Poster #105

Efficacy, Safety, and Tolerability of Efgartigimod in Anti-Acetylcholine Receptor Autoantibody Seronegative Patients With Generalized Myasthenia Gravis: Interim Analysis of ADAPT+ Studies

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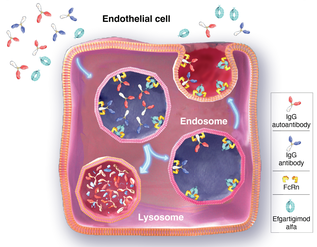
INTRODUCTION

Efgartigimod Mechanism of Action: Blocking Neonatal Fc Receptor



- FcRn recycles IgG, extending its half-life and maintaining its serum concentration[1]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity to FcRn[2,3]
- Efgartigimod was designed to outcompete endogenous IgG, preventing recycling and promoting lysosomal degradation of IgG[2-5]
  - Targeted reduction of all IgG subclasses
  - No impact on immunoglobulins M or A
  - No change in albumin or cholesterol
  - No impact on IgG production or ability to mount an immune response

Clinical Challenges in the Management of AChR-Ab– gMG

- Pathogenic IgG autoantibodies are detectable in most patients with gMG, typically targeting the AChR on skeletal muscle[6]
- 15%–20% of patients with gMG are AChR-Ab–, including ~6% with MuSK antibodies and ~2% with anti-LRP4 antibodies[7]
- Autoantibodies are detectable using highly sensitive cell-based assays in ~30% of patients without detectable autoantibodies by conventional assays[8]
- AChR-Ab– gMG affects a heterogenous and potentially difficult-to-diagnose patient population with high unmet clinical need who have historically been excluded from clinical trials[7]

METHODS

ADAPT was a 26-week, global, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial evaluating efgartigimod in patients with gMG. Participants who completed ADAPT were eligible to be rolled over to ADAPT+[4,a]

adapt myasthenia gravis study

ADAPT[b]
Patients randomized 1:1 to receive cycles of 4 infusions at weekly intervals of 10 mg/kg IV efgartigimod or placebo[3]

adapt+ myasthenia gravis study

ADAPT+ (Open-Label Extension)[c]
Patients received cycles of 4 infusions at weekly intervals of 10 mg/kg IV efgartigimod

Inclusion criteria
- MGFA class II, III, IV
- AChR-Ab seropositive or seronegative
- MG-ADL score ≥5 (>50% nonocular)
- On ≥1 stable gMG treatment[d]
- IgG ≥6 g/L

Diagnosis of AChR-Ab– gMG
- Undetectable AChR-Ab by radioimmunoassay
- ≥1 of the following diagnostic criteria:
  1. Abnormal electrodiagnostic testing
  2. Positive edrophonium chloride test
  3. Demonstrated improvement with oral AChE inhibitors

Efgartigimod AChR-Ab+: n=65
Efgartigimod AChR-Ab–: n=19

1:1

Placebo AChR-Ab+: n=64
Placebo AChR-Ab–: n=19

26 wk (≤3 cycles[e])

N=151

Initiation of new treatment cycle:
- ≥5 weeks between cycles
- MG-ADL score ≥5[f]
- MG-ADL score within 2 points of baseline

Efgartigimod AChR-Ab+: n=61
Efgartigimod AChR-Ab–: n=16

Placebo AChR-Ab+: n=50
Placebo AChR-Ab–: n=18

Part A (1 y) / Part B (2 y)

Initiation of new treatment cycle:
- ≥4 weeks between cycles
- MG-ADL score ≥5[f]
- MG-ADL score within 2 points of baseline

Initiation of new treatment cycle:
- ≥4 wk between cycles
- Per investigator discretion

Note: Beige lines within arrows indicate day of efgartigimod infusion.
[a]Participants who required retreatment but were unable to complete a treatment cycle within the time frame of ADAPT were also eligible to be rolled over to ADAPT+. [b]The ADAPT study was started on August 22, 2018, and was completed on April 6, 2020. [c]The ADAPT+ study was started on March 1, 2019 and current data cutoff was January 31, 2022. [d]Acetylcholinesterase inhibitor, steroid +/or nonsteroidal immunosuppressive therapy. Patients could not change concomitant therapies in ADAPT or during dosing in Part A of ADAPT+. Physicians could change concomitant therapies between doses in Part A and at any time in Part B of ADAPT+. [e]≤3 cycles dosed at ≥8 weeks after initial cycle. [f]With >50% from nonocular items.

SUMMARY

- ADAPT is the first gMG trial to include AChR-Ab– patients
- AChR-Ab– and AChR-Ab+ patients treated with efgartigimod experienced similar response rates, although a higher response to placebo was observed in AChR-Ab– patients compared to AChR-Ab+
- While ADAPT was not powered to demonstrate statistical significance, patients who crossed over from placebo to efgartigimod during ADAPT+ demonstrated improvement in MG-ADL and QMG scores
- Clinically meaningful improvement in MG-ADL scores were observed in ADAPT+ patients across 10 treatment cycles
- Long-term treatment with efgartigimod was well tolerated, with similar rates of AEs observed in ADAPT and ADAPT+ and no notable differences seen in AChR-Ab- patients
- Additional studies assessing the efficacy of efgartigimod in AChR-Ab– patients are warranted

RESULTS

Trial Participants

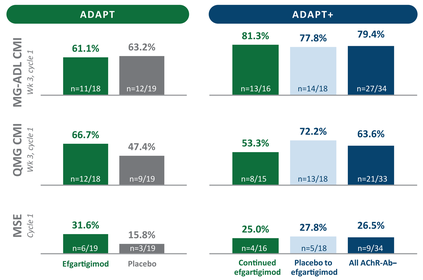
Table 1. Baseline Characteristics

Characteristic	AChR-Ab– Patients: Efgartigimod (n=19)	AChR-Ab– Patients: Placebo (n=19)
Age, mean (SD), y	50.2 (11.6)	44.8 (12.6)
Sex, female, n (%)	17 (89.5)	15 (78.9)
MuSK-Ab+, n (%)	3 (15.8)	3 (15.8)
Time since diagnosis, mean (SD), y	11.7 (11.5)	8.5 (5.2)
Mean (SD) MG-ADL score	9.7 (3.1)	9.8 (2.5)
Mean (SD) QMG score	16.6 (4.6)	16.5 (5.2)
MGFA class at screening, n (%)		
Class II	6 (31.6)	6 (31.5)
Class III	12 (63.2)	13 (68.4)
Class IV	1 (5.3)	0
Prior therapy with NSIST, n (%)	15 (78.9)	14 (73.7)
Baseline gMG therapies, n (%)		
Any NSIST[a]	11 (57.9)	14 (73.7)
Steroids	14 (73.7)	16 (84.2)
AChE Inhibitor	14 (73.7)	10 (52.6)

[a]NSIST: azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate, and/or tacrolimus.

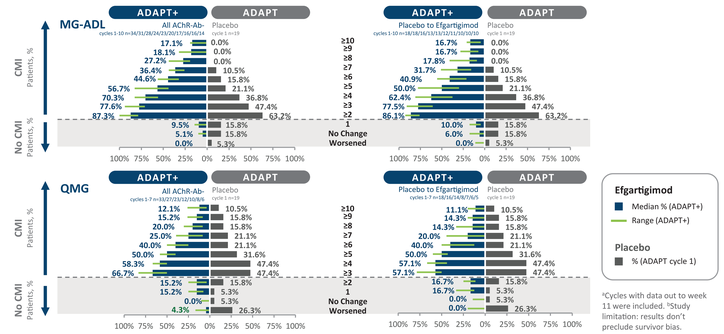
Efficacy of Efgartigimod in AChR-Ab– Patients

Figure 1. Proportion of AChR-Ab– Patients With CMI and MSE in ADAPT and ADAPT+[a,b,c]



[a]CMI defined as ≥2-point improvement in MG-ADL, and ≥3-point improvement in QMG. [b]MG-ADL score of 0–1. [c]Study limitation: assessments in ADAPT+ were not captured at weeks 4–6; MSE would not be captured during that period.[3]

Figure 2. Proportion of AChR-Ab–Patients With Increasing Improvement in MG-ADL and QMG Scores of Cycles in ADAPT+ (WEEK 3[a,b])



[a]Cycles with data out to week 11 were included. [b]Study limitation: results don't preclude survivor bias.

Safety in Overall Trial Population

Table 2. AEs Summary

Treatment-Emergent AE	ADAPT: Placebo (N=83) [34.51 PY] IR[d]	ADAPT: Placebo (N=83) [34.51 PY] n (%)	ADAPT+: Efgartigimod (N=84) [34.86 PY] IR[d]	ADAPT+: Efgartigimod (N=84) [34.86 PY] n (%)	ADAPT+: Efgartigimod (N=145) [217.55 PY] IR[d]	ADAPT+: Efgartigimod (N=145) [217.55 PY] n (%)
AEs[a]	7.8	70 (84)	7.2	65 (77)	3.6	123 (85)
SAEs	0.3	7 (8)	0.1	4 (5)[b]	0.2	34 (23)[b]
≥1 Infusion-related reaction event	0.3	8 (10)	0.1	3 (4)	0.1	15 (10)
Infection AEs	1.2	31 (37)	1.6	39 (46)	0.8	80 (55)
Discontinued study treatment owing to AEs[c]	0.1	3 (4)	0.2	3 (4)	0.1	12 (8)
Severe AEs (grade ≥3)	0.4	8 (10)	0.3	9 (11)	0.3	38 (26)
Death[c]	-	0 (0)	-	0 (0)	<0.1	5 (3)
Most frequent AEs (>10%)						
Nasopharyngitis	0.5	15 (18)	0.3	10 (12)	0.1	20 (14)
URTI	0.2	4 (5)	0.3	9 (11)	<0.1	6 (4)
Urinary tract infection	0.1	4 (5)	0.3	8 (10)	0.1	13 (9)
Headache	1.1	23 (28)	1.2	24 (29)	0.5	36 (25)
Nausea	0.4	9 (11)	0.2	7 (8)	0.1	9 (6)
Diarrhea	0.4	9 (11)	0.2	6 (7)	0.1	14 (10)
COVID-19[e]	-	0 (0)	-	0 (0)	0.1	22 (15)

[a]AEs were predominantly mild or moderate. [b]Only 1 SAE was considered treatment related per investigator. [c]None of the deaths in ADAPT+ were deemed related to efgartigimod administration per the principal investigator. [d]IR was calculated as number of events per total PYs of follow-up. [e]Includes all preferred terms of COVID-19, COVID-19 pneumonia, Coronavirus infection, SARS-COV-2 test positive.

ABBREVIATIONS
AChE, acetylcholinesterase; AChR-Ab, acetylcholine receptor antibody; AE, adverse event; CMI, clinically meaningful improvement; COVID-19, coronavirus 2019; FcRn, Neonatal Fc Receptor; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IR, incidence rate; IV, intravenous; MGFA, Myasthenia Gravis Foundation of America; MG-ADL, Myasthenia Gravis–Activities of Daily Living; MSE, minimal symptom expression; MuSK-Ab, muscle-specific kinase antibody; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; NSIST, nonsteroidal immunosuppressive therapy; POCRI, Patient-Centered Outcomes Research Institute; PY, patient year; QMG, Quantitative Myasthenia Gravis; SAE, serious adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

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