Synopsis

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

Title of Study: A Phase 4, Double-Blind, Randomized, Placebo-Controlled Multicenter Study to Assess the Safety and Efficacy of Adalimumab Used in Conjunction with Surgery in Subjects with Moderate to Severe Hidradenitis Suppurativa

Investigator: Prof. Dr. med. [redacted]

Study Site(s)**:** 45 sites in Belgium, Canada, Columbia, Czech Republic/Czechia, Denmark, France, Germany, Greece, Italy, Mexico, The Netherlands, Norway, Poland, Portugal, Romania, The Russian Federation, Spain, Turkey, The United Kingdom, and US

Publications: None

Studied Period (Years):	**Phase of Development:** 4
First Subject First Visit: 18 July 2016 Last Subject Last Visit: 16 October 2019	

Objective (s):

Primary-

Assess the safety and efficacy of adalimumab prior to surgery in subjects with moderate to severe hidradenitis suppurativa (HS) who are surgical candidates, using hidradenitis suppurativa clinical response (HiSCR) as the assessment measurement.

Secondary-

Assess the impact of adalimumab specifically on the planned HS surgical site before surgery, evaluate the safety and efficacy of adalimumab continued during the perioperative period and after surgery, and evaluate Patient Reported Outcomes (PRO) related to health status, HS-related symptoms (e.g., drainage, swollen skin), physical functioning, treatment satisfaction, and work/activity impairment. The pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) injection in this HS surgical population was as also assessed. The objective was to determine if the inflammatory status of the HS surgical subject alters the PK profile both prior to and after surgery.

Methodology:

Study M15-574 was an interventional, randomized, double-blind (DB), placebo-controlled study. The study duration included a 30-day Screening Period, an initial 12-week DB treatment pre-surgery period (Period A), a 2-week perioperative period with continuation of weekly DB study drug administration (Period B), and a subsequent 10-week DB treatment post-operative period.

Screening Period: The duration of the screening period was to be a minimum of 7 days and a maximum of 30 days.

Methodology (Continued)

Period A: A 12-week DB, placebo-controlled treatment period during which subjects were randomized in a 1:1 ratio to receive adalimumab or matching placebo. The randomization was stratified by baseline Hurley Stage (II versus III) and anatomical location of the planned surgical site (i.e., axilla versus inguinal region). The projected size of the surgical excision established by the designated surgeon during the Screening Period (calculated from a tracing of the outer perimeter onto an acetate sheet or equivalent) was recorded.

Period B: A 2-week DB, placebo-controlled treatment period consisting of Weeks 13 and 14 (the perioperative period). The designated surgeon was to measure and record the surface area of the actual surgery. Surgery was to occur during Week 13. The surgery and post-operative management (e.g., hospitalization, surgical wound care) was per local practice.

Period C: A 10-week DB, placebo-controlled post-operative treatment period occurred from Week 15 through Week 24 (post-operative). No study drug was administered at Week 24, the final study visit. Subjects were able to begin commercial product (as prescribed by the subject's physician) after all Week 24 procedures were completed.

Number of Subjects (Planned and Analyzed):

200 subjects planned; 206 analyzed (intent-to-treat [ITT]).

Diagnosis and Main Criteria for Inclusion:

Key eligibility criteria for Study M15-574 included: male and female subjects between the ages of 18 and 65, inclusive; subject must have skin lesions that are diagnostic of HS for at least 1 year (365 days) prior to the Baseline visit; subject must have at least 3 distinct anatomical regions involved with inflammatory (also termed 'active') HS lesions (including: either an axilla or unilateral inguinal region [limited to the inguino-crural fold and adjacent areas] that requires excisional surgery [hereinafter designated the "HS surgical site"], and with at least one of the other affected HS regions [e.g., contralateral inguinal region, buttocks, inframammary region; hereinafter designated the HS nonsurgical sites] rated as Hurley Stage II or III); subject must have a total abscess and inflammatory nodule (AN) count of greater than or equal to 3 at the Baseline visit within the HS non-surgical sites; the HS surgical site must contain at least one active HS lesion; and the HS surgical site must require excisional surgery and is large enough to require healing by secondary intention as assessed by the designated surgeon.

Key exclusion criteria for Study M15-574 included: subject has a draining fistula count of greater than 20 at the Baseline visit; subject requires surgery at any anatomical site other than an unilateral axilla or inguinal region site; subject requires surgical management prior to Week 13, based on the designated surgeon's assessment; or subject requires, based on the designated surgeon's assessment, excisional surgery with primary closure, partial surgical reduction of the excised area with surgical suture, or reconstruction techniques as the method of closure being most beneficial for the subject.

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

Investigational Product:

Adalimumab

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

Doses:

Period A

On Day 1 subjects received 4 injections (4 adalimumab 40 mg subcutaneous [SC] injections totaling 160 mg or 4 injections of matching placebo). At Week 2, subjects received 2 injections (2 adalimumab 40 mg SC injections totaling 80 mg or 2 injections of matching placebo). Starting at Week 4, subjects received 1 injection (adalimumab 40 mg SC or matching placebo) every week.

Period B

Weeks 13 and 14 (the perioperative period) in which subjects continued adalimumab 40 mg SC or matching placebo (as randomized on Day 1) weekly dosing.

Period C

Week 15 through Week 24, during which the subject continued adalimumab 40 mg SC or matching placebo (as randomized on Day 1) weekly dosing through Week 23. No study drug was administered at Week 24, the final study visit.

Mode of Administration: SC

Bulk Lot Numbers:

Adalimumab: 15-005871, 17-004131, 16-005133,17-002006

Placebo for adalimumab: 15-005865, 16-004292, 17-002248

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects achieving HiSCR at Week 12. HiSCR was defined as at least a 50% reduction in the abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline.

Ranked secondary efficacy variables were:

1. Proportion of subjects achieving HiSCR-es (defined as the HiSCR excluding the HS surgical site) at Week 12;
2. Proportion of subjects achieving HiSCR-es at Week 24;
3. Percent change in surface area of the HS surgical site from Baseline to Week 12; and
4. Proportion of subjects at Week 12 that require a less extensive surgery than the surgical plan (determined at Baseline) or no surgery as determined by the designated surgeon.

Pharmacokinetic:

The pharmacokinetic endpoints were analyzed separately and will be provided in a separate final report.

Safety:

The following safety evaluations were performed during the study: monitoring of adverse events (AE), vital signs, physical examinations, laboratory tests, and product complaints.

Statistical Methods

Efficacy:

The efficacy analysis was conducted among the ITT Population (the ITT population was defined as all subjects who were randomized at the Baseline visit).

In order to evaluate the impact of major protocol deviations on the primary efficacy endpoints, additional sensitivity analyses were performed on a Per-Protocol (PP) Population, which excluded subjects with major protocol deviations that potentially affected the primary efficacy endpoints. Subjects who met any of the following criteria were excluded from the PP Population analysis:

- Subject received less than 75% of planned study drug injections in Period A;
- Subject had no HiSCR post-baseline on or before Week 12;
- Subject had baseline AN count < 3;
- Subject had baseline draining fistula count > 20; and
- Subject took prohibit medication that could potentially affect the assessment of the primary endpoint at Week 12.

A total of 21 subjects entered the study while violating inclusion criterion #4 (subject must have a total AN count of ≥ 3 at the Baseline visit within the HS non-surgical sites), therefore, a sensitivity analysis (post-hoc) was performed to exclude subjects with Baseline AN count < 3 in non-surgical sites.

The primary endpoint to assess the efficacy of adalimumab prior to surgery in subjects with moderate to severe HS was the proportion of subjects achieving HiSCR at Week 12. The primary null hypotheses was that there is no difference in proportion of subjects who achieve HiSCR at Week 12, between the adalimumab and placebo treatment groups. The null hypotheses was tested under a two-sided significance level of 0.05.

The following null hypotheses for ranked secondary endpoints below were tested in a hierarchical order using two-sided significance level of 0.05 only if the null hypothesis for the primary endpoint was rejected:

1. Adalimumab is not different from placebo with respect to the proportion of subjects achieving HiSCR-es at Week 12;
2. Adalimumab is not different from placebo with respect to the proportion of subjects achieving HiSCR-es at Week 24;
3. Adalimumab is not different from placebo with respect to the percent change in surface area of the HS surgical site from Baseline to Week 12; and
4. Adalimumab is not different from placebo with respect to the proportion of subjects at Week 12 that require a less extensive surgery than the surgical plan (determined at Baseline) or no surgery as determined by the designated surgeon.

Pharmacokinetic:

The pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) injection in this HS surgical population was assessed. The objective was to determine if the inflammatory status of the HS surgical subject alters the PK profile both prior to and after surgery.

Safety:

Safety summaries used the safety population, which was defined as all subjects who were in the ITT Population and receive at least 1 dose of study drug. The Safety Population in each period was used for safety analysis. Subjects in the Safety Population were analyzed by treatment group as treated.

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. Study M15-574 demonstrated the superior efficacy of adalimumab over placebo in achieving HiSCR after 12 weeks in the majority of subjects with moderate to severe HS. The primary efficacy variable was met with significantly higher HiSCR rates in subjects receiving adalimumab versus subjects receiving placebo (47.6% of subjects and 34.0% of subjects, respectively; *P* value = 0.049) at Week 12 (pre-surgery period) (nonresponder imputation [NRI]). The observed treatment effect was greater in the sensitivity analysis (excluding subjects with Baseline AN count < 3 in non-surgical sites) with 50.0% of subjects receiving adalimumab versus 32.6% of subjects receiving placebo achieved HiSCR at Week 12 (*P* value = 0.015) (NRI). There were no notable differences among stratification factors.

The HiSCR rates across nonsurgical body regions (HiSCR-es) of subjects receiving adalimumab were higher than subjects receiving placebo at Week 12 (first ranked secondary endpoint; 47.6% vs. 35.0% of subjects, respectively; *P* value = 0.067) and at Week 24 (second ranked secondary endpoint; 51.5% and 31.1% of subjects, respectively; *P* value = 0.003) (NRI). The ranked secondary endpoints did not achieve statistical significance according to the pre-defined hierarchical testing procedure. When the sensitivity analysis (excluding subjects with baseline AN count < 3 in non-surgical sites) was applied, HiSCR-es rates were statistically significantly higher for subjects receiving adalimumab than for subjects receiving placebo at Week 12 (50.0% vs. 32.6% of subjects, respectively; *P* value = 0.016) and at Week 24 (53.3% vs. 27.4% of subjects, respectively; *P* value = < 0.001) (NRI).

For the surgery-related secondary endpoints, there was minimal change in surface area of HS surgical site from Baseline to Week 12 of the actual surgery site observed between dosing regimens; and there was minimal difference in the proportion of subjects requiring less extensive or no surgery at Week 12 between dosing regimens.

At all visits, subjects receiving adalimumab had greater improvements from Baseline in Dermatology Life Quality Index (DLQI), EuroQoL™ Questionnaire (EQ-5D), Hidradenitis Suppurativa Patient's Global Assessment of Skin Pain (HS-PGA-SP) worst skin pain, Hidradenitis Suppurativa Impact Assessment (HSIA) overall score, and Hidradenitis Suppurativa Symptom Assessment-7 day recall (HSSA-7d) compared to subjects receiving placebo.

Pharmacokinetic Results:

The PK results and conclusions will be presented in a separate final PK report.

Safety Results:

The safety profile of subjects receiving adalimumab was comparable to the known safety profile of adalimumab; no new safety signals or unexpected trends were identified.

Approximately 70% of subjects in both dosing regimens had 1 or more treatment-emergent adverse event (TEAE). There were 2 deaths in the study; 1 subject experienced a TEAE of ruptured cerebral aneurysm and died 4 days after receiving the last dose of study drug (Day 69) the event was assessed by the investigator and AbbVie as having no reasonable possibility of relationship to study drug; and 1 subject died Post-Treatment Day 503 due to a primary cause of natural death and a secondary cause of hypertrophic cardiomyopathy. Due to the timing of this event (occurred after the 70-day follow-up call) the relatedness of this event was not assessed by the investigator; however, the event was assessed by AbbVie as having no reasonable possibility of relationship to study drug.

Summary/Conclusion (Continued)

The proportions of subjects who experienced at least 1 SAE or a TEAE leading to study drug discontinuation were low and comparable across dosing regimens. The system organ class with the most frequently reported TEAEs in either dosing regimen were infections and infestations (40.8% of subjects receiving adalimumab and 35.9% of subjects receiving placebo) and skin and SC disorders (33.3% of subjects receiving adalimumab and 24.3% of subjects receiving placebo). The most frequently (≥ 5% of subjects) reported TEAEs by preferred term were nasopharyngitis, procedural pain, hidradenitis, headache, diarrhoea, and arthralgia for subjects receiving adalimumab and nasopharyngitis, hidradenitis, headache, procedural pain, and dizziness for subjects receiving placebo. Most TEAEs were nonserious, mild or moderate in severity, and with no reasonable possibility of relationship to study drug, as assessed by the investigator. The proportions of subjects experiencing adverse events of special interest (AESI) were generally low (< 3%); with the exception of infections and injection site reaction. The occurrences of all AESIs were relatively balanced across dosing regimens.

There were no notable mean changes in laboratory parameter values (hematology, clinical chemistry, and urinalysis) from Baseline. 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.

There were no notable mean changes from Baseline in vital signs values.

One pregnancy was reported during the study which resulted in a live birth without congenital anomaly.

No unexpected drug or device related issues were identified during this study.

Conclusions:

Twelve weeks of treatment with adalimumab in Study M15-574 was efficacious for subjects at reducing the number of HS inflammatory lesions across all body regions (significant increase in HiSCR rate at Week 12), prior to surgery. Adalimumab is an effective and safe adjunctive therapy to surgery, reducing overall inflammatory burden in moderate to severe HS subjects scheduled for surgery without any additional risks to the subjects and significantly decreasing subject's worst skin pain, reducing overall HS symptoms and impact, and further improving quality of life.

Date of Report: 21Feb2020