2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		

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

Coordinating Investigator (Representative of Primary Investigator): [redacted]

Study Sites: 7 sites in Japan

Publications: None

Studied Period (Years): First Subject First Visit: 28 September 2015 Last Subject Last Visit: 20 July 2017 (last 70-day follow-up call)	**Phase of Development:** 3

Objective:

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

Methodology:

Study M14-193 is a Phase 3, multicenter, open-label, single-arm study of adalimumab in Japanese patients with GPP who had a 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.

All subjects received adalimumab in this open-label study. The study included a 30-day Screening Period, a 52-week Treatment Period, and a 70-day Follow-Up Period. A subject's participation in the study was up to 66 weeks.

Number of Subjects (Planned and Analyzed): 10 planned, 10 analyzed

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were ≥ 15 and ≤ 75 years of age with a diagnosis of GPP for at least 60 days prior to Screening, determined by the investigator through subject interview and review of medical history during the Screening period. Subjects were to have had an inadequate response to, demonstrated intolerance to, or had a contraindication to the currently approved treatment for their GPP. Subjects were to have a total skin score of at least 3 and erythema with pustules (skin score of at least 1) in the JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan.

Diagnosis and Main Criteria for Inclusion (Continued):

Ineligible subjects had erythrodermic psoriasis, guttate psoriasis, or subcorneal pustular dermatosis at Screening, drug-induced GPP, or an active skin disease that may have interfered with evaluation of GPP. Subjects who could not taper off of cyclosporine or oral corticosteroid or who could not avoid other anti-tumor necrosis factor-α agents, psoralen plus ultraviolet A or narrow-band ultraviolet B phototherapy, or "Strongest" topical corticosteroid were ineligible. Subjects with a total score of 14 or more in JDA severity index of GPP in GPP Medical Care Guideline 2014 in Japan were also ineligible.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab 40 mg/0.8 mL subcutaneous injection (lot number 15-000609)

Duration of Treatment: 52 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

None

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects achieving clinical response (remission and improvement) at Week 16.

Secondary efficacy variables were the proportion of subjects achieving clinical response and remission over time, change from Baseline in total GPP score (skin and systemic/laboratory test together) and in total skin score and total systemic/laboratory test score separately over time, change from Baseline in JDA severity index of GPP over time, change from Baseline in score of erythema area, erythema area with pustule, and edema area and body surface area over time, change from Baseline in body temperature, change from Baseline in white blood cells, change from Baseline in high sensitivity C-reactive protein (hs-CRP), change from Baseline in serum albumin, proportion of subjects achieving "Mild" in JDA severity index of GPP for patients with "Moderate" or "Severe" at Baseline over time, proportion of subjects achieving treatment success in Physician's Global Assessment (PGA) (reduction of 2 grades) over time, change from Baseline in PGA grade over time, proportion of subjects achieving PGA 0/1, proportion of subjects achieving Psoriasis Area and Severity Index (PASI) 90/75/50, change in PASI from Baseline over time, proportion of subjects achieving Dermatology Life Quality Index (DLQI) = 0 over time, change from Baseline in DLQI score over time, change from Baseline in short form 36 (SF-36) score over time, and proportion of subjects taking systemic and topical co-medication for GPP.

Pharmacokinetic:

Blood samples for adalimumab and anti-adalimumab antibody (AAA) serum concentrations were obtained throughout the study.

Safety:

Adverse events (AEs), laboratory data, physical examinations, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

Descriptive statistics were provided for effectiveness endpoints. Discrete variables were summarized by counts and percentages and continuous variables were summarized by visit with descriptive statistics. The subjects who had missing data for any reason (such as early terminated subjects) were included in the analysis using nonresponder imputation for discrete variables or last observation carried forward (LOCF) for continuous variables.

Pharmacokinetic:

Adalimumab trough serum concentrations were reported at each time point using descriptive statistics. The relationship between adalimumab concentrations and clinical response was determined, as appropriate. AAA was evaluated for each subject and rates of positive AAA were calculated. As appropriate, the effect of AAA on adalimumab PK, efficacy variable(s), and treatment-emergent AEs may have been evaluated. The PK results and conclusions are presented in a separate report.

Safety:

An overview of treatment-emergent AEs, including AEs of special interest, AEs leading to death, and AEs leading to premature discontinuation; AEs by Medical Dictionary for Regulatory Activities preferred term and system organ class; AEs by maximum relationship to study drug; and AEs by maximum severity were summarized by number and percentage. Other safety variables, such as laboratory data, were described by descriptive statistics. In addition, shift tables and listings were provided for abnormal values, whereby the normal range of the analyzing laboratory was used.

Summary/Conclusions

Efficacy Results:

Among the 10 subjects treated with adalimumab in this study, including 5 subjects whose adalimumab dose was escalated to 80 mg every other week (eow), 7 subjects (70.0%, 95% CI: 34.8, 93.3) achieved clinical response at Week 16. Among the 5 subjects who had their adalimumab dose escalated, 4 subjects achieved clinical response at Week 16; the remaining subject who dose escalated discontinued from the study before Week 16. Two of the subjects who responded had previously been treated with infliximab.

Similarly positive results were observed in all secondary efficacy endpoints:

- A clinical response was achieved by 70.0% of subjects at Week 16 and by 50.0% of subjects at Week 52.
- Mean change from Baseline in total GPP score, which comprises both skin score and systemic/laboratory test score, was –4.6 at Week 16 and –6.0 at Week 52. Improvements in skin symptoms (erythema area, erythema area with pustule, and edema area) and systemic/laboratory tests (body temperature, white blood cells, hs-CRP, and serum albumin) continued through Week 52.
- The majority of subjects (8 of 8 subjects at Week 16, 7 of 8 subjects at Week 24, and 5 of 5 subjects at Week 52) reported improvement in PGA from Baseline.
- At Week 16, 5 of 8 subjects (62.5%) achieved treatment success in PGA-GPP and at Week 52, 3 of 5 subjects (60%) achieved treatment success in PGA-GPP.
- At Week 16, 5 subjects achieved a PASI 50 response, 4 subjects achieved a PASI 75 response, and no subjects achieved a PASI 90 response. At Week 52, 4 subjects achieved a PASI 50 response, 3 subjects achieved a PASI 75 response, and 3 subjects achieved a PASI 90 response.
- Subjects had a general improvement in their quality of life, as measured by the mean change from Baseline in DLQI and SF-36 from Baseline until Week 52.
- At Week 16, the JDA severity index of GPP improved from Baseline in 6 of 8 subjects. At Week 52, the JDA severity index of GPP improved from Baseline in 4 of 5 subjects.
- Six of 7 subjects taking systemic co-medication for GPP were able to reduce or eliminate their dosage (dose or dose frequency).

Summary/Conclusions (Continued)

Pharmacokinetic Results:

The PK results and conclusions are presented in a separate report.

Safety Results:

Nine subjects (90%) reported at least 1 AE. The most frequently reported AEs (occurring in > 1 subject) were nasopharyngitis, pruritus, and hypo-albuminaemia. The majority of AEs were nonserious, mild or moderate in severity, and not considered by the investigator to have a reasonable possibility of being related to adalimumab.

No deaths were reported during the study. Three subjects reported 6 serious AEs and 2 subjects reported an AE that led to discontinuation of adalimumab. The most frequently reported AEs of special interest were infections (reported in 7 subjects), 2 of which were serious. The other AEs of special interest reported in the study were generally consistent with the known safety profile of adalimumab.

Two subjects had potentially clinically significant liver function laboratory values during the study that returned to the normal range by the last visit. Shifts to high or low were generally infrequent. Changes in vital signs and urinalysis were clinically unremarkable.

Conclusions:

Open-label adalimumab for 52 weeks was effective in treating Japanese subjects with GPP, even in those who had previously not responded to infliximab treatment. In this study, the primary endpoint (proportion of subjects achieving clinical response) was met. In addition, a number of secondary efficacy endpoints support the effectiveness of adalimumab in these subjects. Further, dose escalation of adalimumab to 80 mg eow induced clinical response in a number of subjects who did not respond to a lower dose. The safety profile of adalimumab treatment in Japanese subjects with GPP is consistent with the experience in other adalimumab clinical trials in subjects with plaque psoriasis and no new safety signals were observed.