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PHARMACOKINETICS

COMPARE: Pharmacokinetic profiles of subcutaneous peginterferon beta-1a and subcutaneous interferon beta-1a over 2 weeks in healthy subjects

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AIM

Subcutaneous (s.c.) peginterferon beta-1a injected once every 2 weeks and s.c. interferon beta-1a injected three times per week (Rebif®) have demonstrated efficacy in relapsing–remitting multiple sclerosis, but direct comparisons of pharmacological activity and tolerability between the two products are lacking. COMPARE was an open label, crossover, pharmacokinetic (PK) study evaluating drug exposure and the safety and tolerability of s.c. peginterferon beta-1a and s.c. interferon beta-1a, over 2 weeks in healthy subjects.

METHODS

Thirty healthy subjects received one dose of peginterferon beta-1a (125 μg s.c.) or six doses of interferon beta-1a (44 μg s.c.) over 2 weeks, followed by the alternate treatment after a 2 week washout period. Drug concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) and PK parameters including cumulative area under the concentration–time curve ($AUC_{0\text{-}336h}$) over 2 weeks and maximum observed serum concentrations (C_{max}) were estimated using a non-compartmental analysis.

RESULTS

The PK analysis population comprised 26 subjects for each treatment. Drug exposure ($AUC_{0\text{-}336h}$) was 60% higher with s.c. peginterferon than with s.c. interferon beta-1a (117.4 ng ml^{-1}h, 95% confidence interval 95.6, 144.3 *vs.* 73.1 ng ml^{-1} h, 95% confidence interval 61.2, 87.3, respectively; $P < 0.0001$). Injection-site reactions (ISRs) were the most common adverse events (AEs) observed with both treatments. Numerically lower frequencies and incidence rates of ISRs, headache, myalgia and chills were observed with s.c. peginterferon beta-1a.

CONCLUSIONS

One dose of s.c. peginterferon delivered significantly greater drug exposure than s.c. interferon beta-1a three times a week over 2 weeks, and a lower frequency of AEs.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Peginterferon beta-1a exhibits reduced clearance and extended half-life compared with non-pegylated interferon beta-1a, permitting reduced frequency of dosing.
- Greater exposure has been observed with peginterferon beta-1a than with intramuscular interferon beta-1a, but direct comparative data for peginterferon beta-1a *vs.* subcutaneous interferon beta-1a are not available.

WHAT THIS STUDY ADDS

- Peginterferon beta-1a provided significantly greater drug exposure, following a single dose, compared with six doses of subcutaneous interferon beta-1a over 2 weeks.
- Higher drug exposure was not associated with increased incidence of side effects. Peginterferon beta-1a demonstrated an improved tolerability profile with respect to injection-site reactions and flu-like symptoms.

Introduction

Interferon beta-based disease-modifying therapies are well-established treatments approved for relapsing forms of multiple sclerosis (RMS). Intramuscular (i.m.) interferon beta-1a (Avonex®, Biogen, Cambridge, MA, USA), subcutaneous (s.c.) interferon beta-1a (Rebif®, Merck Serono, Geneva, Switzerland) and s.c. interferon beta-1b (Betaferon/Betaseron®, Bayer, Leverkusen, Germany; Extavia®, Novartis, Basel, Switzerland) have been available for nearly two decades. The most recent addition to the interferon class, s.c. peginterferon beta-1a (PLEGRIDY®, Biogen, Cambridge, MA, USA), has demonstrated in clinical studies the efficacy, safety and tolerability expected of the interferon class, with a reduced frequency of dosing (one injection every 14 days, whereas the older products are dosed once to several times per week) [1, 2].

The reduced dosing frequency results in part from improved pharmacological properties achieved by conjugation of a polyethylene glycol (PEG) molecule to the native protein to increase molecular size and thereby reduce the rate of clearance by glomerular filtration. Pegylation is an approach that has been used for several protein therapeutics, including pegylated interferons used in the treatment of hepatitis C, which have consistently been found to provide efficacy, safety and tolerability comparable with their unmodified forms [3]. Peginterferon beta-1a was developed by covalent binding of a 20 kDa methoxy-PEG-O-2-methyl propionaldehyde group to the specific alpha-amino group at the N-terminus of interferon beta-1a [4]. Phase 1 studies comparing the pharmacokinetics (PK) of peginterferon beta-1a and i.m. interferon beta-1a demonstrated that pegylation of interferon beta-1a provided a longer terminal half-life ($t_{1/2}$) and greater cumulative area under the curve (AUC), compared with the non-pegylated product, with no peginterferon beta-1a accumulation [5].

Direct comparison of the PK characteristics of peginteferon beta-1a with s.c. interferon beta-1a has not been performed to date. PK characteristics are described in the prescribing information (PI) for each product. However, it is not feasible to make valid comparisons for several reasons, including differences in study design, patient populations, assays techniques and unit disparity. For example, the peginterferon beta-1a PI reports AUC over the 2-week dosing period of approximately 35 ng ml^{-1} h following repeated dosing with peginterferon beta-1a every 2 weeks for 24 weeks in patients with relapsing–remitting multiple sclerosis (RRMS) [6], while the s.c. inteferon beta-1a PI reports AUC over 96 h of 294 ± 81 IU ml^{-1} h following a single s.c. injection of 60 μg in healthy volunteers [7]. The PK profile of peginterferon beta-1a was characterized using an enzyme-linked immunosorbent assay (ELISA) with a range of 31.3–1500 pg ml^{-1} and precision ranging from 4.1% to 11.6% (Invitrogen, Carlsbad, CA, USA), while Phase 1 studies of s.c. interferon beta-1a used an ELISA with precision typically around 25% at concentrations under 2.5 ng ml^{-1} and <20% at higher concentrations [8].

Due to the lack of a more reliable and sensitive assay to determine serum interferon concentrations, particularly during development of first generation interferon treatments, pharmacodynamics (PD) markers, such as neopterin, have often been used to provide an indirect measure of interferon exposure over longer periods of time. However, PD markers have not been shown to correlate with the efficacy of interferon therapy [9, 10], making direct drug exposure a more appropriate endpoint to compare pharmacological activity of different products. Recently, a more sensitive ELISA became available, which has been validated over a range of 5–200 pg ml^{-1} [11]. The new assay was applied in this study to permit direct comparison of the PK profiles of the older generation s.c. interferon beta-1a and the newly approved s.c. peginterferon beta-1a.

In addition, head-to-head trials comparing the safety and tolerability of the pegylated and non-pegylated s.c. therapeutics with different dosing regimens are lacking. While the most common adverse events (AEs) reported in the Phase 3 pivotal trials for both therapies were injection-site reactions (ISRs) and flu-like symptoms [1, 2, 6, 7, 10, 12, 13], data comparing frequency and severity of AEs with the different therapies are not available to date.

This Phase 1 study has been designed to provide a direct comparison of drug exposure, as measured by cumulative AUC over 2 weeks and C_{max}, and to assess comparative safety and tolerability of s.c. peginterferon beta-1a, dosed at 125 μg once every 2 weeks, *vs.* s.c. interferon beta-1a, dosed at 44 μg three times per week, in healthy volunteers. The doses and dosing frequency were selected according to the PI of the respective drugs [6, 7]. The therapeutic dose of peginterferon beta-1a is 125 μg every 2 weeks and the therapeutic dose of interferon beta-1a is 44 μg three times a week.

Methods

Study design and participants

The COMPARE study was an open label, crossover, single centre, Phase 1 study (trial registration: NCT02269930).

Healthy volunteers 18–45 years of age (inclusive) with a body mass index of 19–30 kg m^{-2} and a minimum body weight of 45 kg were assigned to receive either one 125 μg s.c. dose of peginterferon beta-1a or six s.c. doses of 44 μg interferon beta-1a over 2 weeks and then, following a 2-week washout period, receive the alternate treatment (Figure 1). Subjects were assigned to either sequence using a block randomization method with a size of 4. However, a subject was allowed to choose a sequence until 15 subjects were recruited in one group. Subjects were excluded if they had received previous treatment with interferons or pegylated drugs (prescription or investigational), tested positive at screening for human immunodeficiency virus or hepatitis C virus, had current hepatitis B infection or had a history of malignant or premalignant disease including solid tumours or haematologic malignancies. All subjects provided written informed consent after a full explanation of study procedures and the protocol was approved by an Institutional Review Board (Schulman Associates IRB, Cincinnati, OH). The study was conducted in accordance with the US Code of Federal Regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Study procedures

Each subject received a single dose of s.c. peginterferon beta-1a 125 μg on day 1 (treatment sequence 1) or day 29 (treatment sequence 2) based on treatment sequence assignment. Each subject also received six doses of s.c. interferon beta-1a 44 μg administered by qualified clinical research unit staff on days 29, 32, 34, 36, 39 and 41 (treatment sequence 1) or days 1, 4, 6, 8, 11 and 13 (treatment sequence 2) based on treatment sequence assignment. The follow-up period was 4 weeks (±3 days) following the last dose of study drug. PK samples for the evaluation of s.c. peginterferon beta-1a and s.c. interferon beta-1a concentrations were collected and safety assessments were performed as indicated in the study schedules (see Appendix S1). Immunogenicity blood samples were collected on days 1 and 29 pre-dose and at the end of the study on day 43 or 46, for assessment of anti-PEG and anti-interferon beta-1a antibodies. For the prophylactic treatment of flu-like symptoms, all subjects received naproxen or paracetamol (acetaminophen) (when naproxen was not tolerated) within 1 h prior to each dose of study drug, and then approximately every 6 h (or as indicated) for the 24 h following each injection. Subjects received additional doses of naproxen or paracetamol as necessary for relief of interferon-related flu-like symptoms.

Determination of PK parameters

Drug concentration was measured by ELISA, using a commercially available kit (PBL, Piscatway, NJ, USA). Assay parameters were optimized to improve detection of peginterferon beta-1a and non-pegylated interferon beta-1a and assay performance was validated for each compound over the range of 5–200 pg ml^{-1} [11]. Accuracy and precision of the assay were determined by evaluating the performance of assay controls. For peginteferon beta-1a, the percent coefficient of variation (%CV) of quality control samples ranged from 4.2%–6.8% and the percent analytical recovery (%AR) ranged from 105.1–105.4%. For interferon beta-1a, the %CV ranged from 5.4%–7.6% and the %AR varied between 106.7%–108.8%. PK parameters were estimated using a non-compartmental analysis using Phoenix WinNonLin software (Pharsight, Sunnyvale, CA, USA). All post-dose concentrations were above the limit of quantitation through the PK sampling period for both peginterferon beta-1a and interferon beta-1a. Therefore, the method of handling concentrations below the limit of quantitation had no impact on PK parameters. The PK parameters included ($AUC_{0\text{-}336h}$), ($AUC_{0\text{-}72h}$) (s.c. interferon beta-1a only), C_{max}, time to reach C_{max} (t_{max}), apparent total clearance (CL/F), terminal half-life ($t_{1/2}$), apparent volume of distribution (V_d/F), and trough concentration (C_{trough}, measured at pre-dose for repeat dosing). For s.c. interferon beta-1a, all parameters except ($AUC_{0\text{-}336h}$) were calculated for each dose. Ratios of ($AUC_{0\text{-}72h}$), C_{max} and C_{trough} for repeat doses relative to dose 1 were calculated to assess accumulation. Accumulation of peginterferon beta-1a was not assessed in this study, since only a single dose was administered. However, previous multiple dose studies have found no evidence of accumulation [5, 14].

Summary statistics for PK parameters were calculated. Measurements below the lower limit of quantification (LLQ) were set to 0 before statistics were calcuated, except for geometric mean related statistics, which were set to the LLQ. Subjects with pre-dose drug concentrations greater than 5% of C_{max} and subjects positive for anti-drug antibodies were excluded from the primary analysis. All subjects were included in a sensitivity analysis. No formal statistical testing of PK data was planned. *Post-hoc* analysis to compare the geometric mean for ($AUC_{0\text{-}336h}$) of peginterferon beta-1a relative to interferon beta-1a was carried out using a linear mixed effect model with repeated measures including factors for treatment, sequence and period, with ($AUC_{0\text{-}336h}$) being log-transformed. All statistical analyses were performed using SAS 9.3.

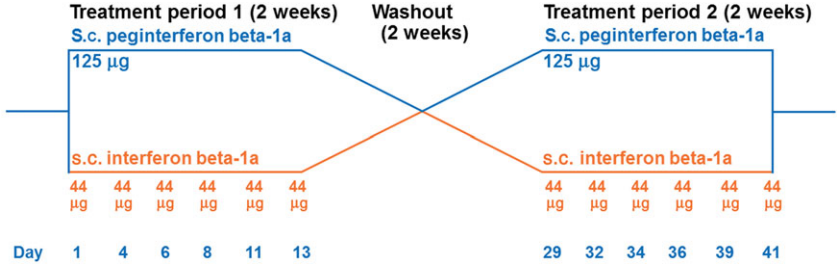

Figure 1
Study design. S.c. subcutaneous

Safety and tolerability evaluation

Safety was monitored by laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, physical examinations, injection-site assessments, immunogenicity assessments, concomitant therapy and procedure recording. All AEs and serious AEs were recorded. Safety data were summarized using descriptive statistics. The incidence (number of subjects experiencing an AE), frequency (total number of occurrences of that AE, including multiple events in the same subject) and incidence rate (calculated as the number of events divided by total number of subject-weeks followed) of AEs were presented by preferred term, coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1.

Testing for the presence and titre of binding antibodies to PEG and interferon beta-1a was performed using validated assays [15].

Results

Subject disposition and characteristics

Thirty subjects were assigned to treatment and received at least one dose of peginterferon beta-1a or interferon beta-1a, with 15 subjects assigned to each treatment sequence. Twenty-nine subjects received peginterferon beta-1a treatment and 29 received interferon beta-1a treatment. Twenty-seven subjects received all doses and completed the study. Of the three who did not complete the study, one subject withdrew consent, one subject was withdrawn by the investigator for non-compliant behaviour and one subject was withdrawn from the study due to an AE (decreased white blood cell count ($<2.5 \times 10^9$ l^{-1}) following four doses of interferon beta-1a 44 µg s.c. in treatment period 1). Subject demographics (Table 1) were similar for the two treatment sequences.

Pharmacokinetics

Peginterferon beta-1a provided higher exposure with respect to both AUC (60% higher over the 2 week cumulative dosing period, $P < 0.0001$) and C_{max}, compared with s.c. interferon beta-1a (Tables 2, 3), with detectable serum concentrations throughout the 2 week dosing period (Figure 2). Peginterferon beta-1a was slowly absorbed with a median t_{max} of 72 h, with individual subject values ranging from 3 h to 168 h. After reaching C_{max}, peginterferon beta-1a was eliminated slowly in a generally monophasic manner. The geometric mean $t_{1/2}$ was 86 h, with individual subject values ranging from 38.7 to 168.3 h.

The s.c. interferon beta-1a serum concentration profile (Figure 2) indicated some accumulation during the first week of treatment, but steady-state was attained by doses 4–5, with dose 6 serving as a good estimate of the steady-state concentration of s.c. interferon beta-1a. Relative to dose 1, geometric mean C_{max}, C_{trough} and ($AUC_{0\text{-}72h}$) for dose 6 increased by approximately 120%, 210% and 150%, respectively. The median t_{max} for s.c. interferon beta-1a following doses 1, 4 and 6 was 12 h and the geometric mean $t_{1/2}$ was 62 h following dose 6.

Sensitivity analyses including all subjects (i.e. including subjects excluded from the primary analysis due to pre-dose drug concentrations >5% of C_{max} or positive for anti-drug antibodies) produced similar results to the main analysis. The geometric mean ($AUC_{0\text{-}336h}$) remained significantly higher with peginterferon beta-1a (109 ng ml^{-1} h, 95% confidence interval [CI] 88.6, 135, $n = 29$) compared with that for s.c. interferon beta-1a (71.1 ng ml^{-1} h, 95% CI 59.5, 85.1, $n = 27$; $P = 0.0002$).

Adverse events

The incidence of treatment-emergent AEs was similar for the pegylated and non-pegylated s.c. interferon beta-1a therapeutics (Table 4). Most of the AEs were mild. ISRs and flu-like symptoms (e.g. myalgia, chills) were among the most common AEs associated with both treatments and most, with

Table 1

Baseline subject demographics

Characteristic	s.c. PEG IFN → s.c. IFN ($n = 15$)	s.c. IFN → s.c. PEG IFN ($n = 15$)	Total ($n = 30$)
Age, years, mean (SD)	33.8 (6.39)	33.9 (6.79)	33.9 (6.48)
Height, cm, mean (SD)	175.5 (10.08)	174.7 (11.92)	175.1 (10.86)
Weight, kg, mean (SD)	78.2 (14.16)	79.8 (10.84)	79.0 (12.42)
Body mass index, kg m^{-2}, mean (SD)	25.3 (3.13)	26.1 (2.66)	25.7 (2.88)
Female, *n* (%)	6 (40)	6 (40)	12 (40)
Ethnicity, *n* (%)			
White	12 (80)	6 (40)	18 (60)
African American	2 (13)	8 (53)	10 (33)
Asian	1 (7)	0 (0)	1 (3)
Other	0 (0)	1 (7)	1 (3)

s.c. IFN, subcutaneous interferon beta-1a; s.c. PEG IFN, subcutaneous peginterferon beta-1a; SD, standard deviation. Population is all subjects who received at least one dose of either treatment and have sufficient pharmacokinetic (PK) data points to determine PK parameters.

Table 2

Drug exposure ($AUC_{0\text{-}336h}$)

($AUC_{0\text{-}336h}$), ng ml^{-1} h (95% CI)	s.c. PEG IFN* (*n* = 26)	s.c. IFN† (*n* = 26)	Percentage difference, %‡	*P* - value
Geometric mean	117 (95.6, 144)	73.1 (61.2, 87.3)	+60.6	< 0.0001*
Mean	131	80.4	+63.5	NA
Median	117	73.0	+59.7	NA

Anti-PEG Ab, anti-polyethylene glycol antibody; CI, confidence interval; NA not applicable; PEG polyethylene glycol; s.c. IFN subcutaneous interferon beta-1a; s.c. PEG IFN subcutaneous peginterferon beta-1a. *Subjects with pre-dose drug concentration > 5% of C_{max} or with anti-PEG Ab titre excluded. †Subjects with pre-dose drug concentration > 5% of C_{max} excluded. ‡Percentage difference = 100 × (mean for peginterferon beta-1a – mean for interferon beta-1a)/mean for interferon beta-1a. *Linear mixed effect model for log-transformed ($AUC_{0\text{-}336h}$) including factors for treatment, sequence and period.

Table 3

Additional pharmacokinetic parameters

Dose	*n*	($AUC_{0\text{-}72h}$), ng ml^{-1} h	C_{max}, pg ml^{-1}	t_{max}, h*	C_{trough}, pg ml^{-1}	V_d/F, l	CL/*F*, l h^{-1}	$t_{1/2}$, h
s.c. PEG IFN†	26		944 (68.1)	72.0 (3.0–168.0)	50 (111.0)	122 (71.1)	1.12 (60.2)	86.0 (37.0)
s.c. IFN‡								
Dose 1	27	6.10 (52.5)	122 (59.9)	12.00 (12.0–24.0)	62 (46.0)			
Dose 2	27		157 (47.9)		118 (37.9)			
Dose 3	27		193 (39.6)		146 (41.2)			
Dose 4	27	13.4 (45.7)	253 (47.7)	12.02 (12.0–24.0)	115 (44.7)			
Dose 5	26		206 (49.3)		174 (49.8)			
Dose 6	26	14.7 (46.2)	266 (46.8)	12.00 (0.0–24.0)	188 (48.0)	321 (56.1)	3.61 (46.0)	61.7 (29.4)

Anti-PEG Ab, anti-polyethylene glycol antibody ($AUC_{0\text{-}72h}$) area under the concentration–time curve from time 0 to 72 h post-dose; C_{max}, maximum serum concentration; CL/*F*, oral clearance; C_{trough}, trough serum concentration; s.c. IFN, subcutaneous interferon beta-1a; S.c. PEG IFN, subcutaneous peginterferon beta-1a; $t_{1/2}$, half-life; t_{max}, time to C_{max}; V_d/F, volume of distribution. Values shown as geometric mean (CV%) unless otherwise specified. *Median (range); †subjects with pre-dose drug concentration > 5% of C_{max} or with anti-PEG Ab titre excluded; ‡subjects with pre-dose drug concentration > 5% of C_{max} excluded.

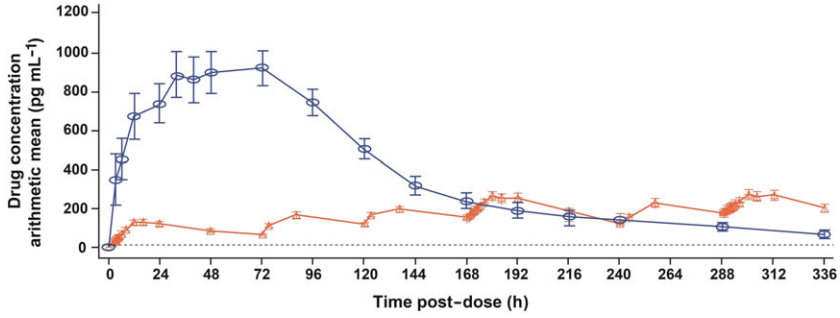

Figure 2

Peginterferon beta-1a and interferon beta-1a serum concentration ±SE over 2 weeks. Dashed lines represent lower limit of quantification (15 pg ml^{-1} for s.c. peginterferon beta-1a; 6 pg ml^{-1} for s.c. interferon beta-1a); *n = 27 for doses 1–4 and n = 26 for doses 5–6. S.c., subcutaneous; SE, standard error. ⬭ s.c. peginterferon beta-1a (n = 26), ⧋ s.c interferon beta-1a (n = 26–27*)

the exception of injection-site pruritus, were more common during s.c. interferon beta-1a three times a week dosing than with peginterferon beta-1a treatment (Table 5, Figure 3). Following each treatment, ≥90% of subjects experienced ISRs. All were mild in severity. The most common ISR was erythema (Table 5, Figure 3). Although the incidence was similar

Table 4

Summary of treatment-emergent AEs

Incidence, *n*	s.c. PEG IFN (*n* = 29)	s.c. IFN (*n* = 29)
AEs (any grade)	28	28
Moderate	3	3
Severe	0	0
Serious	0	0
Treatment-related AEs	28	28
Discontinued due to AE	0	1*

AE, adverse event; s.c. IFN, subcutaneous interferon beta-1a; s.c. PEG IFN, subcutaneous peginterferon beta-1a. *Low white blood cell count; subject discontinued treatment and was withdrawn from study

with peginterferon beta-1a and s.c. interferon beta-1a, the frequency and incidence rate for injection-site erythema were numerically higher with s.c. interferon beta-1a. Injection-site induration and pain also occurred at a higher rate with s.c. interferon beta-1a, while injection-site pruritus, when considered in terms of incidence rate, was similar with each treatment. No clinically relevant differences in vital sign values or laboratory assessments were observed, except for the AE of decreased white blood cell count that led to discontinuation of one patient during s.c. interferon beta-1a treatment.

Immunogenicity

One subject tested positive for anti-PEG antibodies at all sampling time points, including prior to peginterferon beta-1a dosing on day 1 and on days 29 and 46. No AEs considered to be associated with the positive antibody status were reported. No subjects developed anti-interferon antibodies.

It was not possible to assess thoroughly any potential impact of anti-drug antibodies on PK parameters in this study, since the incidence was very low. Only one subject was positive for anti-PEG antibodies, which were present prior to dosing and were likely related to environmental exposure to PEG found in processed foods, over-the-counter medicines, cosmetics and healthcare products [16] rather than peginterferon beta-1a treatment. Analyses of PK parameters including data for this subject were consistent with analyses excluding this subject's data.

Discussion

COMPARE is the first head-to-head study comparing the PK and tolerability profiles of s.c. pegylated interferon beta-1a (PLEGRIDY®) and a non-pegylated s.c. interferon beta-1a (Rebif®). One dose of s.c. peginterferon beta-1a delivered significantly greater drug exposure than s.c. interferon beta-1a three times a week over a 2-week dosing period and a higher maximum serum concentration, despite a lower total dose for peginterferon beta-1a (125 μg *vs.* 264 μg). Detectable drug levels of peginterferon beta-1a were maintained in the circulation over 2 weeks following a single injection.

Drug exposure (AUC) over the dosing period for peginterferon beta-1a every 2 weeks was previously reported as 35 ng m^{-1} h and C_{max} as 280 pg ml^{-1}, following multiple doses of peginterferon beta-1a every 2 weeks in patients with RRMS [14]. The AUC from time 0 to168 h post-dose ($AUC_{0\text{-}168h}$) in healthy subjects in previous studies was 27.2 ng ml^{-1} h and the C_{max} was 342 pg ml^{-1} [5]. The AUC and C_{max} observed in the current study were

Table 5

Incidence, frequency and incidence rate of adverse events (related to study drug) occurring in ≥10% of subjects following either treatment

	s.c. PEG IFN (*n* = 29*)			s.c. IFN (*n* = 29†)		
Adverse event	**Subjects with ≥1 event, *n* (%)**	**Total number of events, *n***	**Incidence rate‡**	**Subjects with ≥1 event, *n* (%)**	**Total number of events, *n***	**Incidence rate‡**
Any event	28 (97)			28 (97)		
Injection-site erythema	26 (90)	29	24.9	27 (93)	125	86.9
Headache	12 (41)	13	11.1	16 (55)	33	22.9
Myalgia	8 (28)	9	7.7	12 (41)	24	16.7
Chills	6 (21)	6	5.1	17 (59)	24	16.7
Injection-site pruritus	5 (17)	5	4.3	3 (10)	4	2.8
Asthenia	4 (14)	4	3.4	6 (21)	6	4.2
Injection-site pain	3 (10)	3	2.6	8 (28)	12	8.3
Injection-site induration	0	0	0	7 (24)	11	7.6
Dizziness	0	0	0	4 (14)	4	2.8
Nausea	0	0	0	3 (10)	7	4.9

S.c. IFN, subcutaneous interferon beta-1a; s.c. PEG IFN, subcutaneous peginterferon beta-1a. *Total number of subject-weeks followed is 116.6; †total number of subject-weeks followed is 143.9; ‡incidence rate = (total number of events/total number of subject-weeks followed) x 100.

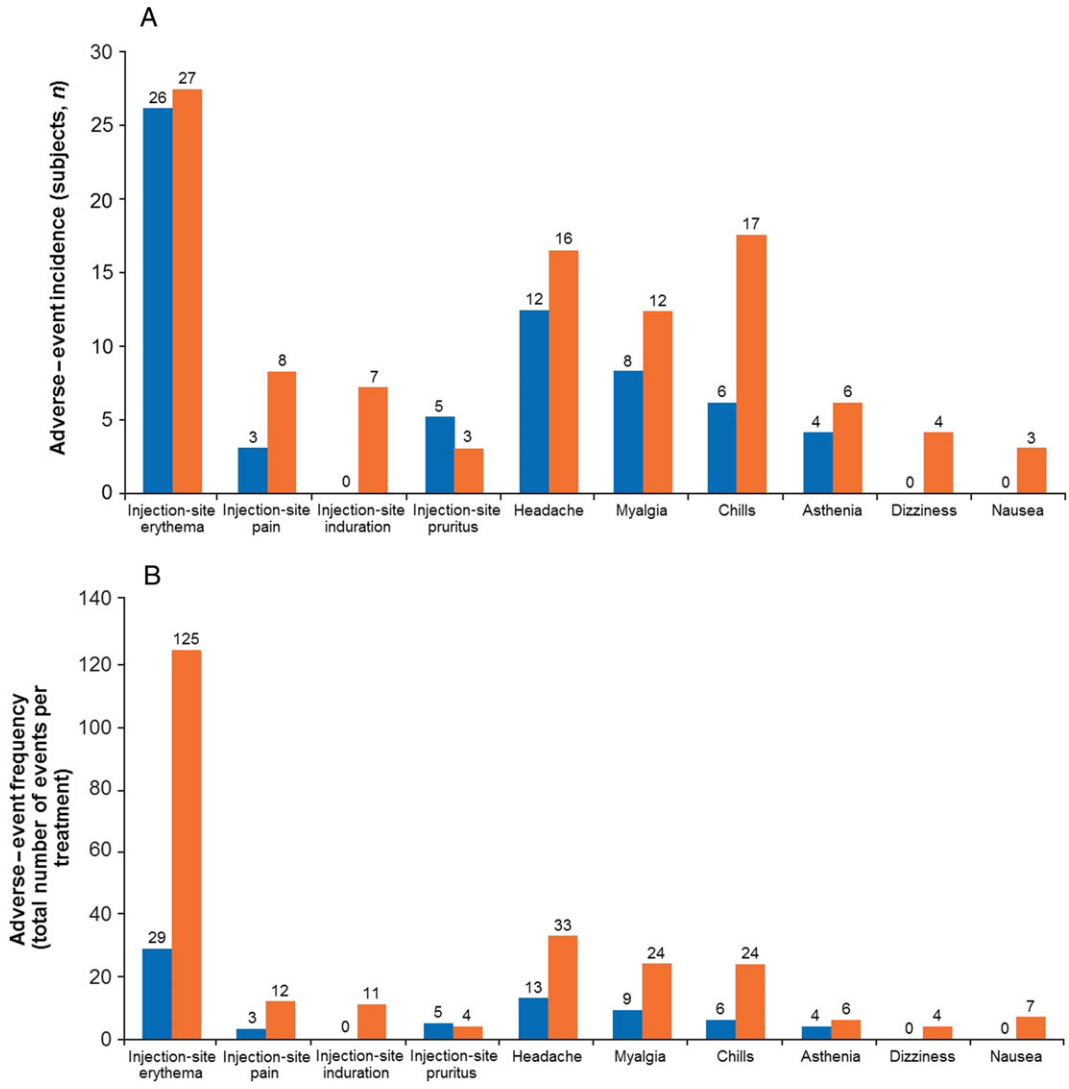

Figure 3

Incidence (A) and frequency (B) of AEs related to study drug occuring in >10% of subjects following either treatment (■) s.c. peginterferon beta-1a (n = 29), (■) s.c. interferon beta-1a (n = 29). AE, adverse event; s.c., subcutaneous

higher for both pegylated and non-pegylated s.c. interferon beta-1a than previously reported. Inter-study variability may contribute partially to the difference. However, since previous studies to characterize peginterferon beta-1a have provided reasonably consistent results in both healthy subjects and RRMS patients [5, 14], it is possible that the major reason for the higher values obtained in this study can be attributed to the utilization of the latest ELISA assay. One plausible explanation is that the current assay was able to capture more stable interferon protein epitopes than the ELISA used in previous PK studies of pegylated and non-pegylated interferon beta-1a. This highlights the necessity of conducting head-to-head studies to permit direct comparisons, rather than attempting to compare products based on values reported in distinct studies.

In the absence of head-to-head clinical comparisons, the potential benefits of greater and continuous drug exposure can only be inferred from other studies linking exposure and efficacy. The efficacy and safety of peginterferon beta-1a, administered every 2 or 4 weeks, was studied in ADVANCE, which was a 2 year, Phase 3, multicentre, randomized, double-blind study with a 1-year placebo controlled period in patients with RRMS. In ADVANCE, peginterferon beta-1a dosed every 2 weeks produced better clinical and radiological outcomes than peginterferon beta-1a dosed every 4 weeks over 2 years [2], which likely relates to the PK profiles of the two regimens, with every 2 weeks dosing providing two-fold greater monthly exposure (AUC) compared with every 4 weeks dosing [14]. Thus, increased exposure to peginterferon beta-1a appears to have led to improved outcomes in ADVANCE. While exposure–response models were established for peginterferon beta-1a [2], there is neither a consistent relationship nor qualitative models to describe the relationship between exposure, PD (such as neopterin) and efficacy and safety across the existing interferons. Thus, direct bridging of the efficacy and safety results of

peginterferon beta-1a to interferon beta-1a using PK or PD parameters is not possible. The benefit to risk profiles of interferon beta-1a (44 μg s.c. three times a week) and peginterferon (125 μg every 2 weeks) remain well established in distinct Phase 3 registrational trials, where significant reductions in relapse rates and risk of disability progression were reported for both therapeutics [1, 6, 7].

S.c. peginterferon beta-1a and s.c. interferon beta-1a were safe and well tolerated when administered in this study. Overall incidence and severity of AEs was similar and AEs were typical of interferon beta therapeutics. The frequency of ISRs and flu-like symptoms were higher during s.c. interferon beta-1a treatment compared with peginterferon beta-1a treatment. The higher frequency of ISRs during s.c. interferon beta-1a treatment is not surprising, given that patients received six injections of s.c. interferon beta-1a compared with a single injection of s.c. peginterferon beta-1a over the 2 week dosing period and demonstrates an important advantage of reduced dosing frequency with peginterferon beta-1a. These results demonstrate that the higher overall drug exposure during peginterferon beta-1a dosing compared with interferon beta-1a dosing was not associated with an increased rate of side effects. Indeed, peginterferon beta-1a appeared better tolerated with respect to flu-like symptoms, as well as ISRs, despite higher overall interferon exposure.

In conclusion, these findings demonstrate that s.c. peginterferon beta-1a provided greater drug exposure, after one injection, than six doses of s.c. interferon beta-1a over 2 weeks. The safety profiles of the pegylated and non-pegylated therapeutics in this study were consistent with previous observations in representative RRMS populations. Approximately 90% of subjects experienced ISRs during each treatment period. However, AE frequencies and incidence rates for ISRs, headaches, myalgia and chills were lower with s.c. peginterferon beta-1a injected once every 2 weeks than with s.c. interferon beta-1a injected three times a week.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from BW) and declare XH, SS, IN, JH, AS, KD, BS and BW had support from Biogen for the submitted work, XH, SS, IN, JH, AS, KD, BS and BW have all been employees and stockholders of Biogen in the previous 3 years and all had no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

XH, SS, IN and BW conceived the study and participated in its design and coordination and helped draft the manuscript. SS performed statistical analyses. JH and AS led safety and tolerability analyses. KD and BS oversaw study conduct and development of the manuscript. All authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Appendix S1 Schedule for safety assessments and collection of PK samples