P1868

Aducanumab Phase 3 Studies: Exposure-Response Analysis Evaluating the Relationship Between Amyloid Removal and Slowing of Clinical Decline on CDR-SB Scores

Kumar Kandadi Muralidharan, Kenneth G. Kowalski, Xiao Tong, Raj Rajagovindan, Samantha Budd Haeberlein, Ivan Nestorov, Eric Masson

Biogen, Cambridge, MA, USA

OBJECTIVE

- To examine whether aducanumab-induced lowering in Aβ-amyloid (Aβ) plaques in the brain, a hallmark of Alzheimer's disease pathophysiology, is associated with attenuation of disease progression as measured by CDR-SB

CONCLUSIONS

- Aducanumab-induced changes in biomarkers of Alzheimer's disease pathophysiology were correlated with changes in clinical measures.
- Exposure-response models detected an aducanumab treatment effect on the CDR-SB in both EMERGE and ENGAGE. The drug effect in both studies was significant, even when effect was estimated separately for each study.
- SUVR–CDR-SB model–based simulations pooled across EMERGE and ENGAGE suggest that aducanumab treatment as a titration to 10 mg/kg without any dose interruption over a period of 18 months is expected to result in 75% reduction in amyloid load and reduction in disease progression by −0.38 units (difference from placebo) on CDR-SB.

2022 International Conference on Alzheimer's and Parkinson's Diseases

Introduction

- Aducanumab is a human monoclonal antibody that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils.[1]
- Aducanumab was granted accelerated approval by the US Food and Drug Administration for the treatment of Alzheimer's disease. According to the US Prescribing Information, treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.[2]
- A robust dose-dependent reduction in brain Aβ plaque levels, as measured by amyloid positron emission tomography, was demonstrated across aducanumab clinical studies (PRIME, EMERGE, and ENGAGE).[1,2]
- An exposure-response model characterizing the relationship between aducanumab exposure and reduction in Aβ levels in the brain has been characterized previously.[3]
- Here, we describe an exposure-response model to characterize the changes in Aβ plaque levels and CDR-SB (primary endpoint) following treatment with aducanumab in the ENGAGE and EMERGE phase 3 studies.

Methods

- Because there are standard uptake value ratio (SUVR) observations for only about one-third of the sample set, the exposure–SUVR model (an indirect response model with induction of plaque elimination) was used to generate ad hoc model imputed typical individual predicted SUVR profiles for all individuals without SUVR observations, based on the individual covariates and the final covariate model.
- The CDR-SB is a bounded scale (0-18), so scaled CDR-SB scores (i.e., CDR-SB/18) were modeled on the logit scale to ensure that predictions of the model were constrained within the bounds of the original scale.
- CDR-SB was modeled sequentially using individual pharmacokinetic-pharmacodynamic parameters incorporated in the data set. SUVR change from baseline calculated as $(SUVR_{BL}-SUVR_{i,j})/(SUVR_{BL}-1)$ was evaluated as a predictor of the CDR-SB response
- Base models were developed, evaluating disease progression and drug effect components. An internal visual predictive check was used to assess predictive performance of the final model on data used in model development
- The analyses were performed using NONMEM® software, version 7.4.3. Postprocessing of model output, including graphical analyses, was performed using R software, version 3.6.0.

Results

- A linear model in the logit-transformed scaled CDR-SB best described the changes over time in the placebo group.
- To account for the considerable variation in disease progression rates, a mixture model was used that assigned subjects to 1 of 3 latent classes: (1) slow progressors (individuals with no progression over the 78-week period); (2) typical progressors; and (3) fast progressors.
- The disease progression model developed based on the placebo data was augmented to include the therapeutic activity of aducanumab as an additive effect and subsequently evaluated based on all randomized subjects from the placebo-controlled periods of EMERGE and ENGAGE.
- Relative to average concentration, the use of SUVR as an exposure marker results in numerically better goodness of fit corresponding to the SUVR–CDR-SB model.
- The model was able to detect a statistically significant drug effect, as indicated by the drug effect slope estimate of 0.136 L.(g.year)−1 with a 95% CI (0.0807 to 0.193) that does not include 0 (Table 1).
- The drug effect was successfully separated from the disease progression rates as evidenced by the consistency of the placebo rate estimates and the class proportions between the placebo and the treatment model.
- Following a series of hypotheses tests, the final model of the exposure-response relationship for CDR-SB did not include a differential effect either between the studies or across the 3 progression classes. The latter is evidence that aducanumab in the 2 studies shares a common pharmacology (Table 2).
- SUVR–CDR-SB model–based simulations pooled across EMERGE and ENGAGE suggest that aducanumab treatment as a titration to 10 mg/kg without any dose interruption over a period of 18 months (Figure 1) is expected to result in 75% reduction in amyloid load and reduction in disease progression by −0.38 units (difference from placebo) on CDR-SB.

Table 1: Parameter Estimates of the Base Population Exposure–CDR-SB Response Model

Parameter	Unit	Disease progression model		Exposure-response model	
		NONMEM estimate	Bootstrap estimate, median (95% CI)	NONMEM estimate	Bootstrap estimate, median (95% CI)
BSL (ApoE ε4 noncarrier)	No unit	2.17	2.17 (2.05 to 2.28)	–	–
BSL (ApoE ε4 carrier)	No unit	2.40	2.40 (2.33 to 2.47)	–	–
BSL	No unit	–	–	2.32	2.32 (2.28 to 2.35)
Slow progressor	y^{-1}	−0.768	−0.768 (−5.00 to −0.538)	−0.724	−0.724 (−0.958 to −0.473)
Typical progressor	y^{-1}	0.278	0.280 (0.233 to 0.328)	0.310	0.312 (0.277 to 0.350)
Fast progressor	y^{-1}	1.12	1.11 (0.972 to 1.39)	1.24	1.25 (1.12 to 1.43)
Prop slow progressors	%	3.20	3.24 (0.54 to 5.91)	3.78	3.86 (2.33 to 6.44)
Prop typical progressors	%	83.5	83.6 (33.1 to 92.8)	85.6	85.7(72.5 to 90.0)
Prop fast progressors	%	13.3	13.2 (1.28 to 66.3)	10.6	10.4 (3.57 to 25.2)
Drug effect	y^{-1}	–	–	0.136	0.136 (0.0807 to 0.193)
Baseline, % CV	No unit	39.6	39.5 (36.5 to 42.5)	41.5	41.5 (39.7 to 43.2)
Rate, % CV	y^{-2}	14.0	14.0 (8.54 to 21.2)	15.1	15.1 (11.8 to 18.9)
Correlation (BSL, rate)	No unit	1	1 (N/A)	1	1 (N/A)
Residual error	No unit	0.335	0.335 (0.322 to 0.347)	0.334	0.333 (0.325 to 0.341)

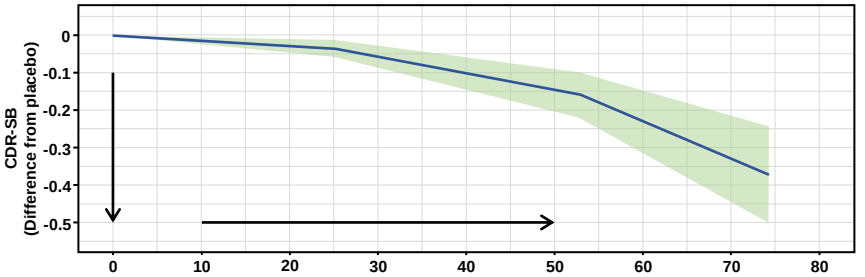
Reported estimates are transformed from logit to linear scale for baseline and proportion parameters; the rate parameters are converted from h^{-1} to y^{-1} by multiplying a factor of 8760; drug effect is converted from a scale of $L.mg^{-1}.h^{-1}$ to $L.g^{-1}.y^{-1}$ by multiplying a factor of 1000 * 8760. A total 4 runs from the placebo and 6 runs from the exposure-response model were skipped while calculating bootstrap summaries.

Table 2: Runs to Investigate the Influence of Study on Drug Effect Using SUVR With Drug Effect Invariant in Typical and Rapid Progressors With Censored Data

Model	Censored runs				
	Run‡	OFV	ΔOFV	BIC	Reference
Trimodal mixture model. Rate in all progression groups estimated. Shared η between IIV (between subject variability) on baseline and rate of progression. Additive drug effect. No study effects. Base model.	715	−50312.16	–	−50219.02	–
Trimodal mixture model. Rate in all progression groups estimated. Shared η between IIV on baseline and rate of progression. Additive drug effect. Drug effect similar in typical and rapid progressor. Drug effect different in slow progressor. No study effects. Reference model.	1105	−50314.21	−2.051	−50211.76	715c
Same structure and random effect as Run 1105. Study impact only on typical-rapid progressor drug effect grouping.	1115	−50319.22	−5.006	−50207.45	1105c
Same structure and random effect as Run 1105. Study impact only on slow progressor drug effect grouping.	1125	−50315.67	−1.462	−50203.91	1105c
Same structure and random effect as Run 1105. Study impact on drug effect in slow and typical-rapid progressor grouping.	1135	−50321.47	−7.261	−50200.40	1105c

ΔOFV denotes change in objective function value between the current run and the reference model. BIC (Bayesian information criteria) = OFV + log(n)*p where, n = 12431 (number of CDR-SB observations) and p = no of parameters (fixed + random effects).

Figure 1: Model-Predicted Treatment Effect Over 18 Months in Subjects Treated With a Titration to 10-mg/kg Aducanumab Regimen



Abbreviations ApoE ε4 = apolipoprotein E ε4 allele; Aβ = amyloid-β; BIC = Bayes information criteria; BSL = baseline; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CV = coefficient of variation; N/A = not applicable; NONMEM = Nonlinear Mixed Effects Modeling; OFV = objective function value; prop = proportion; SUVR = standardized uptake value ratio.

References 1. Sevigny J, et al. *Nature*. 2016;537:50-56; 2. Aduhelm (aducanumab) [prescribing information]. Cambridge, MA: Biogen, Inc; 2021; 3. Kandadi Muralidharan K, et al. *CPT Pharmacometrics Syst Pharmacol.* 2021. Online ahead of print.

Disclosures All authors are employees and shareholders of Biogen Inc; RR was an employee of Biogen at the time of this work and has since left the company.

Acknowledgments This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this presentation was provided by MediTech Media (Atlanta, GA, USA): funding was provided by Biogen.