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 Phase 3 Multicenter, Open-Label, Single Arm Study of the Efficacy and Safety of Adalimumab in Active Ulcer(s) of Pyoderma Gangrenosum in Subjects in Japan		
Investigator: [redacted], MD, PhD		
Study Site(s): 15 sites enrolled subjects in Japan		
Publications: None.		
Studied Period (Years): First Subject First Visit: 27 October 2017 Last Subject Last Visit: 21 April 2020 (Last 70-day follow-up phone call)	**Phase of Development:** 3	
Objective(s): The primary objective of this study was to evaluate the efficacy, safety, and pharmacokinetics (PK) of 26 weeks of adalimumab in subjects in Japan with active ulcer(s) due to pyoderma gangrenosum (PG). Additional secondary objectives were the efficacy, safety, and PK in the subset of subjects who did not achieve healing at Week 26 and received extended adalimumab treatment until Week 52.		
Methodology: Study M16-119 consisted of a 26-week Treatment Period and an additional 26-week Extension Period for those subjects who achieved a partial response (Physician's Global Assessment [PGA] 1, 2, or 3) at Week 26. The aim of this study was to investigate the efficacy, safety, and PK of adalimumab in subjects in Japan with active ulcer(s) due to PG. Approximately 20 subjects with active PG who met all of the inclusion criteria, and none of the exclusion criteria, were planned to be enrolled. This clinical study report (CSR) is the final report that includes data through the last subject's last 70-day follow-up phone call after 52 weeks of treatment. An interim analysis was conducted when the last subject completed the Week 26 visit; the results of the interim analysis were previously reported (R&D/19/0505).		

Number of Subjects (Planned and Analyzed): Approximately 20 subjects planned, 22 subjects enrolled and analyzed.

The Full Analysis Set (FAS) population included all subjects received at least 1 dose of study drug and had at least 1 post-treatment efficacy assessment. The FAS was the primary population for the efficacy analysis. The FAS Population in the Treatment Period (FAS_T) was defined as all subjects who received at least 1 dose of study drug and had at least 1 post treatment efficacy assessment during the Treatment Period. The FAS Population in the Extension Period (FAS_E) was defined as all who received at least 1 dose of study drug and had at least 1 post treatment efficacy assessment during the Extension Period. The Safety Analysis Set (SAS) Population was defined as all subjects who received at least 1 dose of study drug in the study.

Diagnosis and Main Criteria for Inclusion: Key eligibility criteria for Study M16-119 included: male or female subjects ≥ 18 years at the Baseline visit; a diagnosis of ulcerative (classic) PG (including peristomal) made by the investigator; and at least 1 active, measurable ulcer due to classic PG. A subject had to have demonstrated an inadequate response to topical PG therapy or, in the opinion of the investigator, he/she was not a suitable candidate for topical PG treatment. Subjects who were diagnosed as PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) syndrome carrying the identified genetic mutation were eligible to participate in the study.

Key exclusion criteria for Study M16-119 included: subjects with pustular, bullous/atypical, or vegetative variants of PG; subjects with clinical evidence of ulceration that was non-PG related, vasculitis, thrombosis-prone conditions, or monoclonal gammopathy; a histopathological finding that was consistent with a diagnosis other than PG (biopsies were used to exclude alternative etiologies rather than to confirm the diagnosis of PG); receipt of an oral corticosteroid with a prednisolone-equivalent dose of more than 10 mg/day at the Week –2 visit; and prior exposure to adalimumab or previous participation in an adalimumab clinical study.

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

Test Product: Adalimumab 40 mg/0.4 mL solution

Doses: All subjects received open-label (OL) adalimumab 40 mg: 4 injections at Week 0 (160 mg), 2 injections at Week 2 (80 mg), and 1 injection weekly from Week 4 (40 mg) until the study end.

Mode of Administration: Subcutaneous

Lot Numbers: 15-006502 and 18-001079

Duration of Treatment: 26 Weeks (Treatment Period), 52 Weeks (with Extension Period)

Criteria for Evaluation

Efficacy:

The primary analysis was to describe the proportion of subjects achieving PGAR 100 (complete closure for the target PG ulcer) confirmed by digital planimetry at Week 26.

Secondary efficacy endpoints (Treatment Period) regarding the target PG ulcer included the following:

- Proportion of subjects who achieved PGAR 100 at any time point through 26 weeks.
- Proportion of subjects with an IIA Score of 0 for both erythema and border elevation at Week 6 and the proportion at Week 26.
- Mean time to healing (defined as PGAR 100) through Week 26.
- Mean time to relapse (PGAR < 100) of the target PG ulcer that had achieved PGAR 100 prior to Week 26.

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Proportion of subjects who experience relapse (PGAR < 100) of the target PG ulcer
- Percentage change in target PG ulcer area (using Investigator's measurements) at Week 6 and the percentage at Week 26.
- Percentage change in target PG ulcer area (using digital planimetry) at Week 6 and the percentage at Week 26.
- Proportion of subjects achieving PGAR 100 at Week 6.
- Velocities of healing between Week 0 and 6 and the velocity of healing between Week 6 and 26 (velocity of healing is the change in area of the target PG ulcer [in cm^2] divided by the interval [in days] between Baseline and the date of observation, recorded in cm^2/day).

Secondary efficacy endpoints (Treatment Period) utilized to assess the global improvement of a subject included the following (all PG ulcers including the target PG ulcer were to be assessed):

- Proportion of subjects achieving PGA 0 or 1 at Week 6 and the proportion at Week 26.
- Proportion of subjects achieving PGA 0 at Week 6 and proportion at Week 26.
- Change from Baseline in Pain as measured by Numerical Rating Scale (NRS) at Week 6 and change from Baseline at Week 26.
- Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 6 and change from Baseline at Week 26.
- Mean time to occurrence of new PG ulcers through Week 26.
- Change from Baseline in total number of active ulcers (ulcers with a score of 1 or greater in the erythema and/or border elevation categories of the IIA) at Week 26.
- Changes from Baseline in total ulcer area (using Investigator's measurements) at Week 6 and change from baseline at Week 26.
- Changes from Baseline in the proportion of subjects taking analgesics at Week 6 and change from baseline at Week 26.

Extension Period (additional 26-weeks following the Treatment Period) secondary efficacy endpoints included the following:

- Proportion of subjects who achieved PGAR 100 of target PG ulcer at Week 52.
- Mean time to healing of target PG ulcer (defined as PGAR 100) through Week 52.
- Proportion of subjects achieving PGA 0 by visit through Week 52.
- Mean time to occurrence of new PG ulcers through Week 52

Pharmacokinetics:

Provided in separate PK reports.

Safety:

The following safety evaluations were performed during the study: incidence of adverse events (AEs), changes in physical examinations, clinical laboratory tests, and vital signs.

Statistical Methods

Efficacy:

The primary analysis was to describe the proportion of subjects achieving PGAR 100 at Week 26. The number and percentage of subjects achieving PGAR 100 was calculated, as well as the exact 95% confidence intervals (CIs) of the percentages. For the proportion of subjects achieving PGAR 100 at Week 26, the hypothesis testing was carried out using one-sample Chi-square test at threshold level 20% and two-sided significance level 0.05. The primary analysis was carried out in the FAS Population. Non- responder imputation was used as the primary approach for missing values.

Pharmacokinetic:

Provided in separate PK reports.

Safety:

All safety analyses were performed on the safety analysis set. Missing safety data were not imputed.

Summary/Conclusions

Efficacy Results:

Twelve of the 22 enrolled subjects (54.5%) achieved PGAR 100 for the target ulcer at Week 26 (primary efficacy endpoint, Treatment Period) by digital planimetry (P-value < 0.001). In the subgroup analysis of baseline systemic corticosteroid use, 11/16 subjects (68.8%) taking baseline systemic corticosteroids achieved PGAR 100 for the target ulcer at Week 26. However, the number of subjects in the subgroup is too small to be conclusive.

Overall, results for the secondary endpoint analyses were consistent with the primary analysis. During the Treatment Period, the proportion of subjects achieving PGA 0 or 1 showed improvement and steadily increased over time reaching 54.5% at Week 26. A total of 8 subjects (36.4%) achieved PGA 0 by Week 26; 7 subjects (31.8%) were considered completed per protocol, and 1 subject discontinued. The mean change from baseline in NRS pain scale improved over time, and the mean change from Baseline in DLQI continued to improve beyond the level of improvement seen at Week 6.

Nine subjects who achieved a partial response (PGA 1, 2, or 3) at Week 26 of the Treatment Period continued into the Extension Period. Of these, 4 (44.4%) subjects had achieved a PGAR 100 for the target PG ulcer at Week 26; 6 (66.7%) subjects achieved a PGAR 100 for the target PG ulcer at each visit from Week 34 to Week 52. The proportion of subjects who achieved PGA 0 increased from Week 34 (44.4%) through Week 52 (66.7%) during this period. No subject discontinued during the extension.

Pharmacokinetic Results:

PK and immunogenicity (AAA) results and conclusions for the study are presented in separate PK reports.

Summary/Conclusions (Continued)

Safety Results:

The safety profile of adalimumab in subjects in Japan who had active ulcer(s) due to PG was consistent with the known safety profile of adalimumab, and no new safety risk or unexpected trend was identified over the approved indications.

The majority of subjects (81.8%) who received at least 1 dose of study drug experienced at least 1 TEAE, and the proportions of subjects who experienced either a treatment emergent serious AE (SAE) (18.2%) or a TEAE leading to study drug discontinuation (18.2%) were low. The most frequently reported TEAEs by PT were nasopharyngitis (4 subjects) and anaemia, cushingoid, insomnia, eczema, and PG (3 subjects each). Most TEAEs were mild or moderate. Nine (40.9%) subjects experienced TEAEs assessed by the investigator as having a reasonable possibility of being related to study drug. One subject died during Screening due to acute ascending aortic dissection; there were no deaths in subjects who received adalimumab.

There were no notable mean changes from Baseline in laboratory parameter values (hematology, clinical chemistry, and urinalysis). Shifts in hematology, clinical chemistry, and urinalysis values from normal or high at Baseline to low at the final value, or normal or low at Baseline to high at the final value were infrequent and not considered clinically meaningful. No subjects experienced an elevated laboratory value that resulted in discontinuation of study drug. Few subjects had potentially clinically significant (Grade ≥ 3) hematology or clinical chemistry values. No subject met the criteria for a Hy's law case.

There were no notable mean changes from Baseline in vital signs values. No pregnancies or product complaints were reported during the study.

Conclusions:

During the 26-week Treatment Period of this study, and through the 26-week Extension Period of the study for Week 26 partial responders, adalimumab demonstrated efficacy in Japanese subjects with active PG ulcers.

Safety results demonstrated that adalimumab therapy in subjects with active PG ulcers was generally safe and well-tolerated over 52 weeks. The safety profile of adalimumab in subjects in Japan who had an active ulcer(s) due to PG was consistent with the known safety profile of adalimumab, and no new safety risk or unexpected trend was identified over the approved indications.

Overall, these findings support the long-term safety, efficacy, and tolerability of adalimumab for the treatment of active PG ulcers in Japan.