

## 2.0 Synopsis

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| <b>AbbVie Inc.</b>  | <b>Individual Study Table Referring to Part of Dossier:</b><br><br><b>Volume:</b><br><br><b>Page:</b> | <b>(For National Authority Use Only)</b> |
| <b>Name of Study Drug:</b><br>Adalimumab  |   |  |
| <b>Name of Active Ingredient:</b><br>Adalimumab   |   |  |
| <b>Title of Study:</b> A Phase 3 Multicenter, Open-Label, Single Arm Study of the Safety and Efficacy of Adalimumab in Japanese Subjects with Moderate to Severe Hidradenitis Suppurativa   |   |  |
| <b>Investigator:</b> ██████████   |   |  |
| <b>Study Sites:</b> 8 sites in Japan  |   |  |
| <b>Publications:</b> None   |   |  |
| <b>Studied Period (Years):</b><br>First Subject First Visit: 06 September 2016<br>Last Subject Last Visit: 03 April 2019  | <b>Phase of Development:</b> 3  |  |
| <b>Objective:</b> The primary objective of this study is to evaluate the safety and efficacy of adalimumab in Japanese subjects with moderate to severe hidradenitis suppurativa (HS).  |   |  |
| <p> <b>Methodology:</b> This is an open-label, single arm Phase 3 study designed to enroll approximately 15 Japanese subjects in Japan to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.         </p> <p>           The study included a 35-day screening period, an open-label treatment period, and a 70-day follow-up phone call following the last dose of study drug. All subjects were to receive open-label subcutaneous injection of adalimumab 40 mg every week (ew) starting at Week 4, after 160 mg at Week 0 (Baseline) and 80 mg at Week 2, for at least 99 weeks until the time of approval for HS indication, or withdrawal of the marketing application in Japan. A subject's participation in this study was anticipated to be up to 38 months.         </p> <p>           At any time after Week 52, all remaining subjects were given a choice to switch to the 80 mg every other week (eow) dose or continue 40 mg ew. Subjects who consented to receive the 80 mg eow dose received open-label subcutaneous injection of adalimumab 80 mg eow at Week 0x (80 mg eow period) until the end of this study. These subjects had visits at Week 0x, Week 4x, and Week 12x or at the Premature Discontinuation visit. After Week 12x, study visits occurred every 12 weeks until the study end. Subjects who switched to the 80 mg eow dose were allowed to return to 40 mg ew, when the investigator believed it was in the best interest of the subject (e.g., worsening of medication adherence) and if approved by the AbbVie Therapeutic Area Medical Doctor.         </p> |   |  |
| <b>Number of Subjects (Planned and Analyzed):</b> 15 planned; 15 analyzed   |   |  |
| <b>Diagnosis and Main Criteria for Inclusion:</b> Adult male and female subjects who met all the inclusion criteria and who did not meet any of the exclusion criteria were eligible for enrollment into the study. Subjects enrolled in this study are at least 18 years old with a diagnosis of HS. More information about the study design and details of the eligibility criteria can be found in the protocol.   |   |  |

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| <p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b><br/><b>Investigational Product:</b> Adalimumab<br/><b>Doses:</b> 160 mg Week 0 and 80 mg Week 2 followed by 40 mg ew starting at Week 4 followed by 40 mg ew or 80 mg eow after Week 52.<br/><b>Mode of Administration:</b> Subcutaneously (SC)<br/><b>Bulk Lot Number:</b> 15-006502 and 18-001079 (40 mg ew); 18-001078 (80 mg eow)</p>  |
| <p><b>Duration of Treatment:</b> Until approval of HS indication in Japan (at least 99 weeks).</p>   |
| <p><b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b><br/>Not applicable</p>   |
| <p><b>Criteria for Evaluation</b><br/><b>Efficacy:</b> The primary efficacy endpoint was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR was defined as at least a 50% reduction in the total abscess and inflammatory nodule count (abscess and inflammatory nodule [AN] count) with no increase in abscess count and no increase in draining fistula count relative to Baseline.<br/>Study visits were to occur at Weeks –4 and –2 (in the Screening period), Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 or at the Premature Discontinuation visit. After Week 52, study visits were to occur every 12 weeks until the study end. Subjects who consented to receive the 80 mg eow dose were to start at Week 0x (80 mg eow period), Week 4x, and Week 12x or at the Premature Discontinuation visit. After Week 12x, study visits were to occur every 12 weeks until the study end.<br/>Secondary endpoints were:</p> <ol style="list-style-type: none"><li>1. Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12;</li><li>2. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain (Numeric Rating Scale [NRS]30) – at worst (the worst skin pain experienced by the patient due to HS over the last 24 hours) at Week 2; among subjects with Baseline NRS <math>\geq</math> 3;</li><li>3. Change in modified Sartorius scale from Baseline to Week 12.</li></ol> <p><b>Pharmacokinetic:</b> The pharmacokinetics and immunogenicity of adalimumab following SC injection will be assessed in the study.<br/><b>Safety:</b> Adverse events (AE), laboratory data and vital signs will be assessed throughout the study.</p> |
| <p><b>Statistical Methods</b><br/><b>Efficacy:</b><br/>The planned total sample size of 15 for this study provided at least 80.1% power to detect the difference of 35% in the primary endpoint and using one sample Chi-square test at 1 sided 2.5% significant level assuming the threshold response rate at Week 12 of 25% (response rate with no medication) and the expected clinical response rate of 60%.<br/>The full analysis set (FAS) included 15 subjects from sites that complied with GCP and received at least 1 dose of study drug and had at least 1 post-treatment efficacy assessment. The FAS was used for the efficacy analysis. No subjects were excluded from the efficacy analysis.<br/>The 80 mg eow Set included 6 subjects who received adalimumab 80 mg eow after Week 52 in the study. This population was used to assess the safety and efficacy of adalimumab 80 mg eow.</p>  |

### Statistical Methods (Continued)

The primary efficacy endpoint was examined in the following subgroups: Baseline Hurley Stage (II/III), concomitant use of oral antibiotics (yes/no), age group (< 40, 40 to 64, ≥ 65); sex (male or female), duration of HS (< median, ≥ median), weight (< median, ≥ median); body mass index (< 25, 25 to < 30, 30 to < 40, or ≥ 40); current smoking status (yes/no), Baseline C-reactive protein level (< median, ≥ median); Baseline AN count (≤ 5, 6 to 10, 11+); Baseline AN count (< median, ≥ median).

**Pharmacokinetic:** The pharmacokinetics and immunogenicity of adalimumab following SC injection were assessed and summarized in a separate report (R&D/18/0573).

**Safety:** The following safety endpoints were assessed: frequency, relationship, and severity of AEs; vital sign measurements; and clinical laboratory assessments (hematology, chemistry, and urinalysis). The Safety Analysis Set consisted of 15 subjects who received at least 1 dose of study drug. For safety analysis, all AEs with an onset date and all laboratory and vital signs data collected, from the first dose of adalimumab 40 mg ew through 70 days after the last dose of adalimumab 40 mg ew were included. The only exceptions were data collected after a subject switched to adalimumab 80 mg eow, which was excluded from the Safety Analysis Set and will be summarized in the 80 mg eow Set.

The All Adalimumab Treated Population consisted of 15 subjects who received at least 1 dose of adalimumab in the study. This population was used to assess the safety of adalimumab 40 mg ew with and without dose 80 mg eow. The All Adalimumab Treated Population was used for safety analysis only.

### Summary/Conclusions

**Efficacy Results:** The primary efficacy variable in this study was the proportion of subjects achieving HiSCR (defined as at least a 50% reduction in the AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline) at Week 12. The majority of subjects receiving adalimumab 40 mg ew achieved HiSCR at Week 12. Hidradenitis Suppurativa Clinical Response was maintained over time, as evidenced by the majority of subjects sustaining clinical response through the end of the study. The HiSCR response rate was maintained through the end of the study for 4 of 6 subjects who switched to adalimumab 80 mg eow after Week 52. The results from the primary endpoint are supported by improvements in the secondary endpoints of AN count of 0, 1, or 2 at Week 12, NRS30 - at worst at Week 2 among subjects with Baseline NRS - at worst ≥ 3, and modified Sartorius scale from Baseline to Week 12.

There were improved outcomes compared to Baseline in subjects receiving adalimumab 40 mg ew across a number of other clinically relevant endpoints including HiSCR at each visit and over time; these endpoints are AN count 0 or 1, AN50, AN75, and AN100; NRS30 - at worst at each visit and based on a rolling weekly average, NRS30 - on average at each visit and based on a rolling weekly average, mean percent change from Baseline in NRS at worst and on average, mean percent change from Baseline in lesion counts, elimination of inflammatory nodules, non-inflammatory nodules, abscesses, draining fistulas, and non-draining fistulas, erythema score of 1 or 0, and improvement by ≥ 1 Hurley Stage. For subjects who switched to adalimumab 80 mg eow after Week 52, improvements in these efficacy variables were also generally maintained. These outcomes translate to improvements in overall QoL, as measured by improvements in DLQI, TSQM scores for effectiveness and global satisfaction, EQ-5D index and VAS, and HS QoL. These improvements in QoL were also sustained for subjects who switched to adalimumab 80 mg eow after Week 52.

**Pharmacokinetic Results:** Pharmacokinetics and immunogenicity results and conclusion are summarized in a separate report (R&D/18/0573).

**Summary/Conclusions (Continued)**

**Safety Results:** In this open-label study, adalimumab was generally safe and well tolerated, as assessed by frequency of AEs, including serious events, AESI, clinical laboratory values, and vital signs values.

All subjects receiving adalimumab 40 mg ew had at least 1 AE and the majority experienced only 1 AE each. Overall, there were 16 events that were reported in more than 1 subject, with the most frequent ( $\geq 5$  subjects) being influenza and nasopharyngitis. Subjects who switched to adalimumab 80 mg eow experienced 4 TEAEs with no events occurring in more than 1 subject.

No subjects died during the study. A total of 5 subjects experienced at least 1 SAE. Four subjects receiving adalimumab 40 mg ew experienced SAEs of cellulitis (2 events), subcutaneous abscess, deep vein thrombosis, and uterine leiomyoma; the SAEs of cellulitis were considered by the investigator and AbbVie to have a reasonable possibility of being related to study drug. One subject who switched to adalimumab 80 mg eow experienced an SAE of interstitial lung disease considered by the investigator to have a reasonable possibility of being related to study drug.

Adverse Events of Special Interest for treatment-emergent infections were reported in 12 subjects receiving adalimumab 40 mg ew and 2 subjects who switched to adalimumab 80 mg eow. Most of the events were mild to moderate in severity and assessed by the investigator as having no reasonable possibility of relationship to study drug. The AESIs of treatment-emergent serious infection, hematologic disorders, and injection site reactions were reported in  $\leq 15\%$  of subjects receiving adalimumab 40 mg ew.

No safety concerns were identified in the analysis of clinical laboratory and vital signs parameters.

No pregnancies were reported during the study.

No product complaints were identified during the study.

There were no new safety signals or unexpected trends for adalimumab identified as a result of this study. No clinically significant changes in mean laboratory values and urinalysis were observed, and changes in vital signs were not clinically meaningful. The safety profile of adalimumab 40 mg ew treatment observed in this study was expected given the population of moderate to severe HS and was consistent with the experience in other adalimumab clinical trials. The safety profile of subjects who switched to adalimumab 80 mg eow was similar to that of subjects receiving adalimumab 40 mg ew and were consistent with the established adalimumab safety profile.

**Conclusions:** Study M15-573 demonstrated the efficacy of adalimumab 40 mg ew in achieving HiSCR after 12 weeks and maintaining HiSCR for more than 52 weeks in the majority of subjects with moderate to severe HS. This was supported by secondary efficacy endpoints. Similar efficacy was observed following the switch from adalimumab 40 mg ew to adalimumab 80 mg eow dosing. Adalimumab 40 mg ew was generally safe and well tolerated and the safety profile was consistent with previous clinical trials for adalimumab. The safety profile of subjects who switched to adalimumab 80 mg eow was similar to that of subjects receiving adalimumab 40 mg ew. No new safety risks or trends were observed.