Clinical Study Synopsis

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1. Abstract

Acronym/Title	BETAPREDICT - MS patients treated with BETAferon®: PREDICTors of treatment adherence
Report version and date **Author**	Final v1.0, 09 DEC 2020 [redacted] (Bayer Vital GmbH) [redacted]
Keywords	Adherence, clinically isolated syndrome, Interferon beta-1b, psycho-educative training, relapsing remitting multiple sclerosis
Rationale and background	Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating and degenerative disorder of the central nervous system, primarily affecting young adults. A key prerequisite for an effective therapy is that patients follow their physicians' treatment recommendations, i.e. are adherent to therapy. Non-adherence to therapy is a major challenge in patients with chronic diseases requiring a long-term treatment. Systematic analyses 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 of treatment on the individual disease course may be jeopardized and medical resources wasted. Factors determining adherence are complex and multi-layered. We aim to understand potential predictors of adherence by investigating a cohort of MS patients in Germany treated with Betaferon®.

Research question and objectives	The **primary objective** of this study was to determine baseline predictors of adherence to Betaferon® treatment after 12 and 24 months.
	Secondary objectives were 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

	○ self-management mechanisms ○ fatigue ○ cognition • If adherence to Betaferon® treatment was associated with ○ number of relapses at 12 (24) months ○ EDSS change at 12 (24) months ○ utilities of treatment (only baseline and final visit). • In the subgroup of patients participating in the PTMS program evaluation of: ○ treatment adherence ○ depression ○ quality of life ○ self-management mechanisms ○ fatigue ○ cognition ○ social support ○ coping behavior
Study design	Local, prospective, non-interventional, multi-center, observational cohort study.
Setting	The study was conducted in private neurological offices/clinics and neurology departments in Germany specialized in the treatment of MS patients. The study population consisted of male and female patients with relapsing remitting MS (RRMS) or patients with a clinically isolated syndrome (CIS) who were treated with Betaferon® or willing to be treated with Betaferon® and to use the BETACONNECT™ autoinjector. The decision upon treatment with Betaferon® was made at the discretion of the attending physician, according to his/her medical practice. **Main inclusion criteria:** • Patients aged ≥ 18 years with the diagnosis of RRMS or a CIS.

	• Patients on treatment with Betaferon® or if the decision to treat patients with Betaferon® had been made by the attending physician. • Patients using or willing to use the BETACONNECT™ autoinjector for Betaferon® application. • Written informed consent. **Main exclusion criteria:** • Patients receiving any other disease modifying drug. • Contraindications of Betaferon® described in the SmPC. • Patients participating in any other clinical or non-interventional study, evaluating MS therapy. Each patient had the right to refuse further participation in the study at any time and without providing any reason. The investigator documented an initial visit, follow-up visits and a final visit for each patient in the electronic case report form (eCRF). Follow-up visits occurred during routine practice. The study protocol did not define exact referral dates for those visits. Documented visits should have been approximately six months apart. The final visit should have been documented after approximately 24 months. The observation period for each patient should be approximately 24 months. No further selection was made. Patients were enrolled consecutively in order to avoid selection bias. With respect to site selection this study could have potential limited representativeness (convenience sample) as we were looking for experienced specialized sites and departments in the management and treatment of MS.
Subjects and study size, including dropouts	It was planned to collect data from 250 patients with the above mentioned characteristics. Premature treatment discontinuation, which included switching from Betaferon® to other treatments, automatically implied 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). Patients were not be replaced after dropping out. The sample size calculation (250 patients) was 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. It was anticipated, that analyzable data

	from 200 patients was needed to detect potential differences with sufficient confidence.
Variables and data sources	The variables for the primary objectives were: • Compliance to therapy • Persistence of therapy • Overall Adherence to therapy For the primary objective these variables were derived as follows: • Compliance to therapy (%): calculated as ((expected treatment days - missed treatment days)/(expected treatment days)) x 100 • Persistence of therapy (yes, no): this measure allows a view on those patients that completely stop taking their medication vs. those continuing ("persisting") their medication (regardless of the frequency of intake) • Overall adherence to therapy (yes, no): Patients were defined as being adherent to therapy if they fulfilled the following criteria: o They injected ≥80% of the expected Betaferon® dosages and o They did not stop Betaferon® treatment for any reason prior to the time of evaluation • Number of dosages missed was derived from the injection dates recorded via the BETACONNECT™ autoinjector These variables were measured at each follow-up visit. Changes from previous follow-up visit were calculated starting at follow-up visit 2. For the secondary objectives the following variables were collected at each visit (source): • Satisfaction with the BETACONNECT™ autoinjector (patient questionnaire) • Injection site pain (patient questionnaire) • Analgesic use prior to Betaferon® application and flu-like symptoms (patient questionnaire) • Intake of vitamin D, other vitamins and nutrients (CRF) • Depression (CES-D questionnaire) • Health related quality of life (SF-36 survey)

	• Coping mechanisms (Coping with MS Scale; CMSS; only patients participating in the PTMS program) • Self-management mechanisms (Multiple Sclerosis Self-Management Scale-Revised; MSSM-R) • Social support (Inventory of Social Support in Dyads; ISU-DYA; only patients participating in the PTMS program) • Fatigue (Würzburger Fatigue Inventory for MS; WEIMuS) • Cognition (Symbol Digit Modalities Test¸ SDMT) • Number of relapses at 12 and 24 months • Expanded Disability Status Scale (EDSS) • Time to relapse • Utilities of treatment at baseline and final visit (EQ-5D Questionnaire). **Data Sources** The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. The investigator collected treatment related data during initial visit and follow-up visits. Scheduled 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 The investigator documented study-relevant data for each patient in the electronic case report form (eCRF). The analyses of the primary outcome (compliance to therapy) and overall adherence were based on the subgroup of patients with BETACONNECT data. The analyses of the other co-primary endpoint (persistence) and the secondary endpoints were based on the Full Analysis Set (FAS). The analysis of demographic and baseline data was based on the FAS. The analysis of safety and tolerability data was based on the Safety Analysis Set (SAF).

	SAF comprised all patients eligible for the study who received at least one dose of Betaferon. FAS comprised all patients who had injected Betaferon® at least once, had the initial visit after giving the informed consent, and if any further follow-up information was available in the eCRF after initial visit.
Results	**Patients and study duration** • It was planned to enroll 250 patients. Due to the slow recruitment, it was anticipated, that even after prolongation of the enrolment phase it would not be possible to achieve the planed sample size in a reasonable period of time and enrolment was stopped after four years. 165 patients were screened and enrolled in this study between September 2015 and October 2019 • From the 165 enrolled patients, 159 were eligible for inclusion and comprised the Safety Analysis Set (SAF). 153 patients comprised the Full Analysis Set (FAS) • 81 from 153 patients (52.9%) completed the study as planned. 72 from 153patients (47.1%) discontinued the study prematurely • The most frequent reasons for premature study discontinuation were 'other reason' (23.5%), 'adverse event' (7.8%), 'lost to follow-up' (7.2%), and 'switch to other mode of application' (5.2%) • 120 from 153 patients (78.4%) also had BETACONNECT™ data • No patient participated in the PTMS until study enrolment • 73 from 153 patients (47.7%) participated in the PSDMP BETAPLUS **Demographics and baseline characteristics (FAS = 153 patients)** • Mean (SD) age was 42.5 (11.8) years (range: 20.0 to 67.0 years) • 102 patients (66.7%) were female • 54 patients (35.3%) were overweighed (BMI: 25-30) and 23 (15.0%) obese (BMI ≥30) • 73 patients (47.7%) had never smoked, 37 (24.2%) were former smoker and 32 (20.9%) were current smoker

	• 145 patients (94.8%) were diagnosed with RRMS and 8 (5.2%) with CIS • The mean (SD) time since initial diagnosis was 78.9 (85.5) months (range 0.0 to 370.1 months) • Mean (SD) number of demyelinating events/relapses was 0.7 (0.8) during the past 2 years • 108 patients (70.6%) used concomitant medication **Treatments (FAS = 153 patients)** • Pre-treatment: 114 patients (74.5%) received Betaferon injections prior to study enrolment. From these patients 95 used BETACONNECT and 13 used other devices • 38 patients (24.8%) were Betaferon treatment-naïve • Median duration of treatment was 34.4 months (range 0.9 to 264.3 months) • Median duration of the observation was 23.1 months (range 0.9 to 44.0 months) **Primary outcome (primary and co-primary endpoints)** • Median number of injection data entries per patient during the entire study was 265.0, corresponding to the compliance at 24 months • Compliance was high throughout the entire study: Median compliance was 97.9% from baseline to 6 months and decreased to 93.5% from baseline to 24 months • Persistence was high and declined about 15% at the end of study: After 12 months 107 from 153 patients (69.9%) were persistent and 18 patients (1.8%) were possibly persistent. At 24 months 82 from 153 patients (53.6%) were persistent and 25 (16.3%) possibly persistent • Adherence was lower than compliance and persistence: After 12 months 83 from 120 patients (69.2%) were adherent. At 24 months 59 patients (49.2%) were adherent • Median cumulative number of injections missed from baseline to 24 months was 13.0 (mean [SD] 30.2 [39.8]). The median number of injections missed per three-month interval was between 0.0 and 1.0 injection during the entire observational period

	Predictors of compliance, persistence and adherence (model analyses) • Compliance (primary endpoint): o At 12 months: intake of Vitamin D supplements showed a positive impact. The occurrence of hematomas and lipodystrophy showed a negative impact on compliance o At 24 months: in addition the 'general health perceptions at initial visit' (SF-36) had a negative impact on compliance • Persistence (co-primary endpoint): o At 12 months, the duration of treatment showed a positive influence on persistence (p=0.0100). Patients who took "other nutrients or vitamins" were less likely to be persistent (OR=0.161, p=0.0011). o At 24 months, patients already injecting Betaferon® were more likely to be persistent than treatment-naïve patients (OR=3.351, p=0.0154). The factors "age" (p=0.0017) and "limitations in usual role activities because of emotional problems" (p=0.0035) at the initial visit (according to SF-36) had a positive impact on persistence. • Adherence (co-primary endpoint): o At 12 months: "Participating in the PSDMP BETAPLUS" had a positive impact (p=0.0361), whereas using electronic features of the BETACONNECT had a negative impact on adherence (p=0.0540). o At 24 months: Patients already injecting Betaferon® were more likely to be adherent than treatment-naïve patients (OR=4.009, p=0.0352). The factors "age" (p=0.0173) and "limitations in usual role activities because of emotional problems" (p=0.0356) at the initial visit (according to SF-36) had a positive impact on adherence. **Secondary outcomes** **General patient questionnaire:** • **Satisfaction with the BETACONNECT autoinjector (n=126)**: Median (range) satisfaction score was 9.0 (5 to 10) at the initial visit which did not change considerably over time, showing strong satisfaction with the autoinjector throughout the study • **Injection site pain (n=122)**: Median injection site pain score was 3.0 at the initial visit, remaining largely constant over time, corresponding to mild to moderate pain

	• **Analgesics use prior to Betaferon application (n=131):** Over 80% of patients did not use any analgesics prior to the injection at each visit during the study • **Flu-like symptoms (n=131)**: 46 patients (35.1%) reported flu-like symptoms at baseline. The proportion decreased over time to 25.0% at the last follow-up visit 4 and was higher in BETACONNECT-naïve than in experienced patients (e.g. at FU visit 1: 36.6% vs. 26.3%) **Depression (CES-D; n=142)** • Mean (SD) CES-D total score was 14.5 (9.0) at baseline and decreased to 12.7 (10.1) at follow-up visit 4, indicating the severity of depression was low (cut-off score of no depression <15) **Health-related quality of life (SF-36; n=139)** • Initial visit: health concepts that were mostly affected by the disease (i.e. score values < 50) were o limited role activities due to physical problems (mean (SD) 37.1 (19.1)), o social functioning (mean (SD) 39.3 (7.8)), o limited role activities due to emotional problems (mean (SD) 40.3 (18.1)), o vitality (mean (SD) 45.4 (17.8)), and o general health (mean (SD) 47.8 (16.2)) • Score values did not change considerably from baseline to end of study for each of the sub-scales **Self-management mechanism (MSSS; n=145)** • Mean (SD) MSSS total score was 61.7 (11.5) at baseline and remained largely unchanged until follow-up visit 4 (62.3 (11.5)), indicating as relatively high level of self-efficacy **Fatigue and cognition (WEIMuS; n=144)** • Mean (SD) WEIMuS total score was 17.6 (16.3), the mean (SD) subscore for physical fatigue was 9.7 (8.7) and the subscore for cognitive fatigue was 7.9 (8.4) at baseline, corresponding to a rather low level of fatigue. The score values did not change considerably during the course of the study **Utilities of treatment (EQ-5D; n=139)**

	• Mean (SD) EQ-5D weighted index was 0.9 (0.2) at baseline and the final visit, corresponding to a level of almost full health • Mean (SD) EQ-5D VAS was 78.3 (16.9) at baseline and 77.1 (18.1), supporting good health state by the patient's self-perception **Number of relapses (FAS = 153 patients)** • 13 patients (8.5%) had records of one relapse • 12 patients (7.8%) had records of more than one relapse during the observation period • 127 patients (83.0%) did not recorded any relapse • Information was missing for one patient **Kurtzke Expanded Disability Status Scale (EDSS) - (FAS = 153 patients)** • At baseline 91 patients (59.5%) had an EDSS score of 0-2.5 (no to mild disability) and 30 patients (19.6%) had an EDSS score of 3-10 (moderate disability and worse) • Median (range) EDSS was 1.5 (0.0 to 6.5) at baseline (minimal disability) • Scores did not change considerably over time • About 20% of patients had no records of EDSS at each visit **Safety analysis (SAF = 159 patients)** • 109 patients (68.6%) reported 288 treatment emergent adverse events (TEAEs). Most TEAEs (93.4%) were non-serious • 60 patients (37.7%) reported 118 non-serious drug-related TEAEs. The most frequently reported events were 'Injection site erythema', 'Injection site induration' and 'Influenza like illness' in 28, 15 and 12 patients respectively. • 14 patients (8.8%) reported serious TEAEs (19 events). Two patients reported two drug related serious TEAEs ('injection site necrosis' and 'multiple sclerosis relapse') • 17 patients (10.7%) discontinued the study drug due to TEAE. In 13 patients (8.2%) these TEAEs were drug-related • No life-threatening or fatal events were reported in the course of the study

	• Device events: 31 patients (19.5%) reported 34 device events. Device events were not related to an AE/SAE • All reported drug-related TEAE has been described for Betaferon and are listed in the SmPC. • The safety data in this study further support the well-characterized safety and tolerability profile of Betaferon in patients with MS.
Discussion	Most patients in this observational study used the BETACONNECT autoinjector. Compliance, persistence and overall adherence were high during the first 6 months. While compliance remained high, adherence and persistence decreased until the end of the study after up to 2 years of observation. The regularity of injections after 12 months, i.e. compliance, appeared to be negatively affected by the occurrence of hematoma and lipodystrophy, whereas vitamin D intake was positively associated with compliance. In addition the "general health perceptions at initial visit" (SF-36) had also a negative impact on compliance. Clinical variables relating to age, duration of treatment (positively) and vitamin intake (negatively), appeared to predict "staying with the treatment" after 12 months, i.e. persistence. After 24 months of observation, the effect of age, Betaferon® naive patients vs. pretreated patients and "limitations in usual role activities because of emotional problems" (SF-36) had a positive impact on persistence and adherence. During the first year, adherence, which shares aspects of persistence and compliance, was apparently more influenced by external factors like participation in the PSDMP BETAPLUS (positively) and usage of electronic features of the BETACONNECT™ (negatively). The most frequently reported drug-related AEs in the Betapredict study were local skin reactions, including one patient with a serious AE leading to study discontinuation and flu-like symptoms. No new safety issues were identified during the BETAPREDICT study.
Marketing Authorization Holder(s)	Bayer AG
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document (see Annex 1: List of stand-alone documents, which is available upon request.