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PASS INFORMATION

Title	Plegridy® (peginterferon β-1a) Real World Effectiveness and Safety Observational Program
Version identifier of the final study report	V1.0
Date of last version of the final study report	1 August 2022
EU PAS register number	27459
Active substance	L03AB13 peginterferon beta-1a
Medicinal product	Plegridy 63 µg, 94 µg, and 125 µg single use prefilled syringe or prefilled pen
Product reference	EMEA/H/C/2827
Procedure number	Not applicable
Marketing authorisation holder(s)	Biogen Netherlands B.V. Prins Mauritslaan 13 1171 LP Badhoevedorp The Netherlands
Joint PASS	No
Research question and objectives	The purpose of this study is to provide long-term safety and effectiveness data in patients with relapsing forms of multiple sclerosis who were prescribed Plegridy in routine clinical practice.
Countries of study	Global study including approximately 160 sites in the United States, the United Kingdom, the European Union, Australia, Canada, and sites participating in Study 105MS302 or Study 105MS303 in other countries.
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1. ABSTRACT

Title

Plegridy® (peginterferon β-1a) Real World Effectiveness and Safety Observational Program

Keywords

Multiple sclerosis (MS), Plegridy, peginterferon, observational, patient-reported outcomes (PROs).

Rationale and background

For more than 25 years, interferon beta-1a (IFN β-1a) therapy has been successfully used as a disease modifying therapy (DMT) for patients with relapsing forms of multiple sclerosis (RMS) in United States (US) and relapsing-remitting multiple sclerosis (RRMS) in the European Union (EU). Plegridy, in a pivotal Phase 3 study, demonstrated an efficacy and safety profile similar to other IFN β therapies, at a dose of 125 µg administered via subcutaneous (SC) injection every 2 weeks i.e., at a lesser dosing frequency compared with other DMTs. Furthermore, Plegridy® (peginterferon β-1a) has a longer half-life than non-pegylated IFN β-1a.

In order to assess effectiveness of Plegridy in a real-world setting, Biogen has conducted the Plegridy Observational Program (POP), which was a large prospective, observational, longitudinal study to monitor the long-term safety, effectiveness, and health-related quality of life (HRQoL) associated with Plegridy in patients with MS, with a particular interest in evaluation of the tolerability and incidence of flu-like symptoms (FLS) and injection-site reactions (ISRs).

Research question and objectives

The purpose of this study was to better characterize the long-term benefit-risk profile of Plegridy in patients with MS who were prescribed Plegridy under routine clinical care.

Objectives:

The primary objectives of the study were to determine the incidence of serious adverse events (SAEs) and the overall long-term clinical effectiveness of Plegridy in patients with RMS in routine clinical practice.

The secondary objectives of this study were to determine: Plegridy prescription and utilisation adherence patterns; specific long-term clinical effectiveness; incidence of adverse events (AEs) of FLS, ISRs, and AEs (including laboratory abnormalities) leading to treatment discontinuation; effect of FLS on patient-reported effectiveness of and satisfaction with prophylactic management and; change in HRQoL, flu-like symptom (FLS), flu-like symptoms visual analog scale (FLS-VAS), healthcare resource consumption, and treatment adherence over time.

Study design

This study was a global, prospective, observational study in patients with RMS who were newly or currently prescribed Plegridy as per the routine clinical practice. Enrolled

patients were followed for a maximum of 5 years (regardless of treatment discontinuation) or until patient death, withdrawal, or lost to follow-up, whichever occurred first.

Setting

Approximately 160 sites in multiple regions, including the US, the United Kingdom (UK), the EU, Australia, Canada, and sites participating in Study 105MS302 or Study 105MS303 in other countries were included.

Patients and study size, including dropouts

Approximately 1100 patients were planned, and 1208 patients were enrolled in this study.

Variables and data sources

Data from patients with MS were collected in routine clinical practice at Baseline and every 3 months for follow-up Year 1, and then every 6 months in follow-up Year 2 through Year 5. All MS relapse cases were confirmed by the Prescribing Physician.

Results

Primary endpoint and outcome data

Among all patients in the safety analysis population (N=1173), 68.3% (n=801) were reported to have at least 1 treatment-emergent adverse event (TEAE) (95% confidence interval [CI]: 65.5, 70.9). Overall, the incidence rate of treatment-emergent serious adverse events (TESAEs) for all patients with at least 1 TESAE based on 4913.5 patient-years of exposure was 3704.0 per 100,000 patient-years. The incidence rate of treatment-emergent FLS among patients with at least 1 FLS was 47684.5 per 100,000 patient-years across 4913.5 patient-years of exposure. The incidence rate of ISRs was 41273.7 per 100,000 patient-years based on 4913.5 patient-years of exposure. Among the 555 patients assessed for clinical no evidence of disease activity (cNEDA) between Day 0 and Year 6, 370 (66.7%) patients were classified as cNEDA: 192 were Plegridy naïve and 178 were Plegridy prevalent patients; and 105 were newly-diagnosed and 265 were non-newly-diagnosed patients.

Secondary endpoints and outcome data

The overall proportion of patients prescribed Plegridy dosing of 63 µg, 94 µg, and 125 µg was 82.3% (n=964), 78.6% (n=921), and 95.6% (n=1121), respectively. Most patients were prescribed with Plegridy prefilled pen (n=1076, 91.8%) administered every 2 weeks (n=1143, 97.5%).

The adjusted annualized relapse rate (ARR) at 1 year, 2 years, 3 years, 4 years, and more than 4 years was 0.43 (95% CI: 0.27, 0.69), 0.15 (95% CI: 0.11, 0.22), 0.09 (95% CI: 0.05, 0.14), 0.08 (95% CI: 0.05, 0.14), and 0.07 (0.06, 0.08), respectively, representing a general decrease as study duration increased. Overall and across all years, the adjusted ARR was 0.09 (95% CI: 0.08, 0.10).

Overall, 269 (23.0%) patients experienced a relapse, and 826 (70.5%) were censored. The estimated cumulative proportion of patients relapsed at 1 year, 2 years, 3 years, 4 years,

and 5 years was 13.4%, 17.2%, 20.3%, 21.7%, and 22.9%, respectively. Median time to relapse was not estimable due to the limited occurrence of events.

Forty-four (3.8%) patients experienced sustained disability progression, and 553 (47.2%) were censored. The estimated cumulative proportion of patients with disability progression at 1 year, 2 years, 3 years, 4 years, and 5 years was 1.6%, 2.3%, 3.0%, 3.3%, and 3.8%, respectively. Median time to sustained disability progression was not estimable due to the limited occurrence of events.

Of the 1173 patients in the safety analysis population, overall, 308 (26.3%) had at least 1 TEAE leading to treatment discontinuation (corresponding 95% CI: 23.8, 28.9). The incidence rate of all patients with at least 1 TEAE leading to treatment discontinuation was 10257.4 per 100,000 patient-years, corresponding to a total of 504 events across 4913.5 patient-years of exposure.

The mean (SD) number of times patients visited the healthcare provider (HCP) for management of MS at Baseline was 5.6 (12.13), and at 1 year, 2 years, 3 years, 4 years, and 5 years was 4.8 (10.08), 5.0 (10.90), 6.0 (13.42), 4.0 (8.74), and 4.9 (16.56), respectively. Of these visits, most were to a neurologist who specialized in the treatment of MS during the study (Baseline: 37.1% [385/1038], 1 year: 27.7% [163/589], 2 years: 27.8 [153/550], 3 years: 31.8% [147/462], 4 years: 28.6% [106/371], and 5 years: 28.4% [108/380]).

Patient-reported measures

FLS

Overall at Baseline, 37.4% (261/697) of patients reported ‘mild’ muscle ache, chills, fatigue after most recent injection and a similar trend was observed during the 5 year follow-up period with slight fluctuations. Over 40% of patients reported ‘mild’ muscle ache, chills, and fatigue after FLS reducing medication from Baseline (41.6%, 261/628) through 3 years (1 year [44.8%, 203/453]; 2 years [42.0%, 165/393]; 3 years [41.6%, 136/327]). While at 4 years, the category with the highest proportion was ‘absent’ (43.4%, 99/228). This remained consistent at 5 years as 47.2% (116/246) reported ‘absent’. Finally, 47.8% (32/67) reported ‘mild’ muscle ache, chills, and fatigue after FLS reducing medication at 6 years.

FLS-VAS

Overall at Baseline, when asked ‘since your last injection, how satisfied were you with the effectiveness of the medication you took to reduce your flu-like symptoms?’ and ‘since your last injection, how effective was the medication you took to reduce your flu-like symptoms?’ the median response was 9.0 (range: 1 [not effective/not satisfied] to 11 [very effective/ very satisfied]) for both questions and did not change significantly during the study period.

EQ-5D-3L

The majority of the patients reported ‘no problem’ at Baseline for EQ-5D, 3-level (EQ-5D-3L) parameters: mobility (69.1%; 446/645), self-care (93.8%, 605/645), usual activities (66.8%, 431/645), pain and discomfort (50.5%, 326/645), and anxiety and

depression (66.2%, 427/645). These trends remained consistent throughout the study follow-up.

EQ-VAS

At Baseline, the median score observed overall was 80.0 (range: 5 to 100) p-value=0.7900. The median EQ-VAS scores or the median change from baseline in EQ-VAS scores did not change significantly over the follow-up period.

Treatment adherence

At Baseline, overall 86.0% (576/670) of patients reported taking recommended doses of MS treatment in the past 28 days. Adherence to Plegridy treatment post baseline ranged from 71.3% (179/251 at 5.5 years) to 92.3% (492/533 at 3 months) and the proportion of patients who missed 1 or 2 doses of Plegridy ranged from 50.0% (2/4 at 6 years) to 81.1% (30/37 at 3 months).

Discussion

Study 105MS401 was a prospective, global, observational study designed to provide long-term safety and effectiveness data in patients with RMS who have been prescribed Plegridy in routine clinical practice. The safety profile of Plegridy shows that nearly three-quarters of patients experienced an adverse event of special interest (AESI) and nearly 70%experienced at least 1 TEAE during the study. Slightly more than half of patients who discontinued Plegridy withdrew from the study due to AE events. Overall, AESIs were well tolerated and not often severe in nature, consistent with results of previously conducted clinical trials. Additionally, ARR from Baseline through 6 years of observation was shown to decrease overtime, similar to results of previously conducted trials. Utilisation of Plegridy also aligned with Summary of Product Characteristics recommendations and was overall well adhered to amongst POP patients as identified by self-reported PRO measures. Results of this post authorisation safety study (PASS) are informative of real-world treatment of patients with RMS and RRMS and are aligned with other large scale clinical and observational trials in respect to safety and tolerability of Plegridy.

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Please refer to Appendix 15.1.4 for principal investigator details.