**Abbott SA/NV**

[redacted]

**Belgium**

# POST-MARKETING OBSERVATIONAL STUDY (PMOS)
# 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)

## ProAct

| | |
|---|---|
| **Abbott Number:** | **HUM04-28** |
| **Investigational Product:** | **HUMIRA® (Adalimumab)** |
| **Date of protocol:** | **14 April 2004** |
| **Date of Amendment 2:** | **27 June 2005** |
| **Date of Amendment 3:** | **16 February 2006** |
| **Development Phase:** | **NA** |
| Investigator(s): | Multi-center observational study (Investigator information on file at Abbott SA/NV) |

[redacted]

This study will be conducted in compliance with the protocol and all other applicable regulatory and legal requirements.

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# 1 INTRODUCTION

HUMIRA®(adalimumab), a recombinant, full-length immunoglobulin is the first member of a new class of tumour necrosis factor (TNF) antibody compounds, developed to contain exclusively human sequences with a very high affinity for human TNF.

To date, more than 3,000 patients with rheumatoid arthritis (RA) have been treated subcutaneously with HUMIRA®(adalimumab) in controlled trials and more than 6,000 in phase IIIb studies and patient named basis programs in Europe, North America and Australia. HUMIRA®(adalimumab) was administered alone or in combination with methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs) or DMARD combinations.

HUMIRA®(adalimumab) has generally been well tolerated and has demonstrated therapeutic efficacy in the treatment of RA compared to placebo treatment. HUMIRA®(adalimumab) has also shown sustained efficacy in open-label long-term studies, however the data related to patients treated for four and five years is still limited (1, 2).

RA clinical development is largely completed although a number of long-term extension studies and studies for additional indications, e.g. Juvenile Rheumatoid Arthritis and early RA are ongoing.

HUMIRA®(adalimumab) was first approved by the Food and Drug Administration (FDA) for the treatment of patients with RA in the United States of America in December 2002, in Switzerland in April 2003, as well as in several Latin American countries. HUMIRA®(adalimumab) was approved in the European Union in September 2003. "HUMIRA®(adalimumab) is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate. To ensure maximum efficacy, HUMIRA®(adalimumab) is given in combination with methotrexate. HUMIRA®(adalimumab) can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate".

The data from the Psoriatis arthritis (PsA) controlled clinical trials support the conclusion that adalimumab has a favorable benefit/risk ratio in the treatment of subjects with PsA.

As from August 2005 EMEA has granted the approval for the use of Humira® (adalimumab) for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

It is expected that as from June 2006 the indications of HUMIRA®(adalimumab) will be extended with the treatment of adults with active ankylosing spondylitis who have had an inadequate response to conventional therapy. This amendment will be of application after the indication has been approved by EMEA.

For this PMOS, the follow-up observation period is planned for 5 years and is focussed on safety information as well as maintenance of efficacy parameters for HUMIRA®(adalimumab) during normal clinical practice.

## 2 STUDY OBJECTIVES

The objectives of this post-marketing observational study are to:

Observe and assess the long-term use, safety and efficacy of HUMIRA®(adalimumab), as prescribed by the rheumatologist in a normal clinical setting and in accordance with the terms of the European marketing authorization.

Observational statistics will be made on:
- Eventual taper-off of concomitant medication (Corticosteroids and NSAIDs) when being treated with HUMIRA®(adalimumab).
- Evaluations on patient's non-medical complications (number of non-working days, number of days of hospitalization, …)

## 3 INVESTIGATIONAL PLAN

This is a multi-center, uncontrolled observational study of patients who at the time of entry were prescribed with HUMIRA®(adalimumab) following normal clinical practice, with or without other anti-rheumatic treatments, prior to enrollment in this study.

Patients will be followed for 5 years within the post-marketing observational study.

Physicians will be provided with a study kit that includes a protocol, patient informed consent forms, adverse event report forms, and Data Report Forms (DRFs), for each patient to be enrolled. The participating physician will already have provided a prescription to the patient for HUMIRA®(adalimumab), along with instructions for appropriate use according to the European Union (EU) Summary of Product Characteristics (SPC).

Once the physician has determined that the patient meets the inclusion criteria, and the patient has agreed to be included in the observational study, the patient's baseline demographic data, and disease status will be reported in the Baseline DRF. The physician will then follow-up the patient via regular office visits at intervals as determined by routine clinical practice or as recommended by national guidelines.

Patient's safety and efficacy data if they are part of clinical routine will be recorded in the DRFs at Baseline, and regular visits which are closest to Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, Month 30, Month 36, Month 42, Month 48, Month 54, and Month 60. While the physician will likely deem it appropriate and necessary to have the patient return for intermediate visits during the study period, data will be collected via DRFs only at the intervals which correspond closely to those described above. Physicians are encouraged to treat their patients as they would in their routine clinical practice. If treatment with HUMIRA®(adalimumab) is permanently discontinued for any reason, patients will be discontinued from the study and the reason should be recorded. Physicians will be asked to record adverse events up to 3 months after last administration of HUMIRA®(adalimumab) on the DRF of the next scheduled data collection time.

## 3.1 Study Population

Patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis who have been prescribed HUMIRA® (adalimumab) within local reimbursement guidelines for anti-TNF α's may be enrolled in the study.

HUMIRA® (adalimumab) is used in a normal clinical setting according to label.

### 3.1.1 Inclusion Criteria

- Patients with ongoing HUMIRA® (adalimumab) treatment who have been prescribed HUMIRA® (adalimumab) within local reimbursement guidelines.

- Patients must be willing to consent to data being collected and provided to Abbott Laboratories

### 3.1.2 Exclusion Criteria

- Contraindications according to the SPC
- Patients who are actually followed in the ReAlise registry (M03-634)

## 3.2 Safety and Efficacy Variables / Schedule of Assessments

This is a long-term observational study with the objective of documenting safety and efficacy of HUMIRA® (adalimumab) in normal rheumatological clinical practice.

### 3.2.1 Safety Variables

The physician will be asked to document the adverse events on Adverse Events DRFs (see Section 4.0 "Adverse Events/Adverse Event Reporting").

For all serious adverse events (SAEs) reports should be sent by fax to Abbott (for contact information and fax number see Section 4.4 "Adverse Event Reporting").

Special attention for documentation and follow-up is recommended when one of the following adverse events occur:

- malignancy, including lymphoma
- serious infection, including sepsis, tuberculosis and other opportunistic infections
- lupus-like syndrome
- demyelinating disease
- aplastic anaemia and other severe bone marrow suppressions
- congestive heart failure

In case of pregnancy a pregnancy report form (Appendix E) should be faxed to Abbott using the fax number used for SAE forms (Section 4.4)

### 3.2.2 Efficacy Variables

Data on the following individual parameters will be collected if assessed as part of clinical practice at each site:

- 28 joint assessment

- physical function (HAQ)
- inflammatory parameter (ESR, CRP)
- concomitant medication
- change in concomitant steroids, NSAIDs
- assessment of non-medical complications (number of non-working days, number of days of hospitalization, …)

– for patients with polyarticular or oligoarticular erosive psoriatic arthritis:
    - % of the Body Surface Area (BSA) with psoriatic skin lesions
– for patients with oligoarticular erosive psoriatic arthritis:
    - Numerical Rating Scale (score of 0 to 10) for the disease activity in the most important joint by the patient (0 = no disease activity during the previous days, 10 = maximal activity during the previous days)
    - Numerical Rating Scale (score of 0 to 10) for the disease activity in the most important joint by the physician (0 = no disease activity during the previous days, 10 = maximal activity during the previous days)
– For patients with Ankylosing spondylitis the BASDAI will be measured

**Table 1: Schedule of Study Assessments**

| Procedure | Day 1 | Month* 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60 |
|---|---|---|
| Informed Consent | √ | |
| Demographics | √ | |
| | | |
| Safety Data Collection | √ | √ |
| Efficacy Data Collection | √ | √ |
| Concomitant DMARDs, steroids, NSAIDs | √ | |
| Changes in concomitant DMARDs, steroids, NSAIDs | | √ |
| Data Report Form Completion | √ | √ |

* Data collection at regular visits which are closest to time points described

## 3.3 Study Procedures

The following procedures will be performed during the study at the time points specified in Table 1, Schedule of Assessments.

### 3.3.1 Independent Committee Approval

Should the institution/affiliation, and/or national regulation, require an independent committee approval/notification of this protocol, (and related informed consent), then it shall be the investigator's responsibility to secure such approval prior to further initiating any study procedures.

### 3.3.2 Informed Consent

All subjects will provide their consent to releasing their information to Abbott Laboratories (sponsor) on an informed consent form, that is signed and dated by the subject prior to the release of any such information to the sponsor. Before informed consent is obtained, the investigator or designee will explain to the subject or the subject's legally acceptable representative, the nature and purpose of the study and the data to be provided to the sponsor. After the informed consent form is signed, the original informed consent form will be placed in the subject's medical record and a signed copy should be given to the subject. A patient informed consent template is provided in Appendices A (french version) and B (dutch version).

### 3.3.3 Demographics

The physician will determine the patient demographic information at the baseline visit and record it in the Baseline DRF. The demographic information will include date of birth (year of birth if restricted by national regulations) and gender.

### 3.3.4 Patient History

The physician will determine the patient's current status at the Baseline visit and record it in the Baseline DRF. The patient's status will also note concomitant conditions and whether or not these conditions are currently treated. Changes in concomitant medications being taken to treat RA should also be recorded.

### 3.3.5 Treatment Modality

The treatment modality will include thorough information on all treatments prescribed by the physician and received by the patient. Since this is an observational study, the subject will be treated in accordance with the investigator's usual and customary medical practice. Abbott Laboratories will not provide any medication or therapy for this study.

### 3.3.6 Primary Data Collection

The following safety information will be collected: adverse events and serious adverse events. The description of event, start and end date, severity, outcome, causal relationship, and action taken will be recorded.

Data to allow determination of patient's disease activity will be collected. These are 28 joint count of swelling and tenderness (SJC, TJC), physician's global assessment of disease activity, HAQ, ESR and CRP. These data, if available as a result of usual medical practice, will be collected via the DRFs.

**Other Data**

Changes in concomitant DMARDs, steroids, and NSAIDs as well as the administration schedule of HUMIRA® (adalimumab) should be documented in the DRFs.

### 3.3.7 Data Report Form (DRF) Completion and Collection

All data associated with this study will be collected and reported via DRFs on 2-part NCR paper or electronically via the web address and password which will be provided. If using paper DRFs the top copy of the form should be forwarded to the data coordination center, the second copy of the form should be retained at site.

At the baseline visit, the investigator should complete the Baseline Data Report Forms by collecting and reporting on the forms all available required information, including visit date, demographic data, concomitant diseases and medication, etc. If using paper DRFs the enrolment fax should be completed and faxed immediately to the data coordination center.

At subsequent visits corresponding to the schedule of assessments (Table 1), the investigator should complete the appropriate DRF by collecting and reporting on the forms all available information. Since this is an observational study, data from the patient visit following normal clinical practice, which most closely corresponds to the recommended schedule of assessment at Month 3, Month 6, Month 9, Month 12, Month 18, Month 24, Month 30, Month 36, Month 42, Month 48, Month 54, and Month 60 will be accepted.

If the subject is withdrawn from the study at any time or completes the 5-year observation period an Early Termination DRF should be completed.

## 3.4 Withdrawal of Subjects from Study

A subject may withdraw from the study at any time without prejudice. The investigator may discontinue any subject's participation for any reason. If a patient withdraws or is withdrawn from the study, such should be noted, along with the reason for withdrawal, on the Early Termination DRF.

## 3.5 Study Management

Abbott SA/NV will manage the study, collect all study information via DRFs, and complete all statistical analysis of the study, or will contract out parts to a Contract Research Organisation (CRO).

# 4 ADVERSE EVENTS / ADVERSE EVENT REPORTING

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail on the adverse event DRF including the date and time of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "probably related" to study drug, final diagnosis/syndrome (if known) and any action(s) taken. For adverse events to be considered sporadic, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by study-site personnel, or reported spontaneously by the subject, will be recorded.

All adverse events will be followed to a satisfactory conclusion.

## 4.1 Definitions

### 4.1.1 Adverse Event

An **adverse event** is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this 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 protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness (except RA) is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in permanent or temporary discontinuation of treatment with HUMIRA® (adalimumab), necessitate therapeutic medical intervention and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event. However, if a pre-existing condition (except RA) deteriorates unexpectedly during the trial (*e.g.,* surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

### 4.1.2 Serious Adverse Event

If an adverse event meets any of the following criteria, it is to be reported to Abbott as a serious adverse event within 24 hours of occurrence or notification of the study site:

| | |
|---|---|
| **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. |

## 4.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

| | |
|---|---|
| **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. |

## 4.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

| | |
|---|---|
| **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). |

## 4.4 Adverse Event Reporting

In the event of a serious adverse event, whether related to HUMIRA® (adalimumab) or not, the investigator will notify one of the following person by faxing the appropriate adverse event form within 24 hours of being made aware of the serious adverse event.

[redacted]

# 5 DETERMINATION OF SAMPLE SIZE

Since the purpose of this study is to assess the long-term treatment safety, and efficacy of patients treated with HUMIRA® (adalimumab), as many of these patients as are willing to participate in this follow-up will be enrolled. As it is an observational study, no inferential statistical techniques will be applied to data.

## 5.1 Statistical and Analytical Plan

### 5.1.1 Analyzable Populations

Both the efficacy and the safety analysis will be performed on the set of patients who received at least one injection of HUMIRA® (adalimumab).

In addition to the analysis of all patients who received HUMIRA® (adalimumab), certain subgroups may be defined and summarized, e.g. by age, sex, use of certain RA medications.

### 5.1.2 Planned Methods of Statistical Analysis

Demographics and Baseline Characteristics

Demographic and baseline variables will be described by summary statistics. For continuous data, n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum will be presented. For categorical data, absolute and relative frequency will be calculated.

Safety Analyses

Adverse events will be analysed by presenting frequency and percentage. Furthermore, adverse events of special interest, e.g. serious adverse events, or adverse events leading to discontinuation of treatment with HUMIRA® (adalimumab), will be listed.

Efficacy Analysis

The efficacy analysis of continuous variables (e.g. joint count) will be done descriptively by presenting summary statistics and confidence intervals.

## 6 COMPLETION OF STUDY

The investigator will conduct this study in compliance with the protocol and all other applicable regulatory and legal requirements. Abbott SA/NV may terminate this study at any time, either in its entirety or at this site, for reasonable cause provided that written notice is submitted at a reasonable time in advance of the intended termination. The investigator may also terminate the study at their site for reasonable cause, after providing written notice to Abbott SA/NV a reasonable time in advance of the intended termination.

## 7 REFERENCES

1. Breedveld FC, Allaart CF, Rau R, Herborn G, van Riel PLCM, van de Putte LBA, Schattenkirchner M, Kupper H: Sustained efficacy over 4 years with adalimumab in patients with active rheumatoid arthritis. Ann Rheum Dis 2003; 62 (suppl 1): 169, abstract THU0197.

2. Burmester GR, van de Putte LBA, Rau R, Schattenkirchner M, Hartz D, Kupper H: Sustained efficacy of adalimumab monotherapy for more than four years in DMARD-refractory RA. Ann Rheum Dis 2003; 62 (suppl 1): 192-193, abstract THU0275.

# Appendix A
# Subject Information and Consent Form French Version

# Appendix B
# Subject Information and Consent Form Dutch Version

# Appendix C
# Guidance for Joint Evaluation after Preceding Therapeutic Joint Procedures

| **Procedure** | **Joints will not be assessed for:** |
|---|---|
| Intraarticular steroid joint injection | 3 months post injection |
| Joint synovectomy | 3 months post surgery |
| Radiosynoviorthesis | 3 months post synoviorthesis |
| Partial joint endoprosthesis, without synovectomy | 3 months post surgery |
| Partial joint endoprosthesis and total synovectomy | no assessment |
| Total joint endoprosthesis | no assessment |
| Joint resection | no assessment |
| Joint arthrodesis | no assessment |

# Appendix D
# Health Assessment Questionnaire

**In this section we are interested in learning how your illness affects your ability to function in daily life.**

Please tick the response which best describes your usual abilities OVER THE PAST WEEK:

| | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To Do |
|---|---|---|---|---|
| **DRESSING & GROOMING** | | | | |
| Are you able to: | | | | |
| - Dress yourself, including tying shoelaces and doing up buttons? | | | | |
| - Wash your hair? | | | | |
| **RISING** | | | | |
| Are you able to: | | | | |
| - Stand up from a straight chair? | | | | |
| - Get in and out of bed? | | | | |
| **EATING** | | | | |
| Are you able to: | | | | |
| - Cut up your meat? | | | | |
| - Lift a full cup or glass to your mouth? | | | | |
| - Open a new milk carton ? | | | | |
| **WALKING** | | | | |
| Are you able to: | | | | |
| - Walk outdoors on flat ground? | | | | |
| - Climb up five steps? | | | | |

Please tick the response which best describes your usual abilities **OVER THE PAST WEEK**:

| | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To Do |
|---|---|---|---|---|
| **HYGIENE** | | | | |
| Are you able to: | | | | |
| - Wash and dry your body? | | | | |
| - Have a bath? | | | | |
| - Get on and off the toilet? | | | | |
| **REACH** | | | | |
| Are you able to: | | | | |
| - Reach up for and take down a 5 lb object (e.g.: a bag of potatoes) from just above your head? | | | | |
| - Bend down to pick up clothing from the floor? | | | | |
| **GRIP** | | | | |
| Are you able to: | | | | |
| - Open car doors? | | | | |
| - Open jars which have been previously opened? | | | | |
| - Turn taps on and off? | | | | |
| **ACTIVITIES** | | | | |
| Are you able to: | | | | |
| - Go shopping? | | | | |
| - Get in and out of a car? | | | | |
| - Do chores such as vacuuming and gardening? | | | | |

# Appendix E
# Pregnancy Report Form

Investigator Name: _____ Subject Number: _____

Telephone Number: _____ Subject Initials: _____

Date of Birth: _____

**Obstetric History**

Gravida (present pregnancy not included)_____, Para _____, Aborta _____

**Dosing Information**

Dosing of HUMIRA® (adalimumab) Day 1 = _____

**Birth Control Method**

Has the patient used birth control measures? Yes _____ No _____

Unknown _____

**Pregnancy**

Date of 1st positive pregnancy test ( ) serum _____( ) urine _____

Date of last negative pregnancy test _____

Date of HUMIRA® (adalimumab) discontinuation _____

Dates of last menstrual period: Start: _____ End: _____

Estimated number of weeks gestation at 1st positive test _____

Is subject planning to carry pregnancy to term? _____Yes _____ No

Estimated delivery date _____

**Comments:** _____

**Investigator Signature:** _____ **Date:** _____

**Pregnancy Report Sheet (after delivery)**

Date of delivery: _____

Route of delivery: _____

Birth weight/length: _____

Gender: _____

Apgar score: _____

Complications: _____

_____

_____

Outcome: _____

Any abnormalities (major or minor): _____

_____

Labor and delivery report (attach)