

1 Title Page

Abbott GmbH & Co. KG

Documentation Plan AGIL (GER 08-05)

Long term Documentation of the Safety and Efficacy as well as the Effects on Quality of Life and Work Productivity in Patients with Rheumatoid Arthritis under HUMIRA® (Adalimumab) in Routine Clinical Practice (AGIL)

Product Name: HUMIRA®

Type of Study: Non-interventional Study (NIS)

Date: 28-10-2008

Principal Investigator:

[REDACTED]

Biometry

[REDACTED]

Tel
Fax

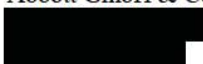
Sponsor:

Abbott GmbH & Co. KG

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This study will be conducted in compliance with this protocol and other applicable regulatory and legal requirements. No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

2 Synopsis

| | |
|---|--|
| Sponsor | Abbott GmbH & Co. KG  |
| Title | Long term Documentation of the Safety and Efficacy as well as the Effects on Quality of Life and Work Productivity in Patients with Rheumatoid Arthritis under HUMIRA® (Adalimumab) in Routine Clinical Practice |
| Short title | AGIL |
| Type of study | Non-interventional study |
| Product, dose, and administration form | Adalimumab (HUMIRA®): 40 mg subcutan (s.c.) every other week |
| Project code | GER 08-05 |
| Indication | Moderate to severe active rheumatoid arthritis (RA) and/or severe, active and progressive RA |
| Study objectives | <p><u>The primary objective</u> of the NIS is to explore the therapeutic success, measured by improvements in the following target variables (with regard to the respective baseline value):</p> <ul style="list-style-type: none"> • The number of missed working days • The self-assessed work ability (WPAI) • The severity of clinical symptoms (number of tender and swollen joints, CRP and ESR, respectively; total score DAS28) • The severity of functional impairment (HAQ) • The health-related quality of life (EQ-5D) <p>All of the patient and disease characteristics which are documented at baseline will be evaluated for their additional impact on the target variables (therapeutic success). Particularly the impact of previous biologic therapies on clinical target variables will be evaluated.</p> <p><u>The secondary objective</u> is to document the therapeutic success by the following variables:</p> <ul style="list-style-type: none"> • The number of physician visits • The number and duration of hospitalization • The number of days of impairment in non-occupational activities • The duration of morning stiffness, pain, exhaustion/fatigue • The reduction of number and dose of concomitant medication • Patient's assessment of adalimumab therapy compared to previous therapies. |

| | |
|----------------------------------|---|
| | Target parameters for safety evaluation of adalimumab are: |
| | <ul style="list-style-type: none"> • The evaluation of safety and tolerability by the documentation and analysis of serious adverse events (SAEs) and adverse events (AEs) • Evaluation of safety and tolerability for subgroups of patients with common frequent concomitant diseases, especially diabetes type II, cardiovascular, liver, and renal insufficiencies, and related concomitant medications. |
| Study population | Adult patients (≥ 18 years) with moderate to severe active RA and/or severe, active and progressive RA |
| Study design | Single-arm, multi-center format, prospective cohort study |
| Treatment duration | 5 years |
| Methodology | Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ), Health Questionnaire Short Form (EQ-5D), WPAI |
| Total number of patients | 2500 Patients |
| Adverse Events | As reported by patients and diagnosed at visits |
| Data analysis plan | The general biometric approach consists of evaluation of changes by descriptive statistical methods, as well as of regression analysis of parameters influencing the therapeutic success and additional subgroup analysis. By forward and backward stepwise regression, those patient and disease characteristics (baseline values of all target parameters, disease duration, previous therapies, demographic and anthropometric data, health-related quality of life etc.) will be selected which show a statistically significant partial correlation with the parameters of therapeutic success at month 3 (improvements in the number of affected joints [DAS28], HAQ, number of missed working days, and WPAI). Due to the clear temporal relation between the baseline values and the treatment effects at month 3, the selected predictors can be interpreted both as causal explanation and as prognosing factors concerning therapy-modifying influencing variables (since an reactive influence of the 3-month values on the baseline values can be ruled out). Additionally, the strength of the relationship between the predictors and the parameters of therapeutic success will be determined. The impact of the variables determined by regression analysis on the therapeutic success will be illustrated by subgroup analysis. The impact of adalimumab therapy on health-related quality of life (EQ-5D), the number of physician visits and hospitalization, the days of impairment in non-occupational activities, and the subjective symptoms (morning stiffness, pain, exhaustion/fatigue) will be descriptively evaluated and additionally analyzed by between-group comparison. Two interim analyses are planned. |
| Planned recruitment phase | March 2009 - March 2012 |
| Planned study duration | March 2009 – March 2018 |
| Product manufacturer | Abbott |

3 Abkürzungen und Definitionen

| | |
|---------|--|
| AE | Adverse event |
| AMG | Arzneimittelgesetz |
| BMI | Body Mass Index |
| CCP | Cyclic citrullinated peptide |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| CRP | C-reactive protein |
| DAS28 | Disease Activity Score 28 |
| DMARD | Disease Modifying Anti-Rheumatic Drug |
| EQ-5D | EuroQol Questionnaire 5 Dimensions |
| ESR | Erythrocyte sedimentation rate |
| FAS | Full analysis set |
| HAQ | Health Assessment Questionnaire |
| Hb | Hemoglobin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NIS | Non-interventional study |
| RF | Rheumatoid factor |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SDV | Source Data Verification |
| WPAI-GH | Work Productivity and Activity Impairment-General Health version |

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5 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints that often results in progressing joint destruction and lead to substantial functional losses, impairment, and reduced quality of life. On the social level, disease-related costs (due to lack of functionality) to be paid by social security systems are increasingly gaining priority (1), (2).

An important cytokine that activates and intensifies inflammation in RA is the tumor necrosis factor α (TNF- α). Introduction of TNF- α inhibitors 10 years ago revolutionized RA treatment options and led to the development of further recombinant antibodies and fusion products, respectively, which are called biologics. Adalimumab is one of these biologics, a human monoclonal antibody against TNF- α , which has been approved in Germany for RA treatment under the trade name HUMIRA® since 2003. Adalimumab inhibits the interaction of TNF- α with its receptors and thus suppresses the biological effect of this proinflammatory cytokine. HUMIRA® is administered as a subcutaneous (sc) injection at a recommended dose of 40 mg every other week.

Several clinical trials have shown that adalimumab both reduces the clinical symptoms of RA and decelerates the structural destruction of the joints, thus significantly improving health-related quality of life.

Patients who had been included in a non-interventional long term study and had been treated with adalimumab under conditions of routine rheumatology practice had been suffering from RA for many years (mean disease duration 12 years) and showed a high disease activity (DAS28 = 5.8). These patients experienced a significant reduction in clinical signs and symptoms of RA after 24 months of adalimumab therapy (interim analysis July 2007). 20 % of patients were in clinical remission and over 40 % had improved in their physical functionality.

Unlike the previous RA documentation, this NIS will put added emphasis on data concerning work productivity and work ability as well as data concerning health-related quality of life. This will result in an according large-scale patient documentation form.

In order to improve quality, all filled questionnaires will be checked for completeness and missing data will be added by written query. A defined percentage of participating physicians will be audited. An independent CRO will perform double data entry, perform plausibility checks and statistically evaluate the data according to criteria determined in the protocol. The results will be published after finalization of the evaluation.

The planned documentation is a non-interventional study (NIS) according to § 4 section 23, point 3, Arzneimittelgesetz (AMG) and will be conducted in compliance with the recommendations of the Verband der forschenden Arzneimittelhersteller (Association of Research-based Pharmaceutical Companies).

6 Rationale

This NIS is designed to provide additional data on treatment effects of adalimumab in the long term treatment in patients with moderate to severe active RA under conditions of routine rheumatology care. In contrast to clinical trials, all patients treated in clinical routine will be included in the NIS, independent of comorbidities, concomitant medication, severity of their illness, or features such as age and gender.

Course of work productivity and work ability, the course of health-related quality of life, and changes in functionality under long term treatment with adalimumab will be documented. The numbers of patients included in the NIS allow identifying and quantifying the impact of disease and patient characteristics on the therapeutic success.

7 Study Objectives

In this NIS, a long term documentation of treatment with adalimumab in RA patients over 60 months with 8 data collection points (visits) is planned. The documentation will be performed by the physician as well as by patient's self-assessment.

The primary objective is to explore the therapeutic success by interim analyses after 12 and 24 months of treatment as well as by the final analysis after 60 months of treatment. Improvements concerning the following target variables will be evaluated (with regard to the respective baseline value):

- the number of missed working days
- the self-assessed work ability (WPAI)
- the severity of clinical symptoms (number of tender and swollen joints, CRP and ESR, respectively; total score DAS28)
- Severity of functional impairment (HAQ)
- The health-related quality of life (EQ-5D)

At month 3, patient and disease characteristics will be evaluated with regard to their additional impact on changes in the number of affected joints (DAS28), in the HAQ, and in the WPAI. The impact on the number of missed working days will be evaluated at month 6.

The secondary objective is to document the therapeutic success by interim analyses at month 12 and 24 months as well as by the final analysis after 60 months. The therapeutic success will be evaluated by the following variables:

- The number of physician visits
- The number and duration of hospitalizations
- The number of days of impairment in non-occupational activities
- The duration of morning stiffness, pain, exhaustion/fatigue

-
- The reduction of number and dose of concomitant medication
 - Patient's assessment of adalimumab therapy compared to previous therapies

Target parameters for safety evaluation of adalimumab are:

- The evaluation of safety and tolerability by the documentation and analysis of serious adverse events (SAEs) and adverse events (AEs).
- Evaluation of safety and tolerability for subgroups of patients with common frequent concomitant diseases, especially diabetes type II, cardiovascular, liver, and renal insufficiencies, and related concomitant medications.

8 Investigational Plan

8.1 Selection of Study Population

This study population will consist of adult patients (≥ 18 years) with moderate to severe active rheumatoid arthritis (RA) who have failed other anti-rheumatic drugs including Methotrexat (MTX) and patients with a severe, active and progressive rheumatoid arthritis (with or without prior MTX).

Patients who have been previously treated with other biologics (including TNF inhibitors) can be included in the NIS.

The inclusion and exclusion criteria adhere to the approved label 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.

Patients to be included will be informed about the NIS and the use of their anonymous data. Patients willing to participate must provide their written informed consent to the investigator before entry into the NIS. The signed informed consent form will be added to the patient’s file.

8.2 Number of Patients to be Enrolled

The NIS will include about 2500 patients in order to provide for the final evaluation of missed working days a sample size of $n = 850$ employed patients who are temporarily on sick leave during the study (see also Section 12.1 “Sample Size Calculation”).

8.3 Investigator Selection Criteria

The data for this NIS will be collected from rheumatology outpatient departments and office-based rheumatologists in Germany routinely treating patients with RA. Physicians from about 200 sites which are spread across all of Germany will participate in this NIS.

Principal Investigator:

[REDACTED]

[REDACTED]

[REDACTED]

8.4 Study Duration

The duration of the whole NIS is estimated to be about 9 years.

Study start: March 2009

Recruiting phase: March 2009 – March 2012

Data completion: March 2017

Data analysis and final report: March 2017 – March 2018

For each individual patient, the NIS starts with the enrollment in the long term documentation at the beginning of the treatment with adalimumab and ends either after 5 years or with the termination of the adalimumab therapy.

8.5 Study Conduct

8.5.1 Schedule of Observations

This NIS will be a single-arm, multi-center, prospective cohort study.

Non-interventional studies are one of several methodical instruments to collect information on drugs available on the market. Their defining characteristic is the lack of influence on the relationship between individual physicians and patients in respect to determining indication as well as choice and conduct of the treatment, while at the same time allowing for the structured and systematic collection of treatment data (see also Section 6). Adalimumab must not be prescribed for the purpose of including a patient in this NIS.

Patients will be informed about the type of therapy, alternate therapies, and risks, and they have to provide a written informed consent to the data collection on the documentation forms before the start of therapy. The presence of the written informed consent is documented on the base documentation form. Before enrollment in the NIS, the patients will be made anonymous. Abbott will only receive access to anonymous data. Abbott can only identify the patients via their patient number.

The visits are scheduled according to the recommendations of the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology): The documentation consists of patient self-assessments as well as assessments by the physician. The following tables provide an overview of the observations to be documented by the physician ([Table 1](#)) and the patient ([Table 2](#)).

Due to long time intervals between the scheduled visits (one year after month 12), interim documentation forms will be provided for non-scheduled visits in order to document clinically significant events.

Table 1. Physician Schedule

| | Month | | | | | | | |
|---|-------|----------------|----------------|----------------|----|----|----|-----------------|
| | 0 | 3 | 6 | 12 | 24 | 36 | 48 | 60 ¹ |
| Demographic data | X | | | | | | | |
| Inclusion criteria | X | | | | | | | |
| Indication HUMIRA® | X | | | | | | | |
| Medical history / change history | X | X | X | X | X | X | X | X |
| Radiologic findings ² | X | | | X | X | X | X | X |
| Previous RA therapies | X | | | | | | | |
| Concomitant diseases and therapies ³ | X | X | X | X | X | X | X | X |
| Current HUMIRA® therapy ⁴ | X | X | X | X | X | X | X | X |
| RA-related concomitant medication ⁴ | X | X | X | X | X | X | X | X |
| Disease activity ⁵ | X | X | X | X | X | X | X | X |
| Current joint status ⁵ | X | X | X | X | X | X | X | X |
| Morning stiffness | X | X | X | X | X | X | X | X |
| Rheumatoid nodules | X | | | | | | | |
| Joint (replacement) surgery | X | | | X | X | X | X | X |
| Laboratory values: CRP, ESG, Hb-value, ⁶ | X | X | X | X | X | X | X | X |
| Laboratory values: RF, CCP ⁶ | X | | | | | | | |
| Laboratory values: Hepatitis B, Hepatitis C, tuberculosis screening, TB prophylaxis (if necessary) ⁶ | X | X ⁷ | X ⁷ | X ⁷ | | | | |
| Adverse events | | X | X | X | X | X | X | X |
| Patient's compliance | | X | X | X | X | X | X | X |

¹ Month 60 or last visit

² after baseline visit (month 0) only if current radiograph is available or if indicated

³ after baseline visit (month 0) only for newly developed diseases or changed therapy

⁴ after baseline visit only for changes in therapy or dose

⁵ Data are part of the DAS28 (Disease Activity Score)

⁶ after baseline visit (month 0) only if data is available or if indicated

⁷ only TB prophylaxis documented

Table 2. Patient Schedule

| | Month | | | | | | | |
|---|-------|---|---|----|----|----|----|----|
| | 0 | 3 | 6 | 12 | 24 | 36 | 48 | 60 |
| Personal data | X | | | | | | | |
| Education | X | | | | | | | |
| Professional status | X | | X | X | X | X | X | X |
| Missed working days (last 6 months) | X | | X | X | X | X | X | X |
| Physician visits and hospitalization (last 6 months) | X | | X | X | X | X | X | X |
| Days of impairment in non-occupational activities | X | | X | | X | X | X | X |
| Work ability (WPAI) | X | X | X | X | X | X | X | X |
| Exhaustion/fatigue (last 7 days) | X | X | X | X | X | X | X | X |
| Pain (last 7 days) | X | X | X | X | X | X | X | X |
| Functionality (HAQ) | X | X | X | X | X | X | X | X |
| Health-related quality of life (EQ-5D) | X | X | X | X | X | X | X | X |
| Patient's assessment of adalimumab therapy compared to previous therapies | | X | X | X | X | X | X | X |
| Participation Abbott Care service program | X | X | X | X | X | X | X | X |

8.5.2 Description of Activities

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

Physician:

Baseline Visit (Month 0)

Demographics and History

Demographic Data (age, gender, height, weight)

Inclusion criteria (moderate to severe active RA and/or severe, active, and progressive RA, signed informed consent)

Exclusion criteria according to Fachinformation (hypersensitivity, active tuberculosis, other severe infections [e.g. sepsis, opportunistic infections], moderate to severe heart insufficiency [NYHA class III/IV])

Indication for the current HUMIRA[®] therapy

Radiological findings of affected joints

History (including initial diagnosis of RA and tobacco use)

Previous therapies: DMARD (MTX, SASP, leflunomid), glucocorticoids, biologics (infliximab, etanercept, rituximab, tocilizumab, abatacept), date of biologic discontinuation

Concomitant diseases and concomitant medication

Current RA therapy

Current HUMIRA[®] therapy

Additional DMARD, systemic glucocorticoids, analgetics, NSAID, COX inhibitors

Current status

Disease activity, joint status (28 joints, tender, swollen), morning stiffness, rheumatoid nodules, previous joint surgery

Laboratory values (RF, CCP, CRP, ESR, Hb-value, hepatitis B, hepatitis C, tuberculosis screening, TB prophylaxis, pregnancy test in women with childbearing potential)

Follow-up Visits (Month 3, 6, 12, 24, 36, 48, 60)

Change history

Current therapy (RA therapy and concomitant medication)

Disease activity

Joint status

Morning stiffness

Joint (replacement) surgery (beginning month 12)

Radiographic findings (beginning month 12)

Laboratory values (CRP, ESR, Hb-value, other laboratory values if indicated)

(S)AE

Patient's compliance

Patient:

Baseline Visit (Month 0)

Personal data

Education

Professional status

Missed working days, days of impairment in non-occupational activities

Physician visit, hospitalization

WPAI, HAQ, and EQ-5D

Exhaustion/Fatigue, pain
Participation in the Abbott Care service program

Follow-up Visits (Month 3, 6, 12, 24, 36, 48, 60)

WPAI, HAQ, and EQ-5D
Exhaustion/Fatigue, pain
Patient's assessment of adalimumab therapy
Participation in the Abbott Care service program

Follow-up Visits (Month 6, 12, 24, 36, 48, 60)

As above, additionally:
Missed working days, days of impairment in non-occupational activities
Physician visits, hospitalization
Changes in the professional status

8.5.3 Scales and Scores

The following scores will be derived from the documented data:

Disease Activity Score (DAS28): The DAS28 indicates the severity of the RA. The score varies between 0 and 10, with 10 indicating the highest degree of severity. The DAS28 is calculated from the following data documented on the physician form:

- Joint status: Number of swollen and tender joints (each with a maximum of 28)
- ESR (mm/1. h) or CRP (mg/l)
- Patient's assessment of current disease activity (from 0 = inactive to 10 = highly active)

The DAS28 is calculated by means of a validated algorithm (4), (5).

Health Assessment Questionnaire (HAQ): The HAQ is the internationally most-used instrument for assessing RA-related functional impairment. The patient has to answer 20 questions concerning impairment in daily activities within the following 8 areas:

- Dressing & Grooming
- Arising

- Eating
- Walking
- Hygiene
- Reach
- Grip
- Activities

Patients assess their functionality over the past week by means of a 4-level scale ranging from 0 (without any difficulty) to 3 (unable to do). The highest (worst) values will be calculated into a mean value which indicates the degree of functional impairment (HAQ Disability Index: 0-3) (8).

WPAI: The WPAI is a questionnaire for the self-assessment of work productivity and activity impairment. In this observational study, the WPAI-GH is used which measures work productivity and activity impairment with reference to general health problems. All dimensions relate to the past seven days. The following dimensions are measured:

- Assessment of employment status
- Assessment of hours missed from work due to health problems and other reasons such as vacation or holidays (total number of hours to be indicated)
- Assessment of hours the patient has actually worked (total number of hours to be indicated)
- Assessment of impairment in work productivity and in regular daily activities (2 assessments with 10 levels each)

The WPAI yields four types of scores:

- ‘activity impairment’
- ‘absenteeism’ (work time missed)
- ‘presenteeism’ (impairment at work/reduced on-the-job effectiveness) and
- ‘work productivity loss’ (overall work impairment/absenteeism plus presenteeism).

Scores were transformed into percentages. Higher scores indicate greater impairment.

EuroQol-5 Dimensions (EQ-5D): The EQ-5D is a generic (not disease specific) instrument for measuring health-related quality of life. The patient questionnaire consists of two parts. The first part includes statements for the following five areas (dimensions):

- agility/mobility
- self-care
- usual activities
- pain, bodily discomfort
- anxiety, depression

For each dimension the patient is asked for a three-level assessment of his health on the current day: “no problems” (1), “some problems” (2), “extreme problems” (3). From the possible combinations of the five three-level areas result 241 different health-statuses.

The second part is a thermometer-scale (EQ-VAS) on which the patients rate their health on the current day between the endpoints “best health imaginable” (100) and “worst health imaginable” (0).

8.5.4 Study Medication

This is a non-interventional observational study with HUMIRA[®]. HUMIRA[®] is used according to the approved label for rheumatoid arthritis and is prescribed by the attending physician. Abbott does not provide any study medication.

HUMIRA[®]-injection is available as ready-to-use syringes and as pre-filled pen (injector, pre-filled/FertigPEN) and includes 40 mg adalimumab.

The recommended dose of HUMIRA[®] for adult patients with RA is 40 mg sc every other week.

9 Adverse Events

9.1 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 the 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 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 of drug abuse.

Spontaneous Abortion: Miscarriage experienced by study subject.

Elective Abortion: Elective abortion performed on study subject.

9.2 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 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.

9.3 Relationship to Pharmaceutical Product

The physician will use the following definitions for any adverse event being collected as an endpoint/data point 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 the 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.**

9.4 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 following the intake of the last dose of physician-prescribed treatment.

9.5 Serious Adverse Event Reporting

In the event of a serious adverse event – whether or not related to Abbott product or comparator, if applicable – the physician will notify the Abbott drug safety identified below within 24 hours of the physician becoming aware of the event. The notification will be performed via fax on the form labeled “Bericht über Schwerwiegende Unerwünschte Arzneimittelwirkungen”:



9.6 Pregnancy Reporting

In the event of a pregnancy, the physician will notify the Abbott drug safety identified below within 24 hours of the physician becoming aware of the pregnancy. The notification will be performed via fax on the base documentation form:



Reported pregnancies will be reported like SAEs.

10 Ethics and Quality

In accordance to the code of conduct of the German pharmaceutical industry, the German principal coordinating investigator [REDACTED] will forward the NIS study protocol to the ethics committee for approval:

[REDACTED]

The patient has to provide a written informed consent to use and/or disclose personal and/or health data before enrollment in the study. This written informed consent will be archived with the patient's file and documented on the report forms. According to § 67 section 6 AMG, the NIS will also be reported to the Kassenärztliche Bundesvereinigung (federal association of physicians), the umbrella organization of health insurance providers, and the responsible federal authority.

All patient data entered in the patient's CRF will be forwarded to Abbott GmbH & Co KG for evaluation - without naming the patient. Each CRF bears a pre-printed patient identification 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.

In-house monitoring of incoming CRF pages with respect to completeness and plausibility will be done by the CRO responsible for data management and statistics. Queries to the study centers will be handled by the sponsor.

Source data verification by the sponsor's monitor at the physician's site is planned for 5% of the documented patients. Informed consent, in- and exclusion criteria, and all available source data will be inspected.

This NIS will be sponsored by Abbott GmbH & Co. KG, [REDACTED]
[REDACTED]

11 Case Report Form

All data specified in Section 8.5 will be collected on paper forms (CRF). For each visit, the CRF includes forms to be completed by the physician as well as forms to be completed by the patient. Each center receives a folder with all documents and forms necessary for the baseline and follow-up documentation of five patients.

Any observation of an adverse event in the time period up to 60 months, beginning with the initiation of HUMIRA® therapy, is to 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 Schwerwiegende Unerwünschte Arzneimittelwirkungen' is to be completed additionally.

12 Data Analysis Plan

All statistical analysis procedures will be described in detail in a Statistical Analysis Plan (SAP). This plan will be developed by the responsible biometrician in collaboration with the sponsor. The SAP will be finalized and approved by the responsible biometrician, the sponsor, and the principle investigator before the database will be opened for the first interim analysis.

12.1 Sample Size Calculation

The primary parameter of this documentation is work productivity, which is captured by the number of missed working days. The sample size calculation is based on the results of an interim analysis of a documentation of adalimumab in RA with 4640 patients, of whom 1417 patients had been employed part time or full time. The mean number of missed working days was 26 days (standard deviation of 55 days) during the last 12 month prior to adalimumab therapy. The correlation between baseline and follow-up report is estimated with $r = 0.5$. According to these numbers, 850 employed patients are required to detect a mean difference of 5 days within 12 months at the 0.05 significance level (two-sided) with a power of 0.80. Since 30 % of patients are employed, a total number of about 2500 employed and non-employed patients are required in order to detect the specified difference in missed working days.

12.2 Analysis Population(s)

The data of all documented patients will be used in the statistical analysis of tolerability and safety of adalimuab. The data of patients whose RA had been treated with adalimuab previously will be excluded from the analysis of efficacy.

12.3 Missing Values

Missing observations will be documented as missing values. Instructions for the minimum documentation required for a patient to be evaluable will be established in the SAP.

All data will be analyzed on the basis of “observed cases”. For the statistical analysis of data concerning the course of disease, the health-related economic parameters and

the health-related quality of life (if related to changes from baseline values), an additional approach will be followed considering only patients with complete data at all visits.

12.4 Level of Significance

Inferential statistics will be performed at a nominal level of significance of 0.05 (two-sided). Due to the exploratory character of the analyses, the resulting p-values will not be adjusted for multiple testing.

12.5 Biometric Concept

The general biometric approach consists of the realization of the analyses described in section 7 “Study Objectives”. The analysis principally uses descriptive statistical methods, supported by regression statistical methods and subgroup analysis.

By forward and backward stepwise regression, those patient and disease characteristics (baseline values of all target parameters, disease duration, previous therapies, demographic and anthropometric data, health-related quality of life etc.) will be selected which show a statistically significant partial correlation with the parameters of therapeutic success at month 3 (improvements in the number of affected joints [DAS28], HAQ, number of missed working days, and WPAI). Due to the clear temporal relation between the baseline values and the treatment effects at month 3, the selected predictors can be interpreted both as causal explanation and as prognosing factors concerning therapy-modifying influencing variables (since an reactive influence of the 3-month values on the baseline values can be ruled out). Additionally, the strength of the relationship between the predictors and the parameters of therapeutic success will be determined.

The impact of the features determined by regression analysis on the therapeutic success will be illustrated by subgroup analysis. Subgrouping will be done according to content-related considerations: Regarding disease activity, patients will be classified into groups with high or low DAS28 values (lower and higher 5.1 units, respectively). Regarding age, patients will be classified into groups with high or low age (lower and higher 40 years, respectively).

The impact of adalimumab therapy on health-related quality of life (EQ-5D), the number of physician visits and hospitalizations, the days of impairment in non-occupational activities, and the subjective symptoms (morning stiffness, pain, exhaustion/fatigue) will be descriptively evaluated and additionally analyzed by between-group comparison.

The tolerability analysis will be based on MedDRA coded AEs and SAEs. Incidence rates will be reported on the “Preferred Term” and “System Organ Class” levels for all patients as well as for subgroups of patients with different degrees of disease activity as well as with different previous and concomitant therapies and diseases.

12.6 Times of Statistical Analyses

Interim analyses are planned after 3 and 5 years after the inclusion of the first patients, so that at month 12 and 24 sufficiently large groups of about 800 patients are available. The general analysis will be performed after closure of the follow-up of the last patient (8 years after starting the study).

13 Final Report and Publications

After the end of the NIS, an Integrated Final Report is generated in cooperation with the Principal Investigator, who also signs the report. The report includes a description of the objectives of the NIS, the employed methods, the results, as well as the conclusions. As the property of Abbott GmbH & Co. KG, the completed CRFs and the report are to be treated as confidential and may not be made accessible to unauthorized persons in any form (publication or presentation) without the explicit approval of Abbott GmbH & Co. KG. The results of this NIS may be published by Abbott GmbH & Co. KG or any of the participating investigators after approval by Abbott GmbH & Co. KG.

14 Literature

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