Poster #481

Efgartigimod: Clinical Development of an FcRn Antagonist for Treatment of IgG-Mediated Autoimmune Neurological Diseases

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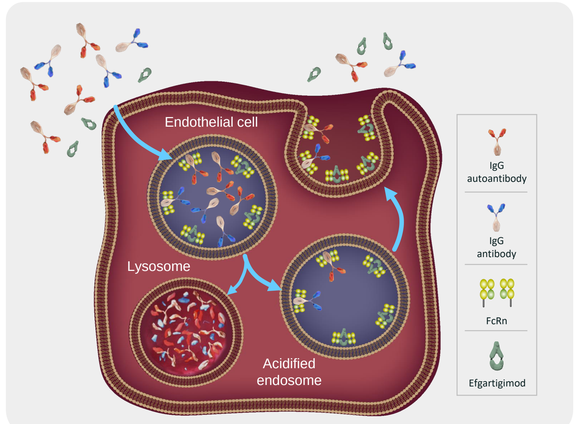
INTRODUCTION

- IgG autoantibodies are thought to play a key role in the pathogenesis of many autoimmune diseases, including chronic inflammatory demyelinating polyneuropathy, generalized myasthenia gravis, and idiopathic inflammatory myopathy/myositis[1]

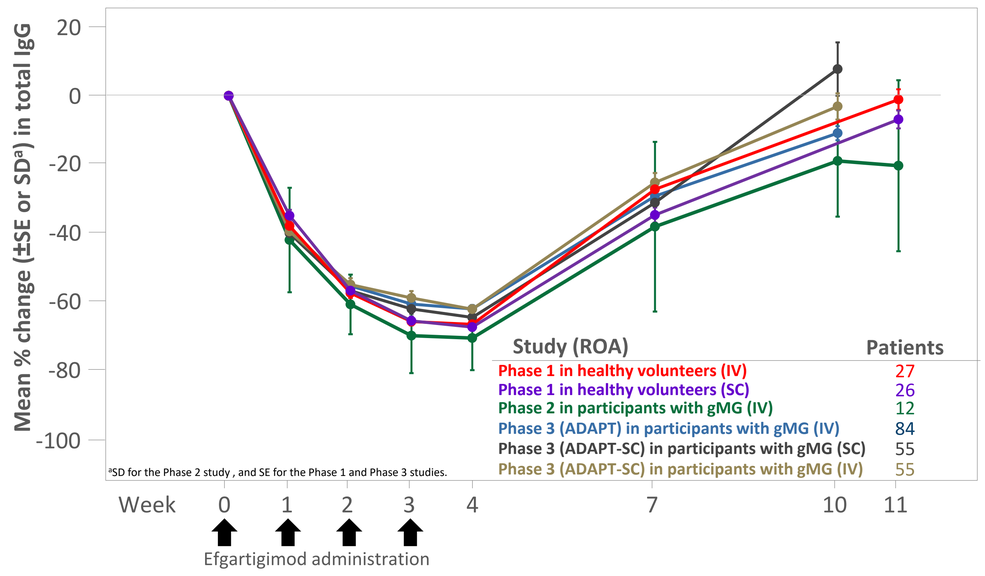
Efgartigimod Mechanism of Action: Blocking FcRn



- FcRn recycles IgG, extending its half-life and maintaining serum concentration[2]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity to FcRn[3,4]
- Efgartigimod was designed to outcompete endogenous IgG, preventing recycling and promoting IgG lysosomal degradation without directly impacting its production[3-7]
  - Targeted reduction of all IgG subtypes
  - No impact on IgM, IgA, IgE, or IgD
  - No reduction in albumin or increase in cholesterol levels

EFGARTIGIMOD REDUCES TOTAL IgG IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH gMG

Figure 1. Total IgG in Healthy Volunteers and Patients With gMG



- Efgartigimod has been shown to reduce pathogenic IgG autoantibody levels in patients with gMG
- Consistent depletion of total IgG levels from baseline was observed with efgartigimod treatment across studies and populations
- Efgartigimod administered IV showed similar, consistent, and transient reductions in IgG levels over multiple cycles in the OLE study ADAPT+
- Similar, consistent, and transient reductions in IgG levels over multiple cycles were observed with efgartigimod PH20 SC in the OLE study ADAPT-SC+

CLINICAL DEVELOPMENT PROGRAM FOR EFGARTIGIMOD IN gMG

Efgartigimod is approved for the treatment of gMG in patients in the US who test positive for AChR antibodies, as add-on to standard therapy in patients in Europe and the UK who test positive for AChR antibodies, and in patients in Japan who test positive or negative for AChR antibodies with insufficient response to steroids or nonsteroid immunosuppressive therapies.

Figure 2. ADAPT/ADAPT+ Study Design

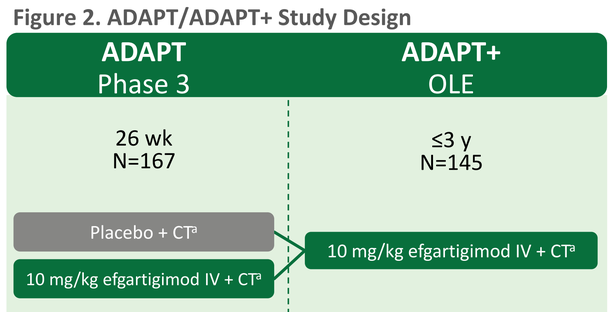
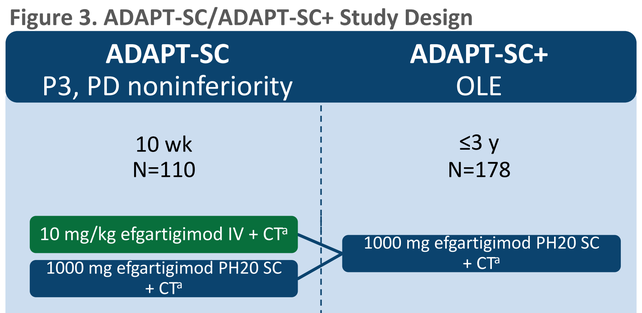


Figure 3. ADAPT-SC/ADAPT-SC+ Study Design



Description

ADAPT was a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial evaluating efgartigimod in participants with gMG. Participants who completed ADAPT were eligible to be rolled over to **ADAPT**

Summary

- Clinically and statistically significant improvements in function (MG-ADL responders, 68%) and strength (QMG responders, 63%) were observed in efgartigimod-treated AChR-Ab+ participants compared with improvements on placebo (30% and 14%, respectively) in cycle 1 of ADAPT
- Similar repeatable and consistent decreases in MG-ADL and QMG scores, as well as IgG and anti-AChR-Ab levels, were seen in AChR-Ab+ participants over multiple cycles in ADAPT+
- Efgartigimod was well tolerated, and most AEs were mild or moderate in severity
- Infections did not increase over time in ADAPT/ADAPT+, with >250 patient-years of patient experience

Status

Complete

Description

ADAPT-SC was a phase 3, noninferiority, randomized, open-label, parallel-group study to evaluate efgartigimod PH20 SC, an additional SC formulation of efgartigimod, in participants with gMG. Participants who completed ADAPT-SC were eligible to be rolled over to **ADAPT-SC+**

Summary

- 1000 mg efgartigimod PH20 SC was noninferior to 10 mg/kg efgartigimod IV in percent reduction from baseline in total IgG levels at day 29 in ADAPT-SC
- Safety and tolerability of efgartigimod PH20 SC were similar to efgartigimod IV in ADAPT-SC, with the exception of injection-site reactions, which were all mild to moderate in severity and did not lead to treatment discontinuation. TEAEs in ADAPT-SC+ were similar to those seen in ADAPT-SC, and no new safety signals were observed
- Efgartigimod PH20 SC treatment resulted in consistent and repeatable reductions in total IgG and anti-AChR-Ab levels in ADAPT-SC+. Improvements in MG-ADL and MG-QOL15r total scores were also achieved over multiple cycles in AChR-Ab+ and overall populations

Status

ADAPT-SC: Complete

ADAPT-SC+: Active, not recruiting

SUMMARY

Efgartigimod is an IgG1 antibody Fc fragment with increased affinity to FcRn, allowing for fewer IgG (auto)antibodies to be recycled back into the bloodstream. Efgartigimod showed consistent depletion of total IgG levels across studies and populations

Therapeutic blocking of FcRn by efgartigimod is approved for the treatment of gMG and is a promising potential therapeutic option for several additional neurological diseases mediated by pathogenic IgG autoantibodies, including CIDP and IIM

Efgartigimod was well tolerated across studies, with most AEs being mild or moderate in severity

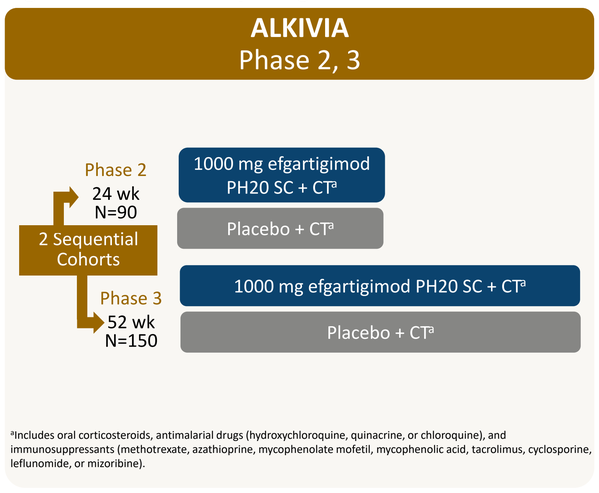
argenx NEUROLOGY PIPELINE

Table 1. argenx Neurology Pipeline

Indication	Formul.	Clinical Trial	Preclinical	Phase 1	Proof of Concept	Phase 2/3	OLE
Generalized myasthenia gravis	**IV**	adapt					
Generalized myasthenia gravis	**SC**	adapt					
Generalized myasthenia gravis (different dosing regimens)	**IV**	adapt					
Generalized myasthenia gravis (in children and adolescents)	**IV**	adapt					
Chronic inflammatory demyelinating polyneuropathy	**SC**	adhere					
Idiopathic inflammatory myopathy/myositis	**SC**	alkivia					

CLINICAL DEVELOPMENT PROGRAM FOR EFGARTIGIMOD IN IIM

Figure 4. ALKIVIA Study Design



Description

ALKIVIA is a phase 2/3, randomized, double-blinded, placebo-controlled, parallel-group, 2-arm, multicenter, operationally seamless study to evaluate the efficacy, safety, tolerability, PD, PK, and immunogenicity of efgartigimod PH20 SC in adult participants with active IIM

Summary

- This trial has a basket study design,[a] and the sequential phase 2 and phase 3 setup will be used to test the efficacy of efgartigimod PH20 SC
- The unblinded phase 2 stage data will be analyzed and used to recommend adaptation of the design of the phase 3 stage
- Efficacy measures will be evaluated using total improvement score (a weighted sum of improvement in 6 core set measures for disease activity), as assessed by the 2016 ACR/EULAR criteria

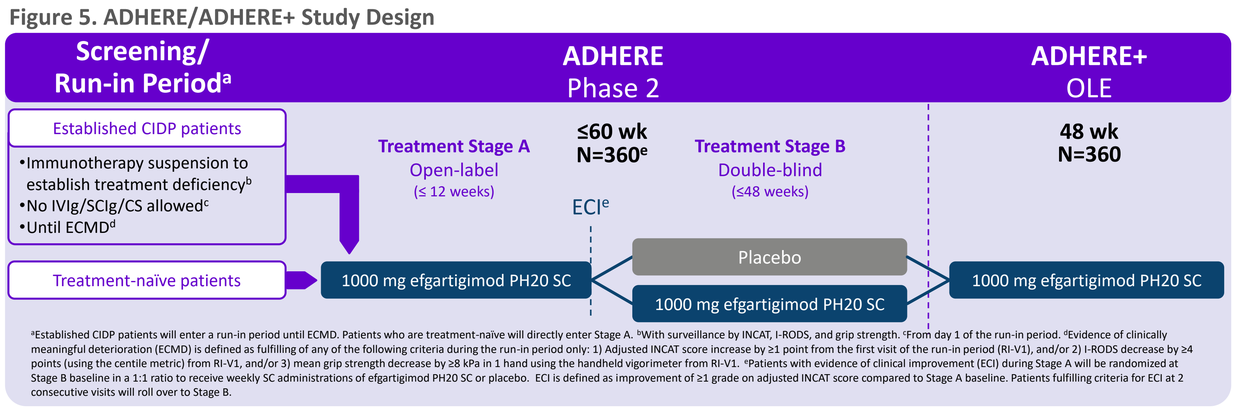
Status

Recruiting

[a]Includes participants with confirmed or probable diagnosis of IIM, as well as one of the following medical histories: diagnosis of DM, JDM, PM (including ASyS), or IMNM.

CLINICAL DEVELOPMENT PROGRAM FOR EFGARTIGIMOD IN CIDP

Figure 5. ADHERE/ADHERE+ Study Design



Description

ADHERE is a phase 2 prospective trial to investigate the efficacy, safety, and tolerability of efgartigimod PH20 SC in adult participants with CIDP

Summary

- During the screening period, diagnosis of CIDP will be confirmed by a CIDP confirmation committee
- The primary objectives of this study are to assess the percentage of participants who are treatment responders and to determine efficacy based on the time needed for the occurrence of the first evidence of clinical deterioration

Status

ADHERE: Recruitment is now closed, with 88 events achieved in the ADHERE trial; top-line data expected in July 2023

ADHERE+: Recruiting

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ABBREVIATIONS: AChR-Ab+, acetylcholine receptor antibody seropositive; ACR, American College of Rheumatology; AEs, adverse events; ASyS, antisynthetase syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; CS, corticosteroid; CT, current treatment; DM, dermatomyositis; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; EULAR, European League Against Rheumatism; FcRn, neonatal Fc receptor; Formul, formulation; gMG, generalized myasthenia gravis; Ig, immunoglobulin; IIM, idiopathic inflammatory myopathy; IMNM, immune-mediated necrotizing myopathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory-Rasch-built Overall Disability Scale; IV, intravenously; IVIg, intravenous immunoglobulin; JDM, juvenile dermatomyositis; MG-ADL, Myasthenia Gravis Activities of Daily Living; OLE, open-label extension; P3, phase 3; PD, pharmacodynamic; PK, pharmacokinetics; PM, polymyositis; QMG, Quantitative Myasthenia Gravis; ROA, route of administration; SC, subcutaneously; SCIg, subcutaneous immunoglobulin; TBD, to be determined; TEAEs, treatment-emergent adverse events.

REFERENCES: 1. Wolfe G, et al. *J Neurol Sci*. 2021;430:118074. **2.** Sesarman A, et al. *Cell Mol Life Sci*. 2010;67(15):2533-2550. **3.** Ulrichts P, et al. *J Clin Invest*. 2018;128(10):4372-4386. **4.** Vaccaro C, et al. *Nat Biotech*. 2005;23(10):1283-1288. **5.** Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526-536. **6.** Nixon AE, et al. *Front Immunol*. 2015;6:176. **7.** Ward ES, et al. *Front Immunol*. 2022;13:892534.

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