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Low Risk of New Flu-like Symptoms in Patients Transitioning from Non-pegylated to Pegylated Interferon Beta-1a and Mitigation with Scheduled Naproxen

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INTRODUCTION

- ALLOW is a Phase 3b, multi-center, randomized, parallel arm study to characterize flu-like symptoms (FLS) in relapsing multiple sclerosis (RMS) patients transitioning from interferon (IFN) beta therapies to peginterferon beta-1a.
- Reported are 48-week key secondary endpoints, including (1) no increase in overall mean FLS severity score over 48 weeks; (2) mean time of FLS onset 12–13 hours after injection; (3) mean FLS duration 17 hours; (4) no clinically meaningful difference in Patient Determined Disease Steps (PDDS) for those patients completing the trial; (5) adverse event (AE) incidence consistent with the Phase 3 pivotal trial ADVANCE.[1]
- Peginterferon beta-1a was well tolerated with an excellent safety profile in IFN-experienced patients.

OBJECTIVES

- To evaluate the incidence and severity of FLS in patients with RMS transitioning from non-pegylated IFN treatment to peginterferon beta-1a and the impact of prophylactic naproxen treatment on FLS.

METHODS

- ALLOW was a 1-year, Phase 3b, open-label, randomized study to characterize FLS in patients with RMS who transitioned from their current IFN-beta therapy to peginterferon beta-1a (Figure 1).
- Study inclusion/exclusion criteria were the following:
  - Inclusion criteria: patients aged 18–65 with RMS who had been treated with a stable dose of IFN for ≥4 months immediately prior to screening.
  - Exclusion criteria: patients with progressive forms of multiple sclerosis, as well as certain pre-defined clinical and laboratory criteria.
- The primary endpoint was the proportion of patients experiencing new or worsening FLS during the first 8 weeks of administering peginterferon beta-1a.
  - New or worsening FLS is defined as ≥2.0 increase in FLS score from FLS score at screening prior to initiation of peginterferon beta-1a.[2]
- Secondary endpoints included the following:
  - FLS severity over 48 weeks and impact of naproxen (500 mg twice daily) on FLS.
  - The onset and duration of FLS following injection with peginterferon beta-1a.
  - The incidence of AEs for the intent-to-treat population over 48 weeks.
  - PDDS, a walking self-assessment scale that ranges from normal = 0 to bedridden = 8, was evaluated at baseline, 12-weeks, and 48-weeks.[3]

RESULTS

Patient Demographics

- Baseline patient characteristics were balanced between the two arms. Although demographics were representative of the RMS population, the average age was older than that enrolled in previous peginterferon beta-1a clinical trials, reflective of a treatment experienced population (Table 1).
- Of 201 patients who were randomized, 81.6% within each arm completed the study.

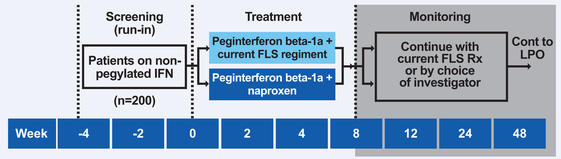
Primary Endpoint

- A majority (89.6%) of patients did not experience new/worsening FLS events during the first 8 weeks of treatment following the transition to peginterferon beta-1a (primary endpoint, previously presented).[4]
  - Prior IFN type did not affect the primary outcome (see Figure 1 footnotes for the most common prior IFNs).

Secondary Endpoints

- FLS severity remained low across all study populations through Week 48, with a majority of FLS being mild to moderate (Figure 2).
  - Naproxen regimen did not reduce FLS severity compared to current FLS regimen.
- Following injection, overall FLS onset occurred between 12.0 and 12.8 hours (mean), and lasted for a median duration of 13.8 to 17.0 hours (Figure 3).
- The most common AEs were injection-site erythema, injection-site reaction (ISR), and influenza-like illness (Table 3).
  - In total, 13.4% of patients discontinued due to an AE, with 6% discontinuing due to ISRs and 2.5% discontinuing due to FLS (data not shown).
- PDDS from baseline to Week 48 was similar (0.83 to 0.94, respectively, with 0 = normal and 1 = mild disability; Figure 4).

Figure 1. ALLOW study design



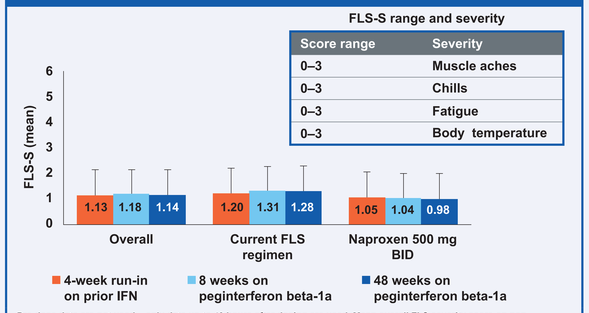
Patients were randomized (1:1) at Week 0 to the current FLS regimen utilized by the trial site or 500 mg naproxen BID. Naproxen 500 mg BID was administered up to 24 hours before peginterferon beta-1a injection and continued for 48 hours after injection.
Maintenance dose 125 mcg peginterferon beta-1a was reached at Week 4 following up-titration over the first four weeks after randomization.
Baseline characteristics in the two treatment arms were well balanced: mean age (years) of patients enrolled = 50; mean RMS duration (years) = 13.5; mean number of relapses within one year of enrollment = 0.2; mean relapses within two years of enrollment = 0.5; mean overall FLS severity score at screening = 1.13; gender was 81.1% female; race was 89.6% Caucasian and 8% African American; compliance with peginterferon beta-1a was greater than 95% over the 48-week period.
BID = two times a day; Cont = continued; FLS = flu-like symptoms; IFN = interferon; LPO = last patient out; RMS = relapsing multiple sclerosis; Rx = prescription

Table 1. Baseline patient characteristics

	Peginterferon beta-1a + current FLS regimen (n=103)	Peginterferon beta-1a + naproxen (n=98)	Total (n=201)
Number of subjects randomized	103 (100%)	98 (100%)	201 (100%)
Number of subjects who completed study	84 (81.6%)	80 (81.6%)	164 (81.6%)
Number of subjects who withdrew from study:	19 (18.4%)	18 (18.4%)	37 (18.4%)
Adverse event	13 (12.6%)	13 (13.3%)	26 (12.9%)
Lost to follow-up	0	0	0
Disease progression	0	0	0
Consent withdrawn	5 (4.9%)	3 (3.1%)	8 (4%)
Investigator decision	0	0	0
Death	0	0	0
Other	1 (1%)	2 (2%)	3 (1.5%)
Number of subjects who discontinued Rx for AE	14 (13.6%)	13 (13.3%)	27 (13.4%)

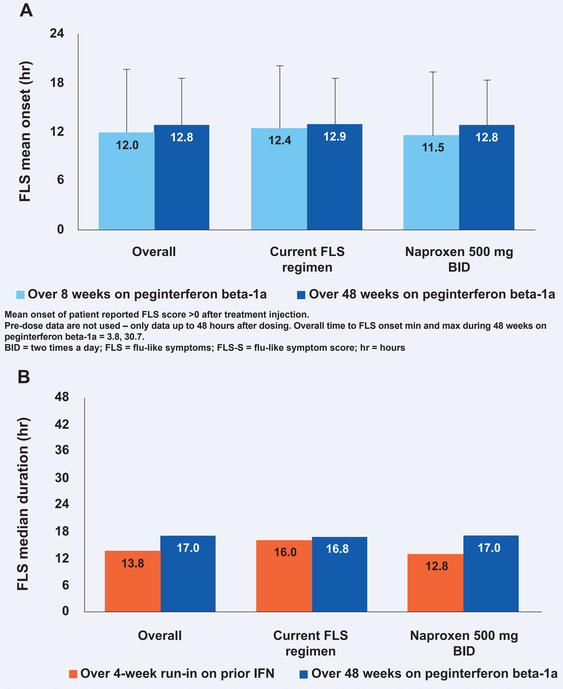
Data are presented as a mean (standard deviation), unless otherwise stated. 50.8% of total patients used IM IFN beta-1a prior to transitioning to peginterferon beta-1a; 27.3% SC IFN beta-1a; 18.9% SC IFN beta-1b. 82% of patients completed the study. The most common concomitant medications taken by patients were ibuprofen (51.5%), vitamin D (34.0%), multivitamin (29.1%), colecalciferol (25.2%), paracetamol (27.2%), acetylsalicylic acid (14.6%), omeprazole (17.5%), fish oil (16.5%), naproxen sodium (16.5%), and naproxen (9.7%). AE incidence reported as severe was 9.4%; 5% were serious AEs.
AE = adverse event; FLS = flu-like symptoms; IFN = interferon; IM = intramuscular; Rx = prescription; SC = subcutaneous

Figure 2. FLS severity over 48 weeks



Pre-dose data are not used – only data up to 48 hours after dosing are used. Mean overall FLS severity score on non-pegylated IFNs during 4-week run-in = 1.13. Overall FLS-S min and max during 4-week run-in on prior IFN = 0, 7.3; overall FLS-S min and max during 48 weeks on peginterferon beta-1a = 0, 6.5.
BID = two times a day; FLS = flu-like symptoms; FLS-S = flu-like symptom score; IFN = interferon

Figure 3. Onset and duration of FLS post-injection over 48 weeks



Mean onset of patient reported FLS score >0 after treatment injection.
Pre-dose data are not used – only data up to 48 hours after dosing. Overall time to FLS onset min and max during 48 weeks on peginterferon beta-1a = 3.8, 30.7.
BID = two times a day; FLS = flu-like symptoms; FLS-S = flu-like symptom score; hr = hours

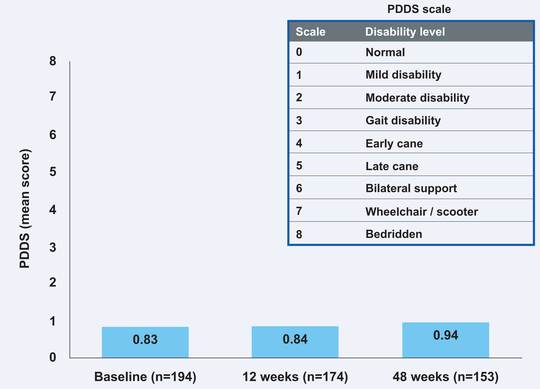
Duration of FLS for a treatment is defined as the sum of hours from the treatment to 48 hours with a FLS score >0. Overall FLS duration min and max (hr) during 4-week run-in period on prior IFN = 6, 42.9; overall FLS duration min and max during 48 week on peginterferon beta-1a = 6, 39.
BID = two times a day; FLS = flu-like symptoms; FLS-S = flu-like symptom score; hr = hours

Table 2. Incidence of adverse events (most common)

Number of subjects experiencing event, n (%)	Peginterferon beta-1a + current FLS regimen (n=103)	Peginterferon beta-1a + naproxen (n=98)
Injection-site erythema	46 (44.7)	34 (34.7)
Injection-site reaction	23 (22.3)	21 (21.4)
Influenza-like illness	11 (11.7)	13 (13.3)
Injection-site pruritus	12 (11.7)	7 (7.1)
Urinary tract infection	9 (8.7)	10 (10.2)
Upper respiratory tract infection	5 (4.9)	10 (10.2)
Headache	9 (8.7)	6 (6.1)
Sinusitis	10 (9.7)	4 (4.1)
Injection-site pain	8 (7.8)	3 (3.1)
Injection-site bruising	4 (3.9)	6 (6.1)
Depression	3 (2.9)	6 (6.1)
Arthralgia	2 (1.9)	7 (7.1)
MS relapse*	1 (1.0)	8 (8.2)

*Mean number of relapses within the year prior to enrollment in ALLOW was 0.2 in both arms. MS relapse AE severity was reported mild in 4 cases, moderate in 4 cases and severe in 1 case. None of the 9 events of MS relapse was assessed as related to the study drug by the Investigators and action taken with study drug was none in all 9 cases. One of the AEs for MS relapse was reported serious. Patients were dosed at least once with peginterferon beta-1a; only post-dose AEs included.
AE = adverse event; FLS = flu-like symptoms; MS = multiple sclerosis

Figure 4. PDDS (walking disability) over 48 weeks



Number of patients reporting in parentheses
PDDS = Patient Determined Disease Steps

CONCLUSIONS

- Peginterferon beta-1a demonstrated a similar safety and tolerability profile in the ALLOW study compared with ADVANCE in patients with RMS:[1]
  - 90% of patients did not experience new or worsening FLS – primary endpoint.[4]
  - Majority of FLS and ISR AEs were mild to moderate, with 2.5% of patients discontinuing for FLS and 6% of patients discontinuing for ISR.
  - FLS mean onset time after injection was 12–13 hours.
  - FLS median duration was 17 hours.
  - Naproxen 500 mg twice-per-day regimen did not significantly reduce FLS severity, onset time, nor duration compared to current FLS regimens utilized by investigative sites in ALLOW (most common: ibuprofen, paracetamol, acetylsalicylic acid, and naproxen).
- No significant increase in mean walking disability (PDDS) was reported by patients who completed the 48-week study.

References

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Disclosures

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RTN: consultant and/or speaker for Acorda, Alkermes, Biogen, EMD Serono, Genentech, Genzyme, EMD Serono, Novartis, Pfizer, Questcor. BH: paid consultant and/or speaker for Acorda, Biogen, EMD Serono, Genzyme, Mallinckrodt, Novartis, and Teva. SW: paid consultant, speaker and/or contract researcher for Acorda, Bayer, Biogen, EMD Serono, Genzyme, Novartis, Questcor, Receptos, Genentech/Roche, and Teva. DH: paid consultant and/or speaker for Biogen, Novartis, and Teva Neuroscience. XY and BW are/were at the time of the study employees and stockholders of Biogen.

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