Population PK/PD analysis for efgartigimod Phase 3 study in myasthenia gravis patients

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Introduction

- Efgartigimod (ARGX-113) is a human IgG1 antibody antibody fragment and a neonatal Fc receptor (FcRn) antagonist that has been developed for the treatment of patients with severe autoimmune diseases mediated by pathogenic immunoglobulin G (IgG) autoantibodies.
- FcRn has a specific role in IgG homeostasis by recycling IgG, rescuing it from lysosomal degradation.
  - IgG is taken up by cells and binds to FcRn at the relatively acidic conditions in the early endosome.
  - Bound IgG does not enter the lysosome, in contrast to other unbound immunoglobulins, and is therefore rescued from lysosomal degradation.
  - FcRn returns IgG to the cell surface where at more neutral conditions it is released back to the circulation.
- Efgartigimod has a high FcRn affinity at both physiologic and acidic pH and, consequently, outcompetes endogenous IgG binding, thereby preventing FcRn-mediated recycling and causing increased endogenous IgG degradation.
- In patients with generalized myasthenia gravis (gMG), by blocking FcRn recycling, efgartigimod lowered antibodies against the acetylcholine receptor (AChRAb).

Objectives

- To support the development of efgartigimod for gMG by modelling the efgartigimod pharmacokinetics (PK) as well as the effects of efgartigimod on total IgG and AChRAb change from baseline.
- To identify covariate effects for PK and total IgG.
- To assess the impact of covariate in the PK model on the area under the effect curve over 168 hours ($AUC_{0\text{-}168h}$) after the fourth dose.

Methods

Existing models for PK, total IgG, and AChRAb were available from the PK/PD efgartigimod analyses in healthy subjects (Phase 1) [1,2], and gMG patients (Phase 2) [3]. These models were used as a starting point for the PK/PD analyses performed for the Phase 3 study in the gMG patient population.

- The analysis was performed by means of non-linear mixed-effects modelling (NONMEM, version 7 level 4.3) [4]) in combination with PsN (version 4.7.0).
- Exploratory analyses and post-processing of NONMEM output were performed using R (version 3.4.4) [5] and Rstudio (version 1.1.463) [6] and in-house developed modelling interface.

Data

The existing models for PK, total IgG, and AChRAb were optimized using the data from the ADAPT Phase 3 study (ARGX-113-1704 [7]) in patients with gMG. ARGX-113-1704 was a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial designed to evaluate the efficacy, safety, and tolerability of efgartigimod in patients with gMG as well as the impact of efgartigimod treatment to affect patient quality of life and ability to perform normal daily activities. Patients were randomized in a 1:1 ratio to receive efgartigimod IV 10 mg/kg or placebo in treatment cycles of four infusions at weekly intervals. A schematic of the trial design is shown in Figure 1.

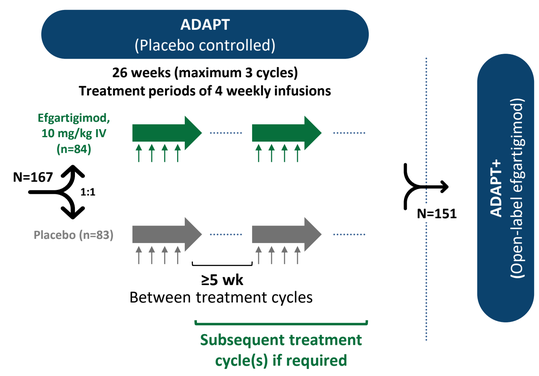

Figure 1 *Schematic representation of the design for the Phase 3 study ARGX-113-1704 [7]*

Model

- The PK model consisted of a three-compartmental model with linear clearance (CL) and the volume of the two peripheral compartments (V2 and V3) were assumed to be equal [3]. Based on the covariate analysis, weight and eGFR were found to be statistically significant covariates for CL. Further, weight was found to be a covariate for the volume of the central compartment (V1).
- To reflect the mechanism of action, the total IgG model consisted of an indirect response turnover model, in which efgartigimod stimulated the degradation rate of total IgG (k_{out}). An Emax model was implemented to capture the saturable effect of efgartigimod on k_{out} [3]. An effect of weight was found to be statistically significant on the potency (EC_{50}).
- Further, a PK/total IgG/AChRAb model was developed, in which the change from baseline of AChRAb is directly linked to the change from baseline of total IgG, under the assumption that AChRAb is part of the total IgG pool.
- The schematic of the PK/total IgG/AChRAb model is shown in Figure 2.
- Parameters were precisely estimated, as shown in Tables 1 (PK) and 2 (total IgG and AChRAb). For each endpoint, parameters were estimated sequentially.

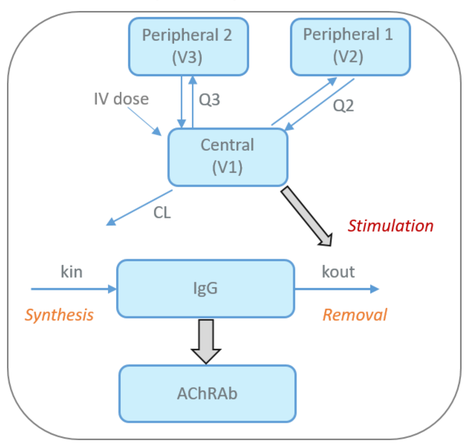

Figure 2 *Schematic of the PK/total IgG/AChRAb model*

Parameter	Estimate [RSE%]
CL (L/h)	0.108 [2.50%]
V1 (L)	3.31 [3.40%]
Q2 (L/h) FIXED	0.00511 [-]
V2 = V3 (L)	4.72 (6.90%)
Q3 (L/h)	0.242 [20.9%]
Weight on V1	0.590 [14.7%]
eGFR on CL	0.453 [18.4%]
Weight on CL	0.272 [17.2%]
ω^2 CL	0.0177 [17.1%] (CV%: 13.4)
ω CLxV1	0.0160 [37.2%] (CV%: 51.2)
ω^2 V1	0.0527 [28.7%] (CV%: 23.3)
σ^2 Add error (in log)	0.127 [17.8%] (SD: 0.356)

Table 1 *Parameter estimates final PK model*

Parameter	Estimate [RSE%]
BL-tIgG (ug/mL)	7744 [2.14%]
k_{out}-tIgG (1/h)	0.00198 [3.74%]
Emax-tIgG (-) FIXED	4.87 [-]
EC_{50}-tIgG (ng/mL)	41407 (6.82%)
Weight on EC_{50}	0.741 [24.1%]
BL-AChRAb (nmol/L)	17.7 [12.4%]
α-AChRAb (-)	1.02 [2.52%]
ω^2 BL-tIgG	0.0735 [11.7%] (CV%: 27.6)
ω^2 EC_{50}-tIgG	0.192 [23.9%] (CV%: 46.0)
ω^2 BL-AChRAb	3.32 [10.5%] (CV%: 516)
σ^2 Prop error tIgG	0.0214 [5.79%] (SD: 0.146)
σ^2 Prop error AChRAb	0.0220 [11.5%] (SD: 0.148)

Table 2 *Parameter estimates final total IgG and AChRAb models*

Results

The final PK model adequately described efgartigimod concentration, as shown in the prediction-corrected Visual Predictive Checks (VPCs) in Figure 3.

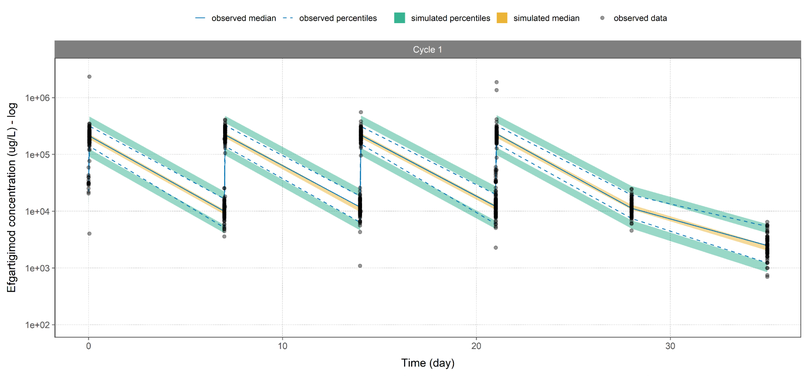

Figure 3 *Prediction-corrected VPCs: PK of efgartigimod in Cycle 1 for all patients in ADAPT. Cycles 2 and 3 were captured equally well (not shown).*

- The impact of body weight and eGFR effect on $AUC_{0\text{-}168h}$ after the fourth infusion in the gMG population was assessed by simulations of extreme values (Figure 6).

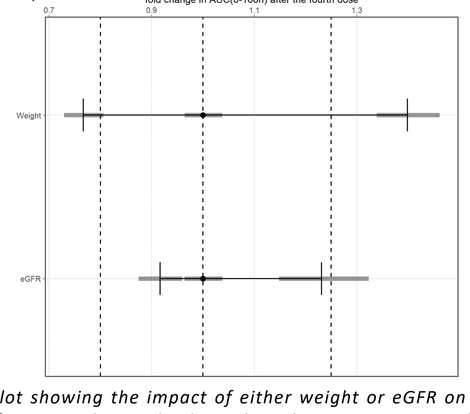

Figure 6 *Forest plot showing the impact of either weight or eGFR on AUC_{0-168h} after the fourth weekly infusion. Body weight dependent dosing was assumed in the simulation. For body weight, from left to right: 5th (53 kg) and 95th (129.8 kg) percentiles from ADAPT study. For eGFR, from left to right: 95th (122.4 mL/min/1.73m²) and 5th (62.2 mL/min/1.73m²) percentiles from ADAPT study. Grey areas: 90% CI based on uncertainty.*

The final total IgG and AChRAb models adequately described the change from baseline of total IgG and AChRAb concentrations, as shown in the VPCs in Figures 4 and 5, respectively.

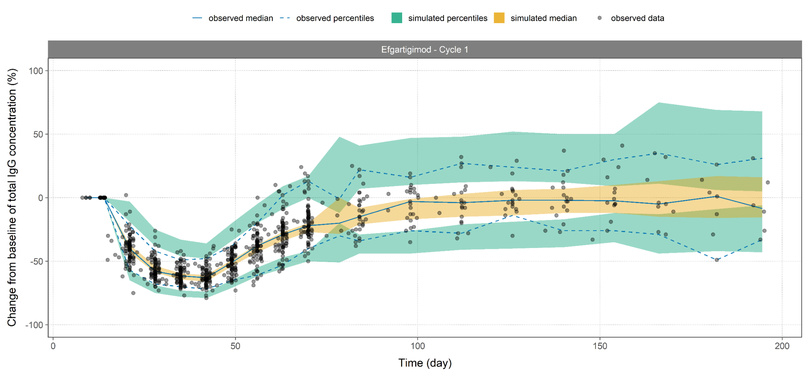

Figure 4 *VPCs: change from baseline of total IgG concentration in all patients from ADAPT study in Cycle 1. Cycles 2 and 3 were captured equally well (not shown).*

- The results suggested that the increase in exposure with increase in body weight is mainly driven by the increase in the absolute dose administered and to a lesser extent by the weight effect on CL (Table 3).
- Compared to a reference subject (eGFR = 100.27 mL/min/1.73m²), eGFR values of 62.2 mL/min/1.73m² (5th percentile) and 122.4 mL/min/1.73m² (95th percentile) are associated, respectively, with +23% (90%CI: +15%, +32%) and -8% (90%CI: -13%, -4%).

	Body weight	Relative $AUC_{0\text{-}168h}$ difference compared to a reference subject of median body weight and eGFR (76.05 kg and 100.27 mL/min/1.73m²)
Body-weight based dosing	53 kg (5th percentile)	-23% (90%CI: -27%, -19%)
	129.8 kg (95th percentile)	+48% (90%CI: +41%, +55%)
Fixed absolute dose (760.5 mg)	53 kg (5th percentile)	+10% (90%CI: +5%, +16%)
	129.8 kg (95th percentile)	-13% (90%CI: -17%, -9%)

Table 3 *Body weight effect on AUC_{0-168h} after the fourth weekly infusion. Body weight based and fixed absolute dosing. Percentiles were based on the ADAPT study.*

The change from baseline of AChRAb was found to be proportional to the total IgG change from baseline, as indicated by the estimate of the power coefficient (α-AChRAb in Table 2). This confirmed the assumption of AChRAb was part of the total IgG pool.

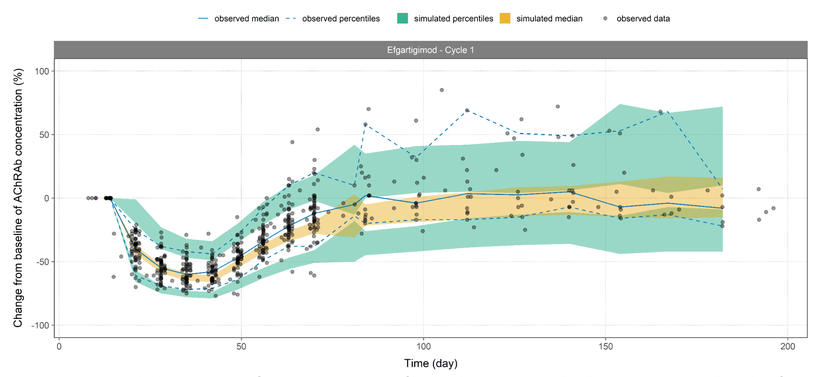

Figure 5 *VPCs: change from baseline of AChRAb concentration in all patients from ADAPT study in Cycle 1. Cycles 2 and 3 were captured equally well (not shown).*

- The median and 90% CI of the $AUC_{0\text{-}168h}$ ratio for mild renal impairment patients, as compared to patients with normal renal function, were estimated to be 1.28 (1.19, 1.37) (red bar in Figure 7).
- The simulated range of the $AUC_{0\text{-}168h}$ ratio based on 10000 replicates of the original dataset (black bar in Figure 7, 1.22 (1.14, 1.30), 1.13 (1.06, 1.21), and 1.30 (1.22, 1.40)) was in agreement with the observed $AUC_{0\text{-}168h}$ ratio.

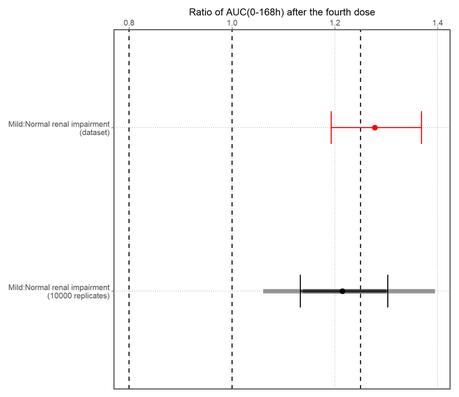

Figure 7 *Forest plot to investigate potential differences in AUC_{0-168h} after the fourth weekly infusion between mild renal impairment (eGFR ≥60 mL/min/1.73m² but < 90 mL/min/1.73m²) and patients with normal renal function (eGFR ≥ 90 mL/min/1.73m²). Body weight dependent dosing was assumed in the simulation. Grey areas: 5th and 95th percentiles of the 10000 ratios and their 90% CI based on uncertainty and IIV.*

Conclusion

- PK of efgartigimod was successfully linked to change from baseline in total IgG and AChRAb. Covariates were identified for both PK and total IgG change from baseline and allowed for simulations on the impact of these covariates in gMG patients, to support the development of efgartigimod.
- An apparent increase in EC_{50} with increasing body weight was found. Despite a higher clearance and lower potency in patients with higher body weight, similar levels of total IgG suppression are achieved: in the model, the lower potency could compensate for a higher exposure.
- The final model linking PK, total IgG, and AChRAb served as a good basis for evaluation of the effects of efgartigimod on clinical responses in patients with gMG.

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