14.3) | 174 (13.0) | 88 (14.4) | 598 (14.9) |
| Upper respiratory tract infection | 70 (4.7) | 86 (5.7) | 56 (6.4) | 36 (5.9) | 23 (8.2) | 166 (12.4) | 93 (15.2) | 505 (12.6) |
| Urinary tract infection | 17 (1.1) | 16 (1.1) | 8 (0.9) | 10 (1.6) | 7 (2.5) | 43 (3.2) | 23 (3.8) | 126 (3.1) |
| Pharyngitis | 14 (0.9) | 22 (1.5) | 9 (1.0) | 5 (0.8) | 5 (1.8) | 47 (3.5) | 12 (2.0) | 114 (2.8) |
| Influenza | 13 (0.9) | 19 (1.3) | 4 (0.5) | 7 (1.1) | 5 (1.8) | 33 (2.5) | 23 (3.8) | 110 (2.7) |
| Bronchitis | 11 (0.7) | 19 (1.3) | 12 (1.4) | 7 (1.1) | 8 (2.9) | 41 (3.1) | 20 (3.3) | 125 (3.1) |
| Conjunctivitis | 11 (0.7) | 11 (0.7) | 1 (0.1) | 2 (0.3) | 5 (1.8) | 20 (1.5) | 9 (1.5) | 62 (1.5) |
| Gastroenteritis | 10 (0.7) | 10 (0.7) | 10 (1.1) | 3 (0.5) | 2 (0.7) | 23 (1.7) | 10 (1.6) | 89 (2.2) |
| Sinusitis | 9 (0.6) | 16 (1.1) | 11 (1.3) | 8 (1.3) | 3 (1.1) | 40 (3.0) | 19 (3.1) | 134 (3.3) |
| Gastroenteritis viral | 8 (0.5) | 4 (0.3) | 1 (0.1) | 4 (0.7) | 4 (1.4) | 15 (1.1) | 13 (2.1) | 44 (1.1) |
| Viral upper respiratory tract infection | 9 (0.6) | 9 (0.6) | 5 (0.6) | 4 (0.7) | 1 (0.4) | 19 (1.4) | 12 (2.0) | 72 (1.8) |
| Oral herpes | 7 (0.5) | 5 (0.3) | 1 (0.1) | 4 (0.7) | 4 (1.4) | 20 (1.5) | 10 (1.6) | 67 (1.7) |
| Rhinitis | 6 (0.4) | 14 (0.9) | 6 (0.7) | 7 (1.1) | 3 (1.1) | 27 (2.0) | 13 (2.1) | 65 (1.6) |
| Ear infection | 6 (0.4) | 3 (0.2) | 3 (0.3) | 1 (0.2) | 2 (0.7) | 12 (0.9) | 4 (0.7) | 40 (1.0) |
| Folliculitis | 5 (0.3) | 8 (0.5) | 2 (0.2) | 2 (0.3) | 1 (0.4) | 12 (0.9) | 10 (1.6) | 53 (1.3) |
| Oral candidiasis | 3 (0.2) | 3 (0.2) | 0 | 0 | 4 (1.4) | 21 (1.6) | 1 (0.2) | 60 (1.5) |
| Cellulitis | 3 (0.2) | 4 (0.3) | 6 (0.7) | 3 (0.5) | 2 (0.7) | 25 (1.9) | 3 (0.5) | 46 (1.1) |

n (%)
a) Subjects who received brodalumab 140 mg Q2W through Week 52
b) Subjects who received brodalumab 210 mg Q2W through Week 52
c) Subjects who received ustekinumab through Week 52
d) All brodalumab-treated subjects

The incidences of serious injections were 2.8% (5 of 177 subjects) in Japanese Pool 1; 0.5% (7 of 1491 subjects) in the brodalumab 140 mg Q2W group, 0.5% (7 of 1496 subjects) in the brodalumab 210 mg Q2W group, 0.3% (2 of 613 subjects) in the ustekinumab group, and 0.2% (2 of 879 subjects) in the placebo group in Pool A; and 1.0% (42 of 4019) in all brodalumab-treated subjects and 0.8% (5 of 613) in ustekinumab-treated subjects in Pool B. There were no major differences in the incidence among the treatment groups. In Pool C, the incidence of serious adverse events in the "Infections and infestations SOC" was 1.3% in all brodalumab-treated subjects (59 of 4461 subjects, 1.2 events per 100 subject-years); the main events were cellulitis in 11 subjects (0.2%, 0.2 events per 100 subject-years); pneumonia, urinary tract infection, and appendicitis in 4 subjects each (0.1%, 0.1 events per 100 subject-years); and sepsis, diverticulitis, and gastroenteritis in 3 subjects each (0.1%, 0.1 events per 100 subject-years), etc.

Japanese Pool 1 included 1 subject with a history of tuberculosis, but had no occurrence of adverse events in the "Tuberculous infections HLT." In Pool C, latent tuberculosis (2 subjects) and erythema induratum (1 subject) were reported as adverse events in the "Tuberculous infections HLT." The subjects with latent tuberculosis did not develop tuberculosis. The erythema induratum resolved without study drug discontinuation and its causal

relationship to study drug was ruled out by the investigator. At present, these findings have not suggested the possibility of initial tuberculosis infection or reactivation of latent tuberculosis associated with brodalumab.

In Pool C, 1 subject had hepatitis C, but its causal relationship to study drug was ruled out by the investigator.

The results presented above show no trend towards a substantially higher incidence of infections in brodalumab-treated subjects than in placebo- or ustekinumab-treated subjects. However, the possibility of infections associated with brodalumab cannot be ruled out in light of its mechanism of action, and serious infections occurred in subjects treated with brodalumab, etc. Given these findings, brodalumab should be used at medical institutions where infections, etc. can be managed adequately, and precautionary statements and warnings will be included in the informative materials for healthcare professionals and in the WARNINGS section and the IMPORTANT PRECAUTIONS section of the package insert. Furthermore, brodalumab has not been administered to patients with active tuberculosis in the clinical studies; therefore the possibility of brodalumab-induced reactivation of tuberculosis in patients with a history of tuberculosis cannot be completely ruled out. Thus brodalumab will be contraindicated in patients with serious infection or active tuberculosis, and patients with infection or suspected infection and patients with a history of tuberculosis will be listed in the CAREFUL ADMINISTRATION section of the package insert. Moreover, the occurrence of serious infections, etc. will continue to be evaluated via post-marketing surveillance.

PMDA's view:
The possibility of serious infections associated with brodalumab cannot be ruled out in light of its pharmacological actions; and serious infections were reported in clinical studies. Thus patients and healthcare professionals using brodalumab should be alerted to the possibilities of infections, in the same manner as those using other approved biological products. To date, no initial tuberculosis infection or reactivation of latent tuberculosis has been noted in patients receiving brodalumab. However, patients and healthcare professionals using brodalumab should be alerted to the possibility of the onset of tuberculosis as well, in the same manner as those using other approved biological products, because the number of patients assessed and the observation period in clinical studies were not sufficient to evaluate the risk of tuberculosis, and because a report suggested an association between the IL-17 signaling pathway and the development of tuberculosis (*J Immunol*. 2010; 184: 4414-22). The occurrence of serious infections and tuberculosis in patients treated with brodalumab should continue to be evaluated via post-marketing surveillance. The applicant should take safety measures thoroughly for prevention and early detection of serious infections, in cooperation with dermatologists, who play the main role in treating psoriasis, and with specialists capable of detecting and treating serious infections [see 7.R.8 Post-marketing safety measures].

**7.R.3.2 Fungal infections including candidiasis**

The applicant's explanation on the occurrence of fungal infections including candidiasis in patients treated with brodalumab:
The risk of fungal infections including candidiasis was assessed in patients treated with brodalumab because the IL-17 signaling pathway plays a central role in the mucosal defense to *Candida albicans* (*Eur J Immunol*.

2012; 42: 2246-54, *J Exp Med*. 2010; 207: 299-308, etc.).

Table 52 shows the main adverse events in the "Fungal infectious disorders (High Level Group Term [HLGT])" reported in clinical studies. In Pool A and Pool B, the incidence of fungal infections tended to increase dose-dependently in subjects receiving brodalumab, with a tendency towards a higher incidence in brodalumab-treated subjects than in placebo- or ustekinumab-treated subjects. In Pool C, the incidence of fungal infections was 6.6% (295 of 4461 subjects, 7.2 events per 100 subject-years). Pool C had serious adverse events in the "Fungal infectious disorders HLGT" (coccidioidomycosis in 1 subject and cryptococcal meningitis in 1 subject); the outcome was "resolved" for both events. In Japanese Pool 2, the incidences of events in the "Fungal infectious disorders HLGT" were 6.8% (5 of 73) in subjects receiving brodalumab 140 mg Q2W and 25.0% (18 of 72) in subjects receiving brodalumab 210 mg Q2W. The most common event was tinea pedis (4.1% [3 of 73] in subjects receiving brodalumab 140 mg Q2W, 13.9% [10 of 72] in subjects receiving brodalumab 210 mg Q2W).

Table 52. Adverse events in the Fungal infectious disorders HLGT reported by ≥3 brodalumab-treated subjects (Pool A and Pool B)

| | Pool A (Induction phase) | | | | Pool B (through Week 52) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Constant brodalumab 140 mg Q2W | Constant brodalumab 210 mg Q2W | Ustekinumab | All subjects receiving brodalumab |
| N | 1491 | 1496 | 879 | 613 | 280 | 1335 | 613 | 4019 |
| Fungal infectious disorders (HLGT) | 17 (1.1) | 36 (2.4) | 8 (0.9) | 6 (1.0) | 11 (3.9) | 68 (5.1) | 18 (2.9) | 212 (5.3) |
| Oral candidiasis | 3 (0.2) | 3 (0.2) | 0 | 0 | 4 (1.4) | 21 (1.6) | 1 (0.2) | 60 (1.5) |
| Vulvovaginal candidiasis | 3 (0.2) | 1 (0.1) | 0 | 0 | 3 (1.1) | 3 (0.2) | 1 (0.2) | 11 (0.3) |
| Tinea pedis | 2 (0.1) | 10 (0.7) | 0 | 2 (0.3) | 1 (0.4) | 11 (0.8) | 4 (0.7) | 28 (0.7) |
| Vulvovaginal mycotic infection | 2 (0.1) | 3 (0.2) | 3 (0.3) | 1 (0.2) | 0 | 4 (0.3) | 4 (0.7) | 18 (0.4) |
| Oesophageal candidiasis | 2 (0.1) | 1 (0.1) | 0 | 0 | 0 | 1 (0.1) | 0 | 3 (0.1) |
| Oral fungal infection | 2 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.4) | 5 (0.4) | 0 | 14 (0.3) |
| Tinea versicolour | 1 (0.1) | 1 (0.1) | 2 (0.2) | 1 (0.2) | 0 | 3 (0.2) | 2 (0.3) | 9 (0.2) |
| Skin candida | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 6 (0.1) |
| Candida infection | 0 | 4 (0.3) | 0 | 0 | 0 | 3 (0.2) | 0 | 10 (0.2) |
| Intertrigo candida | 0 | 2 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.1) | 0 | 3 (0.1) |
| Genital candidiasis | 0 | 2 (0.1) | 0 | 0 | 0 | 1 (0.1) | 0 | 4 (0.1) |
| Fungal infection | 0 | 1 (0.1) | 1 (0.1) | 1 (0.2) | 0 | 3 (0.2) | 2 (0.3) | 14 (0.3) |
| Fungal skin infection | 0 | 1 (0.1) | 0 | 1 (0.2) | 0 | 2 (0.1) | 2 (0.3) | 5 (0.1) |
| Body tinea | 0 | 1 (0.1) | 0 | 0 | 1 (0.4) | 4 (0.3) | 0 | 8 (0.2) |
| Tinea cruris | 1 (0.1) | 1 (0.1) | 0 | 0 | 0 | 4 (0.3) | 1 (0.2) | 7 (0.2) |
| Onychomycosis | 0 | 1 (0.1) | 0 | 0 | 0 | 3 (0.2) | 0 | 8 (0.2) |
| Tinea infection | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 3 (0.1) |

n (%)

The possibility of fungal infections associated with brodalumab cannot be ruled out in light of its pharmacological actions. In clinical studies, the incidence of fungal infections tended to be higher in brodalumab-treated subjects than in placebo- or ustekinumab-treated subjects. Thus, warnings and precautions about the risk of tinea and candidiasis will be provided in the package insert.

PMDA's view:

Attention should be paid to the possible development of fungal infections during treatment with brodalumab, because a report suggested that the IL-17 signaling pathway plays a central role in the mucosal defense to *Candida albicans* (*Eur J Immunol*. 2012; 42: 2246-54), and because the incidence of fungal infections tended to be higher in brodalumab-treated subjects than in placebo- or ustekinumab-treated subjects in clinical studies. Since

the number of patients studied is limited at present, the occurrence of fungal infections as well as other infections should continue to be evaluated via post-marketing surveillance.

**7.R.3.3 Inflammatory bowel diseases (Crohn's disease and ulcerative colitis)**

The applicant explained the occurrence of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) in patients treated with brodalumab.

The applicant's explanation:

Reports on the role of IL-17 in different colitis models are inconsistent: some reports suggested the involvement of IL-17 in the pathogenesis of colitis in an animal model (*Biochem Biophys Res Commun*. 2008; 377: 12-6, *J Exp Med*. 2008; 205: 1063-75, etc.), but another report suggested a protective function for IL-17A (*Nat Immunol*. 2009; 10: 603-9).

The toxicity studies revealed no brodalumab-related effects on the intestine, but the pharmacology studies in different colitis models showed exacerbation of disease or lack of therapeutic efficacy after administration of the mouse surrogate antibody of brodalumab [see 3.2.3 Effects in mouse models of inflammatory bowel disease]. Thus, the risk of inflammatory bowel disease in patients treated with brodalumab was assessed.[50]

In Pool A, no patients receiving brodalumab experienced events related to inflammatory bowel diseases including Crohn's disease.

In Pool C, inflammatory bowel disease-related events occurred in 0.8% (35 of 4461) of all brodalumab-treated subjects: enteritis (6 subjects); haematochezia (5 subjects); rectal haemorrhage (4 subjects); colitis, duodenal ulcer, and gastritis erosive (3 subjects each); ulcerative colitis and gastric ulcer (2 subjects each); Crohn's disease, enterocolitis, ulcer, lower gastrointestinal haemorrhage, lip erosion, colitis microscopic, and erosive oesophagitis (1 subject each). Of these events, serious events were duodenal ulcer (3 subjects); and enteritis, gastritis erosive, Crohn's disease, enterocolitis, and lower gastrointestinal haemorrhage (1 subject each). In Pool C, 2 subjects had ulcerative colitis and 2 subjects had a history of ulcerative colitis, but none of them experienced a worsening or relapse of ulcerative colitis. The subject with a history of ulcerative colitis experienced 1 event of Grade 1 diarrhoea, but its causal relationship to study drug was ruled out.

In Japanese Pool 1, inflammatory bowel disease-related events occurred in 6.8% (12 of 177) of subjects: abdominal pain upper and constipation (5 subjects each); and abdominal pain, mucosal inflammation, and anal haemorrhage (1 subject each). No serious events were reported.

The results presented above do not suggest brodalumab-associated risk of new onset of inflammatory bowel disease or worsening of ulcerative colitis in patients with psoriasis. However, the possibility of worsening of Crohn's disease cannot be ruled out in light of its pharmacological actions. Further, patients with Crohn's disease showed worsening of symptoms in clinical studies (Studies 200900702 and 20100008 [conducted in patients with Crohn's disease]). Thus, patients with active Crohn's disease will be listed in the CAREFUL ADMINISTRATION section of the package insert, and precautions will be provided also in the

[50] Patients with Crohn's disease were excluded from psoriasis clinical studies.

informative materials for healthcare professionals. The occurrence of Crohn's disease will continue to be evaluated via post-marketing surveillance. Foreign clinical studies in patients with Crohn's disease were terminated due to the risk of exacerbation of Crohn's disease.

PMDA's view:
Although there has been no evidence for the risk of inflammatory bowel disease associated with brodalumab, given that the symptoms of active Crohn's disease tended to worsen in clinical studies in patients with Crohn's disease, etc., it is appropriate to list patients with active Crohn's disease in the CAREFUL ADMINISTRATION section of the package insert. However, as the number of patients assessed and the observation period in clinical studies were not sufficient to evaluate the risk of Crohn's disease and ulcerative colitis, an investigation of the occurrence of Crohn's disease and ulcerative colitis in patients treated with brodalumab needs to be continued via post-marketing surveillance.

**7.R.3.4 Neutropenia**
The applicant's explanation on the occurrence of neutropenia in patients treated with brodalumab:
A reduction in neutrophil count in IL-17 receptor A-deficient mice is considered attributable to reduced production of granulocyte colony-stimulating factors in nonhemopoietic cells (*J Immunol*. 2008; 181:1357-64). Neutropenia has been reported in clinical studies of other agents that target the IL-17 signaling pathway. Analyses of neutropenia were performed because of these findings.

Table 53 shows neutropenia-related adverse events in clinical studies. In Pool A, there was no trend towards a higher incidence in the brodalumab group than in the placebo group. In Pool C, 1 subject experienced serious neutropenia, which resolved following treatment discontinuation. In Pool C, neutrophil count $<0.5\times10^9$/L was observed in 4 subjects without associated infections. In Japanese Pool 1, the incidence of neutropenia was 1.1% (2 of 177 subjects), the incidence of neutrophil count decreased was 0.6% (1 of 177 subjects), and the incidence of white blood cell count decreased was 0.6% (1 of 177 subjects).

The possibility of neutropenia associated with brodalumab cannot be ruled out in light of its pharmacological actions, and neutropenia-related adverse events were reported in clinical studies. Therefore, precautionary statements will be provided in the package insert and in the informative materials for healthcare professionals, and the occurrence of neutropenia will continue to be evaluated via post-marketing surveillance.

Table 53. Neutropenia-related adverse events (Pool A and Pool C)

| | Pool A (Induction phase) | | | | Pool C (Entire treatment period) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Overall brodalumab 140 mg Q2W | Overall brodalumab 210 mg Q2W | Ustekinumab /Brodalumab | Combined brodalumab group |
| N | 1491 | 1496 | 879 | 613 | 279 | 1291 | 564 | 4461 |
| Neutropenia [a)] | 7 (0.5) | 10 (0.7) | 0 | 3 (0.5) | 2 (0.7) | 7 (0.5) | 2 (0.4) | 27 (0.6) |
| Leukopenia | 3 (0.2) | 2 (0.1) | 2 (0.2) | 1 (0.2) | 1 (0.4) | 2 (0.2) | 0 | 9 (0.2) |
| Neutrophil count decreased [a)] | 2 (0.1) | 3 (0.2) | 0 | 1 (0.2) | 0 | 4 (0.3) | 1 (0.2) | 8 (0.2) |
| Neutrophil count abnormal | 2 (0.1) | 2 (0.1) | 0 | 1 (0.2) | 0 | 3 (0.2) | 0 | 5 (0.1) |
| White blood cell count abnormal | 2 (0.1) | 1 (0.1) | 1 (0.1) | 0 | 0 | 3 (0.2) | 1 (0.2) | 7 (0.2) |
| White blood cell count decreased | 0 | 1 (0.1) | 0 | 2 (0.3) | 0 | 1 (0.1) | 1 (0.2) | 5 (0.1) |
| Pancytopenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Number of subjects with neutrophil count decreased | | | | | | | | |
| $\geq 1.0\times10^9$ /L and $<1.5\times10^9$ /L | 13 (0.9) | 19 (1.3) | 3 (0.3) | 2 (0.3) | 6 (2.2) | 34 (2.6) | 5 (0.9) | 102 (2.3) |
| $\geq 0.5\times10^9$ /L and $<1.0\times10^9$ /L | 3 (0.2) | 7 (0.5) | 0 | 0 | 1 (0.4) | 6 (0.5) | 0 | 19 (0.4) |
| $<0.5\times10^9$ /L | 2 (0.1) | 0 | 0 | 1 (0.2) | 1 (0.4) | 0 | 0 | 4 (0.1) |

n (%)
a) Events were counted based on the physicians' reports.

PMDA's view:

The occurrence of neutropenia is expected from the pharmacological properties of brodalumab, and the incidence of neutropenia tended to be higher in brodalumab-treated subjects than in placebo-treated subjects in clinical studies. This suggests the possibility of neutropenia associated with brodalumab. Some subjects receiving brodalumab had a neutrophil count $<0.5\times10^9$/L, and decreased neutrophil count associated with brodalumab may induce infections. Therefore, precautionary statements about neutropenia, etc. associated with brodalumab should be included in the package insert. Further, the occurrence of neutropenia and its association with infections should continue to be evaluated via post-marketing surveillance.

### 7.R.3.5 Malignant tumors

The applicant's explanation on the risk of malignant tumors in patients treated with brodalumab:

The results of a 6-month repeat-dose toxicity study in cynomolgus monkeys did not suggest the carcinogenic potential of brodalumab. However, the risk of malignant tumors was assessed because the role of IL-17 in malignancy has not been elucidated (the IL-17 signaling pathway has been reported to have both pro-tumor and anti-tumor functions [see 5.4 Carcinogenicity]), and because malignant tumors are serious events.

Table 54 shows malignancy-related events in Pool A and Pool B. In the combined brodalumab group in Pool C, the following events occurred (in addition to the events reported in Pool B): basal cell carcinoma (4 subjects); squamous cell carcinoma of skin (3 subjects); prostate cancer (2 subjects); squamous cell carcinoma, neoplasm skin, colon cancer, bladder transitional cell carcinoma, rectal cancer, and invasive ductal breast carcinoma (1 subject each). The exposure-adjusted rate of non-melanoma skin cancer-related events was 0.5 events per 100 subject-years.

Table 54. Malignancy-related events (Pool A and Pool B)

| | Pool A (Induction phase) | | | | Pool B (through Week 52) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Constant brodalumab 140 mg Q2W | Constant brodalumab 210 mg Q2W | Ustekinumab | All subjects receiving brodalumab |
| N | 1491 | 1496 | 879 | 613 | 280 | 1335 | 613 | 4019 |
| Malignancies (adjudicated) [a)] | 3 (0.2) | 3 (0.2) | 0 | 1 (0.2) | 0 | 12 (0.9) | 8 (1.3) | 28 (0.7) |
| Basal cell carcinoma | 2 (0.1) | 0 | 0 | 0 | 0 | 4 (0.3) | 6 (1.0) | 13 (0.3) |
| Pancreatic carcinoma | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 |
| Bladder cancer | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Penile squamous cell carcinoma | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Squamous cell carcinoma | 0 | 1 (0.1) | 0 | 0 | 0 | 3 (0.2) | 1 (0.2) | 4 (0.1) |
| Prostate cancer | 0 | 0 | 0 | 1 (0.2) | 0 | 0 | 1 (0.2) | 2 (<0.1) |
| Adenocarcinoma pancreas | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 2 (<0.1) |
| Bile duct adenocarcinoma | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Breast cancer | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Oesophageal carcinoma | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Small intestine carcinoma metastatic | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Bowen's disease | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 |
| Squamous cell carcinoma of skin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Follicle centre lymphoma, follicular grade I, II, III | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |

n (%)

a) Events in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC adjudicated by Amgen as malignancies.

In Japanese Pool 1, the reported events in the "Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC" were skin papilloma (6.8%, 12 of 177 subjects), seborrhoeic keratosis (1.1%, 2 of 177 subjects), lipoma (0.6%, 1 of 177 subjects), neoplasm skin (0.6%, 1 of 177 subjects), pyogenic granuloma (0.6%, 1 of 177 subjects), prostate cancer (0.6%, 1 of 177 subjects), and hepatocellular carcinoma (0.6%, 1 of 177 subjects).

The standardized incidence ratio (SIR) for malignancies in Pool C [95% CI] was calculated from the US National Cancer Institute Surveillance Epidemiology and End Results (SEER) database. The SIRs were 0.91 [0.58, 1.37] (Pool C/the world's general population), 0.96 [0.39, 1.98] (Pool C/the European general population), and 0.90 [0.45, 1.61] (Pool C/the US general population). This suggested no trend towards higher risk of malignant tumors in brodalumab-treated patients than in the general population. The follow-up time-adjusted rate of malignancies (adjudicated) in Pool C [95% CI] was 0.9 [0.68, 1.20] events per 100 subject-years. This was lower than the rate of malignancy-related events with another psoriasis treatment (n = 36,465.5 subject-years): 1.429 [1.309, 1.557] events per 100 subject-years (CTD5.3.5.3-6).

The incidences of malignancies in Japanese and foreign clinical studies were similar to that in the general population. The incidence of malignancy-related events showed no brodalumab dose-response relationship. In Pool B, the incidence of malignancy-related events was lower with brodalumab than with ustekinumab. The follow-up time-adjusted rate of malignancies was lower with brodalumab than with another psoriasis treatment. Therefore, there has been no evidence for the risk of malignant tumors associated with brodalumab, and no specific measures against malignant tumors are needed at present.

PMDA's view:

Although no evidence for the risk of malignant tumors has been found at present, a warning/precaution about the risk of malignant tumors should be included in the WARNINGS section of the package insert, because brodalumab may possibly affect the anti-tumor mechanism. Generally, many patients with psoriasis have

experienced phototherapy or immunosuppressants and are particularly at risk of developing skin cancer. Therefore, the occurrence of malignancies including skin cancer in patients treated with brodalumab should be monitored via post-marketing surveillance.

**7.R.3.6 Cardiovascular events**

The applicant explained the occurrence of ischemic cerebrovascular and cardiac events and MACE (myocardial infarction, stroke, cardiovascular death) in patients treated with brodalumab.

The applicant's explanation:

Reports have suggested that the IL-17 signaling pathway acts as a precipitating factor by inducing inflammation during cardiac repair following myocardial infarction (*Int J Cardiol*. 2013; 163: 326-34, *J Am Coll Cardiol*. 2012; 59: 420-9) and plays a proatherogenic role in atherosclerosis and acute coronary syndrome (*Circ Res*. 2012; 110: 675-87, *J Immunol*. 2010; 185: 5820-7). The pharmacological effects of brodalumab suggest that brodalumab plays a protective role in myocardial remodeling and atherogenesis. However, analyses of cardiovascular events were performed because patients with psoriasis often have cardiovascular disease as well as typical risk factors for cardiovascular events, such as diabetes mellitus, hypertension, dyslipidemia, smoking, and obesity (*J Am Acad Dermatol*. 2006; 55: 829-35).

Table 55 shows ischemic cerebrovascular and cardiac events and MACE[51] that occurred in clinical studies. In Japanese Pool 1, the incidence of blood creatine phosphokinase increased was 1.1% (2 of 177 subjects), the incidences of electrocardiogram T wave inversion, myocardial infarction, myocardial ischaemia, and Prinzmetal angina were all 0.6% (1 of 177 subjects). In all subjects from the clinical studies of other psoriasis treatments (including biologics) (n = 19498.5 subject-years), the incidence rate of MACE [95% CI] was 0.451 [0.362, 0.556] events per 100 subject-years. This was not significantly different from the incidence rate of MACE in clinical studies for brodalumab (0.56 [0.37, 0.82] events per 100 subject-years).

No specific measures against cardiovascular events are needed at present, because all of the subjects who experienced MACE had cardiovascular risk factors, and because there was no trend towards an increased risk of cardiovascular events in patients treated with brodalumab.

[51] In Studies 20120102, 20120103, and 20120104, adverse events suspected of MACE were adjudicated in a blinded manner by a Cardiovascular Events Committee. Adjudication was not implemented in other foreign clinical studies or Japanese clinical studies.

Table 55. Ischemic cerebrovascular and cardiac events and MACE (Pool A and Pool C)

| | Pool A (Induction phase) | | | | Pool C (Entire treatment period) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Overall brodalumab 140 mg Q2W | Overall brodalumab 210 mg Q2W | Ustekinumab /Brodalumab | Combined brodalumab group |
| N | 1491 | 1496 | 879 | 613 | 279 | 1291 | 564 | 4461 |
| Ischaemic cerebrovascular conditions (SMQ) | 1 (0.1) | 1 (0.1) | 0 | 1 (0.2) | 0 | 2 (0.2) | 0 | 10 (0.2) |
| Cerebrovascular accident | 1 (0.1) | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 3 (0.1) |
| Cerebral infarction | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Transient ischaemic attack | 0 | 0 | 0 | 1 (0.2) | 0 | 0 | 0 | 2 (<0.1) |
| Carotid artery stenosis | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Ischaemic stroke | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.1) |
| Cerebral ischaemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Ischaemic heart disease (SMQ) | 4 (0.3) | 0 | 1 (0.1) | 1 (0.2) | 3 (1.1) | 9 (0.7) | 0 | 46 (1.0) |
| Angina pectoris | 2 (0.1) | 0 | 0 | 0 | 1 (0.4) | 2 (0.2) | 0 | 14 (0.3) |
| Angina unstable | 1 (0.1) | 0 | 0 | 0 | 1 (0.4) | 1 (0.1) | 0 | 4 (0.1) |
| Myocardial infarction | 1 (0.1) | 0 | 0 | 0 | 1 (0.4) | 3 (0.2) | 0 | 17 (0.4) |
| Myocardial ischaemia | 0 | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 2 (<0.1) |
| Acute myocardial infarction | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 4 (0.1) |
| Blood creatine phosphokinase increased | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 2 (<0.1) |
| Electrocardiogram T wave inversion | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Coronary artery disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 (0.1) |
| Arteriosclerosis coronary artery | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (<0.1) |
| Arteriospasm coronary | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Coronary artery occlusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Ischaemic cardiomyopathy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Electrocardiogram T wave abnormal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |
| Acute coronary syndrome | 0 | 0 | 0 | 1 (0.2) | 0 | 0 | 0 | 0 |
| MACE [a)] | 3 | 0 | 0 | 0 | 1 (0.4) | 5 (0.4) | 0 | 27 (0.6) |
| Myocardial infarction | 2 (0.1) | 0 | 0 | 0 | 1 (0.4) | 4 (0.3) | 0 | 18 (0.4) |
| Stroke | 1 (<0.1) | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 7 (0.2) |
| Cardiovascular death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (<0.1) |

n (%), a) Pool C for MACE is based on phase III studies only (277 subjects receiving brodalumab 140 mg Q2W, 1278 subjects receiving brodalumab 210 mg Q2W, 564 subjects treated with ustekinumab/brodalumab, 4270 brodalumab-treated subjects)

PMDA's view:

Although an increased risk of cardiovascular adverse events associated with brodalumab has not been suggested at present, the effects of brodalumab on the cardiovascular system should continue to be evaluated because the number of patients assessed in clinical studies was not sufficient to evaluate the risk of cardiovascular adverse events.

**7.R.3.7 Depression and suicide/self-injury**

The applicant's explanation on the occurrence of depression and suicide/self-injury in patients treated with brodalumab:

Multiple research reports have indicated the association between systemic inflammation and depression, but the association of the IL-17 signaling pathway with depression or suicide/self-injury and other psychiatric disorders has not been elucidated. The 1-, 3-, and 6-month repeat-dose studies in cynomolgus monkeys have shown no behavioral pharmacological changes attributable to brodalumab.

During the development of brodalumab, among approximately 6000 subjects who received study drug in foreign clinical studies, 7 subjects experienced suicide/self-injury-related events (completed suicide [3 subjects], suicide

attempt [3 subjects], suicidal ideation [1 subject]; a causal relationship to study drug was ruled out by both the investigator and Amgen Inc. for all events[52]). Thus, "suicidal ideation and behavior" were identified as important potential risks, and the C-SSRS and PHQ-8 were introduced to all the then-ongoing clinical studies of brodalumab to assess suicidality and the severity of depressive symptoms.

Against the above background, analyses for depression and suicide/self-injury were performed.

Table 56 shows adverse events in the "depression (excluding suicide/self-injury) SMQ" or the "suicide/self-injury SMQ" that occurred in Pool A and Pool B. The incidence in the brodalumab group was similar to that in the placebo or ustekinumab group.

Table 56. Depression (excluding suicide/self-injury) (SMQ), depression, depressed mood, and suicide/self-injury (SMQ) (Pool A and Pool B)

| | Pool A (Induction phase) | | | | Pool B (through Week 52) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Constant brodalumab 140 mg Q2W | Constant brodalumab 210 mg Q2W | Ustekinumab | All subjects receiving brodalumab |
| N | 1491 | 1496 | 879 | 613 | 280 | 1335 | 613 | 4019 |
| Depression (excluding suicide/self-injury) (SMQ) | 13 (0.9) | 11 (0.7) | 9 (1.0) | 6 (1.0) | 4 (1.4) | 15 (1.1) | 19 (3.1) | 82 (2.0) |
| Depression | 9 (0.6) | 5 (0.3) | 5 (0.6) | 3 (0.5) | 2 (0.7) | 9 (0.7) | 10 (1.6) | 55 (1.4) |
| Depressed mood | 2 (0.1) | 1 (0.1) | 1 (0.1) | 2 (0.3) | 2 (0.7) | 1 (0.1) | 5 (0.8) | 9 (0.2) |
| Suicide/self-injury (SMQ) | 0 | 1 (0.1) | 0 | 0 | 0 | 4 (0.3) | 2 (0.3) | 6 (0.1) |
| Suicide attempt | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.1) | 1 (0.2) | 1 (<0.1) |
| Suicidal ideation | 0 | 0 | 0 | 0 | 0 | 2 (0.1) | 1 (0.2) | 3 (0.1) |
| Intentional overdose | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 1 (<0.1) |
| Intentional self-injury | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (<0.1) |

n (%)

In the combined brodalumab group in Pool C, the incidence of "depression (excluding suicide/self-injury) SMQ" was 2.5% (112 of 4461 subjects). The most common events were depression (1.7%, 75 of 4461 subjects) and depressed mood (0.3%, 14 of 4461 subjects). In Pool C, events in the "suicide/self-injury SMQ" occurred in 16 subjects by the time of data cutoff for regulatory submission (March to September 2014) and then in 11 subjects by the data cutoff in March 2015. Of the events reported by the 16 subjects by the time of data cutoff for regulatory submission, the adverse event reported by 1 subject was reclassified as a medical history in the subsequent data cleaning. The suicide/self-injury-related adverse events reported by 26 subjects consisted of completed suicide (3 subjects), intentional overdose (1 subject), suicide attempt (4 subjects), suicidal behavior (2 subjects), intentional self-injury (1 subject), suicidal ideation (17 subjects; 1 subject also had suicide attempt and 2 subjects also had suicidal behavior), and suicidal depression (1 subject). A causal relationship to study drug could not be ruled out for 1 case of completed suicide, 2 cases of suicide attempt, 7 cases of suicidal ideation, and 1 case of suicidal depression, but all of these subjects (except for 1 subject with suicide attempt and 2 subjects with suicidal ideation) had current or past psychiatric disorders such as depression. The follow-up time-adjusted rates of these adverse events were as follows: suicide/self-injury-related adverse events, 0.33 per 100 subject-years; completed suicide-related events, 0.05 per 100 subject-years; suicidal behavior-related events, 0.14 per 100 subject-years; suicidal ideation-related events, 0.23 per 100 subject-years.[53]

[52] Of these events, completed suicide (1 subject) and suicide attempt (1 subject) were noted in a clinical study in patients with rheumatoid arthritis.
[53] Completed suicide-related events: completed suicide and intentional overdose. Suicidal behavior-related events: completed suicide, intentional overdose, suicide attempt, suicidal behavior, and intentional self-injury. Suicidal ideation-related events: suicidal ideation and suicidal depression.

In a foreign clinical study in patients with rheumatoid arthritis (CTD5.3.5.4-4, Study 20090402), 1 subject receiving brodalumab 210 mg Q2W completed suicide, but its causal relationship to study drug was ruled out by the investigator. In Japanese Pool 1, the incidences of adverse events in the "Psychiatric disorders SOC" were 0.6% (1 of 177 subjects) for dysthymic disorder and 0.6% (1 of 177 subjects) for suicide attempt. In Study 4827-005, 1 subject receiving brodalumab 140 mg Q4W had suicide attempt, but its causal relationship to study drug was ruled out by the investigator.

The C-SSRS[54] and PHQ-8[55] scores assessed in foreign phase III studies (Studies 20120103, 20120104) are shown in Tables 57 and 58. There was no trend towards substantially higher scores in the combined brodalumab group than in the ustekinumab group.

Table 57. Most severe suicidal ideation based on C-SSRS through Week 52 in foreign phase III studies (Studies 20120103 and 20120104) (Safety analysis set)

| | Brodalumab 140 mg Q2W [a)] | Brodalumab 210 mg Q2W [b)] | Combined brodalumab [c)] | Ustekinumab [d)] |
|---|---|---|---|---|
| Subjects with past suicidality | N = 0 | N = 3 | N = 17 | N = 9 |
| Score ≥1 | 0 | 0 | 3 (17.6) | 1 (11.1) |
| Score 4 or 5 | 0 | 0 | 1 (5.9) | 0 |
| Score 4 or 5, or suicidal behavior | 0 | 0 | 1 (5.9) | 0 |
| Subjects with no past suicidality | N = 25 | N = 74 | N = 497 | N = 104 |
| Score ≥1 | 2 (8.0) | 3 (4.1) | 16 (3.2) | 1 (1.0) |
| Score 4 or 5 | 0 | 0 | 0 | 0 |
| Score 4 or 5, or suicidal behavior | 0 | 0 | 0 | 0 |

n (%)
a) Subjects who received brodalumab 140 mg Q2W through Week 52
b) Subjects who received brodalumab 210 mg Q2W through Week 52
c) All brodalumab-treated subjects
d) Subjects who received ustekinumab through Week 52

Table 58. Maximum PHQ-8 total score through Week 52 in foreign phase III studies (Studies 20120103 and 20120104) (Safety analysis set)

| | Brodalumab 140 mg Q2W (N = 15) | Brodalumab 210 mg Q2W (N = 145) | Combined brodalumab (N = 474) | Ustekinumab (N = 78) |
|---|---|---|---|---|
| 0-4 (None-minimal) | 13 (86.7) | 116 (80.0) | 388 (81.9) | 69 (88.5) |
| 5-9 (Mild) | 2 (13.3) | 23 (15.9) | 68 (14.3) | 6 (7.7) |
| 10-14 (Moderate) | 0 | 4 (2.8) | 11 (2.3) | 2 (2.6) |
| 15-19 (Moderately Severe) | 0 | 1 (0.7) | 5 (1.1) | 1 (1.3) |
| 20-24 (Severe) | 0 | 1 (0.7) | 2 (0.4) | 0 |

n (%)

The combined data from clinical studies of other approved or investigational drugs for psoriasis were analyzed to determine the incidence rates [95% CI] (events per 100 subject-years) of the following events: depression (serious and non-serious), 1.378 [1.149, 1.638]; completed suicide, 0.028 [0.012, 0.055]; suicide attempt, 0.040 [0.011, 0.101]; and suicidal ideation and behavior-related events, 0.109 [0.023, 0.320] (CTD5.3.5.3-6). The incidence rate of suicide/self-injury-related events tended to be higher in clinical studies of brodalumab than in clinical studies of other psoriasis treatments. This may be due to differences in the total subject-years of follow-up.

[54] Suicidal ideation was graded on a 5-point scale: 1 = wish to be dead; 2 = active suicidal ideation, non-specific; 3 = active suicidal ideation with method, but no plan; 4 = active suicidal ideation with intent to act, but no plan; 5 = active suicidal ideation with specific plan and intent. The question about the presence or absence of suicidal behavior was answered for the most severe suicidal ideation. Patients with suicidal ideation severity categories 4 or 5, or any suicidal behavior were identified as positive cases, and referred to a mental health professional and discontinued from study drug.

[55] The 8 items of depressive symptoms in the past 2 weeks are scored separately on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day). The scores are summed to yield a total score.

As described above, no mechanism of action that can explain the association between brodalumab and suicide/self-injury has been identified, and the occurrence of suicide/self-injury was unlikely related to brodalumab. However, suicide/self-injury will be classified as important potential risks to continue to evaluate the risks, because the incidence rate of suicide/self-injury-related events tended to be higher in clinical studies of brodalumab than in clinical studies of other psoriasis treatments, and because suicide/self-injury is serious in nature. Since many of the subjects with suicide/self-injury had a history of depression, suicidal ideation, or suicide attempt, patients in severe psychotic state such as depression, suicidal ideation, and suicide attempt or those with such psychiatric history will be listed in the CAREFUL ADMINISTRATION section of the package insert, and precautionary statements will be provided also in the informative materials for healthcare professionals. Moreover, post-marketing information on the occurrence of suicide-related events will be collected.

PMDA's view:
Many of the 26 subjects with suicide/self-injury-related events (completed suicide [3 subjects], intentional overdose [1 subject], suicide attempt [4 subjects], suicidal behavior [2 subjects], intentional self-injury [1 subject], suicidal ideation [17 subjects; 1 subject also had suicide attempt and 2 subjects also had suicidal behavior], suicidal depression [1 subject]) had risk factors for suicide/self-injury such as psychiatric disorders. Suicidality and depression assessments based on the C-SSRS and PHQ-8 showed no trend towards worsening of scores with brodalumab. Thus, at present, there are no findings clearly suggesting the association between depression and suicide/self-injury-related events and treatment with brodalumab. However, it is understandable to list patients with current or past depression/depressive state and patients with a history of suicidal ideation or suicide attempt in the CAREFUL ADMINISTRATION section, as explained by the applicant, because there were also events for which a causal relationship to brodalumab could not be ruled out. Since the number of patients assessed and the observation period in clinical studies were limited and were not sufficient to evaluate the neuropsychiatric effect of brodalumab, it is necessary to monitor the occurrence of suicide/self-injury-related events, etc. following treatment with brodalumab after the market launch and take actions as needed.

PMDA will discuss this issue and specific measures to ensure proper use, based on comments from the Expert Discussion.

**7.R.3.8 Hypersensitivity and injection site reaction**

The applicant's explanation on the occurrence of hypersensitivity and injection site reaction in patients treated with brodalumab:
Brodalumab is a monoclonal antibody preparation for subcutaneous injection and the possibility of hypersensitivity reaction and injection site reaction cannot be ruled out. Thus, analyses of hypersensitivity and injection site reaction were performed.

Table 59 shows adverse events in the "Hypersensitivity SMQ" or the "Injection site reaction AMQ" that occurred in Pool A and Pool C. No anaphylaxis was reported. In Pool C, serious events of rash, dermatitis, contact dermatitis, erythema, and urticaria (1 subject each) occurred. There were no differences in the trend of occurrence of injection site reaction between ustekinumab-treated subjects and brodalumab-treated subjects, but the

incidence of hypersensitivity tended to be higher in subjects on long-term brodalumab than in ustekinumab-treated subjects. Of 281 adverse events in the "Injection site reaction AMQ," 3 led to treatment interruption, but not treatment discontinuation.

Table 59. Hypersensitivity- or injection site reaction-related events reported by ≥4 brodalumab-treated subjects (Pool A and Pool C)

| | Pool A (Induction phase) | | | | Pool C (Entire treatment period) | | | |
|---|---|---|---|---|---|---|---|---|
| | Brodalumab 140 mg Q2W | Brodalumab 210 mg Q2W | Placebo | Ustekinumab | Overall brodalumab 140 mg Q2W | Overall brodalumab 210 mg Q2W | Ustekinumab/ Brodalumab | Combined brodalumab group |
| N | 1491 | 1496 | 879 | 613 | 279 | 1291 | 564 | 4461 |
| **Hypersensitivity (SMQ)** | 39 (2.6) | 26 (1.7) | 27 (3.1) | 8 (1.3) | 20 (7.2) | 64 (5.0) | 13 (2.3) | 227 (5.1) |
| Pruritus | 18 (1.2) | 10 (0.7) | 14 (1.6) | 5 (0.8) | 10 (3.6) | 15 (1.2) | 2 (0.4) | 71 (1.6) |
| Contact dermatitis | 7 (0.5) | 5 (0.3) | 2 (0.2) | 2 (0.3) | 1 (0.4) | 4 (0.3) | 2 (0.4) | 13 (0.3) |
| Rhinitis allergic | 7 (0.5) | 2 (0.1) | 4 (0.5) | 0 | 0 | 3 (0.2) | 0 | 9 (0.2) |
| Urticaria | 4 (0.3) | 5 (0.3) | 2 (0.2) | 4 (0.7) | 1 (0.4) | 4 (0.3) | 0 | 10 (0.2) |
| Rash | 3 (0.2) | 3 (0.2) | 0 | 0 | 1 (0.4) | 6 (0.5) | 0 | 14 (0.3) |
| Hypersensitivity | 3 (0.2) | 3 (0.2) | 3 (0.3) | 0 | 0 | 4 (0.3) | 0 | 9 (0.2) |
| Conjunctivitis | 3 (0.2) | 0 | 0 | 0 | 2 (0.7) | 1 (0.1) | 0 | 14 (0.3) |
| Eczema | 2 (0.1) | 5 (0.3) | 1 (0.1) | 1 (0.1) | 1 (0.4) | 6 (0.5) | 3 (0.5) | 14 (0.3) |
| Eosinophil count increased | 2 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.4) | 2 (0.2) | 0 | 4 (0.1) |
| Dermatitis | 2 (0.1) | 0 | 0 | 0 | 2 (0.7) | 3 (0.2) | 0 | 11 (0.2) |
| Seasonal allergy | 2 (0.1) | 0 | 0 | 0 | 1 (0.4) | 3 (0.2) | 0 | 8 (0.2) |
| Skin exfoliation | 2 (0.1) | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 4 (0.1) |
| Pruritus generalised | 1 (0.1) | 3 (0.2) | 3 (0.3) | 1 (0.2) | 1 (0.4) | 4 (0.3) | 1 (0.2) | 7 (0.2) |
| Dermatitis allergic | 1 (0.1) | 2 (0.1) | 1 (0.1) | 0 | 1 (0.4) | 1 (0.1) | 0 | 7 (0.2) |
| Erythema | 1 (0.1) | 2 (0.1) | 1 (0.1) | 0 | 1 (0.4) | 3 (0.2) | 1 (0.2) | 7 (0.2) |
| Eosinophilia | 1 (0.1) | 0 | 2 (0.2) | 0 | 0 | 1 (0.1) | 0 | 4 (0.1) |
| Injection site urticaria | 0 | 1 (0.1) | 0 | 1 (0.2) | 0 | 1 (0.1) | 0 | 4 (0.1) |
| Injection site rash | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 2 (0.4) | 4 (0.1) |
| **Injection site reaction (AMQ)** | 25 (1.7) | 23 (1.5) | 11 (1.3) | 12 (2.0) | 13 (4.7) | 35 (2.7) | 11 (2.0) | 146 (3.3) |
| Injection site pain | 7 (0.5) | 9 (0.6) | 3 (0.3) | 4 (0.7) | 2 (0.7) | 8 (0.6) | 2 (0.4) | 40 (0.9) |
| Injection site erythema | 6 (0.4) | 5 (0.3) | 3 (0.3) | 3 (0.5) | 2 (0.7) | 4 (0.3) | 0 | 25 (0.6) |
| Injection site reaction | 5 (0.3) | 1 (0.1) | 0 | 1 (0.2) | 5 (1.8) | 6 (0.5) | 4 (0.7) | 26 (0.6) |
| Injection site bruising | 4 (0.3) | 4 (0.3) | 2 (0.2) | 1 (0.2) | 2 (0.7) | 3 (0.2) | 2 (0.4) | 24 (0.5) |
| Injection site swelling | 2 (0.1) | 2 (0.1) | 0 | 0 | 0 | 1 (0.1) | 1 (0.2) | 8 (0.2) |
| Injection site pruritus | 2 (0.1) | 0 | 1 (0.1) | 1 (0.2) | 0 | 4 (0.3) | 1 (0.2) | 11 (0.2) |
| Vessel puncture site bruise | 2 (0.1) | 0 | 0 | 1 (0.2) | 1 (0.4) | 1 (0.1) | 1 (0.2) | 4 (0.1) |
| Injection site haemorrhage | 1 (0.1) | 3 (0.2) | 2 (0.2) | 1 (0.2) | 1 (0.4) | 5 (0.4) | 1 (0.2) | 10 (0.2) |
| Injection site oedema | 0 | 1 (0.1) | 0 | 0 | 1 (0.4) | 3 (0.2) | 0 | 5 (0.1) |
| Injection site induration | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.1) | 0 | 4 (0.1) |
| Injection site rash | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 2 (0.4) | 4 (0.1) |
| Injection site haematoma | 0 | 0 | 0 | 0 | 0 | 2 (0.2) | 0 | 4 (0.1) |
| Injection site urticaria | 0 | 1 (0.1) | 0 | 1 (0.2) | 0 | 1 (0.1) | 0 | 4 (0.1) |

n (%); SMQ, Standardised MedDRA queries; AMQ, Amgen-defined medical queries

In Japanese Pool 2, the incidences of "Hypersensitivity SMQ" were 30.1% (22 of 73 subjects) for brodalumab 140 mg and 45.8% (33 of 72 subjects) for brodalumab 210 mg. The main events were contact dermatitis (140 mg, 9.6% [7 of 73 subjects]; 210 mg, 11.1% [8 of 72 subjects]), eczema (140 mg, 8.2% [6 of 73 subjects]; 210 mg, 8.3% [6 of 72 subjects]), seasonal allergy (140 mg, 2.7% [2 of 73 subjects]; 210 mg, 9.7% [7 of 72 subjects]), and allergic rhinitis (140 mg, 2.7% [2 of 73 subjects]; 210 mg, 4.2% [3 of 72 subjects]). Contact dermatitis occurring in 1 subject was a serious event. In Japanese Pool 2, the incidences of "Injection site reaction AMQ" were 5.5% (4 of 73 subjects) for brodalumab 140 mg and 2.8% (2 of 72 subjects) for brodalumab 210 mg. The main events were injection site bruising (140 mg, 1.4% [1 of 73 subjects]; 210 mg, 1.4% [1 of 72 subjects]), injection site pain (140 mg, 2.7% [2 of 73 subjects]), etc. No serious events were reported.

Based on the above, precautionary statements about hypersensitivity and injection site reaction will be included in

the package insert and in the informative materials for healthcare professionals. An investigation of the occurrence of hypersensitivity reaction will be continued via post-marketing surveillance.

PMDA's view:
No serious hypersensitivity-related adverse events were reported in clinical studies. However, as brodalumab is a monoclonal antibody preparation that may possibly cause hypersensitivity reactions including shock and anaphylaxis, precautionary statements should be included in the package insert and the occurrence of hypersensitivity reaction, injection site reaction, etc. should continue to be evaluated via post-marketing surveillance.

In conclusion, close attention should be paid to the possible occurrence of adverse events (especially serious infections, etc.) due to the effect the IL-17 signaling pathway inhibition on the immune system. However, brodalumab was not shown to have a tendency toward a higher risk of such events than ustekinumab, the comparator used in clinical studies of brodalumab. Therefore, such events can be managed by taking safety measures as in the case of other approved biological products. The safety information from the Japanese subpopulation also suggested no particularly noteworthy events in Japanese patients with psoriasis. However, because brodalumab has been used by only a limited number of patients, information on such adverse events should be collected via post-marketing surveillance to further characterize the safety profile of brodalumab.

**7.R.4 Dosage and administration**

As shown below, the applicant explained the rationale for the proposed dosage and administration: "The usual adult dosage is 210 mg of Brodalumab (Genetical Recombination) administered subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks."

- In a Japanese phase II study (Study 4827-002), pairwise comparisons showed statistically significant differences between placebo and each brodalumab dose (70, 140, 210 mg) in the percent improvement in PASI score. The percent improvement in PASI score was highest for brodalumab 210 mg [see 7.1.1 Japanese phase II study].
- As shown in Table 60, a Japanese long-term treatment study (Study 4827-003) demonstrated consistently higher efficacy of brodalumab 210 mg compared to 140 mg through Week 52.
- In foreign phase III studies (Studies 20120102, 20120103, 20120104), the PASI 75 and 100 response rates and sPGA success (0 or 1) rate at Week 12 tended to be consistently higher in the brodalumab 210 mg group than in the brodalumab 140 mg group [see 7.2 Phase III studies].
- In foreign phase III studies (Studies 20120103, 20120104), the PASI 100 response rate at Week 12 was statistically significantly higher in the brodalumab 210 mg group than in the ustekinumab group [see 7.2 Phase III studies].
- As shown in Table 61, the sPGA success (0 or 1) rate at Week 52 was higher in the brodalumab 210 mg/210 mg Q2W group than in other groups in foreign phase III studies (Studies 20120103, 20120104).
- The possibility that body weight affects the efficacy of brodalumab has been suggested (Table 46). As shown in Tables 62 and 63, the PASI 75 response rate in subjects weighing ≤70 kg was similar in both the

brodalumab 140 and 210 mg groups. However, a 210 mg dose is probably required to achieve PASI 100 response (a clinically important outcome) in all body weight categories.

- The clinical studies of brodalumab have raised no particular safety concerns about brodalumab 210 mg [see 7.R.3 Safety].
- The efficacy of brodalumab 210 mg in Japanese patients with psoriatic arthritis, pustular psoriasis, or erythrodermic psoriasis has been suggested, with no safety concerns [see 7.1 Phase II studies and 7.2.5 Japanese clinical study].

Table 60. Efficacy endpoints over time in Japanese long-term treatment study (Study 4827-003)

| Time point | Dose | PASI 75 | PASI 90 | PASI 100 | sPGA success (0 or 1) | BSA involvement |
|---|---|---|---|---|---|---|
| Week 0 [a)] | 140 mg | 46.6 (34/73) | 37.0 (27/73) | 19.2 (14/73) | 47.9 (35/73) | 23.1 ± 24.3 |
| | 210 mg | 59.7 (43/72) | 52.8 (38/72) | 30.6 (22/72) | 56.9 (41/72) | 18.1 ± 23.1 |
| Week 12 | 140 mg | 85.3 (58/68) | 79.4 (54/68) | 38.2 (26/68) | 83.8 (57/68) | 7.8 ± 16.5 |
| | 210 mg | 97.2 (70/72) | 93.1 (67/72) | 52.8 (38/72) | 94.4 (68/72) | 4.0 ± 11.4 |
| Week 24 | 140 mg | 83.1 (54/65) | 78.5 (51/65) | 44.6 (29/65) | 81.5 (53/65) | 6.1 ± 14.6 |
| | 210 mg | 95.8 (69/72) | 91.7 (66/72) | 48.6 (35/72) | 93.1 (67/72) | 3.1 ± 10.4 |
| Week 52 | 140 mg | 87.5 (56/64) | 81.3 (52/64) | 50.0 (32/64) | 79.7 (51/64) | 4.7 ± 12.1 |
| | 210 mg | 95.7 (66/69) | 88.4 (61/69) | 56.5 (39/69) | 92.8 (64/69) | 2.3 ± 7.6 |

% (n/N), Mean (%) ± SD for BSA involvement
a) Subjects randomized to placebo or brodalumab 70 mg in Japanese phase II study (Study 4827-002) are included.

Table 61. sPGA success (0 or 1) rate at Week 52 in foreign phase III studies (Pooled data from Studies 20120103 and 20120104) (NRI)

| 140 mg/140 mg Q8W | 140 mg/140 mg Q4W | 140 mg/140 mg Q2W | 140 mg/210 mg Q2W | 210 mg/140 mg Q8W | 210 mg/140 mg Q4W | 210 mg/140 mg Q2W | 210 mg/210 mg Q2W |
|---|---|---|---|---|---|---|---|
| 7.7 (13/169) | 14.2 (48/337) | 39.2 (133/339) | 58.5 (197/337) | 2.9 (5/173) | 10.3 (35/339) | 48.4 (165/341) | 64.9 (220/339) |

% (n/N), Dose through Week 12 (all Q2W)/Dosage regimen from Week 12 to Week 52

Table 62. PASI 75 and 100 response rates at Week 12 by body weight in Japanese phase II study (Study 4827-002) (NRI)

| | ≤60 kg | >60 kg and ≤70 kg | >70 kg and ≤80 kg | >80 kg and ≤90 kg | >90 kg and ≤100 kg | >100 kg |
|---|---|---|---|---|---|---|
| PASI 75 | | | | | | |
| 140 mg | 87.5 (7/8) | 100 (8/8) | 70.0 (7/10) | 66.7 (4/6) | 66.7 (2/3) | 50.0 (1/2) |
| 210 mg | 100 (7/7) | 100 (10/10) | 100 (8/8) | 87.5 (7/8) | 100 (3/3) | 0 (0/1) |
| PASI 100 | | | | | | |
| 140 mg | 50.0 (4/8) | 25.0 (2/8) | 40.0 (4/10) | 16.7 (1/6) | 33.3 (1/3) | 50.0 (1/2) |
| 210 mg | 71.4 (5/7) | 70.0 (7/10) | 62.5 (5/8) | 37.5 (3/8) | 66.7 (2/3) | 0 (0/1) |

% (n/N)

Table 63. PASI 75 and 100 response rates at Week 12 by body weight in foreign phase III studies
(Pooled data from Studies 20120102, 20120103, and 20120104) (NRI)

| | ≤60 kg | >60 kg and ≤70 kg | >70 kg and ≤80 kg | >80 kg and ≤90 kg | >90 kg and ≤100 kg | >100 kg and ≤110 kg | >110 kg and ≤120 kg | >120 kg and ≤130 kg | >130 kg |
|---|---|---|---|---|---|---|---|---|---|
| PASI 75 | | | | | | | | | |
| 140 mg | 92.2 (83/90) | 89.3 (134/150) | 77.6 (197/254) | 72.0 (219/304) | 65.9 (162/246) | 50.0 (86/172) | 46.9 (53/113) | 34.4 (22/64) | 26.2 (17/65) |
| 210 mg | 94.7 (89/94) | 86.8 (145/167) | 91.4 (223/244) | 88.9 (263/296) | 87.1 (210/241) | 80.3 (139/173) | 85.7 (78/91) | 74.5 (41/55) | 57.7 (56/97) |
| PASI 100 | | | | | | | | | |
| 140 mg | 54.4 (49/90) | 44.7 (67/150) | 38.2 (97/254) | 27.6 (84/304) | 18.3 (45/246) | 14.5 (25/172) | 8.8 (10/113) | 1.6 (1/64) | 0 (0/65) |
| 210 mg | 67.0 (63/94) | 48.5 (81/167) | 52.5 (128/244) | 42.9 (127/296) | 33.2 (80/241) | 39.3 (68/173) | 25.3 (23/91) | 21.8 (12/55) | 12.4 (12/97) |

% (n/N)

PMDA's conclusion:

As explained by the applicant, the proposed dosage and administration for brodalumab ("The usual adult dosage is 210 mg of Brodalumab [Genetical Recombination] administered subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.") is acceptable for the following reasons:

- In all of the Japanese phase II study (Study 4827-002) and foreign clinical studies (Studies 20090062, 20120102, 20120103, 20120104) in patients with plaque psoriasis, brodalumab 210 mg remained superior to 140 mg in efficacy endpoints (e.g., the PASI 75 response rate) for 52 weeks of treatment. This suggests that a dose of 210 mg every 2 weeks is required to maintain the efficacy of brodalumab.
- The PASI 100 response rate, a clinically relevant outcome, was higher in the brodalumab 210 mg group than in the brodalumab 140 mg group across the body weight subgroups.
- No major safety concerns have been raised about brodalumab 210 mg.

**7.R.5 Indications**

PMDA considers that brodalumab should be used in patients who have had an inadequate response or intolerance to standard therapies for psoriasis, namely phototherapy or systemic therapy with cyclosporine, etretinate etc., in view of the data submitted, the discussion presented in 7.R.2 and 7.R.3, and the following facts: (1) brodalumab has the potential risk of serious and fatal infections, etc., as with other biological products already approved for the treatment of psoriasis; (2) the long-term safety of brodalumab has not fully been characterized.

PMDA thus concluded that, as with other approved biological products, brodalumab should be indicated for "treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have had an inadequate response to conventional therapies," as proposed by the applicant.

**7.R.6 Clinical positioning**

**7.R.6.1 The position of brodalumab among other approved biological products**

The applicant's explanation on the position of brodalumab among other approved biological products:

Table 64 shows the efficacy results for ustekinumab (the comparator in phase III studies of brodalumab) and the results from the pivotal clinical studies of other approved biological products: Adalimumab (Genetical Recombination) (hereinafter referred to as adalimumab), Infliximab (Genetical Recombination) (hereinafter referred to as infliximab), and Secukinumab (Genetical Recombination) (hereinafter referred to as secukinumab). Although comparison results among different studies should be interpreted with care, brodalumab 210 mg had an earlier onset of efficacy compared with other approved biological products, and the PASI 75 response rate at the time of primary endpoint assessment tended to be higher with brodalumab 210 mg than with other approved biological products. A pairwise comparison showed a statistically significant difference between brodalumab 210 mg and ustekinumab in the PASI 100 response rate in foreign phase III studies (Studies 20120103, 20120104).

Table 64. Comparison of the efficacy of brodalumab and other biological products in patients with psoriasis

| | | Brodalumab | | Ustekinumab | | Adalimumab | Infliximab | | Secukinumab |
|---|---|---|---|---|---|---|---|---|---|
| Dosing regimen | | 210 mg administered subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks | | Subcutaneous injection of 45 mg (subjects weighing ≤100 kg) or 90 mg (subjects weighing >100 kg) at Weeks 0 and 4 | | 80 mg administered subcutaneously at Week 0 followed by 40 mg every 2 weeks | 5 mg/kg administered intravenously at Weeks 0, 2, and 6 | | 300 mg administered subcutaneously at Weeks 0, 1, 2, 3, 4, and 8 |
| Primary endpoint | | PASI 75 response rate at Week 12 | | 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 Week 12 |
| Study ID | | 20120103 | 20120104 | 20120103 | 20120104 | Japanese clinical study (M04-688) | Japanese clinical study | Pooled foreign studies | Pooled data from multi-regional (A2302) and foreign clinical studies (A2303, A2308, A2309) |
| PASI 75 response rate with proposed or approved dosing regimen | Week 1 | 4.6 (28/612) | 2.4 (15/624) | 0 | 0.3 (1/313) | | | | 0.6 (4/686) |
| | Week 2 | 24.7 (151/612) | 20.4 (127/624) | 2.7 (8/300) | 3.5 (11/313) | 2.3 (1/43) | 2.9 (1/34) | 5.4 (38/710) | 3.4 (23/686) |
| | Week 4 | 60.8 (372/612) | 58.5 (365/624) | 19.0 (57/300) | 14.1 (44/313) | 14.0 (6/43) | 47.1 (16/34) [a] | 60.8 (428/704) [a] | 36.7 (252/686) |
| | Week 8 | 81.4 (498/612) | 80.1 (500/624) | 56.3 (169/300) | 51.8 (162/313) | 41.9 (18/43) | | | 71.9 (493/686) |
| | Week 12 | 86.3 (528/612) | 85.1 (531/624) | 70.0 (210/300) | 69.3 (217/313) | 53.5 (23/43) | 68.6 (24/35) [b] | 79.3 (566/714) [b] | 79.4 (545/686) |
| | Week 16 | | | | | 62.8 (27/43) | | | |

% (n/N), a) Assessed at Week 6, b) Assessed at Week 10

In foreign phase III studies of brodalumab, no events showed a particularly higher incidence in the brodalumab group than in the ustekinumab group [see 7.2.2 Foreign phase III study and 7.2.3 Foreign phase III study]. The incidences of the main adverse events with brodalumab in Japanese clinical studies (Studies 4827-002, 4827-003, 4827-004, 4827-005) and in foreign clinical studies (Studies 20090062, 20090403, 20120102, 20120103, 20120104) were compared with those with other approved biological products. As shown in Table 65, no events showed a particularly higher incidence with brodalumab than with other drugs.

Table 65. Adverse events with brodalumab vs. other biological products (Pooled data from Japanese or foreign clinical studies)

| | Brodalumab | | Ustekinumab | | Adalimumab | | Infliximab | | Secukinumab | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Japan (177) | Foreign [a] (4461) | Japan (126) | Foreign (2266) | Japan (163) | Foreign (1696) | Japan (114) | Foreign (1564) | Japan (207) | Foreign (3430) |
| Total exposure time | 275.2 subject-years | 5448.8 subject-years | 11.7 weeks (mean) | 33.7 weeks (mean) | 396 subject-years | 1684.2 subject-years | 427.5 days (mean) | 42.0 weeks (mean) | 170.0 subject-years | 2724.6 subject-years |
| Serious infections and infestations | 5 (2.8) | 59 (1.3) | 1 (0.8) | 15 (0.7) | 4 (2.5) | 21 (1.2) | 2 (1.8) | 23 (1.5) | 3 (1.4) | 40 (1.2) |
| Candida (HLT) | 11 (6.2) | 137 (3.1) | 1 (0.8) | 8 (0.4) | 1 (0.6) | 3 (0.2) | 4 (3.5) | 22 (1.4) | 4 (1.9) | 69 (2.0) |
| Injection site reaction | 34 (19.2) | 701 (15.7) | 5 (4.0) | 268 (11.8) | 88 (54.0) | — | 16 (14.0) | 465 (29.7) | 13 (6.3) | 397 (11.6) |
| Hypersensitivity | 0 | 9 (0.2) | 0 | 5 (0.2) | — | — | 2 (1.8) | 48 (3.1) | — | 8 (0.2) |
| Neutropenia | 2 (1.1) | 27 (0.6) | 0 | 2 (0.1) | — | — | 0 | 16 (1.0) | 0 | 16 (0.5) |
| Suicidal ideation and behavior | | | | | | | | | | |
| Completed suicide (PT) | 0 | 1 (<0.1) [b] | 0 | 0 [c] | — | 1 (<0.1) | 0 | 0 | 0 | 0 |
| Suicide attempt (PT) | 1 (0.6) | 6 (0.1) [d] | 0 | 1 (<0.1) | — | — | 0 | 3 (0.2) | 0 | 0 |
| Suicidal ideation (PT) | 0 | 15 (0.3) [e] | 0 | 1 (<0.1) | — | 2 (0.1) | 0 | 0 | 0 | 1 (<0.1) |

n (%); —, unknown/unavailable

a) Foreign data on suicidal ideation and behavior in subjects receiving brodalumab are based on data collected by the data cutoff in March 2015 (4464 subjects, 7894.6 subject-years)

b) Intentional overdose (PT) (1 subject). In addition, completed suicide (PT) (3 subjects) occurred outside the exposure period.

c) After the data cutoff, 1 case of completed suicide was reported.

d) These 6 cases consist of suicide attempt (PT) (3 subjects), suicidal behavior (PT) (2 subjects), and intentional self-injury (PT) (1 subject). In addition, suicide attempt (PT) (1 subject) occurred outside the exposure period.

e) These 15 cases consist of suicidal ideation (PT) (14 subjects) and suicidal depression (PT) (1 subject). In addition, suicidal ideation (PT) (3 subjects) occurred outside the exposure period.

As shown by the results above, brodalumab showed greater improvement in skin symptoms than other biological products, with a favorable safety profile. Brodalumab therefore can become a first-line biologic for patients with psoriasis. As shown in Tables 46 and 66, brodalumab demonstrated high efficacy also in patients with previous biologic use, with no adverse events of particular concern. Therefore, brodalumab can become a therapeutic option also for patients who have had an inadequate response to other approved biological products and patients who discontinued other approved biologic therapy for safety reasons.

Table 66. Main adverse events in subjects with or without previous biologic use (Pool C)

| | Previous biologic use | |
|---|---|---|
| | Yes (N = 1262) | No (N = 3008) |
| All adverse events | 1025 (81.2) | 2434 (80.9) |
| Nasopharyngitis | 207 (16.4) | 491 (16.3) |
| Upper respiratory tract infection | 153 (12.1) | 424 (14.1) |
| Arthralgia | 139 (11.0) | 303 (10.1) |
| Headache | 93 (7.4) | 246 (8.2) |
| Back pain | 78 (6.2) | 140 (4.7) |
| Hypertension | 71 (5.6) | 143 (4.8) |
| Sinusitis | 71 (5.6) | 97 (3.2) |

n (%)

PMDA's view:

The applicant's opinion that brodalumab is useful compared with ustekinumab is acceptable, because a pairwise comparison showed a statistically significant difference between brodalumab and ustekinumab in the PASI 100 response rate in foreign phase III studies, and because there were no major differences in the incidence of adverse events, etc. between brodalumab and ustekinumab. However, at present, brodalumab cannot be regarded as a first-line biologic, because no clinical studies have been conducted to directly compare brodalumab with biologics other than ustekinumab, and because it is difficult, at present, to fully evaluate the differences in the safety profile between brodalumab and other approved biologics because of the limited clinical experience with brodalumab. In future, the clinical positioning of brodalumab will be discussed at relevant academic societies, etc., based on clinical study data on brodalumab as well as the results of a post-marketing surveillance and reports from studies conducted properly in and outside Japan. PMDA has no objection to the applicant's view that brodalumab can become a therapeutic option for patients who have had an inadequate response to other approved biological products and patients who discontinued other approved biologic therapy because of poor tolerability. The applicant should collect information about patients switching from other biologics and appropriately provide the information to healthcare professionals.

**7.R.6.2 Concomitant use of existing therapy**

The applicant explained the concomitant use of brodalumab with topical therapy (e.g., corticosteroids, vitamin D3 derivatives), phototherapy, systemic therapy (e.g., cyclosporine, oral corticosteroids, methotrexate), or other biologics.

The applicant's explanation:

In Japanese clinical studies (Studies 4827-002, 4827-003, 4827-004, 4827-005), the incidence of infections and infestations did not clearly differ between subjects receiving concomitant topical corticosteroids (79.0% [79 of 100 subjects]) and subjects not receiving concomitant topical corticosteroids (62.3% [48 of 77 subjects]). However, as only limited data are available on concomitant use of brodalumab with corticosteroids, etc., adequate caution should be exercised against the possible occurrence of adverse reactions to topical treatments or skin infections in patients receiving brodalumab and topical corticosteroid therapy. In Foreign Study 20101227, the risk of infections and infestations was 134.8 events per 100 subject-years in subjects receiving concomitant systemic therapy (oral corticosteroids and methotrexate) and 98.6 events per 100 subject-years in subjects not receiving concomitant systemic therapy; the concomitant systemic therapy thus did not lead to a clear increase in the risk of infection. No major concerns about the concomitant use of brodalumab with topical corticosteroids, oral corticosteroids, or methotrexate have been suggested. Since there is no clinical experience with brodalumab in combination with phototherapy, other biologics, or cyclosporine, brodalumab should not be used with these therapies as a rule. Meanwhile, phototherapy may be used in some patients with refractory psoriatic skin lesions, and other biologics or cyclosporine may temporarily be used with brodalumab in order to prevent flares when switching to brodalumab. Therefore, healthcare professionals should determine whether to use concomitant immunosuppressive systemic therapy or phototherapy after fully weighing its risks and benefits, and should carefully monitor patients for serious infections and skin cancer, etc. during the combination therapy. The OTHER PRECAUTIONS section of the package insert will state that the safety and efficacy of brodalumab in combination with immunosuppressive systemic therapy or phototherapy have not been established.

PMDA's view:

Only limited data are currently available on the safety of brodalumab in combination with other systemic therapy or phototherapy. The combination use of different biologics has been reported to result in an increased incidence of serious infections in patients with rheumatoid arthritis, although there have been no case reports on the use of brodalumab with other biologics. Therefore, in addition to the measures proposed by the applicant, the package insert, etc. should advise against the concomitant use of brodalumab with other biologics. The applicant should collect information on the efficacy and safety of brodalumab in combination with other psoriasis treatments via post-marketing surveillance and appropriately provide the information to healthcare professionals.

**7.R.7 Self-administration**

The applicant explained the efficacy and safety of self-administered brodalumab based on the data from Japanese long-term treatment studies (Studies 4827-003, 4827-005).

The applicant's explanation:

In a Japanese long-term treatment study (Study 4827-003), 28.8% (21 of 73) of subjects in the brodalumab 140 mg group and 22.2% (16 of 72) of subjects in the brodalumab 210 mg group performed multiple self-injections for up to 40 weeks after Week 12. The PASI 75/90/100 response rates in these subjects are shown in Table 67. The response rates remained constant before and after the start of self-administration.

Table 67. PASI 75/90/100 response rates in subjects who performed self-injections in Japanese long-term treatment study (Study 4827-003)

| | | 140 mg Q2W | 210 mg Q2W |
|---|---|---|---|
| At start of self-administration | PASI 75 | 85.7 (18/21) | 100.0 (16/16) |
| | PASI 90 | 76.2 (16/21) | 100.0 (16/16) |
| | PASI 100 | 28.6 (6/21) | 56.3 (9/16) |
| At last time point | PASI 75 | 81.0 (17/21) | 100.0 (16/16) |
| | PASI 90 | 66.7 (14/21) | 93.8 (15/16) |
| | PASI 100 | 33.3 (7/21) | 50.0 (8/16) |

% (n/N)

Among the 37 subjects who performed multiple self-injections of brodalumab in the Japanese long-term treatment study (Study 4827-003), the incidences of adverse events were 81.1% (30 of 37 subjects) before the start of self-administration and 70.3% (26 of 37 subjects) after the start of self-administration. Adverse events reported by ≥2 subjects after self-injection were back pain (8.1%, 3 of 37 subjects), somnolence (5.4%, 2 of 37 subjects), allergic rhinitis (5.4%, 2 of 37 subjects), and xeroderma (5.4%, 2 of 37 subjects). A causal relationship to study drug was ruled out for all events.

In 60 subjects who performed multiple self-injections of brodalumab in a Japanese long-term treatment study (Study 4827-005), the main adverse events were nasopharyngitis (18.3%, 11 of 60 subjects), dental caries (6.7%, 4 of 60 subjects), tinea pedis (6.7%, 4 of 60 subjects), periodontitis (5.0%, 3 of 60 subjects), back pain (5.0%, 3 of 60 subjects), and contact dermatitis (5.0%, 3 of 60 subjects), etc. A causal relationship to study drug could not be ruled out for 2 cases of nasopharyngitis, 2 cases of periodontitis, and 1 case of tinea pedis. No injection site reaction-related events were reported after self-administration in either study.

The results presented above suggest that there are no particular problems with the efficacy and safety of self-administered brodalumab. Whether to allow patients to self-administer brodalumab should be determined carefully by their physician. Self-injection will be allowed only in patients who have received adequate education and training, have learned brodalumab-related risks (and how to manage them), and are able to perform self-injection reliably. Accordingly, the applicant will prepare explanatory materials used by physicians when providing education and training for patients, and a patient guide that provides information on the procedures for self-injection and the points to note.

PMDA's view:
No particular problems with the safety and efficacy of self-injected brodalumab have been suggested up to now. However, as only limited data are available on the safety and efficacy of self-injected brodalumab in Japanese patients with psoriasis, the efficacy and safety should continue to be evaluated via post-marketing surveillance, etc. A management scheme must be established for patients starting self-injection by using examples from the experiences with similar drugs in Japan.

**7.R.8 Post-marketing safety measures**

The applicant's explanation on post-marketing safety measures:
In view of the safety profile, etc. of brodalumab, it is important to ensure that brodalumab is used under the supervision of a physician who is familiar with the diagnosis and treatment of psoriasis at a facility capable of managing adverse drug reactions such as serious infections in cooperation with other departments/medical

institutions. Therefore, relevant warnings and precautions will be provided in the package insert, and informative materials for healthcare professionals will be developed and distributed so as to promote the proper use of brodalumab. Furthermore, in the light of suicide/self-injury-related events that were reported in Japanese and foreign clinical studies, physicians will be advised (1) to interview patients to confirm whether they have current or past psychiatric disorder before determining the appropriateness of brodalumab therapy, and (2) to closely monitor the clinical course of patients who have started treatment with brodalumab.

PMDA's view:

Brodalumab has so far posed no safety concerns greater than those associated with other approved biological products. However, the clinical experience with long-term brodalumab therapy is limited. As with other approved biological products, further information should be collected on the occurrence of serious infections, etc., which are common risks to immunosuppressive drugs. Thus, in addition to the measures proposed by the applicant, long-term post-marketing surveillance should be conducted to collect relevant information on such risks. Brodalumab should be used under the supervision of a physician who is familiar with the diagnosis and treatment of psoriasis, and adverse drug reactions such as serious infections should be managed in cooperation with a physician with knowledge and experience in the treatment of infections. The applicant must ensure, via post-marketing surveillance, that brodalumab is used in cooperation with other departments/medical institutions also in routine clinical practice.

In order to promote the proper use of brodalumab, the applicant should develop informative materials for healthcare professionals (e.g., physicians) and a patient information leaflet that explains the risks associated with brodalumab in a proper and comprehensive manner. Post-marketing safety information should be provided to healthcare professionals and patients in an appropriate and timely manner.

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

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

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

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

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

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

PMDA has concluded that the data submitted demonstrate the efficacy of brodalumab in the treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have had an inadequate

response to conventional therapies has been demonstrated, and show acceptable safety in view of the benefits indicated by the data submitted. Brodalumab, a biologic with a novel mechanism of action, is clinical meaningful because it offers a new therapeutic option for patients with psoriasis. PMDA considers that the occurrence of adverse events (e.g., serious infections) during long-term treatment should be further investigated via post-marketing surveillance.

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

**Review Report (2)**

May 18, 2016

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Lumicef Subcutaneous Injection 210 mg Syringe |
| **Non-proprietary Name** | Brodalumab (Genetical Recombination) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 30, 2015 |

## 1. Content of the Review

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

### 1.1 Efficacy, dosage and administration, and indications

At the Expert Discussion, the expert advisors supported PMDA's conclusions on efficacy, dosage and administration, and indications for Lumicef Subcutaneous Injection 210 mg Syringe (the product) as described in the Review Report (1).

### 1.2 Safety

At the Expert Discussion, the expert advisors made the following comments and supported PMDA's conclusions on the safety of brodalumab as described in the Review Report (1).

- In view of the safety profile of brodalumab, the applicant needs to take safety measures in collaboration with the relevant academic societies, as in the case of other approved biological products. In particular, the occurrence of serious infections, malignant tumors, and suicide-related events, etc. during long-term treatment with brodalumab should continue to be evaluated after the market launch.
- At present, it is difficult to draw any conclusions on an association between brodalumab and suicide-related events, in view of the occurrence of suicide-related events (e.g., suicidal ideation, suicide attempt, and completed suicide) and the C-SSRS and PHQ-8 scores during treatment with brodalumab. However, healthcare professionals should be advised to carefully administer brodalumab to patients with a history of depression, depressive state, suicidal ideation, or suicide attempt, and to monitor the clinical course of such patients, because the association of brodalumab with suicide-related events cannot be ruled out, and because suicide-related events occurred more frequently in subjects with a history of depression or suicidal ideation, etc.

- At present, much remains unclear about the risk of suicide-related events associated with brodalumab. Therefore, it is important to provide information appropriately to healthcare professionals and patients so as to avoid the situation where excessive precaution about suicide-related events leads to a reluctance to use brodalumab in patients who need it.

### 1.3 Risk management plan (draft)

In view of the Review Report (1) "7.R.8 Post-marketing safety measures" and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for brodalumab should include the safety and efficacy specifications presented in Table 68, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 69.

Table 68. Safety and efficacy specifications in the risk management plan (draft)

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| · Serious infections<br>· Serious hypersensitivity<br>· Exacerbation of Crohn's disease in patients with active Crohn's disease<br>·Neutrophil count decreased | ·Malignant tumors<br>· Immunogenicity<br>· Inflammatory bowel disease<br>· Suicide/self-injury-related events | None |
| Efficacy specification | | |
| · Efficacy in routine clinical settings | | |

Table 69. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| · Early Post-marketing Phase Vigilance<br>· Specified drug use-results survey<br>· Post-marketing clinical study [a)] | · Early Post-marketing Phase Vigilance<br>· Develop and distribute a guide for proper use to healthcare professionals.<br>· Develop and distribute informative materials for self-injection to healthcare professionals and patients<br>· Ensure that information on the proper use is provided before the delivery of the product. |

a) The ongoing Study 4827-005 will be reclassified as a post-marketing clinical study after approval, and continued until the product can be prescribed at medical institutions.

Accordingly, PMDA instructed the applicant to conduct post-marketing surveillance to address the above issues.

The applicant's explanation:

As shown in Table 70, a specified drug use-results survey involving patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, or erythrodermic psoriasis who have had an inadequate response to conventional therapies (a total of 600 patients in safety analysis cases, an observation period of 52 weeks) will be conducted to evaluate the long-term safety and efficacy of brodalumab in routine clinical settings. Key survey items are serious infections, serious hypersensitivity, neutrophil count decreased, inflammatory bowel disease, malignant tumors, and suicide/self-injury-related events. After the completion of the observation period, patients will be followed up for 3 years from the start of treatment to collect data on serious infections and malignant tumors, in order to further evaluate the long-term safety of brodalumab.

Table 70. Outline of use-results survey plan (draft)

| | |
|---|---|
| Objective | To confirm the long-term safety and efficacy of brodalumab in routine clinical settings. |
| Survey method | Central registry system |
| Population | Patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, or erythrodermic psoriasis who have had an inadequate response to conventional therapies |
| Observation period | 52 weeks from the start of treatment (patients will be followed up for 3 years from the start of treatment, regardless of whether they continue or discontinue treatment.) |
| Planned sample size | 600 patients (Safety analysis cases) |
| Main survey items | · Key survey items: neutrophil count decreased, serious infections, serious hypersensitivity, inflammatory bowel disease (Crohn's disease and exacerbation of Crohn's disease in patients with active Crohn's disease, etc.), malignant tumors, suicide/self-injury-related events<br>· Patient characteristics (duration of disease, severity, current or past medical conditions, etc.)<br>· Previous therapies<br>· Administration of brodalumab<br>· Concomitant therapies<br>· Laboratory tests<br>· Adverse events (including the development of malignant tumors)<br>· Efficacy |

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (5.3.5.1-1, 5.3.5.1-3, 5.3.5.1-5, 5.3.5.2-1, 5.3.5.2-4, 5.3.5.2-5) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection verified that the clinical studies as a whole were conducted in compliance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issues at some trial sites, although the issues had no significant impact on the overall assessment of the studies. The heads of the relevant medical institutions were notified of these issues as the findings requiring improvement.

**Findings requiring improvement**

Trial sites

- Protocol deviations (noncompliance with the rules for re-randomization, failure to ensure that no exclusion criteria were met [a washout period from previous therapy])

## 3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indications and dosage and administration, with the following condition. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs. The product is classified as a biological product.

**Indications**

Treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis in patients who have had an inadequate response to conventional therapies

**Dosage and Administration**

The usual adult dosage is 210 mg of Brodalumab (Genetical Recombination) administered subcutaneously at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

**Condition of Approval**

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