Real-world Characterization of Flu-Like Symptom Severity and Duration in Patients with RRMS: Interim Analysis of the Peginterferon Beta-1a POP Study

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Conclusions

- Peginterferon beta-1a–naive (PEG-naive) patients were more likely than PEG-experienced patients to experience flu-like symptoms (FLS) and discontinue peginterferon beta-1a treatment due to FLS.
- For patients in both subgroups who experienced FLS, symptoms tended to be mild or moderate, were stable or decreased over time, and were well managed by FLS medication.
  - The proportions of patients in both subgroups experiencing mild FLS symptoms increased over time, while the proportions experiencing moderate FLS symptoms decreased over time.
  - The proportion of PEG-experienced patients experiencing severe FLS symptoms also declined over time.
  - Symptom severity was associated with symptom duration.
- The long-term results of this real-world study may help set patient expectations for FLS and facilitate FLS management for individual patients treated with peginterferon beta-1a, particularly those initiating treatment.

Introduction

- Subcutaneous peginterferon beta-1a 125 µg every 2 weeks is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS).[1]
- The PLEGRIDY® Observational Program (POP; ClinicalTrials.gov identifier NCT02230969) is an ongoing 5-year phase 4 study of the long-term safety and effectiveness of peginterferon beta-1a in a broad patient population under real-world conditions.
  - During the pivotal phase 3 study, ADVANCE, one of the most frequently reported adverse events (AEs) was FLS, such as pyrexia, myalgia, and chills.[2]
  - One of the primary objectives of the POP study is to evaluate the incidence of AEs, including FLS, in patients with RRMS receiving peginterferon beta-1a in routine clinical practice.
  - Key secondary objectives include assessing the patient-reported severity and duration of FLS as well as using the FLS–Visual Analogue Scale (FLS-VAS) to evaluate the patient-reported effectiveness of, and satisfaction with, prophylactic management of FLS.

Objectives

- Evaluate the real-world incidence and patient experience of FLS, and assess correlations between FLS severity and duration in patients with RRMS receiving peginterferon beta-1a.

Methods

- POP is ongoing at approximately 150 sites in 14 countries.
- This second interim analysis included patients with up to 36 months of treatment in POP as of September 2017.
- Patients could enter POP if they were initiating or already receiving peginterferon beta-1a. For this analysis, patients were classified based on when they had initiated peginterferon beta-1a treatment:
  - *PEG-naive* patients had started treatment ≤31 days prior to POP enrollment.
  - *PEG-experienced* patients had started treatment >31 days prior to POP enrollment.
- The duration and severity of patient-reported FLS (muscle ache, chills, and fatigue) and the effectiveness of FLS medication in reducing the severity of these symptoms were assessed for each treatment group.
  - Correlations between FLS severity and duration were also assessed in each treatment group.
- Patient-reported effectiveness of, and satisfaction with, prophylactic FLS management was assessed using the FLS-VAS starting at baseline and every 3 months thereafter.

Results

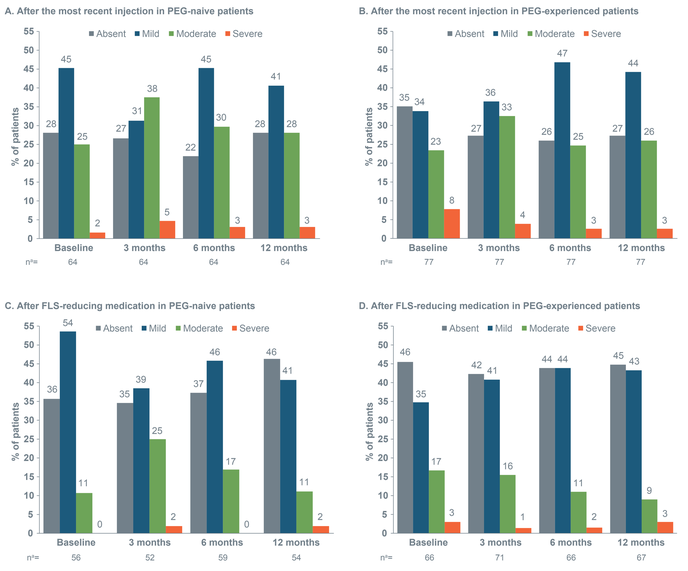
- A total of 963 patients were evaluated in the second interim analysis; 511 (53%) were PEG-naive and 452 (47%) were PEG-experienced (Table 1).
- The overall safety profile was consistent with that reported in the first interim analysis[2] and the phase 3 trial,[3] and no new safety signals were observed (data not shown).
- A higher proportion of PEG-naive than PEG-experienced patients experienced at least 1 FLS (48% vs 28%; Table 2).
- PEG-naive patients were more likely to discontinue treatment due to FLS than PEG-experienced patients (15% vs 3%; Table 2).
- Of patients reporting FLS severity following their most recent peginterferon beta-1a injection, more than 90% of both PEG-naive and PEG-experienced patients had either no symptoms or mild or moderate symptoms over 12 months (Figure 1A, B).
  - The proportion of PEG-experienced patients with severe FLS symptoms generally declined from baseline to 12 months (Figure 1B).
- In both the PEG-naive and PEG-experienced groups, a smaller proportion of patients taking FLS-reducing medications reported moderate or severe symptoms from baseline through 12 months overall (Figure 1C, D) compared with all patients reporting FLS after their most recent dose (Figure 1A, B).
- Over 12 months, median patient-reported FLS-VAS scores for prophylactic medication effectiveness and satisfaction with medication effectiveness were ≥8 out of 10 in each group.
- At 3 months, equal proportions of PEG-naive patients reported FLS durations of ≤24 hours and >24 hours (Figure 2A), whereas PEG-experienced patients were more likely to report an FLS duration of ≤24 hours than >24 hours (Figure 2B).
  - The proportion of PEG-naive patients reporting FLS of >24 hours did not generally change over 12 months (stabilizing at approximately 50% over months 3–12; Figure 2A), while the proportion of PEG-experienced patients reporting FLS of >24 hours declined from 42% at 3 months to 34% at 12 months (Figure 2B).
- Generally, more patients who reported mild FLS experienced symptoms for ≤24 hours (vs >24 hours), whereas more patients who reported moderate or severe FLS experienced symptoms for >24 hours (vs ≤24 hours). These trends were consistent over 12 months in both the PEG-naive and PEG-experienced subgroups (Figure 3).

Table 1. Baseline demographics and disease characteristics of PEG-naive and PEG-experienced patients

Characteristic	PEG-naive (n=511)	PEG-experienced (n=452)	Overall (N=963)
Age at enrollment, mean (SD), years	**43.8 (12.8)**	**44.2 (12.4)**	**43.9 (12.6)**
<40, n (%)	201 (39)	174 (38)	375 (39)
≥40, n (%)	310 (61)	278 (62)	588 (61)
Female, n (%)	**397 (78)**	**345 (76)**	**742 (77)**
Ethnicity			
White, n (%)	141 (28)	168 (37)	309 (32)
Other, n (%)	23 (4)	24 (5)	47 (5)
Not reported, n (%)	347 (68)	260 (58)	607 (63)
Diagnosis of RRMS, n (%)	**503 (98)**	**443 (98)**	**946 (98)**
Age at MS diagnosis, mean (SD), years	**36.1 (10.4)**	**36.3 (10.5)**	**36.2 (10.4)**
No. of relapses in prior year, mean (SD)	**0.5 (0.7)**	**0.4 (0.7)**	**0.5 (0.7)**
EDSS score, mean (SD)	**1.9 (1.5)**	**1.8 (1.4)**	**1.8 (1.5)**
<4.0, n (%)	112 (90)	70 (90)	294 (90)
≥4.0, n (%)	13 (10)	8 (10)	33 (10)
Prior use of DMT, n (%)	**377 (74)**	**342 (76)**	**719 (75)**
IM IFN beta-1a	213 (42)	194 (43)	407 (42)
SC IFN beta-1a	98 (19)	93 (21)	191 (20)
SC IFN beta-1b	83 (16)	76 (17)	159 (22)
Glatiramer acetate	67 (13)	57 (13)	124 (13)
Teriflunomide	11 (2)	16 (4)	27 (3)
Dimethyl fumarate	46 (9)	46 (10)	92 (10)
Fingolimod	18 (4)	14 (3)	32 (3)
Natalizumab	13 (3)	12 (3)	25 (3)

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; IM, intramuscular; MS, multiple sclerosis; SC, subcutaneous; SD, standard deviation.
Percentages shown represent the proportion of total patient populations.

Figure 1. Self-reported severity of FLS after (A, B) most recent injection and (C, D) FLS-reducing medication in (A, C) PEG-naive and (B, D) PEG-experienced patients



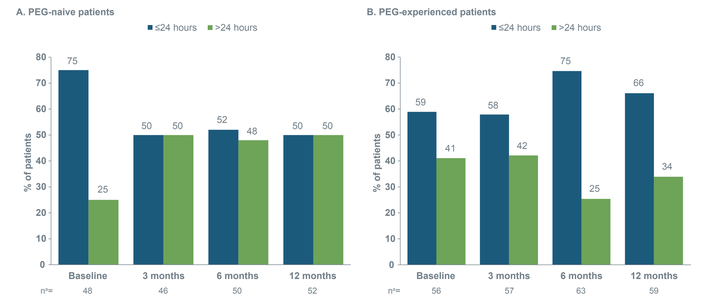
*Patients who completed protocol-scheduled visits from baseline through month 12.

Table 2. Incidence of AEs and serious AEs in PEG-naive and PEG-experienced patients

Category, n (%)	PEG-naive (n=511)	PEG-experienced (n=452)
Patients with at least 1 FLS	**246 (48)**	**128 (28)**
Influenza-like illness	133 (26)	74 (16)
Chills	91 (18)	26 (6)
Headache	56 (11)	17 (4)
Myalgia	63 (12)	33 (7)
Pyrexia	45 (9)	18 (4)
Feeling cold	2 (<1)	0 (0)
Back pain	2 (<1)	0 (0)
Pelvic pain	1 (<1)	0 (0)
Rhinorrhea	1 (<1)	0 (0)
Any FLS leading to treatment discontinuation	**76 (15)**	**13 (3)**
Influenza-like illness	20 (4)	7 (2)
Headache	15 (3)	4 (1)
Myalgia	10 (2)	1 (<1)
Chills	8 (2)	0 (0)

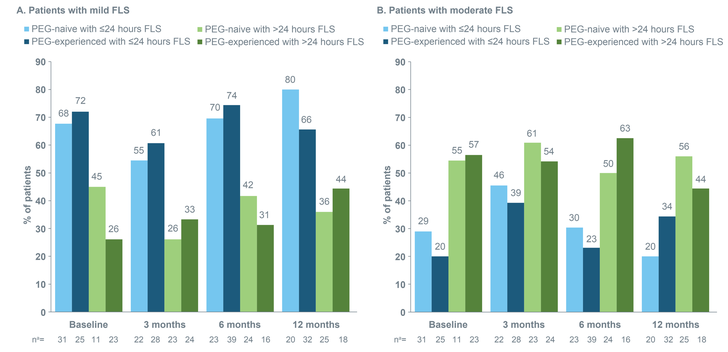
For AEs and serious AEs leading to treatment discontinuation, only those with an incidence ≥1% in either treatment group are shown.

Figure 2. Self-reported percentage of (A) PEG-naive and (B) PEG-experienced patients reporting FLS duration ≤24 hours or >24 hours



*Patients who completed protocol-scheduled visits from baseline through month 12.

Figure 3. Percentage of PEG-naive and PEG-experienced patients who experienced (A) mild FLS or (B) moderate FLS after last injection by FLS duration



*Patients who completed protocol-scheduled visits from baseline through month 12.

References 1. PLEGRIDY (pegylated interferon beta-1a) [prescribing information]. Cambridge, MA: Biogen; 2015; 2. Salavetti M, *et al.* Presented at ECTRIMS-ACTRIMS; October 25–28, 2017; Paris, France. Poster EP1627; 3. Kieseier BC, *et al. Mult Scler.* 2015;21:1025-1035. **Disclosures** MLN, OM, CW: employees and stockholders of Biogen. MS: grant support and speaker honoraria from Biogen. JY: employee of Biogen at the time of these analyses. SW: paid consultant, speaker, and/or contract researcher for Acorda, Bayer, Biogen, EMD Serono, Genentech/Roche, Genzyme, Novartis, Questcor, Receptos, Teva. **Acknowledgments** This study was sponsored by Biogen (Cambridge, MA). All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this poster and take responsibility for the integrity of the work as a whole. Biogen provided funding for medical writing and editorial support in the development of this poster; John Watson, PhD, of Ashfield Healthcare Communications (Middletown, CT) wrote the first draft of the poster based on input from authors, and Joshua Safran of Ashfield Healthcare Communications copyedited and styled the poster per congress requirements. Biogen reviewed and provided feedback on the poster to the authors. The authors had full editorial control of the poster and provided their final approval of all content.