## Observational Study Information

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| **Acronym / Title** | **BETAPREDICT** - MS patients treated with BETAferon®: PREDICTors of treatment adherence |
| **Protocol version identifier** | Version 1.0 |
| **Date of last version of protocol** | 12.02.2015 |
| **IMPACT study number** | 18016 |
| **Study type** | ☐ non-PASS<br>☒ PASS Joint PASS: ☐ YES ☒ NO |
| **EU PAS register number** | Study not yet registered |
| **Active substance** | Cytokines, Interferones, Interferon beta-1b |
| **Medicinal product** | Betaferon®, (BAY 86-5046) |
| **Product reference** | EU/1/95/003/012 ATC Code: L03AB08 |
| **Procedure number** | N/A |
| **Marketing authorization holder(s)** | Bayer Healthcare AG, 51368 Leverkusen, Germany |
| **Research question and objectives** | The **primary objective** of this study is to determine baseline predictors of adherence to Betaferon® treatment after 12 and 24 months (co-primary end-point).<br>**Secondary objectives** are to evaluate at each visit:<br>• Satisfaction with the BETACONNECT™ autoinjector,<br>• Injection site pain,<br>• Flu-like symptoms following Betaferon® application,<br>• Analgesic use prior to Betaferon® application,<br>• Intake of vitamin D, other vitamins, and nutrients,<br>• If adherence to Betaferon® treatment is associated with:<br>▪ depression,<br>▪ health related quality of life,<br>▪ coping mechanisms*,<br>▪ self-management mechanisms, |

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| | ▪ social support*,<br>▪ fatigue, and<br>▪ cognition.<br>• If adherence to Betaferon® treatment at 12 (24) months is associated with number of relapses at 12 (24) months.<br>• If adherence to Betaferon® treatment at 12 (24) months is associated with EDSS change at 12 (24) months.<br>• .<br>• If adherence to Betaferon® treatment is associated with utilities of treatment (only baseline and final visit).<br>• With respect to the subgroup of patients participating in the PTMS program (participants from PTMS centers vs. participants from non-PTMS centers):<br>▪ At each visit, if the PTMS program is associated with:<br>• treatment adherence,<br>• depression,<br>• quality of life,<br>• self-management mechanisms,<br>• fatigue,<br>• cognition.<br>• In the subgroup of patients participating in the PTMS program:<br>▪ At each visit evaluation of:<br>• social support,<br>• coping behavior.<br><br>*only for patients participating in the PTMS program. |
| **Country(-ies) of study** | Germany |
| **Author** | Prof. Dr. med. Markus Schürks, MSc<br>Medical Project Leader<br>Neurology, Immunology & Ophthalmology<br>Building K56, 51368 Leverkusen, Germany |
| OS Template-Protocol Version | v2.0, 11 April 2014 |

## Marketing authorization holder

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| Marketing authorization holder(s) | Bayer Healthcare AG, 51368 Leverkusen, Germany |
| MAH contact person | Morgan Hugosson<br>Bayer Pharma AG<br>Müllerstr. 178, 13353 Berlin, Germany |

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

# 1 Table of contents

## 2 List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical (Classification System) |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DMP | Data Management Plan |
| EC | European Commission |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicine Agency |
| ENCePP | European Network of Centers in Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GPP | Good Publication Practice |
| GVP | Good Pharmacovigilance Practice |
| ICH | International Conference of Harmonization |
| HEOR | Health Economics and Outcomes Research |
| IEC | Independent Ethics Committee |
| INN | International Nonproprietary Name |
| IRB | Institutional Review Board |
| IT | Information Technology |
| MAH | Marketing Authorization Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | Not Applicable |
| OS | Observational Study |
| PAS | Post-Authorization Study |
| PASS | Post-Authorization Safety Study |
| QPPV | Qualified Person Responsible For Pharmacovigilance |

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| QRP | Quality Review Plan |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| WHO DD | World Health Organization Drug Dictionary |

# 3 Responsible parties

## 3.1 Sponsor / MAH

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## 3.2 Collaborators / Committees

Contact details on the coordinating and / or principal investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Table 2: List of stand-alone documents, Annex 1) which is available upon request.

Administrative changes of responsible persons and / or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

## 4 Abstract

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| **Acronym / Title** | BF1502, **BETAPREDICT** - MS patients treated with **BETA**feron®: **PREDICT**ors of treatment adherence |
| **Protocol version identifier** | Version 1.0 |
| **Date of last version of protocol** | 2015-02-12 |
| **IMPACT study number** | 18016 |
| **Study type** | ☐ non-PASS<br>☒ PASS Joint PASS: ☐ YES ☒ NO |
| **Author** | Prof. Dr. med. Markus Schürks, MSc<br>Medical Project Leader<br>Neurology, Immunology & Ophthalmology |
| **Rationale and background** | Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating and degenerative disorder of the central nervous system, primarily affecting young adults. The key prerequisite for an effective therapy is that patients follow their physicians' treatment recommendations, i.e. are compliant or adherent to therapy. However, non-adherence to therapy is a major challenge in all chronic diseases requiring long-term treatment. Systematic analyses aiming to determine predictors of adherence among MS patients in general and among those treated with Betaferon® in particular are scarce. Adherence among MS patients is low, constituting a serious public health challenge. Potential benefits on the individual disease course may be jeopardized and medical resources wasted. Factors determining adherence are complex and multi-layered; hence, we aim to comprehensively understand potential predictors of adherence by investigating a representative cohort of MS patients in Germany treated with Betaferon®. |
| **Research question and objectives** | The **primary objective** of this study is to determine baseline predictors of adherence to Betaferon® treatment after 12 and 24 months (co-primary end-point).<br>**Secondary objectives** are to evaluate at each visit:<br>• Satisfaction with the BETACONNECT™ autoinjector,<br>• Injection site pain,<br>• Flu-like symptoms following Betaferon® application, |

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| | • Analgesic use prior to Betaferon® application,<br>• Intake of vitamin D, other vitamins, and nutrients,<br>• If adherence to Betaferon® treatment is associated with:<br>  ▪ depression,<br>  ▪ health related quality of life,<br>  ▪ coping mechanisms*,<br>  ▪ self-management mechanisms,<br>  ▪ social support*,<br>  ▪ fatigue, and<br>  ▪ cognition.<br>• If adherence to Betaferon® treatment at 12 (24) months is associated with number of relapses at 12 (24) months.<br>• If adherence to Betaferon® treatment at 12 (24) months is associated with EDSS change at 12 (24) months.<br>• .<br>• If adherence to Betaferon® treatment is associated with utilities of treatment (only baseline and final visit).<br>  • With respect to the subgroup of patients participating in the PTMS program (participants from PTMS centers vs. participants from non-PTMS centers):<br>  ▪ At each visit, if the PTMS program is associated with:<br>  • treatment adherence,<br>  • depression,<br>  • quality of life,<br>  • self-management mechanisms,<br>  • fatigue,<br>  • cognition.<br>• In the subgroup of patients participating in the PTMS program:<br>  ▪ At each visit evaluation of:<br>  • social support,<br>  • coping behavior.<br><br>*only for patients participating in the PTMS program. |

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| **Study design** | Local, prospective, non-interventional, multi-center, observational cohort study. The study will be conducted in private neurological offices/clinics and neurology departments in Germany specialized in the treatment of MS patients. |
| **Population** | It is planned to collect data from 250 patients aged ≥ 18 years with relapsing remitting multiple sclerosis (RRMS) or a clinically isolated syndrome (CIS) who are treated with Betaferon® or will be treated with Betaferon and are willing to use the BETACONNECT™ autoinjector. The decision upon treatment with Betaferon® is made at the discretion of the attending physician, according to his/her medical practice. |
| **Variables** | The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits. |
| **Data sources** | Treating physician or designated medical person, medical records, routine measurements (e.g. EDSS), patient questionnaires. |
| **Study size** | The sample size calculation is based on Analysis of Variance (ANOVA) aiming to identify the number of patients needed to detect a given difference in compliance between three groups of patients, since the maximum number of groups or categories for our covariates under investigation will be three (e.g. smoking [current, past, never]). We have chosen a difference of 7% in adherence between groups as clinically meaningful. Overall comparison: to account for a standard deviation of 10% (alpha=0.1; power=0.80) and 20% incomplete or missing data, we will need to enroll a total of 240 patients. Pairwise comparison: to account for a standard deviation of 10% (alpha=0.05; power=0.80) and 20% missing or incomplete data we will need to enroll a total of 250 patients. |
| **Data analysis** | Statistical analyses will be of explorative and descriptive nature. All issues concerning patient validity, data consistency checks, permissible data modifications will be described in detail in the Data Management Plan. All statistical issues including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan. All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for |

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| | Regulatory Activities (MedDRA) version. |
| **Milestones** | Start of data collection: Q2 2015<br>End of recruitment: Q4 2016<br>End of data collection: Q4 2018<br>Final report of study results: Q1 2019 |

## 5 Amendments

None.

## 6 Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrollment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document.

Definitions:

- Start of study: first center initiated
- Start of data collection: FPFV
- End of data collection: LPLV
- Recruitment period: time from FPFV to LPFV
- End of study: 12 months after database clean / database closure but no later than 24 months after last patient last visit
- Observation period: time-window for data collection (FPFV to LPLV)
- Final report: Final report of study results 12 months after database close

Table 1: Milestones

| **Milestone** | **Planned date** |
|---|---|
| Start of study & data collection | Q2 2015 |
| Recruitment period | Q2 2015 until Q4 2016 |
| End of data collection | Q4 2018 |
| Interim statistical analysis | primary analysis will be at 12 and 24 months after inclusion |

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| Final report of study results | Q1 2019 |

## 7 Introduction: Background and Rationale

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating and degenerative disorder of the central nervous system, primarily affecting young adults.[1] MS presents with a chronic disease course and cannot be cured.

A number of established[2] and new medications[3] are available that were shown to modify disease course by reducing relapse rates and/or delaying disease and disability progression. However, optimal treatment response can only be achieved through early initiation[4-6] and continuous long-term treatment.[7]

The key prerequisite for an effective self-administered therapy is that patients follow their physicians' treatment recommendations, i.e. are compliant or adherent to therapy. In contrast, patients missing doses or interrupting therapy fare worse than patients adhering to their treatment regimen.[7-9] Furthermore, adherence was shown to have a direct effect on healthcare resource utilization and may thus affect healthcare costs.[9, 10]

However, non-adherence to therapy is a major challenge in all chronic diseases requiring long-term treatment.[11] Non-adherence rates among patients with MS taking disease-modifying drugs (DMDs) are particularly high reaching about 50% after 2 years of drug initiation.[12]

The World Health Organization has suggested that improving treatment adherence may have a larger effect on society and health than most major therapeutic advances.[13] In general, there are various methods to improve adherence,[11, 14] which may be grouped into the main categories:

- Improving patient care/patient centricity, including:
    - Improving communication between physicians and patients
    - Patient education
    - Extended clinic opening hours, thus shorter waiting times

and

- Improving medication application to enhance ease of use and tolerability, including:
    - Improved dosing schedules
    - Adequate management of side effects
    - Improvement in drug formulation

- Improvements in drug-delivery devices (for certain drugs)

These approaches focus on *external factors* and answer the question: "What can we do to help the patient/improve his/her adherence?" However, it is equally important to address the question: "How receptive is the patient for any of these factors/for help?" This refers to elucidating *internal factors* among MS patients including for example:

- disease-specific factors (disease duration, fatigue, disability, cognition, etc.),
- comorbidity (cognition, depression, anxiety, etc.),
- coping ability (acceptance of disease, perceived ineffectiveness of treatment, etc.),
- family support,
- demographic background, etc.

For example, MS patients suffer from increased mental health comorbidity compared to controls,[15] and treatment adherence has been associated with emotional status, personality, and cognition[16] as well as depression.[17] Further, more than half of non-adherent patients indicate "forgetting to take the medication" as the underlying reason,[18, 19] suggesting that a more detailed investigation of this behaviour may be warranted.

Systematic analyses aiming to determine predictors of adherence among MS patients in general and among those treated with Betaferon® in particular are scarce.

Some previous studies have looked at factors associated with non-adherence among MS patients in general. However, the definition of adherence may vary by study design and source of data (claims data vs. patients derived data).[11, 20] Further, many studies differ with respect to study design, source population investigated, duration of follow-up, focus of potential predictors investigated, etc. For example, a previous prospective cohort study among patients using various DMDs identified amount of alcohol consumed, history of missed doses, lower education and previous relapses as negative predictors of adherence after a mean follow-up of 2.4 years.[8] In addition, in the international MSBase registry younger age at treatment initiation and higher EDSS scores were predictive of DMD discontinuation.[21] A prospective study over 12-weeks among patients taking Copaxone® identified self-efficacy and self-injection competence as a positive predictor of adherence.[22] With respect to Betaferon® is has previously been reported that depression, quality of life and autoinjectors were predictors of adherence at two years, while coping styles were not.[23] However, the results may not be representative to the German population, since participants were primarily from the Middle East.

Some studies have reported differences in adherence between available DMDs.[24, 25] Hence, focusing on a well-characterized group of patients such as those treated with Betaferon® is advisable at the design stage to avoid confounding by mode of medication administration (injection vs. oral),

frequency of injection (Betaferon® vs. Rebif® vs. Avonex® vs. Copaxone®), medication group (interferones vs. glatiramer acetate), etc. Furthermore, in a heterogeneous group of patients (1) any factor that may be important for all MS patients might not be detectable because of the background data noise or a larger than necessary sample size would be required to detect it and (2) we may not be able to detect factors for adherence that are specific for Betaferon®.

Adherence among MS patients is low, constituting a serious public health challenge. Potential benefits on the individual disease course may be jeopardized and medical resources wasted. Factors determining adherence are complex and multi-layered; hence, we aim to comprehensively understand potential predictors of adherence by investigating a representative cohort of MS patients in Germany treated with Betaferon® by performing a prospective, observational study over two years in a real-world setting. This will help us to identify patients at risk of non-adherence early and to provide timely and individualized support. In order to have the right focus it is important to remember that our main interest is adherence to therapy, which refers to the drug being delivered into the patient's body. This may appear trivial; however, reporting methods of adherence (e.g. counting pills, verbal reportings, diaries) are indirect and for various reasons may not represent the true drug intake/application frequency. For the present study we will focus on patients using the BETACONNECT™ autoinjector, which automatically records every injection. During office visits it allows read-out of the stored injection data via a validated USB interface. This will avoid recall bias and allow an almost "direct" evaluation of therapy adherence. The BETACONNECT™ is a new electronic autoinjector, available in Germany since May 2014. Patients can obtain the device free of charge from their treating physician or nurse. The majority of patients on Betaferon® in Germany are using any kind of autoinjector for convenience reasons and many have opted for the BETACONNECT™ over the past eight months. It is expected that almost all new and existing Betaferon® patients in Germany will be using the BETACONNECT™ autoinjector by mid-2015.

As part of the study we also plan to evaluate whether the **P**sycho-educative **T**raining for patients with **MS** (PTMS)[26] may affect treatment adherence among patients using Betaferon®. The PTMS program is group-based trainings program that has been developed in 2009 and has been advanced since. It aims at helping patients deal with their MS as well as supporting them in developing a positive perspective of their lives, despite suffering from a chronic condition. The key focuses of the program are adequately coping with the disease, self-motivation for the required therapy, and continuity of treatment to ensure compliance/adherence.

The PTMS has been developed by a group of collaborating neurologists and psychologists. We have identified six neurology clinics, specialized in the treatment of MS offering the program as part of their clinical routine.

During clinical routine, the MS nurse or the treating neurologist recommends participation in the PTMS program if there is indication for inadequate coping, incompliance or deficit in knowledge about the disease. In general this pertains to all newly diagnosed patients, but also for example to experienced patients with "needle fatigue". Interested patients with the confirmed diagnosis of MS will be evaluated by a group leader. Exclusion criteria are severe depression or severe cognitive impairment. Groups consist of six to ten patients. The 90 minute sessions will be held with one to two weeks between each session until a series of 10 sessions has been completed. Sessions are mostly led by an experienced psychologist or MS nurse; however, sessions three, four and nine will be led by a physician or social worker. The program comprises knowledge transfer, exchange of experiences, role play, discussions, and self-reflection via diary.

The endpoints pertaining to the evaluation of the PTMS program, coping mechanisms, and social support will only be evaluated in patients from the six centers offering the program.

Approximately 90% of Betaferon® patients in Germany participate in the BETAPLUS® nurse support program. Hence, a subgroup analysis among those patients—while feasible—may not yield additional information and is not planned.

# 8 Research questions and objectives

## 8.1 Primary objective

The primary objective of this study is to determine baseline predictors of adherence to Betaferon® treatment after 12 and 24 months (co-primary end-point).

## 8.2 Secondary objective(s)

Secondary objectives are to evaluate at each visit:

- Satisfaction with the BETACONNECT™ autoinjector,
- Injection site pain,
- Flu-like symptoms following Betaferon® application,
- Analgesic use prior to Betaferon® application,
- Intake of vitamin D, other vitamins, and nutrients,
- If adherence to Betaferon® treatment is associated with:
    - depression,
    - health related quality of life,
    - coping mechanisms*,
    - self-management mechanisms,
    - social support*,

    - fatigue, and
    - cognition.
- If adherence to Betaferon® treatment at 12 (24) months is associated with number of relapses at 12 (24) months.
- If adherence to Betaferon® treatment at 12 (24) months is associated with EDSS change at 12 (24) months.
- If adherence to Betaferon® treatment is associated with utilities of treatment (only baseline and final visit).
- With respect to the subgroup of patients participating in the PTMS program (participants from PTMS centers vs. participants from non-PTMS centers):
    - At each visit, if the PTMS program is associated with:
        - treatment adherence,
        - depression,
        - quality of life,
        - self-management mechanisms,
        - fatigue,
        - cognition.
- In the subgroup of patients participating in the PTMS program:
    - At each visit evaluation of:
        - social support,
        - coping behavior.

*only for patients participating in the PTMS program.

All of the patient reported outcomes listed are pertinent to the study question, since they either constitute typical complaints by patients or comorbidities often associated with MS. They are hypothesized to be among the main variables determining adherence (see analysis section). The results are meant to help the attending physician guide the patient and focus on the most important variables at baseline determining adherence over time. Further, it is important to evaluate if any of these variables changes over time (secondary objectives), in order to help the treating physician adjust his focus during the course of the treatment. We would like to emphasize that we are not collecting these data for the purpose of learning anything new about these complaints or the comorbidities *per se*, but we need to record them in order to understand which of these are predictors of adherence. Number of relapses or changes in EDSS may be reasons to terminate treatment. While we do not have this information at baseline, we aim to collect this incident information during the study course (secondary

objectives). This will help evaluating if number of relapses of changes in EDSS is associated with adherence at any of the follow-up visits.

# 9 Research methods

## 9.1 Study design

The BETAPREDICT study is a local, prospective, non-interventional, company-sponsored, multi-center, single arm observational cohort study. The study will be conducted in doctor's offices run by neurologists as well as hospitals and neurology departments across Germany specialized in the treatment of MS patients. All institutions accept patients covered by public or private health insurance as well as self-pay patients. For each patient, the investigator will document data in standardized electronic case report forms (eCRF) at initial, follow-up and the final visit. It is planned to collect data from 250 patients with relapsing remitting multiple sclerosis (RRMS) or patients with a clinically isolated syndrome (CIS) who are treated with Betaferon® or will be treated with Betaferon® and are willing to use the BETACONNECT™ autoinjector in order to determine baseline predictors of adherence to Betaferon® treatment after 12 and 24 months. The decision upon treatment with Betaferon® is made at the discretion of the attending physician, according to his/her medical practice.

### 9.1.1 Primary endpoint(s)

The term "adherence" as used in this protocol is used as an umbrella term capturing various aspects of how patients follow their treatment regimen, including "compliance", "persistence", and "overall adherence". Hence, the primary endpoints will be the following:

The primary endpoint is:

- Compliance to therapy (%)

Co-primary endpoints are:

- Persistence of therapy (yes, no)
- Overall adherence to therapy (yes, no)

### 9.1.2 Secondary endpoint(s)

The secondary endpoints are:

- Satisfaction with the BETACONNECT™ autoinjector
- Injection site pain
- Flu-like symptoms

- Analgesic use prior to Betaferon® application
- Intake of vitamin D, other vitamins, and nutrients
- Depression
- health related quality of life
- coping mechanisms*
- self-management mechanisms
- social support*
- fatigue
- cognition
- number of relapses at 12 and 24 months
- EDSS change at 12 and 24 months
- utilities of treatment

*to be evaluated only in the subgroup of patients participating in the PTMS program.

### 9.1.3 Strengths of study design

This is a prospective, non-interventional, multi-center, single arm cohort study with patients with relapsing remitting multiple sclerosis (RRMS) or patients with a clinically isolated syndrome (CIS) who are treated with Betaferon® or will be treated with Betaferon® and are willing to use the BETACONNECT™ autoinjector a routine clinical practice setting. This study will include patients from a more diversified and less selected patient population than in a clinical trial setting, using fewer eligibility criteria to be as representative as possible.

## 9.2 Setting

The study will be conducted in in private neurological offices/clinics and neurology departments across Germany specialized in the treatment of MS patients. For each patient, the investigator will document data in standardized electronic case report forms (eCRF) at initial, follow-up and the final visit. It is planned to collect data from 250 patients with relapsing remitting multiple sclerosis (RRMS) or patients with a clinically isolated syndrome (CIS) who are treated with Betaferon® or will be treated with Betaferon® and are willing to use the BETACONNECT™ autoinjector in order to determine baseline predictors of adherence to Betaferon® treatment after 12 and 24 months. The decision upon treatment with Betaferon® is made at the discretion of the attending physician, according to his/her medical practice.

### 9.2.1 Eligibility

The study population will consist of male & female patients with relapsing remitting multiple sclerosis (RRMS) or patients with a clinically isolated syndrome (CIS) who are treated with Betaferon® or will be treated with Betaferon® and are willing to use the BETACONNECT™ autoinjector according to the attending physician's decision.

### 9.2.2 Inclusion criterion/criteria

- Patients aged ≥ 18 years with the diagnosis of relapsing remitting multiple sclerosis or a clinically isolated syndrome.
- Patients must be on treatment with Betaferon® or the decision to treat patients with Betaferon® has been made by the attending physician.
- Patients must be using or willing to use the BETACONNECT™ autoinjector for Betaferon® application.
- Written informed consent must be obtained.

### 9.2.3 Exclusion criterion/criteria

- Patients receiving any other disease modifying drug.
- Contraindications of Betaferon® described in the Summary of Product Characteristics.
- Patients participating in any other clinical or non-interventional study, evaluating MS therapy.

### 9.2.4 Withdrawal

Each patient has the right to refuse further participation in the study at any time and without providing any reason. A patient's participation is to be terminated immediately upon his/her request. In this non-interventional study, withdrawal from the study is independent of the underlying treatment. On the other hand, premature discontinuation of treatment, which includes switching from Betaferon® to other treatments, automatically implies end of documentation. While fully respecting the patient's rights, the investigator should seek to obtain the reason and record this on the Case Report Form (CRF).

### 9.2.5 Replacement

Patients will not be replaced after drop out.

### 9.2.6 Representativeness

No further selection than outlined in Sections 9.2.1 – 9.2.3 should be made and patients should be enrolled consecutively in order to avoid selection bias. With respect to site selection this study could have potential limited representativeness (convenience sample) as we are looking for experienced specialized sites & departments in the management and treatment of MS.

### 9.2.7 Visits

The investigator documents an initial visit, follow-up visits and a final visit for each patient in the case report form (CRF). Follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits. However, documented visits should be approximately six months apart. The final visit is to be documented after approximately 24 months. The observation period for each patient is therefore approximately 24 months.

**Enrollment / Initial visit**

Once a patient is found eligible for inclusion, the investigator will inform the patient about the study. Where applicable, this will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

Typical information to be collected at the baseline visit includes:

- Date of visit
- Date of birth (at least year)
- Sex (female, male)
- Race / ethnicity (Caucasian, asian, black, other)
- Height (cm)
- Weight (kg)
- Smoking (current, past, never)
- Employment status (employed, retired, keeping house, student, seeking work, self-employed, other, not reported)
- Education level (elementary education, secondary education, college or university education, not reported)
- Marital status (married/partnership, single)
- Medical history
    - Concomitant diseases
    - Concomitant medication
        - Trade name or INN
        - Start date (at least year)
        - Stop date or "continued"
        - Daily dose, if applicable
        - Indication
- Intake of vitamin D supplements (yes vs. no; if yes which dosage?)
- Intake of other nutrients or vitamins (yes vs. no)

- Specific MS history
    - Date of first clinical event suggestive of MS (DD/MM/YYYY)
    - Date of initial diagnosis (DD/MM/YYYY)
    - diagnostic criteria
        - according to McDonald criteria
        - according to Poser criteria (CDMS)
    - Number of further demyelinating events/relapses (number during past 2 years)
        - If number >0: date of onset (DD/MM/YYYY), ongoing
    - Concomitant diseases of special interest
        - Depression
        - Anxiety
        - Fatigue
    - Betaferon® administration record
        - Betaferon® treatment (ongoing/naive)
        - Date of first Betaferon® injection (DD/MM/YYYY)
    - Current application form for Betaferon® (prior to study)
        - Manual injection (yes/no)
        - Use of auto-injection device (yes/no)
            - If Yes, please tick (BETACONNECT™, BETACOMFORT®, BETAJECT Comfort®, BETAJECT lite®, other)
    - Treatment days with Betaferon® during last month
        - Number of expected treatment days
        - Number of true treatment days
        - N/A
    - Participation in the BETAPLUS® nurse support program (yes/no)
    - Participation in the PTMS program (yes/no)
    - injection-site reactions (yes vs. no; if yes: redness, other discoloration, hematoma, induration, lipodystrophy, necrosis; if yes: mild, moderate, severe)
    - previous use of other MS drugs (yes/no; if yes please specify)
- Examination results
    - EDSS

- Local skin reactions (yes/no)
    - If yes; please tick

      a) (redness, other discoloration, hematoma, induration, lipodystrophy/-atrophy, necrosis)

      b) (mild, moderate, severe)
- Patient Questionnaire (QQ) results available (yes/no), if yes
    - please send back
- SF-36 results available (yes/no), if yes
    - please send back
- EQ-5D results available (yes/no), if yes
    - please send back
- CES-D results available (yes/no), if yes
    - please send back
- WEIMuS results available (yes/no), if yes
    - please send back
- SDMT results available (yes/no), if yes
    - please send back
- CMSS results available (yes/no)*, if yes
    - please send back
- MSSM-R results available (yes/no), if yes
    - please send back
- ISU-DYA results available (yes/no)*, if yes
    - please send back

*only for patients participating in the PTMS program.

**Follow-up visits during treatment**

Typical information to be collected at follow-up visits include:

- Date of follow-up visit (DD/MM/YYYY)
- Study continued (yes/no), if no
    - please complete end of observation visit

- Smoking (current, past, never)
- Employment status (employed, retired, keeping house, student, seeking work, self-employed, other, not reported)
- Marital status (married/partnership, single)
- Concomitant diseases
- Concomitant medication
    - Trade name or INN
    - Start date (at least year)
    - Stop date or "continued"
    - Daily dose, if applicable
    - Indication
- Disease course
    - Number of further demyelinating events/relapses (enter 0 if no further event since last visit)
        - If number >0: date of onset (DD/MM/YYYY)/ongoing
- Specific MS history
    - BETACONNECT™ auto-injector device still used (yes/no)
        - If no, please tick: Betaferon® treatment (ongoing/prematurely discontinued/unknown)
        - If ongoing, please specify which way of injection is used
            - Manual injection, BETACOMFORT®, BETAJECT Comfort®, BETAJECT lite®, other
        - If prematurely discontinued
            - last date of Betaferon® injection (DD/MM/YYYY)
            - reason [adverse event (please complete AE page), lack of efficacy, pregnancy, patient's wish, choice of other treatment (please specify)]
- Treatment days with Betaferon® since last visit
    - Number of expected treatment days
    - Number of true treatment days
- Local skin reactions (yes/no)
    - If yes; please tick

        - a) (redness, other discoloration, hematoma, induration, lipodystrophy/-atrophy, necrosis)
        - b) (mild, moderate, severe)
- Participation in the BETAPLUS® nurse support program (yes/no; if no, please specify termination date)
- Participation in the PTMS program (yes/no; if no, please specify termination date)
- Intake of vitamin D supplements (yes vs. no; if yes which dosage?)
- Intake of other nutrients or vitamins (yes vs. no)
- EDSS
- Patient QQ results available (yes/no), if yes
    - please send back
- SF-36 results available (yes/no), if yes
    - please send back
- CES-D results available (yes/no), if yes
    - please send back
- WEIMuS results available (yes/no), if yes
    - please send back
- SDMT results available (yes/no) [only follow-up visit 2], if yes
    - please send back
- CMSS results available (yes/no)*, if yes
    - please send back
- MSSM-R results available (yes/no), if yes
    - please send back
- ISU-DYA results available (yes/no)*, if yes
    - please send back
- Change of concomitant medication compared to last visit (yes/no), if yes
    - Please fill out Concomitant Medication page
- Did adverse events or device events occur since the last visit (yes/no), if yes: Please fill out Adverse Event Report/Device Event Report

*only for patients participating in the PTMS program.

**Final Visit and End of Observation period**

The final data collection (last visit) is after approximately 24 months, at discontinuation of therapy or at end of study (whatever is earlier). At this final observation point, the patient's condition and a treatment assessment will be documented, including:

- Date of follow-up visit (DD/MM/YYYY)
- Study continued (yes/no), if no
    - please complete end of observation visit
- Smoking (current, past, never)
- Employment status (employed, retired, keeping house, student, seeking work, self-employed, other, not reported)
- Marital status (married/partnership, single)
- Medical history
    - Concomitant diseases
    - Concomitant medication
        - Trade name or INN
        - Start date (at least year)
        - Stop date or "continued"
        - Daily dose, if applicable
        - Indication
- Disease course
    - Number of further demyelinating events/relapses (enter 0 if no further event since last visit)
        - If number >0: date of onset (DD/MM/YYYY)/ongoing
- Specific MS history
    - BETACONNECT™ auto-injector device still used (yes/no)
        - If no, please tick: Betaferon® treatment (ongoing/prematurely discontinued/unknown)
        - If ongoing, please specify which way of injection is used
            - Manual injection, BETACOMFORT®, BETAJECT Comfort®, BETAJECT lite®, other
        - if prematurely discontinued
            - last date of Betaferon® injection (DD/MM/YYYY)

- reason [adverse event (please complete AE page), lack of efficacy, pregnancy, patient's wish, choice of other treatment (please specify)]

- Treatment days with Betaferon® since last visit
    - Number of expected treatment days
    - Number of true treatment days
- Local skin reactions (yes/no)
    - If yes; please tick
        - a) (redness, other discoloration, hematoma, induration, lipodystrophy/-atrophy, necrosis)
        - b) (mild, moderate, severe)
- Participation in the BETAPLUS® nurse support program (yes/no; if no, please specify termination date)
- Participation in the PTMS program (yes/no; if no, please specify termination date)
- Intake of vitamin D supplements (yes vs. no; if yes which dosage?)
- Intake of other nutrients or vitamins (yes vs. no)
- EDSS
- Patient QQ results available (yes/no), if yes
    - please send back
- SF-36 results available (yes/no), if yes
    - please send back
- EQ-5D results available (yes/no), if yes
    - please send back
- CES-D results available (yes/no), if yes
    - please send back
- WEIMuS results available (yes/no), if yes
    - please send back
- SDMT results available (yes/no), if yes
    - please send back
- CMSS results available (yes/no)*, if yes
    - please send back
- MSSM-R results available (yes/no), if yes

- please send back

- ISU-DYA results available (yes/no)*, if yes
    - please send back
- Change of concomitant medication compared to last visit (yes/no), if yes
    - Please fill out Concomitant Medication page
- Did adverse events or device events occur since the last visit (yes/no), if yes: Please fill out Adverse Event Report/Device Event Report

*only for patients participating in the PTMS program.

## 9.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits. The investigator documents the study-relevant data for each patient in the electronic case report form (eCRF). All variables as indicated in **Table 1** are routinely collected during regular office visits. The CRF is available upon request (see Table 2: List of stand-alone documents, Annex 1).

**Table 1: Tabulated overview on variables collected during the study**

| Variables | Initial visit | Follow-up visit 1 | Follow-up visit 2 | Follow-up visit 3 | Final visit |
|---|---|---|---|---|---|
| Demography | X | | | | |
| Employment status | X | X | X | X | X |
| Education | X | | | | |
| Smoking | X | X | X | X | X |
| Vitamin D intake | X | X | X | X | X |
| Other vitamin or nutrient intake | X | X | X | X | X |
| Medical history | X | | | | |
| Specific MS history | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X |
| Concomitant diseases | X | X | X | X | X |
| Disease course | | X | X | X | X |
| Expanded Disability Status Scale | X | X | X | X | X |
| Local skin reactions | X | X | X | X | X |

| | | | | | |
|---|---|---|---|---|---|
| Expected/true treatment days | X | X | X | X | X |
| Symbol Digit Modalities Test (SDMT) | X | | X | | X |
| Participation in the BETAPLUS® nurse support program | X | X | X | X | X |
| Participation in the PTMS program | X | X | X | X | X |
| Satisfaction with current way of Betaferon® injection | X | X | X | X | X |
| Injection site pain with current way of Betaferon® injection | X | X | X | X | X |
| Flu-like symptoms following application of Betaferon® | X | X | X | X | X |
| Prophylactic analgesic use prior to Betaferon® injection with current way of injection | X | X | X | X | X |
| Using electronic features of BETACONNECT™ | X | X | X | X | X |
| CES-D questionnaire (depression) | X | X | X | X | X |
| SF-36 questionnaire (HrQoL) | X | X | X | X | X |
| EQ-5D (utilities) | X | | | | X |
| WEIMuS questionnaire (fatigue) | X | X | X | X | X |
| MSSM-R questionnaire (self-management) | X | X | X | X | X |
| CMSS questionnaire (coping)* | X | X | X | X | X |
| ISU-DYA Inventory (social support)* | X | X | X | X | X |
| Adverse Events | | X | X | X | X |
| Medical Device related events and PTCs (including use errors) | | X | X | X | X |
| Reason for end of observation | | | | | X |

*only for patients in centers, where the PTMS program is offered

### 9.3.1 Variables to determine the primary endpoint(s)

The variables for our primary objective are:

- Compliance to therapy
- Persistence of therapy
- Overall Adherence to therapy

They will be derived in the following way:

Adherence to therapy:

In the medical literature there is no commonly agreed upon definition of adherence. The term adherence has largely replaced the term compliance, as it implies a less directive way of treatment, but acknowledges the patient's participation in the treatment plan in the sense of a shared-decision-making. Beyond this difference in definition both terms refer to the same aspect of treatment, specifically to what extend patient treatment behaviors match the treatment plan. Adherence may be measured in various ways.[27, 28] For our study we will ascertain adherence in different ways to account for different aspects of patient treatment behavior:

1. Compliance in percentage—this measure allows a general appreciation of the average patient treatment behavior (and spread) in the whole cohort investigated. It will be calculated as follows:

   Compliance (%) = ((expected # of treatment days during observation period - missed # of treatment days during observation period)/(expected # of treatment days during observation period))*100

2. Persistence (dichotomous, yes vs. no)—this measure allows a special view on those patients that completely stopped taking their medication vs. those continuing ("persisting") their medication (regardless of the frequency of intake)

3. Overall adherence—this measure will combine compliance and persistence to account for and allow comparison with studies basing their analysis on the "medication possession ratio" (MPR).[28] Patients will be defined as being adherent to therapy if they fulfill the following criteria:

   a. They have been at least 80% compliant, i.e. injected ≥80% of the expected Betaferon® dosages[20, 24, 25, 28] and

   b. They have not dropped out of the study prior to the time of evaluation (i.e. they did not stop Betaferon® treatment for any reason including switching to another medication prior to the time of evaluation).

Based on this definition adherence will be a dichotomous variable, which can be either "yes" or "no".

4. Number of dosages missed - to further characterize and quantify non-compliance we will also calculate the number of dosages missed[8]

For this study "compliance" in percentage will be our primary outcome variable while persistence and adherence will be considered as co-primary outcome variables.

We will evaluate each of these measures at each of the follow-up visits as well as change from previous follow-up visit starting at follow-up visit 2.

Ascertainment of injection data:

Given the electronic features of the BETACONNECT™ auto-injector, which automatically records injections, we will be able to obtain an unbiased number of injections from patients using this device.

### 9.3.2 Variables to determine the secondary endpoint(s)

These outcome variables for secondary objectives will be collected at each visit:

- Satisfaction with the BETACONNECT™

  Satisfaction will be evaluated with the following question on the *patient questionnaire*:

  - Overall how would you rate your satisfaction with the BETACONNECT™ autoinjector device on a scale from 0 to 10, where "0" means "not satisfied at all" and "10" means "entirely satisfied"? Please mark one of the boxes below.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|

- Injection site pain

  Injection site pain will be evaluated with the following question on the *patient questionnaire*:

  - Overall, when using the BETACONNECT™ auto-injector, how would you rate your intensity of injection site related pain on a scale from 0 to 10, where "0" means "no pain at all" and "10" means the "worst possible pain"? Please mark one of the boxes below.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|

- Usage of analgesics prior to Betaferon® injection & Flu-like symptoms

  Patients will be asked the following questions on the *patient questionnaire*:

  - When using Betaferon® are you using any analgesics prior to injection?
    a. No
    b. Yes
  - When using Betaferon®, do you experience flu-like symptoms like fever, myalgia, chills, or headaches?
    a. No

b. Yes

- Depression

  *Center for Epidemiologic Studies Depression Scale (CES-D)/ Allgemeine Depressionsskala (ADS-L)*

  The CES-D is a self-administered questionnaire to measure symptoms of depression experienced during the past week.[29] It includes 20 items comprising six scales reflecting major dimensions of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance.
  For this study we will use the ADS-L, which is the validated German translation of the CES-D.[30]

- Health related quality of life

  *Short Form-36*

  The SF-36 is a multi-purpose, short-form health survey with 36 questions designed for use in clinical practice and research, health policy evaluations, and general population surveys.[31] The SF-36 includes one multi- item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone. Each scale is directly transformed into a 0-100 scale.

- Coping mechanisms*

  *The Coping with MS Scale (CMSS)*

  The CMSS is a multidimensional coping inventory to assess different ways people with MS respond to illness-related stressors.[32] It consists of 29 items covering seven categories (problem solving, physical assistance, emotional release, avoidance, personal health control, acceptance, energy conservation). Each item can be rated on a seven-point scale (1=not stressful at all to 7=extremely stressful).

- Self-management mechanisms

  *Multiple Sclerosis Self-Management Scale-Revised (MSSM-R)*

The MSSM-R is a brief and multidimensional scale for research and clinical applications.[33] It was created as an instrument that addresses both the multidimensional nature of self-management in general and those aspects of self-management that may be specific to the experience of persons with MS. It consists of 24 items, each of which can be scored on a 5-point Likert scale (1= I completely disagree to 5=I completely agree). Factor analysis has identified the following five subscales: (1) Healthcare provider relationship and communication; (2) treatment adherence/barriers; (3) Social/family support; (4) MS knowledge and information; and (5) Health maintenance behavior. The composite scale has been found to be correlated with quality of life, self-efficacy, and functional impact scales.

- Social support*

  *Inventory of Social Support in Dyads (Inventar zur sozialen Unterstützung in Dyaden; ISU-DYA)*

  In order to examine supportive interactions within stressful situations it is necessary to consider both providers' and recipients' reports (the "dyad"). The ISU-DYA was developed to retrospectively assess support as well as mobilization behavior in a specific stressful episode from both perspectives of the dyad. Factor analysis has identified five mobilization scales (1. requesting feedback and advice; 2. demanding help; 3. search for physical contact; 4. emotional expression; 5. ostentatious withdrawal) and three support scales (1. emotional, 2. informational, 3. instrumental support).

- Fatigue

  *Würzburger Fatigue Inventory for MS (Würzburger Erschöpfungs-Inventar bei Multipler Sklerose; WEIMuS)*

  The WEIMuS is a two-dimensional, easy to use self-administered questionnaire in order to appropriately assess MS-associated fatigue.[34] The questionnaire consists of two scales covering both "physical fatigue" (8 items) and "cognitive fatigue" (9 items). Each item can be scored on a scale from 0 to 4.

- Cognition

  *The Symbol Digit Modalities Test (SDMT)*

  The SDMT is used to investigate cognitive functioning over time and in response to treatment with high sensitivity.[35] It is brief and easy to administer, screening for possible motor, visual, learning, or other cerebral dysfunction. The SDMT involves a simple substitution task. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Because examinees can give either written or spoken responses, the test is well suited for use with

individuals who have motor disabilities or speech disorders. Because it involves only geometric figures and numbers, the SDMT is relatively culture free as well and can be administered to individuals who do not speak English.

- number of relapses at 12 and 24 months

- EDSS (Expanded Disability Status Scale)

- utilities of treatment (only at baseline and final visit)
  *Derived from the **EQ5-D** questionnaire*
  The EQ-5D is a health questionnaire providing a one dimensional quality of life assessment.[36] The score ranges from 5 (very good) to 15 (extremely low). It was developed in 1987 by an international interdisciplinary group consisting of physicians, psychologists, philosophers, economists, nurses, and sociologists. The questionnaire evaluates five dimensions of health: mobility, ability to care for oneself, activities of daily life, pain, and anxiety.

### 9.3.3 Demography

For demographic / socio-demographic assessment, the following data will be recorded:

- Date of birth (at least year)
- Sex (female, male)
- Race / ethnicity (Caucasian, asian, black, other)
- Height (cm)
- Weight (kg)
- Marital status (married/partnership, single)
- Employment status (employed, retired, keeping house, student, seeking work, self-employed, other, not reported)
- Education level (elementary education, secondary education, college or university education, not reported)
- Smoking (current, past, never)
- Intake of vitamin D supplements (yes vs. no; if yes which dosage?)
- Intake of other nutrients or vitamins (yes vs. no)

### 9.3.4 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that were present before start of therapy with Betaferon, independent on whether or not they are still present. They have to be documented in the Medical History / Concomitant Diseases section. Concomitant diseases of special interest are depression, anxiety, and fatigue.

For any co-morbidity, the diagnosis, the start and the stop date/ongoing have to be documented.

### 9.3.5 Prior and concomitant medication

All medication taken before study start (initiated and stopped before study start) is termed prior medication. Prior medication meeting the criteria listed below are considered to be relevant to the study indication have to be documented:

- disease-modifying drugs or immunosuppressants for treatment of MS
- medication to treat MS associated symptoms like depression, fatigue or spasticity

All medication taken in addition to the product for any indication (either initiated before study start or during the study) is termed concomitant medication.

Information to be collected for medication includes: trade name or INN, start date, stop date/ongoing, dose, unit, frequency, application route, indication.

### 9.3.6 Exposure / treatment

Information on Betaferon to be documented include:

- Start and stop date
- Dose
- Expected number of treatment days
- True number of treatment days
- injection-site reactions (yes vs. no; if yes: redness, other discoloration, hematoma, induration, lipodystrophy, necrosis; if yes: mild, moderate, severe)
- flu-like symptoms (yes vs. no)
- Prophylactic analgesic use prior to injection (yes vs. no)

### 9.3.7 Assessment of therapy

N/A

### 9.3.8 Visits

- Initial visit: baseline
- Follow-up visit 1: after approximately 6 months
- Follow-up visit 2: after approximately 12 months
- Follow-up visit 3: after approximately 18 months
- Final visit: after approximately 24 months

## 9.4 Data sources

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's investigator is able to identify the patient based on the patient identification code.

## 9.5 Study Size

Based on the following considerations we plan to enroll a total of 250 patients into our study:

We have performed a sample size calculation based on an Analysis of Variance (ANOVA) aiming to identify the number of patients needed to detect a given difference in compliance between three groups of patients, since the maximum number of groups or categories for our covariates under investigation will be three (e.g. smoking [current, past, never]). Most of the covariates have only two categories (e.g. participation in the BETAPLUS® program [yes, no]). There are no data available as to which change in compliance might be regarded as clinically meaningful; however, following internal and external discussions we think that a 7-10% change should be achieved. We have conservatively chosen a 7% difference.

In *table 1* we present the maximum sample sizes needed to detect a difference of 7% in the overall comparison for a predictor with three groups/categories assuming an alpha=0.1in order to have a power of 80%. The sample size is given for a range of standard deviations (SD; 8%, 10%) and assuming different distributions for the predictor groups/categories (1:1:1, 5:2:1).

*Table 1*: sample size calculation for the overall comparison (alpha=0.1)

| Difference in compliance (%) | SD 8% | | SD 10% | |
|---|---|---|---|---|
| | Group ratio | Group ratio | Group ratio | Group ratio |

| | 1:1:1 | 5:2:1 | 1:1:1 | 5:2:1 |
|---|---|---|---|---|
| 7 | **63** | **128** | **99** | **192** |

As sketched in the table 63 patients would be needed for example to detect a difference of 7% if the standard deviation is 8% and the group ratio 1:1:1. For an extreme group ratio of 5:2:1 the required sample size would be 128. If the standard deviation is 10% we would need a sample size of 192 for a group ratio of 5:2:1.

Hence, in order to be able to detect potential differences with sufficient confidence we would need analyzable data from 192 patients.

The required sample size to detect a difference of seven percent with the same power (80%) will be lower, if a covariate has less than three categories. Further, the sample size will be lower if the true difference in compliance due to a covariate is larger than 7%.

To further account for 20% incomplete or missing data with respect to our primary outcome variable "compliance" (measured in percentage) over the 2 year follow-up we would need to enroll a total of 240 patients. This adjustment is necessary, since for patients who drop out of the study and/or do not wish to have their data read out of the device as well as those lost to follow-up accurate calculation of compliance will not be possible.

Categorical covariates identified as potential predictors in the overall test will be further analyzed using pairwise comparisons, which will affect sample size.

Hence, in *table 2* we present the maximum sample sizes needed to detect a difference of 7% in the pairwise comparison for a predictor with three groups/categories assuming an alpha=0.05 in order to have a power of 80%.

*Table 2*: sample size calculation for the pairwise comparison (alpha=0.05)

| Difference in compliance (%) | SD 8% | | SD 10% | |
|---|---|---|---|---|
| | Group ratio 1:1:1 | Group ratio 5:2:1 | Group ratio 1:1:1 | Group ratio 5:2:1 |

| | | | | |
|---|---|---|---|---|
| 7 | **66** | **128** | **99** | **200** |

As sketched in the table 66 patients would be needed for example to detect a difference of 7% if the standard deviation is 8% and the group ratio 1:1:1. For an extreme group ratio of 5:2:1 the required sample size would be 128. If the standard deviation is 10% we would need a sample size of 200 for a group ratio of 5:2:1.

Hence, in order to be able to detect potential differences with sufficient confidence we would need analyzable data from 200 patients.

To further account for 20% incomplete or missing data with respect to our primary outcome variable "compliance" (measured in percentage) over the 2 year follow-up we would need to enroll a total of 250 patients.

Subgroup analysis with respect to the PTMS program

For the secondary objective of evaluating an association between participation in the PTMS program and adherence we will have >90% power to detect a difference of 7% based on a t-test assuming various group sizes (assumptions: 7% difference in compliance between PTMS centers and non-PTMS centers; SD 8% or 10%; alpha=0.05; group sizes: 30 vs. 100, 30 vs. 220, 60 vs. 190, 90 vs. 160).

Sample size calculation was performed using the "proc power"' procedure with the "one way anova" statement in SAS 9.2.

## 9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. The injection-related data stored in the BETACONNECT™ will be downloaded via a USB cable to the computer of the attending physician from there it can be uploaded into the eCRF. A validated software application for this procedure has been specifically developed by the manufacturer of the BETACONNECT™ "Medicom" and is already in use in the non-interventional study BETAEVAL. Information on the EDC system is available upon request (see BF1502_EDC_manual_final_yyyymmdd, Table 2: List of stand-alone documents, Annex 1). Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see BF1502_DMP_final_yyyymmdd Table 2: List of stand-alone documents, Annex 1).

For information on quality control, refer to section 9.8.

## 9.7 Data analysis

### 9.7.1 Statistical considerations

Statistical analyses will be of explorative and descriptive nature. P-values <0.05 will be considered as statistically significant unless stated otherwise.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All analyses will be performed for the total study population (overall analysis) or when defined otherwise within a valid subpopulation. Patients receiving at least one dose of Betaferon® will be included in the analysis. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics).

There will be no further documentation of patients fulfilling the following criteria (end of observation visit will be documented): 1. patients terminating Betaferon® treatment including those stopping treatment overall or switching to other treatments; 2. patients lost to follow-up; and 3. patients choosing to terminate study participation for any reason. During the final visit (in case of premature termination) the investigator should try to identify the date, when Betaferon® treatment was discontinued. If this date cannot be identified or approximated, e.g. if a patient is lost to follow-up, the date of the last documented visit should be chosen. Further, the investigator should make every effort to identify the reason, why a patient decides to terminate the study. Reasons for study termination will be displayed using descriptive statistics.

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request (see BF1502_SAP_final_yyyymmdd Table 2: List of stand-alone documents, Annex 1).

The first pre-specified analyses will be performed after the dataset for the 12-month follow-up is complete, the final analysis will be performed at the end of the study, which is the date the analytical dataset is completely available (all data for the 24-month follow-up are available).

### 9.7.2 Analysis of demography, disease details, prior and concomitant medication and other baseline data

Descriptive statistics will be used to summarize data on demographics, baseline characteristics, diagnosis, concomitant diseases, concomitant medication, and questionnaire scales and scores using mean (± SD), median, minimum, maximum for continuous variables, and category counts and frequencies (percentages) for categorical variables. Concomitant diseases on the case report form correspond to MedDRA terms. Concomitant medication will be coded using WHO's drug dictionary. Data will be recorded at each of the visits which will enable us to acknowledge and evaluate changes over time.

We will perform analyses for data obtained at each of the scheduled visits.

### 9.7.3 Analysis of treatment data

Summary statistics will be provided for start of treatment, end of treatment, treatment duration, and reasons for treatment discontinuation.

### 9.7.4 Analysis of primary outcome(s)

Our primary analysis will be after 12 and 24 months of observation; however, we will also perform analyses for the visits in between.

For the analyses of our primary outcome compliance we will use descriptive statistics to characterize compliance (in percent) by calculating mean (±SD), median, min, and max. This will include a stratified analysis according to the patients' pre-study experience with the BETACONNECT™, i.e. new patients vs. experienced patients.

We will then investigate the association between baseline covariates and compliance in percentage using Analysis of Variance (ANOVA) and linear regression. First, we will use ANOVA to investigate mean differences in compliance for each of the categorical covariates. Second, we will use linear regression with compliance as the dependent variable and each of the covariates as independent variables. We will investigate univariate associations and then build a multivariable-adjusted model accounting for all covariates. With respect to the ANOVA analysis we will chose covariates as potential predictors that show a univariate association in the overall comparison using the F-test with a $p \leq 0.1$ and further investigate those in pairwise comparisons using both univariate and multivariable models. Finally, employing linear regression models, we will use a stepwise selection procedure to determine predictors of compliance, considering all covariates as potential predictors.

For the analyses of our co-primary endpoints we will likewise use descriptive statistics to characterize persistence and overall adherence (yes, no) using category counts and frequencies (percentages). This will include stratified analyses according to the patients' pre-study experience with the

BETACONNECT™, i.e. new patients vs. experienced patients. In further analyses we will use logistic regression to investigate the association between baseline covariates as the independent variables and persistence and overall adherence as the dependent variables. The regression analyses will include investigating univariate associations, multivariable-adjusted associations, and finally as stepwise selection procedure to determine predictors of persistence and overall adherence, similar to the analysis of the endpoint compliance.

All demographic and clinical covariates will be considered as potential predictors, specifically: age (linear), sex (female, male), body mass index (BMI; $kg/m^2$), marital status (married/partnership, single), employment status (employed, retired, keeping house, student, seeking work, self-employed, other, not reported), educational level (elementary education, secondary education, college or university education, not reported), concomitant diseases, number of concomitant diseases (0, 1, ≥2), baseline EDSS (≤3, >3), number of relapses during year prior to enrolment (0, 1, >1), CIS vs. RRMS, intake of vitamin D supplements (yes vs. no; if yes which dosage?), intake of other nutrients or vitamins (yes vs. no), smoking (never, past, present), new patients vs. patients already on Betaferon®, concomitant medication, number of concomitant medications (0, 1, ≥2), MS duration, duration of treatment, previous usage of BETACONNECT™ (BETACONNECT™-naïve vs. BETACONNECT™-experienced), usage of electronic features of BETACONNECT™, injection site pain (Numerical Analog Scale), injection-site reactions (yes vs. no; if yes: redness, other discoloration, hematoma, induration, lipodystrophy, necrosis; if yes: mild, moderate, severe), flu-like symptoms (yes vs. no), participation in the BETAPLUS® nurse support program (yes vs. no), SDMT score, health related quality of life, depression, fatigue, participation in the PTMS program, CMSS*, MSSM-R, ISU-DYA*, WEIMuS.

*only among patients participating in the PTMS program.

Depending on the number of patients previously exposed to the BETACONNECT™ and those newly introduced to the device, we will also perform the above mentioned analyses in the two groups separately, since adherence may differ. For multivariable-adjusted analyses in the BETACONNECT™–naïve group we will not include the variable "prior usage of BETACONNECT™", while for the BETACONNECT™-experienced group we will adjust for a linear variable "duration of prior BETACONNECT™-use" (measured in months) instead. We will further reduce the number of covariates to account for smaller numbers of patients in these subgroups if necessary.

### 9.7.5 Analysis of secondary outcome(s)

Descriptive statistics will be used to summarize data from questionnaire scales and scores as well as clinical data using mean (± SD), median, minimum, maximum for continuous variables, and category

counts and frequencies (percentages) for categorical variables. Concomitant diseases on the case report form correspond to MedDRA terms. Concomitant medication will be coded using WHO's drug dictionary. Data will be recorded at each of the visits which will enable us to acknowledge and evaluate changes over time.

We will perform analyses for data obtained at each of the scheduled visits.

We will use linear or logistic regression analysis (depending on the outcome scale) to evaluate the association between participation in the PTMS program and adherence to Betaferon® treatment as well as between participation in the PTMS program and depression, health related quality of life, self-management mechanisms, fatigue, and cognition at each visit as well as change of these variables over time.

### 9.7.6 Analysis of safety data

Patients who took at least one dose of Betaferon® and provide sufficient information whether they had an adverse event or not (i.e. who have a follow-up visit page and/or an adverse event page) will be eligible for safety analysis (safety analysis set). The full analysis set (FAS) will include all patients who have data available at baseline as well as at least from one post-baseline visit.

Adverse events will be summarized using the MedDRA coding system. Event rates for single adverse events will be calculated based on the total number of patients valid for safety analysis. Adverse events will be categorized according to relation, seriousness, discontinuation of therapy, action taken and outcome. Special attention will be paid to serious adverse events and unexpected or unlisted ADRs.

Category counts and frequencies (percentages) will be calculated for overall tolerability.

All patients will be presented with all details from the AE report form.

Device events will be summarized using the MedDRA coding system. Event rates for device events will be calculated based on the total number of patients valid for safety analysis.

Further details of the safety analysis are described in the SAP.

### 9.7.7 Bias, confounding and effect-modifying factors

In general data collected in this study may suffer from biases (e.g. interviewer bias, either by systematic differences in data recording or different interpretation of information on exposure or outcome for different patients, reporting as well as selection bias). Information bias with respect to

injection data will be avoided since the autoinjector automatically records injection related data; however information obtained from patients may suffer from recall bias, which is inherent to the study design. Further, prospective studies are prone to bias from loss to follow-up or change in methods over time. To decrease reporting bias source data verification will be performed in at least 10% of the sites. Sites will be selected according to several criteria, main criteria for site selection will be: availability of suitable patients and an equal geographical distribution. Patients should be enrolled consecutively. Investigators should select patients to be documented in the study only based on eligibility according to inclusion and exclusion criteria. No further selection should be applied. However, sites agreeing to participate in the study may not be equally distributed across Germany; hence, patients enrolled may not be representative of all German MS patients.

Primary and secondary outcome variables will be analyzed with regard to different baseline factors. However, unknown and unmeasured risk factors for the outcome variables will exist and might lead to confounding when comparing results in different subgroups and when comparing study results with historical results from clinical studies.

For the secondary objectives we will also evaluate post-baseline variables with respect to adherence. Potential bias may arise from reciprocal influence of these variables on each other during the study course, requiring extreme caution when interpreting these results.

Both BETACONNECT™-naïve and BETACONNECT™-experienced patients will be included in the study. Regarding experienced patients it needs to be considered that this group of patients may be "positively selected" with respect to adverse effects, i.e. they may still be using the device because they experience no or only mild adverse effects. We will address this by performing stratified analyses in the naïve and experienced groups in addition to the overall group and also investigate for interaction by adding an interaction term between the variables "previous usage of BETACONNECT™" and "compliance/adherence" to the multivariable-adjusted models.

The consideration of treatment-naïve and -experienced patients with respect to usage of the device (BETACONNECT™) as well as with respect to usage of the drug (Betaferon®) also leads to another aspect: patients experiencing injection-related adverse effects like skin reactions (in the past and during course of study) may differ from those not experiencing adverse effects with respect to adherence (non-adherent patients may not be exposed to risk of skin reactions, while on the other hand, skin reaction may induce non-adherence). One way to address this potential "reverse causation" bias is to group study participants according to their experience with the device or the drug. Hence, by performing separate analyses as described in the previous paragraph we will also be able to appreciate "reverse causation".

## 9.8 Quality control

### 9.8.1 Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer. All results will be verified by an independent data analyst at the selected CRO.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see BF1502_DMP_final_yyyymmdd Table 2: List of stand-alone documents, Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA)[37]. The documentation is available upon request (see BF1502_EDC_system validation_final_yyyymmdd>, Table 2: List of stand-alone documents, Annex 1).

### 9.8.2 Quality review

In a subset of patients (at least 10% of all patients) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see BF1502_QRP_final_yyyymmdd Table 2: List of stand-alone documents, Annex 1).

### 9.8.3 Storage of records and archiving

The sponsor will make sure that all relevant documents of this non-interventional study including CRFs and other patient records will be stored after end or discontinuation of the study for at least 10 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to also store documents for a retention period of at least 10 years.

#### 9.8.4 Certification/qualification of external parties

N/A

### 9.9 Limitations of the research methods

This prospective observational cohort study provides the opportunity to collect data of real-life treatment adherence that can be analyzed and disseminated in a timely manner. However, this study is a single arm cohort study without a comparison group. Thus, in addition to subgroup analyses within this study, the results can only be compared with historical data from other studies. Such a comparison is prone to bias and confounding as historical data may differ by method of ascertainment and the data ascertained in our study may not be available.

In general caution needs to be exercised when investigating associations between variables collected in observational studies, since they may be spurious and generated by study inherent biases. Hence, any association identified needs to be carefully examined with respect to causality, i.e. if certain criteria for causality apply (e.g. criteria by Bradford Hill).

### 9.10 Other aspects

N/A

## 10 Protection of human subjects

### 10.1 Ethical conduct of the study

This study is an observational study where Betaferon is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

### 10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012[38]). Recommendations given by other organizations will be followed as well (e.g. EFPIA[39], ENCePP[40]). ICH-GCP guidelines will be followed whenever possible.

### 10.3 Independent ethics committee (IEC) or institutional review board (IRB)

Documented approval from appropriate IECs/IRBs will be obtained for all participating sites prior to study start. When necessary, an extension, amendment or renewal of the IEC / IRB approval must be obtained and also forwarded to the sponsor. The IEC / IRB must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to applicable laws and regulations.

### 10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing.The investigator must have the IECs / IRB written approval / favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

### 10.5 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

### 10.6 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the sponsor. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

# 11 Management and reporting of adverse events/adverse reactions

## 11.1 Definition

### 11.1.1 Definition of (serious) adverse events/reactions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.[41]

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).
The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator product
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a product is implied by the use of the term "adverse event".

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to Betaferon.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before subject's inclusion in the study (i.e. elective or scheduled surgery) or
- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant

special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

### 11.1.2 Definition of Device Events

A device event includes but is not limited to:

- A malfunction or deterioration in the characteristics or performance. A malfunction or deterioration should be understood as a failure of the DEVICE to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.
- Unanticipated adverse reaction or unanticipated side effect
- Interactions with other substances or products
- Degradation/destruction of the DEVICE (e.g. fire)
- Inappropriate therapy
- An inaccuracy in the labeling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended users.
- Use error

Device Event Category:

Device malfunction

Failure of DEVICE to meet its performance specifications or otherwise perform as intended when used in accordance with the Instructions for Use (IFU).

Device failure

Failure of DEVICE to perform or function as intended, including any deviations from the performance specifications or intended use.

Use Error

Use errors are preventable handling or technique errors including slips, lapses, mistakes, deviation from the instructions for use including reasonably foreseeable misuse. Use errors are to be distinguished from medication errors.

Product Technical Complaint (PTC)

A PTC is any report received from a third party (written, electronic or verbal communication) about a potential or alleged failure of a product in its quality (including the identity, durability, reliability,

safety, efficacy or performance) or suspect counterfeit. The complaint may or may not represent a potential risk to the customer.

Device Event Evaluation:

Incident

Any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Any event which meets all three basic reporting criteria (A-C) is considered an Incident and must be reported to the relevant National Competent Authority. The criteria are that:

A) An event has occurred

B) The device is suspected to be a contributory cause of the Incident.

C) The event led, or might have led, to death or serious deterioration in state of health of a patient, or user, or other person

Near Incident

Any Incident that did not lead to death or serious deterioration in health, but it might do if it occurred again under less fortunate circumstances or without intervention of healthcare personnel. This may include cases without any medical event reported.

Unanticipated

A deterioration in state of health is considered unanticipated if the condition leading to the event was not considered in the Reference Safety Information (RSI), like the Medical Device Core Data Sheet (MDCDS).

Non-incident

Any device event that did not lead to a serious deterioration of health or death.

Serious deterioration in state of health

A serious deterioration in state of health (also known as serious injury) can include (non-exhaustive list):

a) life-threatening illness,

b) permanent impairment of a body function or permanent damage to a body structure,

c) a condition necessitating medical or surgical intervention to prevent a) or b) Examples:

- clinically relevant increase in the duration of a surgical procedure,
- a condition that requires hospitalization or significant prolongation of existing hospitalization.

d) foetal distress, foetal death or any congenital abnormality or birth defects.

## 11.2 Collection

Starting with the first application of Betaferon, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF / EDC system and forwarded to the sponsor within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness). For each AE, the investigator must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

All device related events must be documented on the device related CRF form or in the CRF / EDC system and in case of incidents/near incidents and deficiencies also on the PTC form(s). Non-incidents must be forwarded to the sponsor within 7 calendar days of awareness while incidents/near-incidents must be reported immediately (within 24 hours).

If a pregnancy occurs during the study, although it is not a serious adverse event, it should be documented and forwarded to the sponsor within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby collected.

The documentation of any AE / SAE /device event ends with the completion of the observation period of the patient. However, any AE / SAE - regardless of the relationship and the seriousness - occurring up to 30 days after the last dose of Betaferon has to be documented and forwarded to the sponsor within the given timelines, even if this period goes beyond the end of observation.

As long as the patient has not received any Betaferon AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the patient's medical history.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

## 11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with Betaferon that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI[42]) and according to national regulations by the sponsor; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the sponsor for SAEs related Betaferon treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Non-Incidents

The outcome of all reported non-incidents will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Near-incidents, Incidents

Device-related near-incidents, and incidents occurring under treatment with BETACONNECT® that qualify for expedited reporting will be submitted to the relevant authorities according to all applicable medical device regulations by the sponsor; however, all investigators must obey local legal requirements.

All device-related events will be forwarded to the pharmacovigilance country person being responsible for device event processing. Product technical complaints not related to an AE/SAE will be forwarded to the Bayer quality department under bv-complaint@bayerhealthcare.com. The outcome of all

reported incidents/near-incidents (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant clinical trial authorities will be done by the sponsor for reportable device events while submission to the competent device authority will be done by the device manufacturer.

For any device related events occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

### 11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

## 12 Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

The results of this study are intended to be published as papers in peer-reviewed journals and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines[43], STROBE[4444]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the sponsor.

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## Annex 1: List of stand-alone documents

**Table 2: List of stand-alone documents**

| Number | Document Name / Reference number | Date | Title |
|---|---|---|---|
| 1 | BF1502_Status_Report_final_yyyymmdd <draft> | Tbd | Investigator list |
| 2 | BF1502_CRF_final_yyyymmdd <draft> | Tbd. | CRF |
| 3 | BF1502_EDC_manual_final_yyyymmdd <draft> | Tbd. | EDC System |
| 4 | BF1502_DMP_final_yyyymmdd <draft> | Tbd. | DMP |
| 5 | BF1502_SAP_final_yyyymmdd <draft> | Tbd. | SAP |
| 6 | BF1502_EDC_system_validation_final_ yyyymmdd <draft> | Tbd. | EDC System Validation |
| 7 | BF1502_QRP_final_yyyymmdd <draft> | Tbd. | QRP |

* Draft versions are indicated by date and <draft> in brackets. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage.

## Annex 2: ENCePP Checklist for Study Protocols (Revision 2, amended)

### Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

| **Study title:** |
|---|
| **BETAPREDICT** - MS patients treated with BETAferon®: PREDICTors of treatment adherence |

| **Study reference number:** |
|---|
| Impact 18016 / BF1502 |

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 14 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 14 |
| 1.1.3 Study progress report(s) | ☐ | ☒ | ☐ | |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | 14 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 1 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 14 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 11,15-18 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 18f |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 22 |
| 2.1.4 Which formal hypothesis (-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | | | | |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| | ☐ | ☐ | ☒ | |

Comments:

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design) | ☒ | ☐ | ☐ | 20 |
| 3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | 20f |
| 3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 31-33 |

Comments:

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 22 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 14; 21 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 22 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 21 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 21 |
| 4.2.5 Co-morbidity? | ☒ | ☐ | ☐ | 22; 37 |
| 4.2.6 Seasonality? | ☐ | ☐ | ☒ | |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 22 |

Comments:

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure) | ☒ | ☐ | ☐ | 22; 37 |
| 5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study) | ☒ | ☐ | ☐ | 22 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 22; 37 |
| 5.4 Is exposure classified based on biological mechanism of | | | | |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| action and taking into account the pharmacokinetics and pharmacodynamics of the product? | ☐ | ☒ | ☐ | |
| 5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☒ | ☐ | ☐ | 20ff |

Comments:

| **Section 6: Endpoint definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 6.1 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | 20 |
| 6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 17 |

Comments:

| **Section 7: Confounders and effect modifiers** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders) | ☒ | ☐ | ☐ | 45 |
| 7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect) | ☒ | ☐ | ☐ | 45 |

Comments:

| **Section 8: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.) | ☒ | ☐ | ☐ | 30-36 |
| 8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.) | ☒ | ☐ | ☐ | 30-36 |
| 8.1.3 Covariates? | ☒ | ☐ | ☐ | 30-36 |
| 8.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 30-36 |
| 8.2.2 Endpoints? (e.g. date of occurrence, multiple event, | ☒ | ☐ | ☐ | 30-36 |

| **Section 8: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| severity measures related to event)<br>8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.) | ☒ | ☐ | ☐ | 30-36 |
| 8.3 Is a coding system described for: | | | | |
| 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) | ☒ | ☐ | ☐ | 41 |
| 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) | ☒ | ☐ | ☐ | 41 |
| 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) | ☒ | ☐ | ☐ | 41 |
| 8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 38 |

Comments:

| **Section 9: Study size and power** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 9.1 Is sample size and/or statistical power calculated? | ☒ | ☐ | ☐ | 38-40 |

Comments:

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 10.1 Does the plan include measurement of excess risks? | ☐ | ☐ | ☒ | |
| 10.2 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 41-44 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 41-44 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 41-44 |
| 10.5 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 41-44 |
| 10.6 Does the plan describe methods addressing effect modification? | ☐ | ☒ | ☐ | |

Comments:

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 11.1 Is information provided on the management of missing data? | ☒ | ☐ | ☐ | 46 |
| 11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 46-47 |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 11.3 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 46 |
| 11.4 Does the protocol describe possible quality issues related to the data source(s)? | ☒ | ☐ | ☐ | 46 |
| 11.5 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 46 |

Comments:

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss: | | | | |
| 12.1.1 Selection biases? | ☒ | ☐ | ☐ | 47 |
| 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | 44-45; 47 |
| 12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 47 |
| 12.3 Does the protocol address other limitations? | ☒ | ☐ | ☐ | 47 |

Comments:

| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described? | ☒ | ☐ | ☐ | 47 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 48f |

Comments:

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | 14 |

Comments:

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 55 |

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 55 |

Comments:

| |
|---|
| |

Name of the main author of the protocol: Prof. Dr. Markus Schürks

Date: 12/02/2015

Signature: _____

## Annex 3: Additional information

N/A

## Annex 4: Description of Amendments

N/A