**Background:** PEGylated interferon beta-1a (PEG IFNβ-1a) is being developed to reduce dosing frequency and improve patient convenience, while maintaining the established efficacy and safety of IFNβ-1a. **Objectives:** To determine the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability profile of single or multiple doses of PEG IFNβ-1a. **Methods:** Two randomized, blinded phase 1 studies were conducted in healthy volunteers: a phase 1a single-dose (SD) study compared intramuscular (IM) or subcutaneous (SC) PEG IFNβ-1a (63, 125, or 188 μg) with IFNβ-1a IM 30 μg; a phase 1b multiple-dose (MD) study compared SC PEG IFNβ-1a (63, 125, or 188 μg) every 2 or every 4 weeks with placebo. Serum IFNβ-1a levels were evaluated by enzyme-linked immunosorbent assay (ELISA) and cell-based activity assays. Neopterin and 2',5'-oligoadenylate synthetase (2',5'-OAS), were measured using an enzyme immunoassay and quantitative reverse transcriptase polymerase chain reaction, respectively. PK/PD parameters were calculated using noncompartmental analysis. Safety and tolerability were evaluated in both studies. **Results:** In the SD study, higher exposures and longer half-life for IFNβ were observed following SC or IM administration of PEG IFNβ-1a of at least 63 μg (6 MIU) compared with IFNβ-1a IM 30 μg (6 MIU). Neopterin and 2',5'-OAS showed prolonged elevations with PEG IFNβ-1a at these doses. Serum IFNβ-1a concentration peaked around 24 to 36 hours post-dose, followed by a monophasic decline with a median half-life of 33 to 67 hour. PK and PD parameters in the IM and SC routes were similar. In the MD study, the PK of PEG IFNβ-1a was similar to that in the SD study, and no drug accumulation was observed. Serum neopterin levels peaked at approximately 72 hours, returning to baseline approximately 10 days postdose. There was no evidence of decrease in pharmacologic responses following multiple doses. The safety and tolerability of PEG IFNβ-1a was similar to what has been observed historically for IFNβ-1a IM 30 μg. **Conclusions:** PEG IFNβ-1a was safe and well tolerated. Dose-related increases in exposure to IFNβ and PD activity were observed with PEG IFNβ-1a at or above 63 μg compared with IFNβ-1a IM 30 μg. Results of these phase 1 studies support further clinical development of PEG IFNβ-1a as a potentially safe, efficacious, and convenient treatment option for patients with MS.

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