Scandinavian Development Services

Statistical Analysis Plan

Study Code: P15-692

Study title: Post Marketing Observational Study to Assess Quality of Life Changes in Swedish Patients with Moderate or Severe Hidradenitis Suppurativa after 6 Months on Adalimumab Treatment (HOPE study)

Final version 1.0

April 27, 2017

[redacted] _____ _____

Study Statistician Signature Date

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TRIAL FULL TITLE	Post Marketing Observational Study to Assess Quality of Life Changes in Swedish Patients with Moderate or Severe Hidradenitis Suppurativa after 6 Months on Adalimumab Treatment (HOPE study).
BASED ON CLINICAL STUDY PROTOCOL VERSION	Protocol P15-692 incorporating Amendment 1 and Administrative change 1
EUDRACT NUMBER	
SAP VERSION	Final version 1.0
SAP VERSION DATE	April 27, 2017
STUDY STATISTICIAN	[redacted] Scandinavian Development Services
COORDINATING/ PRINCIPAL INVESTIGATORS	
SAP AUTHORS	[redacted] Scandinavian Development Services Danderyd, Sweden

1 Table of contents

1 Introduction

Hidradenitis Suppurativa (HS) also known as acne inversa, is a painful, chronic, skin disease characterized by recurrent inflamed nodules and abscesses, which may rupture to form fistulas and subsequent scarring. The most commonly involved anatomic locations are the axillary and sub-mammary folds, the inguino-crural, the gluteal and perineal areas.

HS has a severely negative effect on patients quality of life.[1,2] It typically presents with painful, deep-seated nodules, which either resolve spontaneously, persist as non-tender nodules, or progress to form abscesses. Abscesses typically rupture and release purulent drainage. Abscesses and nodules may heal with scarring and the formation of fistulas or sinus tracts. Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. The physical and psycho-social morbidity associated with en bloc excision of scarred axillary, inguinal, or groin skin is substantial. Rare complications of HS include fistula formation into urethra, bladder, rectum, or peritoneum, lymphedema of the limbs or scrotal elephantiasis, and squamous cell carcinomas of the skin originating from HS lesions.

HS affects approximately 1 % of the general population. [3,4] Disease onset is typically after puberty. Disease prevalence decreases from 1.5% in those <25 years of age to 0.5% in those older than 55 years of age. It affects women from 2 to 5 times more commonly than men. Several factors may predispose a person to HS, including genetics, cigarette smoking, and obesity.[5]

Compared to other dermatological diseases (e.g. acne psoriasis, atopic eczema and skin tumors) the impact, measured by the Dermatology Life Quality Index (DLQI), is significantly greater. Although this is shown in studies from different parts of the world there is only limited information available on the Quality of Life in Swedish HS patients and there are no national registries capturing this information.

2 Study objectives

2.1 Primary Objectives

The objectives of this observational study is to assess the changes in QoL, skin pain, work productivity/activity and health related problems before and after 6 months treatment with Adalimumab of Swedish patients with moderate to severe HS in real-life and as per routine clinical care.

2.2 Secondary Objectives

None

3 Study details

3.1 Study design

This is a Post Marketing Observational Study (PMOS), an open, non-interventional study. The patients will be treated in accordance with normal routine care and the drug will be prescribed in accordance with the approved labeling (Summary of Product Characteristics), i.e. AbbVie will not be involved in the supply of Adalimumab.

Patients will be included in the study at the time the physician has decided to change their current treatment to Adalimumab for any reason. The decision to prescribe Adalimumab should be clearly separated from and preceding the decision to include the patient in the study. The patients will be assessed during routine visits at the clinic at baseline (inclusion) and after approximately 4 weeks, 12 weeks and 24 weeks. Data will be collected from the patient's medical records, by investigator assessment and by patient questionnaires as described in section 9.1.1 Study Flow Chart and in Section 9.3 Variables.

3.1.1 Study Flow Chart

Patients that have been prescribed Adalimumab as per routine care will asked to participate in this study. In accordance with routine care, a patient will be seen by the patient's physician at baseline (inclusion) and approximately 4, 12 and 24 weeks after the first dose of Adalimumab.

Parameters	Baseline	Week 4	Week 12	Week 24
Informed consent	X			
Demographic/baseline data	X			
Dermatology Life Quality Index (DLQI)	X	X	X	X

EuroQol (EQ-5D)	X	X	X	X
Patient's Global Assessment of Skin Pain (NRS)	X	X	X	X
Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)	X	X	X	X
Hidradenitis Suppurativa Impact Assessment (HSIA)	X	X	X	X
Hidradenitis Suppurativa Clinical Response (HiSCR)	X	X	X	X
Serious Adverse Event		X	X	X
Pregnancy Reporting		X	X	X
Concomitant Medication	X	X	X	X
Surgical Treatment	X	X	X	X
Missed Adalimumab doses		X	X	X

3.2 Number of patients

3.2.1 Sample size calculations

With 50 evaluable patients, the power is 90% based on a change in DLQI of -5.4, and an assumed standard deviation of 11.5 and type I error of 5% (two-sided). The drop-out rate is considered to be low, approximately 5% after 12 weeks, which will have a minimal impact on the power (decreased to 88%).

3.2.2 Interim analysis

An interim analysis will be performed in Q2 of 2017 for administrative reasons. No statistical analyses will be presented and no adjustments regarding this interim analysis are planned for the final analysis.

3.3 Randomization

NA This is a Post Marketing Observational Study

3.4 Database lock

When the database has been declared to be complete and accurate, the database will be locked and declared clean file. Any changes to the database after that time can only be made by joint written agreement between the project manager, the data manager and the statistician.

4 Analysis Sets

4.1 Definition of analysis data sets

The analysis of data will be based on different subsets according to the purpose of analysis, i.e. for effectiveness and safety respectively. The decision regarding validity of data for each of the analysis sets will be made before database lock.

4.2 Baseline analysis set

The Baseline analysis set will include all enrolled patients, with the exception of subjects who had no baseline data collected.

The Baseline analysis set will be used for presenting baseline characteristics.

4.3 Effectiveness analysis sets

4.3.1 Full analysis Set (FAS), (modified Intention-to-treat(ITT)

The FAS will include all enrolled patients, with the exception of subjects who were enrolled and not treated with any dose of adalimumab, or who had no baseline or post baseline data collected for the primary endpoint Dermatology Life Quality Index (DLQI). In case all of a patients post baseline assessments of DLQI are outside visit windows, the patient is excluded from FAS.

The FAS will be used for baseline characteristics and analysis of effectiveness.

4.3.2 Per protocol analysis set (PP)

Criteria for the determination of the PP population will be finalized prior to database lock, and will include the following:

- Study subjects included in FAS
- Study subjects meeting all inclusion criteria and none of the exclusion criteria
- Study subjects with a valid 12 week assessment(according to visit windows) for the primary endpoint Dermatology Life Quality Index
- Study subjects who up until the valid 12 week assessment have less than 4 missed doses of Adalimumab

The PP analysis set will be used as sensitivity analysis for the primary effectiveness endpoint.

4.4 Safety analysis set

The safety analysis set will include all subjects given at least one dose of adalimumab and for whom follow-up safety data are available. Subjects/data will be summarised and analysed according to the total dose dispensed.

The Safety analysis set will be used for analysis of safety endpoints.

5 Endpoints

5.1 Primary endpoint

- Changes in Dermatology Life Quality Index (DLQI) at 12 weeks

  DLQI is the sum of 10 sub items, each ranging from 0 to 3. Minimum and maximium of DLQI is 0 and 30 respectively.

5.2 Secondary endpoints

- Change in DLQI at 4 and 24 weeks
- Change in Patient's Global Assessment of Skin Pain (NRS) at 4, 12 and 24 weeks.

  NRS consists of two Visual Analogue Scale response questions :

  Patient’s response on each question can range from 0 to 10
- Change in items of EuroQol (EQ-5D) at 4, 12 and 24 weeks

  EQ-5D consists of 5 sub-items:

  Mobility
  Self-care
  Usual Activities
  Pain/Discomfort
  Anxiety/Depression

  each classified into levels 1 to 3 where 3 is most severe.
- Change in EuroQol (EQ-5D) VAS score at 4, 12 and 24 weeks

- Change in items of Hidradenitis Suppurativa Impact Assessment (HSIA) at 4, 12 and 24 weeks.

  HSIA consist of 18 sub items of which 16 range from 0 to 10 and 2 items register time at work/school and time away from work/school because of HS.

- Change in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) at 4, 12 and 24 weeks

  The WPAI consists of six questions regarding productivity and impairment:
  (Q1) Currently employed
  (Q2) Hours missed due to specified problem
  (Q3) Hours missed for other reasons
  (Q4) Hours actually worked
  (Q5) Degree problem affected productivity while working
  (Q6) Degree problem affected regular activities

  From above questions, four scores will be calculated:
  Percent work time missed due to problem: [Q2/(Q2+Q4)]*100
  Percent impairment while working due to problems: (Q5/10)*100
  Percent overall work impairment due to problem:
  {Q2/(Q2+Q4) +[(1- (Q2/(Q2+Q4)))*(Q5/10)]}*100
  Percent impairment while doing regular activities: (Q6/10)*100

- Hidradenitis Suppurativa Clinical Response (HiSCR) at 4, 12 and 24 weeks

  HiSCR is a clinical endpoint focusing on assessment of HS inflammatory signs and symptoms that will determine the clinical effectiveness of Adalimumab.
  HiSCR requires:
  - At least a 50% reduction in the total abscess and inflammatory nodule count (AN count) relative to baseline, and
  - No increase in abscess count, and
  - No increase in draining fistula count.

  In first bullet AN count is defined as sum of abcess count and inflammatory nodules count.

5.3 Safety endpoints

- Non-serious Adverse events

As the safety profile of Adalimumab is stable and well established, non-serious events will not be actively solicited as these events are not likely to further contribute

to the understanding of the safety profile of the product. Any non-serious reports will be collected as spontaneous reports if notified to AbbVie.

- Serious Adverse events

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

In the CRF the response to the following question is registered at 4, 12 and 24 week visits:

Has any SAE(s) occurred since last visit?

6 Analysis Methods

The final statistical analyses will be performed at Scandinavian Development Services AB, Danderyd, Sweden by using the SAS ® version 9.3 or higher.

Continuous variables will be summarized using descriptive statistics (n, mean, SD, min, median, max). Categorical variables will be summarized in frequency tables (frequency and proportion). Graphical presentations, e.g. describing the change over time, will be used as appropriate, and individual patient data will be listed.

The primary and secondary endpoints (change in DLQI, Patient's Global Assessment of Skin Pain (NRS), EQ-5D VAS score and WPAI:SHP at 4, 12 and 24 weeks) will be analyzed using paired samples t-tests or non-parametric methods such as Wilcoxon signed rank test as appropriate.

HiSCR is a dichotomous response variable which will be analysed descriptively presenting proportion HiSCR with binomial exact 95% confidence interval.

The change at 12 weeks will be of primary interest.

Visit windows regarding 4, 12 and 24 weeks assessments following first dose of Adalimumab will decide the validity of assessment.

- Baseline Last assessment before first dose of Adalimumab
- 4 weeks Day (4*7)-(3*7) <= 4 weeks <= Day (4*7)+(3*7)

- 12 weeks Day (12*7)-(4*7) <= 12 weeks <= Day (12*7)+(4*7)
- 24 weeks Day (24*7)-(7*7) <= 24 weeks <= Day (24*7)+(7*7)

Assessments outside these visit windows will not be part of input for summaries by visit. Such assessments will only be presented in listings.

When multiple assessments are found inside the same visit window the assessment most close to the planned visit day (day 28, 84 or 168) will be selected. In case two assessments are equally close to the planned visit day, one X days before and the other X days after planned day, the later of the assessments will be selected. The assessments which was not selected will only be presented in listings.

No adjustment for multiple comparisons will be made.

6.1 Interim analysis

6.1.1 Purpose of the interim analysis

Slow patient recruitment has delayed the study and to provide data according to original plan an interim analysis will be performed in Q2 2017. No formal statistical tests will be performed on the interim data.

No adjustment of final analysis will be made regarding the blinded interim analysis.

6.1.2 Planned Schedule of the interim analysis

NA. Choice of timepoint for Interim analysis is based on administrative reasons.

6.1.3 Scope of adaptations

NA. No actions will be taken based on the descriptive interim analysis.

6.1.4 Methods to minimize bias in the type I error rate

NA. Since this is a Post Marketing Observational Study of one single treatment no method can be applied to minimize bias.

6.1.5 Practical measures to minimize bias

None. Preserving data integrity is not possible since the purpose of the interim analysis is to provide information to investigators and to publish data.

Assignment of personnel to perform the interim analysis

Since purpose of Interim analysis is to provide information to investigators and to publish data the praxis of not allowing SDS personnel to be involved both in interim and final analysis is relaxed.

Limiting access of data and results within SDS

Since purpose of Interim analysis is to provide information to investigators and to publish data the praxis of not allowing access to interim data for SDS personnel involved in final analysis is relaxed. This includes personnel possibly involved in production of protocol amendments, the SAP and data base lock.

Communicating interim results to sponsor

The Baseline characteristics and endpoints listed below will be analyzed descriptively and presented to Sponsor. Continuous Baseline characteristics will be summarized using descriptive statistics (n, mean, SD, min, median, max). Categorical baseline variables will be summarized in frequency tables (frequency and proportion).
Effectiveness endpoints DLQI, NRS, HSIA and HiSCR will be presented in listings.

- Baseline demographics
  - Age
  - Gender
  - Smoking status
  - BMI
  - Time from first HS symptoms to HS diagnosis
    Time point for first HS symptom is registered as year of symptom.
    In calculation of time from first HS symptom to HS diagnosis all symptom starts are assumed to have begun on June 30 except for when symptom starts in year of HS diagnosis. In the latter case symptoms is assumed to have started on January 1.
  - Time from HS diagnosis to start of Humira treatment start.
  - Relevant Medical history(Current and Previous)
  - Proportion Hurley II och III (from HiSCR)
  - WPAI compontents including WPAI-score

- DLQI components including DLQI-score
  Patient data (no summary) at BL, week 4 and 12.

- NRS, Patient data (no summary) at BL, week 4 and 12 for
  - Worst pain during last 7 days
  - Average pain during last 7 days

- HSIA components

Patient data (no summary) at BL, week 4 and 12

- HiSCR responders/ non-responders
  Patient data (no summary) at BL, week 4 and 12

Interim results will be based on all enrolled patients. Visit windows will not be used in interim analysis.

Documentation and storage

Interim data, scripts and outputs will be stored in a secure folder at SDS server.

6.2 General principles

In general, descriptive statistics will be presented for all effectiveness variables and safety variables, as appropriate. Continuous variables will be summarised by descriptive statistics (sample size [n], mean, standard deviation, minimum, median, and maximum value) by treatment group. Categorical data will be summarised in frequency tables showing number of patients, frequency and percentage of occurrence by treatment group.

Graphical presentations will be used, as appropriate and individual patient data will be listed.

6.2.1 Missing data

In general imputation of missing observations will not be performed.
Missing data will be reported descriptively.

6.2.2 Multiple comparisons

No adjustment for multiple comparisons will be made.

6.2.3 Treatment group comparisons

NA This is a Post Marketing Observational Study analyzing only one treatment group

6.2.4 Derived variables

For endpoints which are of index type (sums of sub-item scores) the CRF sometimes provide space where investigator can register the sum of sub-item scores. If QC process finds inconsistencies between sub-items and investigators total score the total score can be set to missing by the QC process.

It has been decided to disregard the investigators derived sums of sub-item scores and instead calculate these in the analysis database.

For information about derived analysis endpoints please see sections 5.1 and 5.2.

6.3 Study population results

Characteristics of patients prior to the start of dosing will be tabulated. The characteristics that will be summarised for baseline include subject demographics, disease characteristics including medical history, and prior and concomitant medications.

6.3.1 Disposition

The number and percentage of patients that reached the various stages of the study (e.g. enrolled, completed study). Reason for withdrawal will be listed. The number and percentage of patients in the different patient population analysis sets (FAS, PP, Safety) will also be tabulated.

6.3.2 Medical history

Concurrent illness and medical history will be reported as a listing for all enrolled patients.

6.3.3 Demographics and baseline patient characteristics

Demographics (gender, age, length, weight, BMI, ethnic background and smoking) will be presented as a table for the baseline visit.

6.4 Effectiveness analyses

Effectiveness analyses will be based on the Full analysis Set (FAS), as described in earlier sections, using paired samples t-tests or non-parametric methods such as Wilcoxon signed rank test as appropriate for numerical endpoints. Dichotomous response variables which will be analysed descriptively presenting proportion of responders with binomial exact 95% confidence interval.

The PP analysis set will be used as sensitivity analysis for the primary effectiveness endpoint.

6.5 Safety analyses

Responses to the CRF question “Has any SAE(s) occurred since last visit?” will be summarized descriptively for the 4, 12 and 24 week visits.

7 Changes of Analyses from Protocol

It was specified in Protocol that HiSCR was to be analyzed using t-test or non-parametric methods such as Wilcoxon signed rank-test.

HiSCR is a dichotomous response variable which will be analysed descriptively presenting proportion HiSCR with binomial exact 95% confidence interval.

It was specified in Protocol that HSIA and EQ5D was to be analyzed using t-test or non-parametric methods such as Wilcoxon signed rank-test.

No total scores for HSIA or EQ5D will derived. Both endpoints will be analyzed descriptively presenting result by sub-item. The EQ5D VAS score has however been added as one variable to be analysed using paired samples t-tests or non-parametric methods such as Wilcoxon signed rank test as appropriate

8 References

The numbered references present in section 1 Introduction are found in the Study protocol.