Population analysis of MG-ADL total score of efgartigimod IV Phase 3 study in myasthenia gravis patients: application of a bounded-integer model

Marostica E [1], Ahsman M [1*], Van Bragt T [2], Noukens J [2], Vis P [1], T'joen C [3], Ulrichts P [3], Guglietta A [4], Rossenu S [3], van Steeg T [1]

[1]LAP&P Consultants BV, Leiden, The Netherlands, [2]Curare Consulting BV, The Netherlands, [3]argenx BV, Belgium, [4]Former argenx BV, Belgium, *current affiliation: Merck Sharp & Dohme LLC, Rahway, NJ, USA

Contact: info@lapp.nl

Introduction

- Efgartigimod (ARGX-113), a human IgG1 antibody fragment and a neonatal Fc receptor (FcRn) antagonist, has been developed for the treatment of severe autoimmune diseases mediated by pathogenic immunoglobulin G (IgG) autoantibodies.
- Efgartigimod has a high affinity for FcRn and, consequently, outcompetes endogenous IgG binding, thereby preventing FcRn-mediated recycling and causing increased endogenous IgG degradation.
- In patients with generalized myasthenia gravis (gMG), efgartigimod lowered pathogenic antibodies directed against the acetylcholine receptor (AChRAb).
- Myasthenia Gravis Activities of Daily Living (MG-ADL) total score is a standardized 8-item patient-reported scale, used to assess MG symptoms and effects on daily activities.
- MG-ADL score data can be treated as either continuous or ordered categorical.
- Continuous modelling approach: residual error can produce predictions outside the expected range; data transformations allow the model to predict extreme values exclusively along the asymptote.
- Ordered categorical modelling approach: it requires many parameters and cannot predict outside the range of observations.
  - Bounded integer model [1]: it respects the integer nature of the data and it is parsimonious

Objectives

- To develop a model for MG-ADL score that enables the prediction of responder rates after placebo or efgartigimod treatment in the ADAPT Phase 3 study ARGX-113-1704 [2].

Methods

Previously developed PK/PD models [3] were linked to the MG-ADL score:

- Non-linear mixed-effects modelling (NONMEM, version 7 level 5.0) [4]) was used for the analysis.
- A continuous model and the bounded integer (BI) model [1] were developed using first-order conditional estimation method with interaction (FOCE-I) and Laplacian method, respectively.
- Post-processing of output was performed using R (version 3.4.4) [5] and Rstudio (version 1.1.463) [6] and in-house developed modelling interface.
- Developed MG-ADL score models were validated by simulating 1000 individual profiles, based on which the median and 5th and 95th percentiles of the responder rate in treatment Cycle 1 were derived (Table 3).
- Responder definition: patient who showed a reduction of MG-ADL score of at least 2 points (compared to cycle baseline) at response onset and for the next four consecutive visits after the onset, with the first of these decreases occurring at the latest one week after the last infusion.

Data

The ADAPT Phase 3 study (ARGX-113-1704 [2]) was a randomized, double-blind, placebo-controlled, multicenter 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.

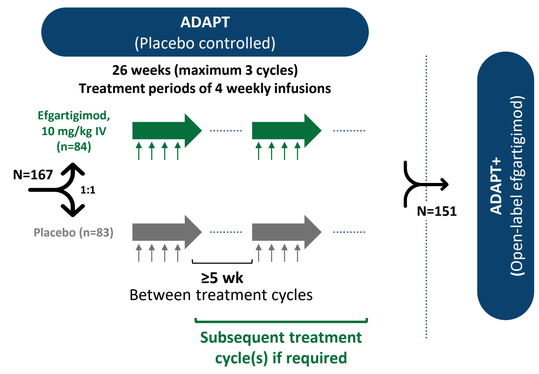

Figure 1 *Schematic representation of the design for the ADAPT Phase 3 study [2]*

MG-ADL total score data were assumed to be categorical in nature and the possible categories are many, as the scale ranges from 0 to 24 [7,8]

Model

- Efgartigimod PK was described through a three-compartmental model with linear clearance [3].
- 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 used to capture the saturable effect of efgartigimod on total IgG, which was directly linked to the reduction of AChRAb [3].
- ***Continuous approach***: the total IgG/AChRAb model was extended to include an effect compartment linking the AChRAb reduction to the changes in MG-ADL score. Further, a placebo model with a time-varying exponential function was incorporated to describe the reduction in the MG-ADL score over time due to placebo.

$$MGADL = BL_{MG-ADL} \cdot effect_{drug} + effect_{placebo} \qquad effect_{drug} = \left({AChRAb_{delay}(t)}/{BL_{AChRAb}}\right)^{\alpha_{MG-ADL}} \qquad effect_{placebo} = -P_{max} \cdot \left(1 - exp^{\left(\frac{\log(2)}{T_{plac}} \cdot t\right)}\right)$$

- ***Categorical approach***: a BI model was used [1], in which the baseline reflects the probability of MG-ADL score being in a specific category. As compared to the continuous approach, the reduction in AChRAb was directly linked to MG-ADL score. A Markovian component (PM) to account for serial correlation between observations was also estimated.

$$MGADL = BL_{MG-ADL} - effect_{drug} + effect_{placebo} \qquad effect_{drug} = \left({AChRAb\,(t)}/{BL_{AChRAb}}\right)^{\alpha_{MG-ADL}} - 1$$

- To apply the BI model, a sequential approach was needed, as the population PK/total IgG/AChRAb model was optimized using FOCE-I, whereas for the BI model, the Laplacian estimation method was required. Therefore, the PK/total IgG/AChRAb model was used to simulate individual AChRAb concentrations at the time points of MG-ADL score observations.
- Overall, MG-ADL score parameters were precisely estimated, as shown in Table 1 for the continuous model and in Table 2 for the BI model. In the continuous model (Table 1), IIV on the drug effect parameters was not precisely estimated (RSE% > 50%), but it was needed to describe the individual profiles.

- The schematic of the total IgG/AChRAb/MG-ADL score model is shown in Figure 2.

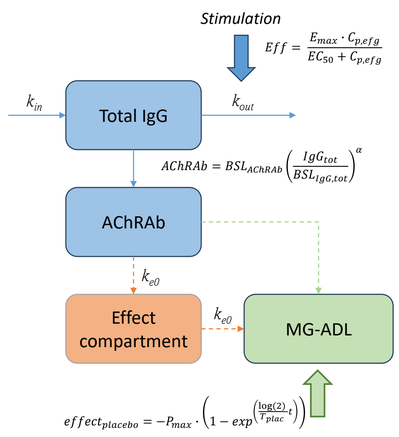

Figure 2 *Schematic of the total IgG/AChRAb/MG-ADL score model. Blue: elements of the underlying PD model; orange: effect compartment used in the continuous approach; green: MG-ADL model (including placebo effect) which is directly linked to AChRAb reduction in the BI model and indirectly linked (through the effect compartment) in the continuous approach.*

Parameter	Estimate [RSE%]
BL_{MG-ADL}	8.93 [1.84%]
α_{MG-ADL}	0.260 [31.8%]
k_{e0}	0.0181 [11.8%]
P_{max} [a]	2.08 [7.02%]
T_{plac} (h) [b]	152 [8.49%]
ω^2 BL_{MG-ADL}	0.0953[16.4%] (CV%: 31.6)
ω^2 α_{MG-ADL}	1.70 [93.5%] (CV%: 212)
σ^2 add error	3.48 [12.6%]

Table 1 *Parameter estimates **continuous** model.*
[a] P_{max} is the maximal placebo effect;
[b] T_{plac} is the time needed to reach half P_{max}

Parameter	Estimate [RSE%]
BL_{MG-ADL} [a]	-0.249 [9.28%]
α_{MG-ADL} [b]	-0.313 [11.1%]
P_{max} [c]	0.309 [1.77%]
T_{plac} (h) [d]	138 [10.8%]
PM	0.366 [7.41%]
SD	0.247 [5.20%]
ω^2 BL_{MG-ADL}	0.114 [13.3%] (CV%: 34.7)
ω^2 α_{MG-ADL}	0.117 [1.71%] (CV%: 35.3)

Table 2 *Parameter estimates final **BI** model.*
[a] baseline estimate for MG-ADL on cumulative probabilities (i.e. -0.249 corresponds to a baseline MG-ADL score of 9;
[b] α_{MG-ADL} is the drug effect parameter;
[c] P_{max} is the maximal placebo effect;
[d] T_{plac} is the time needed to reach half P_{max})

Results

- PK, total IgG, and AChRAb models adequately described observations from the ADAPT study and parameters were precisely estimated [3].
- Both the continuous and categorical models adequately described MG-ADL score data and their IIV across treatment cycles in the ADAPT study. Visual predictive checks (VPCs) for Cycle 1 only are shown in Figures 3 and 4, for the continuous and BI models, respectively.

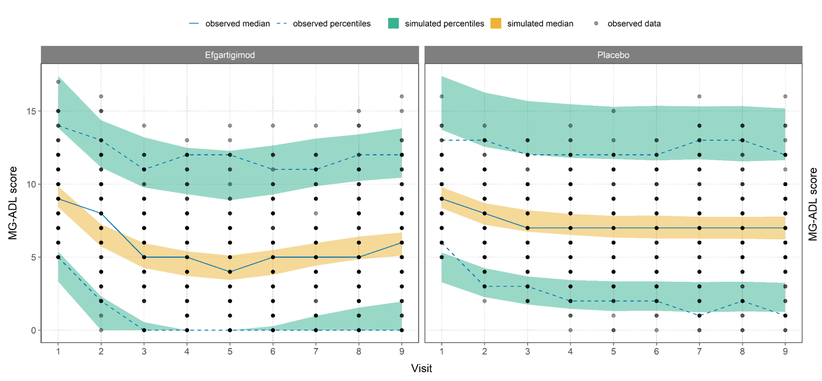

Figure 3 *VPCs obtained with the **continuous** model: MG-ADL score in all patients from ADAPT study in Cycle 1. Cycles 2 and 3 were captured equally well (not shown).*

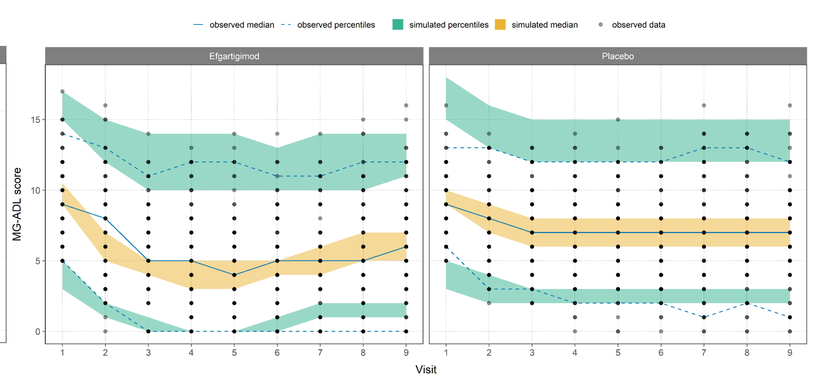

Figure 4 *VPCs obtained with the **BI** model: MG-ADL score in all patients from ADAPT study in Cycle 1. Cycles 2 and 3 were captured equally well (not shown).*

- The continuous model consistently underpredicted median responder rates in the ADAPT study [9] for both placebo and efgartigimod.
- In addition, the 95% PI did not overlap with the observed responder rate per treatment group, indicating that the prediction significantly differed from the observed responder rate (Table 3).
- The BI model predicted responder rates in line with the observed ones for placebo and efgartigimod (Table 3).

Table 3 *Observed and predicted responder rates for placebo and efgartigimod in the ADAPT Phase 3 study.*

Treatment	Median responder rate (%)		
	Observed	Continuous Predicted (95% PI)	BI Predicted (95% PI)
Placebo	37.3	21.7 (13.3 – 31.4)	38.6 (27.7 – 48.2)
Efgartigimod	67.9	54.8 (44.0 – 65.5)	65.5 (54.8 – 76.2)

- The BI model has the advantage that it is able to describe (and predict) data equal to zero. As such, it is superior in performance especially in predicting responder rates. Further, the Markovian component, providing a higher probability that an observation has the same value as the previous one in time [1], led to a better description of the data, as well as a match between predicted and observed responder rates (Table 3).

- One of the limitations of the current model was that inter-treatment cycle data could not be included in the analysis (only data from Visits ≤ 9, i.e. 5 weeks after the last infusion, in each treatment cycle were analyzed). A new treatment cycle was initiated by a physician based on specific guidelines. The initiation of re-treatment was dependent on both MG-ADL score and assessment of the physician. Consequently, the re-treatment is not predictable based on MG-ADL score alone.

Conclusion

- The BI model was able to adequately describe the MG-ADL score data and predict the responder rates in patients with gMG receiving either placebo or efgartigimod.
- The developed BI model was suitable to perform clinical trial simulations to support further development of efgartigimod in patients with gMG.
- In addition, the model included the link between autoantibody reduction and clinical improvement.

[1] Wellhagen GJ, Kjellsson MC and Karlsson MO, A bounded integer model for rating and composite scale data, AAPS Journal, 21 (4) (2019). https://doi.org/10.1208/s12248-019-0343-9.
[2] argenx BV. Clinical Study Report ARGX-113-1704: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness (ADAPT), 18 August 2020.
[3] Marostica E, et al., Population PK/PD analysis for efgartigimod Phase 3 study in myasthenia gravis patients, 31st PAGE Meeting (2023).
[4] Beal S, Sheiner LB, Boeckmann A and Bauer RJ, NONMEM User's Guides. Icon Development Solutions, Ellicott City, MD, USA (1989-2009).
[5] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria (2013) URL https://www.R-project.org.
[6] RStudio Team. RStudio: Integrated Development Environment for R. RStudio, Inc.,Boston, MA (2017) URL http://www.RStudio.com/.
[7] Muppidi S, The myasthenia gravis-specific activities of daily living profile, Annals of the New York Academy of Sciences, 1274 (1), 114-119 (2012). https://doi.org/10.1111/j.1749-6632.2012.06817.x.
[8] Wolfe GI, et al., Myasthenia gravis activities of daily living profile, Neurology, 52(7) (1999). https://doi.org/10.1212/WNL.52.7.1487.
[9] Bril V, et al., Effect of efgartigimod on muscle group subdomains in participants with generalized myasthenia gravis: post hoc analyses of the phase 3 pivotal ADAPT study, European Journal of Neurology (2023). https://doi.org/10.1111/ene.16098.