1. Title Page

ABBOTT Laboratories

Postmarketing Observational Study to Evaluate the Safety and Efficacy of HUMIRA® (adalimumab sc) for the Treatment of Moderate to Severe Crohn's Disease in daily clinical practice

Incorporating Amendment 1

Product Name:	HUMIRA®	
Type of Study:	Observational Study	
Date:	22 July 2011	
CRO:	n.n.	
Biometrics (Affiliate contact)	[redacted]	[redacted]
Sponsor	ABBOTT GmbH&Co KG Max Planck-Ring 2 D-65205 Wiesbaden	Phone:++49-6122-582516 Fax: ++49-6122-562866

This study will be conducted in compliance with this protocol and other applicable regulatory and legal requirements

2. Table of Contents

3. Introduction

Crohn's Disease is one of the major forms of inflammatory bowel disease manifested by focal asymmetric, transmural, and granulomatous inflammation affecting any segment of the gastrointestinal tract (1). The general prevalence in the European population is estimated as 0.1–0.2%. Epidemiologies of Crohn's disease reveal a north-south gradient: Crohn's disease appears to be more common in the northern latitudes. The incidence is estimated from 8/100,000 with a prevalence of 151/100,000 in the UK to an incidence of 4/100,000 with a prevalence of 37/100,000 in Germany (2-4). At present, the aetiology of Crohn's disease is unknown, however, a number of possible explanations for its pathogenesis exist. Genetic susceptibility, infectious agents and environmental factors have all been suggested to play a role in the pathogenesis of the disease; the aetiology of Crohn's disease is currently believed to be multifactorial. Risk factors that predispose to Crohn's disease include: (i) being of Caucasian race and (ii) a family history of Crohn's disease, (iii) living in a westernized society, (iv) smoking and (v) diet. Crohn's disease typically affects people in the age of 15-30 years and there is a higher incidence of the disease in women (5). Genetic as well as clinical analyses demonstrate that Crohn's disease comprises syndromes rather than one disease suggesting that different subgroups might be formed that have different etiology and probably different treatment needs (6).
In Crohn's disease therapy there are two major needs. First is the rapid induction of remission particular with regard to the lag of response of conventional immunosuppressive agents such as azathioprine up to 8 weeks and more. Second, in Crohn's disease the relapse rate is high and there are not enough options for an effective maintenance treatment available. Conventional therapy consists of corticosteroids, azathioprine or methotrexate. However, there still is a group of patients that cannot be treated successfully using conventional therapy. In addition, life quality of patients still is low and the side effects of steroids and other drugs should not be forgotten. With the introduction of biological agents, such as anti-TNF-α antibodies, the goals of therapy have advanced, including induction of remission with bowel healing as well as reduction in the rate of complications, surgeries and mortality (7, 8). Current therapy for moderate to severe Crohn's disease is based on 'step-up' algorithms, which initiate treatment with corticosteroids followed by immunomodulatory agents, and defer therapy with biological agents until patients become refractory to conventional therapeutics (9). Recent data suggest that induction therapy with an anti-TNF-α antibody and azathioprine in recent-onset Crohn's disease (i.e. 'top-down' approach) might be superior to current step-up algorithms to induce clinical remission (10, 11).

Adalimumab is a recombinant full-length human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. Adalimumab is comprised of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not lymphotoxin (TNF-β). Adalimumab has been approved for therapeutic use in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

In Crohn's disease Adalimumab was shown to be effective in 4 controlled clinical studies in subjects with moderate to severe active Crohn's disease, including more than 1400 patients. CLASSIC I was a 4 week trial that showed the effectiveness of Adalimumab in the induction of remission of CD in anti-TNF naïve moderate to severe Crohn's disease patients. The trial assessed three different Adalimumab dosing regimens, with prior efficacy of the dosing regimen of 160 mg at week 0 and 80 mg at week 2. GAIN demonstrated the effectiveness of Adalimumab at the 160 mg (week 0) and 80 mg (week 2) loading dose, for the induction of remission in Crohn's disease patients who had loss of response, or were intolerant to infliximab. CHARM was the pivotal efficacy and safety trial for the maintenance use of Adalimumab in Crohn's disease demonstrating the significant efficacy of Adalimumab compared with placebo in sustained remission over 1 year. The study population included both anti-TNF naïve and anti-TNF experienced patients. In CLASSIC II patients of CLASSIC I were continued and received either 40 mg every other week or 40 mg every week over 1 year. The trial demonstrated the effectiveness of both these regimens on sustained remission of Crohn's disease (12, 13).

4. Rationale

Hypothesis is that Adalimumab is well tolerated under every day's conditions during long-term application in patients with Crohn's disease.

Adalimumab has recently received marketing authorization in Germany for the treatment of severe active Crohn's disease in patients not responding to the adequate therapy with steroids and/or one conventional immunosuppressive drug. This PMOS is designed to collect long-term data on the safety and efficacy of Adalimumab in patients with moderate to severe Crohn's disease in everyday clinical usage, prescribed in accordance

with the terms of the marketing authorization. Data on the safety and efficacy of Adalimumab will be collected from initial dosing and up to 60 months of therapy.

Well-designed observational cohort studies including a very strict study protocol and monitoring, are indispensable to complement the knowledge gained from randomized controlled trials with important real-life data. The gain in experience was recently demonstrated in the German register RABBIT in rheumatoid arthritis patients. RABBITT provided information that the majority of patients with various comorbidities, concomitant medications, dosing schemes, and disease states, who would not fulfill the inclusion criteria of a major trial, benefit from biologic therapy (14).

5. Study Objective

The primary objective of the non-investigational study (PMOS) is to demonstrate long-term efficacy and safety of Adalimumab in patients with Crohn's disease under routine conditions and to evaluate the proportion of patients achieving remission and the time to remission induction.

Secondary objectives include: Improvement/resolution of signs and symptoms of the acute Crohn's disease (CDAI –100), rate of adverse events, and long-term improvement of patients QOL.

Further, the observation study protocol enables physicians to characterize patients that fulfill criteria for Adalimumab treatment thus ensuring the requirements of reimbursement.

6. Investigational Plan

6.1 Selection of the Study Population

The study population will consist of patients with severe Crohn's disease.

Inclusion criteria: The inclusion criteria are as stated in the German Summary of Product Characteristics (SPC) 'Fachinformation' for HUMIRA®

Exclusion criteria: The exclusion criteria are as stated in the German Summary of Product Characteristics (SPC) 'Fachinformation' for HUMIRA®

No additional inclusion and exclusion criteria are applicable since this project is non-interventional and Adalimumab will be used in a normal clinical setting according to the approved label.

Patients must provide the written informed consent to the investigator before entry into the PMOS.

6.2 Number of Patients to be Enrolled

The PMOS will include up to 2000 patients with active moderate to severe Crohn's disease.

6.3 Investigator Selection Criteria

The data for this observational study will be collected from IBD centers in Germany, and office based GI-specialists. Institutions, which have the capacity to enroll a minimum of five patients for Adalimumab in this observational study, will be included. Based on this, up to 400 sites will participate in the study.

6.4 Study Duration

The observation period for each individual patient starts with the administration of the initial dose of Adalimumab and ends after 60 months.

6.5 Study Conduct

This postmarketing observational study will be conducted in a single-arm, multi-center format.

Observational studies are intended to gather findings in the use of marketable medicinal products. Their special feature is that they do not influence, as far as this is possible, the physician in charge of the treatment in his diagnosis or choice and implementation of therapy for the individual case.

Adalimumab must not be prescribed for the purpose of including a patient in this observational study. Physicians are encouraged to treat their patients as in routine clinical practice. The patient is only identified for the study after the decision on the therapy had been made.

Patients who have active severe Crohn's disease and start treatment with Adalimumab in normal clinical settings according to label are documented. Adalimumab will be administered by sc injection. The dose regimen is recommended following the approved label: Either an initial dose of 160 mg adalimumab sc at Week 0 followed by 80 mg adalimumab sc at Week 2, or an initial dose of 80 mg adalimumab sc at Week 0 followed by 40 mg adalimumab sc at Week 2. Starting at Week 4 all subjects will receive 40 mg every other week (eow) sc in an open-label fashion. The PMOS documentation starts with the first application of Adalimumab, and is repeated at month 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60.

The follow-up observation period is planned for five years and is focused on maintenance of efficacy and safety information during normal clinical settings. The physicians will follow up the patient via regular office visits at intervals as determined by routine clinical practice or as recommended by national guidelines. It is expected that follow up visits will be performed every three months during the first year and every six months during the subsequent four years. Baseline and follow up visits will be reported on different forms. Failure to observe these usual practice intervals of patient visits will not constitute a breach or violation of the protocol.

The following data will be documented (if assessed in routine care):

Baseline Demographic Data (month 0)

Age
Gender
Height
Weight
Smoking behavior

Informed Consent

Informed consent signed by patient

Medical History

History of Crohn's disease

- Date of first diagnosis
- First manifestation of Crohn's disease

Local of luminal disease

Fistula

Stenoses

Extra-intestinal manifestation

Crohn´s related surgery (incl. bowel surgery & number of surgeries)

Concomitant diseases

Cconcomitant medication (Crohn´s related)

Crohn's disease activity before treatment

CDAI

Current manifestation of Crohn's disease and extraintestinal manifestation (EIM)

Laboratory values (leukocyte and thrombocytes count, hematocrit, C-reactive protein, gamma-glutamyl transpeptidase)

Pre-medication (Crohn's related): 5-ASA/Suflasalazine, steroids, immuno-suppressants, TNF-inhibitors (incl. duration of treatment, reason for discontinuation; for prior adalimumab treatment: additionally documentation of former maintenance dose and interval), other biologicals

Average number of moderately severe to severe bouts of active disease per year over the past 3 years

Examinations prior to initiation of adalimumab therapy

Tuberculosis diagnostics & result (only if adalimumab therapy recently started)

Imaging techniques for disease activity assessment (i.e. endoscopy, ultrasonography, MRI or CT scan)

Mucosal healing status

Status for chronic hepatitis B

Initiation of adalimumab therapy

Date of initiation

Dose & interval

Follow-up Data (months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60)

Weight

Adalimumab treatment continued/abrogated (reason for abrogation)

Adverse events/SAE

Crohn's disease activity during treatment

CDAI

Current manifestation of Crohn's disease, Fistula and EIM (incl. comparison of current disease activity with previous visit)

Crohn´s related surgery since last visit (incl. bowel surgery & number of surgeries)

Mucosal healing

Change of adalimumab treatment (incl. change in dose & interval; if discontinued: reason for discontinuation; restart)

Change of concomitant Crohn's-related medication (steroids, immunosuppressants, antibiotics)

Laboratory values (leukocyte and thrombocytes count, hematocrit, C-reactive protein, gamma-glutamyl transpeptidase)

Imaging techniques for disease activity assessment since last visit (i.e. endoscopy, ultrasonography, MRI or CT scan)

Patients Questionnaire (months 0, 3, 6, 12, 24, 30, 36, 42, 48, 54, 60)

S-IBDQ (standard questionnaire)

Crohn´s related hosptalization (within previous 3 months; incl. number of hopitalizations, duration of hospitalization)

Crohn´s related work productivity impairment (within previous 3 months)

Final Data (month 60)

Global assessement of efficacy and safety, change of current Crohn's related medication, and adverse events

6.5.1 Description of Activities

For all study centers participating at the CARE Crohn's study (Phase IIIb) a follow-up in the PMOS is provided.

6.5.2 Product Supply

Abbott will not supply any product, because it is a postmarketing observational study. Adalimumab is used according to the approved marketing label and is to be prescribed by the physician under usual and customary practice of physician prescription according to the §47 AMG (German Arzneimittelgesetz).

7 Adverse Events

7.1 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 Subject An event that results in the death of a subject.

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 subject is hospitalized and prolongs the subject'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 subject. 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 subject 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). 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.

Spontaneous Abortion Miscarriage experienced by study subject.

Elective Abortion Elective abortion performed on study subject.

7.2 Severity

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

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

Moderate The adverse event causes the subject discomfort and interrupts the subject's usual activities.

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

7.3 Relationship to Pharmaceutical Product

The physician will use the following definitions for any adverse event being collected as an endpoint/datapoint in the study and for all serious adverse events, to assess the relationship of the adverse event to the use of the pharmaceutical product:

Probably Related An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.

Possibly Related An adverse event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.

Probably Not Related An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.

Not Related An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator's opinion of possibly, probably not, or not related to pharmaceutical product is given, an alternate etiology must be provided by the investigator for the adverse event.

7.4 Serious Adverse Event Collection Period

Serious adverse events will be reported to Abbott 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, whichever is longer, following the intake of the last dose of physician-prescribed treatment.

7.5 Serious Adverse Event Reporting

In the event of a serious adverse event, whether related to Abbott product or comparator, (if applicable) or not, the physician will notify the Abbott contact person identified below within 24 hours of the physician becoming aware of the event.

Any adverse drug reaction that occurs is recorded by the treating physician using a separate "Adverse drug reaction report" form, labeled 'Bericht über unerwünschte Arzneimittelwirkungen'.

In case of a severe adverse event this form is sent by the treating physician within 24 hours to Bernd Matiba, Abbott GmbH & Co. KG, Max-Planck-Ring 2, 65205 Wiesbaden-Delkenheim, phone: (06122/58-2975, fax: (06122/58-1628).

7.6 Pregnancy Reporting

In the event of pregnancy, the physician will notify the Abbott contact person identified in Section 7.5 within 24 hours of the physician becoming aware of the pregnancy

8 Ethics and Quality

The German Drug Law defines an observational study as a data collection on routine use of medication, prescribed in the usual manner in accordance with the terms of the marketing authorization. In accordance to the code of contact of the German pharmaceutical industry the PMOS study protocol as well as the patients information and consent form will has been forwarded to the ethics committee of the German principal coordinating investigator Prof. Dr. M. Neurath/Mainz for approval. The investigator will document the patients written consent and authorization to use and/or disclose personal and/or health data in the patients chart.

All patient data entered in the patient's case report form will be forwarded - without naming the patient - for evaluation to Abbott GmbH & Co KG and the biometrician online or in paper version. Each case report form bears a pre-printed patient identity number, which replaces the patient's initials. The date of birth will be replaced by the

patient's age at the start of the study. Accordingly, the patient's identity will not be disclosed to Abbott GmbH & Co. KG.

The data collection forms inclusive adverse event and serious adverse drugs reaction forms will be checked during data entry for missing or inconsistent data. These data will be completed through the use of data queries, if possible.

9 Case Report Forms

See also **6.5 Study conduct** for details

Data will be collected online or in paper version. The study comprises 4 different questionnaires to collect baseline data, data on therapeutic efficacy and safety during therapy with HUMIRA®, a final report on efficacy and safety and a patient questionnaire (German S-IBDQ).

Each study center receives either online permission to a database or binders with a set of sheets for data collection, depending on the technical equipment of the centre. The required data should be entered in to the data sheets using the physicians' documentation. Any observation of an adverse event in the time period up-to 60 months, beginning with the initiation of HUMIRA® therapy, must be documented on the "Adverse Event Form", labeled 'Bericht über unerwünschte Ereignisse' and checked for severity. If the event fulfills the serious criterion (Serious Adverse Event) the "Adverse drug reaction report" form, labeled 'Bericht über unerwünschte Arzneimittelwirkungen' must be completed in addition.

10 Data Analysis Plans

All statistical analysis procedures are described in detail in a statistical analysis plan. This plan will be established by the biometric before the database will be opened for the first interims analysis, and signed by the sponsor, the principle investigator and the biometric.

10.1 Sample size calculation

For this postmarketing observational study no sample size calculation was performed. The sample size of 2000 should lead to a sufficient number of patients with data at month 60 to perform adequate long-term safety and effectiveness analysis, assuming an annual drop-out rate of 20% to 30%.

10.2 Study population

The study population contains data of all documented patients. According to chapter 5 the objective of the study is the Adalimumab therapy in patients with Crohn's disease under routine conditions. Therefore a separate analysis for intention to treat population and per protocol population is not planned.

10.3 Missing values

According to chapter 6.5 failures to the common practice intervals of patient visits will not constitute a breach or violation of the protocol. All missing values are documented as missing and not replaced. Instructions for the minimum documentation for each patient will be established in the statistical analysis plan.

10.4 Biometric concept

The aims of the biometric concept for the statistical analysis include:

- Assessment of the safety of the Adalimumab therapy by evaluation and registration of side effects
- Assessment of the efficacy of the Adalimumab therapy by evaluating the proportion of patients achieving remission (remission as defined according to CDAI or HBI scores)
- Assessment of factors of influence to remission (logistic regression models), e.g. duration of therapy, concomitant medication in the medical history, extra-intestinal manifestation, kind of Crohn's disease (fistula, stenoses)
- Assessment of the duration until remission
- Assessment of factors influencing time until remission (Cox regression models)
- Assessment of centre effects
- Subgroup analyses based on the results of the regressions analyses

10.5 Statistical analyses

The study population will be described including all documented variables (absolute and relative frequency, mean, median, quantiles, range etc.). The incidence of side effects of

the Adalimumab therapy will be described according to the physician's statement. The level of statistical significance is established to 5%, a multiple fit to a global level of significance is not planned.

10.6 Times of statistical analyses

A 12 months interim evaluation is scheduled during the study, the general analysis is performed after finishing of the follow-up of the last patient (approx. ten years after starting the study).

11 Final Report and Publications

On the basis of the statistical analysis an Integrated Final Report is generated according to Abbott SOP Q-12-06-001.

12 References

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