Upstream Targeting: Rethinking MG Treatment Through Active C1s Inhibition

Expert Panel

TUAN VU
MD

PUSHPA NARAYANASWAMI
MD

STOJAN PERIC
MD, PHD

SHAHAR SHELLY
MD

AGENDA

Introduction to dianthus therapeutics and claseprubart

Clinical and treatment gaps

Panel discussion part 1: clinical and treatment gaps

aC1s inhibition mode of action animation

Upstream inhibition of the classical pathway

MaGic phase 2 results

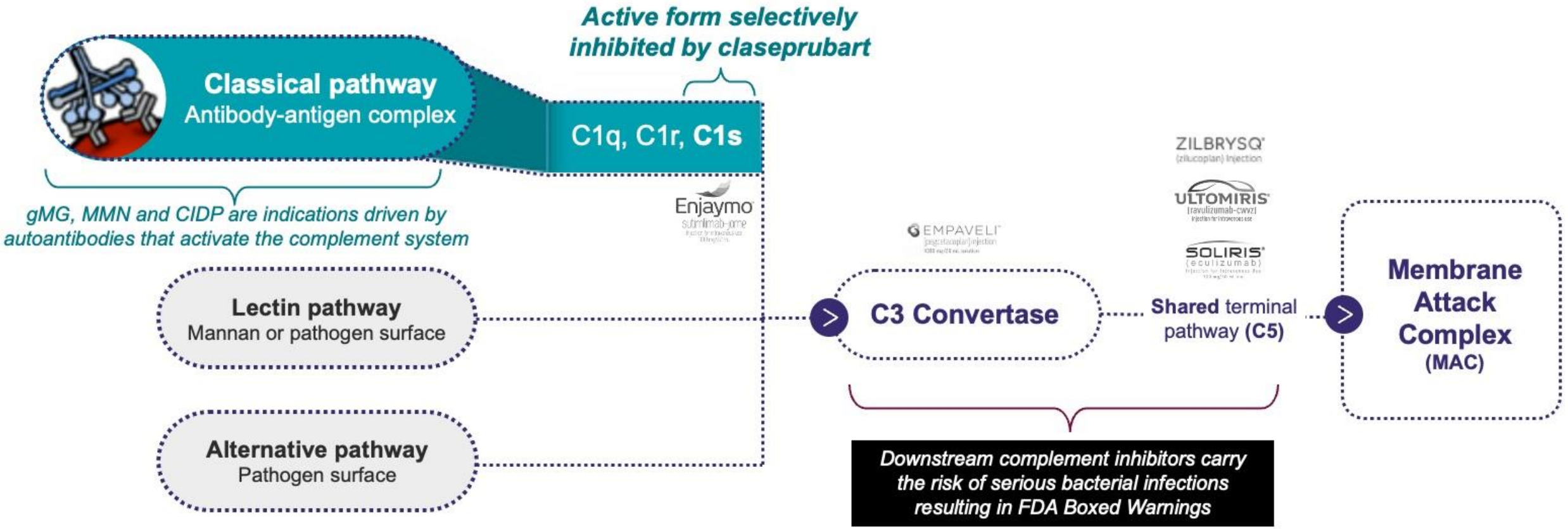
Panel discussion part 2: feedback on MaGic results and potential of c1s inhibition

Phase 3 and future outlook

Claseprubart is an investigational agent that is not approved as a therapy in any indication in any jurisdiction worldwide.

Selectively targeting classical pathway aims to provide effective but safer complement inhibition

Targeting aC1s aims to deliver efficacy demonstrated with terminal inhibitors while preserving the critical immune activity of lectin and alternative pathways, leading to a lower risk of infection and no FDA boxed warning/REMS



C1s is a clinically validated target in the classical complement pathway with an FDA approved therapy

1

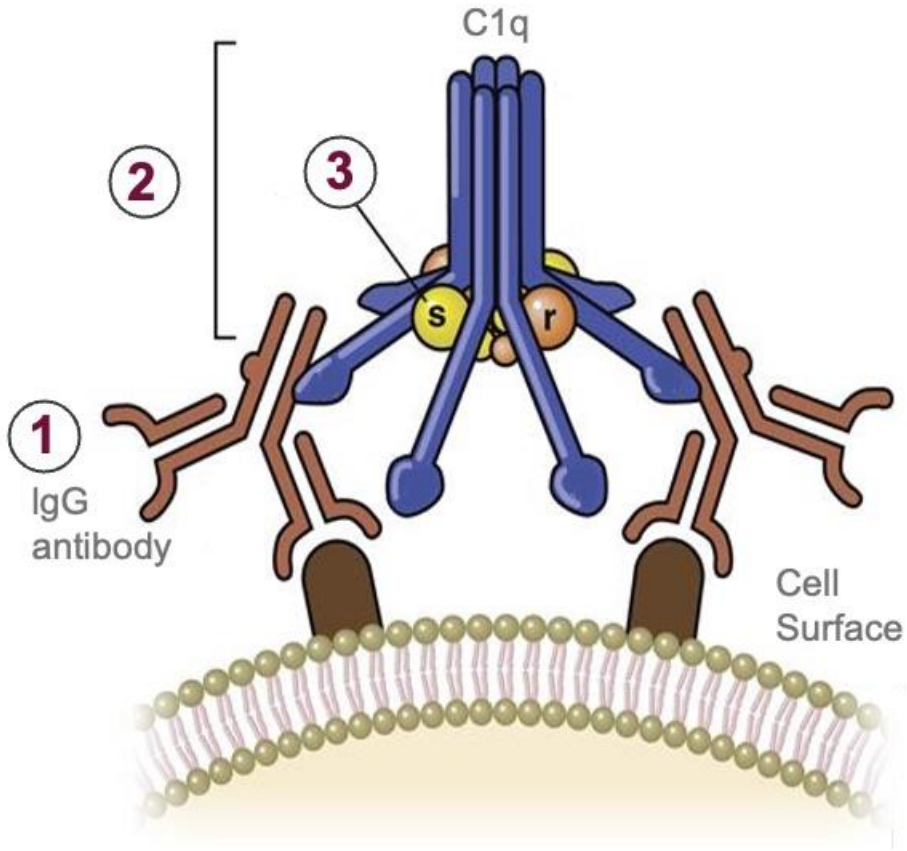
Classical pathway
The only pathway activated by the presence of IgG and IgM, which bind to the **C1 complex**

2

The C1 complex
The initial component of the classical complement pathway consisting of C1q, C1r and C1s

3

Active C1s
A serine protease that executes catalytic function of the C1 complex, leading to MAC formation



C1s is the only target of the C1 complex with an FDA approved therapy

Enjaymo, FDA approved in 2022 for CAD, is a C1s inhibitor but is not selective to the active form and dosed I.V. at 6,500-7,500mg every two weeks

Active C1s inhibition has recently demonstrated clinical benefit in CIDP

Riliprubart results show clinical PoC for inhibiting active C1s in autoimmune neuromuscular diseases

Enjaymo information sourced from prescribing information

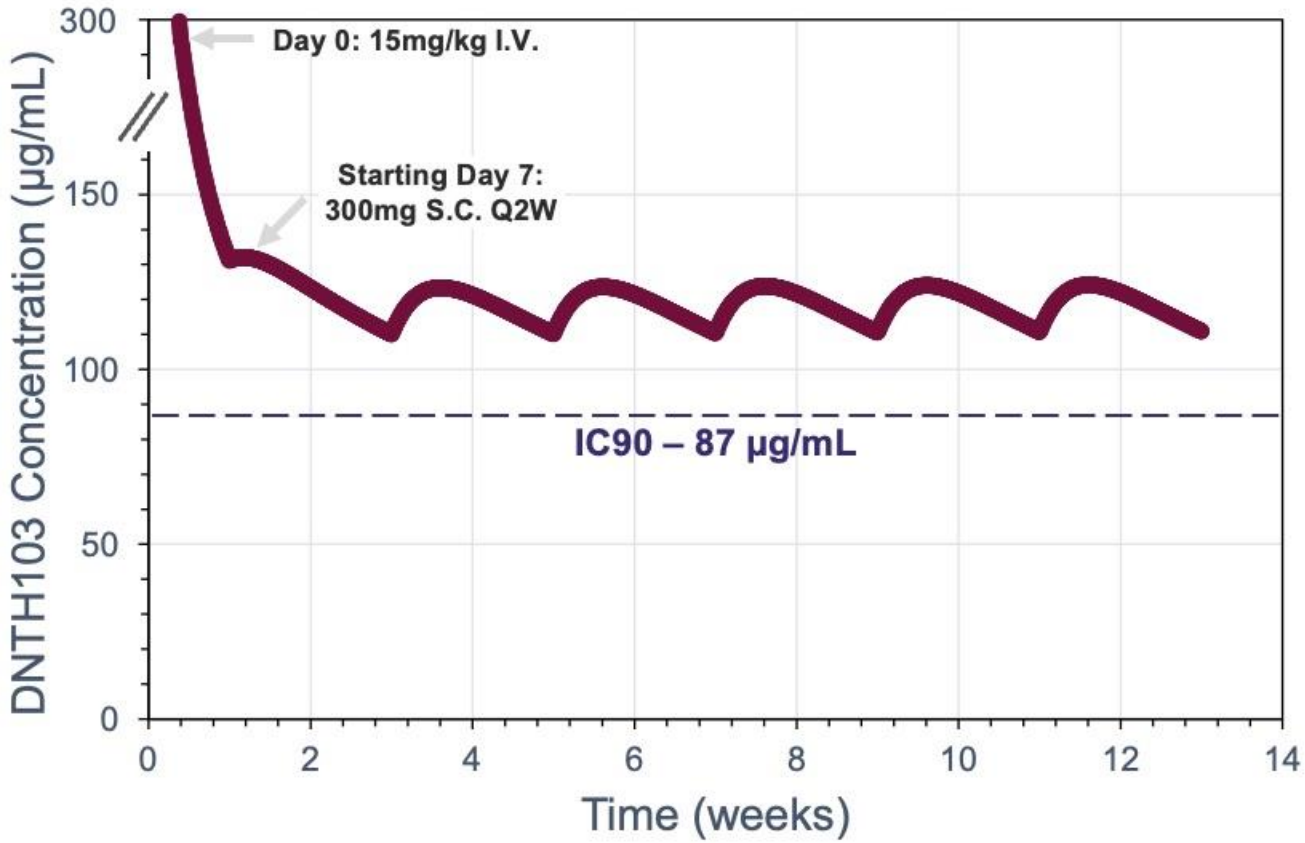
Claseprubart phase 1 data confirms potent inhibition of the classical pathway as a Q2W S.C. injection

Ph. 1 Data Confirms

- ~60-day half-life
- IC90 calculated at 87 µg/mL

Dosing Modeled

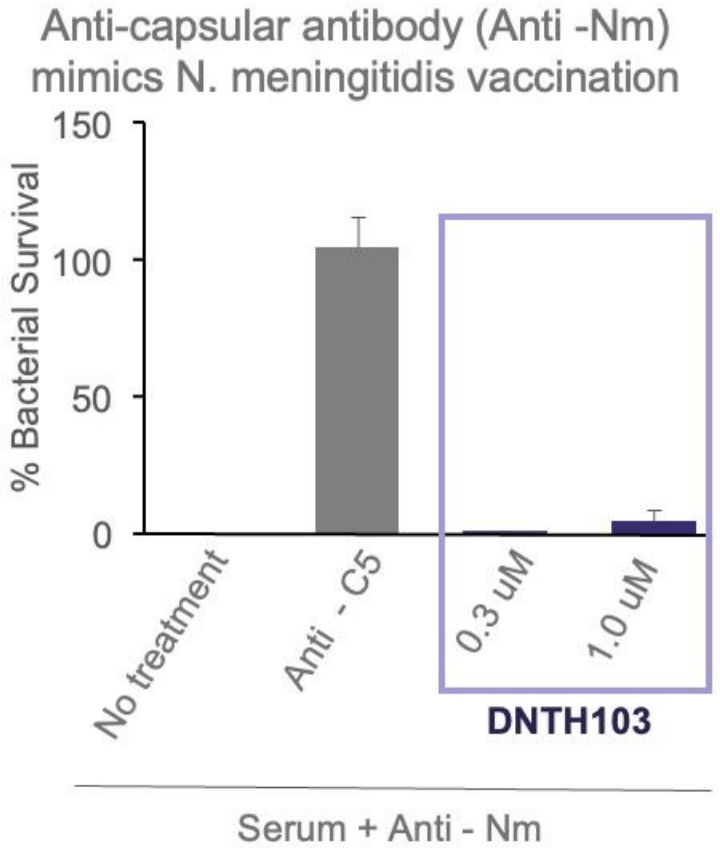
- 15mg/kg I.V. on Day 0
- 300mg S.C. Q2W starting Day 7



Simulation using data from 60 healthy volunteers dosed across multiple cohorts demonstrates potent inhibition with infrequent S.C. dosing

Claseprubart *in vitro* study indicates lower risk of *neisseria meningitidis* infections

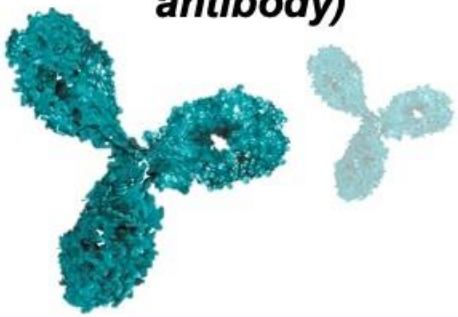
- Protection against infection is a critical function of the complement pathway
- **DNTH103 selectively inhibits** the **classical pathway**, leaving the alternative and lectin-activated defense pathways intact
- An *in vitro* assay measured **antibody-dependent complement-mediated killing of *N. meningitidis*** in the presence of **DNTH103** and **anti-C5 (ravulizumab*)**
- In this assay, **DNTH103 maintained bacterial killing**, potentially leading to a decreased risk of infection vs. C5 inhibitors



Results further validate the potential differentiated safety profile for DNTH103 as a selective classical pathway inhibitor consistent with ENJAYMO, an approved C1s inhibitor without an FDA Boxed Warning or REMS

* Engineered using patent sequence

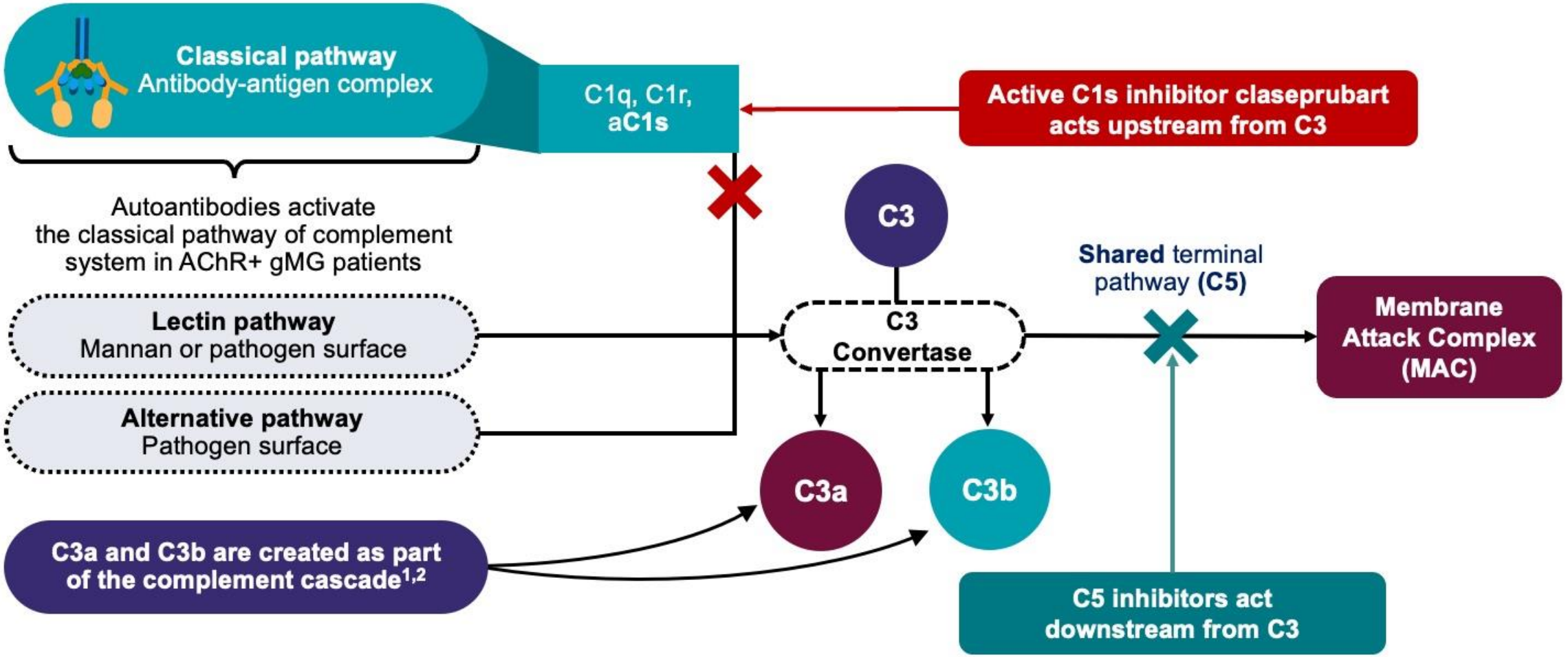
Claseprubart rapidly advancing in three clinical trials with multiple catalysts in 2026

Program (Target)	Target Population	2024	2025	2026
 ***Claseprubart (S.C. Active C1s antibody)***	**Generalized Myasthenia Gravis (gMG)** >100,000 U.S. patients		Ph. 2 MaGic data reported Q3'25	Initiate Ph. 3 trial 2026
	Multifocal Motor Neuropathy (MMN) >10,000 U.S. patients	Initiated Ph. 2 trial Q3'24		Top-line Ph. 2 data 2H'26 ★
	**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** >40,000 U.S. patients	Initiated Ph. 3 trial Q4'24		Interim Responder Analysis 2H'26 ★

Claseprubart has the potential to address significant unmet needs in multiple classical pathway-driven diseases with its best-in-class target product profile

gMG: >100,000 gMG U.S. patients from Komodo claims data accessed 2013-2025; approx. 85% of gMG patients have AChR autoantibody-driven disease https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7033452/#
CIDP & MMN: Komodo claims data 2013-2025, adjusted to account for 70% capture of real-world patient counts for biologic treated patients; CIDP adjusted to account for 27% misdiagnosed

Pro-inflammatory split products C3a and C3b have potential negative effects on NMJ pathology beyond MAC in gMG



AChR+, acetylcholine receptor-positive; gMG, generalized myasthenia gravis

Pro-inflammatory split products C3a and C3b have potential negative effects on NMJ pathology beyond MAC in gMG

C3a and C3b Are Elevated in AChR+ gMG – Both Cause Inflammatory Damage[1,2]

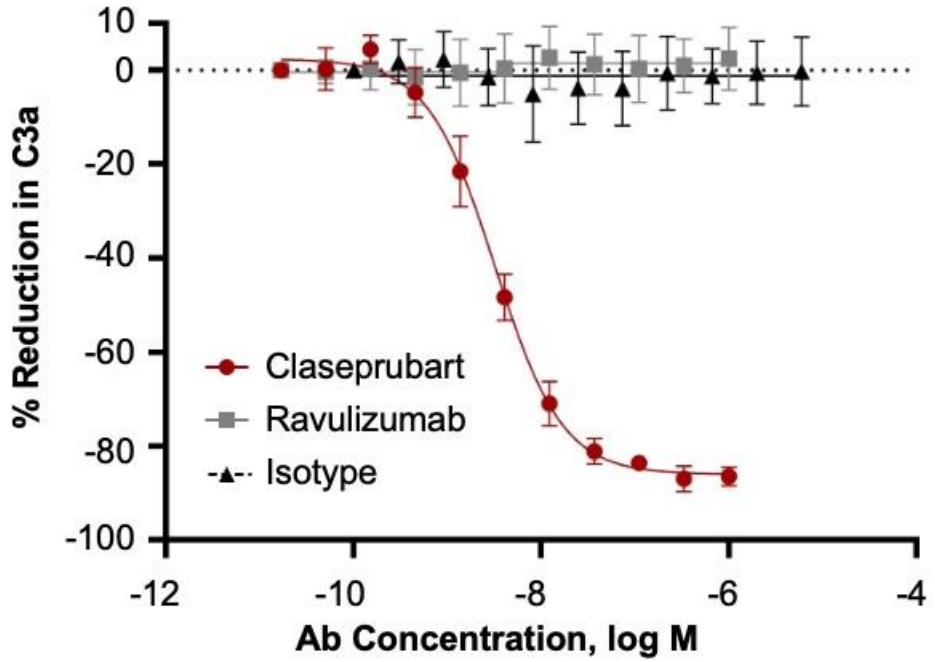
C3a	C3b
• Anaphylotoxin[2,3] • Initiates mast cell degranulation[4] • Promotes neutrophil-mediated acute phase reactions[5] driven by pro-inflammatory cytokines[6] – particularly IL-6 in gMG[7] • Has the potential to directly act on NMJ via smooth muscle contraction and endothelial permeability[8]	• Opsonin[3] • Forms part of an amplification loop that perpetuates a cycle of complement activation[3] • Facilitates integrin-mediated phagocytois[3]

AChR+, acetylcholine receptor-positive; gMG, generalized myasthenia gravis; IL, interleukin; NMJ, neuromuscular junction

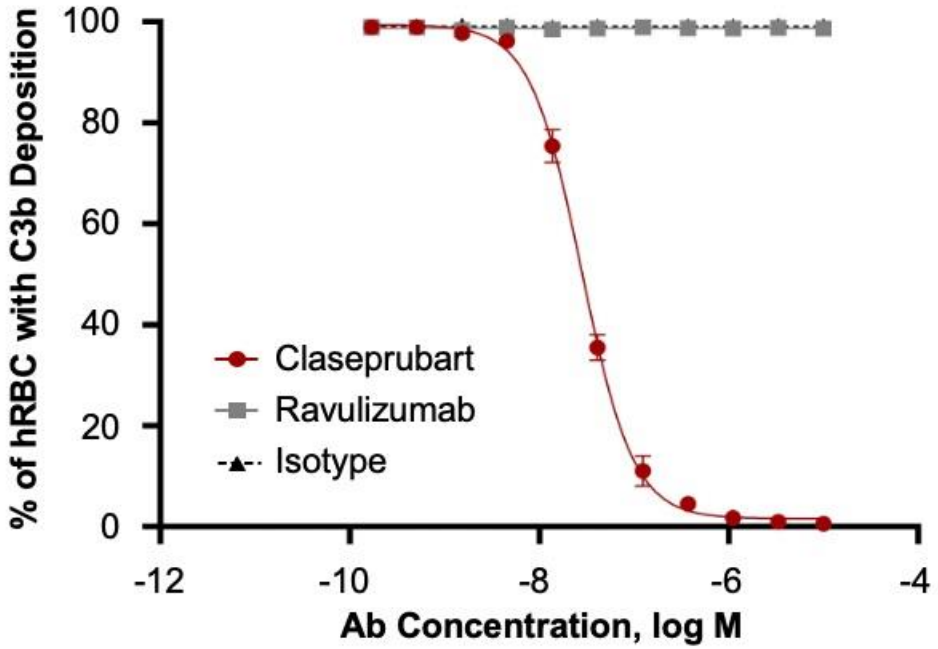
1. Stascheit F, et al. *Eur J Neurol* 2023;30:1409–16; 2. Iacomino N, et al. *Biomedicines* 2022;10; 3. Watanabe-Kusunoki K, Anders HJ. *J Autoimmun* 2024;145:103216; 4. Nilsson G, et al. *J Immunol* 1996;157:1693–8; 5. Riaz B, Sohn S. Cells 2023;12; 6. Wang Y, et al. J Neurol 2025;272:489; 7. Uzawa A, et al. J Neuroimmunol 2021;358:577634; 8. Drouin SM, et al. *J Immunol* 2001;166:2025–32; 2015;2:e119

Claseprubart potently prevents the creation of pro-inflammatory split products C3a And C3b vs ravulizumab

C3a Formation[1]



C3b Deposition[2*]



Upstream inhibition prevents the creation of C3a and C3b in addition to MAC, providing potential benefits beyond terminal inhibitors for AChR+ gMG patients

1. C3a Formation Assay: Human C3a ELISA specific to C3a-desArg with no cross-reactivity to C3 (N=3)
2. C3b Deposition Assay: Ab-sensitized hRBC triggered by complement-positive sera to deposit C3b on the hRBC surface, measured by flow cytometry (N=3)

*Enjaymo (sutimlimab) targets the C1s complement protein, which prevents C3b deposition on red blood cells, thereby stopping hemolysis and improving anemia in patients with cold agglutinin disease (Jager U, et al. Blood 2019;133:893–901)

Presentation at the AANEM Annual Meeting, October 29 – November 1, 2025, San Francisco, California

Top-line results for MaGic, a phase 2 trial of claseprubart (DNTH103), an active C1s inhibitor, in generalized myasthenia gravis

MAGIC

Pushpa Narayanaswami,* Sankalp Gokhale, Caitlin M Briggs, Uzma Siddiqui, Simrat Randhawa, Matt I Truman, Luke Hickey, Shahar Shelly, Stojan Peric, Tuan Vu, John Vissing

***Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, United States**

Claseprubart is an investigational agent that is not approved as a therapy in any indication in any jurisdiction worldwide.

Disclosures

Pushpa Narayanaswami has received research support from AHRQ, PCORI, NIH, Alexion.

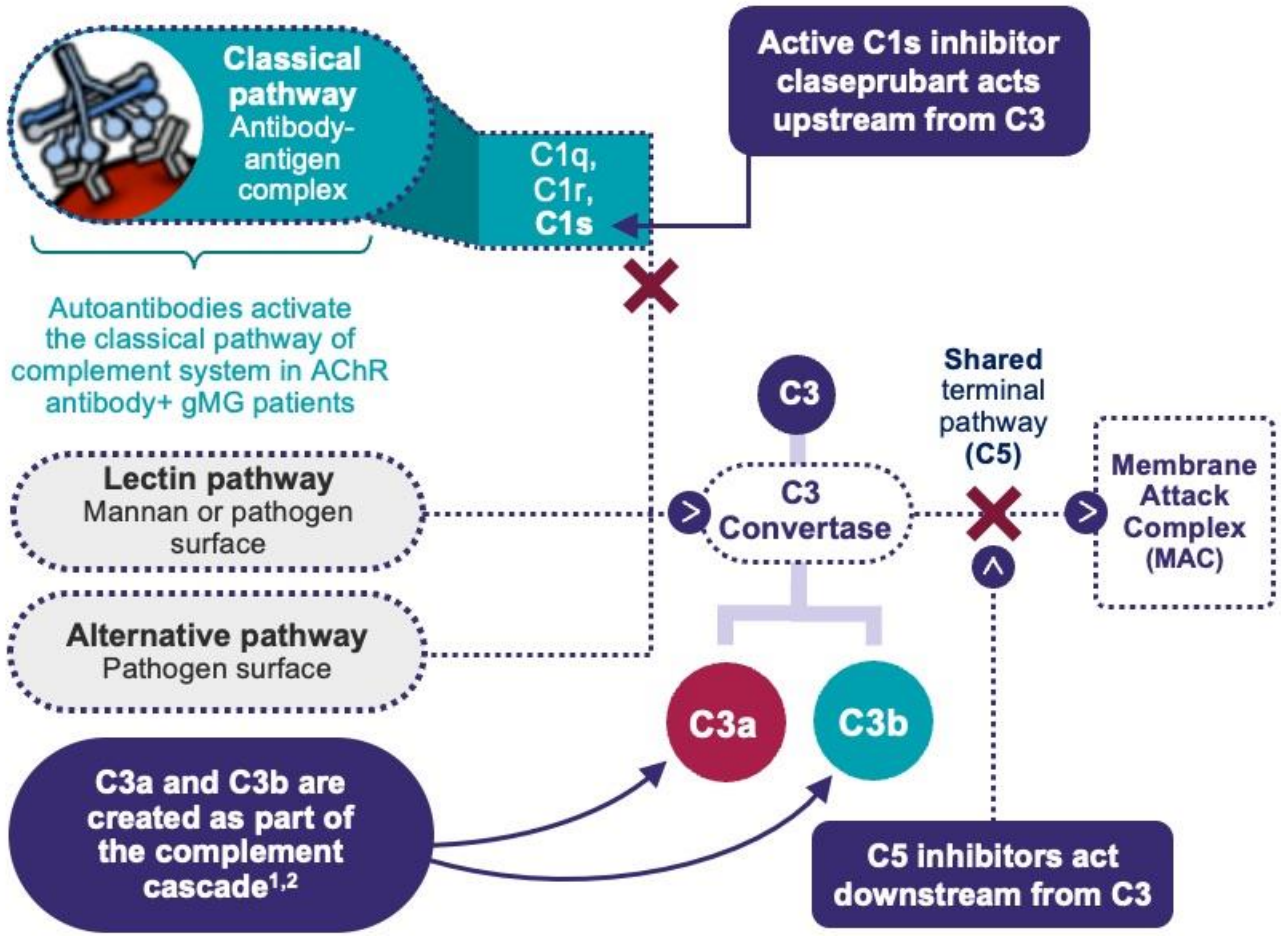
She has served as advisor/consultant for Alexion/ Astra-Zeneca, Argenx, Amgen, Cartesian, CVS, Dianthus Therapeutics, EMD-Serono, GSK, Immuneabs, Immunovant, Johnson & Johnson, Novartis, UCB, Viridian.

She serves on Data Monitoring Boards for Sanofi (ended), Argenx, NMD-pharma.

She receives royalties from Springer Nature.

Introduction

- Claseprubart (DNTH103) targets the classical complement pathway through active C1s (aC1s) inhibition.
- Claseprubart is the first aC1s inhibitor evaluated in generalized myasthenia gravis (gMG).
- Unlike C5 inhibition, which blocks all complement pathways (classical, lectin, and alternative) downstream, claseprubart aC1s inhibition specifically targets the classical pathway upstream, offering a more focused approach, with the potential to reduce the activity of upstream components, including C3a and C3b
- Claseprubart preserves lectin and alternative complement activity, which may address MG disease pathology while reducing the risk of severe encapsulated bacterial infections seen with broad C5 inhibition.



MaGic Trial: https://clinicaltrials.gov/study/NCT06282159

MaGic is a global Ph. 2 trial in AChR antibody + gMG patients

A global, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and PK/PD of claseprubart administered SC following initial loading dose

Highlights

- **Design:** ~60 male and female subjects randomized to receive either claseprubart or placebo for 13 weeks
- **Inclusion:** ≥18 years old with AChR antibody+ gMG
- **Dosing:** 15 or 20mg/kg IV loading dose followed by 300mg or 600mg SC Q2W starting Day 7

Endpoints

- **Primary:** Safety
- **Secondary/exploratory:** Efficacy (MG-ADL, QMG MSE, MGC, MG-QoL-15r)

MAGIC

Trial enrollment exceeded target, with 65 participants enrolled

MaGic Trial: https://clinicaltrials.gov/study/NCT06282159

AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis score; MGC, Myasthenia Gravis Composite score); Q2W, once every 2 weeks; QoL15r, Quality of Life scale; RCT, randomized, controlled trial; SC, subcutaneous

Participant baseline characteristics were generally well balanced across arms

AChR antibody + gMG participants	Placebo (N=22)	Claseprubart 300mg Q2W (N=21)	Claseprubart 600mg Q2W (N=22)
Age, mean (SD), years	52.2 (16.5)	57.1 (13.7)	55.3 (12.0)
Male, n (%)	13 (59%)	14 (67%)	10 (45%)
Weight, mean (SD), pounds	195.0 (48.0)	192.5 (35.5)	179.0 (35.4)
Duration of disease, median (range), years	7.7 (0.4–21.2)	3.0 (0.5–22.1)	7.6 (1.0–37.3)
MG-ADL score at baseline, mean (SD)	8.5 (2.9)	8.2 (2.2)	8.4 (2.6)
QMG score at baseline, mean (SD)	14.2 (5.8)	12.2 (2.7)	12.2 (3.6)
MG Composite score at baseline, mean (SD)	15.0 (7.8)	16.3 (4.5)	16.0 (5.3)
MG-QoL-15r score at baseline, mean (SD)	14.3 (7.0)	15.4 (6.6)	14.9 (5.9)
MGFA class at screening, n (%)			
II	7 (32%)	11 (52%)	12 (55%)
III	12 (55%)	10 (48%)	9 (41%)
IVa	3 (14%)	0 (0%)	1 (5%)
Prior thymectomy, n (%)	8 (36%)	6 (29%)	7 (32%)
Baseline corticosteroid use, n (%)	19 (86%)	17 (81%)	20 (91%)
Number of ISTs at baseline, n (%)			
1	11 (50%)	10 (48%)	12 (55%)
>1	11 (50%)	11 (52%)	10 (45%)
FcRn use in prior 24 months, n (%)	0 (0%)	1 (5%)	0 (0%)
Prior complement use, n (%)	0 (0%)	0 (0%)	0 (0%)

gMG, generalized myasthenia gravis; SD, standard deviation; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; QMG, Quantitative Myasthenia Gravis score; MGFA, Myasthenia Gravis Foundation of America clinical classification; IST, immunosuppressive therapy; MGC, Myasthenia Gravis Composite; MG-QOL-15r, Myasthenia Gravis quality of life 15 revised.

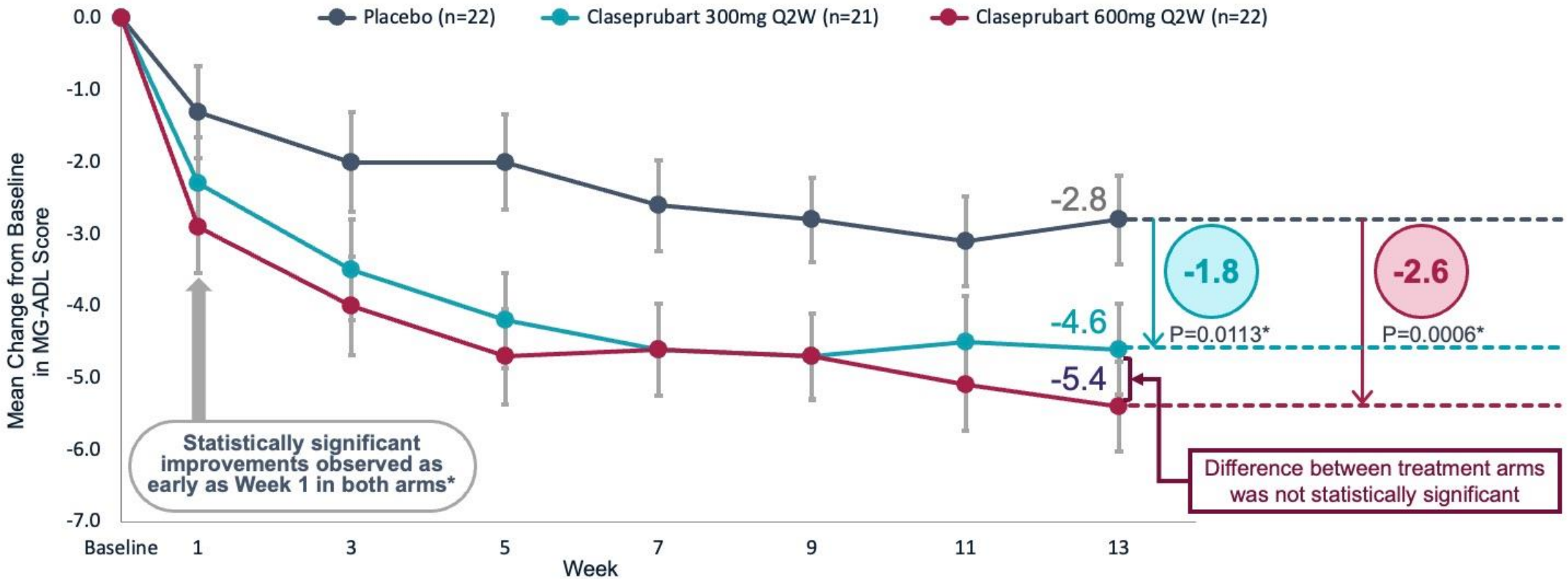
Claseprubart was generally well tolerated, with a favorable, potentially differentiated safety profile in Phase 2

	Placebo (N=22)	Claseprubart 300mg Q2W (n=21)	Claseprubart 600mg Q2W (n=22)
Clinical adverse events (AEs)[1]	11 (50.0%)	13 (61.9%)	15 (68.2%)
Related serious AEs	1 (4.5%)	0 (0%)	0 (0%)
RCT discontinuation due to related AE	0 (0%)	0 (0%)	0 (0%)
Infections	10 (45.5%)	5 (23.8%)	6 (27.3%)
Related serious infections	1 (4.5%)	0 (0%)	0 (0%)
Injection site reactions[2]	0 (0%)	2 (9.5%)	2 (9.1%)
Newly positive for anti-nuclear antibodies (ANA)[3]	0 (0%)	1 (5.9%)	8 (36.4%)
Rashes	0 (0%)	0 (0%)	0 (0%)
Arthralgia	1 (4.5%)	1 (4.8%)	0 (0%)

Comparable clinical safety profile to placebo with remarkably benign administration, no infection signal and no symptoms indicative of autoimmune activation

(1) Excludes events in the investigations System Organ Class (MedDRA).
(2) All injection site reactions were mild to moderate.
(3) Represents participants who were ANA negative at baseline and tested positive at ≥1:320 at any point during RCT (percentages calculated from n=17 for 300mg arm and n=22 for 600mg arm). An ANA titer of ≥1:320 was an exclusion criterion for the clinical trial protocol. At end of RCT (Week 13), 2 of the 8 patients in 600mg arm tested negative for ANA, 2 of the 8 patients in 600mg arm remained positive but at <1:320.

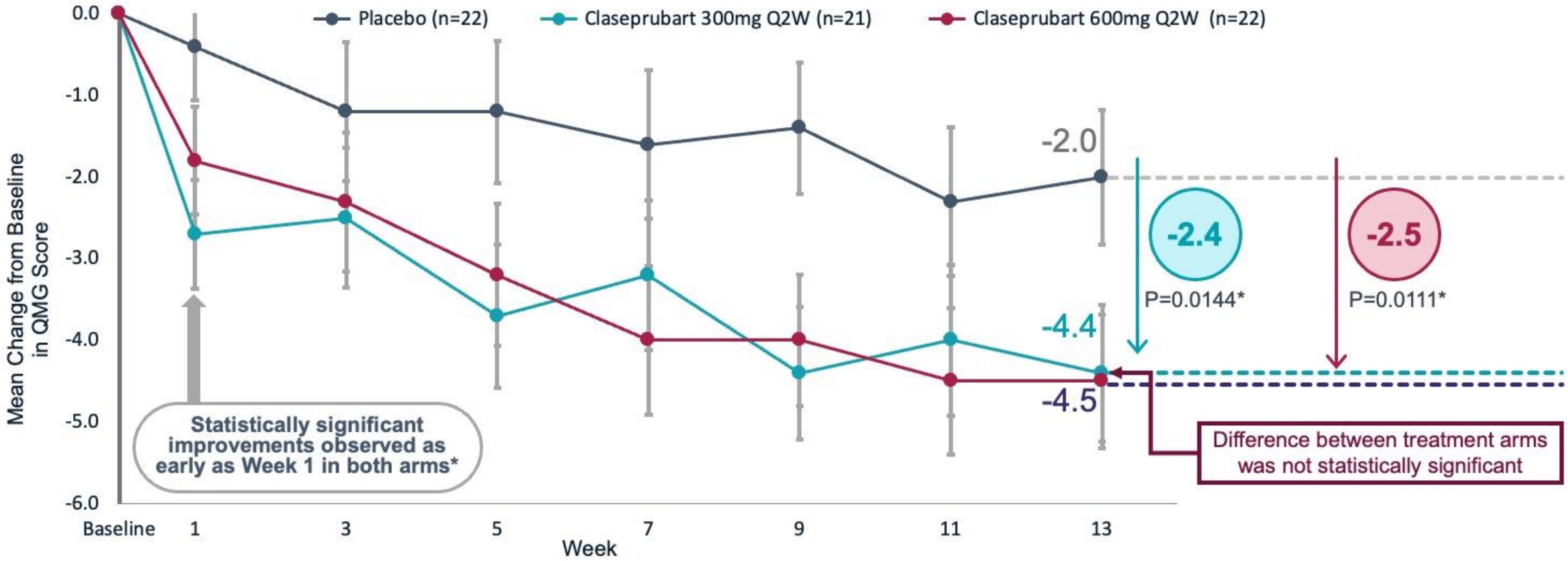
Claseprubart arms demonstrated rapid, sustained, and clinically meaningful improvements in MG-ADL score



MG-ADL improvements for participants treated with claseprubart were rapid, sustained, clinically meaningful and statistically significant as early as Week 1

The change from baseline in MG-ADL was analyzed using a mixed effect model for repeated measures (MMRM) with treatment group, visit, treatment by visit interaction, stratification factors, and baseline measure included.
Bars represent standard error of the mean.
*One-sided p-values are presented for comparisons of claseprubart vs placebo, with any p-value below 0.1 considered nominally statistically significant.

Claseprubart arms demonstrated rapid, sustained, and clinically meaningful improvements in QMG score



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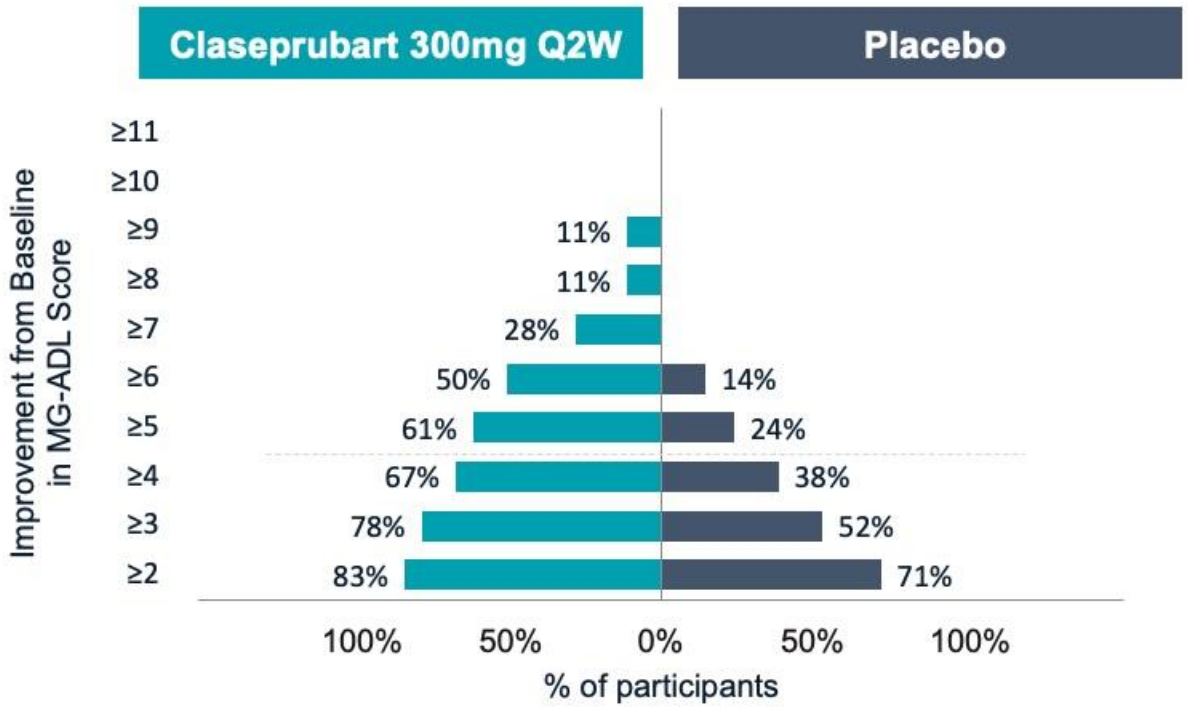
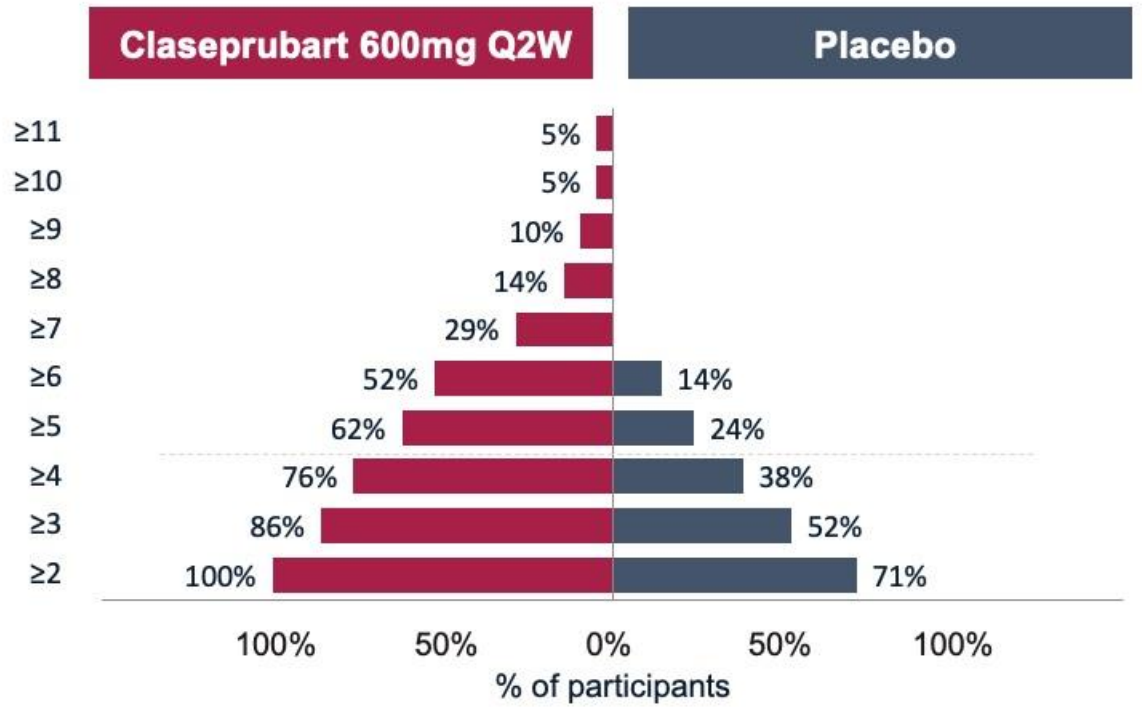
>60% of participants on claseprubart 300mg and 600mg achieved ≥5 point improvement in MG-ADL

Improvement in MG-ADL Total Score

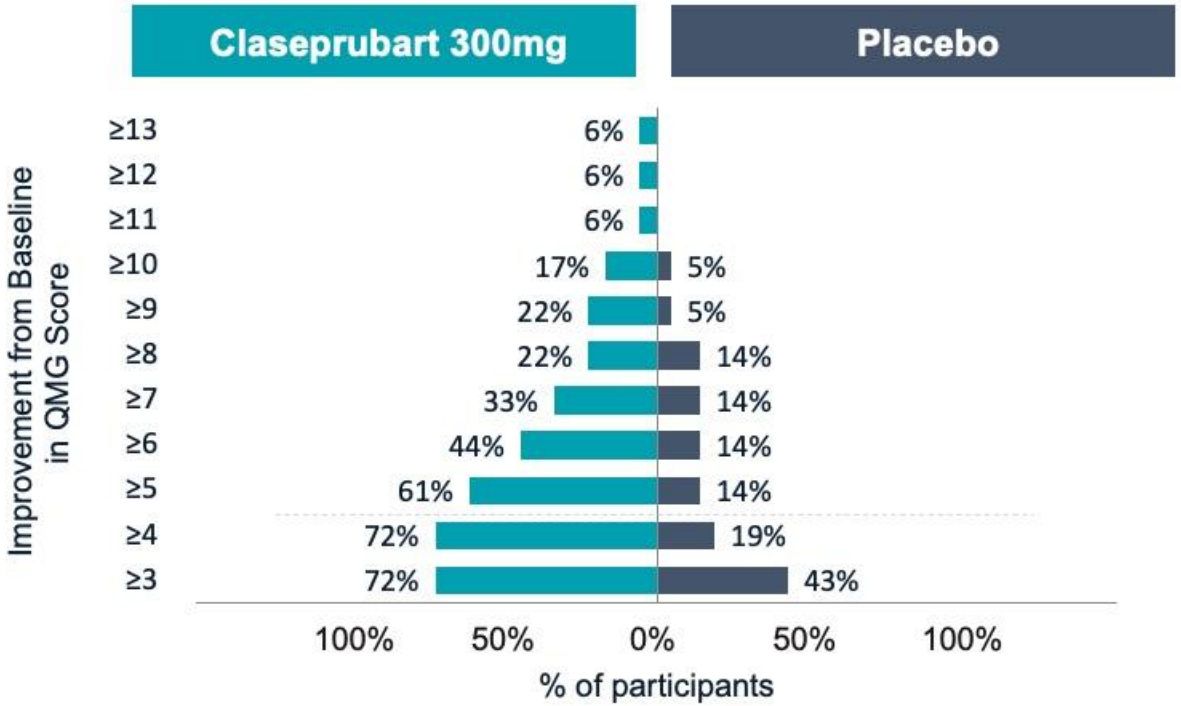


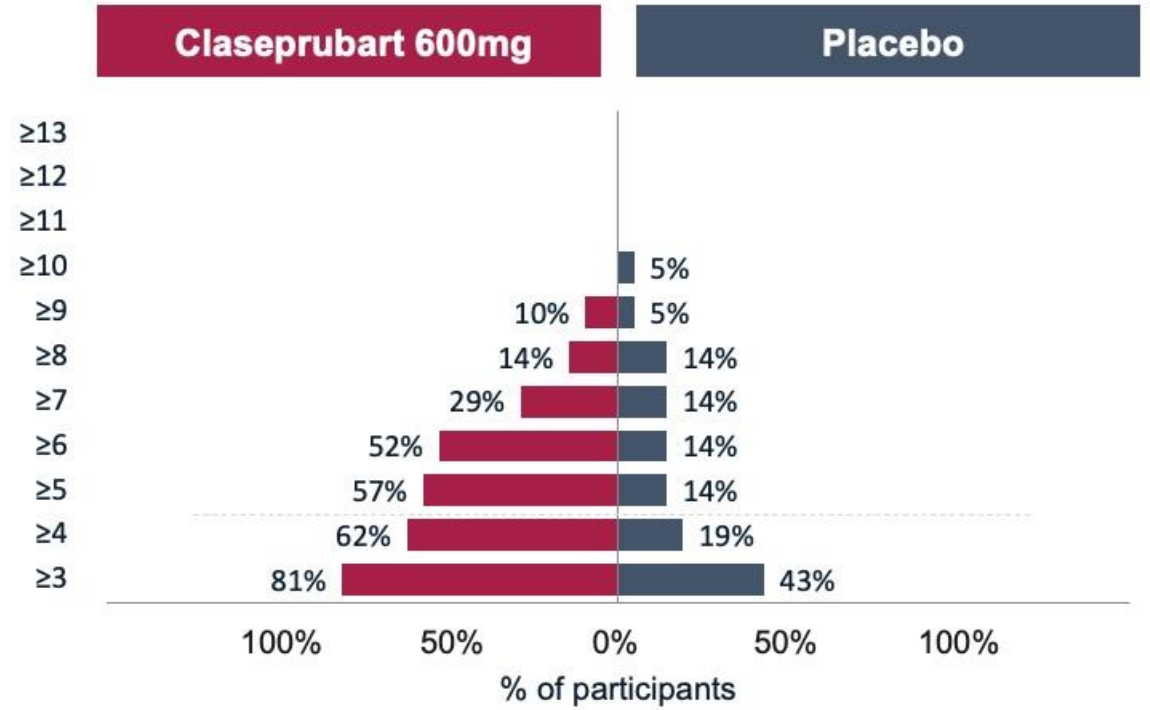


Participants across both treatment arms achieved robust improvements in MG-ADL at Week 13

>60% of participants on claseprubart 300mg achieved ≥5 point improvement in QMG

Improvement in QMG Total Score

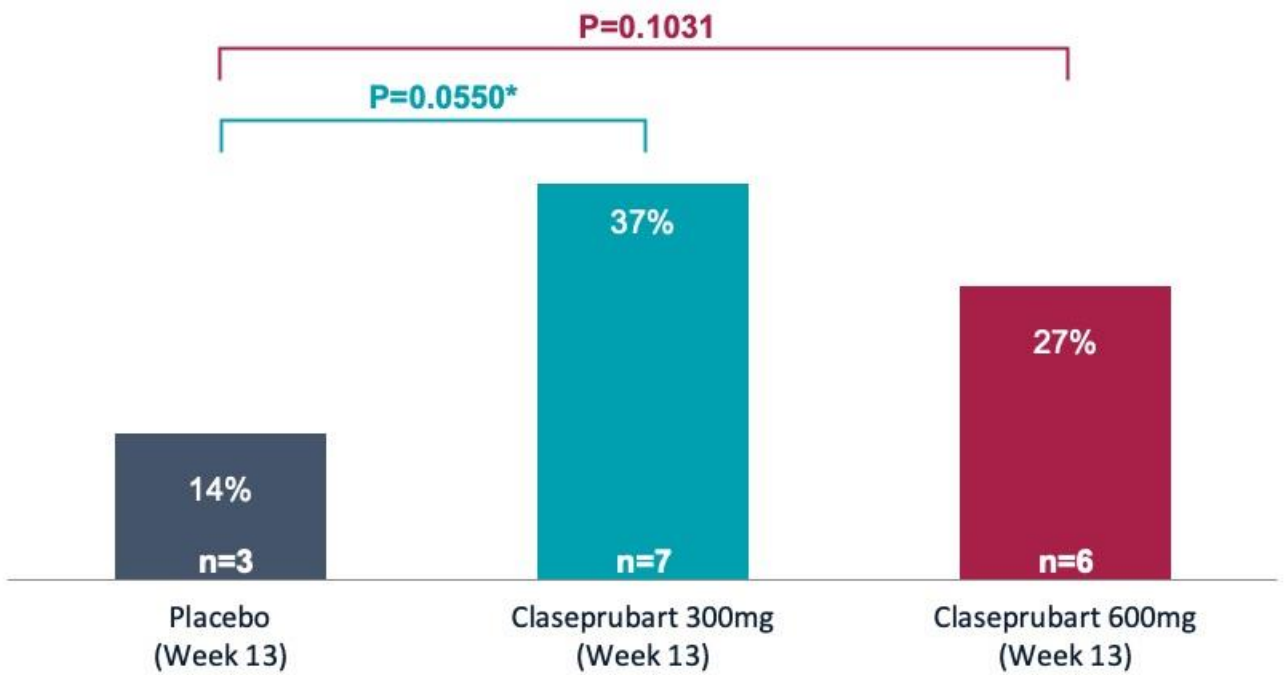




Participants across both treatment arms achieved robust improvements in QMG at Week 13

37% of 300mg claseprubart-treated participants achieved Minimal Symptom Expression on MG-ADL at Week 13

Minimal Symptom Expression (MSE)
% of Participants Achieving MG-ADL Score of 0 or 1 at Week 13



The proportion of participants who achieve MSE was analyzed using a logistic regression with terms for treatment group, stratification factors, and baseline MG-ADL included.
*One-sided p-values are presented for comparisons of claseprubart vs placebo, with any p-value below 0.1 considered nominally statistically significant.

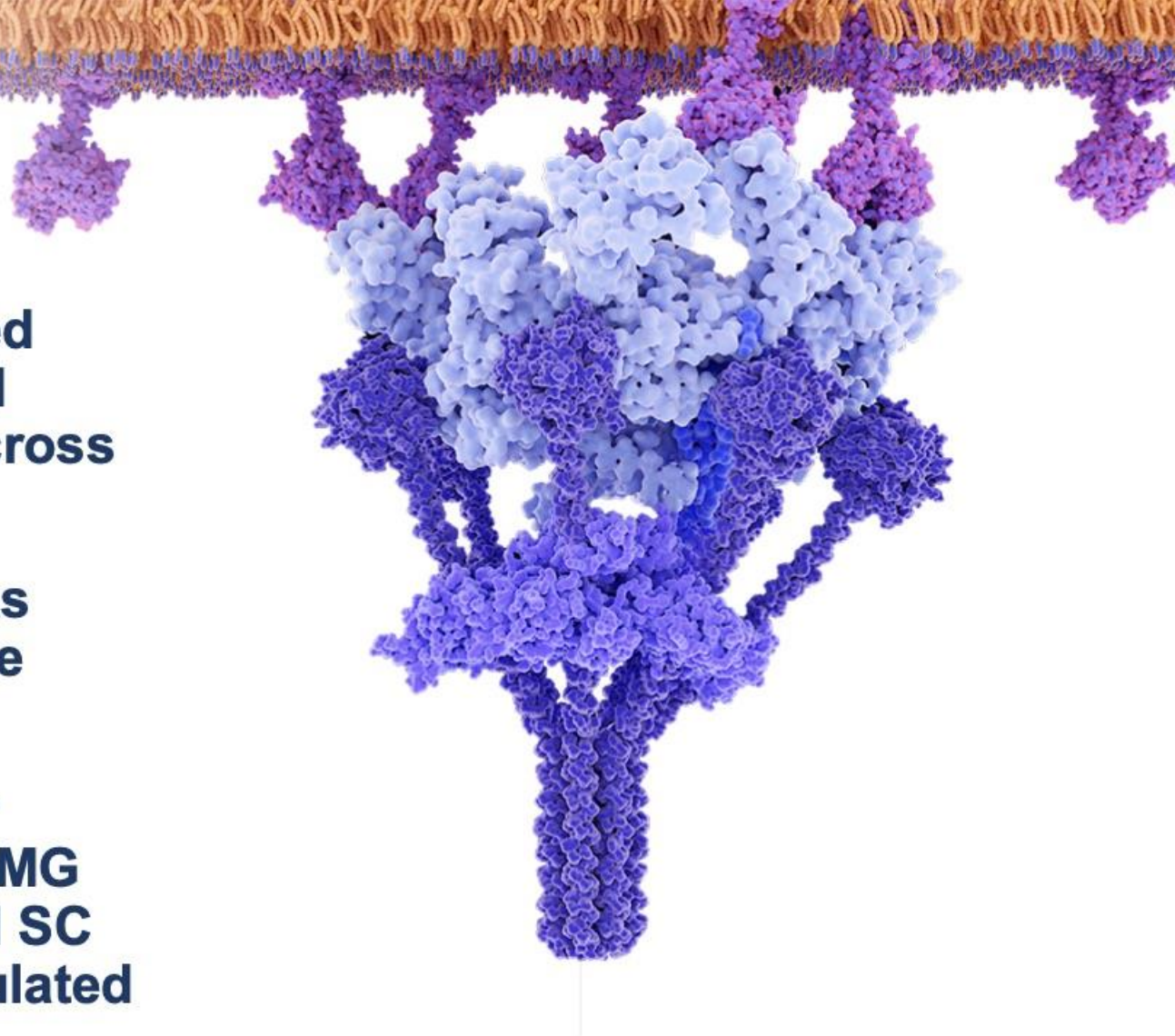
Across key efficacy measures, claseprubart demonstrated equally robust and clinically meaningful responses

	Placebo	Claseprubart 300mg Q2W		Claseprubart 600mg Q2W	
		Absolute	Placebo-adjusted	Absolute	Placebo-adjusted
MG-ADL mean change from baseline at Week 13	-2.8	-4.6	-1.8 *(P=0.0113)**	-5.4	-2.6 *(P=0.0006)**
QMG mean change from baseline at Week 13	-2.0	-4.4	-2.4 *(P=0.0144)**	-4.5	-2.5 *(P=0.0111)**
MSE at Week 13	14%	37%	23% *(P=0.0550)**	27%	13% *(P=0.1031)*
MGC mean change from baseline at Week 13	-3.1	-8.7	-5.6 *(P=0.0008)**	-8.6	-5.5 *(P=0.0008)**
MG-QoL-15r mean change from baseline at Week 13	-3.9	-6.1	-2.2 *(P=0.0414)**	-5.4	-1.5 *(P=0.1122)*

Claseprubart 300mg Q2W treatment arm achieved statistical significance vs. placebo across all five key efficacy measures

*One-sided p-values are presented for comparisons of claseprubart vs placebo, with any p-value below 0.1 considered nominally statistically significant.

Conclusions



- **Claseprubart treatment was well tolerated and resulted in clinically meaningful and statistically significant improvements across key assessments**
- **The benefit/risk profile of both doses was similar, supporting research focus on the lower dose**
- **Claseprubart has the potential to deliver meaningful benefit to AChR antibody+ gMG patients via infrequent self-administered SC injections and a reduced risk of encapsulated bacterial infections versus C5 inhibitors**

AChR, acetylcholine receptor; gMG, generalized myasthenia gravis; Q2W, once every other week; Q4W, once every 4 weeks; SC, subcutaneous

THANK YOU TO ALL OUR PATIENT PARTICIPANTS
MaGic Principal Investigators

Ana Azanjac-Arsic
Cynthia Bodkin
Urszula Chyrchel-Paszkiewicz
Gordana Djordjevic
Dori, Amir
Erik Ensrud
Marc Feinberg
Laura Fionda
Folkens, Eric
Miriam Freimer
Nils Gilhus
Raghav Govindarajan
Mariusz Grudniak
Kelly Gwathmey

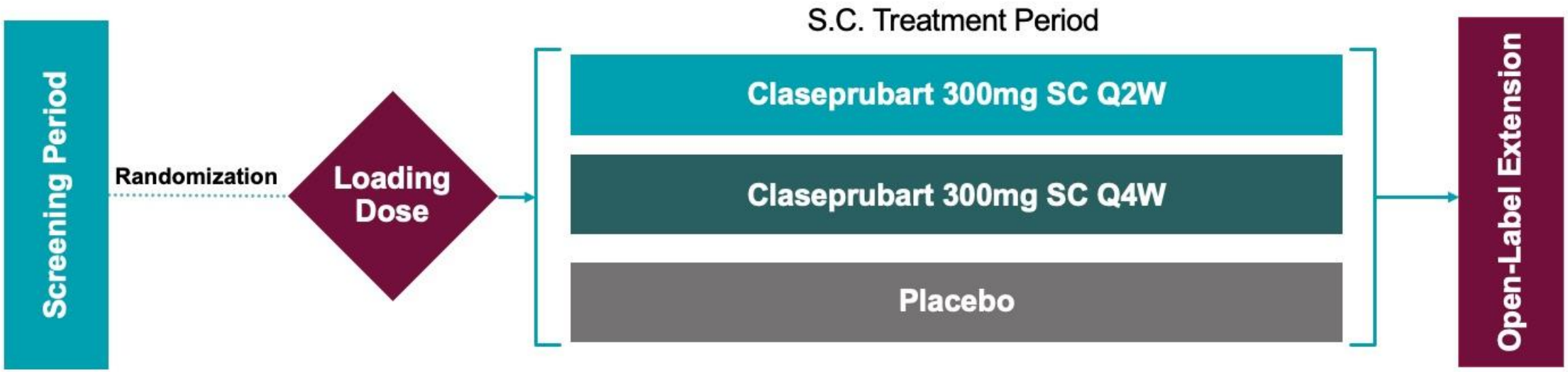
Ali Habib
Petr Hon
Andreea Illinca
Raffaele Iorio
Arnaldo Isa
Gustavo Jose
Zita Jovin
Agnieszka Kulaga
Hani Kushlaf
Susana del Valle Liwacki
Lopez, Pablo
Michelangelo Maestri Tassoni
Lorenzo Maggi
Peter McAllister

Aleksandra Nadaj-Pakleza
Pushpa Narayanaswami
Thy Nguyen
Michael Nicolle
Fatima Pagani Cassara
Mamatha Pasnoor
Stojan Peric
Dragana Petrovska Cvetkovska
Maria Philip
Nicolai Preisler
Roberto Daniel Rey
Lukasz Rzepinski
Ahmad Sabouni
Francesco Sacca

Sabrina Sacconi
Amit Sachdev
Radi Shahien
Aziz Shaibani
Shahar Shelly
Sheetal Shroff
Kumaraswamy Sivakumar
Agnieszka Slowik
Marek Smilowski
Guilhem Sole
Adnan Subei
Dario Tavolini
Anneke J van der Kooi
Tuan Vu
James Winkley

Phase 3 trial design pending regulatory feedback

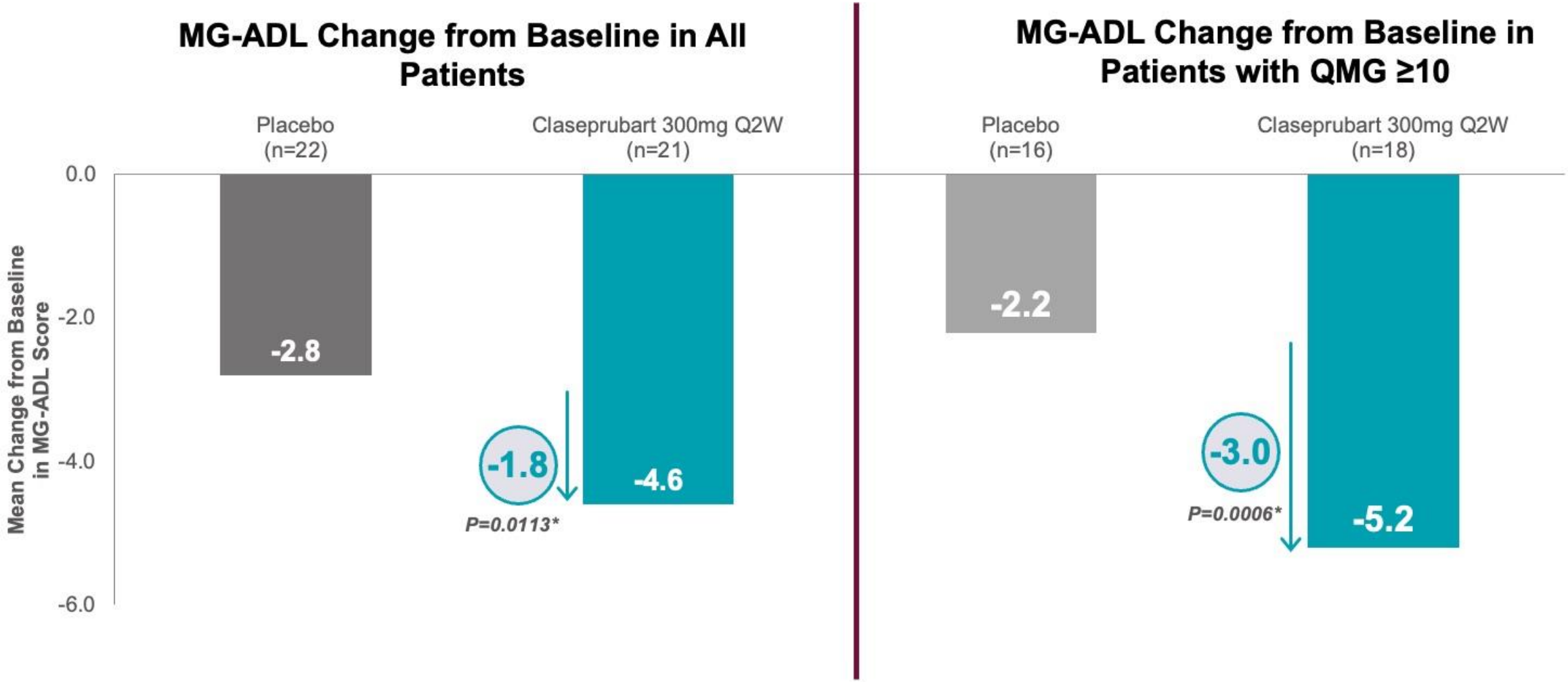
Evaluate 300mg Q4W based on early PK/PD data from Phase 2 OLE



- **Primary Endpoint:** Change from Baseline to end of RCT in Myasthenia Gravis Activities of Daily Living (MG-ADL) scale score
- **Key Inclusion criteria:**
  - Adult males and females, between the ages of 18 - 80 years of age at screening.
  - Myasthenia Gravis Activities of Daily Living (MG-ADL) 6 or more, both at screening and confirmed prior to randomization.
  - Quantitative Myasthenia Gravis assessment score: ≥10, both at screening and confirmed prior to randomization.

PD, pharmacodynamics; PK, pharmacokinetics; Q2W, once every other week; Q4W, once every 4 weeks; SC, subcutaneous; TBD, to be determined

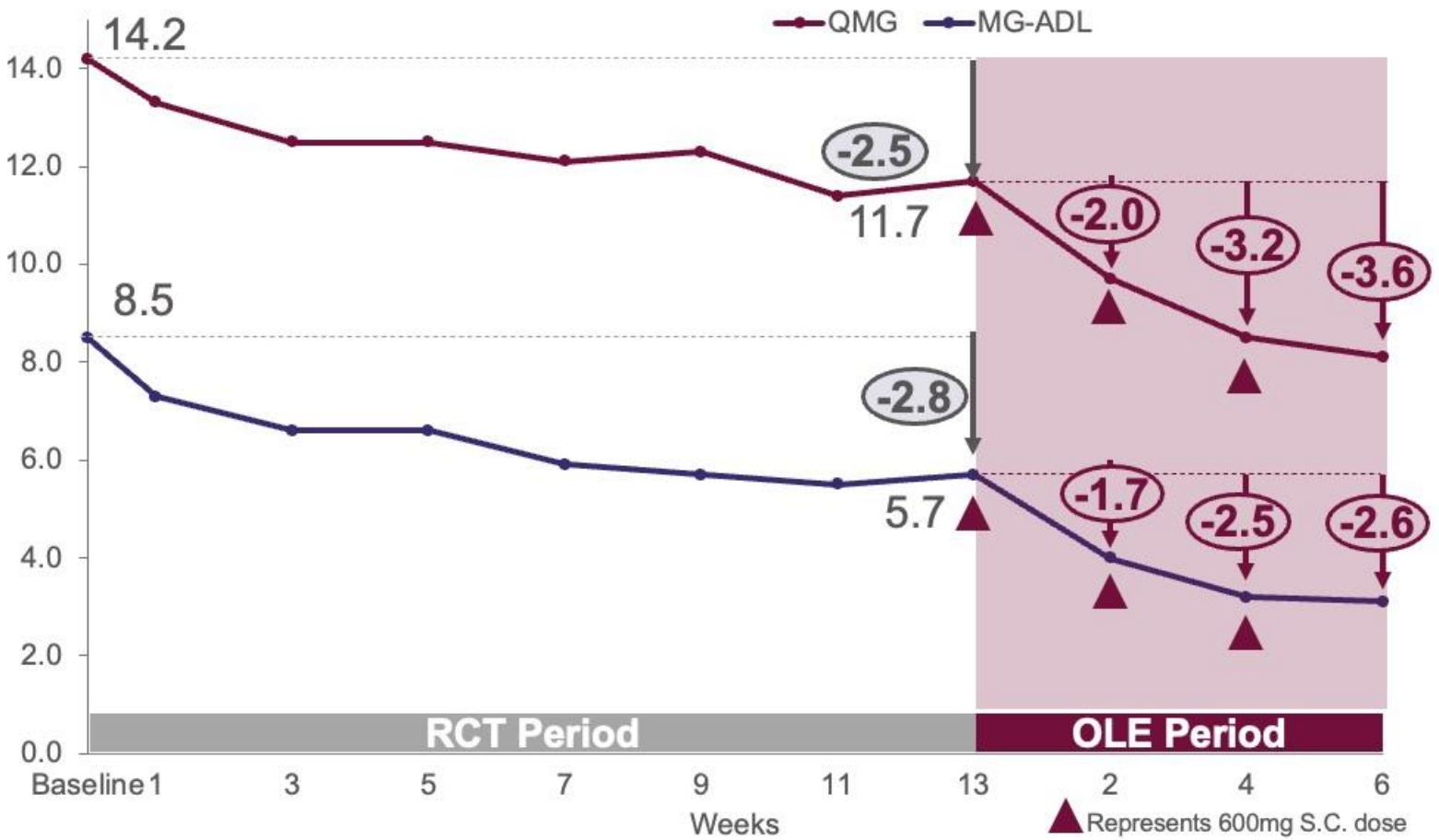
Mean change in MG-ADL score from baseline at week 13 in patients with QMG ≥10



The change from baseline in ADL was analyzed using a mixed effect model for repeated measures (MMRM) with treatment group, visit, treatment by visit interaction, stratification factors, and baseline measure included.
*One-sided p-values are presented for comparisons of claseprubart vs placebo, with any p-value below 0.1 considered nominally statistically significant.

Rationale for adding 300mg Q4W in addition to 300mg Q2W in future ph. 3 study

Mean Change in MG-ADL and QMG Score from RCT Baseline to OLE Week 6



OLE Data Support 300mg Q4W Dosing in Future Ph. 3 Study

- Placebo patients switching over to OLE receive 600mg Q2W with no loading dose
- PK of ~65 µg/mL after two 600mg Q2W doses is substantially lower than estimated 300mg Q2W steady state PK of 100-120 µg/mL
- Following two 600mg Q2W doses, maximum reduction in MG-ADL is achieved and is stable in subsequent weeks
- Growing evidence that lower levels of complement inhibition (<90%) may be sufficient for efficacy in gMG[1]

The change from RCT baseline in MG-ADL and QMG were separately analyzed using a mixed effect model for repeated measures (MMRM) with randomized treatment group, visit, randomized treatment by visit interaction, stratification factors, and baseline measure included. All patients received claseprubart in OLE.

[1] https://newsroom.regeneron.com/node/31216/pdf