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PROTOCOL SYNOPSIS

Title	PERFECT Subcutaneous Interferon beta therapy in multiple sclerosis patients and characterization of injection site reactions and flu-like symptoms under daily practice setting
Protocol No.	GER-PEG-16-10988
EU PAS register number	EUPAS21013
Active substance	Peginterferon beta-1a, Interferon beta-1a, Interferon beta-1b
Medicinal products	Subcutaneous (SC) Interferon beta therapies (SC Peginterferon beta-1a ,SC Interferon beta-1a, SC Interferon beta-1b) Plegridy®, Betaferon®, Extavia®, Rebif®
Study design	Multicenter non-interventional, cross-sectional, open-label voluntarily post-authorization safety study (PASS)
Population	Adult patients with relapsing-remitting multiple sclerosis (RRMS), currently stable on a SC Interferon beta treatment for at least three months
Participating countries	Germany
Number of study sites	Approximately 100
Number of patients	Approximately 1,600 - 1,800
Research question and objectives	This single point survey based on a standardized questionnaire was conducted to investigate injections site reactions (ISR) and flu-like symptoms (FLS) in adult RRMS patients receiving a SC Interferon beta therapy. Additionally, a better insight in the patient's management of ISR and FLS in daily life was expected. By asking the patient, physician and MS nurse the same questions independently, it was anticipated to gain information on how the perspectives of patients, MS nurses and physicians may differ
Inclusion criteria	• Ability to understand the purpose of the study and provide signed and dated informed consent • At least 18 years at time of informed consent • Diagnosed relapsing-remitting multiple sclerosis • Currently receiving a SC Interferon beta treatment (label conform) • Stable on SC Interferon beta treatment for three months or longer (switch between SC Interferon beta treatments possible)
Exclusion criteria	• Contraindications according to the "Fachinformation" (German equivalent to Summary of Product Characteristics [SmPC]) • Therapy with Glatiramer acetate or intramuscular (IM) Interferon beta-1a • Participation in a non-interventional or interventional clinical study of Biogen
Treatment	All patients were treated with their current SC Interferon beta medication according to the Fachinformation and were managed according to clinical practice.

Study duration per patient	The study participation started with signature of informed consent and ended with completion of the patient questionnaire. As both actions had to be done during the same visit at the study site, the patient's study duration was expected to be less than one day.
Planned Study Period	The study period started after first site initiation with the identification and enrollment of patients meeting the eligibility criteria. Recruitment was planned for 18 months and 3 more months were assumed until all questionnaires from patients, physicians and MS nurses had been collected and cleaned. The end of study was defined as end of overall data collection when the complete analysis dataset is available. The Sponsor was able to terminate or prolong this study at any time, after informing the participating sites.
Study procedure / Assessments	Due to the non-interventional character of the study, patients were treated according to the routine clinical practice at each site. Thus, there were no extra treatments or examinations besides the routine treatment except that the patient was asked to complete the patient questionnaire at a single point of time during a regular site visit according to routine clinical care. In all cases, the decision to treat patients with SC Interferon beta had been made prior to the decision to include the patient in the study and the SC Interferon beta treatment was administered according to the Fachinformation. After the site had been initiated, a patient eligible according to the inclusion/exclusion criteria was informed about the study and the written Informed Consent was collected. The physician then handed out the standardized paper questionnaire as NCR form (Non Carbon Required) to the patient which had to be completed directly during the same visit. The original of the completed questionnaire was handed back to the site and was stored in a sealed envelope to keep MS nurses and physicians blinded in order to be able to answer the same questions independently of the patient and each other via Electronic Data Capture (EDC) system. The physician and the MS nurse both also documented patient's baseline characteristics in the EDC system. The original of the completed patient questionnaire was sent to the Contract Research Organization (CRO) for entry in the study database (a copy remained on-site). Serious adverse events under Plegridy® were to be reported by the sites.
Data Sources	• The patient's medical record from which the site transfered data into the electronic Case Report Form (eCRF) • The completed paper patient questionnaire
Study endpoints	Primary endpoints: • Number and proportion of patients with at least one ISR as reported by the patient

	• Number and proportion of patients with at least one FLS as reported by the patient Secondary endpoints: • Number and proportion of patients with at least one ISR/FLS as reported by the MS nurse • Number and proportion of patients with at least one ISR/FLS as reported by the physician Following endpoints were assessed by patients, nurses and physicians, respectively: o Type and frequency of ISR/FLS o Duration of ISR/FLS o Usual time of occurrence of ISR/FLS o Interference of ISR/FLS with patient's daily activities assessed by a visual analogue scale ranging from '0' (not at all) to '10' (extremely). o Number and proportion of patients taking treatment/actions to relieve the ISR/FLS o Number and proportion of patients with at least one self-administered treatment/action resulting in disappearance of ISR/FLS or relief of ISR/FLS o Number and proportion of patients with reducing/increasing frequency of ISR/FLS compared to previous therapy. o Number and proportion of patients with reducing/increasing intensity of ISR/FLS compared to previous therapy.
Statistical analysis	This study is an observational study with focus on a patient's questionnaire at a single point of time. All documented data were analyzed by descriptive statistics, that is, no formal statistical hypothesis was formulated and no statistical tests were carried out. All analyses were performed based on the data set of patients who were eligible for participation according to inclusion criteria and completed the questionnaire. If a patient omitted a specific question he was set to missing in all analyses referring to this question. No data imputation was performed. Since this is an exploratory study and no formal hypothesis-testing was carried out, there is no formal sample size calculation. The sample size of this study depended on how many patients completed the questionnaire and were eligible to participate in this observation. In total about 4,700 questionnaires were planned to be handed out across 100 sites. Approximately 1,600 - 1,800 completed patient questionnaires were expected to be returned (40% return rate expected). Categorical variables were summarized descriptively by absolute frequencies and percentages. The denominator for all percentages

	was the total number of patients, within the respective group, unless otherwise indicated. Percentages were presented to one decimal place and were not displayed for zero frequencies. A row denoted "Missing" was included in all tabulations to clearly indicate the completeness of the collected data. Continuous variables were described by number of patients (n), number of patients with missing values (Nmiss), mean, standard deviation (SD), median, quartiles, minimum and maximum. Subgroup analyses were performed with respect to patient's disease history and patient's previous and current MS therapy. The primary endpoints were evaluated in following subgroups: • Age group (<40 years, ≥40 years) • Gender (male, female) • Time since RRMS had been diagnosed (≤1 year, >1-2 years, >2-5 years, >5 years) • Current SC Interferon beta therapy (Plegridy® /Betaferon®, Extavia®, Rebif®) • Duration of exposure of current Interferon beta therapy (≤3 months, >3-6 months, >6-12 months, >1-2 years, >2-3 years, >3 years) • Type of skin (Celtic, Nordic, mixed, Mediterranean, dark, black) • Number of previous MS therapies (0, 1, 2, >2) • Application form of prior MS therapy before switching to current (injection, oral, other) • ccurrence of ISR under previous therapy (yes, no) • Occurrence of FLS under previous therapy (yes, no) A full statistical analysis plan was available before any analyses were performed.

3. SUMMARY OF RESULTS AND CONCLUSIONS

Number of Subjects (Planned and Analyzed):

The study projection was for 1,600-1,800 subjects to participate in the study; 626 subjects were enrolled, and data from 603 subjects were analyzed.

Criteria for Evaluation:

The completed questionnaires of 603 patients, 545 physicians, and 599 nurses were evaluated with regard to primary and secondary endpoints

Results:

Primary objectives:

- 505 (83.7%) of patients experienced at least one ISR under current therapy
- 407 (67.5%) of patients experienced at least one FLS under current therapy

Secondary objectives:

- 394 (65.8%) of MS nurses reported at least one ISR and 304 (50.8%) at least one FLS under current therapy
- 306 (56.1%) of physicians reported at least one ISR and 261 (47.9%) at least one FLS under current therapy
- The ISR ‘Redness’ was almost always experienced by 232 (38.5%) of patients and documented by 123 (31.2%) of MS nurses and 86 (28.1%) of physicians. The FLS ‘Aching limbs’ was almost always experienced by 89 (14.8%) of patients and documented by 33 (10.9%) of MS nurses and 34 (13.0%) of physicians
- Usual duration of ISR was indicated as 2-3 days by 111 (18.4%) of patients, 90 (22.8%) of MS nurses, and 64 (20.9%) of physicians and of FLS as less than half a day by 155 (25.7%) of patients, 81 (26.6%) of MS nurses, and 54 (20.7%) of physicians
- Usual time of occurrence of ISR was documented as ‘Within one day after the injection’ by 196 (32.5%) of patients, 156 (39.6%) of MS nurses, and 125 (40.8%) of physicians and of FLS ‘About 2 to 6 hours after the injection’ by 183 (30.3%) of patients, 110 (36.2%) of MS nurses, and 83 (31.8%) of physicians
- Interference of ISR on daily activities (assessed by a visual analogue scale ranging from ‘0’ [not at all] to ‘10’ [extremely]), was 1.0 (median) reported by patients and 2.0 by MS nurses and physicians and of FLS as 4.5 by patients, 4.0 by MS nurses, and 4.3 by physicians
- 172 (33.0%) of patients performed actions to relieve ISR and 88 (22.3%) of MS nurses and 52 (17.0%) of physicians reported that patients performed actions to relieve ISR. Regarding FLS 351 (76.0%) of patients performed actions to relieve FLS and 224 (73.7%) of MS nurses and 189 (72.4%) of physicians reported that patients performed actions to relieve FLS
- The disappearance of ISR symptoms with self-administered treatment/action was reported by 26 (4.3%) patients, 12 (13.6%) MS nurses and 7 (13.5%) physicians . Relief of ISR symptoms with self-administered treatment/action was reported by 127 (21.1%) patients, 59 (67.0%) MS nurses and 44 (84.6%) physicians. The disappearance of FLS

symptoms with self-administered treatment/action was reported by 163 (27.0%) patients, 81 (36.2%) MS nurses and 63 (33.3%) physicians . Relief of FLS with self-administered treatment/action was reported by 211 (35.0%) patients, 153 (68.3%) nurses and 133 (70.4%) physicians

- Occurrence of ISR compared to previous therapy was reported as less frequent by 65 (10.8%) of patients, 42 (19.2%) of MS nurses, and 48 (24.6%) of physicians and as more frequent by 42 (7.0%) of patients, 24 (11.0%) of MS nurses, and 19 (9.7%) of physicians. Duration of FLS compared to previous therapy was reported as lasting less long by 55 (9.1%) of patients, 27 (12.4%) of MS nurses, and 28 (14.4%) of physicians and as lasting longer by 37 (6.1%) of patients, 25 (11.5%) of MS nurses, and 15 (7.7%) of physicians
- Intensity of ISR compared to previous therapy was reported as less bothering by 96 (1.59%) of patients, 55 (25.1%) of MS nurses, and 50 (25.6%) of physicians and as more bothering by 14 (2.3%) of patients, 14 (6.4%) of MS nurses, and 13 (6.7%) of physicians. Intensity of FLS compared to previous therapy was reported as less bothering by 67 (11.1%) of patients, 38 (17.4%) of MS nurses, and 34 (17.4%) of physicians and as more bothering by 25 (4.1%) of patients, 17 (7.8%) of nurses, and 12 (6.2%) of physicians

Conclusions:

- The majority of patients experienced at least one ISR and/or FLS under current Interferon beta therapy
- Occurrence of ISR and FLS was reported to a lower rate by MS nurses and physicians compared to the data provided by patients
- Mostly, MS nurses were more aware of the patient´s discomfort and actions to relieve/prevent symptoms than physicians
- Duration and interference with daily activities of ISR and FLS were slightly overestimated by MS nurses and physicians compared to the data provided by patients