270

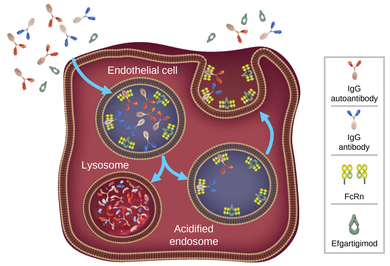
Dose Selection and Clinical Development of Efgartigimod PH20 SC in Participants With gMG

Tuan Vu,[1] James F. Howard Jr,[2] Yuebing Li,[3] Denis Korobko,[4] Marek Smilowski,[5] Li Liu,[6] Sophie Steeland,[6] Jana Podhorna,[6] Jan Noukens,[7] Tonke Van Bragt,[7] Kimiaki Utsugisawa,[8] Jan L. De Bleecker,[9] Renato Mantegazza,[10] and the ADAPT-SC Study Group

[1]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, Florida; [2]Department of Neurology, The University of North Carolina, Chapel Hill, North Carolina; [3]Cleveland Clinic, Cleveland, Ohio; [4]State Budgetary Healthcare Institution of Novosibirsk Region "State Novosibirsk Regional Clinical Hospital," Novosibirsk, Russia; [5]Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland; [6]argenx, Ghent, Belgium; [7]Curare Consulting BV, The Netherlands; [8]Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan; [9]Ghent University Hospital, Ghent, Belgium; [10]Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

INTRODUCTION

Efgartigimod Mechanism of Action: Blocking FcRn

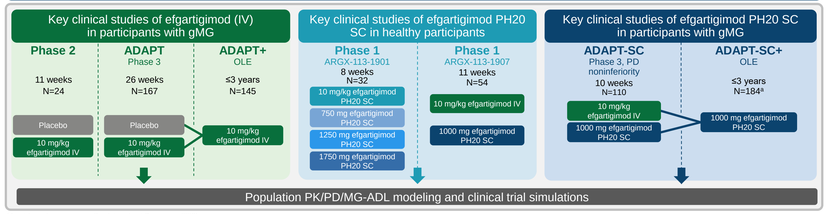


- FcRn recycles IgG to extend its half-life and maintain its high serum concentration[1]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered to have increased affinity for FcRn and outcompete endogenous IgG[2,3]
- Efgartigimod binding to FcRn prevents IgG recycling and promotes its lysosomal degradation, thus reducing IgG levels without directly impacting IgG production[2-5]
  - Targeted reduction of all IgG subtypes[2,4]
  - No impact on IgM, IgA, IgE, or IgD[2,5]
  - No reduction in albumin or increase in cholesterol levels[4-6]
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid SC administration of larger volumes[7,8]
- PK/PD modeling and phase 3 data (ADAPT-SC) suggest 4 once-weekly administrations of 1000 mg efgartigimod PH20 SC and 10 mg/kg efgartigimod IV result in comparable decreases in IgG levels[7]

METHODS

- Modeling and simulations using PK and PD data from healthy participants informed dose selection of efgartigimod PH20 SC **(Figure 1)**
- A bridging approach was applied to show that 4 once-weekly administrations of 1000 mg efgartigimod PH20 SC were noninferior to 4 once-weekly administrations of 10 mg/kg efgartigimod IV with respect to the percentage change from baseline in total IgG level at Day 29

Figure 1. Efgartigimod PH20 SC Bridging Strategy



[a]As of the interim analysis 2 cutoff date of December 2022.

SUMMARY

- **Studies of efgartigimod IV in patients with gMG established a clear association between reduction in total IgG level and improved clinical outcomes, suggesting that a bridging approach based on reduction in total IgG level/PD between efgartigimod IV and efgartigimod PH20 SC was feasible**
- **Data from healthy participants showed that 1000 mg efgartigimod PH20 SC had similar PD effects as 10 mg/kg efgartigimod IV**
- **1000 mg dose of efgartigimod PH20 SC is appropriate, as no clinically relevant effect of body weight on exposure was observed in a PK/PD analysis**
- **ADAPT-SC confirmed the PD noninferiority of 4 once-weekly administrations of 1000 mg efgartigimod PH20 SC to 10 mg/kg efgartigimod IV in participants with gMG**
- **Clinical improvements in ADAPT-SC, as determined by MG-ADL score, were consistent between the SC and IV treatment arms**

RESULTS

Studies with efgartigimod IV in participants with gMG established association between PD and clinical outcomes

- 10 mg/kg efgartigimod IV administered in cycles of once-weekly infusions for 4 weeks was demonstrated to be well tolerated and efficacious in patients with gMG in the ADAPT phase 3 study
- Strong associations between reductions in both total IgG and AChR-Ab levels and improvement in the MG-ADL total scores were observed in the placebo-controlled ADAPT (*P*<.0001; **Figure 2)** and phase 2 studies (data not shown)
- Maximum improvement in MG-ADL score, and nadir values of total IgG and AChR-Ab levels, occurred at Week 4 of each cycle (1 week after last infusion)
- These results suggest reduction in total IgG level can be considered an appropriate PD marker for efficacy

Data from healthy participants showed that 1000 mg efgartigimod PH20 SC had similar PD effects as 10 mg/kg efgartigimod IV

Phase 1 in Healthy Participants (ARGX-113-1901)

- **Design:** Healthy participants received a single SC dose of 750 mg, 1250 mg, 1750 mg, or 10 mg/kg efgartigimod coformulated with rHuPH20
- **Results:** Following a single administration of efgartigimod PH20 SC, the maximal % reduction from baseline in total IgG level was between 38.5% and 55.3% and occurred around Day 14 **(Figure 3)**
- **Safety:** AEs were mild to moderate in severity; most frequently reported TEAEs[a] included injection site reactions,[b] diarrhea, nasopharyngitis, and back pain
- **Conclusions:** Modeling based on these data suggested 1000 mg efgartigimod PH20 SC would have similar PD effects as 10 mg/kg efgartigimod IV, and the 1000-mg dose was subsequently evaluated in ARGX-113-1907

[a]Occuring in ≥20% of participants in either treatment group. [b]Including injection site erythema, bruising, and pain.

Phase 1 in Healthy Participants (ARGX-113-1907)

- **Design:** Healthy participants received 4 once-weekly administrations of 1000 mg efgartigimod PH20 SC or 10 mg/kg efgartigimod IV
- **Results:** When given in 4 once-weekly administrations, 1000 mg efgartigimod PH20 SC was noninferior to 10 mg/kg efgartigimod IV in total IgG level reduction at Day 29, with maximal reductions in total IgG levels between 65.7% and 67.5% **(Figure 4)**
- **Safety:** AEs were mild to moderate in severity; most common TEAEs[a] were injection site erythema, headache, injection site hematoma, catheter site hematoma, paresthesia, and diarrhea
- **Conclusions:** These data confirmed the selection of 1000 mg efgartigimod PH20 SC dose

[a]Occuring in ≥10% of participants in either treatment group.

Population PK/PD Modeling of Simulated Exposure ($AUC_{0\text{-}168h}$) With Various Covariates

- After 4 once-weekly administrations, exposure (as measured by AUC) of 10 mg/kg efgartigimod IV and 1000 mg efgartigimod PH20 SC was comparable. Ratios and 90% CI of the simulated exposure ($AUC_{0\text{-}168h}$) fell within the bioequivalence criteria of 0.8 to 1.25
- 1000-mg dose of efgartigimod PH20 SC is appropriate, as no clinically relevant effect of body weight on exposure was observed in a PK/PD analysis

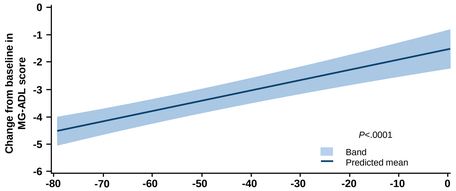
ADAPT-SC confirmed the PD noninferiority of 1000 mg efgartigimod PH20 SC to 10 mg/kg efgartigimod IV in participants with gMG

- After 1 treatment cycle (4 once-weekly administrations), reduction in total IgG level at Day 29 in participants who received 1000 mg efgartigimod PH20 SC was noninferior[a] to participants who received 10 mg/kg efgartigimod IV in the overall population **(Figure 5)**
- Total IgG and AChR-Ab percent change from baseline as well as change from baseline in MG-ADL total scores was similar between the 2 treatment arms in the AChR-Ab+ population **(Figure 6)**
- AEs were mild to moderate in severity; most frequently reported[a] TEAEs included injection site rash, headache, and injection site erythema

[a]Noninferiority margin of 10% based on % change from baseline in total IgG levels.

[a]Occuring in ≥10% of participants in the efgartigimod PH20 SC treatment group. The percentage of patients experiencing any injection site reaction decreased with each injection from 21.8% with injection 1 to 10.2% with injection 4. ISRs were mild to moderate in severity and did not lead to treatment discontinuation. Most were transient and resolved without treatment.

Figure 2. Statistical Modeling of the Association Between MG-ADL Score and Total IgG Levels in Participants With gMG Treated With Efgartigimod IV During ADAPT[a]



[a]mITT analysis set (n=84). To minimize potential modeling bias, only Week 1 to Week 6 data from all cycles in ADAPT were included.

Figure 3. Mean Percentage Change From Baseline in Total IgG Levels in Healthy Participants

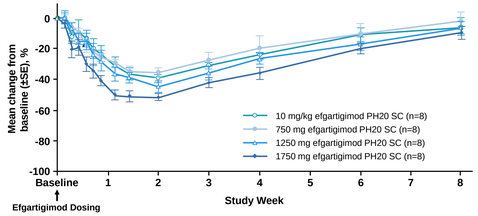


Figure 4. Mean Percentage Change From Baseline in Total IgG Levels in Healthy Participants

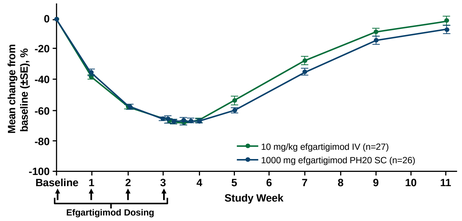


Figure 5. Percentage Change From Baseline in Total IgG Levels at Day 29 in ADAPT-SC
Overall Population

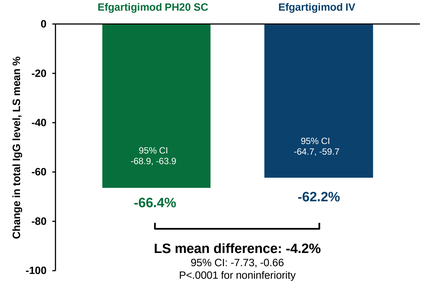
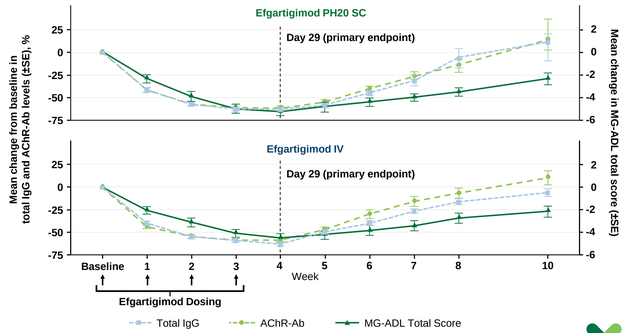


Figure 6. Mean Percentage Change From Baseline in Total IgG Levels, AChR-Ab Levels, and Mean Change in MG-ADL Total Score in ADAPT-SC
AChR-Ab+ Population



ABBREVIATIONS
AChR-Ab, acetylcholine receptor antibody; AE, adverse event; $AUC_{0\text{-}168h}$, area under the concentration-time curve from time 0 up to 168 hours; Fc, fragment crystallizable region; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; Ig, immunoglobulin; ISR, injection site reaction; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intention-to-treat; OLE, open-label extension; PD, pharmacodynamic; PK pharmacokinetic; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; TEAE, treatment-emergent adverse event.

REFERENCES
1. Ulrichts P, et al. *J Clin Invest*. 2018;128(10):4372-4386. **2.** Vaccaro C, et al. *Nat Biotechnol*. 2005;23(10):1283-1288. **3.** Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526-536. **4.** Nixon AE, et al. *Front Immunol*. 2015;6:176. **5.** Ward ES, et al. *Front Immunol*. 2022;13:892534. **6.** Study ARGX-113-2001 (ADAPT-SC) Clinical Trial Protocol v2.0, 02 Jul 2021. **7.** Locke KW, et al. *Drug Deliv*. 2019;26(1):98-106.

ACKNOWLEDGMENTS AND DISCLOSURES: The authors gratefully acknowledge the ADAPT trial participants and investigators.
TV: argenx, CSL Behring, Allergan/AbbVie, Alexion/AstraZeneca, UCB, Horizon/Viela Bio, Regeneron, Janssen/Momenta, Cartesians, and Sanofi. **JFH:** Alexion, AstraZeneca Rare Disease, argenx, Biologix, AcademicCME, Cartesian, Centers for Disease Control and Prevention, F. Hoffmann-LaRoche, Horizon Therapeutics, Merck EMB Serono, MGFA, Medscape CME, Muscular Dystrophy Association, NIH, NMD, Novartis, PCORI, PeerView CME, PlatformQ CME, Ra/UCB, Regeneron, Sanofi US, Takeda, Tolerranzia AB, and Zai Labs. **YL:** argenx, UCB, Alexion, Catalyst, and Immunovant. **DK:** Roche, Novartis Russia, Sanofi, Merck, Janssen (Johnson & Johnson), UCB, argenx, Horizon, Bristol-Myers Squib, and BIOCAD. **MS** has no disclosures to report. **LL, SS,** and **JP** are employees of argenx. **JN** and **TVB:** Curare Consulting and argenx. **KU:** argenx, UCB, Janssen, Viela Bio, Chugai Pharma, Mitsubishi Tanabe, Alexion, and the Japan Blood Products Organization. **JLDB:** argenx, Alexion, CSL, UCB, Alnylam, and Sanofi Genzyme. **RM:** Alexion, argenx, Ra, BioMarin, Catalyst, UCB, Teva, Merck, Roche, and Biogen.
The ARGX-113-1901, ARGX-113-1907, ADAPT/ADAPT+, and ADAPT-SC/ADAPT-SC+ studies were funded by argenx. Medical writing and editorial support was provided by PRECISION Value & Health and funded by argenx.

Presented at the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Annual Meeting; November 1-4, 2023; Phoenix, Arizona