

A Phase 3 Study to Evaluate the Efficacy and Safety of Telitacicept in Patients With Generalized Myasthenia Gravis: UPSTREAM MG Trial Design Update

Ali A. Habib,¹ Mamatha Pasnoor,² Tuan Vu,³ Bhupendra O. Khatri,⁴ Gil I. Wolfe,⁵ Amit Sachdev,⁶ Said Beydoun,⁷ George G. Li,⁸ Shaida Khan,⁹ Lawrence Meinert,¹⁰ Jeremy Sokolove,¹⁰ Kristl G. Claeys,¹¹ Francesco Saccà,¹² James F. Howard Jr¹³

¹Department of Neurology, University of California Irvine, Orange, CA, USA; ²University of Kansas Medical Center, Kansas City, MO, USA; ³University of South Florida Morsani College of Medicine, Tampa, FL, USA; ⁴Center for Neurological Disorders, The Regional Multiple Sclerosis Center, Milwaukee, WI, USA; ⁵University at Buffalo, Buffalo, NY, USA; ⁶Department of Neurology and Ophthalmology, Michigan State University, East Lansing, MI, USA; ⁷Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; ⁸MEDSOL Clinical Research Center, Port Charlotte, FL, USA; ⁹Department of Neurology, UT Southwestern Medical Center, Dallas, TX, USA; ¹⁰Vor Biopharma Inc., Boston, MA, USA; ¹¹Department of Neurology, University Hospitals Leuven, and Laboratory for Muscle Diseases and Neuropathies, KU Leuven, Leuven, Belgium; ¹²Università degli Studi di Napoli Federico II, Napoli, Italy; ¹³University of North Carolina School of Medicine, Chapel Hill, NC, USA

INTRODUCTION

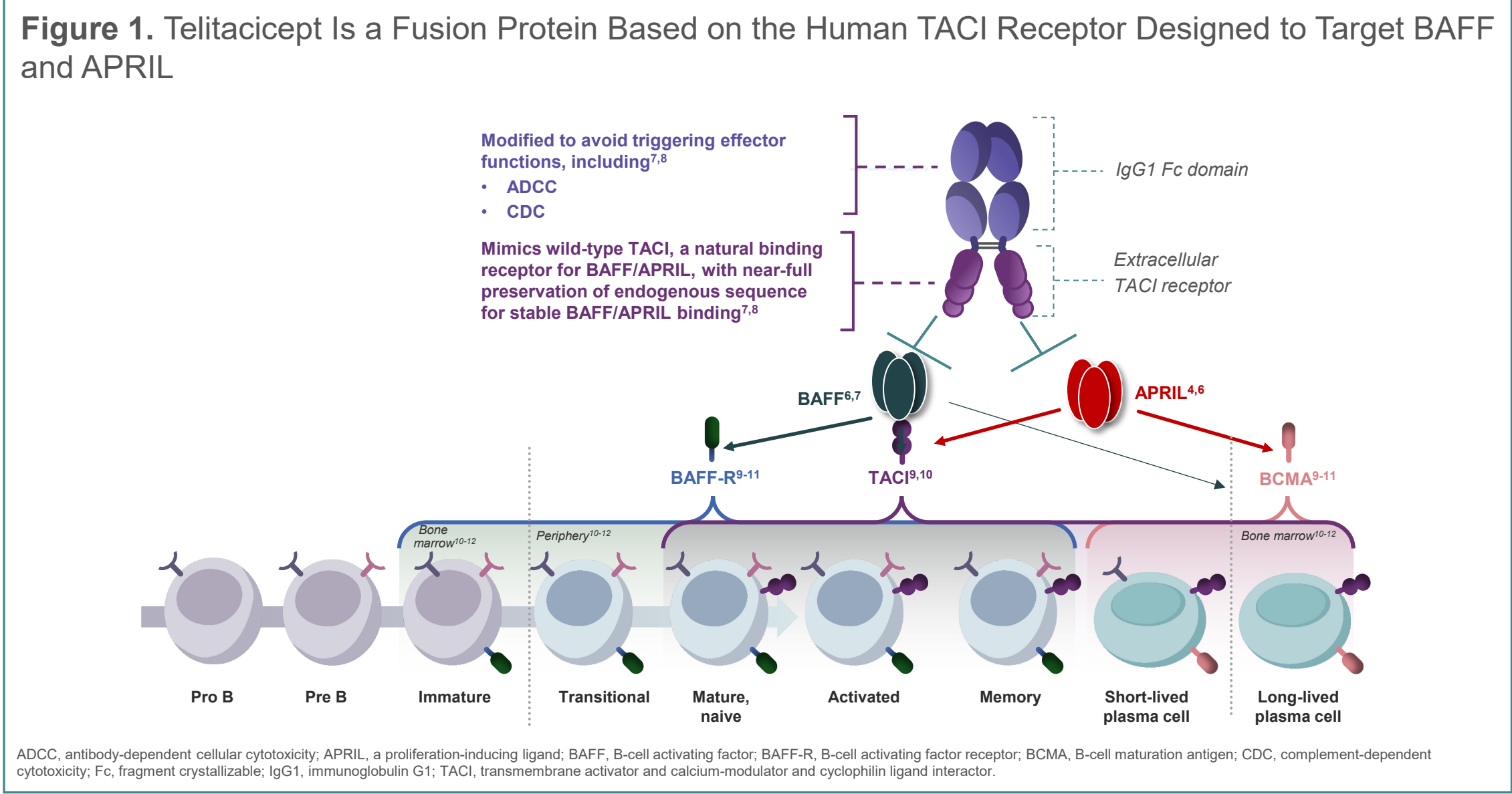
Myasthenia gravis (MG) is an autoimmune neuromuscular disease in which autoreactive B cells produce pathogenic autoantibodies that target the postsynaptic membrane of the neuromuscular junction^{1,2}

The predominant clinical manifestation is fatigable muscle weakness, which affects limb, respiratory, bulbar, and ocular muscle function²

Current therapies for generalized myasthenia gravis (gMG) primarily manage symptoms, induce nonspecific immunosuppression, or inhibit downstream immune function at the neuromuscular junction^{1,3,4}

Telitacicept is a novel, fully human transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI)-Fc fusion protein that inhibits B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), 2 cytokines that play critical roles in B-cell development, maturation, and survival⁵⁻⁸

Through its dual inhibition of BAFF and APRIL, telitacicept modulates B-cell maturation, survival, and differentiation, which ultimately may reduce pathogenic autoantibodies implicated in gMG (**Figure 1**)^{6,7}



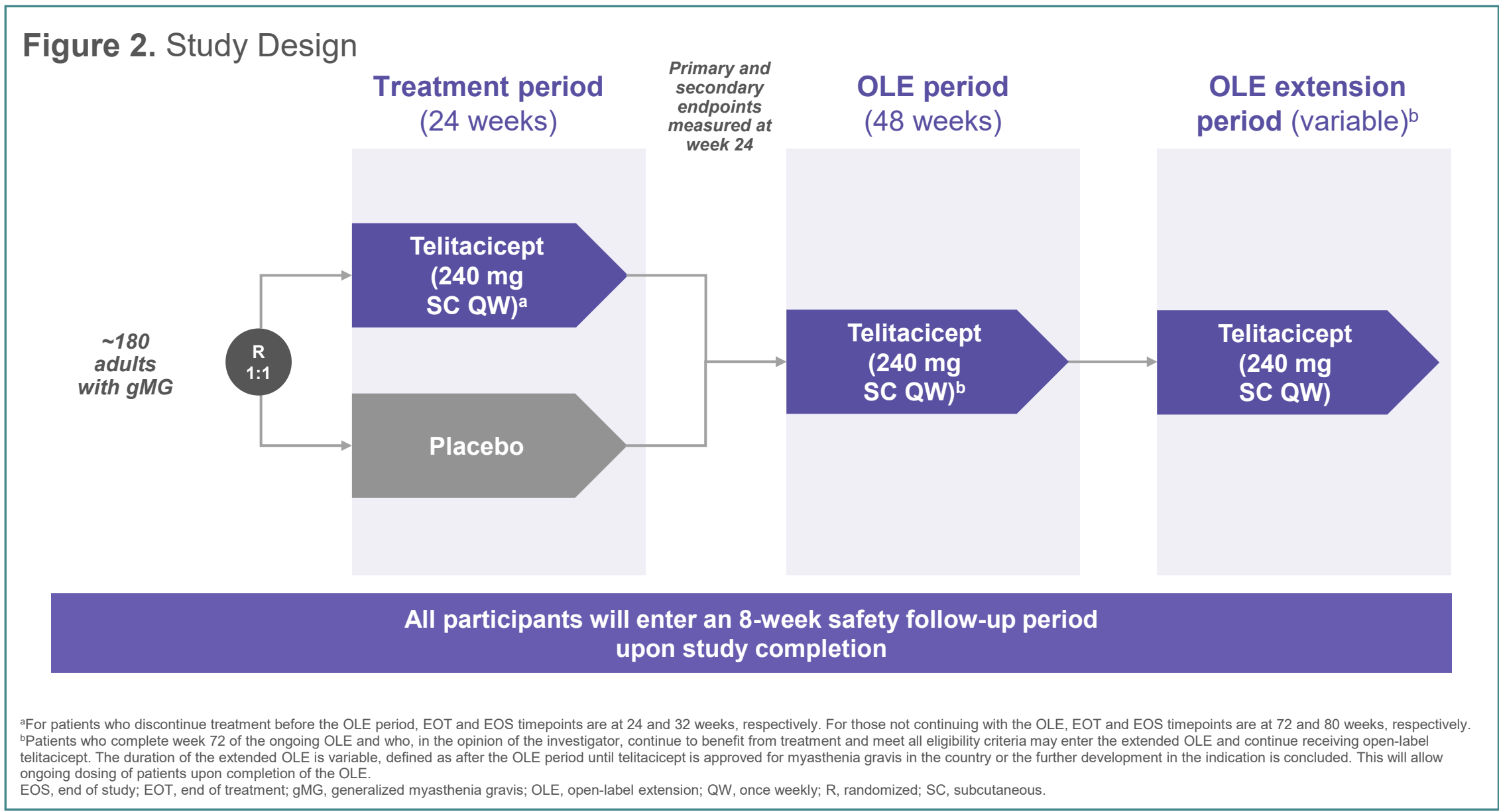
- Data from multicenter, phase 2 (NCT04302103) and phase 3 (NCT05737160) studies of telitacicept conducted in China showed efficacy and safety in adults with AChR antibody-positive gMG¹³⁻¹⁷
- In the phase 3 trial^{16,17}
 - The **primary endpoint** was met: change from baseline in MG-ADL score at week 24 of **-5.74** in the telitacicept 240-mg QW group and **-0.91** in the placebo group ($p<0.001$)¹⁶
 - ≥3-point reduction** in MG-ADL score in 98.1% and 12.0% of patients treated with telitacicept and placebo (difference, 86.1%; 95% CI, 76.4–95.8; $p<0.001$)¹⁶
 - Telitacicept was generally well tolerated
 - Most adverse events were mild to moderate in severity^{16,17}
- Here, we present the study design of an ongoing, global, phase 3, double-blind, placebo-controlled study (NCT06456580) in adults with gMG in order to understand the effect of BAFF/APRIL inhibition by telitacicept in a heterogeneous international population¹⁸

AChR, acetylcholine receptor; MG-ADL, Myasthenia Gravis Activities of Daily Living; QW, once weekly.

METHODS

Study Design

- UPSTREAM MG is randomizing ~180 patients with gMG 1:1 to receive either placebo or telitacicept subcutaneously weekly (**Figure 2**)
- UPSTREAM MG consists of a screening period of ≤4 weeks; a 24-week, double-blind, placebo-controlled phase; and a 48-week open-label extension (OLE)
 - This is followed by an additional extended OLE period, which has a variable duration until telitacicept is available or further development in the indication is concluded (**Figure 2**)



^aFor patients who discontinue treatment before the OLE period, EOT and EOS timepoints are at 24 and 32 weeks, respectively. For those not continuing with the OLE, EOT and EOS timepoints are at 72 and 80 weeks, respectively.

^bPatients who complete week 72 of the ongoing OLE and who, in the opinion of the investigator, continue to benefit from treatment and meet all eligibility criteria may enter the extended OLE and continue receiving open-label telitacicept. The duration of the extended OLE is variable, defined as after the OLE period until telitacicept is approved for myasthenia gravis in the country or the further development in the indication is concluded. This will allow ongoing dosing of patients upon completion of the OLE.

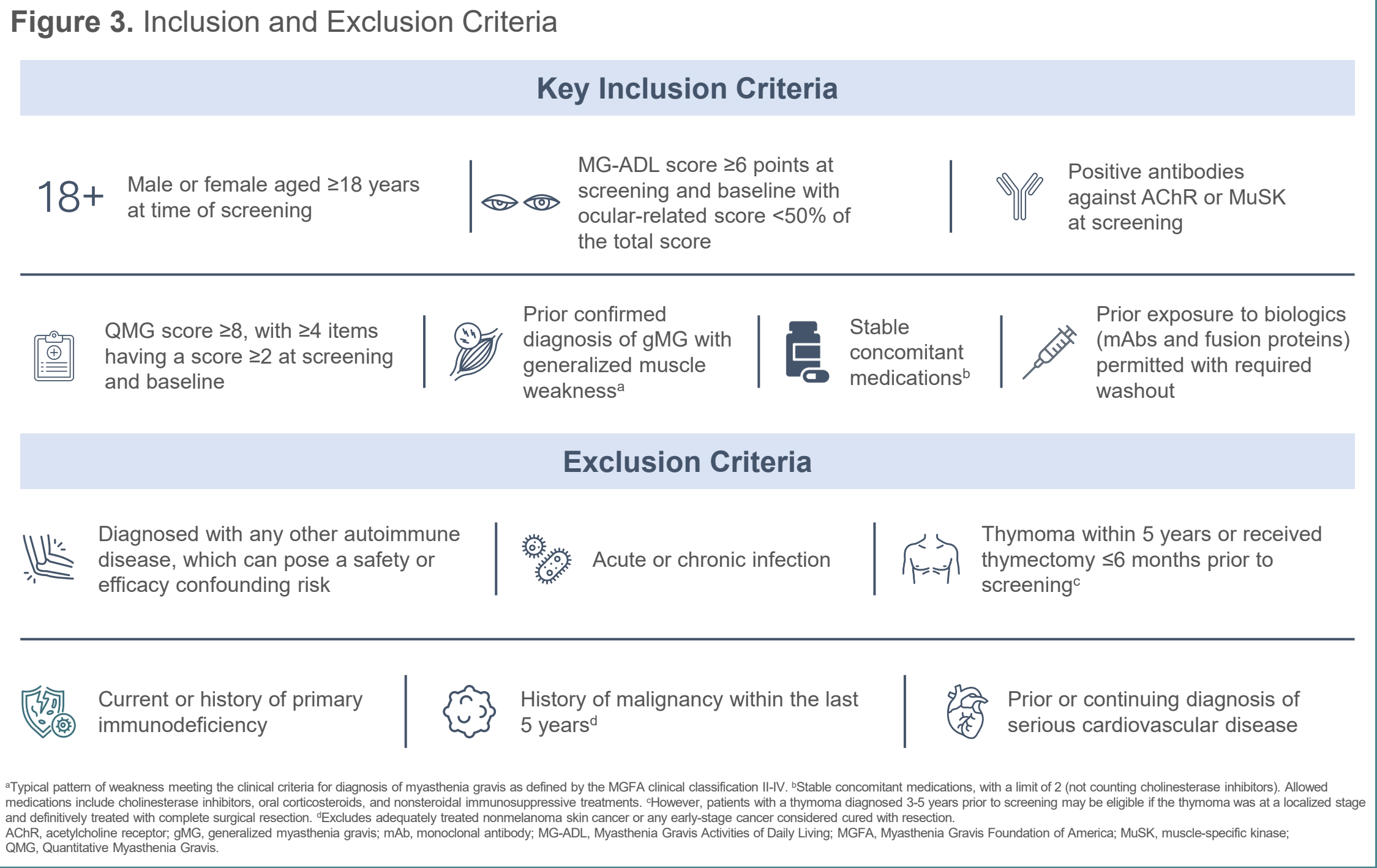
EOT, end of treatment; EOS, end of study; EOT, end of treatment; gMG, generalized myasthenia gravis; OLE, open-label extension; QW, once weekly; R, randomized; SC, subcutaneous.

Endpoints

- The primary endpoint is the change from baseline in MG-ADL score at week 24
- Secondary efficacy endpoints include
 - Change from baseline in Quantitative Myasthenia Gravis (QMG) score at week 24
 - Change from baseline in MG Quality of Life 15-item Revised scale (MG-QOL15r) at week 24
 - Proportion of patients with a ≥2-point decrease in MG-ADL score at week 24
 - Proportion of patients with a ≥3-point decrease in QMG score at week 24
 - Proportion of patients who achieved minimal symptom expression (defined as having an MG-ADL score of 0 or 1) at week 24
- Incidence of adverse events and evaluation of other vital signs and safety laboratory measurements will also be used to assess the safety and tolerability of telitacicept

Eligibility Criteria

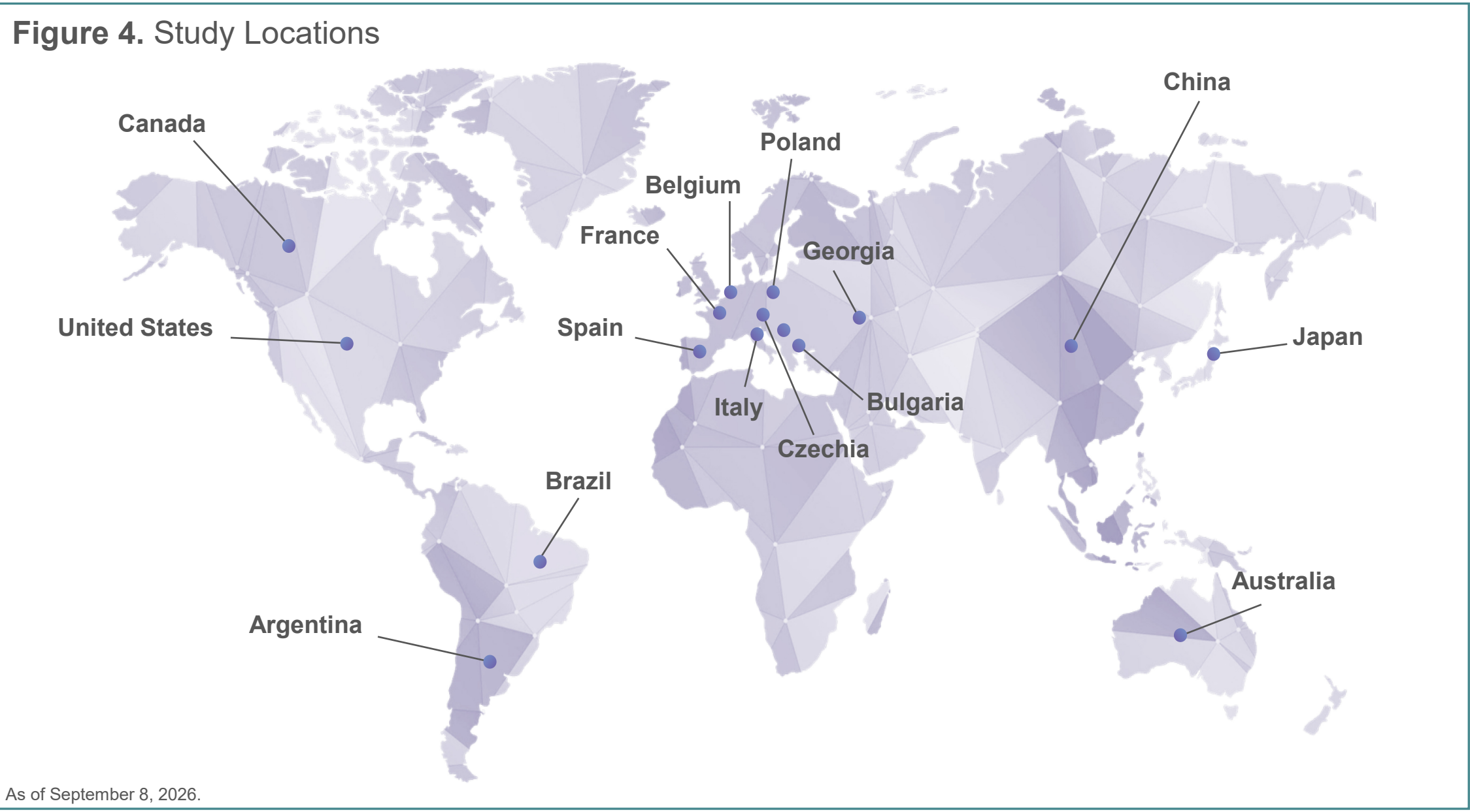
- Inclusion and exclusion criteria are outlined in **Figure 3**
- Patients may also have received up to 2 stable concomitant medications (not counting cholinesterase inhibitors) for the treatment of gMG if they meet the stability criteria prior to baseline
 - Varying standard-of-care regimens are allowed, including cholinesterase inhibitors, oral corticosteroids, and nonsteroidal immunosuppressive treatments
- Patients who have recently received prohibited immunosuppressants (pimecrolimus, vincristine, vinblastine, or cyclophosphamide) other than protocol-permitted stable concomitant medications, biologics, or other agents were excluded
 - Washout periods were required for prohibited medications, including any prior biologic or intravenous immunoglobulin use
- Patients were excluded if they have a chronic or acute infection



RESULTS

Study Locations

- Study enrollment is completed across 15 countries with top-line results anticipated in the first half of 2027
- Study locations are shown in **Figure 4**



CONCLUSIONS

- A global, phase 3, pivotal, multicenter, randomized, double-blind, placebo-controlled trial with a long-term OLE period is ongoing to evaluate the efficacy and safety of telitacicept in a global patient population
- Results from this study will augment the established efficacy and safety of BAFF/APRIL inhibition with telitacicept in a broader heterogeneous population

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Conflicts of Interest: Kristl G. Claeys has received speaker/advisory board honoraria from Alexion, Alnylam, Amicus, argenx, Biogen, CSL Behring, Jansen, Janssen Pharmaceuticals, Lupin, Pfizer, Roche, Sanofi-Genzyme, UCB, and Vertex. Francesco Saccà has received public speaking honoraria from Alexion, argenx, Biogen, Genpharm, Johnson & Johnson, MedPharma, Medipharma, Neopharm Israel, UCB, and Zai Lab. He has also received compensation for advisory boards or consultation fees from Alexion, Amgen, argenx, AstraZeneca, AveXis, Biogen, Dianthus, Johnson & Johnson, Lexov, Novartis GmbH, Resto, UCB, and Zai Lab. He is principal investigator in clinical trials for Alexion, argenx, Dianthus, Immunovant, Inc., Leadant, Lexov, Novartis, Pilenia, RemeGen, and Sanofi. Ali A. Habib has received research support/honoraria from Alexion/AstraZeneca, Amgen, Argenx, Cabaletta Bio, Cartesian, COUR Pharmaceuticals, GSK Biopharma, Grifols, Immunovant, Inc., Janssen/Janssen & Johnson, Kyverna, Merck, MGNel (grant number: US4NS115054), Nkarta, NMD Pharma, Novartis, Regeneron, and UCB; has served on a Data and Safety Monitoring Board for Genentech/Roche, Immunis, and the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke; and has served on a Trial Steering Committee for Dianthus, Janssen/Janssen & Johnson, and Kyverna. Richard J. Nowak has received research support from Alexion Pharmaceuticals, argenx, Amnexus Biosciences, Inc., Genentech Inc., Grifols, S.A., Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Myasthenia Gravis Foundation of America (MGFA), NIH, Ra Pharmaceuticals, Inc. (now UCB S.A.), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). Mamatha Pasnoor is a University of Kansas site principal investigator for RemeGen MG trial; served as medical advisor or consultant for Alexion, Amgen, Amnexus, argenx, BMS, Catalyt, CSL Behring, Grifols, Immunovant, Inc., Janssen, Johnson & Johnson, Momenta, Takeda, and Tatum BCT; serves on the board of directors for the Myasthenia Gravis Association. Gil I. Wolfe serves as an advisor for Alexion, argenx, BPL, Canopy, Cartesian, Dianthus, Grifols, Johnson & Johnson, Takeda, and UCB and receives research support from Immunovant, Inc., Novartis, Roche, and Vor. Tuan Vu is a University of South Florida site principal investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR, Dianthus Therapeutics, EMD Serono, ImmunAbs, Immunovant, Inc., Johnson & Johnson, NMD Pharma, Novartis, Regeneron, UCB, and Vor. He has served as a speaker for Alexion/AstraZeneca Rare Disease, Amgen, argenx, and CSL Behring and participated on advisory boards for Alexion/AstraZeneca Rare Disease, Amgen, argenx, Dianthus Therapeutics, ImmunAbs, Johnson & Johnson, NMD Pharma, Regeneron, and Vor. Jeremy Sokolove is an employee of Vor Bio and owns company stock. James F. Howard Jr has received research funding (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, Merck EMD Serono, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, and UCB Bioscience. He has served as medical advisor or consultant for Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Cartesian Therapeutics, CoreVitas, Curie bio, H. Lundbeck A/S, Japan Tobacco Company, Kyverna Therapeutics, Merck EMD Serono, NMD Pharma, Novartis Pharmaceuticals, Regeneron Pharmaceuticals, Seismic Therapeutics, TG Therapeutics, Toleranzia AB, and UCB Bioscience. He has received speaker fees from AcademicCME, CheckRare CME, PeerView CME, Physicians' Education Resource (PER) CME, and PlatformQ CME.



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