

## 1.0 Abstract

### Title

Long term Documentation of the Safety and Efficacy as well as the Effects on Work Productivity in Patients with Moderate to Severe Plaque Psoriasis treated with HUMIRA® (Adalimumab) in Routine Clinical Practice (LOTOS)

### Keywords

HUMIRA® (Adalimumab); Plaque Psoriasis; Work Productivity; Clinical Practice

### Rationale and Background

Psoriasis is a systemic inflammatory skin disease with a prevalence of up to 3% of the European Population (1-3); in Germany, about 2 million people are affected (4). Psoriasis is associated with certain concomitant diseases such as cardiovascular diseases, metabolic syndrome, diabetes and depression. The high burden of disease caused by the symptoms and comorbidities results in a significantly reduced quality of life, combined with considerable direct and indirect medical expenses (5,6). Systemic treatments for moderate to severe chronic plaque psoriasis include antibodies against the pro-inflammatory cytokine Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) (7). One TNF- $\alpha$ -antibody is adalimumab (brand name HUMIRA®), a completely human monoclonal TNF- $\alpha$ -antibody, that was shown to be safe and effective in patients with moderate to severe chronic plaque psoriasis in several studies since its first approval in the European Union for psoriasis in 2007 (8-12). HUMIRA® is administered as a subcutaneous (sc) injection at a recommended dose of 40 mg every other week (eow) (13).

This non-interventional study (NIS) was designed to document long-term data on the efficacy and tolerability of HUMIRA® in the treatment of patients with moderate to severe chronic plaque psoriasis under conditions of routine care including data of patient groups that are usually excluded from clinical trials, e.g., due to comorbidities, varied concomitant medication.

---

Based on data of clinical utility of once weekly administration of HUMIRA<sup>®</sup> 40 mg in patients with psoriasis showing inadequate response to HUMIRA<sup>®</sup> 40 mg given eow (15), the SmPC (Summary of Product Characteristics, "Fachinformation") for HUMIRA<sup>®</sup> was adapted in November 2015. The possibility of a once-weekly regimen in psoriasis patients with insufficient response to the bi-weekly regimen after 16 weeks of therapy, at the earliest, as well as that of returning to dosing HUMIRA<sup>®</sup> eow, once sufficient response was achieved was included in the recommendations for treatment (13). Based on these changes it was indicated to amend the study protocol for alignment with the following rationale:

- a) To collect real-life data of the clinical impact and safety of dose escalation of HUMIRA<sup>®</sup>.
- b) To assess in a large real-world psoriasis population which patients receive a dose escalation and when. What are the results of the dose escalation with regard to a large panel of established parameters on disease signs and symptoms as well as quality-of-life.
- c) To analyze the benefit of dose escalation with regard to long-term drug survival rates of HUMIRA<sup>®</sup> compared to previously reported registry data.

### **Research Question and Objectives**

The primary objectives were:

- to explore changes in health-related care utilization data by the evaluation of
    - the number of missed working days
    - the number of visits to doctor's office
    - the number and duration of hospitalizations
    - the self-assessed work ability
-

- to explore efficacy for different subgroups by the analysis of
  - changes in the Psoriasis Area and Severity Index (PASI) (16)
  - the number of patients achieving a PASI 75 response
- to evaluate safety by
  - the documentation and analysis of serious adverse events (SAE) and adverse events (AE)

Secondary objectives included:

- the exploration of changes in quality of life measurements (Dermatology Life Quality Index [DLQI] (17), EuroQol-5D [EQ-5D] (18))
- the exploration of the influence of the body mass index (BMI) and body weight on efficacy measurements (PASI)
- the evaluation of the physician's assessment of the antipsoriatic treatment with HUMIRA®
- the evaluation of patients' assessments of the antipsoriatic treatment with HUMIRA®
- the evaluation of the safety and tolerability of the HUMIRA® treatment for subgroups of patients with common concomitant diseases, especially diabetes type I and II, cardiovascular, liver, and renal insufficiencies, and related concomitant medications.

The following secondary objectives were additionally included through the amendment of the study protocol:

- Itch Visual Analogue Scale (Itch VAS)
  - Palmoplantar Psoriasis Area Severity Index (pPASI)
  - Reasons for and duration of dose escalation
  - Median drug survival rates of different dosing regimes
  - PASI (mean, min, max) at start of the dose escalation
  - Assessment of Psoriasis Scalp Severity Index (PSSI)
-

- Target Nail Psoriasis Severity Index (target-NAPSI) (19)

In addition, a substudy was conducted termed "Long-term Documentation of Risk Factors of Metabolic Syndrome and Cardiovascular Disease in Patients with Moderate to Severe Plaque Psoriasis Treated with HUMIRA® in Routine Clinical Practice (LOTOS Metabolism)" ([Appendix 5](#) and [6](#)):

The research question explored in this substudy was whether treatment with HUMIRA® altered lipid and glucose metabolism or cardiovascular risk factors in patients with psoriasis. The primary objectives were:

- To explore the effects of HUMIRA® therapy on the parameters of metabolic and cardiovascular risk
- To explore whether there exists a correlation between therapeutic effectiveness on skin disease and changes in the parameters of metabolic and cardiovascular risk

### **Study Design**

Single-arm, multi-center, prospective cohort study

### **Setting**

The data for this NIS were collected from dermatology outpatient departments and office-based dermatologists in Germany routinely treating patients with psoriasis. The sites were distributed throughout Germany.

The decision to initiate HUMIRA® therapy was taken independently by the physician. The aim of the study was to start documentation after initiation of the HUMIRA® treatment and to end documentation either after 5 years (2 years for patients included after the amendment of the study protocol) or with the termination of the HUMIRA® therapy.

---

## **Patients and Study Size, Including Dropouts**

The study population consisted of patients with moderate to severe chronic plaque psoriasis (psoriasis vulgaris). The patients had to be at least 18 years of age at the start of the investigation and provided written informed consent. Patients had to be able to understand the study objective and to complete patient reported outcomes questionnaires. The inclusion and exclusion criteria adhered to the approved label as stated in the German SmPC for HUMIRA®. No additional inclusion and exclusion criteria were applicable since this project was non-interventional.

The NIS planned to include sufficient patients to provide 850 assessable documentations at Month 60.

## **Variables and Data Sources**

### **Original protocol (LOTOS patients)**

The documentation consisted of patient self-assessments as well as assessments by the physician.

#### Physician:

- Demographics, inclusion and exclusion criteria, previous psoriasis therapies (Month 0)
  - Medical history/change history, HUMIRA® therapy, concomitant therapies including psoriasis-related ones, concomitant diseases, psoriasis disease activity, laboratory values, nail involvement (Month 0, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60)
  - Adverse Events (Month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60)
  - Photographic documentation (patient's file) (Month 0, 3, 6, 12, 24, 26, 48, 60)
  - Clarification of Psoriatic Arthritis, PsA (Month 0, 60)
  - Final data (Last Visit): Final evaluation of the therapeutic response, change of current psoriasis-related medication, adverse events, end of observation
-

Patient:

- Personal data, professional status (Month 0)
- Patient questionnaires: Quality of Life (Month 0, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60)
- Patient questionnaires: Work Ability, Work Productivity, Disease-related Expenses (Month 0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60)
- Health Assessment Questionnaire Disability Index (HAQ) in case of PsA diagnosis (Month 0, 60)
- Patient's assessment of HUMIRA<sup>®</sup> therapy (Month 6, 12, 24, 36, 48, 60)

**Amendment (LOTOS Amendment patients)**

Long-term documentation of treatment with HUMIRA<sup>®</sup> over 24 months was included according to the amendment to the study protocol. The documentation was performed by the physician as well as by patients' self-assessment and included:

Physician:

- Demographics, inclusion and exclusion criteria, previous psoriasis therapies (Month 0)
- Medical history/change history, HUMIRA<sup>®</sup> therapy, concomitant therapies including psoriasis-related ones, concomitant diseases, psoriasis disease activity, laboratory values, nail involvement (Month 0, 4, 8, 12, 18, 24)
- Adverse Events (Month 4, 8, 12, 18, 24)
- Photographic documentation (Month 0, 4, 8, 12, 18, 24)
- Clarification of Psoriatic Arthritis, PsA (Month 0)
- Final data (Last Visit): Final evaluation of the therapeutic response, change of current psoriasis-related medication, adverse events, end of observation

Patient:

- Personal data, professional status (Month 0)
-

- Patient questionnaires: Quality of Life (Month 0, 4, 8, 12, 18, 24)
- Patient questionnaires: visits to the physician's office and hospital stays, Work Ability, Work Productivity (Month 0, 8, 12, 18, 24)
- HAQ in case of PsA diagnosis (Month 0, 24)
- Patient's assessment of HUMIRA® therapy (Month 8, 12, 24)

**Documented data was derived from the following scores:**

- Psoriasis Area and Severity Index (PASI)
- Body surface area (BSA) (20)
- Physicians global assessment (PGA) (21)
- Dermatology Life Quality Index (DLQI)
- EuroQol-5 Dimensions (EQ-5D)
- Work Ability Index (WAI (22)), modified

Scales and scores added additionally through the amendment of the study protocol:

- Target Nail Psoriasis Severity Index (target-NAPSI)
- Itch Visual Analogue Scale (Itch VAS)
- Palmoplantar Psoriasis Area Severity Index (pPASI) (23)
- Psoriasis Scalp Severity Index (PSSI) (24)

**Results**

Overall, 5205 patients (LOTOS patients n = 4793, LOTOS Amendment patients n = 412) were analyzed in the safety analysis set (SAF) and 3684 patients (LOTOS patients n = 3390, LOTOS Amendment patients n = 294) in the full analysis set (FAS).

During the course of the study, treatment with HUMIRA® was associated with strong improvements in health-related care utilization and employment-related outcomes. The ratio of patients which were under medical treatment due to psoriasis during the

---

past 6 months showed a statistically significant decrease for all visits (all p-values < 0.0001, McNemar's test). At Month 6, 7.4% of the LOTOS patients that were under medical treatment at baseline were not under medical treatment anymore. Patients that were not under medical treatment at baseline (2.28%) were under medical treatment at Month 6. This improved to 12% (shift from being under medical treatment to not being under medical treatment anymore) and 2.2% (shift from not being under medical treatment to being under medical treatment), respectively, at Month 12. The "Current work ability compared with lifetime best" (ranging from 0 (being unable to work) to 10 (currently best work ability)) and the proportion of patients with psoriasis-related work absenteeism / restraint in non-professional activities and duties improved statistically significantly throughout the study for both LOTOS and LOTOS Amendment patients. Mean work ability improved from 6.3 at baseline to 8.2 at Month 60 for LOTOS patients; for LOTOS Amendment patients from 6.6 at baseline to 7.4 at Month 24.

HUMIRA<sup>®</sup> therapy was also shown to be highly effective by both the physician as well as patient measures of disease activity. Mean PASI scores significantly decreased during the study (all p < 0.0001 for LOTOS and all p < 0.05 for LOTOS Amendment patients, paired t-test): from 18.5 at baseline to 2.1 at Month 60 for LOTOS patients and from 17.3 at baseline to 2.8 at Month 24 for LOTOS Amendment patients. Simultaneously, PASI 75 responder rates increased for both LOTOS and LOTOS Amendment patients during the course of the study (from 43.4% at Month 3 to 82.6% at Month 60 for LOTOS patients and from 44.3% at Month 4 to 76.5% at Month 24. Other outcome measures including PsA characteristics, BSA, PGA, characteristics of nail involvement, pPASI and PSSI also all showed improvements during the course of the study.

The improvements observed in patient-reported outcomes (DLQI, EQ-5D, HAQ and itch-VAS) indicate that decreases in disease activity were accompanied by improvements in quality of life and functional improvements.

---



With the amendment the collection of real-life data on dose escalation was included in the study protocol. Results indicate that dose escalations are rarely conducted under HUMIRA® treatment.

No unexpected adverse events (AEs) were observed in the course of the study. Overall, 1089 (20.92%) patients had at least one AE and 512 (9.84%) patients at least one SAE reported. Relationship to treatment was reported for at least one AE for 658 (13.73%) of the LOTOS patients and 41 (9.95%) of the LOTOS Amendment patients. For SAEs, these were 238 (4.97%) of the LOTOS patients and 39 (9.47%) of the LOTOS Amendment patients. During the course of the study, 11 deaths and 1 neonatal death were documented.

### **Discussion**

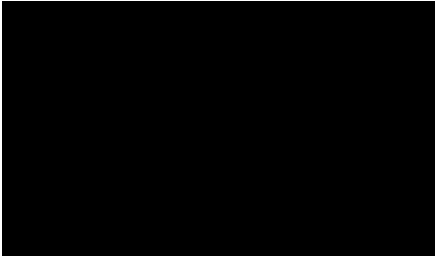
Treatment with HUMIRA® for up to 60 (LOTOS patients) and 24 (LOTOS Amendment patients) months during routine clinical care had a favorable impact on health-related care utilization, employment-related and clinical outcomes in adult patients with psoriasis. Dose escalations were documented for the LOTOS Amendment patients and turned out to be less common than anticipated in daily routine care. The results of this NIS support the conclusion that HUMIRA® is effective and safe during long-term therapy of adult patients with psoriasis in Germany.

### **Marketing Authorization Holder(s)**

AbbVie Deutschland GmbH & Co.KG  
Knollstrasse, 67061 Ludwigshafen, Germany

---

**Names and Affiliations of Principal Investigators**



After start of the amendment and as of August 24th, 2018:

