

Pharmacokinetics, Pharmacodynamics, and Safety of Peginterferon Beta-1a in Subjects with Normal or Impaired Renal Function

The Journal of Clinical Pharmacology
2015, 55(2) 179–188
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Clinical Pharmacology
DOI: 10.1002/jcph.390

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Abstract

Peginterferon beta-1a was efficacious in a Phase 3 relapsing multiple sclerosis trial, and its safety profile was consistent with other beta interferons. This study evaluated the impact of renal impairment on the pharmacokinetics and pharmacodynamics (neopterin elevation; a biomarker of pharmacological activity induced by interferon beta-1a) of peginterferon beta-1a following a single subcutaneous dose at 63 μg ($n = 5$) or 125 μg ($n = 30$). The results showed a fractional increase in area-under-the-concentration-time curve (AUC [30–53%]) and peak serum concentration (C_{max} [26–42%]) in subjects with mild, moderate, and severe renal impairment, versus healthy subjects; AUC and C_{max} were similar for healthy subjects and end-stage-renal-disease patients receiving hemodialysis. Pharmacokinetic simulation showed that the steady state concentration overlapped in the majority of healthy subjects and subjects with severe renal impairment. Neopterin baseline, peak concentration, and AUC increased as renal function decreased. Peginterferon beta-1a was well tolerated in all groups. These results do not warrant peginterferon beta-1a dose adjustment in subjects with renal impairment.

Keywords

clinical trial, multiple sclerosis, pegylation

All currently approved injectable treatments for multiple sclerosis (MS) require frequent (from daily to weekly) administration, which can inconvenience patients suffering from a debilitating chronic disease. Pegylated interferon beta-1a (peginterferon beta-1a) is in development as a less frequently-injected subcutaneous (SC) therapy for relapsing MS (RMS) that may provide similar safety and efficacy to currently available interferons.¹ In a pivotal Phase 3 study that dosed 1512 RMS patients, peginterferon beta-1a 125 μg administered SC once every two weeks reduced annualized relapse rate by 36%, risk of relapse by 39%, and risk of disability progression by 38%, when compared with placebo at the end of year 1.² Other magnetic resonance imaging (MRI) endpoints, such as new or newly-enlarging T2 hyperintense and gadolinium-enhancing lesions, were also significantly reduced versus placebo. A once every four week dosing regimen was also included in this study; while peginterferon beta-1a every 4 weeks also had a significant effect on the clinical endpoints, the reduction relative to placebo in clinical and MRI endpoints was numerically greater in the every 2 week group compared with the every 4 week group.

Interferons, as small proteins, are cleared primarily through renal catabolism and excretion;³ pegylation can increase the apparent size of a biomolecule, reducing the glomerular filtration rate, extending the biomolecule's

half-life, enhancing its in vivo activity through prolonged systemic drug exposure, and enabling less frequent dosing.^{1,4} Therefore, to extend the half-life of interferon beta-1a, peginterferon beta-1a was formed via attachment of a 20-kDa methoxy poly(ethyleneglycol) (peg) polymer to the alpha-amino group of the N-terminus of interferon beta-1a, which is not critical for binding to the type 1 interferon receptor.⁵ In Phase 1 studies in healthy subjects, compared with non-pegylated interferon beta-1a, peginterferon beta-1a (125 μg) had a longer half-life (~ 2 days versus ~ 1 day), increased exposure (maximum serum concentration [C_{max}] and area under the serum

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Submitted for publication 2 May 2014; accepted 2 September 2014.

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ClinicalTrials.gov: NCT01119781.

concentration curve through 168 hours [AUC_{168h}]), and prolonged and higher elevations in well-characterized pharmacodynamic (PD) markers of type 1 interferon receptor activation (serum neopterin and 2'-5'-oligoadenylate synthetase),⁶ supporting the contention that pegylation of interferon beta-1a would allow for less frequent dosing.

Although pegylation reduces the contribution of the renal system to overall clearance and increases the significance of alternative clearance routes (e.g., hepatic⁷), renal clearance may still comprise the major clearance pathway. For instance, it was shown that the AUC of 10-kDa pegylated interferon alpha-2b was increased in subjects with moderate and severe renal impairment vs. healthy subjects, which necessitated a 25–50% dose reduction in patients with renal impairment.^{8–9} The objective of this study was to investigate whether renal impairment impacts the pharmacokinetics (PK) of peginterferon beta-1a and to provide dose adjustment guidance in MS patients with renal impairment. A population PK model was developed and simulation was carried out to predict and compare the steady state peginterferon beta-1a concentration–time profiles between healthy subjects and subjects with severe renal impairment.

Neopterin (D-erythro-1',2',3'-trihydroxypropylpterin), a well-characterized biomarker induced by interferon beta-1a in vivo, is a product of the activity of guanosine triphosphate-cyclohydrolase I and is produced by macrophages and monocytes. It is an indicator of immune system activation.^{10–11} It is known that neopterin is cleared in the kidney and that increasing renal impairment might affect the kinetics of neopterin concentration following peginterferon beta-1a treatment.^{12–13} Concentrations of neopterin were monitored as an exploratory marker of PD activity. Tolerability and adverse events (AEs) data were also collected in this study.

Methods

Study Design and Subjects

The protocol was approved by each site's institutional review board. All subjects provided written informed consent before entering the study, which was conducted according to International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

This was a single-dose, open-label, multicenter Phase 1 study (ClinicalTrials.gov Identifier: NCT01119781) in healthy subjects and subjects with renal impairment or end-stage renal disease (ESRD). Renally-impaired subjects were included if they had stable renal disease (no change in disease status) for 1 month before enrollment (determined by the investigator), with laboratory and clinical findings consistent with renal impairment.

Creatinine clearance (CrCl) was defined by the following Cockcroft–Gault equation:¹⁴

$$(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85 \text{ if female}) / (72 \times \text{serum creatinin in mg/dL}) \quad (1)$$

For analytical comparison only, subjects were also categorized according to renal impairment estimated glomerular filtration rate (GFR) calculated using the following modification of the diet in renal disease (MDRD) equation:

$$175 \times \text{serum creatinin in (in mg/dL)}^{-1.154} \times \text{age (in years)}^{-0.203} \times 1.212 (\text{if patient is black}) \times 0.742 (\text{if female}) \quad (2)$$

After a 28-day screening period, subjects were enrolled into one of five groups, categorized according to Committee for Medicinal Products for Human Use (CHMP) guidance¹⁵ on estimated CrCl values. Healthy subjects and those with mild, moderate, or severe renal impairment (as defined in Table 1) were required to have two estimates of CrCl within 25% of each other, obtained >5 days and ≤6 months apart. ESRD subjects were required to have hemodialysis two to three times per week. Each healthy subject was matched with an ESRD subject with respect to age (±10 years) and weight (±20%). Stable medication regimens used for at least 30 days pre-dose to treat conditions related to renal impairment or underlying disease states, and for prophylaxis, were permitted during the study. Exclusion criteria included a history of any clinically unstable major disease or recent serious infection.

All subjects received one subcutaneous dose of peginterferon beta-1a, starting with 63 µg in three subjects with mild renal impairment before proceeding to subjects with more severe renal impairment and a dose of 125 µg. Three subjects with mild renal impairment and two subjects with severe renal impairment received a single 63 µg dose (a dose that should yield concentrations no greater than those previously tested, and shown to be well tolerated⁶), to assess safety and tolerability profiles prior to administering the target 125 µg dose; six subjects from each of the five groups received a single 125 µg dose.

Blood Sampling

Blood samples for PK analyses of peginterferon beta-1a were collected pre-dose, and at 6, 12, 24, 36, 48, 72, 96, 168, 240, 336, 408, 504, 576, and 672 hours post-dose. PD samples were collected at the same timepoints, except 6 and 12 hours post-dose. Subjects with ESRD were dosed when hemodynamically stable (approximately 2 hours post-hemodialysis). Subsequent dialysis was scheduled three days post-dosing to minimize impact on C_{max}. PK

Table 1. Baseline Subject Demographics and Renal Disease Etiology

	Normal renal function (n = 6) (CrCl >80 mL/min)	Mild renal impairment (n = 9) (CrCl >50 mL/min – ≤80 mL/min)	Moderate renal impairment (n = 6) (CrCl >30 mL/min – ≤50 mL/min)	Severe renal impairment (n = 8) (CrCl ≤30 mL/min)	ESRD on hemodialysis (n = 6) (Require hemodialysis two to three times a week ^a)
Age, years, mean (SD)	47.7 (5.79)	68.2 (5.26)	59.7 (10.1)	65.6 (6.72)	46.5 (1.52)
Sex, n (%)					
Male	4 (67)	7 (78)	4 (67)	3 (38)	4 (67)
Female	2 (33)	2 (22)	2 (33)	5 (63)	2 (33)
Height, cm, mean (SD)	167 (10.2)	172 (6.20)	168 (13.53)	163 (8.42)	179 (7.97)
Weight, kg, mean (SD)	82.0 (15.2)	84.4 (14.4)	79.3 (21.8)	71.2 (9.77)	87.9 (19.2)
BMI, mean (SD)	29.5 (4.33)	28.5 (3.28)	27.8 (5.28)	26.8 (4.10)	27.4 (4.94)
CrCl ^b (mL/min), mean (SD)	111 (14)	70.1 (8.6)	39.2 (6.8)	23.5 (3.9)	–

^aCrCl could not be estimated in these patient.

^bBy Cockcroft–Gault equation.

Three subjects in the mild renal impairment function group and two subjects in the severe renal impairment group received a single dose of peginterferon beta-1a 63 µg. After ascertaining that the 63 µg dose was well tolerated, six patients each group received a single dose of peginterferon beta-1a 125 µg. BMI, body mass index; CrCl, creatinine clearance; ESRD, end-stage renal disease; SD, standard deviation.

and PD samples were also taken before (within 4 hours) and after (between 1 and 4 hours) dialysis through Day 8.

Safety and Tolerability Assessment

Safety and tolerability evaluations included physical examination for vital signs, subject's injection-site pain assessment, clinician's injection-site assessment, monitoring for AEs, hematology, blood chemistry, urinalysis, and electrocardiograms. These assessments were conducted pre-dose and up to 35 days post-dose.

Determination of Serum Concentration of Peginterferon Beta-1a and Neopterin

Serum peginterferon beta-1a concentrations were evaluated using a validated enzyme-linked immunosorbent assay (ELISA; Invitrogen, Carlsbad, CA, USA) with a lower limit of quantitation (LLOQ) of 31.3 pg/mL and an upper limit of quantitation (ULOQ) of 1500 pg/mL. Precision, expressed as percent coefficient of variation (%CV) and evaluated using assay controls, ranged from 1.5 to 6.1%. Neopterin concentrations were evaluated using a validated competitive binding enzyme immunoassay (ImmuchemTM, MP Biomedicals, Santa Ana, CA, USA). The quantitation range of the neopterin assay was 1.3 ng/mL (LLOQ) to 101 ng/mL (ULOQ), with precision (%CV of assay controls) ranging from 3.6 to 5.7%.

Immunogenicity Assay

Immunogenicity assessments were performed to determine pre-existing anti-PEG antibodies. Serum anti-PEG antibody levels were evaluated using a three tier sandwich ELISA method (Biogen Idec Inc., Cambridge, MA, USA). Anti-PEG antibodies detected in the screening assay were evaluated for specificity by competition with

excess PEG. Samples confirmed as positive were then evaluated to determine levels of reactivity in a titer assay. Results for anti-PEG antibodies were listed per subject at baseline (Day 1) time-point.

Calculation of PK and PD Parameters Using Non-compartmental Analysis

PK parameters from non-compartmental analysis (NCA) included C_{max} , time to peak serum concentration (t_{max}), AUC from time 0 to 336 hours post-dose (AUC_{336h} ; specified as peginterferon beta-1a concentrations had dropped below the LLOQ by 336 hours), apparent clearance (CL/F , where F represents bioavailability), and terminal half-life ($t_{1/2}$). PD parameters included baseline neopterin concentration, area under effect–time curve from time 0 to 672 hours post-dose ($E_{AUC672h}$), peak effect (E_{peak}), and time to peak effect (E_{Tmax}); $E_{AUC672h}$ and E_{peak} were calculated following baseline correction.

Population PK Model

The PK model consists of a one-compartment model with first-order absorption rate (K_a) and linear elimination rate (K_{10}). K_{10} was parameterized as:

$$K_{10} = CL/V_C + INDEX_{dialysis} \times K_{dialysis} \quad (3)$$

in which V_C represents volume of distribution of the central compartment, CL represents total clearance, $INDEX_{dialysis}$ indicates hemodialysis status (0 = off; 1 = on), and $K_{dialysis}$ represents drug elimination rate by hemodialysis. Because no reference intravenous data were available, bioavailability (F) was not identifiable and was fixed as 1. K_a and K_{10} could not be differentiated and

the individual K_a was constrained to be greater than individual K_{10} as:

$$(DK_a + CL_i/V_{C_i}) \quad (4)$$

where DK_a represents the typical value of the difference between absorption rate and elimination rate and was constrained to be greater than zero, and i represents subject index. The ESRD subjects were excluded during the model development process and were included for the final model with separate theta values (typical values) for CL and V_C .

Inter-subject variance (ω^2) for PK parameters was assumed to have a log-normal distribution and added one-at-a-time, judged by numerical stability and decrease of objective function value. Residual error was modeled using an exponential error model:

$$C = C \times \exp(\varepsilon) \quad (5)$$

where ε represents random error. Once the structural and stochastic model was finalized, the impact of renal function on CL was tested. No other parameters were tested due to the limited subject number and narrow demographic range. $CrCl$, $MDRD-GFR$, and serum concentration of creatinine were tested using Perl-speaks-NONMEM (PsN) software (version 3.5.3), including linear, power, and exponential relationship with CL . The following linear relationship between $CrCl$ and CL was identified to produce the most significant decrease of objective function value:

$$CL = TVCL \times (1 + CL_CrCl_COV \times (CrCl - 31.00)) \quad (6)$$

where $TVCL$ represents the typical CL value for subjects with a $CrCl$ of 31 mL/min, a value provided by PsN Stepwise Covariate Model (scm) which was close to the median $CrCl$, and CL_CrCl_COV represents coefficient for $CrCl$ covariate.

Model Evaluation

Diagnostic plots were produced to assess goodness-of-fit for each model during development, such as individual concentration–time plots for both observed data and predicted data, conditional weighted residual (CWRES) diagnostic plots.^{16,17} The final PK model was evaluated using visual predictive check (VPC). One thousand simulations were carried out using the parameter estimates of the final model without uncertainty. The 2.5th, 50th (median), and 97.5th percentiles of observed data were compared to the 95% CI of the corresponding percentile of the simulated data.

Simulation

Simulations were performed to compare PK profiles between healthy subjects and subjects with severe renal

impairment. Subjects with their demographic data from the current study were used for simulation. One thousand simulations with parameter uncertainty were carried out following multiple doses of 125 μ g every other week to obtain steady state concentration–time profiles. PK parameters were simulated using the final parameter estimates and the covariance matrix from the final model. Medians and the 5th and 95th percentiles of the simulated concentration–time profiles for the two groups were compared.

To investigate the impact of hemodialysis on drug removal, simulations were carried out for subjects with different hemodialysis schedules (thrice-weekly), including: Schedule 1, prior to peginterferon beta-1a dosing and at 3, 5, and 7 days post-dose (representing the schedule of the current study); Schedule 2, at 2, 4, 6, and 9 days post-dose; Schedule 3, at 1, 3, 5, and 8 days post-dose; Schedule 4, at 0.5 hours, 3, 5, 7, and 10 days post-dose. Inter-subject variance and random error were fixed at zero for these simulations.

Modeling Software and Hardware

PK and PD NCAs were conducted using “plasma model” (200-202; PhoenixTM, WinNonlin[®], Pharsight, Sunnyvale, CA, USA) with extravascular input in Phoenix WinNonLin software version 1.1 (Pharsight, Sunnyvale, CA, USA). NONMEM (ICON plc, Dublin, Ireland, version 7.2) was used for population PK analysis with Intel Fortran compiler (Intel Corporation, Santa Clara, California, USA, version 12.1). Pre- and post-analysis data assembly, manipulations, and diagnostic plots were carried out using SAS software (SAS Institute Inc., Cary, NC, USA, version 9.3) and R software (R Foundation for Statistical Computing, Vienna, Austria, version 15.1). All PK models were run with 2–8 parallel cores on an HP 20-node cluster, each node with 2 quad-core Intel Xeon E5630 (160 cores in total) at 2.53 GHz and 24–60 GB of RAM.

Results

Subjects

Thirty-five subjects were enrolled and all completed the study. Baseline demographics are presented in Table 1. Mean age was 58.9 (range 36–75) years; subjects in the normal and ESRD renal function groups were younger (mean age 47.7 and 46.5 years, respectively) than subjects in the mild, moderate, and severe renal function groups (mean age 68.2, 59.7, and 65.6 years, respectively). The majority of subjects were male (63%). The overall mean body mass index of the safety population was 27.9 kg/m^2 (range 20.9–35.9 kg/m^2), and was similar across all renal function groups. Mean height (169.5 cm overall) and weight (80.7 kg) were also similar across the groups. Mean $CrCl$ values were 111, 70.1, 39.2, and 23.5 for

subjects classified as having normal renal function ($\text{CrCl} > 80 \text{ mL/min}$) and mild ($\text{CrCl} > 50 \text{ mL/min}$ to $\leq 80 \text{ mL/min}$), moderate ($\text{CrCl} > 30 \text{ mL/min}$ to $\leq 50 \text{ mL/min}$), and severe ($\text{CrCl} \leq 30 \text{ mL/min}$) renal impairment, respectively. The majority (28/35) subjects were classified into the same renal function groups using both the CrCl^{14} and MDRD-GFR methods.

Pharmacokinetics

Mean (\pm standard error of mean [SEM]) serum peginterferon beta-1a concentrations are presented in Figures 1a and 1b for subjects who received a single 125 μg dose ($n = 6/\text{group}$). Corresponding NCA PK parameters are shown in Table 2. Peginterferon beta-1a serum concentrations reached a peak at approximately 1–2 days post-dose, followed by a gradual decline. By 14 days post-dose, peginterferon beta-1a concentrations had dropped below the LLOQ in all subjects. Peginterferon beta-1a exposure increased with increasing renal impairment except for ESRD subjects. In subjects with mild, moderate, and severe renal impairment, a 30%, 40%, and 53% increase in geometric mean $\text{AUC}_{336\text{h}}$, and a 27%, 26%, and 42% increase in geometric mean C_{max} were observed, respectively, compared to healthy subjects. In contrast, $\text{AUC}_{336\text{h}}$ and C_{max} were similar between the ESRD and healthy groups. An approximately 24% decrease in peginterferon beta-1a concentration was

observed following each hemodialysis (Figure 1b), indicating that hemodialysis partially removed the drug from systemic circulation. The geometric mean $t_{1/2}$ of peginterferon beta-1a was approximately 2 days for subjects with normal renal function or mild or moderate renal impairment, and approximately 3 days in subjects with severe renal impairment. For subjects with ESRD who received hemodialysis three times in a week, the apparent $t_{1/2}$ was approximately 2 days, similar to that of healthy subjects.

Classification of renal function using the MDRD-GFR method resulted in estimates of exposure to peginterferon beta-1a similar to those reported for the CrCl method. Geometric mean ratios of $\text{AUC}_{336\text{h}}$ values (compared with healthy individuals) for subject classified using CrCl and MDRD-GFR were 1.30 vs. 1.13, 1.41 vs. 1.40, 1.53 vs. 1.62, and 0.88 vs. 0.90 for subjects with mild, moderate, and severe renal impairment and ESRD, respectively.

Supplementary Figure S1a shows the correlation between CL/F and CrCl . Linear regression analysis (excluding ESRD subjects; $n = 29$) yielded the following equation (the 95% confidence interval [CI] of the slope was 0.0732–0.414):

$$\text{CL/F (mL/min)} = 27.7 + 0.244 \times \text{CrCl (mL/min)} \quad (7)$$

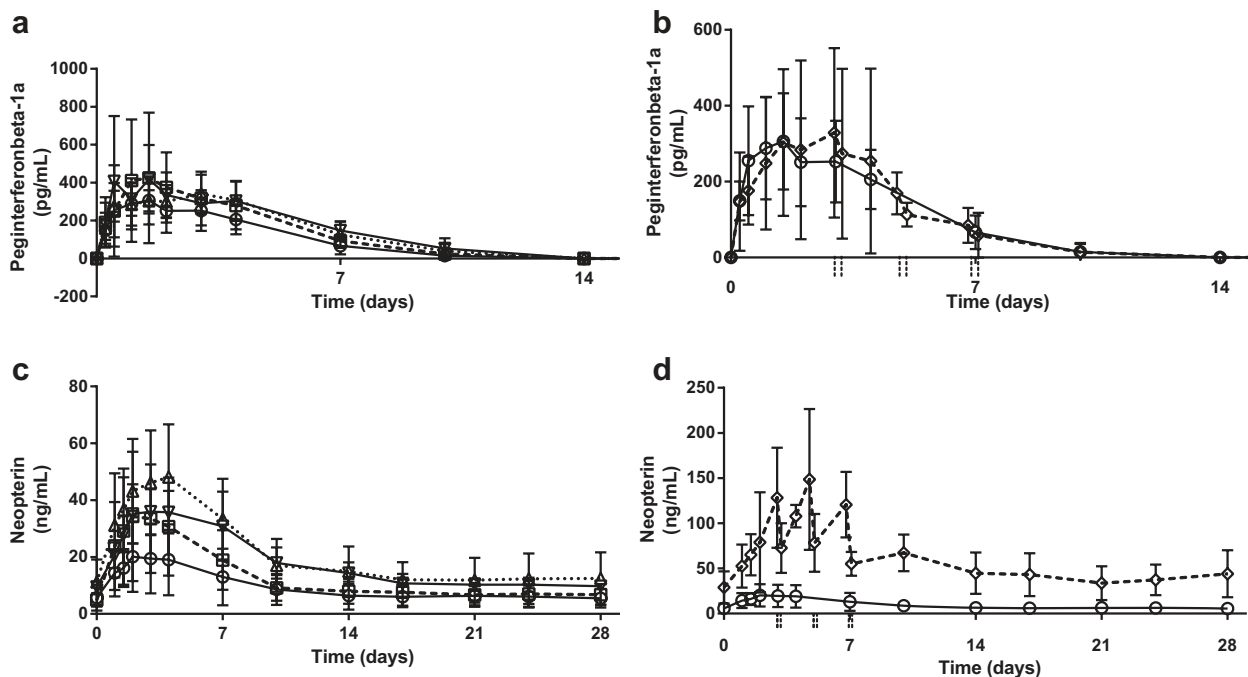


Figure 1. Mean (\pm SD) serum concentration of peginterferon beta-1a (a and b) and neopterin (c and d) after a single subcutaneous dose of 125 μg peginterferon beta-1a in healthy subjects (circle), subjects with mild (square), moderate (triangle), or severe (inverted triangle) renal impairment, or subjects with end-stage renal disease (ESRD) undergoing hemodialysis (diamond). Data for healthy subjects and individuals with mild, moderate, or severe renal impairment are shown on parts a and c. Data for healthy subjects and individuals with ESRD are shown on parts b and d. Vertical broken lines in parts b and d indicate time window of hemodialysis for subjects with ESRD.

Table 2. Geometric Mean (Percent Coefficient of Variation [%CV]) Pharmacokinetic and Pharmacodynamic Parameters for a Single Dose of Peginterferon Beta-1a 125 µg Administered Subcutaneously Across the Different Renal Populations

PK parameters	Normal renal function (n = 6)		Mild renal impairment (n = 6)		Moderate renal impairment (n = 6)		Severe renal impairment (n = 6)		ESRD on hemodialysis (n = 6)	
	A (n = 6)	B (n = 4)	A (n = 6)	B (n = 6)	A (n = 6)	B (n = 6)	A (n = 6)	B (n = 8)	A (n = 6)	B (n = 6)
AUC _{336h} (h · ng/mL)	35.0 (38.2)	34.3 (49.7)	45.6 (45.5)	38.6 (24.2)	48.9 (34.7)	48.2 (46.2)	53.5 (28.3)	55.7 (25.0)	31.0 (75.0)	31.0 (75.0)
C _{max} (pg/mL)	308 (51.5)	258 (53.6)	392 (63.3)	366 (35.1)	389 (27.4)	413 (57.8)	438 (52.1)	441 (43.5)	286 (74.2)	286 (74.2)
CL/F (L/h)	3.25 (32.6)	3.30 (42.6)	2.61 (43.7)	3.08 (23.0)	2.47 (35.2)	2.47 (44.9)	1.99 (29.1)	1.98 (24.6)	3.79 (68.8)	3.79 (68.8)
T _{max} (hours)	37.0 (75.3)	49.4 (48.9)	37.0 (44.1)	27.5 (51.6)	41.6 (94.1)	35.3 (77.0)	28.0 (80.9)	36.8 (92.6)	52.0 (44.8)	52.0 (44.8)
t _{1/2} (hours)	52.4 (25.9)	58.9 (20.6)	50.6 (32.4)	47.5 (29.4)	47.5 (27.0)	46.9 (31.8)	77.8 (37.2)	70.2 (37.8)	44.2 (34.6)	44.2 (34.6)
PD parameters										
Baseline neopterin concentration (ng/mL)	4.7 (68.6)	4.90 (94.1)	4.5 (49.3)	4.32 (33.6)	9.5 (66.2)	7.81 (84.2)	9.4 (13.8)	9.22 (24.2)	22.1 (49.1)	22.1 (49.1)
Neopterin E _{AUC672h} (h · µg/mL)	2.4 (50.1)	2.28 (65.9)	4.6 (68.4)	3.55 (52.6)	6.1 (54.5)	6.06 (63.9)	5.6 (49.6)	5.54 (51.7)	21.1 (33.5)	21.1 (33.5)
Neopterin E _{peak} (ng/mL)	13.8 (49.1)	13.0 (63.8)	26.6 (65.7)	20.5 (43.8)	35.2 (43.5)	35.0 (56.9)	30.5 (25.9)	31.6 (33.1)	105.3 (50.9)	105 (50.9)
Neopterin E _{Tmax} (hours)	54.9 (36.2)	63.1 (34.7)	66.0 (27.5)	62.9 (36.3)	69.2 (57.9)	57.7 (56.9)	64.6 (58.3)	68.8 (50.7)	115.7 (32.9)	116 (32.9)

A = as defined by CrCl values (calculated using the Cockcroft-Gault equation); B = as defined by estimated glomerular filtration rate values (calculated using the MDRD equation); AUC_{336h} = AUC from time 0 to 336 hours post-dose; C_{max} = peak serum concentration; CL/F = apparent peginterferon beta-1a clearance; ESRD = end-stage renal disease; t_{1/2} = terminal half-life; T_{max} = time to reach peak serum concentration; E_{AUC672h} = area under the concentration curve after baseline correction through 672 hours post-dose; E_{peak} = peak concentration after correcting for baseline; MDRD = modification of the diet in renal disease; PK = pharmacokinetic; PD = pharmacodynamic.

Based on this equation, a CrCl of 100 mL/min corresponded to a typical CL/F of 52.1 mL/min, while a CrCl of 0 mL/min (y-intercept) corresponded to a CL/F of 27.7 mL/min. The extrapolation suggested that non-renal clearance of peginterferon beta-1a accounted for 53% (27.7/52.1) with a 95% CI of 30% to 82%, with renal clearance accounting for slightly less than half of the total clearance (47%).

Linear regression analysis of the correlation between CL/F and MDRD-GFR yielded the following equation (the 95% confidence interval [CI] of the slope was 0.0193–0.435):

$$\text{CL/F (mL/min)} = 30.8 + 0.227 \times \text{MDRD} - \text{GRF (mL/min/1.73 m}^2\text{)} \quad (8)$$

Similarly, extrapolation based on this equation suggested that non-renal clearance of peginterferon beta-1a account for 58% of total clearance, consistent with the extrapolation-based CrCl equation (Supplementary Figure S1b).

Pharmacodynamics

Mean (±SEM) serum neopterin concentrations following peginterferon beta-1a administration are presented in Figures 1c and 1d for subjects who received a single 125 µg dose. Corresponding NCA PD parameters are shown in Table 2. Neopterin concentrations increased in all subjects after peginterferon beta-1a treatment, confirming the pharmacological activity of the drug. Peak neopterin concentration was reached 2–4 days post-dose, followed by a gradual decline to baseline concentrations in approximately 2–2.5 weeks. The healthy group and mild renal impairment group had similar geometric mean neopterin baseline; the moderate and severe renal impairment groups had an approximately twofold greater and the ESRD group showed a fivefold greater neopterin baseline compared with the healthy group. Following peginterferon beta-1a administration, 1.9-, 2.5-, 2.3-, and 8.8-fold increases in geometric mean E_{AUC672h}, and 1.9-, 2.6-, 2.2-, and 7.6-fold increases in E_{peak} were observed in subjects with mild, moderate, or severe impairment or with ESRD, respectively, compared with healthy subjects. In ESRD subjects, hemodialysis seemed to be the major mechanism for neopterin clearance, with a 46% geometric mean decrease in neopterin concentration from pre- to post-hemodialysis (Figure 1d).

Population PK Model

The parameter estimates of the final PK model are listed in Table 3. Inclusion of CrCl as a covariate for total clearance (CL) resulted in a marginal decrease of 8.36 in the objective function value ($P < 0.05$). The stochastic model included ω^2 for CL, volume (V), K_a, and CL for ESRD subjects (CL_ESRD), and V for ESRD subjects

Table 3. Population Pharmacokinetic Model Parameters (Fixed and Random Effects), Including % Relative Standard Error

Parameter	Definition	Estimated value	Relative standard error (%)
CL (L/h)	Typical clearance value for subjects with a CrCl of 31 mL/min	2.12	11
V (L)	Volume of distribution	229	9.9
DKa (h^{-1})	Difference between absorption rate and elimination rate	0.0448	16
CL_CrCl_COV	Coefficient for CrCl covariate	0.00500	45
CL_ESRD (L/h)	Clearance for ESRD subjects	2.76	12
V_ESRD (L)	Volume of distribution for ESRD subjects	305	39
K_{dialysis} (h^{-1})	Elimination rate by hemodialysis	0.0454	47
ω^2_{Ka}	Inter-subject variance of Ka	0.166	46
ω^2_{CL}	Inter-subject variance of CL	0.106	37
ω^2_{V}	Inter-subject variance of V	0.194	33
COV _{V,CL}	Covariance of V and CL	0.123	37
$\omega^2_{\text{CL_ESRD}}$	Inter-subject variance of CL for ESRD subjects	0.182	80
$\omega^2_{\text{V_ESRD}}$	Inter-subject variance of V for ESRD subjects	0.561	40
COV _{V,CL_ESRD}	Covariance of V and CL for ESRD subjects	0.245	92
SD	Coefficient of random error	0.234	6.4
σ^2	random error	1 Fixed	NA

CrCl, creatinine clearance; ESRD, end-stage renal disease.

(V_ESRD), with a covariance between CL and V, as well as between CL_ESRD and V_ESRD. The final PK model described both the central trend and the variability of the data from this study, judged by diagnostic plots and VPC plot. The VPC plot (presented as Supplementary Figure S2) shows median values well-aligned between the observed and simulated drug concentrations and almost all observed values falling within the 5–95th percentiles. All other goodness-of-fit diagnostic plots also showed that the data were adequately described by the model (plots not shown).

Based on the final estimates, the relationship between CL and CrCl was described by the following equation (expressed in the same format as the previous equation from the NCA analysis, with good agreement between NCA and population PK parameters):

$$\text{CL/F (mL/min)} = 29.8 + 0.176 \times \text{CrCl (mL/min)} \quad (9)$$

Extrapolation based on final parameter estimate suggested that non-renal clearance accounted for 63% of total clearance assuming a typical subject with CrCl of 100 mL/min, within the 95% CI predicted from the linear regression of the NCA CL ([30%, 82%]). The absorption rate estimate was 0.0556 h^{-1} , corresponding to an absorption half-life of 12.5 hours, which suggests that absorption of peginterferon beta-1a was almost complete (>95%) 3 days after administration. The typical value of V was greater than the typical values of V for other groups (305 vs. 229 L), which might be due to water retention in the ESRD subjects. Based on the drug elimination rate by hemodialysis

(K_{dialysis}) estimate (0.0454 h^{-1}), the model predicted a 20% concentration drop following a 4-hour hemodialysis session, which was within the random error, compared to the observed concentration decrease (24%) following each hemodialysis. The hemodialysis schedule was at 3, 5, and 7 days post-dose. Based on the typical values, 23% of the dosed drug was removed by hemodialysis. Other hemodialysis schedules were also simulated; hemodialysis occurring at 2, 4, and 6 days or at 1, 3, and 5 days showed 26% or 22% drug removal.

Simulation

Simulated steady-state PK profiles for peginterferon beta-1a 125 μg administered every 2 weeks showed that the majority of 5th–95th concentration intervals overlapped between subjects with normal renal function and subjects with severe renal impairment (Figure 2). C_{max} increased slightly, as shown by a simulated median C_{max} ([5th, 95th]) of 373 ([187, 798]) pg/mL for subjects with severe renal impairment, in contrast to 346 ([170, 724]) pg/mL for healthy subjects. Consistent with the observed AUC increase, simulated median AUC ([5th, 95th]) was 42.3 ([24.0, 74.0]) ng·h/mL for healthy subjects, compared with 61.6 ([35.0, 114]) ng·h/mL for subjects with severe renal impairment, showing a 46% increase while the majority of the range overlapped.

Simulation of different hemodialysis schedules confirmed that hemodialysis timing does not significantly change the amount of drug removed by hemodialysis (Figure 3), accounting for 20–27% of the dose with four different schedules (Schedules 1–4).

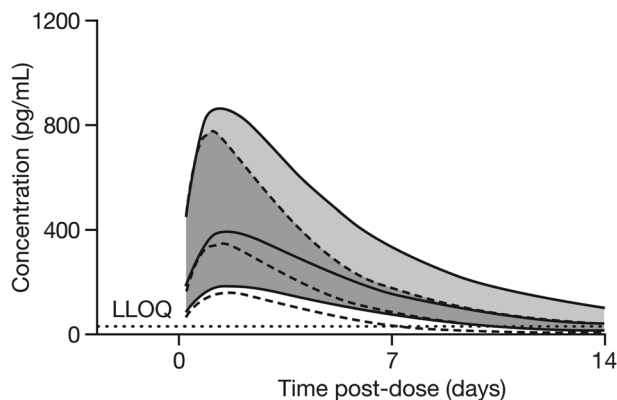


Figure 2. Simulated PK profiles at steady state for subjects with normal renal function or with severe renal impairment. The dashed lines from top to bottom represent the 95th, 50th, and 5th concentration percentiles of the concentration profile in healthy subjects, respectively; the solid lines represent the 95th, 50th, and 5th concentration percentiles of the concentration profile in subjects with severe renal impairment, respectively; the dotted line represents the lower limit of quantitation (LLOQ; 31.3 pg/mL).

Immunogenicity

One subject tested positive for anti-PEG antibodies at baseline ($n = 1$ in ESRD group; anti-PEG antibody titer of 100).

Safety

The incidence of AEs was similar between groups (Supplementary Table S3). The most common AEs were chills, headache, influenza-like illness, and pyrexia; no subjects withdrew because of AEs. No meaningful relationships were observed between changes in the type or incidence of AEs and degree of renal impairment. One serious AE (SAE) was reported in the ESRD group (gastroenteritis), which was assessed by the study investigator to be unrelated to the study treatment. There were no reports of death in the study. No clinically significant changes from baseline in hematology, coagulation or blood chemistry laboratory values, physical examination, electrocardiography, or vital signs were observed.

Discussion

This study showed that exposure to SC peginterferon beta-1a was marginally increased in subjects with decreased renal function, compared with healthy subjects. Exposure to peginterferon beta-1a was similar in subjects with ESRD undergoing hemodialysis, and in those with normal renal function. Consistent results were seen for exposure to peginterferon beta-1a, regardless of whether renal impairment was classified according to CrCl or MDRD-GFR.

Extrapolation using a non-compartmental analysis or using population PK model indicated that non-renal clearance accounted for 53% or 62% of total peginter-

feron beta-1a clearance, respectively. Hepatic catabolism has been shown to be important for clearance of pegylated (40-kDa) interferon alpha-2a.¹⁸ A tissue distribution study in mice showed that murine interferon beta was distributed across multiple tissues, including kidney, liver, spleen, and lung.¹⁹ Catabolism could potentially occur in these tissues and multiple clearance pathways reduce the likelihood of drug accumulation in cases of organ insufficiency.

Data for ESRD subjects suggest that hemodialysis partially removes peginterferon beta-1a from the systemic circulation; simulation of different hemodialysis schedules confirmed that hemodialysis timing does not significantly change the amount of drug removed by hemodialysis (20–27% of dosed drug was removed by dialysis across four different schedules).

Concentrations of neopterin, an established marker of type 1 interferon receptor activation, increased in all subjects after administration of peginterferon beta-1a, confirming the pharmacological activity of peginterferon beta-1a. Increases in neopterin $E_{AUC672h}$ and E_{peak} with the severity of renal impairment might have been due to reduced renal clearance of neopterin and possibly due to increased exposure to peginterferon beta-1a. It is known that neopterin is cleared in the kidney and that increasing renal impairment results in greater neopterin accumulation, particularly in subjects with ESRD, due to activation of cellular immune response and changes in blood coagulation molecules upon exposure to hemodialysis.^{12–13} These increases in neopterin concentrations are unlikely to be clinically relevant, as there was no corresponding increase in AEs, SAEs, or shifts in laboratory parameters, and no correlation between neopterin concentrations and clinical efficacy has been reported. Additionally, no toxicity of neopterin has been reported.²⁰ Therefore, the neopterin PD parameters were not relevant in consideration of dose adjustment, but provided supportive information on the maintenance of peginterferon beta-1a pharmacological activity in renally-impaired subjects.

Single SC doses of peginterferon beta-1a 125 μ g were well tolerated in subjects with renal impairment, with no meaningful difference in the type or incidence of AEs or laboratory assessments between renally-impaired and healthy subjects. The safety profile of peginterferon beta-1a 125 μ g SC in this study reflects that previous observations in Phase 1 trials,^{1,6} which were suggestive of a safety profile similar to that of non-pegylated interferon beta-1a. Additionally, the pivotal Phase 3 study showed that peginterferon beta-1a was well tolerated and demonstrated a favorable safety profile, consistent with the well-established safety profile of beta interferons currently used to treat MS; there was no evidence of a relationship between the incidence of influenza-like illness and exposure to peginterferon beta-1a.² Overall, the fractional increase in exposure in subjects with

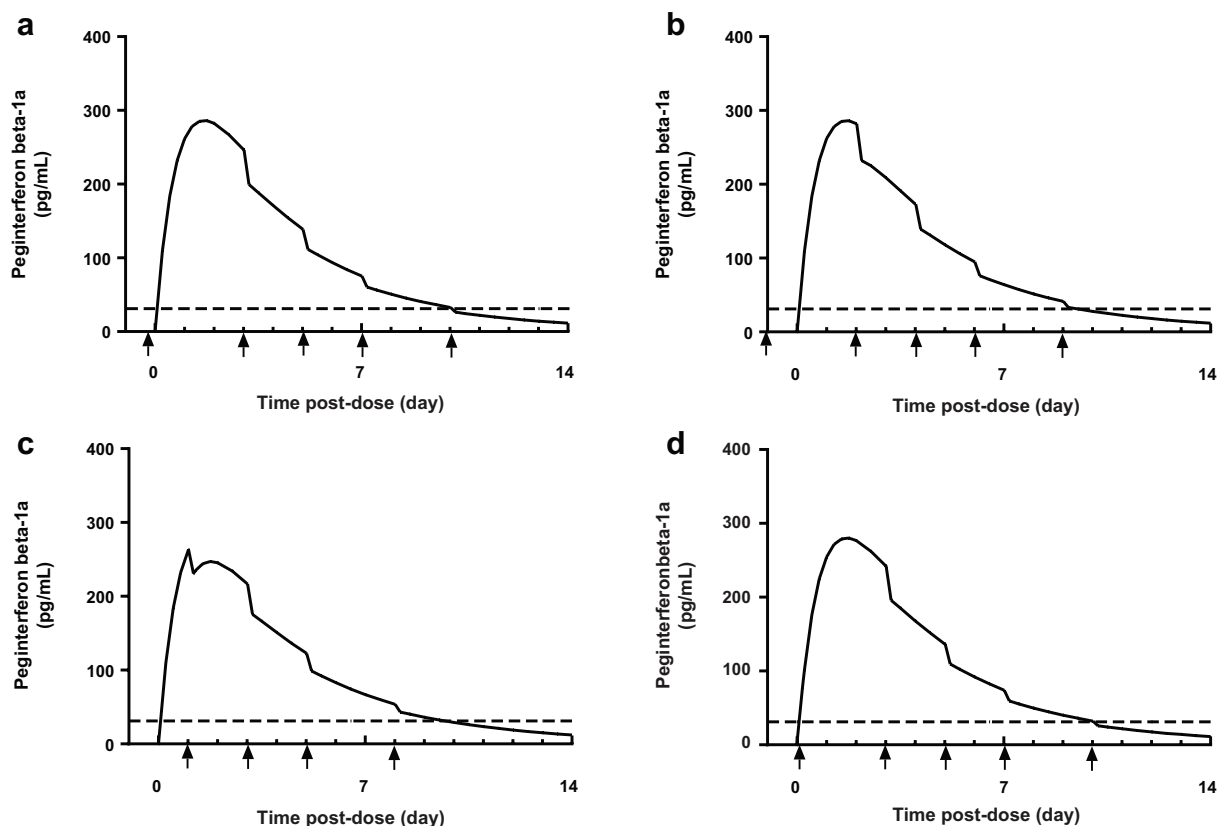


Figure 3. Simulated PK profiles for ESRD subjects under different schedules for hemodialysis. (a) Schedule 1: prior to peginterferon beta-1a dosing and at 3, 5, and 7 days post-dose (representing the schedule of the current study); (b) Schedule 2: at 2, 4, 6, and 9 days post-dose; (c) Schedule 3: at 1, 3, 5, and 8 days post-dose; (d) Schedule 4: at 0.5 hours, 3, 5, 7, and 10 days post-dose. Solid line: simulation peginterferon beta-1a concentration; dashed line: LLOQ (31.3 pg/mL); arrows: hemodialysis events.

varying degrees of renal impairment was not considered clinically significant and no dose adjustment appears to be necessary for patients with renal impairment receiving peginterferon beta-1a. An evaluation of the PK and PD of peginterferon beta-1a in the Phase 3 study is currently underway and will be the subject of a subsequent publication to assess whether MS disease changes drug disposition, and whether the current study interpretation is applicable to MS patients.

In comparison, analyses of another pegylated interferon, 10-kDa peginterferon alpha-2b, showed that renal impairment can affect drug exposure, with a greater elevation in exposure seen with decreased renal function.^{8–9,21} In a single-dose PK study, AUC increased by 27%, 77%, and 107% in subjects with mild, moderate, or severe renal impairment, respectively;⁸ in a multiple dose PK study, AUC increased by 30% and 120% in patients with moderate or severe renal impairment, respectively.⁹ Variation in the impact of renal impairment on the PK of these two pegylated interferon agents could be explained by differing molecular sizes (with peginterferon beta-1a having a larger 20-kDa pegylation attachment), as this can increase steric hindrance for renal clearance and reduce the contribution of renal clearance. Another difference

was that peginterferon alpha-2b is administered more frequently (once weekly) than peginterferon beta-1a (once every two weeks). Given that $t_{1/2}$ was similar between peginterferon beta-1a and peginterferon alpha-2b (52.7–77.8 hours vs. 40.0–65.6 hours), this may suggest that more accumulation of peginterferon alpha-2b could be expected during the chronic treatment of patients in the clinic than peginterferon beta-1a at steady state. Consequently, a dose reduction of 25% and 50% was recommended for peginterferon alpha-2b for subjects with moderate and severe renal impairment, respectively.

Participants were categorized to renal function groups based on recommended regulatory guidelines available at the time of study design (CHMP¹⁵ and Food and Drug Administration [FDA]²²), which was slightly different from the updated draft FDA guidance on PK studies in renal impairment subjects,²³ and versus 2012 Practice Guidelines from Kidney Disease Improving Global Outcomes (KDIGO).²⁴ However, subjects were evenly distributed across the whole renal function spectrum and linear regression analyses, which utilized data from all subjects other than ESRD subjects; this enabled calculation of clearance based on different classification systems, which provided similar results.

In conclusion, this study indicates that renal impairment marginally increases exposure to SC peginterferon beta-1a in subjects with mild, moderate, and severe renal impairment, whereas a similar exposure profile was seen between healthy subjects and ESRD subjects undergoing hemodialysis. Peginterferon beta-1a was well tolerated in healthy subjects and subjects with various degrees of renal impairment, and incidence of AEs were similar across groups. Based on these results, no dose adjustments in subjects with various severities of renal impairment are warranted.

Acknowledgments

We wish to thank the subjects who volunteered for this study and the site staff members who help to conduct the study. The study was sponsored by Biogen Idec Inc. (Cambridge, MA, USA). The authors were assisted in the preparation of the manuscript by Shelley Davies PhD, a professional medical writer contracted to CircleScience (Tytherington, UK), part of KnowledgePoint360, an Ashfield Company. Writing support was funded by the study sponsor.

Declaration of Conflicting Interests

XH, AS, SS, YZ, JG, SH, IN are the employees of Biogen Idec Inc., own stocks and have stock options in Biogen Idec Inc. IN also has stocks in other pharmaceutical companies. TM is an employee of Orlando Clinical Research Center, WS is an employee of New Orleans Center for Clinical Research and MM is an employee of Prism Research.

Funding

The study was sponsored by Biogen Idec Inc. (Cambridge, MA, USA).

References

- Kieseier BC, Calabresi PA. PEGylation of interferon- β -1a: a promising strategy in multiple sclerosis. *CNS Drugs*. 2012;26(3):205–214.
- Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A. Pegylated interferon beta-1a in relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. *Lancet Neurol*. 2014;13:657–665.
- Wills RJ. Clinical pharmacokinetics of interferons. *Clin Pharmacokinet*. 1990;19(5):390–399.
- Jain A, Jain SK. PEGylation: an approach for drug delivery. A review. *Crit Rev Ther Drug Carrier Syst*. 2008;25(5):403–447.
- Baker DP, Lin EY, Lin K, et al. N-terminally PEGylated human interferon- β -1a with improved pharmacokinetic properties and in vivo efficacy in melanoma angiogenesis model. *Bioconjug Chem*. 2006;17(1):179–188.
- Hu X, Miller L, Richman S, et al. A novel PEGylated interferon beta-1a for multiple sclerosis: safety, pharmacology, and biology. *J Clin Pharmacol*. 2012;52(6):798–808.
- Webster R, Didier E, Harris P, et al. PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. *Drug Metab Dispos*. 2007;35(1):9–16.
- Gupta SK, Pittenger AL, Swan SK, et al. Single-dose pharmacokinetics and safety of pegylated interferon- α 2b in patients with chronic renal dysfunction. *J Clin Pharmacol*. 2002;42(10):1109–1115.
- Gupta SK, Swan SK, Marbury T, et al. Multiple-dose pharmacokinetics of peginterferon α -2b in patients with renal insufficiency. *Br J Clin Pharmacol*. 2007;64(6):726–732.
- Murr C, Widner B, Wirleitner B, Fuchs D. Neopterin as a marker for immune system activation. *Curr Drug Metab*. 2002;3(2):175–187.
- Berdowska A, Zwirska-Korczala K. Neopterin measurement in clinical diagnosis. *J Clin Pharm Ther*. 2001;26(5):319–329.
- Estelberger W, Weiss G, Petek W, Paletta B, Wachter H, Reibnegger G. Determination of renal clearance of neopterin by a pharmacokinetic approach. *FEBS Lett*. 1993;329(1–2):13–16.
- Lhee HY, Kim H, Joo KJ, Jung SS, Lee KB. The clinical significance of serum and urinary neopterin levels in several renal diseases. *J Korean Med Sci*. 2006;21(4):678–682.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41.
- Committee for Medicinal Products for Human Use (CHMP). Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function. London: European Medicines Agency (EMA); 2004.
- Food and Drug Administration (FDA). Guidance for industry. Population pharmacokinetics. 1999. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133184.pdf> (accessed 30 June 2014).
- European Medicines Agency (EMA). Guideline on reporting the results of population pharmacokinetic analyses. 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf (accessed 30 June 2014).
- Modi MW, Fulton Jeffrey S, Buckmann DK, Wright Teresa L, Moore David J. Clearance of pegylated (40 kDa) interferon α -2a Pegasys is primarily hepatic. *Hepatology*. 2000;32:371A.
- Mihara Y, Kuratsu J, Takaki S, et al. Distribution of mouse interferon- β in normal and brain tumour-bearing mice. *Acta Neurochir (Wien)*. 1991;109(1–2):46–51.
- Drug Bank. Neopterin. 2013. <http://www.drugbank.ca/drugs/DB02385#taxonom> (accessed 30 June 2014).
- PegIntron[®]. (peginterferon α -2b) Prescribing Information. Kenilworth, NJ: Schering Corporation; 2003–2009.
- Food and Drug Administration (FDA). Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, 1998. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072127.pdf> (accessed 7 July 2014).
- Food and Drug Administration (FDA). Guidance for industry pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. Draft guidance. 2010. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> (accessed 30 June 2014).
- Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2012. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf (accessed 7 July 2014).

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