## 1.0 Title Page

# Clinical Study Protocol M14-193

# A Multicenter, Open-Label Study of Adalimumab in Japanese Subjects with Generalized Pustular Psoriasis

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| AbbVie Investigational Product: | Adalimumab |
| Date: | 08 June 2015 |
| Development Phase: | 3 |
| Study Design: | This is a multicenter, open-label study of adalimumab in Japanese subjects with Generalized Pustular Psoriasis. |
| Investigator: | Multicenter: Investigator information is on file at AbbVie |
| Sponsor*: | AbbVie GK (Japan) |
| Sponsor/Emergency Contact: | [redacted] |

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

## 1.1 Synopsis

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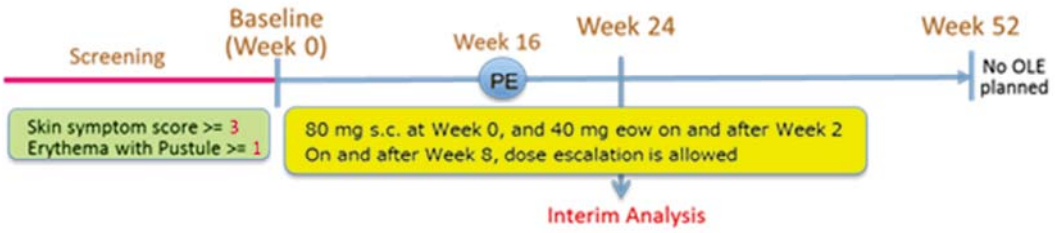
| **AbbVie Inc.** | **Protocol Number:** M14-193 |
| **Name of Study Drug:** Adalimumab | **Phase of Development:** 3 |
| **Name of Active Ingredient:** Adalimumab | **Date of Protocol Synopsis:** 08 June 2015 |
| **Protocol Title:** A Multicenter, Open-label Study of Adalimumab in Japanese Subjects with Generalized Pustular Psoriasis | |
| **Objective:**<br>The primary objective is to investigate efficacy, safety and pharmacokinetics of adalimumab in Japanese subjects with Generalized Pustular Psoriasis (GPP). | |
| **Investigators:** Multicenter Trial (Investigator information on file at AbbVie). | |
| **Study Sites:** Approximately 10 sites in Japan | |
| **Study Population:** Male and female Japanese subjects ≥ 15 and ≤ 75 years of age with a diagnosis of GPP. GPP patients with previous infliximab exposure can be enrolled. | |
| **Number of Subjects to be Enrolled:** 10 subjects | |
| **Methodology:**<br>This study is a 52-week trial. The study will include a 30-day screening period, 52-week open-label active treatment period, and a subsequent 70-day follow-up period after the last dose.<br>Subjects will be Japanese patients diagnosed as GPP with total skin score of at least 3 and erythema with pustule (skin score of at least 1) in Japan Dermatology Association (JDA) severity index of GPP in GPP Medical Care Guideline 2014.<br>Subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled and treated subcutaneously with adalimumab 80 mg at the Baseline for initial dose and then 40 mg eow on and after Week 2 until Week 50. Dose-escalation to 80 mg eow is allowed if subjects have inadequate response (i.e., minimal improvement, unchanged or worsened) on or after Week 8. Dose reduction is not allowed throughout the study period for the dose-escalated subjects.<br>The primary efficacy variable is the proportion of subjects achieving Clinical Response (CR) at Week 16. CR is defined as the reduction of skin score of 1 (if the subject's Baseline skin score is 3) or 2 (if the subject's Baseline skin score is 4 or higher) relative to Baseline, according to JDA severity index of GPP in GPP Medical Care Guideline 2014.<br>Study visits will occur at Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52, and at the Premature Discontinuation visit if the subject discontinues prior to Week 52. No open label extension (OLE) study is planned after this 52-week study. | |

**Methodology (Continued):**




Adverse events will be collected throughout the study. Subjects who complete this study or who decide to withdraw the study participation will have a Day 70 follow-up phone call following their last dose of study drug to determine the status of any ongoing adverse events (AEs) or serious adverse events (SAEs), or the occurrence of any new AEs or SAEs.

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

The following Inclusion/Exclusion criteria are for subjects enrolled in this study.

**Main Inclusion:**

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol. If the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.
2 Male or female ≥ 15 and ≤ 75 years of age at the Baseline visit.
3. Subject must have a diagnosis of Generalized Pustular Psoriasis (GPP) for at least 60 days prior to Screening and determined by the Investigator through subject interview and review of medical history during the Screening Period.
4. Subject must have had an inadequate response to, or demonstrated intolerance to, or have a contraindication to the currently approved treatment for their GPP (excluding infliximab).
5. Subject must have total skin score of at least 3 and erythema with pustules (skin score of at least 1) in Japan Dermatology Association (JDA) severity index of GPP in GPP Medical Care Guideline 2014 in Japan at Baseline.
6. Subject may be included if they have previously experienced a benefit for their GPP from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of GPP related symptoms, "infliximab secondary failure") or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss of response or lack of tolerability will be required.
7. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential who must have negative result of pregnancy test performed at the Screening and at the Baseline. Female subject of childbearing potential is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Inclusion (Continued):**

8. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.
9. Subject has a negative TB Screening Assessment (including a PPD test and/or Quantiferon-TB Gold test, or equivalent) and negative chest x-ray (CXR) (posterior anterior [PA] and lateral view). If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis prior to Baseline.
10. Subject is judged to be in good general health, as determined by the Principal Investigator based upon the results of a medical history, physical examination, laboratory profile, chest x-ray, and a 12-lead electrocardiogram (ECG) performed during the Screening.

**Main Exclusion:**

1. Subject has erythrodermic psoriasis, guttate psoriasis, or subcorneal pustular dermatosis at Screening.
2. Subject diagnosed drug-induced GPP.
3. Total score of 14 or more in JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan.
4. Subject has other active skin disease (e.g., urticarial, atopic dermatitis) or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of GPP, with the exception of footpad trichophytosis (athlete's foot).
5. Subject who cannot taper off cyclosporine until Week 8 after the Baseline and during the study. Subject who cannot taper etretinate to 20 mg/day at the maximum dose prior to the Baseline.
6. Subjects who is receiving oral corticosteroid more than 10 mg/day at the Baseline, and cannot taper off until Week 4 after the Baseline and during study.
7. Subject who received granulocyte and monocyte adsorption apheresis (GMA) therapy for at least 28 days prior to the Baseline and cannot avoid this therapy during the study.
8. Subjects who received any investigational agents of chemical or biologic nature (including anti-IL17 agents), which would be efficacious to GPP or psoriasis-related skin disease for at least 28 days or 5 half-lives of the drug prior to the Baseline, whichever is longer, and during the study.
9. Subjects who received ustekimumab for at least 84 days prior to the Baseline and during the study.
10. Subject who cannot avoid PUVA or narrow-band UVB phototherapy for at least 14 days prior to the Baseline and during the study.
11. Subject who cannot avoid "Strongest" corticosteroid in Japanese classification of topical therapy for at least 14 days prior to the Baseline and during the study. The other topical therapies including corticosteroids ("Very strong," "Strong," "Medium" and "Weak" in Japanese classification), vitamin D3 and topical tacrolimus can be allowed to use concomitantly.
12. Subject who cannot avoid anti-tumor necrosis factor (TNF) agent other than infliximab and adalimumab (including but not limited to etanercept [Enbrel], golimumab [Simponi] or certolizumab pegol [Cimzia]) for at least 28 days prior to the Baseline and during the study.
13. Prior exposure to adalimumab.

**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Exclusion (Continued):**

14. Subject who has previous used infliximab:
    - and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction, or
    - who used infliximab ("secondary treatment failure") within 42 days prior to the Baseline.
15. Prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalitis (PML) (i.e., natalizumab [Tysabri], rituximab [Rituxan], efalizumab [Raptive]).
16. Subject with any active viral infection that makes the subject an unsuitable candidate for the study based on the investigator's clinical assessment.
17. Hepatitis B: HBs Ag positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBs Ab positive subjects.
18. Subject with known hypersensitivity to the excipients of adalimumab.
19. Positive pregnancy test at the Screening (serum) or the Baseline (urine).
20. Female who is breast-feeding or considering becoming pregnant during the study.
21. History of clinically significant drug or alcohol abuse in the last 12 months.
22. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
23. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and/or any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.
24. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix.
25. Chronic recurring infections or active TB.
26. Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to Baseline or oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline.
27. History of invasive infection (listeriosis, histoplasmosis), human immunodeficiency virus (HIV).
28. Screening laboratory and other analysis show any of the following abnormal results:
    - AST, ALT > 1.75 × upper limit of the reference range;
    - WBC count < $3.0 \times 10^9$/L;
    - Electrocardiogram (ECG) – with clinically significant abnormalities
    - Total bilirubin ≥ 3 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Serum creatinine > 1.6 mg/dL.
29. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

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| **Investigational Products:** | Adalimumab |
| **Doses:** | 80 mg starting at Baseline (Week 0) and 40 mg eow on and after Week 2 until Week 50. Dose escalation to 80 mg eow is allowed for subjects who do not have appropriate response and meeting dose escalation criteria on or after Week 8. Dose reduction is not allowed after dose escalation until the study end. Treatment of study drug will not occur at Week 52. |
| **Mode of Administration:** | Subcutaneous injection (SC) |

**Duration of Treatment:** 52 weeks

**Criteria for Evaluation:**

**Efficacy:**

The primary efficacy endpoint is the proportion of subjects achieving Clinical Response (CR) at Week 16. CR is defined as reduction of skin score of 1 (if the subject's Baseline skin score is 3) or 2 (if the subject's Baseline skin score is 4 or higher) relative to Baseline, according to JDA severity index of GPP in GPP Medical care guideline 2014 in Japan.

**Pharmacokinetic:**

Blood samples will be collected for the measurement of serum adalimumab concentrations at the Baseline and Weeks 2, 4, 8, 12, 16, 24, 36, and 52 or at the Premature Discontinuation visit. Blood samples will be collected for the measurement of anti-adalimumab antibody (AAA) at the Baseline, Weeks 8, 16, 24, 36, and 52 or at the Premature Discontinuation visit. Blood samples will be also collected prior to dose escalation.

**Safety:**

Adverse events, laboratory data and vital signs will be assessed throughout the study.

**Statistical Methods:**

**Efficacy:**

The primary efficacy variable is the proportion of subjects achieving Clinical Response (remission and improvement) at Week 16;

Secondary variables, to be analyzed at each scheduled visit, include:

- Proportion of subjects achieving Clinical Response (except Week 16, which is the primary endpoint).
- Proportion of subjects achieving remission.
- Change from the Baseline in total GPP score (skin and systemic/laboratory test).
- Change from the Baseline in JDA severity index of GPP.
- Change and Percent change from the Baseline in total skin score.
- Change from the Baseline in total systemic/laboratory test score.
- Change from the Baseline in score of erythema area (overall) and BSA (BSA of GPP).
- Change from the Baseline in score of erythema area with pustule and BSA.
- Change from the Baseline in score of edema area and BSA.

**Statistical Methods (Continued):**

**Efficacy:**

- Change from the Baseline in Body temperature.
- Change from the Baseline in WBC.
- Change from the Baseline in hs-CRP.
- Change from the Baseline in serum Albumin.
- Proportion of subjects achieving "Mild" in JDA severity index of GPP for patients with "Moderate" or "Severe" at Baseline.
- Proportion of subjects achieving Treatment Success in PGA (reduction of 2 grades).
- Change from the Baseline in PGA grade.
- Proportion of subjects achieving PGA 0/1 for patients with PGA grade at least 2 at Baseline.
- Proportion of subjects achieving PASI 90.
- Proportion of subjects achieving PASI 75.
- Proportion of subjects achieving PASI 50.
- Change and Percent change from the Baseline in PASI score.
- Proportion of subjects achieving DLQI = 0.
- Change from the Baseline in DLQI score.
- Change from the Baseline in SF-36 score.
- Proportion of subjects taking systemic co-medication for GPP (etretinate, MTX).
- Proportion of subjects taking topical co-medication for GPP (corticosteroid, vitamin D3, tacrolimus).

**Determination of the Sample Size:**

GPP is designated as the specified rare and intractable disease in Japan and patient number is quite limited. Assuming the Clinical Response rate of adalimumab in GPP is similar to PASI 75 response in plaque psoriasis, 50% to 60% as expected response rate in adalimumab treatment and 10% as a threshold response rate is hypothesized.

A sample size of 6 to10 provides over 90% power to detect the difference between expected Clinical Response rate (50% to 60%) and threshold response rate (with no medication, 10%) in GPP, using a one sample Chi-square test with 2.5% one-sided significance level. Using Fisher's exact test, an exact binomial test with a nominal 0.025 one-sided significance level will have 82% power to detect the difference between the threshold proportion of 10% and the expected proportion of 50%.

Therefore, the target number of subjects is set 10 subjects, taking the study feasibility into consideration.

**Statistical Methods (Continued):**

**Determination of the Sample Size (Continued):**

| Threshold Response Rate | Expected Response Rate | Actual Power | No of Subjects |
|---|---|---|---|
| 10% | 50% | 91.2% | 10 |
| 10% | 55% | 91.6% | 8 |
| 10% | 60% | 90.3% | 6 |

**Pharmacokinetic:**

Adalimumab trough serum concentrations will be reported at each time point using descriptive statistics. The relationship between adalimumab concentrations and Clinical Response improvement will be determined as appropriate.

**Immunogenicity:**

AAA will be evaluated for each subject and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment emergent adverse events may be evaluated.

**Safety:**

Adverse events (AEs), laboratory data and vital signs are the safety parameters in this study. Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose day of the study medication and within 70 days after the last dose of the study medication. Treatment-emergent AEs will be summarized separately for the first half period (Week 0 to Week 24), the second half period (Week 24 to Week 52), and entire period (Week 0 to Week 52).

An overview of treatment-emergent AEs, including AEs of special interest, AEs leading to death and AEs leading to PD, AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage. Other safety variables like laboratory data will be described by descriptive statistics. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

## 1.2 List of Abbreviations and Definition of Terms

**Abbreviations**

| | |
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| AAA | Anti-adalimumab Antibody |
| ADA | Adalimumab |
| AE | Adverse event |
| ALT | Alanine Transaminase |
| ANA | Antinuclear Antibody |
| AST | Aspartate Transaminase |
| BCG | Bacillus Calmette-Guérin |
| BUN | Blood Urea Nitrogen |
| CDC | Centers for Disease Control and Prevention |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| dsDNA | Double-stranded Deoxyribonucleic Acid |
| ECG | Electrocardiogram |
| EU | European Union |
| eCRF | Electronic Case Report Form |
| eow | every other week |
| ew | every week |
| FDA | Food and Drug Administration |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GMA | Granulocyte and Monocyte absorbent Apheresis |
| GPP | Generalized Pustular Psoriasis |
| hs-CRP | high-sensitivity C-Reactive Protein |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IGRA | Interferon-Gamma Release Assay |
| IRB | Institutional Review Board |
| JDA | Japanese Dermatological Association |
| LOCF | Last Observation Carried Forward |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |

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|---|---|
| MTX | Methotrexate |
| NRI | Non-Responder Imputation |
| PA | Posterior-anterior |
| PASI | Psoriasis Area and Severity Index |
| PD | Premature Discontinuation |
| PGA | Physician's Global Assessment |
| PK | Pharmacokinetics |
| POR | Proof of Receipt |
| PML | Progressive Multifocal Leukoencephalopathy |
| PPD | Purified Protein Derivative |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SDP | Study Designated Physician |
| TB | Tuberculosis |
| TNF | Tumor Necrosis Factor |

## 2.0 Table of Contents

## List of Tables



## List of Figures



## List of Appendices

# 3.0 Introduction

Generalized Pustular Psoriasis (GPP) is severe form of psoriasis and inflammatory disease of undetermined cause, which is characterized by generalized cutaneous erythema along with acute pyrexia as well as multiple sterile pustules. This disease has a very low incidence in Japan, and the effective treatments are limited. Therefore, it is designated as a specified rare and intractable disease by the Ministry of Health, Labour and Welfare (MHLW).

GPP may either be preceded by plaque psoriasis, or arise without a prior history of plaque psoriasis, classically after withdrawal of systemic glucocorticosteroids,[1] and recently the studies for disease pathogenesis have been identified specific gene region susceptible to GPP.[2] GPP is characterized by pyrexia with chills and extensive skin erythema, where tender pustules form and then coalesce into lakes of pus. Desquamation from the pustules occurs thereafter, which is accompanied by nail plate changes (thickening and onycholysis), complaint of general malaise, and with a high frequency, mucosal symptoms, arthritis, and eye symptoms. These symptoms significantly impair quality of life (QOL) and markedly affect daily living. GPP is also characterized by multiple recurrences, and rarely, patients experience capillary leak syndrome, respiratory failure, or secondary amyloidosis, and are also at risk for death from cardiac or circulatory failure, general debility, and infections.

In the acute phase of the disease, GPP requires intense management of the general condition. Once the symptoms are relatively stable, management of skin symptom is important. In Japan, some systemic treatments are approved: etretinate, cyclosporine, and infliximab. All these treatments are demonstrated to be effective for GPP, and improve skin symptom and patient QOL. However, etretinate is teratogenic and causes liver disorder, while cyclosporine sometimes causes renal disorder and hypertension. For these reasons, their use cannot be continued for long-term disease management in some patients from the safety point of view. Infliximab, which contains murine protein, may rarely cause anaphylactic symptoms. Loss of response (secondary failure patients) has

been also observed during treatment for the long-term use, and actions to be taken for such reduced response are clinically significant. These limitations of current treatments highlight the need for new therapeutic options for GPP.

Adalimumab (genetical recombination), a fully human anti-human tumor necrosis factor-α (TNFα) monoclonal antibody, exhibits the efficacy by inhibiting action of TNFα which plays an important role in the pathology of psoriasis. Since adalimumab contains no murine protein, neutralizing antibodies to the drug is less likely to be produced, and it is less of a risk for occurrence of the anaphylactic symptom and expected to cause fewer cases of reduced response by continued use. In Japan, adalimumab has been approved for indications of rheumatoid arthritis, plaque psoriasis, arthritic psoriasis, Crohn's disease, ankylosing spondylitis, juvenile idiopathic arthritis, ulcerative colitis, and intestinal Behcet's disease.

In Japan, the Medical care guideline for GPP 2014[3] recommends the following systemic treatments for GPP: etretinate, cyclosporine, methotrexate (not approved for GPP in Japan), and TNFα inhibitors such as infliximab and adalimumab as the committee's opinion. The report from the overseas experts meeting (Medical Board of the National Psoriasis Foundation)[4] and the psoriasis treatment guideline in the United Kingdom[5] also recommend the use of anti-TNFα preparations (e.g., infliximab and adalimumab) for GPP.

While adalimumab has not been investigated in overseas or Japanese clinical studies in GPP patients, case reports[6-10] for clinical use of adalimumab in GPP patients and results of the post-marketing surveillance (all-case surveillance) conducted in Japan suggest the effectiveness of adalimumab in GPP patients.

As described above, adalimumab was expected to be an effective treatment for GPP patients who have no adequate response to the existing treatments (except for biologics) and secondary failures with infliximab treatment. In 2011, the Japanese Dermatological Association submitted a request for an indication of an unapproved drug to MHLW to propose GPP as an additional indication of adalimumab. In response to this request, MHLW invited company opinions about use of adalimumab for GPP on 15 November. In

January 2012, AbbVie submitted an opinion that Public Domain Submission is appropriate for the approval of additional indication. On 23 March 2012, however, such application was not adopted by the Study Group on Unapproved and Off-label Drugs of High Medical Need for the following reasons: infliximab, a similar drug with the same indication, had been already approved; adalimumab was not considered to be positioned as a standard treatment in overseas because it had not been approved for treatment of GPP in 6 major foreign countries (e.g., major European countries and the United States) and there had been no clinical study globally. Therefore, the sponsor planned to conduct a clinical study in Japan for the approval of an indication for GPP to meet the unmet medical needs.

The purpose of this study is to evaluate efficacy, safety and pharmacokinetics of adalimumab dose regimen approved for plaque Ps in Japan (80 mg at Week 0 by subcutaneous injection, followed by 40 mg every other week [eow] on and after Week 2, and dose escalation to 80 mg eow is allowed if the adequate response is not obtained) in Japanese GPP patients who had an inadequate response to the currently approved treatment.

## 3.1 Benefits and Risks

This study is the first clinical trial in patients diagnosed with generalized pustular psoriasis on adalimumab in the world, and expected clinical use of this drug in Japan. The dose regimen planned in this study is 80 mg for initial loading dose subcutaneously followed by 40 mg every other week (eow) on and after Week 2 until study end, which is the same dose regimen in Ps approved in Japan. Dose escalation to 80 mg eow is allowed if subjects have inadequate response on or after Week 8 and meet the dose escalation criteria. Reasonable efficacy is expected not only in the patients who had inadequate response to the existing therapies, but also in the infliximab-secondary failures, which have been reported to being increased in Japan. The safety of this dose regimen is supported by the safety data of clinical studies in plaque psoriasis (Studies M04-688 and M04-702).

## 3.2 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in US and EU for the treatment of Rheumatoid Arthritis in 2002 and 2003, respectively, and subsequently the Pharmaceuticals and Medical Devices Agency in Japan in 2008. Additional indications have been approved in the US and EU including Psoriasis, Psoriatic Arthritis, Axial Spondylitis, Crohn's Disease, Juvenile Arthritis, and Ulcerative Colitis. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

## 3.3 Safety Information

Adalimumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial subject exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the

pre-clinical toxicology, metabolism, pharmacology, and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in a Food and Drug Administration (FDA)-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects who are 30 years old or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event Reporting.

# 4.0 Study Objective

The primary study objective is to investigate efficacy, safety and pharmacokinetics of adalimumab in Japanese patients with generalized pustular psoriasis (GPP).

# 5.0 Investigational Plan

## 5.1 Overall Study Design and Plan: Description

This is a Phase 3, multicenter, open-label, single-arm study of adalimumab dosing regimens (80 mg at Week 0 by subcutaneous injection, followed by 40 mg every other week [eow] on and after Week 2 until Week 50) in Japanese patients with generalized pustular psoriasis with total skin score of at least 3 and erythema with pustule (skin score of at least 1) in Japan Dermatology Association (JDA) severity index of GPP in GPP Medical Care Guideline 2014. Dose escalation to 80 mg eow is allowed for subjects who do not have adequate response on or after Week 8.

The study is designed to enroll 10 subjects at approximately 10 sites in Japan to meet scientific and regulatory objectives in alignment with ethical considerations.

This study will include:

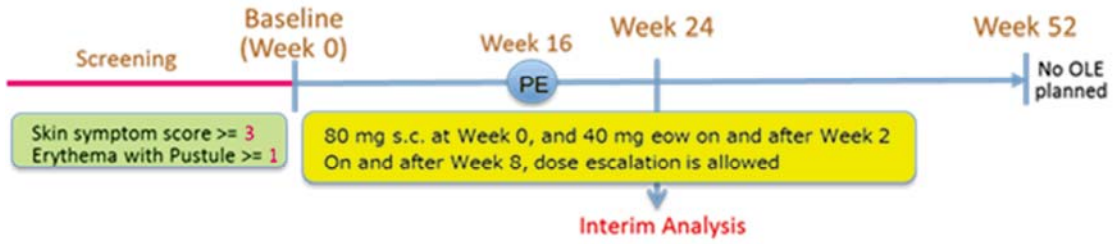
- A 30-day Screening Period
- A 52-Week Treatment Period
- A 70-Day Follow-Up Period

A subject's participation in the study is anticipated to be up to 66 weeks. There is a ± 7-day window for all study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window.

Study visits for clinical and safety assessments will be performed at Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52, and at the Premature Discontinuation visit if the subject discontinues prior to Week 52. No open label extension (OLE) study is planned after this 52-week study. Blood samples will be collected for clinical laboratory test, adalimumab serum concentrations, anti adalimumab antibody (AAA) levels, as indicated in Table 1. In addition, photography of skin lesion will be performed in subjects who consent to it in pre-selected sites.

A schematic of the study design is presented in Figure 1.

**Figure 1. Study Schematic**




## Screening Period

The Screening Period begins at the Screening Visit and continues through to Baseline Visit (Week 0). Screening Assessments will include medical history, physical

examination, chest x-ray, electrocardiogram (ECG), laboratory results including pregnancy testing, all of which will be reviewed by the study site to confirm selection criteria are met prior to enrolling the subject.

Subjects who meet all eligibility criteria during the Screening Period (Section 5.2.1 and Section 5.2.2) will enter the 52-Week Treatment Period. The length of time between Screening and the Baseline Visits must allow time for lab results. The Screening period (30 days, ± 7 days is granted around all study visits) may be extended as necessary for subjects who require initiation of prophylactic anti-tuberculosis (TB) therapy, or in case of external, not subject-related circumstances (e.g., due to delay of availability of screening test results).

Subjects who initially screen fail for the study may be permitted to re-screen following re-consent. There is no minimum period of time a subject must wait to re-screen for the study. The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. If the subject had a complete initial screening evaluation including the assessment of a purified protein derivative (PPD) test (or equivalent), or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold or equivalent), chest x-ray, and ECG, these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed. All other screening procedures will be repeated. As appropriate, sites should contact the AbbVie SDP to confirm if subjects may be re-screened.

**52-Week Treatment Period**

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the 52-Week Treatment Period.

All subjects enrolled in the study will be allocated at Baseline (Week 0) to the same adalimumab dose regimen at the investigation site. The dose regimen will be 80 mg at Baseline (Weeks 0) by subcutaneous injection followed by 40 mg eow on and after Week 2 until Week 50 as shown in Figure 1. Dose-escalation to 80 mg eow will be allowed for

subjects who do not have adequate response (e.g., minimal improvement, unchanged or worsened) on or after Week 8. No dose reduction is allowed after dose escalation.

Subjects will return to the study site at scheduled visits and complete study procedures for each visit as outlined in Section 5.3.1.1.

For subjects who are on oral steroids at the Baseline, their steroid dose must be tapered off for 4 weeks (until Week 4) and withdrawn for the rest of the study period. For subjects who are on cyclosporine at the Baseline, the treatment must be tapered off for 8 weeks (until Week 8) and withdrawn for the rest of the study period.

Throughout the study, subjects who are on etretinate (maximum dose of 20 mg/day at the Baseline), MTX, azathioprine, or salazosulfapyridine will be continued on their stable dose or have their dose of GPP-specific concomitant medications decreased as specified in Section 5.2.3.2. Dose escalation is not allowed for these treatments.

No study drug will be administered at the final visit.

**70-Day Follow-Up/Premature Discontinuation**

Subjects may discontinue adalimumab treatment at any time during study participation (Section 5.4). Subjects who end study participation early will have a premature discontinuation (PD) Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing AEs.

## 5.2 Selection of Study Population

Ten subjects will be enrolled at approximately 10 investigation sites in Japan.

Male and female subjects who meet all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of the protocol are eligible to be enrolled into the study.

### 5.2.1 Inclusion Criteria

1. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol. If the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent.
2. Male or female ≥ 15 and ≤ 75 years of age at the Baseline visit.
3. Subject must have a diagnosis of Generalized Pustular Psoriasis (GPP) for at least 60 days prior to Screening and determined by the Investigator through subject interview and review of medical history during the Screening Period.
4. Subject must have had an inadequate response to, or demonstrated intolerance to, or have a contraindication to the currently approved treatment for their GPP (excluding infliximab).
5. Subject must have total skin score of at least 3 and erythema with pustules (skin score of at least 1) in JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan at Baseline.
6. Subject may be included if they have previously experienced a benefit for their GPP from infliximab and discontinued its use due to a subsequent loss of response (i.e., judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of GPP related symptoms, "infliximab secondary failure"), or intolerance (i.e., in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication). Confirmed documentation indicating loss of response or lack of tolerability will be required, see Section 10.1 and Appendix Q.
7. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential who must have negative result of pregnancy test performed at the Screening and at the Baseline. Female subject of childbearing potential is practicing an approved method of birth

control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control which result in a low failure rate when used consistently and correctly are:

- Condoms, sponge, foams, jellies, diaphragm, intrauterine devices (IUDs), or intrauterine hormone releasing system (IUS);
- Sexual abstinence (when in line with preferred and usual lifestyle of the subject);
- A vasectomized partner;
- Hormonal contraceptives for at least 90 days prior to study drug administration.

Note: low-dose progestin-only oral contraceptives are not considered adequate.

8. If female, subject is not breast-feeding throughout the study and for 150 days after last dose.

9. Subject has a negative TB Screening Assessment (including a PPD test and/or Quantiferon TB Gold test, or equivalent) and negative chest x-ray (CXR) (posterior anterior [PA] and lateral view). If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis prior to Baseline (Section 5.3.1.1).

10. Subject is judged to be in good general health, as determined by the Principal Investigator based upon the results of a medical history, physical examination, laboratory profile, chest x-ray, and a 12 lead electrocardiogram (ECG) performed during the Screening.

**Rationale for the Inclusion Criteria**

| | |
|---|---|
| 1 | In accordance with good clinical practice (GCP) |
| 2 – 10 | In order to select the appropriate subject population with a disease status representative of the target population for evaluation |

### 5.2.2 Exclusion Criteria

1. Subject has erythrodermic psoriasis, guttate psoriasis, or subcorneal pustular dermatosis at Screening.
2. Subject diagnosed drug-induced GPP.
3. Total score of 14 or more in JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan.
4. Subject has other active skin disease (e.g., urticarial, atopic dermatitis) or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of GPP, with the exception of footpad trichophytosis (athlete's foot).
5. Subject who cannot taper off cyclosporine until Week 8 after the Baseline and during the study. Subjects who cannot taper etretinate to 20 mg/day at the maximum dose prior to the Baseline.
6. Subject who is receiving oral corticosteroid more than 10 mg/day at the Baseline, and cannot taper off until Week 4 after the Baseline and during study.
7. Subject who received granulocyte and monocyte adsorption apheresis (GMA) therapy for at least 28 days prior to the Baseline and cannot avoid this therapy during the study.
8. Subjects who received any investigational agents of chemical or biologic nature (including anti-IL17 agents), which would be efficacious to GPP or psoriasis-related skin disease for at least 28 days or 5 half-lives of the drug prior to the Baseline, whichever is longer, and during the study.
9. Subjects who received ustekimumab for at least 84 days prior to the Baseline and during the study.
10. Subject who cannot avoid PUVA or narrow-band UVB phototherapy for at least 14 days prior to the Baseline and during the study.
11. Subject who cannot avoid "Strongest" corticosteroid in Japanese classification of topical therapy for at least 14 days prior to the Baseline and during the study.

12. Subject who cannot avoid anti-tumor necrosis factor (TNF) agent other than infliximab and adalimumab (including but not limited to etanercept [Enbrel], golimumab [Simponi] or certolizumab pegol [Cimzia]) for at least 28 days prior to the Baseline and during the study.
13. Prior exposure to adalimumab.
14. Subject who has previous used infliximab:
    - and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction, or
    - who used infliximab ("secondary treatment failure") within 42 days prior to the Baseline.
15. Prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy (PML) (i.e., natalizumab [Tysabri®], rituximab [Rituxan®], efalizumab [Raptiva®]).
16. Subject with any active viral infection that makes the subject an unsuitable candidate for the study based on the investigator's clinical assessment.
17. Hepatitis B: HBs Ag positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBs Ab positive subjects.
18. Subject with known hypersensitivity to the excipients of adalimumab.
19. Positive pregnancy test at the Screening (serum) or the Baseline (urine).
20. Female who is breast-feeding or considering becoming pregnant during the study.
21. History of clinically significant drug or alcohol abuse in the last 12 months.
22. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
23. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and/or any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.

24. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix.
25. Chronic recurring infections or active TB.
26. Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to Baseline or oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline.
27. History of invasive infection (e.g., listeriosis, histoplasmosis), human immunodeficiency virus (HIV).
28. Screening laboratory and other analysis show any of the following abnormal results:
    - AST, ALT > 1.75 × upper limit of the reference range;
    - WBC count < $3.0 \times 10^9$/L;
    - Electrocardiogram (ECG) – with clinically significant abnormalities;
    - Total bilirubin ≥ 3 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
    - Serum creatinine > 1.6 mg/dL.
29. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

**Rationale for the Exclusion Criteria**

| | |
|---|---|
| 1, 2 | To avoid medical conditions that may compromise the ability to identify subjects with the correct diagnosis or to interpret medical importance of clinical results |
| 3, 18, 21 | To exclude subjects who maybe at increased risk for protocol non-adherence or premature discontinue |
| 4 – 15 | To avoid bias for the evaluation of efficacy and safety by concomitant or prior use of other medications or treatments |

| | |
|---|---|
| 16, 17, 19, 20, 22 – 28 | To reduce the risk to subjects or others and/or to exclude underlying conditions that would compromise the subject's safety |
| 29 | To maintain the integrity of other aspects of study conduct, including, subject sampling, treatment procedures, etc. |

### 5.2.3 Prior and Concomitant Therapy

#### 5.2.3.1 Prior Therapy

Any non-GPP medication or vaccine (including over-the-counter or prescription medicines, vitamins, mineral supplements, and herbal supplements) that the subject is receiving within 30 days prior to Baseline, is receiving at the time of Enrollment, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF). Medication for PPD test and injection solvents does not need to record as far as adverse events derived from these drugs are not occurred.

GPP-specific medications and therapies (including but not limited to cyclosporine, etretinate, MTX, oral or topical corticosteroids, topical vitamin D3, phototherapy, or GMA) that the subject has received within 90 days of Baseline should be recorded on the appropriate page of the eCRF and should include the date(s) of administration and dosages, and reason(s) for termination of the treatment (if appropriate). Subjects who failed to respond (within the past 1 year) or were intolerant (within the past 5 years) to treatment will have date(s) of administration, dosages including maximum dose, and reasons for discontinuation recorded in appropriate eCRF, as long as these information is available in the medical records.

For subjects previously treated with infliximab, the infliximab history will be recorded, including the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment.

The AbbVie SDP identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapies.

In addition for subjects age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their labels and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

#### 5.2.3.2 Concomitant Therapy

Doses of etretinate (tapered to 20 mg/day at maximum dose prior to the Baseline), MTX, azathioprine, or salazosulfapyridine taken at Baseline will be continued and remain stable throughout the study. Doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities or improvement of GPP skin lesion according to the discretion of the investigator. Dose escalation of these treatments will not be allowed.

Doses of topical corticosteroids ("Very strong," "Strong," "Medium" and "Weak" in Japanese classification), topical vitamin D3, or topical tacrolimus taken at the Baseline will be continued without dose escalation. Dose escalation (increase of amount for use) of topical corticosteroids is allowed only to use lower classes of drugs. Doses may be decreased or terminated in the event of moderate-to-severe treatment-related toxicities or improvement of GPP skin lesion according to the discretion of the investigator.

For subjects who are on oral steroids at the Baseline, their steroid dose must be tapered off for 4 weeks (until Week 4) and withdrawn for the rest of the study period. For subjects

who are on cyclosporine at the Baseline, the treatment must be tapered off for 8 weeks (until Week 8) and withdrawn for the rest of the study period.

Changes in all concomitant medications will be assessed at each study visit from Baseline (Week 0) through Week 52/PD Visits. Any changes will be documented, including the reason for the change of dose will be documented in the source documents and captured on the appropriate eCRF page.

Prophylaxis treatment with isoniazid for TB will be recorded. Even if a subject prematurely discontinues the study, isoniazid treatment should be continued for 9 months considering the best interest of the subject at the discretion of the investigator.

Any vaccine (except for live vaccines) administered during the study will be recorded in the eCRF as a concomitant medication.

#### 5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following:
  - Etanercept (Enbrel®);
  - Infliximab (Remicade®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Golimumab (Simponi®);
  - Certolizumab pegol (Cimzia®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®);

- Vedolizumab (Entyvio®).
- Anti-IL-17 agents (Secukinumab, Ixekizumab, Brodalumab), including 28 days prior to Baseline and during the study.
- GMA, including 28 days prior to Baseline and during the study.
- Live vaccines, during the study and for 70 days after the last dose of study drug.
- Tofacitinib (Xeljanz®).
- Recreational or medical marijuana use 14 days prior to Baseline and during the study.
- Intravenous corticosteroid use or topical "Strongest" corticosteroid in Japanese Classification is prohibited within 14 days prior to Baseline and during the study.
- Investigational drugs of a chemical or biologic nature or investigational procedures are prohibited within 28 days or 5 half-lives (whichever is longer) of the drug prior to Baseline and during the study.

The AbbVie SDP identified in Section 6.1.5 should be contacted if there are any questions regarding prohibited therapy.

## 5.3 Efficacy, Pharmacokinetic, and Safety Assessments/Variables

### 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in Section 5.3.1.1. All subjects must meet the study selection criteria outlined in Section 5.2.1 and Section 5.2.2 in order to be enrolled into the study.

## Table 1. Study Activities

| Activity | Screening (Day –30 to Day –1) | Baseline[a] (Day 1) | Wk 2 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 | Wk 52 or Premature Discontinuation Visit | Unscheduled Study Visit | 70-Day Call |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Assign Subject ID Number | X | | | | | | | | | | | | | | | | | |
| Subject Background | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X[b] | | | | | | | | | | | | | | | | |
| Medical/Surgical History | X | X[b] | | | | | | | | | | | | | | | | |
| Prior and Concomitant Therapy Assessment | X | X[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Alcohol Use | X | | | | | | | | | | | | | | | | | |
| Tobacco Use | X | | | | | | | | | | | | | | | | | |
| Physical Exam[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Chest X-Ray[d]/12-Lead ECG[e] | X | | | | | | | | | | | | | | | X[f] | X[g] | |
| TB Screening[h] | X | | | | | | | | | | | | | | | | | |
| Vital Signs | X[i] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Pregnancy Tests | X[j] | X[k] | | | | | | | | | | | | | | X[k] | | |
| General Labs[l]: Blood Chemistry and Hematology | X | X[m] | X | X | X | X | X | | X | | | X | | | | X | X[s] | |

## Table 1. Study Activities (Continued)

| Activity | Screening (Day –30 to Day –1) | Baseline[a] (Day 1) | Wk 2 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 | Wk 52 or Premature Discontinuation Visit | Unscheduled Study Visit | 70-Day Call |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urinalysis[n] | X | X | | | X | | X | | X | | | X | | | | X | | |
| HIV Screen[o] | X | | | | | | | | | | | | | | | | | |
| Hepatitis B Screen[p] | X | | | | | | | | | | | | | | | | | |
| Hepatitis C Screen | X | | | | | | | | | | | | | | | | | |
| Antinuclear Antibody (ANA)/Anti-Double-Stranded DNA (dsDNA)[q] | X | | | | | | | | | | | | | | | | | |
| Photography[r] | | X | X | X | X | X | X | | X | | | X | | | | X | | |
| GPP Skin Score and BSA, Systemic/Laboratory Score | X | X | X | X | X | X | X | | X | | | X | | | | X | X[s] | |
| PGA | X | X | X | X | X | X | X | | X | | | X | | | | X | X[s] | |
| PASI Score | X | X | X | X | X | X | X | | X | | | X | | | | X | X[s] | |
| DLQI | | X | | | X | | X | | X | | | X | | | | X | | |
| SF-36 | | X | | | X | | X | | X | | | X | | | | X | | |
| Dispense Study Drug | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X[s] | |
| Administer Study Drug[t] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X[s] | |
| PK Measurements[u] | | X | X | X | X | X | X | | X | | | X | | | | X | X[s] | |
| AAA Measurements[u] | | X | | | X | | X | | X | | | X | | | | X | X[s] | |

## Table 1. Study Activities (Continued)

| Activity | Screening (Day –30 to Day –1) | Baseline[a] (Day 1) | Wk 2 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 | Wk 52 or Premature Discontinuation Visit | Unscheduled Study Visit | 70-Day Call |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monitor Adverse Events[v] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Follow-Up Phone Call | | | | | | | | | | | | | | | | | | X[w] |

Footnote for Table 1;

a. The Baseline visit date will serve as the reference for all subsequent visits. A ± 7-days window is permitted around scheduled study visits.

b. Update inclusion/exclusion, medical/surgical history, and prior and concomitant therapy information to assure subject eligibility.

c. Physical examinations performed at Screening, Week 24 and Week 52/PD Visits will be full physical examinations. Physical exams performed at all other visits will be symptom-based.

d. Chest x-ray (CXR) includes posterior-anterior [PA] **and** lateral views. Subjects with normal chest x-ray within 90 days of Screening will not require a repeat chest x-ray, if documentation is available.

e. Subjects with normal ECG within 90 days of Screening will not require a repeat ECG, if documentation is available.

f. Subjects will have a repeat CXR or ECG at Week 52 or the appropriate Premature Discontinuation visit, only if in the opinion of the investigator, clinically significant AEs develop during the study that warrant a repeat.

g. Subjects can have a repeat CXR/ECG at any time during the study as warranted based on the opinion of the Investigator.

h. Subjects with negative latent TB test(s) (In case a subject received both a PPD test and IGRA, both must be negative) within 90 days of Screening will not require a repeat latent TB test, if documentation is available. PPD skin test is to be read 48 to 72 hours after placement.

i. Height will be measured at the Screening only.

j. All females of childbearing potential will have a serum pregnancy test at the Screening that is performed at the central laboratory.

k. All females of childbearing potential will have a urine pregnancy test at the Baseline and Week 52 or Premature Discontinuation visits at the central laboratory. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to start of the treatment in the study. Urine pregnancy test at the Baseline will be performed also at site to confirm negative result on site. If the result at site is positive, treatment with study drug should not be started until the serum pregnancy test at the central laboratory is confirmed negative.

l. Subject should be fasting. Please refer to the laboratory manual for further instructions.

## Table 1. Study Activities (Continued)

m. Laboratory assessments will only need to be repeated at the Baseline if the time between blood sampling for Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

n. Dipstick urinalysis will be conducted by the central laboratory at all required study visits. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

o. Subjects will be tested for HIV and documented that the test has been performed. This testing is to be done at the central laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

p. Subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

q. Anti-dsDNA will be measured if ANA is positive.

r. Photographs of skin lesion will be taken at the time points above in subjects who agree to do in the pre-selected sites.

s. When dose escalation is decided on unscheduled visit or on any visit when the data collection is not planned, the investigator must assess skin lesion (GPP skin score, BSA, PGA and PASI score), and perform blood sampling for laboratory test and PK/AAA prior to dose escalation. Body temperature will come from Vital Signs. Additional study drug dispense may be necessary, if appropriate.

t. Administration of study drug will be performed after all assessments and examinations scheduled for that day have been completed. Study drug will be administered every other week in the investigator's office or at subject's home after training of self-injection to ensure proper technique.

u. Blood samples for the measurement of adalimumab and AAA concentrations will be collected prior to dosing.

v. All AEs reported from the time of study drug administration until 70 days following discontinuation of study drug administration will be collected. SAEs and protocol-related nonserious AE will be collected from the time the subject signed the study-specific informed consent until 70 days following discontinuation of study drug administration.

w. Site personnel will contact all subjects by phone 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AE/SAEs.

#### 5.3.1.1 Study Procedures

The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of drug concentration and antibody measurements (discussed in Section 5.3.2), and the collection of adverse event (AE) information (discussed in Section 6.1.4). All study data will be recorded in source documents and on the appropriate eCRFs.

**Informed Consent**

At the Screening visit, the subject will sign and date a study specific, Institutional Review Board (IRB) approved, informed consent form before any study procedures are performed or any medications are withheld from the subject. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

**Assignment of Subject Identification Number**

After obtaining the informed consent, the investigator will assign a subject identification number to each subject and record it in the subject screening/registration sheet (Screening Log, Appendix D). This record will be used for the management of the subjects.

The subject identification number consists of 4 digits; the first 2 digits refer to the investigation site (presented in the site list) and the last 2 digits refer to specific subjects (ascending number) within each site. The unique number will be used repeatedly, if the subject is re-screened for this study.

**Subject Background**

Year of birth, sex, race and ethnicity will be recorded at the Screening Visit.

**Inclusion/Exclusion Criteria**

Subjects will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria at both the Screening and Baseline Visits.

**Assessment of Eligibility at the Screening Visit**

The investigator will assess the eligibility of each subject according to the inclusion and exclusion criteria. The following information will be sent by email or facsimile to the sponsor's CRA within 3 days;

- Subject identification number,
- IC signed date,
- sex,
- age,
- total skin score,
- next scheduled visit date.

**Assessment of Eligibility at the Baseline Visit (Prior to the Initiation of Treatment)**

The investigator will make the final assessment of eligibility according to the inclusion and exclusion criteria based on the latest information obtained during the Screening period. The results of the eligibility assessment and GPP skin scores will be sent within 5 days by email or facsimile to the sponsor's CRA. The worksheet for the eligibility assessment and the scores of skin lesions will be kept as the source document.

**Medical (including Medication) and Surgical History**

A complete medical and surgical history, as well as history of alcohol and tobacco use, will be obtained from each subject during the Screening Period. Medical history will include GPP-related medical history (which includes GPP-onset date) and non-GPP-related medical history. An updated medical history will be obtained at the Baseline Visit to ensure that the subject still qualifies for enrolling in the study.

All previous therapies used for GPP within 90 days prior to Baseline will be recorded in the appropriate eCRF. Information on any treatment failure (failure to respond within the past 1 year and/or intolerant within the past 5 years) will be also recorded in the eCRF, see Section 5.2.3.1.

A detailed history with respect to loss of response and/or intolerance to infliximab will be documented in the subject's source documents. Documentation will include the investigator's judgment based on the conditions defined in Appendix Q.

A detailed medical history with respect to TB exposure also needs to be documented. This information needs to include Bacillus Calmette-Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or residence or work in TB-endemic locations.

**Physical Examination**

A physical exam will be performed at the designated study visits as outlined in Table 1. Physical examinations performed at Screening, Week 24 and Week 52/PD Visits will be full physical examinations, whereas physical examinations performed at all other visits will be symptom-based.

Physical examination findings that are related to subject's medical history will be captured on the appropriate medical history eCRF.

**Chest X-Ray**

All subjects will undergo a standard chest x-ray (PA **and** lateral views) at the Screening Visit to rule out the presence of TB or other clinically relevant findings. The chest x-ray will not be required if the subject had a previous normal chest x-ray within 90 days of Screening, provided all protocol required documentation is available at the site (as outlined below). A computerized tomography will be performed for more precise assessment, if necessary.

In the assessment of the chest x-ray, a radiologist/physician must note the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. The CXR reports require the signature of both the radiologist/physician who read the films and the Principal Investigator. If it is the

site's policy that the radiologist/physician does not sign the final report, the report must include the date of the procedure, the name of the interpreting radiologist/physician and at a minimum must be signed and dated by the Principal Investigator.

Subjects can have a repeat chest x-ray at any time during the study as warranted based on the opinion of the investigator.

**12-Lead Electrocardiogram (ECG)**

A resting 12-lead ECG will be performed at the designated study visits as outlined in Table 1. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. Any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF using the following conventions as appropriate:

- Normal
- Abnormal – not clinically significant
- Abnormal – clinically significant
- Unable to evaluate

The original ECG tracing, signed and dated by a qualified physician or local reader and the investigator, will be retained in the subject's record at the study site and monitored by the responsible sponsor's CRA.

For subjects with a normal ECG taken within 90 days of screening, a repeat ECG at screening will not be required, provided all protocol required documentation is available. If there are other findings that are clinically significant, the Principal Investigator must contact the SDP before enrolling the subject.

Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the investigator.

**TB Screening**

Subjects should be screened for TB using either PPD or IGRA. A PPD skin test (known as tuberculin skin test) will be placed in each investigation site or an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T SPOT TB test) will be performed in the central laboratory during the Screening Period for all subjects including those with a prior history of BCG administration. If a subject had a negative PPD or IGRA test within 90 days prior to screening, and all protocol required documentation is available, this test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. In case a subject received both a PPD test and IGRA, both must be negative.

Subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours after placement when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The induration must be recorded in mm not as positive or negative. The absence of induration should be recorded as "0 mm," not "negative." Subjects who have had an ulcerating reaction to a PPD skin test in the past should not be re-exposed and should not be tested at Screening but will be considered PPD-positive.

If the IGRA test is indeterminate, the site should repeat the test with another blood sample or perform a PPD test. If the second IGRA test is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis.

If the PPD or the IGRA test is positive or the subject has a chest x-ray indicative of latent TB, the subject will be required to initiate and have taken at least 2 weeks of an ongoing course of Center for Disease Control (CDC) recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy.

Subjects with a prior history of latent TB that have a documented completion of the CDC recommended or local guideline recommended prophylaxis may be permitted to enroll. If

the subject has a prior history of latent TB but has not completed or received prophylaxis, prophylaxis must be initiated for at least 2 weeks before enrolling into the study.

Newly initiated prophylactic treatment should be captured on the concomitant medications page in the eCRF and in the source documents. Prior therapy should be captured in medical history.

**Vital Signs**

Vital sign determinations of diastolic and systolic blood pressure in the sitting position, pulse rate (counted for at least 30 seconds), respiratory rate, body temperature (oral), and body weight will be obtained at each visit prior to blood draws. Weight measurements of subjects (with clothes on) will be obtained at each visit using the same measuring instrument. Height will be measured at the Screening Visit only. All measurements will be recorded in metric units.

**Pregnancy Tests**

A serum pregnancy test will be performed on all women of childbearing potential at Screening by the central laboratory. Urine pregnancy tests will be performed at the Baseline Visit (prior to start of treatment with test drug), and at the Week 52/PD for all women of childbearing potential by the central laboratory.

If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Urine pregnancy test at the Baseline will be performed also at the investigation site to confirm negative result on site. If the result at site is positive, treatment with study drug must not be started until the serum pregnancy test at the central laboratory is confirmed negative.

**Laboratory Assessments**

Samples obtained for the laboratory tests will be collected as indicated in Table 1. Laboratory assessments will only need to be repeated at the Baseline if the time between blood sampling for Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

Blood draws should be performed in fasting status after completion of questionnaires (DLQI and SF-36), efficacy assessments and vital sign determinations during a study visit, but before study drug administration, if applicable. Additional laboratory tests may be obtained when clinically warranted. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A certified central laboratory chosen for the study will provide instructions regarding the collection, processing, and shipping of sample for the clinical laboratory tests indicated in Table 2. The laboratory results will be reported by the central laboratory to the investigation site where they will be reviewed, signed and dated by the investigator.

The last clinical laboratory test value obtained prior to the first treatment will serve as the baseline laboratory test values. Laboratory abnormalities are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

**Table 2. Clinical Laboratory Tests**

| Hematology | Clinical Chemistry | Urinalysis[a] |
|---|---|---|
| Hematocrit<br>Hemoglobin<br>Red Blood Cell count<br>White Blood Cell count<br>Neutrophils (Stab, Seg)<br>Bands (Stab)<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelet count (estimate not acceptable) | Blood Urea Nitrogen (BUN)<br>Creatinine<br>Total bilirubin<br>Serum glutamic-pyruvic transaminase/alanine transaminase (SGPT/ALT)<br>Serum glutamic-oxaloacetic transaminase/aspartate transaminase (SGOT/AST)<br>Alkaline phosphatase<br>Sodium<br>Potassium<br>Calcium<br>Inorganic phosphorus<br>Uric acid<br>Cholesterol<br>Total protein<br>Glucose<br>Triglycerides<br>Albumin<br>hs-CRP | Specific gravity<br>Ketones<br>pH<br>Protein<br>Blood<br>Glucose |
| **Additional Blood Samples Collected** | | |
| β-hCG (serum pregnancy test)<br>QuantiFERON-TB Gold or T-SPOT TB (IGRA)<br>HIV<br>HBV<br>HCV<br>ANA<br>anti-dsDNA – *if ANA positive*<br>Pharmacokinetic, Anti-adalimumab antibody | | |

a. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

## Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits as listed in Table 2. A microscopic analysis will be performed by the central laboratory, in

the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

**HIV Screen**

All subjects will be tested for antibodies to the Human Immunodeficiency Virus (HIV) at Screening and documented that the test has been performed. This testing will be done at the central laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

**Hepatitis B Screen**

All subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing the results below do not require HBV DNA PCR qualitative testing, and can be eligible to the study;

- HBs Ab (–) and HBc Ab Total (–)
- HBs Ab (+) and HBc Ab Total (–)
- HBs Ab (+) and HBc Ab Total (+)

**Hepatitis C Screen**

All subjects will be tested for the presence of the Hepatitis C Virus (HCV) at Screening. A positive result for the hepatitis C will be exclusionary.

**Antinuclear Antibody and Anti-Double-Stranded DNA**

ANA will be performed and if positive, anti-dsDNA will be performed at Screening as indicated.

**Photography**

Photography of skin lesions will be recorded for subjects who agree to be taken in the pre-selected sites at the time points noted in Table 1. Photography will be used for referring changes of skin lesions from the Baseline over time, for the selected skin lesions at the discretion of the investigator. When photography is conducted, it will be recorded in the medical record appropriately.

**Skin Lesions Outcome Assessments**

The assessor must be a dermatologist or experienced physician. The site will make every attempt to have the same investigator perform the assessment of skin lesions throughout the study for each subject.

**GPP Skin Score and BSA (Body Surface Area)**

Skin lesion will be observed and assessed BSA for each skin symptom (erythema, erythema with pustule, and edema [Appendix J]) and to calculate skin score (Appendix H) at the time points indicated in Table 1. BSA of GPP is relevant to BSA of erythema in GPP.

BSA, a proportion of skin lesion area in the total body surface area will be determined. The following should be taken into account for the assessment that four anatomic sites – the head, upper extremities, trunk, and lower extremities correspond to approximately 10%, 20%, 30%, and 40% of body surface area, respectively, and the palm corresponds approximately 1% of BSA. BSA below 1% should be round up to integer number in the assessment.

**Systemic Symptom/Laboratory Test Score**

Systemic symptom/Laboratory test score in JDA severity index of GPP will be calculated from the result of Vital signs (body temperature) and Laboratory test (WBC, hs-CRP and serum Albumin) at the time points indicated in Table 1 (Appendix K).

**PGA (Physician's Global Assessment)**

A Physician's Global Assessment (PGA) of disease severity will be performed by the investigator at the time points indicated in Table 1. The PGA is static and refers to the subject's disease state at the time of the assessment and is not a comparison with the subject's previous disease state, whether at the Baseline or at the previous visits (Appendix L).

**Psoriasis Area and Severity Index Score (PASI Score)**

A qualified investigator will assess the PASI score (Appendix M) at the time points indicated in Table 1. All raw data used to determine the PASI score will be recorded on a worksheet (Appendix N) and entered to eCRF. The PASI score will be calculated on the EDC system automatically.

**DLQI (Dermatology Life Quality Index)**

Subjects will complete a DLQI questionnaire (Appendix O) at the Baseline, Weeks 8, 16, 24, 36 or 52/PD visit. The subject will complete the questionnaire by oneself or with the aid of site personnel, if necessary, before the investigator performs any clinical assessment to avoid biasing the subject's response. Sites will review the subject's questionnaires/assessments to make sure that they are complete before the subject completes the study visit and clarify any discrepancies with the subject before the visit is over to ensure accuracy.

**SF-36v2™ Health Status Survey**

The SF-36v2™ form contains 36 total questions targeting a subject's functional health and well-being, as well as his/her psychometric physical and mental health. Subjects will

complete the SF-36 at the visits indicated in Table 1 (Appendix P). The subject will l complete the questionnaire by oneself or with the aid of site personnel, if necessary, before the investigator performs any clinical assessment to avoid biasing the subject's response. Sites will review the subject's questionnaires/assessments to make sure that they are complete before the subject completes the study visit and clarify any discrepancies with the subject before the visit is over to ensure accuracy.

**Study Drug Dispensing/Administration**

Study drug will be administered to subjects by study site medical staff, by him/herself or by a designee (friend, family member or health care professional) throughout the study. The date and time (the nearest minute) that study drug is dosed will be recorded after injection.

When subjects hope for self-injection, he/she or a designated family member or friend will be trained to administer study medication during the first visit or appropriate times of visit, under the supervision of trained medical personnel to reinforce proper aseptic SC injection technique including the management of study drug at home. This training must be documented in the subject's source document. Detailed instructions and training for the administration of adalimumab are provided in Appendix F.

A ± 7-day dosing window is allowable for scheduled study dosing dates. For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

Subjects will maintain a Subject Dosing Sheet for all study medication administered outside of the study visit (i.e., at home). The Subject Dosing Sheet will be reviewed and verified for compliance at each site visit by the study personnel. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Sheet is presented in Appendix G.

The site staff will maintain all the information of study drug medication including those performed at the investigation site, and record appropriately for each subject.

For subjects who cannot/will not self-administer study drug or do not have adequate support (family member, friend or healthcare professional) at home, administration will occur in the investigation site.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home, subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction. If subjects are unable to reach his/her study site or experience life-threatening symptoms, they will be instructed to call an emergency number or proceed to the nearest emergency room and then inform the site as soon as possible.

Study drug is dispensed by the site staff or pharmacists in the site following the subject's treatment schedule. The first two doses of study drug will be administered on site at the Baseline Visit. On and after Week 2, necessary number of study drug packages will be prescribed and dispensed to the subjects to take home who hope for self-injection.

The site staff will remind the subject to take the syringe(s) in the correct order before opening a new package, when applicable. Subjects must be reminded to take correct number of the syringe in the order dispensed by the site staff. The site staff should count all remaining on site visits to dispense the correct number of study drug.

The subject must be instructed to return all used and unused study drug (syringes), sharp containers and empty boxes at each visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.5 and Section 5.5.6.

**Adverse Events**

Adverse events will be assessed at every study visit from Baseline through the Final/Early Termination visit, and during the 70-day phone call or clinic visit (if applicable). For those subjects who terminate the study early, a phone call or routine clinic visit should occur approximately 70 days after last dose of study medication to obtain follow-up information on any ongoing or new AEs. In addition, serious adverse events and protocol-related non-SAE will be collected from the time the subject signs the study-specific informed consent. Refer to Section 6.0 and Appendix R for additional information.

### 5.3.2 Drug Concentration Measurements

#### 5.3.2.1 Collection of Samples for Analysis

Blood samples for adalimumab and anti-adalimumab antibody (AAA) assays will be obtained at the time points as indicated in Table 1.

The date and time that each blood sample is collected will be recorded to the nearest minute in the source document and on the appropriate eCRF.

**Collection of Samples for Adalimumab and AAA Assays**

Blood samples for adalimumab and AAA assays will be collected by venipuncture into appropriately labeled 4 mL evacuated serum collection tubes (one tube for adalimumab and one tube for AAA) without gel separator immediately prior to dosing. Sufficient blood will be collected to provide approximately 2 mL serum for adalimumab assay and 2 mL serum for AAA assay. Please refer to the laboratory manual for further instructions. Serum for assay will be frozen and transferred to the central laboratory for storage until the shipment to the measurement facilities.

A maximum of 15 samples (not including unscheduled visit sample collections) are planned to be collected per subject for adalimumab (9 samples) and AAA (6 samples) assays. The total number of samples planned (not including unscheduled visit sample

collections) will not exceed 90 (9 samples × 10 subjects) for the adalimumab assay and 60 (6 samples × 10 subjects) for the AAA assay.

Additional blood sample for measurement of adalimumab and AAA assays will be collected prior to dosing and whenever a subject is scheduled to be dose escalated.

#### 5.3.2.2 Handling/Processing of Samples

The blood samples for adalimumab and AAA assays will be labeled with the type of sample, the protocol number, the subject number, the week and the assay type (pharmacokinetic [PK]-Adalimumab or AAA). Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory.

#### 5.3.2.3 Disposition of Samples

Frozen samples will be packed in dry ice (pellet form) sufficient to last 7 days during transport. Samples will be shipped by the central laboratory pursuant to instructions from the sponsor. An inventory of the samples will be included in the package for shipment.

#### 5.3.2.4 Measurement Methods

Serum concentrations of adalimumab and AAA will be determined using a validated ligand binding assay (LBA) method under the supervision of the Bioanalysis Department at AbbVie.

### 5.3.3 Efficacy Variables

#### 5.3.3.1 Primary Variable

The primary efficacy variable is the proportion of subjects achieving Clinical Response (remission and improvement) at Week 16.

For the efficacy assessment criteria, see Appendix I.

#### 5.3.3.2 Secondary Variables

Secondary efficacy variables, to be analyzed at each scheduled visit, include:

1. Proportion of subjects achieving Clinical Response (expect Week 16, which is the primary endpoint).
2. Proportion of subjects achieving remission.
3. Change from the Baseline in total GPP score (skin and systemic/laboratory test).
4. Change from the Baseline in JDA severity index of GPP.
5. Change and Percent change from the Baseline in total skin score.
6. Change from the Baseline in total systemic/laboratory test score.
7. Change from the Baseline in score of erythema area (overall) and BSA (BSA of GPP).
8. Change from the Baseline in score of erythema area with pustule and BSA.
9. Change from the Baseline in score of edema area and BSA.
10. Change from the Baseline in Body temperature.
11. Change from the Baseline in WBC.
12. Change from the Baseline in hs-CRP.
13. Change from the Baseline in serum Albumin.
14. Proportion of subjects achieving "Mild" in JDA severity index of GPP for patients with "Moderate" or "Severe" at the Baseline.
15. Proportion of subjects achieving Treatment Success in PGA (reduction of 2 grades).
16. Change from the Baseline in PGA grade.
17. Proportion of subjects achieving PGA 0/1 for patients with PGA grade at least 2 at Baseline.
18. Proportion of subjects achieving PASI 90.

19. Proportion of subjects achieving PASI 75.
20. Proportion of subjects achieving PASI 50.
21. Change and Percent change from the Baseline in PASI score.
22. Proportion of subjects achieving DLQI = 0.
23. Change from the Baseline in DLQI score.
24. Change from the Baseline in SF-36 score.
25. Proportion of subjects taking systemic co-medication for GPP (etretinate, MTX).
26. Proportion of subjects taking topical co-medication for GPP (corticosteroid, vitamin D3, tacrolimus).

#### 5.3.3.3 Safety Variables

Safety will be assessed by adverse events, laboratory data and vital signs during the entire study period.

### 5.3.4 Pharmacokinetic Variables

Pharmacokinetic

Serum concentrations of adalimumab at each scheduled sampling time will be reported. Changes in serum adalimumab concentration in subjects who get dose-escalated will also reported.

Immunogenicity

The number and percentage of subjects who develop AAA will be determined.

## 5.4 Removal of Subjects from Therapy or Assessment

### 5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol.

Subjects will be withdrawn from the study immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie SDP.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie SDP (Section 5.2 and Section 7.0).
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie SDP.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- Subject has dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie SDP.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the PD Visit must be completed within

2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final phone call will be made to the subject approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last dose of study drug and the primary reason for PD. The information will be recorded on the appropriate eCRF page.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent.

### 5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

## 5.5 Treatments

### 5.5.1 Treatments Administered

Subjects will receive adalimumab 80 mg (2 syringes) at Baseline (Week 0) by subcutaneous injection. At and after Week 2, subjects will receive 40 mg (1 syringe)

every other week (eow) subcutaneously until Week 50. No study drug administration will occur at Week 52.

**Dose Escalation**

For subjects who meet dose escalation criteria on or after Week 8, 80 mg (2 syringes) doses will be administered subcutaneously every other week until study end. No dose reduction will be allowed after dose escalation throughout the study. The dose escalation criteria are defined as the subjects who do not achieve Clinical Response (i.e., minimal improvement, unchanged or worsened) on or after Week 8 (Appendix I).

Prior to dose escalation, the observation result of skin lesions (GPP skin score, PGA and PASI score) will be recorded. Blood draw for the laboratory test (including WBC, hs-CRP and serum albumin for systemic/laboratory score) and measurement of pharmacokinetics and AAA will be also performed, prior to dose escalation.

### 5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3.

**Table 3. Study Drugs**

| Drug | Dosage Form | Device | Formulation | Manufacturer |
|---|---|---|---|---|
| Adalimumab | Parenteral | Pre-filled syringe | 40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH | AbbVie |

#### 5.5.2.1 Packaging and Labeling

Investigational product will be packaged in 0.8 mL syringe containing adalimumab 40 mg/0.8 mL. Each dosing package contains 2 pre-filled syringes. The carton label will contain the following information as required per country requirements.

- Sponsor's name and address
- Study protocol number
- Study drug name
- Storage conditions
- Manufacturing number
- Expiry date
- Display of "for clinical trial"

All labels must remain affixed to study medication at all times, and should never be removed for any reason.

Detailed instructions and training for the administration of study drug supplies are provided in Appendix F.

#### 5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study medication drug ***must not be frozen*** at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded on a temperature log to record proper function. Malfunctions or any temperature excursion must be reported to the sponsor immediately. Study medication should be quarantined and not dispensed until AbbVie GPRD deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study.

### 5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique identification number by the Investigator at the site at the Screening visit. Subjects who meet all entry criteria in Section 5.2.1 and none of the exclusion criteria in Section 5.2.2 will be assigned to the treatment arm. Subjects will be referred to using the subject identification number assigned at the Screening.

Study drug will be dispensed and/or administered at the study visits summarized in Table 1. The investigator will record the number of study drug and the date of initial dosing in the subject's screening/registration sheet. The site will send the results of the eligibility assessment and GPP skin score within 5 days by email or facsimile to the sponsor's CRA.

### 5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

If a subject should forget to administer the injection of study medication on his/her regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of his/her next scheduled dose. The subject should not administer two doses on the same day except the first dose at the Baseline visit and after dose escalation.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all self-dosing information on the Subject Dosing Sheet (Appendix G).

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. The extra syringe(s) should be returned to the study site full. The subject should resume his/her regular dosing schedule based on the first dosing date at Baseline.

### 5.5.5 Treatment Compliance

The investigator or his/her designated and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The subject or his/her qualified designee, or site personnel will administer all doses of study drug. In order to document compliance with treatment regimen for subjects conducting self-injection, the subject will be given a Subject Dosing Sheet (Appendix G) to record necessary dosing information including injection dates and times. Compliance information will be verified at every site visit and documented on the appropriate eCRF by making a dosing performance record per subject. Subjects will be counseled on missed doses of medication. If the subject does not return IP boxes and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the dosing sheet is returned before completing on the applicable eCRF page.

### 5.5.6 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying the manufacturing number in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the site on a Site Drug Accountability log including date received, the manufacturing number, date

dispensed, subject number, and the identification with date of the person dispensing the drug.

**For Subjects Dosing at Home**

Each subject will be given his/her own Sharps disposal container to store used pre-filled syringes. Empty IP boxes and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty Boxes and returned Sharps containers will be retained until the sponsor's CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via study medication logs, source documents, empty IP boxes and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened.

The unused pre-filled syringes will be returned by the CRA and used pre-filled syringes will be discarded by the site, after drug accountability has been completed at the site.

## 5.6 Discussion and Justification of Study Design

### 5.6.1 Discussion of Study Design and Choice of Control Groups

Study M14-193 is a multicenter, open-label, single arm study of adalimumab dosing regimen of adalimumab in Japanese subjects with generalized pustular psoriasis (GPP). No placebo arm is planned due to limited GPP patient number in Japan and the purpose of this study is to investigate whether efficacy is achieved with the approved dose regimen in plaque psoriasis and to detect any safety concerns in GPP patients. This study design was endorsed by PMDA.

### 5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The clinical efficacy measurement used in this study (JDA severity index of GPP, BSA, and PASI score) has been used in multiple clinical trials in assessing disease activity in

subjects with GPP. PGA was newly established by AbbVie, and this was endorsed by clinical experts and PMDA.

### 5.6.3 Suitability of Subject Population

Subjects with GPP who meet all inclusion criteria and none of the exclusion criteria are eligible for this study. The specific subject population chosen was based on unmet medical needs of currently available medical therapies as well as previous anti-TNF therapy (infliximab) that demonstrated effectiveness in GPP. This was endorsed by PMDA.

### 5.6.4 Selection of Doses in the Study

Dose regimen was determined based on efficacy and safety data from the adult Ps population from Study M04-688, and observed long-term safety data from Ps study (Study M04-702) in Japan, according to the PMDA's advice.

**Dose Escalation Criteria**

When the enrolled subject would respond inappropriately during the course of the study, dose can be escalated to 80 mg eow on or after Week 8. The safety of 80 mg eow was confirmed in Studies M04-688/M04-702 Japanese Ps studies. The dose escalation criterion is when efficacy of subjects does not achieve the clinical response (i.e., minimal improvement, unchanged or worsened) at the time of evaluation. Time of dose escalation was justified from the result that the mean percentage change for the baseline in PASI score almost reached a steady state by Week 8 in Ps study.

## 6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe)

Complaints associated with any component of this investigational product must be reported to the Sponsor. For adverse events as medical complaints, please refer to Section 6.1, and for product complaints, please refer to Section 6.2.

## 6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

### 6.1.1 Definitions

#### 6.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention (Section 6.2) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

#### 6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a SAE within 24 hours of the site being made aware of the serious adverse event.

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |

| | |
|---|---|
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

### 6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

| | |
|---|---|
| **Mild** | The adverse event is transient and easily tolerated by the subject. |
| **Moderate** | The adverse event causes the subject discomfort and interrupts the subject's usual activities. |
| **Severe** | The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening. |

The CTCAE v4.0 – JCOG (Japanese translation JCOG version on 09 April 2013) can be used as a reference as appropriate.

### 6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

| | |
|---|---|
| **Reasonable Possibility** | An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event. |
| **No Reasonable Possibility** | An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event. |

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, other cause of event must be provided by the investigator for the serious adverse event.

### 6.1.4 Adverse Event Collection Period

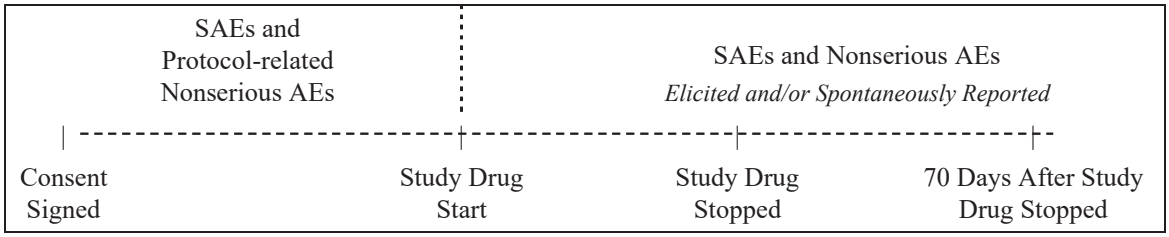
All adverse events reported from the time of study drug administration until 70 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious AEs will be collected from the time the subject signed the study-specific informed consent. Adverse event information will be collected and recorded on the appropriate eCRFs.

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs.

All SAEs and AEs of Special Interest, as defined by AbbVie, reported during the 70-day follow-up phone call must be captured in the clinical database (Appendix R). The end of trial is the last subject contact, i.e., the 70-day follow-up call.

Adverse event information will be collected as shown in Figure 2.

**Figure 2. Adverse Event Collection**




### 6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the investigator will notify the AbbVie Clinical Pharmacovigilance within 24 hours of the site being aware of the event by entering the SAE or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the Rave® EDC system or if Rave® is not operable, should be documented on the SAE Non-case report form (CRF) forms and send to the AbbVie Clinical Pharmacovigilance within 24 hours of the site being made aware of the adverse event.

**Email:** [redacted]

**FAX to:**

For safety concerns, contact Medical Science Group at:

[redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Study Designated Physician:

[redacted]

Secondary Contact (Regional Medical Monitor):

[redacted]

Should in case of subject safety concerns or medical emergencies the Primary or Secondary Study Designated Physician be unavailable, please call the following central back-up number:

| **Phone:** | [redacted] |
|---|---|

The principal investigators will provide documentation of all serious adverse events to the Director of the investigation site and the sponsor.

### 6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

## 6.2 Product Complaint

### 6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

### 6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

## 6.3 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (see Section 6.1.1.2 for definitions). Study medication may be

restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

## 7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations.

For the purposes of the protocol, reportable deviations are defined as:

- Subject entered into the study even though she/he did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying IEC/Institutional Review Board (IRB), regulatory authorities (if appropriate), and the following AbbVie Clinical Monitor(s):

| Primary Contact: | Alternate Contact: |
|---|---|
| [redacted] | |

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

The Investigator will record all protocol deviations in the appropriate medical records at site.

# 8.0 Statistical Methods and Determination of Sample Size

## 8.1 Statistical and Analytical Plans

Complete, specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAPs will be finalized prior to the database lock.

### 8.1.1 Analysis Population

The following populations will be used for analyses in this study:

Full Analysis Set (FAS) population includes all subjects who complied with GCP and received at least one dose of study drug and had at least one post-treatment efficacy

assessment. FAS is the primary population for the efficacy analysis. In general, efficacy analysis will be performed for all subjects regardless dose escalation.

The Safety set consists of all subjects who received at least one injection of study drug.

Pharmacokinetic assessments will be conducted on all subjects who were administered at least one dose of study drug and have at least one post-dose sample collected for the determination of serum adalimumab concentration.

### 8.1.2 Planned Methods of Statistical Analysis

Descriptive statistics will be provided. These include the number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and counts and percentages for discrete variables. The analysis will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

### 8.1.3 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized using descriptive statistics.

### 8.1.4 Statistical Analyses of Efficacy

#### 8.1.4.1 Primary Efficacy Variable

The primary efficacy endpoint is the proportion of subjects achieving Clinical Response (remission and improvement) at Week 16.

Clinical Response is defined as reduction of 1 (if the subject's Baseline skin score is 3) or 2 (if the subject's Baseline skin score is 4 or higher) relative to Baseline, according to JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan (Appendix I).

#### 8.1.4.2 Secondary Efficacy Variables

Discrete variables will be summarized by counts and percentages, and continuous variables will be summarized by descriptive statistics on the items below at each visit.

The subjects who have missing data for any reason such as early terminated subjects will be included into analysis using NRI for discrete variables or LOCF for continuous variables.

For secondary efficacy variables, see Section 5.3.3.2.

### 8.1.5 Statistical Analyses of Safety

Adverse events (AEs), laboratory data and vital signs are the safety parameters in this study. Treatment-emergent AEs are defined as events that begin or worsen either on or after the first dose day of the study medication and within 70 days after the last dose of the study medication. Treatment-emergent AEs will be summarized separately for the first half period (Week 0 to Week 24), the second half period (Week 24 to Week 52), and entire period (Week 24 to Week 52).

An overview of treatment-emergent AEs, including AEs of special interest, AEs leading to death and AEs leading to PD, AEs by MedDRA preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage. Other safety variables like laboratory data will be described by descriptive statistics. In addition, shift tables and listings will be provided for abnormal values, whereby the normal range of the analyzing laboratory will be used.

Safety of 40 mg eow and dose escalation may be also summarized separately.

### 8.1.6 Other Statistical Analyses of Efficacy

The subgroup analysis listed below is planned. Proportion of subjects achieving Clinical Response (remission and improvement) at Weeks 16, 24, and 52.

- Dose escalation: (without dose escalation, with dose escalation)
- Previous infliximab experience (infliximab naïve, prior exposure to infliximab)

### 8.1.7 Interim Analysis

An interim analysis of the primary endpoint and secondary efficacy variables as well as safety data collected from Baseline through Week 24 will be performed after the last subject in FAS population completes the 24-week period of the study. A database lock will be performed and any discrepant data will be clarified before the lock.

### 8.1.8 Pharmacokinetic Analyses

Pharmacokinetic

Adalimumab trough serum concentrations will be reported at each time point using descriptive statistics. The relationship between adalimumab concentrations and Clinical Response will be determined as appropriate.

Immunogenicity

AAA will be evaluated for each subject and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated.

## 8.2 Determination of Sample Size

GPP is designated as the specified rare and intractable disease in Japan and patient number is quite limited. Assuming the clinical response rate of adalimumab in GPP is similar to that in plaque psoriasis, 50% to 60% as expected response rate in adalimumab treatment and 10% as a threshold response rate is hypothesized.

A sample size of 6 to 10 provides over 90% power to detect the difference between expected Clinical Response rate (50 to 60%) and threshold response rate (with no medication, 10%) in GPP, using a one sample Chi-square test with 2.5% one-sided significance level. Using Fisher's exact test, an exact binomial test with a nominal 0.025 one-sided significance level will have 82% power to detect the difference between the threshold proportion of 10% and the expected proportion of 50%.

Therefore, the target number of subjects is set 10 subjects, taking the study feasibility into consideration.

| Threshold Response Rate | Expected Response Rate | Actual Power | No of Subjects |
|---|---|---|---|
| 10% | 50% | 91.2% | 10 |
| 10% | 55% | 91.6% | 8 |
| 10% | 60% | 90.3% | 6 |

# 9.0 Ethics

## 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

## 9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

## 9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement, including the acceptability of photography of skin lesion, will be reviewed and signed and dated by the subject, and the person who administered the informed consent. If the subject is < 20 years old, a subject's parent or legal guardian must be explained and willing to give written informed consent. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

### 9.3.1 Informed Consent Form and Explanatory Material

The Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

### 9.3.2 Revision of the Consent Form and Explanatory Material

When important new information related to the subject's consent becomes available, the Principal Investigator will revise without delay the consent form and explanatory material based on the information and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue in the study or not. The Investigator will also provide further explanation using the revised consent form and explanatory material and will obtain written consent from each subject of their own free will to continue participating in the study. If the subject is < 20 years old, a subject's parent or legal guardian must be explained and willing to give written informed consent.

## 10.0 Source Documents and Case Report Form Completion

### 10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' dosing diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The following assessments that will be completed by subjects on paper will be considered source documentation:

- DLQI
- SF-36 version 2.0

The following contents recorded in eDRF may also be used as source, and will require an Investigator approval on the eCRF as verification of the accuracy of the information:

- Route of drug administration
- Effect of the pre-treatment for GPP
- Reasons for pre-treatment and concomitant treatment for GPP
- Diagnostics, time course, severity, frequency and relationship to study drug, alternative etiology, medication for recovery, and seriousness for either SAEs or Nonserious AEs
- Investigator's comments
- Reason for Premature discontinuation for subject
- Reason why the physician or nurse performed injection of study drug, after self-injection started (if applicable)

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

## 10.2 Case Report Forms

Case Report Forms (CRFs) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. Data entry should be completed within 5 days after a subject visit or results are available. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system, except for subject-completed questionnaires, which will be completed on paper by the subject then transcribed into the

EDC system by site personnel. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or AbbVie's representatives). AbbVie (or AbbVie's representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media. The following assessments will be completed by subjects on paper:

- DLQI
- SF-36 version 2.0

Site staff will verify completion of these forms. All questionnaires must be legible and completed in indelible ballpoint ink. Any necessary corrections are to be made by drawing a single line through the incorrect entry and writing in the revision, the date of the correction, the reason for the correction, and the initials of the study subject who is making the correction. Data are not to be obliterated by blacking out, using correction fluid or by erasing the original entry.

The questionnaire administrator will review the questionnaire for completeness and accuracy. The subject-completed questionnaires will be transcribed into the EDC system by study personnel. The completed paper questionnaire will be considered source documentation.

## 11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF, Subject Questionnaires and Subject Dosing Sheet completion, and specimen collection methods.

The AbbVie CRA will monitor each site throughout the study, and source document verification will be performed.

All data entered in the database will be verified at AbbVie. Any discrepancies will be reviewed. The data will be reviewed and computer logic checks will be run to identify items such as inconsistent study dates. A manual review of selected line listings also will be performed at the end of the study. Queries will be generated in the EDC system. Any necessary corrections will be made to the eCRF.

The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

## 12.0 Use of Information

All information concerning adalimumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, to the FDA and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (Screening Log, with subject's name). This list will be maintained at the site. When a copy is provided to AbbVie, the site should carefully consider that it never include any subject identifying information by obscuring subject's name with a heavy black marker until the relevant information can no longer be seen.

## 13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Director of the Site and the sponsor. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Director of the Site and the sponsor. The investigator will provide a final report to the Director of the Site following conclusion of the study, and the Director of the Site will inform the summary of the report to IRB and the sponsor.

The Director of the Site must retain any records related to the study according to local requirements. If the Director of the Site is not able to retain the records, he/she must notify the sponsor to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

## 14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

| | |
|---|---|
| Protocol Title: | A Multicenter Open-label Study of Adalimumab in Japanese Subjects with Generalized Pustular Psoriasis |
| Protocol Date: | 02 June 2015 |

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

## 15.0 Reference List

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## Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

## Appendix B. List of Protocol Signatories

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | [redacted] | Clinical |
| | | Data and Statistical Sciences |
| | | Clinical Pharmacokinetics and Pharmacodynamics |
| | | Clinical |
| | | Clinical |
| | | Clinical, Japan Development |
| | | Data and Statistical Sciences, Japan Statistics |
| | | Clinical, Japan Development |

## Appendix C. Clinical Expense and Compensation

**Expenditure of the Clinical Expense**

The sponsor will pay the expenses related to this study to the investigative site in accordance with "Special Healthcare Expenditure." The expenses of screening test, etc. will be paid based on the contract concluded with each investigative site. To lighten the burden imposed on the subject with participation to the study, transportation expenses, etc. will be paid to the subjects via participating investigative site in accordance with the rules of the investigative site.

**Compensation for Health Impairment and Insurance**

1. If a subject suffers some sort of health impairment due to this study, the investigative site will provide treatment and take other necessary measures. Among the expenses required for the treatment, the amount not covered by health insurance that the patient must pay directly will be borne by the sponsor only when the event is associated with the use of the study drug.
2. When a subject suffers health impairment during this study and a dispute occurs or might occur between the investigative site and the subject, the investigative site will immediately report this to the sponsor and resolve it. The sponsor will cooperate with the investigative site in resolving any issues or problems.
3. When the investigative site must compensate subject for any health impairment caused by this study, the compensation paid by the investigative site and the expenses related to any dispute will be borne in full by the sponsor, except in cases where the responsibility for the problem is attributed to the investigative site. This shall not apply to cases where the health impairment occurred because the investigative site performed the study with marked deviation from the GCP or the protocol or because of a deliberate action or a major error by the investigative site.
4. When a subject suffers health impairment during this study and liability for compensation arises, the sponsor will compensate in accordance with the SOP regarding the compensation prepared in advance.

5. The sponsor will obtain clinical study insurance and will take other necessary measures to cover the claims and compensation required in such cases.

## Appendix D. Screening Log – Sample

| Name of the Investigation Site |
|---|
| |

| # | Subject ID Number | Subject's Name | | Sex | Age | Date of Informed Consent | Sending info to the Sponsor's CRA | Date of the First Administration | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | Last | First | | | | | | |
| 1 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 2 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 3 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 4 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 5 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 6 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 7 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |
| 8 | | | | M / F | | 20__ _mon_ _day_ | ☐ | 20__ _mon_ _day_ | |

20___ _mon__ _day__ Principal Investigator's Signature _____

## Appendix E. Eligibility Assessment Form for Enrollment

| FAX Number | Reporter | |
|---|---|---|
| AbbVie GK<br>03-4577-1017 | Study Institution | |
| | Department | Dermatology |
| | Investigator's name | |

| Subject ID Number | | Date of Informed Consent | Date of Eligibility Assessment |
|---|---|---|---|
| _____ | | 20__ mon day | 20__ mon day |
| Sex | Age | Total Skin score | Score of Erythema with Pustule |
| M / F | | | |

## Inclusion Criteria

| Yes | No | Not Applicable | | |
|---|---|---|---|---|
| ☐ | ☐ | | 1 | Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol. If the subject is < 20 years old, a subject's parent or legal guardian must be willing to give written informed consent. |
| ☐ | ☐ | | 2 | Male or female ≥ 15 and ≤ 75 years of age at the Baseline visit. |
| ☐ | ☐ | | 3 | Subject must have a diagnosis of Generalized Pustular Psoriasis (GPP) for at least 60 days prior to Screening and determined by the Investigator through subject interview and review of medical history during the Screening Period. |
| ☐ | ☐ | | 4 | Subject must have had an inadequate response to, or demonstrated intolerance to, or have a contraindication to the currently approved treatment for their GPP (excluding infliximab). |
| ☐ | ☐ | | 5 | Subject must have total skin score of at least 3 and erythema with pustules (skin score of at least 1) in JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan at Baseline. |
| ☐ | ☐ | | 6 | Subject may be included if they have previously experienced a benefit for their GPP from infliximab and discontinued its use due to a subsequent loss of response or intolerance. Confirmed documentation indicating loss of response or lack of tolerability will be required. |

| Yes | No | Not Applicable | | |
|---|---|---|---|---|
| ☐ | ☐ | ☐ The subject is male, or female without childbearing potential | 7 | If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential who must have negative result of pregnancy test performed at the Screening and at the Baseline. Female subject of childbearing potential is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. |
| ☐ | ☐ | ☐ The subject is male | 8 | If female, subject is not breast-feeding throughout the study and for 150 days after last dose. |
| ☐ | ☐ | | 9 | Subject has a negative TB Screening Assessment (including a PPD test and/or Quantiferon TB Gold test, or equivalent) and negative chest x-ray (CXR) (posterior anterior [PA] and lateral view). If the subject has evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis prior to Baseline. |
| ☐ | ☐ | | 10 | Subject is judged to be in good general health, as determined by the Principal Investigator based upon the results of a medical history, physical examination, laboratory profile, chest x-ray, and a 12 lead electrocardiogram (ECG) performed during the Screening. |

## Exclusion Criteria

| Yes | No | Not Applicable | | |
|---|---|---|---|---|
| ☐ | ☐ | | 1 | Subject has erythrodermic psoriasis, guttate psoriasis, or subcorneal pustular dermatosis at Screening. |
| ☐ | ☐ | | 2 | Subject diagnosed drug-induced GPP. |
| ☐ | ☐ | | 3 | Total score of 14 or more in JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan. |
| ☐ | ☐ | | 4 | Subject has other active skin disease (e.g., urticarial, atopic dermatitis) or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of GPP, with the exception of footpad trichophytosis (athlete's foot). |
| ☐ | ☐ | | 5 | Subject who cannot taper off cyclosporine until Week 8 after the Baseline and during the study. Subject who cannot taper etretinate to 20 mg/day at the maximum dose prior to the Baseline. |

| Yes | No | Not Applicable | | |
|---|---|---|---|---|
| ☐ | ☐ | | 6 | Subjects who is receiving oral corticosteroid more than 10 mg/day at the Baseline, and cannot taper off until Week 4 after the Baseline and during study. |
| ☐ | ☐ | | 7 | Subject who received GMA (granulocyte and monocyte adsorption apheresis) therapy for at least 28 days prior to the Baseline and cannot avoid this therapy during the study. |
| ☐ | ☐ | | 8 | Subjects who received any investigational agents of chemical or biologic nature (including anti-IL17 agents), which would be efficacious to GPP or psoriasis-related skin disease for at least 28 days or 5 half-lives of the drug prior to the Baseline, whichever is longer, and during the study. |
| ☐ | ☐ | | 9 | Subjects who received ustekimumab for at least 84 days prior to the Baseline and during the study. |
| ☐ | ☐ | | 10 | Subject who cannot avoid PUVA or narrow-band UVB phototherapy for at least 14 days prior to the Baseline and during the study. |
| ☐ | ☐ | | 11 | Subject who cannot avoid "strongest" corticosteroid in Japanese classification of topical therapy for at least 14 days prior to the Baseline and during the study. |
| ☐ | ☐ | | 12 | Subject who cannot avoid anti-tumor necrosis factor (TNF) agent other than infliximab and adalimumab (including but not limited to etanercept [Enbrel], golimumab [Simponi] or certolizumab pegol [Cimzia]) for at least 28 days prior to the Baseline and during the study. |
| ☐ | ☐ | | 13 | Prior exposure to adalimumab. |
| ☐ | ☐ | | 14 | Subject who has previous used infliximab:<br>• and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction,<br>or<br>• who used infliximab ("secondary treatment failure") within 42 days prior to the Baseline. |
| ☐ | ☐ | | 15 | Prior exposure to medications that have a potential or known association with progressive multifocal leukoencephalitis (PML) (i.e., natalizumab [Tysabri], rituximab [Rituxan], efalizumab [Raptive]). |
| ☐ | ☐ | | 16 | Subject with any active viral infection that makes the subject an unsuitable candidate for the study based on the investigator's clinical assessment. |

| Yes | No | Not Applicable | | |
|---|---|---|---|---|
| ☐ | ☐ | | 17 | Hepatitis B: HBs Ag positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBs Ab positive subjects. |
| | | | 18 | Subject with known hypersensitivity to the excipients of adalimumab. |
| ☐ | ☐ | ☐ The subject is male, or female without childbearing potential | 19 | Positive pregnancy test at the Screening (serum) or the Baseline (urine). |
| ☐ | ☐ | ☐ The subject is male | 20 | Female who is breast-feeding or considering becoming pregnant during the study. |
| ☐ | ☐ | | 21 | History of clinically significant drug or alcohol abuse in the last 12 months. |
| ☐ | ☐ | | 22 | History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease. |
| ☐ | ☐ | | 23 | History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and/or any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study. |
| ☐ | ☐ | | 24 | Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix. |
| ☐ | ☐ | | 25 | Chronic recurring infections or active TB. |
| ☐ | ☐ | | 26 | Infection(s) requiring treatment with intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 28 days prior to Baseline or oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline |
| ☐ | ☐ | | 27 | History of invasive infection (listeriosis, histoplasmosis), human immunodeficiency virus (HIV). |

| Yes | No | Not Applicable | | |
|---|---|---|---|---|
| ☐ | ☐ | | 28 | Screening laboratory and other analysis show any of the following abnormal results:<br>• AST, ALT > 1.75 × upper limit of the reference range;<br>• WBC count < $3.0 \times 10^9$/L;<br>• Electrocardiogram (ECG) – with clinically significant abnormalities;<br>• Total bilirubin ≥ 3 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome.<br>• Serum creatinine > 1.6 mg/dL. |
| ☐ | ☐ | | 29 | Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study. |

## Appendix F. Injection Instructions – Sample Pre-Filled Syringe

**Subject Instructions**

**0.8 mL dose**

**(Administered as a single dose-pre-filled syringe)**

**Protocol M14-193**

**Tables of Contents**

- Dosing Schedule
- General Information
- Injection Procedures

**Study Drug Dosing Schedule**

Subject Number: _____

You will require subcutaneous injections throughout the study.

You will receive the following number of injections during this study:

- Baseline visit (the first visit to receive study medication for this study), you will receive 2 injections at the investigation site subcutaneously.
- On or after Week 2 until Week 50, you will receive 1 injection (1 syringe from 1 package) subcutaneously.
- If the Investigator considers dose escalation is appropriate on or after Week 8, you will receive 2 injections (1 package).
- If you prefer to self-injection at home (or any place outside the investigation site), you will be allowed to do it after the site staff qualifies your skill of the administration procedures.

**For all doses, packages of study medication must be used in the order dispensed.**

Please return all used and unused syringes and empty boxes to the clinic on your next visit. Used syringes should be placed in the special sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

**General Information**

- Pre-filled syringes will be labeled "Adalimumab."
- Store all adalimumab pre-filled syringes in your refrigerator NOT in the freezer. Should the syringes accidentally become frozen, call your study doctor's office.
- Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study medications. ***Pre-filled syringes (used and unused) & empty boxes must be returned to the study center at each visit*.** Used syringes will be disposed of in a sharps container provided to you.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms, **call** _____, or proceed to your nearest emergency room.

## Injection Procedures

### 1. Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one package with the prefilled syringe(s) of adalimumab from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused syringe(s) to the refrigerator.

You will need the following items for each dose:

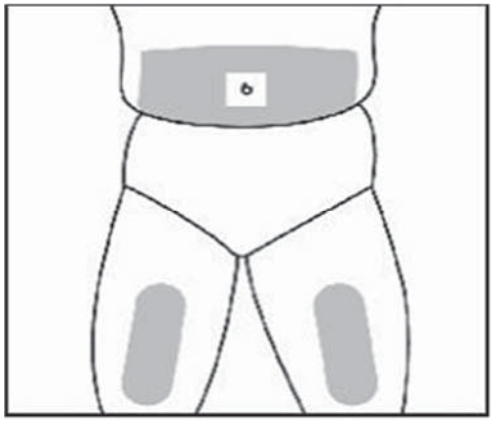
- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

**2. Choosing and preparing an injection site**



- Wash your hands well.
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.

**3. How to prepare your adalimumab dose for injection with a Prefilled Syringe**

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg prefilled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay.
- Do not shake the syringe.

**4. Injecting Adalimumab**

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly.
- You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject adalimumab. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. Do not use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the adalimumab is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container.

**5. Training of "Dosing at home" for Japanese subjects**

Training will include:

a. Guidebook and DVD
   - How to transport and storage the study drug
   - How to perform self-injection
   - How to treat and collect the used syringe
   - How to do when the subject's physical condition is changed suddenly
   - How to fill in self-injection dosing sheet

b. Practice of the SC injection under supervision by a physician or nurse

Following cases may expect to occur;

1. The same training course is necessary when a family member will perform subcutaneous injection.
2. If a subject gives up "dosing at home" or investigator decides a subject can no longer perform the self-injection appropriately, study drug should be administered by an investigator or nurse.
3. If the subject wants to terminate "dosing at home" or continuation of "dosing at home" becomes difficult, investigator should record the circumstances on the medical record and the study should continue with treatment by an investigator or nurse. In this case, record of Subject Dosing Sheet is not necessary afterward.

4. Even after the subject initiated "dosing at home," it is acceptable that an investigator or nurse performs the SC injection at the site, depending on the situation (e.g., time of dose escalation, this is not a protocol deviation). The reason why an investigator or nurse performed the injection should be recorded in the subject's medical record.
5. If the self-injection was once terminated and the subject wants to re-start it, investigator should confirm the subject can perform the self-injection appropriately. If it occurs after a long period (ca. 3 months or longer), investigator must confirm again the subject or his/her family member can perform the SC injection appropriately.

## Appendix G. Subject Dosing Sheet for Self-Injection – Sample

M14-193 Subject ID:

| # | Date | Wk | Number of Syringes | Time of Administration | Was the Entire Volume Injected? | Person Who Administer | Place | Injection Site (1st Syringe) | Comments (Injection Site Of 2nd Syringe etc.) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2015/xx/xx | 0 | 2 | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | no problem |
| 2 | | 2 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 3 | | 4 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 4 | | 6 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 5 | | 8 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 6 | | 10 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 7 | | 12 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 8 | | 14 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 9 | | 16 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 10 | | 18 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 11 | | 20 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 12 | | 22 | | : | Y/N | Patient / Family | Home / Hospital | R/L, Abdomen/Thigh | |
| 13 | | | | : | | | | | |
| 14 | | | | : | | | | | |
| 15 | | | | : | | | | | |

## Appendix H. Severity Assessment Criteria from the Medical Care Guideline for Pustular Psoriasis (Generalized)

### Total GPP Score and JDA Severity Index of GPP

Total GPP score = skin score + systemic/laboratory test score

JDA severity index of GPP: Mild (0 – 6), Moderate (7 – 10), Severe (11 – 17)

### (1) Evaluation of Skin Score (0 – 9)

| | Severe | Moderate | Mild | None |
|---|---|---|---|---|
| Erythema area (overall)*1 | 3 | 2 | 1 | 0 |
| Erythema area with pustules*2 | 3 | 2 | 1 | 0 |
| Edema area*2 | 3 | 2 | 1 | 0 |

*1 % of body surface area (severe, ≥ 75%; moderate, ≥ 25% and < 75%; mild, < 25%).

*2 % of body surface area (severe, ≥ 50%; moderate, ≥ 10% and < 50%; mild, < 10%).

### (2) Evaluation of Systemic/Laboratory Test Score (0 - 8)

| Score | 2 | 1 | 0 |
|---|---|---|---|
| Pyrexia (°C) | ≥ 38.5 | 38.5 > ≥ 37 | 37 > |
| White blood cell count (/μL) | ≥ 15,000 | 15,000 > ≥ 10,000 | 10,000 > |
| CRP (mg/dL) | ≥ 7.0 | 7.0 > ≥ 0.3 | 0.3 > |
| Serum albumin (g/dL) | 3.0 > | 3.8 > ≥ 3.0 | ≥ 3.8 |

## Appendix I. Efficacy Assessment Criteria

(1) The clinical response categories were defined according to the total skin score at Baseline.

| Skin score at Baseline / Reduction in skin score | | Skin Score = 0 | ≥ ⊿3 | ⊿2 | ⊿1 | Increase in Skin Score |
|---|---|---|---|---|---|---|
| 4 – 9 | Remission | Improvement | Improvement | Minimal improvement | Unchanged | Worsened |
| 3 | Remission | Remission | Improvement | Improvement | Unchanged | Worsened |

- Clinical Response rate (%) = (Remission and Improvement)/number of treated patients *100

(2) Dose escalation criteria

In case subjects do not achieve improvement or remission (i.e., Minimal improvement, unchanged or worsened) on or after Week 8.

## Appendix J. Observation of Skin Lesions – Example

**Assessor Requirements**

- The assessor must be a dermatologist or experienced physician.
- The same assessor must determine all skin lesion assessment for any individual subject throughout the trial. A backup assessor is only allowed in case of emergency or special situation when the designated assessor is unable to perform the evaluation. The backup assessor must be a dermatologist or an experienced physician.

**Assessment of Skin Lesion and Record**

Skin lesion should be an erythema, erythema with pustule, or edema, which is typical for GPP.

The Area (size) of erythema, erythema with pustule, or edema of each part of body will be assessed and recorded. Skin score of each skin lesion and total skin score will be calculated automatically, according to the scoring criteria by severity scores of 0 – 3 where higher scores denote worse conditions.

The site should make every attempt to have the same investigator conduct these assessments throughout the study for each subject.

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

## Appendix K. Skin Lesion Evaluation Form (GPP) and Scoring Form for Systemic Symptoms – Example

| | | Area of Skin Lesion (Body Surface Area) | | |
|---|---|---|---|---|
| | | Erythema (E) | Erythema with Pustule (P) | Edema (D) |
| Head | (max. 10%) | ☐☐ % | ☐☐ % | ☐☐ % |
| Upper extremity | (max. 20%) | ☐☐ % | ☐☐ % | ☐☐ % |
| Body Trunk | (max. 30%) | ☐☐ % | ☐☐ % | ☐☐ % |
| Lower extremity | (max. 40%) | ☐☐ % | ☐☐ % | ☐☐ % |
| Total | (max. 100%) | ☐☐ % | ☐☐ % | ☐☐ % |
| Scoring Criteria | | 3: ≥75%,<br>2: 75% > ≥ 25%,<br>1: 25% > | 3: ≥ 50%,<br>2: 50% > ≥ 10%,<br>1: 10% > | 3: ≥ 50%,<br>2: 50% > ≥ 10%,<br>1: 10% > |
| Skin score (0 – 3) | | ☐ | ☐ | ☐ |
| Total Skin score (0 – 9) | | ☐ | | |

BSA below 1% should be round up to integer number.

### Scoring Form for Systemic Symptoms (GPP) – Example

| | Pyrexia (Body temp., °C) | WBC (/μL) | CRP (mg/dL) | Serum albumin (g/dL) |
|---|---|---|---|---|
| Measurement | ☐☐.☐ | ☐☐☐☐☐ | ☐☐.☐ | ☐.☐ |
| Scoring Criteria | 2: ≥ 38.5<br>1: 38.5 > ≥ 37<br>0: 37 > | 2: ≥ 15,000<br>1: 15,000 > ≥ 10,000<br>0: 10,000 > | 2: ≥7.0<br>1: 7.0 > ≥ 0.3<br>0: 0.3 > | 2: < 3.0<br>1: 3.8 > ≥ 3.0<br>0: ≥ 3.8 |
| Systemic score (0 – 2) | ☐ | ☐ | ☐ | ☐ |
| Total Systemic score (0 – 8) | ☐ | ☐ | ☐ | ☐ |

| JDA severity index in GPP: (Total Skin score ☐ + Total Systemic score ☐) |
|---|

## Appendix L. PGA Scale for Generalized Pustular Psoriasis

The Physician's Global Assessment of Generalized Pustular Psoriasis (PGA-GPP) is a 6-point scale used to measure the severity of skin disease at the time of the qualified investigator's evaluation of the subject. The degree of overall severity will be evaluated using the following categories: erythema, pustulation, and edema.

Scoring Instructions:

If a subject has signs of erythema, pustulation, or edema intermediate between two grades, then the subject's erythema, postulation, or edema grade should be assigned the higher of the two grades. For example, if a subject's erythema is considered to be worse than 'mild' but less than 'moderate,' the subject's erythema grade should be considered 'moderate.'

The subject's score is an arithmetic average (mean) of the grades for erythema, pustulation, and edema, rounded to the nearest whole integer. For example, if a subject's erythema is moderate (3), **pustulation** is mild (2), and edema is moderate (3), the average grade is 2.67, which is rounded to the nearest whole integer of 3, giving the subject a score of 'moderate.'

| Grade | Erythema | Pustulation | Edema | Score |
|---|---|---|---|---|
| 0 | No evidence of erythema | No evidence of postulation | No evidence of edema | Cleared, except for residual discoloration |
| 1 | Faint erythema | Scattered isolated pustules | Minimal edema | Minimal |
| 2 | Light red coloration | A cluster of non-confluent pustules involving 1 skin location | Mild edema | Mild |
| 3 | Moderate red coloration | Clusters of non-confluent pustules involving more than 1 skin location | Moderate edema | Moderate |
| 4 | Bright-red coloration | A confluent 'lake of pus' in 1 skin location | Marked edema | Severe |
| 5 | Dusky to deep-red coloration | Confluent 'lakes of pus' in more than 1 skin location | Severe edema | Very severe |

'Treatment Success' is defined by at least 2 grade improvement relative to baseline:

- Very severe → Moderate or better
- Severe → Mild or better
- Moderate → Minimal or better
- Mild → Cleared

## Appendix M. Psoriasis Area and Severity Index (PASI)

**Assessor Requirements**

- The assessor must be a dermatologist or experienced physician.
- The same assessor must determine all PASIs for any individual subject throughout the trial. A backup assessor is only allowed in case of emergency or special situation when the designated assessor is unable to perform the evaluation. The backup assessor must be a dermatologist or an experienced physician and have attended the PASI training session of the investigator meeting or have been trained by a physician who attended the investigator meeting.

**PASI Scoring**

Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The below table outlines the characteristics seen with each category:

| | Erythema[a] | Desquamation | Induration |
|---|---|---|---|
| **0 = none** | No redness | No scaling | No elevation over normal skin |
| **1 = slight** | Faint redness | Fine scale partially covering lesions | Slight but definite elevation, typically edges indistinct or sloped |
| **2 = moderate** | Red coloration | Fine to coarse scale covering most of all of the lesions | Moderate elevation with rough or sloped edges |
| **3 = marked** | Very or bright red coloration | Coarse, non-tenacious scale predominates covering most or all of the lesions | Marked elevation typically with hard or sharp edges |
| **4 = very marked** | Extreme red coloration; dusky to deep red coloration | Coarse, thick, tenacious scale over most or all lesions; rough surface | Very marked elevation typically with hard sharp edges |

a. Do not include residual hyperpigmentation or, hypopigmentation as erythema.

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to < 30%
- 3 = 30% to < 50%
- 4 = 50% to < 70%
- 5 = 70% to < 90%
- 6 = 90% to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10%, 20%, 30%, and 40% of body surface area, respectively, the PASI score is calculated using the formula.

$$PASI = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$$

Where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and *h*, *u*, *t*, and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI ranges from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest degree.

**References for PASI**

1. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
2. Marks R, Barton SP, Shuttleworth D, et al. Assessment of disease progress in psoriasis. Arch Dermatol. 1989;125(2):235-40.

## Appendix N. Work Sheet for PASI score

Evaluation Date: 20 / mon. / day

Subject ID:

**BSA**

| Site | BSA | BSA (%) | BSA per Site (%) | Area Score |
|---|---|---|---|---|
| Head | max.10% | _____ % | ×10 = | $A_h$ _____ |
| Upper extremity | max. 20% | _____ % | × 5 = | $A_u$ _____ |
| Trunk | max.30% | _____ % | × 3.3 = | $A_t$ _____ |
| Lower extremity | max. 40% | _____ % | × 2.5 = | $A_l$ _____ |
| Total | 100% | | | |

Area score: 0 (0), 1 (10% >), 2 (30% > ≥ 10%), 3 (50% > ≥ 30%), 4 (70% > ≥ 50%), 5 (90% > ≥ 70%), 6 (100% ≥ ≥ 90%)

**PASI Extent** **0** (no symptom), **1** (mild), **2** (moderate), **3** (severe), **4** (very severe)

| | Items | Head (H) | Upper Extremity (U) | Trunk (T) | Lower Extremity (L) |
|---|---|---|---|---|---|
| 1. | Extent of Erythema (E) | $E_h$ _____ | $E_u$ _____ | $E_t$ _____ | $E_l$ _____ |
| 2. | Extent of Induration (I) | $I_h$ _____ | $I_u$ _____ | $I_t$ _____ | $I_l$ _____ |
| 3. | Extent of Desquamation (D) | $D_h$ _____ | $D_u$ _____ | $D_t$ _____ | $D_l$ _____ |
| 4. | Sum (1 + 2 + 3) | | | | |
| 5. | Area score (A) | $A_h$ _____ | $A_u$ _____ | $A_t$ _____ | A _____ |
| 6. | Score per site (4 × 5) | | | | |
| 7. | Portion of BSA | × 0.10 | × 0.20 | × 0.30 | × 0.40 |
| 8. | PASI score per site (6 × 7) | | | | |
| 9. | | | PASI score (sum of 8) | | |

## Appendix O. Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life **OVER THE LAST WEEK**. Please tick √ one box for each question.

| Question | Response | |
|---|---|---|
| 1. Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | |
| 2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | |
| 3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 4. Over the last week, how much has your skin influenced the **clothes** you wear? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 5. Over the last week, how much has your skin affected any **social** or **leisure** activities? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 6. Over the last week, how much has your skin made it difficult for you to do any **sport**? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |

| Question | | Response | | | |
|---|---|---|---|---|---|
| 7. | Over the last week, has your skin prevented you from working or studying?<br>If "no," over the last week how much has your skin been a problem at **work** or **studying**? | Very much<br>A lot<br>A little<br>Not at all | ☐<br>☐<br>☐<br>☐ | Not relevant | ☐ |
| 8. | Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**? | Very much<br>A lot<br>A little<br>Not at all | ☐<br>☐<br>☐<br>☐ | Not relevant | ☐ |
| 9. | Over the last week, how much has your skin caused any sexual difficulties? | Very much<br>A lot<br>A little<br>Not at all | ☐<br>☐<br>☐<br>☐ | Not relevant | ☐ |
| 10. | Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time? | Very much<br>A lot<br>A little<br>Not at all | ☐<br>☐<br>☐<br>☐ | Not relevant | ☐ |

Please check you have answered EVERY question. Thank you.

**Appendix P. SF-36**

Please see SF-36, version 2.0.

## Your Health and Well-Being

**This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!***

**For each of the following questions, please mark an ☒ in the box that best describes your answer.**

**1. In general, would you say your health is:**

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**2. <u>Compared to one year ago</u>, how would you rate your health in general now?**

| Much better now than one year ago | Somewhat better now than one year ago | About the same as one year ago | Somewhat worse now than one year ago | Much worse now than one year ago |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports | ☐1 | ☐2 | ☐3 |
| b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐1 | ☐2 | ☐3 |
| c. Lifting or carrying groceries | ☐1 | ☐2 | ☐3 |
| d. Climbing several flights of stairs | ☐1 | ☐2 | ☐3 |
| e. Climbing one flight of stairs | ☐1 | ☐2 | ☐3 |
| f. Bending, kneeling, or stooping | ☐1 | ☐2 | ☐3 |
| g. Walking more than a mile | ☐1 | ☐2 | ☐3 |
| h. Walking several hundred yards | ☐1 | ☐2 | ☐3 |
| i. Walking one hundred yards | ☐1 | ☐2 | ☐3 |
| j. Bathing or dressing yourself | ☐1 | ☐2 | ☐3 |

**4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Cut down on the <u>amount of time you</u> spent on work or other activities | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| b. <u>Accomplished less</u> than you would like | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| c. Were limited in the <u>kind</u> of work or other activities | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort) | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Cut down on the amount of time you spent on work or other activities | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| b. Accomplished less than you would like | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| c. Did work or other activities less carefully than usual | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

| Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**7. How much bodily pain have you had during the past 4 weeks?**

| None | Very mild | Mild | Moderate | Severe | Very Severe |
|---|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |

**8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

| Not at all | Slightly | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>:**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Did you feel full of life? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| b. Have you been very nervous? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| c. Have you felt so down in the dumps that nothing could cheer you up? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| d. Have you felt calm and peaceful? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| e. Did you have a lot of energy? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| f. Have you felt downhearted and depressed? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| g. Did you feel worn out? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| h. Have you been happy? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| i. Did you feel tired? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

**11. How TRUE or FALSE is each of the following statements for you?**

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|---|---|---|---|---|---|
| a. I seem to get sick a little easier than other people | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| b. I am as healthy as anybody I know | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| c. I expect my health to get worse | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| d. My health is excellent | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

***THANK YOU FOR COMPLETING THESE QUESTIONS***

## Appendix Q. Guidelines to Evaluate Loss of Response and Intolerance to Infliximab

To enroll in this study, subjects who have previously been exposed to infliximab must meet one of the two conditions defined below.

**Loss of Response**

A subject to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of symptoms after a full and adequate course of infliximab based on the investigator's assessment.

**Intolerance to Infliximab**

A subject is defined as intolerant when, in the opinion of the investigator, therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication.

## Appendix R. 70-Day Follow-Up Phone Call – Sample

Site Name/Number: _____

Subject Number: _____

**Please contact subjects who discontinue adalimumab 70 days following study drug discontinuation.**

Date of Call: _____

- ☐ Lost to Follow-up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt.)
- ☐ No Events Reported
- ☐ N/A subject started adalimumab therapy after the end of study participation

**List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.)**

_____

_____

_____

_____

_____

**If events are listed above, your monitor will review and retrieve the appropriate eCRF pages during their next visit.**

Please fax all completed forms to:

[Name] at XXX-XXX-XXXX

# Document Approval

Study M14193 - A Multicenter, Open-Label Study of Adalimumab in Japanese Subjects with Generalized Pustular Psoriasis

**Version:** 1.0 **Date:** 09-Jun-2015 05:58:49 PM **Company ID:** 06092015-00F9F680DADA24-00001-en

| Signed by: | Date: | Meaning Of Signature: |
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| [redacted] | | Approver |
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