

Exposure-Response Analysis of Peginterferon Beta-1a in Subjects with Relapsing Remitting Multiple Sclerosis

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INTRODUCTION

- Previous Phase 1 studies provide evidence that peginterferon beta-1a provides potential for increased biologic activity and more convenient, less frequent dosing compared with non-pegylated IFN beta-1a¹ with:
 - A longer terminal half-life ($t_{1/2}$)
 - Greater exposure (peak serum concentration [C_{max}] and area under the curve [AUC])
- A pivotal Phase 3 study (ADVANCE) has been conducted to determine the efficacy and safety of peginterferon beta-1a in patients with RRMS.
 - The pharmacokinetics of peginterferon beta-1a in RRMS patients were characterized in ADVANCE. Previously, the data was analyzed using non-compartmental analysis.² Covariates that impacted pharmacokinetics were explored using a 2-stage method. In this study, population analyses were carried out to develop a population pharmacokinetic model and to identify covariates that impacted pharmacokinetic parameters significantly.
 - Both every 2 weeks (Q2W) and every 4 weeks (Q4W) dosing regimen showed statistically greater annualized relapse rate reduction, relative to placebo group, while greater efficacy was observed for Q2W versus Q4W.³ Considering Q4W provided more convenience, the option of Q2W vs. Q4W was not a clear cut. An exposure-response analysis would provide more insight onto if the observed better efficacy was driven by greater exposure.

OBJECTIVES

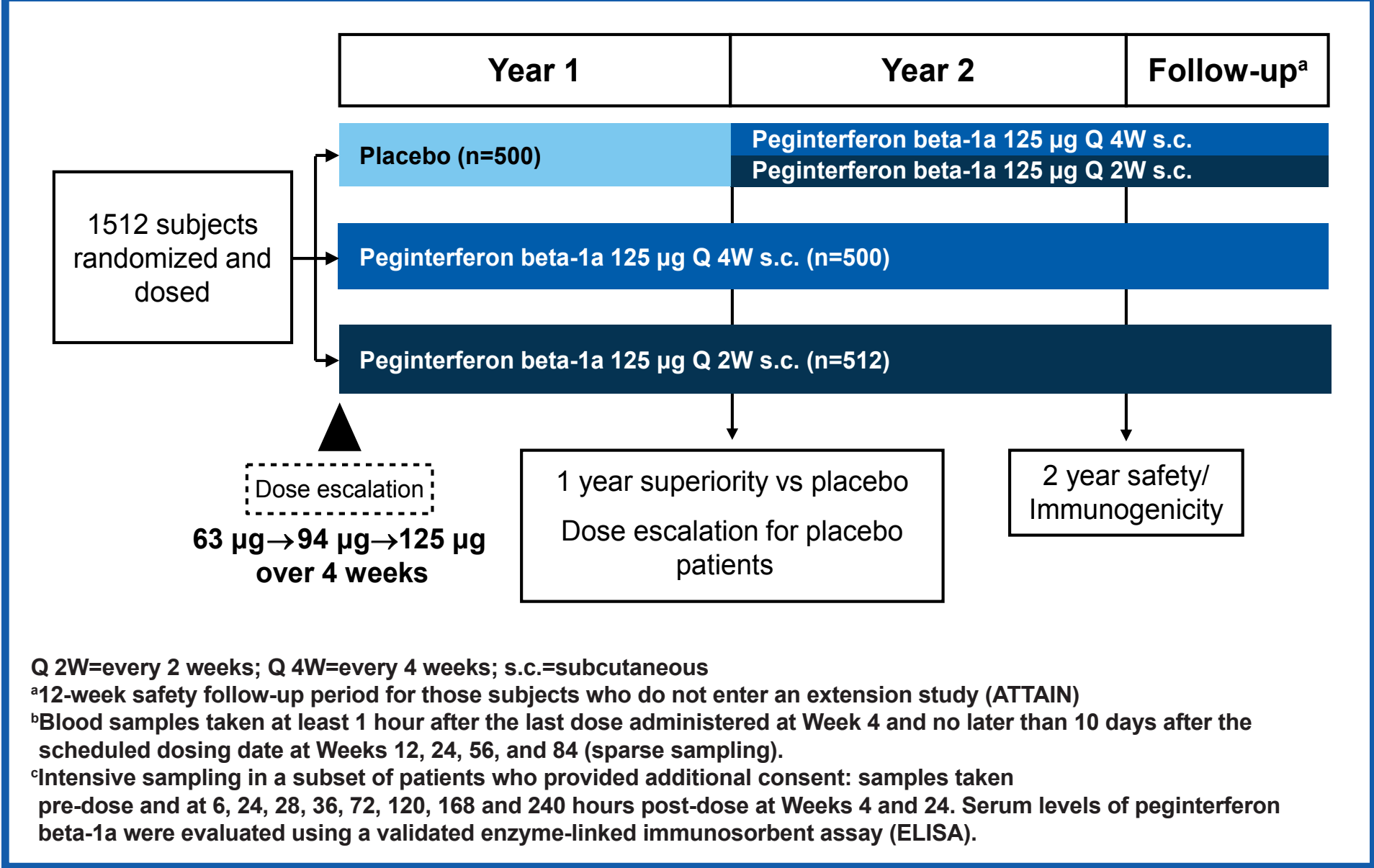
- To establish a population pharmacokinetic model of peginterferon beta-1a in patients with RRMS in the ADVANCE study.
- To describe the relationship between peginterferon beta-1a exposure and ARR.

METHODS

Study Design and Procedures

- ADVANCE was a 2-year, multicenter, randomized, double-blind, parallel-group, Phase 3 study, with a placebo arm during the first year (NCT00906399; Figure 1).³

Figure 1. ADVANCE phase 3 study design



Population Pharmacokinetic Model

- Peginterferon beta-1a serum concentrations were fitted to a pharmacokinetic model using non-linear mixed-effects modelling implemented in NONMEM V7.2.0.⁴
- The population pharmacokinetic model was based on a one-compartment model with a first-order absorption rate, in which body mass index (BMI) was identified as a significant covariate.

$$CL = TVCL * \left(\frac{BMI}{23.75}\right)^m \quad V = TVV * \left(\frac{BMI}{23.75}\right)^n$$

CL = clearance; TVCL = typical value for CL; BMI = body mass index; V = volume of distribution; TVV = typical value for V

Post-hoc Pharmacokinetic Parameters

- Final pharmacokinetic parameter estimates were generated by bootstrapping results based on the final pharmacokinetic model, performed using Perl-speaks-NONMEN (PsN) software (version 3.5.3).
- The median values from the bootstrapping results were used to derive individual post hoc pharmacokinetic parameters.
- Peginterferon beta-1a exposure was represented by monthly cumulative AUC for each subject, which was derived from individual post-hoc Clearance (CL) value using the following equation:

$$Cumulative\ AUC = DOSE * N / CL$$

Dose = 125 µg; N = number of doses over 4 weeks (2 for Q2W group, 1 for Q4W group); CL = post-hoc clearance for each subject

Exposure-Response Model

- The response variable for this analysis was 1-year relapse data for the placebo treatment group and 2-year relapse data for the active treatment groups.

- Four models were tested to describe the relapse data.

- Poisson model:

$$n_{relapse, i} \sim Poisson(\hat{\lambda} \cdot t_i)$$

$n_{relapse, i}$ = number of relapses for subject i; $\hat{\lambda}$ = population annualized relapse rate; t_i = treatment duration

- Poisson-lognormal model:

$$n_{relapse, i} \sim Poisson(\lambda_i \cdot t_i)$$

$$\log(\lambda_i) \sim N(\log(\hat{\lambda}), \sigma^2)$$

$n_{relapse, i}$ = number of relapses for subject i; $\hat{\lambda}$ = population annualized relapse rate; t_i = treatment duration

- Zero-inflated poisson model:

$$n_{relapse, i} \sim Poisson(\lambda \cdot t_i \cdot I_i)$$

$$I_i \sim Bernoulli(p)$$

I_i = value 0 or 1, and follows Bernoulli distribution; p = the probability of I_i being 1

- Poisson-gamma model

$$n_{relapse, i} \sim Poisson(\lambda_i \cdot t_i)$$

$$\lambda_i \sim gamma(\alpha, \alpha/\hat{\lambda})$$

α = shape factor of gamma distribution; $\hat{\lambda}$ = mean of the gamma distribution, which are the same for all subjects in the baseline model

- Baseline model was selected based on deviance information criteria (DIC).

- The relationship between AUC and ARR was described by a log-linear relationship.

$$\log(\hat{\lambda}_i) = \log(\lambda_0) + b \cdot AUC_i$$

$\hat{\lambda}_i$ = mean ARR for subject i; λ_0 = mean baseline ARR; AUC = cumulative monthly AUC in subject i

- Other covariates tested included baseline Expanded Disability Status Scale (EDSS) score, baseline relapse rate (number of relapses in 3 years before study entry divided by 3), age, gender, baseline McDonald Criteria, baseline Gd+ lesion volume, 6-month after study entry Gd+ lesion volume, 6-month after study entry 2-weighted lesion volume. Covariates that yielded the greatest DIC decrease were included in the model until addition of covariate produced no decrease. The relationship between ARR and covariates is shown below.

$$\log(\hat{\lambda}_i) = \log(\lambda_0) + b \cdot AUC_i + c \cdot P_i$$

P_i = the covariate value for subject i

Software

- Pharmacokinetic model was developed using NONMEM version 7.2.⁴ The exposure-ARR was developed using WinBUGS (Imperial college and MRC, UK, version 1.4.3).^{5,6} Data preparation and plots were carried out using R software (R Foundation for Statistical Computing, Vienna, Austria, version 2.15.3).

RESULTS

Pharmacokinetic Parameter Estimates

- The pharmacokinetic parameter estimates based on bootstrapping are shown in Table 1.

Table 1. Bootstrap result of the final pharmacokinetic model					
	Mean	Standard Error	Medians	2.5th Percentile	97.5 Percentile
OFV	445	80.1	448	281	604
V (L)	440	39	440	360	540
CL (L/h ⁻¹)	3.2	0.13	3.3	3	3.5
DKA (h ⁻¹)	0.21	0.02	0.21	0.16	0.26
SD1	0.57	0.02	0.56	0.53	0.61
m	0.8	0.13	0.77	0.55	1.1
n	0.033	0.0071	0.035	0.016	0.046
ω^2_{CL}	0.16	0.062	0.14	0.049	0.34
ω^2_v	0.34	0.066	0.35	0.18	0.47

OFV = objective function value; CL = clearance; V = volume of distribution; DKA = difference between absorption rate and elimination rate; SD = coefficient of random error; m = exponent for clearance as a function of body mass index; n = exponent for volume of distribution as a function of body mass index; ω^2_{CL} = inter-subject variance of CL; ω^2_v = inter-subject variance of V

Exposure-Response Model

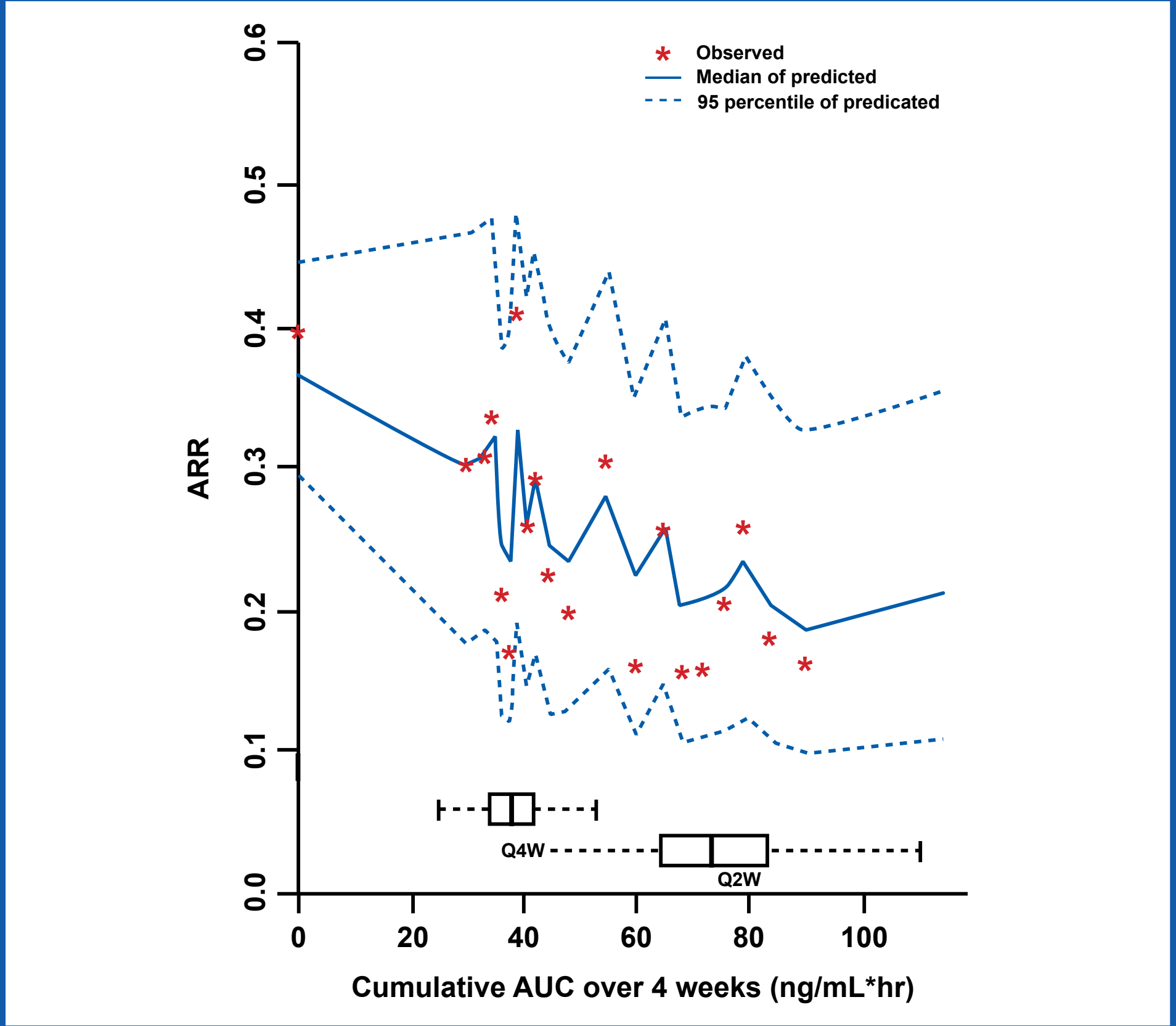
- The parameter estimates for the four baseline models and the final model are shown in Table 2. The Poisson-Gamma model yielded the lowest DIC than other three models, thus, selected as the baseline model for further exploration.
- Among all covariates tested, incorporation of Gd+ lesion volume at 6 month in addition to cumulative monthly AUC yielded the greatest DIC decrease.
- For the final model, the time-series SEs were less than 5% of the parameter estimates, indicating the sampling number was sufficient to estimate the parameters.
- A negative slope (b=-0.00482) confirmed that ARR decreased with cumulative AUC. Based on the median model parameter estimates, the median AUC of the Q4W and Q2W group, 38.0 and 73.1 ng/mL*hr, was associated with a 17% and 30% ARR reduction over the placebo group, assuming the same Gd+ lesion volume. Comparing the Gd+ lesions among the three treatment groups, the mean Gd+ lesion volume at 6-month was 0.215, 0.198 and 0.0519 cm³, which was associated with 5% and 0.5% ARR reduction for the Q4W and Q2W groups, respectively, compared with the placebo group.

- The relationship between peginterferon beta-1a AUC and ARR for observed data and model predicted data is illustrated in Figure 1. The alignment between the observed ARR and model predicted ARR indicated that the data was well described by the final model.
- The slope for ARR reduction in the plot was steep in the Q4W AUC range, especially at below median AUC. In contrast, the slope started to level off in the Q2W AUC range. Although the model did not show that Q2W dosing regimen had achieved a maximal reduction in ARR, it demonstrated that the observed better efficacy of Q2W dosing regimen as compared with the Q4W dosing regimen was driven by its greater peginterferon beta-1a exposure. Of note, the plot also indicated that there were large portion of subjects receiving sub-optimal treatment in the Q4W group.

Table 2. Summary of AUC-relapse model parameter estimates

		DIC	Para-meters	Mean	SD	Time-series SE	Median	2.50%	97.50%
Baseline Model	Poisson	799	Deviance	797	1.42	0.0184	797	796	802
			$\hat{\lambda}$	0.406	0.0305	0.000372	0.406	0.348	0.468
	Zero-inflated Poisson	1799	Deviance	677	47.4	1.93	676	590	774
			$\hat{\lambda}$	0.572	0.086	0.00301	0.567	0.419	0.753
			p	0.725	0.0967	0.00392	0.716	0.558	0.938
	Log-normal Poisson	789	Deviance	734	28.9	2.91	735	677	787
			$\hat{\lambda}$	0.343	0.0445	0.00373	0.342	0.259	0.433
			τ	4.16	4.38	0.817	2.86	1.26	13.3
			σ	0.585	0.167	0.0193	0.592	0.274	0.892
	Poisson-gamma	783	Deviance	734	34.9	4.33	735	664	791
			$\hat{\lambda}$	0.405	0.0331	0.00138	0.404	0.343	0.473
Final Model	Poisson-gamma Model	2145	Deviance	1880	50.1	0.915	1880	1780	1980
			λ_0	0.323	0.0285	0.00052	0.322	0.271	0.382
			α	0.815	0.118	0.00216	0.804	0.608	1.07
			b	-0.00477	0.00164	3.00E-05	-0.00482	-0.00799	-0.00159
			c	0.325	0.0879	0.00161	0.325	0.163	0.506

Figure 2. Relationship between cumulative AUC and ARR



CONCLUSIONS

- Peginterferon beta-1a pharmacokinetics were well described by a one-compartment model with linear kinetics. BMI was the most significant covariate that impacted both clearance and volume distribution.
- The relapse counts were described by a poisson-gamma distribution. The relationship between cumulative monthly AUC and ARR was described by a log-linear relationship. Six-month Gd+ volume was shown to be the most predictive covariate for 2-year ARR.
- The model supported Q2W based on the better efficacy associated with greater exposure and the large portion of subjects receiving sub-optimal treatment in the Q4W treatment group.

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Disclosures

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XH, YH, YC, SL, IN: employees of Biogen Inc.

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