POST-MARKETING OBSERVATIONAL STUDY

PROTOCOL HUM04-28

A five-year, post-marketing observational study to follow-up patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis who are treated with HUMIRA® (adalimumab)

Version	Date	Status
1.0	26 November 2018	Final

Approvals

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1. METHODOLOGY

The purpose of this statistical analysis plan is to provide detailed information on the statistical analysis of the data of the ProAct study. The plan is based on the quotation dated 18 October 2017 and the mail dated 4 April 2017.

1.1 Study Objective

To evaluate the effectiveness and safety of adalimumab for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) in real life clinical practice.

1.2 Available data

The questionnaires table, as received on 5 February 2018, contained 47378 records, of which 5947 baseline visits. This database has been adapted by hardcoding in the programmation in order to resolve inconsistencies, double patients, misclassification of visits, add additional visit CRF pages, add additional AE pages. A total of 5920 patients of which 2836 rheumatoid arthritis patients, 1127 psoriatic arthritis patients (of which 197 Oligoarticular PsA) and 1957 ankylosing spondylitis patients were included in the analysis.

The parameter DAS28 was entered in the database from the moment the new Belgium reimbursement criteria for Humira were in place (2010).

Visits were scheduled at baseline, months 3, 6, 9 and 12, then every 6 months till 5 years.

1.3 Patient Population

All patients are to be considered in the analysis.

1.4 Data Handling

All data handling rules used during the analysis will be described in the section Methodology of the Statistical Report.

‘LT’ visits are visits added in the database for patients who were lost to follow-up in order to close the patient in the database. These visits will not be taken into account for any analysis.

1.5 Derived Data

- Study duration (year) = (visit date of last visit – visit date of baseline visit)/365.25

- Completed patients: patients with >= 1734 days study duration

- Treatment duration (year):

  For completed patients:

  (Date of last visit – Date of baseline visit)/365.25

  For not completed patients:

  Sum of number of weeks/52, months/12 and years patient has been on drug documented on the last visit
  If missing: (Date of last visit – Date of baseline visit)/365.25

  Note: Some patients stopped Humira temporaly. The periods of not taken Humira are not taken into account for the analysis. These patients will be considered as having taken Humira during the complete study.

- Treatment duration category:
  0 to 3 months
  > 3 to 6 months
  > 6 to 9 months
  > 9 to 12 months
  > 12 to 18 months
  > 18 to 24 months
  > 24 to 30 months
  > 30 to 36 months
  > 36 to 42 months
  > 42 to 48 months
  > 48 to 54 months
  > 54 to 60 months
  > 60 months

- For the purpose of the analysis of the evolution of parameters over time, follow-up visits will be classified into time windows, defined upon the number of days between Visit 1 and the date of each subsequent visit (PERIOD = Date of follow-up visit - Date of Visit 1)

  - Period = Date of visit – Date of baseline visit
  - Month 3 window: 1 <= period <= 137 days
  - Month 6 window: 138 <= period <= 228 days
  - Month 9 window: 229 <= period <= 319 days
  - Month 12 window: 320 <= period <= 456 days
  - Month 18 window: 457 <= period <= 639 days
  - Month 24 window: 640 <= period <= 821 days
  - Month 30 window: 822 <= period <= 1004 days

- Month 36 window: 1005 <= period <= 1186 days
- Month 42 window: 1187 <= period <= 1368 days
- Month 48 window: 1369 <= period <= 1551 days
- Month 54 window: 1552 <= period <= 1733 days
- Month 60 window: 1734 <= period <= 1916 days

Each visit will be classified in a time window. If the date of the visit is completely missing, it will be assumed that the visit took place on the target day of the window as indicated on top of the follow-up page. If more than one follow-up visit is classified into the same time window, the visit closest to the target day is retained. If within a time window there are two visits at the same distance from the target day, the visit which comes first (e.g. before the target date) is retained. If there are two visits on the same date, the first record is retained.

- BASDAI responder: a relative improvement in BASDAI of >= 50%
- DAS28 category: <2.6, ≥2.6 and ≤3.2, >3.2
- Serious adverse event = event where at least one criteria of seriousness is present
- An adverse event is considered to start in a certain year if the difference between start date and date of baseline (=AEPER) is in the following windows:
  - Year 1: 0 <= AEPER < 365.25
  - Year 2: 365.25 <= AEPER < 730.5
  - Year 3 730.5 <= AEPER < 1095.75
  - Year 4: 1095.75 <= AEPER < 1461
  - Year 5: 1461 <= AEPER < 1826.25

2 STATISTICAL ANALYSIS

The analysis of the baseline data and prior anti-TNF treatment will be performed broken down by indication (RA, PsA, AS). Within each indication, baseline data will also presented broken down by completed/not completed patients. Statistical tests will be performed to compare baseline data for patients completed/not completed the study.

The analysis of treatment duration and the evolution of different parameters over time, will be performed broken down by indication (RA, PsA, AS).

The analysis of adverse events will be performed for all patients together and broken down by indication (RA, PsA, AS):

- Overall
- Per year (up to 5 years)
- By cumulative yearly period (till 5 years)
- Incidence
- Incidence divided by total exposure to treatment (till 5 years).
- Reason for seriousness
- Serious adverse events: number of patients and incidence by system organ class and preferred term
- Non-serious adverse events: number of patients by system organ class and preferred term

If an adverse event has no onset date, the observation date will be taken as onset date. Events that are coded with multiple MedDRA Terms will be counted as separate event.

The percentages in the adverse event table are calculated as follows:

Table	Nominator	Denominator
Number of patients with an adverse event per year.	Number of patients treated in that year with at least one adverse event in that year.	Number of patients treated in that year.
Number of patients with an adverse event per cumulative year	Number of patients with at least one adverse event in that year or before.	Number of patients.
Number of adverse events by total exposure to treatment	Number of adverse events in that year or before.	The sum of the patients' treatment exposure time in that year or before.

The following tables will be presented:

Rheumatoid Arthritis

1 Baseline Characteristics– All Patients and Broken Down by Early Termination
1.1 Age
1.2 Gender
1.3 Disease Duration Before Inclusion
1.4 Anti-TNF use Before Inclusion
1.4.1 Anti-TNF Naïve / Experienced
1.4.2 Types of Anti-TNF use Before Inclusion
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