Poster #017

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

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in collaboration with the ADAPT-SC Study Group

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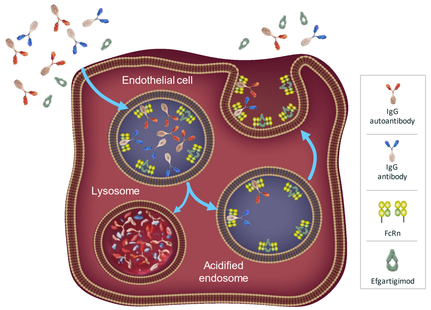
INTRODUCTION

Efgartigimod Mechanism of Action: Blocking FcRn

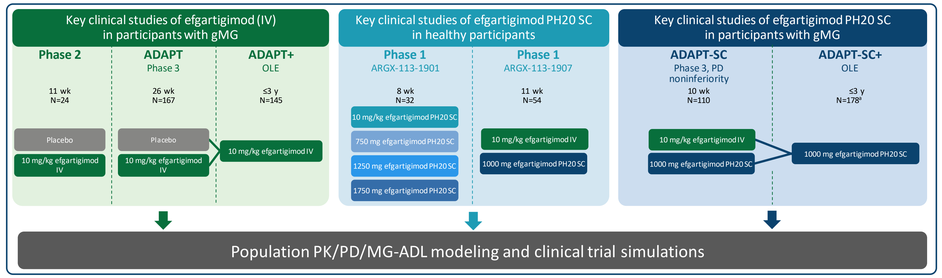


- Efgartigimod is a human IgG1 Fc fragment engineered for increased affinity to FcRn, which prevents recycling of IgG without impacting its production[1-5]
  - Targeted reduction of all IgG subclasses
  - No impact on IgM, IgA, IgE, and IgD
  - No reduction in albumin levels
  - No increase in cholesterol
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid SC administration of larger volumes[6,7]

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 demonstrate that 4 weekly administrations of 1000 mg efgartigimod PH20 SC were noninferior to 4 weekly administrations of 10 mg/kg efgartigimod IV with respect to the percentage change from baseline in total IgG at Day 29

Figure 1. Representation of Efgartigimod PH20 SC Bridging Strategy



[a]As of the interim analysis 1 cutoff date of March 2022.

SUMMARY

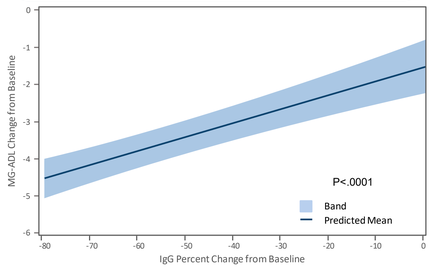
- **Studies of efgartigimod IV in patients with gMG established a clear association between reduction in total IgG and improved clinical outcomes, suggesting that a bridging approach based on total IgG reduction/PD between efgartigimod IV and efgartigimod PH20 SC was feasible**
- **Data from healthy participants demonstrated 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 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, 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*<0.0001; Figure 2)** and phase 2 studies (data not shown)
- Maximum improvement in MG-ADL, 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 total IgG reduction can be considered an appropriate PD marker for efficacy

Figure 2. Statistical Modeling on the Association Between MG-ADL and Total IgG 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.

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

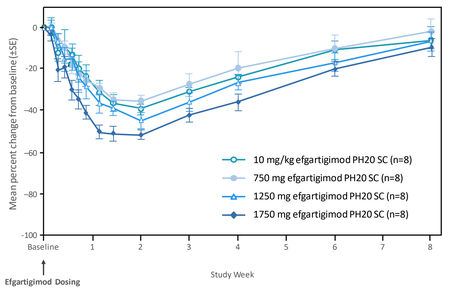
Phase 1 in Healthy Participants (ARGX-113-1901)

- **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 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

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

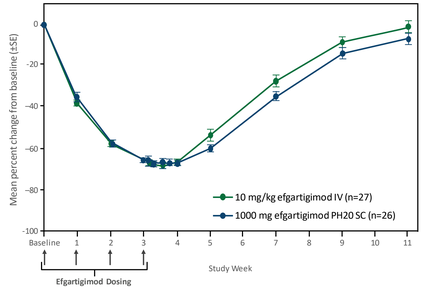
- **Design:** Healthy participants received 4 weekly administrations of 1000 mg efgartigimod PH20 SC or 10 mg/kg efgartigimod IV
- **Results:** When given in 4 weekly administrations, 1000 mg efgartigimod PH20 SC was noninferior to 10 mg/kg efgartigimod IV in total IgG level reduction at Day 29, with maximal total IgG reductions of between 65.7%-67.5% **(Figure 4)**
- **Safety:** Most 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

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



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

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



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

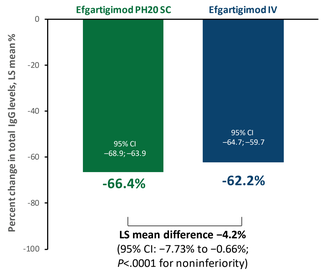
Population PK/PD Modeling of Simulated Exposure ($AUC_{0\text{-}168h}$) With Various Covariates

- After 4 weekly administrations, exposure (as measured by AUC) of 10 mg/kg efgartigimod IV and 1000 mg efgartigimod PH20 SC were comparable. Ratios and 90% CI of the simulated exposure ($AUC_{0\text{-}168h}$) fell within the bioequivalence criteria of 0.8-1.25
- 1000 mg dose of EFG 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

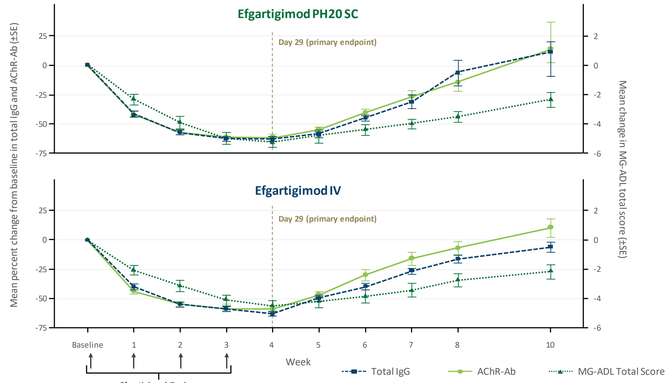
- After 1 treatment cycle (4 weekly administrations), total IgG reduction at Day 29 in participants who received 1000 mg efgartigimod PH20 SC was noninferior[a] to participants who received 10 mg/kg efgartigimod IV in the overall population **(Figure 5)**
- Total IgG and AChR-Ab percent change from baseline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

Figure 5. Change (%) From Baseline in Total IgG Levels at Day 29 in ADAPT-SC
Overall population



[a]Noninferiority margin of 10% based on % change from baseline in total IgG levels.[b]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. The majority were transient and resolved without treatment.

Figure 6. Percent Change From Baseline in Total IgG, AChR-Ab levels, and Change in MG-ADL Total Score in ADAPT-SC
AChR-Ab+ population



ABBREVIATIONS
AChR-Ab, acetylcholine receptor antibody; AE, adverse event; AUC, area under curve; Fc, fragment crystallizable region; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; Ig, immunoglobulin; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living; OLE, open-label extension; PD, pharmacodynamics; PK pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SE, standard error; TEAE, treatment-emergent adverse event.

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1. Ulrichts P, et al. *J Clin Invest*. 2018;128(10):4372-4386. **2.** Vaccaro C, et al. *Nat Biotech*. 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.

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