Amendment History for Protocol:

"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)"

LOTOS GER-07-06 (November 9th 2007)

Amendment I (06/2016)

Product Name:	HUMIRA®
Type of Study:	Non-interventional Study (PMOS)
Date	23-6-2016
Principal Investigator	Dr. Sandra Philipp, [redacted]
Sponsor	ABBVIE GmbH & CO KG Max-Planck-Ring 2 D-65205 Wiesbaden

Reason for change:

The study protocol of November 9th, 2007 was based on a maintenance treatment regimen of adalimumab 40 mg administered in 2-week intervals. Since initiation of the LOTOS study a trial by Leonardi et al. (see reference) has demonstrated clinical utility considering both efficacy and safety parameters of a once weekly administration of adalimumab 40 mg in patients with psoriasis showing inadequate response to adalimumab 40 mg given every other week. Based on these data the scientific information for adalimumab was adapted in Nov 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, was included in the recommendations for treatment as well as that of returning to dosing adalimumab every other week, once sufficient response was achieved. To allow for changes between treatment regimens and pertinent changes in efficacy and safety to be documented at time points other than the planned (regular) visits, CRFs for additional visits (=tandem inter visit documentation, IVD) in between regular intervals defined in the protocol are provided in addition to the amendment of several sections of the study protocol.

The purpose of this amendment is to incorporate the changes summarized below.

- **Page 1, Section 1.0, Title Page. Updated Sponsor Contact**

Rationale for change: Update of sponsor name to AbbVie (formerly Abbott) and address:

AbbVie Deutschland GmbH & Co. KG, Mainzer Str. 81, 65189 Wiesbaden

Phone +49 611 / 1720-0, FAX +49 611 / 1720-1244

AbbVie is replacing Abbott throughout the whole protocol.

- **Page 6, Section 5.0, Rationale. Text added**

Rationale for change: Text added to existing text to provide a clear rationale and scientific information background for the amendment.

New text added:

Since initiation of the LOTOS study a trial by Leonardi et al. has demonstrated clinical utility (considering both efficacy and safety parameters) of once weekly administration of adalimumab 40 mg in patients with psoriasis showing inadequate response to adalimumab 40 mg given every other week. Based on these data the scientific information for adalimumab was adapted in Nov 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 adalimumab every other week, once sufficient response was achieved was included in the recommendations for treatment. Based on these changes it is indicated to amend this study protocol for alignment with the following rationale:

a) To collect real-life data of the clinical impact and safety of dose escalation of adalimumab.

b) To assess in a large real-world psoriasis population which patients receive a dose escalation, when they receive it and what outcome the dose escalation brings with regard to a large panel of established parameters on disease signs and symptoms as well as quality-of-life parameters.

c) To analyze the value of dose escalation with regard to long-term drug survival rates of adalimumab compared to previously reported registry data.

- **Page 6, Section 6.0, Study Objective. Text added**

Rationale for change: Text added to existing text to provide an overview of amended documentation procedure. Previous primary and secondary objectives are still valid and new secondary objectives are added to meet amendment requirements.

New text added (changes or additions are marked):

In this NIS, a long term documentation of treatment with HUMIRA® over 24 months with 6 data collection points (visits) is planned. The documentation will be performed by the physician as well as by patients' self-assessment.

Amended secondary objectives:

- reasons for and duration of dose escalation
- median drug-survival rates of different dosing regimens
- PASI (mean, min, max) at start of the dose escalation
- Target Nail Psoriasis Severity Index (target NAPSI)
- Itch Visual Analogue Scale (Itch VAS)
- Palmoplantar Psoriasis Area Severity Index (pPASI)
- Assessment of Psoriasis Scalp Severity Index (PSSI)

- **Page 8, Section 7.4, Study Duration. Update of dates according to amendment**

Rationale for change: Recruiting phase, data completion and dates for data analysis as well as final report updated to meet amendment requirements.

New text <u>replacing</u> text in section 7.4:

Recruiting phase: Oct 2016-Oct 2018

Data completion: Oct 2020

Data analysis and final report: June 2021

For each individual patient, the NIS starts with the enrollment into the long term documentation at the beginning of the treatment with HUMIRA® and ends either after 2 years or with the termination of the HUMIRA® therapy.

- **Page 9, Section 7.5.1, Study Conduct. Update of observations schedule**

Rationale for change: To clarify additionally needed documentation for those subjects who are escaleted from ADA 40mg eow to ew due to insufficient therapeutic response.

New text <u>replacing</u> text on page 9, section 7.5.1 starting with "The observational study documentation starts with the first application of adalimumab…":

New text added:

- The observational study documentation starts with the first application of adalimumab and is repeated at month 4, 8, 12, 18, 24. Any time after 16 weeks of adalimumab treatment, patients with insufficient therapeutic response as judged by the treating physician may be switched to adalimumab 40 mg weekly and back to adalimumab 40 mg every other week, based on their efficacy and safety data on the weekly regimen. Therefore additional documentation of changes in dose regimen (adalimumab eow to ew, according to label) at date of updosing and after another 16 weeks (= tandem inter visit documentation, IVD) independent of further dose regimen will be necessary. Documentation of an additional visit will encompass all data as assessed at a regular visit using the same set of CRF pages.
- The follow-up observation period is planned for two years.

Physician schedule:

	Month					
	0	4	8	12	18	24
Demographic data	X					
In- and exclusion criteria	X					
Medical history / Change history	X	X	X	X	X	X
Previous psoriasis therapies	X					
HUMIRA® therapy	X	X	X	X	X	X
Psoriasis-related concomitant medication	X	X	X	X	X	X
Other diseases and therapies*	X	X	X	X	X	X
Clarification PsA	X					
BSA	X	X	X	X	X	X
PASI	X	X	X	X	X	X
PGA	X	X	X	X	X	X
Nail involvement	X	X	X	X	X	X
Laboratory values	X	X	X	X	X	X
Photographic documentation	X	X	X	X		X
Adverse events		X	X	X	X	X
Final evaluation						X**
End of observation						X**
Target NAPSI	X	X	X	X	X	X
Itch VAS	X	X	X	X	X	X
pPASI	X	X	X	X	X	X
PSSI	X	X	X	X	X	X

*after baseline visit (month 0) only for newly developed diseases

** month 24 or last visit

Patient schedule:

	Month					
	0	4	8	12	18	24
Personal data and risk factors	X					
Professional status	X					
DLQI	X	X	X	X	X	X
EQ-5D	X	X	X	X	X	X
Number of psoriasis-related visits to the physician's office and	X		X	X	X	X
Psoriasis-related work absenteeism	X		X	X	X	X
Work ability WAI	X		X	X	X	X
Functionality HAQ	X*					X*
Patient's assessment of HUMIRA® therapy			X	X		X

* only in case of PsA diagnosis

- **Page 13, Section 7.5.2, Description of Activities. Update of activities to fit with new timeframe of the study**

Rationale for change: The observational study documentation starts with the first application of adalimumab and is repeated at month 4, 8, 12, 18, 24. The follow-up observation period is planned for two years.

All described activities for physician and patient are adjusted to meet the above mentioned timeline and are terminated after completion of the follow-up period of two years. Activities scheduled for month 3 and month 6 will be conducted at month 4 and month 8 respectively.

- **Page 15, Section 7.5.3, Scales and Scores. Update of scores to be derived from documented data**

Rationale for change: Scores added to meet documentation requirements for changes in dose regimen (matching with added secondary objectives).

Scores added:

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

- **Page 17, Section 8, Adverse Events. Update of safety language**

Rationale for change: Incorporation of new AbbVie safety language to meet up to date requirements.

New added text (changes or additions are underlined):

8.1. Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient: An event that results in the death of a patient.

Life-Threatening: An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization: An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.

Prolongation of Hospitalization: An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.

Congenital Anomaly: An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity: An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome: An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2. Severity

The physician will use the following definitions to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse SAEs.

Mild: The adverse event is transient and easily tolerated by the patient.

Moderate: The adverse event causes the patients discomfort and interrupts the patient's usual activities.

Severe: The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

Instructions and Strategies:

Note that in certain cases (e.g., oncology drugs), it may make sense to use different categories for rating adverse event severity than those presented in this guideline as the standard (e.g., the NCI Common Toxicity Criteria).

8.3. Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility

An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.

No Reasonable Possibility

An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event.

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

8.4. Serious Adverse Event Collection Period

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.

8.5. Serious Adverse Event Reporting

In the event of a SAE, the physician will:

- For events from patients using an AbbVie product – notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the event.

Arzneimittelsicherheit, AbbVie GmbH & Co. KG,
Max-Planck-Ring 2
65205 Wiesbaden
Telephone: [redacted]
Fax: [redacted]

8.6. Pregnancy Reporting

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 8.5 within 24 hours of the physician becoming aware of the pregnancy.

Note: Reported pregnancy occurrences must be forwarded to GMS Postmarketing Safety using the appropriate form.

Note: Information regarding pregnancy outcome will be requested from the investigator 4 and 12 weeks postpartum, as applicable.

- **Page 22, Section 10.0, Case Report Forms. Update of observation time**

Rationale for change: Time period of observation up to 24 months (instead of 60 months)

New added text:

Any observation of an adverse event in the time period up to 24 months, beginning with the initiation of HUMIRA® therapy…

New added text:

- *For regression analysis* at the end of the study, patients with dose escalation (ew) and patients without dose escalation (eow) will be "matched" according to a list of defined co-variables (such as age, gender, disease duration, body weight, PASI and DLQI at baseline, co-medication, level of education, season (calendar) of start adalimumab therapy, adherence).
- *For the comparison of drug persistence rates* between patients with dose escalation and patients without dose escalation, persistence is defined as the treatment duration on adalimumab from baseline to discontinuation of adalimumab for any reason except pregnancy and remission.
- *Reasons for up-titration* of adalimumab and extent/duration of up-titration will be assessed.
- *For the comparison of safety and tolerability* between patients with dose escalation and patients without dose escalation, tolerability analysis will be based on MedDRA coded AEs and SAEs. AEs will be summarized by "Preferred Term" and "System Organ Class".

- **Page 25, Section 13.0, References. Text added**

Rationale for change: Reference added to provide the scientific publication that forms the basis/rationale for planned amendment.

Reference added:

11. Leonardi C, Sobell JM, Crowley JJ, Mrowietz U, Bao Y, Mulani PM, Gu Y and Okun MM. Efficacy, safety and medication cost implications of adalimumab 40 mg weekly dosing in patients with psoriasis with suboptimal response to 40 mg every other week dosing: results from an open-label study. British Association of Dermatologists 2012 167, 658–667.

Signature Page

This Amendment I (06/2016) to LOTOS GER-07-06 (November 9th 2007) was reviewed in GMA-RC on May 23 2016 and is herewith approved.

07/20/2016

MD, PHD

Vice President, Immunology & Biotherapeutics

Global Medical Affairs, GPRD