American Academy of Neurology 2025 Annual Meeting

April 9, 2025

Efficacy and Safety of Autologous BCMA-directed mRNA CAR T-Cell Therapy in Generalized Myasthenia Gravis: Results from a Phase 2b Randomized Placebo-controlled Trial

Tuan Vu, Hacer Durmus Tekce, Michael Rivner, Sheetal Shroff, Thomas Ragole, Bennett Myers, Mamatha Pasnoor, George Small, Chafic Karam, Mithila Vullaganti, Amanda Peltier, Gregory Sahagian, Marc H. Feinberg, Adam Slansky, Carolina Barnett-Tapia, Zaeem Siddiqi, Milos D. Miljkovic, Hafsa Kamboh, Tahseen Mozaffar, James F. Howard, Jr, for the MG-001 Study Team.

COI Disclosures

- Consultant and/or on speaker bureaus for Alexion/AstraZeneca Rare Disease, Amgen, argenx, CSL Behring, Dianthus, ImmunAbs, NMD Pharma, and Johnson & Johnson.
- Research or grant support related to myasthenia gravis from Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesians, COUR, Dianthus, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron, and UCB.

Myasthenia gravis is a rare, progressive autoimmune disease with significant unmet need

>120,000

Patients in the U.S. and EU

Significant unmet need remains

Characterized by debilitating fatigue and muscle weakness

Limbs

Respiratory

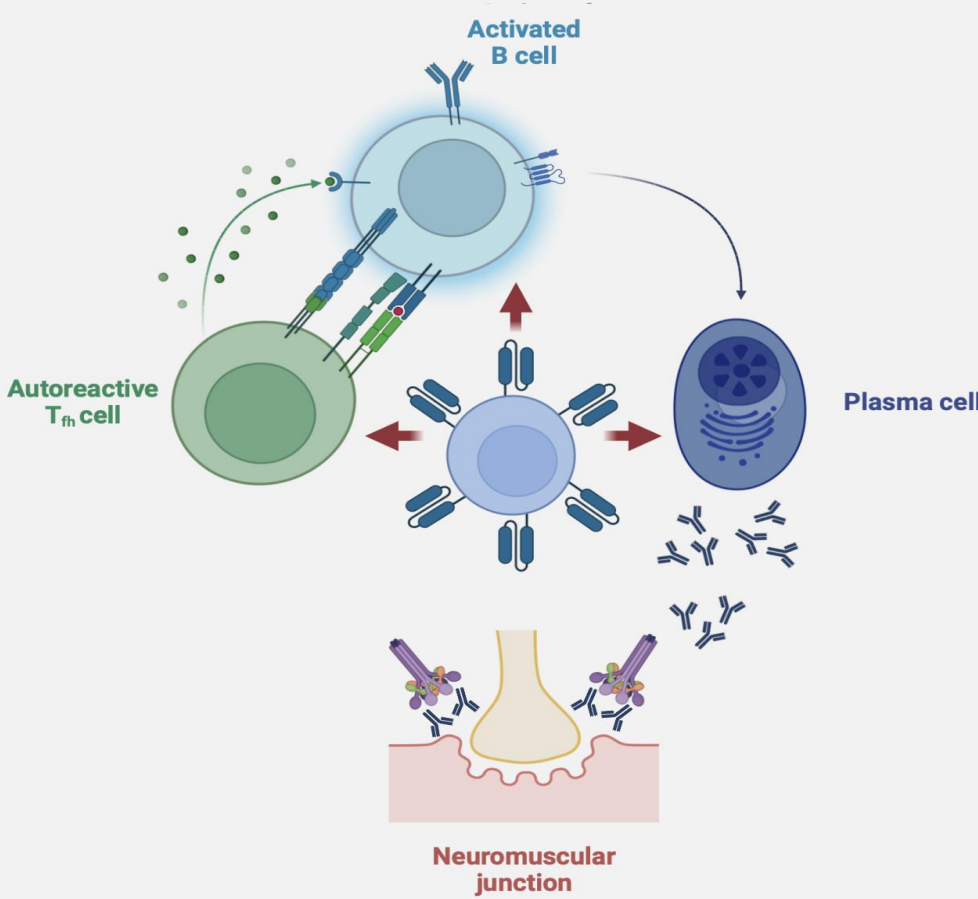
Ocular

Facial

Current treatments require chronic or frequent administration and have limited durability

Descartes-08 is an autologous BCMA-directed mRNA CAR-T in clinical development for gMG

- **Engineered by transfection of autologous CD8+ T cells with mRNA encoding anti-BCMA CAR**
  - **B-cell Maturation Antigen (BCMA)**, a surface antigen preferentially expressed on plasma cells, plasmablasts and plasmacytoid dendritic cells
  - **BCMA can be dysregulated in autoimmune conditions** leading to excessive autoantibody production
  - Descartes-08 was designed to target and delete BCMA+ cells
- **Granted U.S. FDA orphan and RMAT designations for generalized myasthenia gravis**



FDA, Food and Drug Administration
RMAT, Regenerative Medicine Advanced Therapy

mRNA CAR-T engineering may expand the reach of potent cell therapy products to address potential autoimmune indications

No Lymphodepletion

No requirement for cell proliferation → no expected need for pre-treatment chemotherapy → no Grade 3-4 cytopenias

Administered Outpatient

Convenient dosing schedule

Reduced patient burden and lower indirect cost

Delivered at Therapeutic Levels

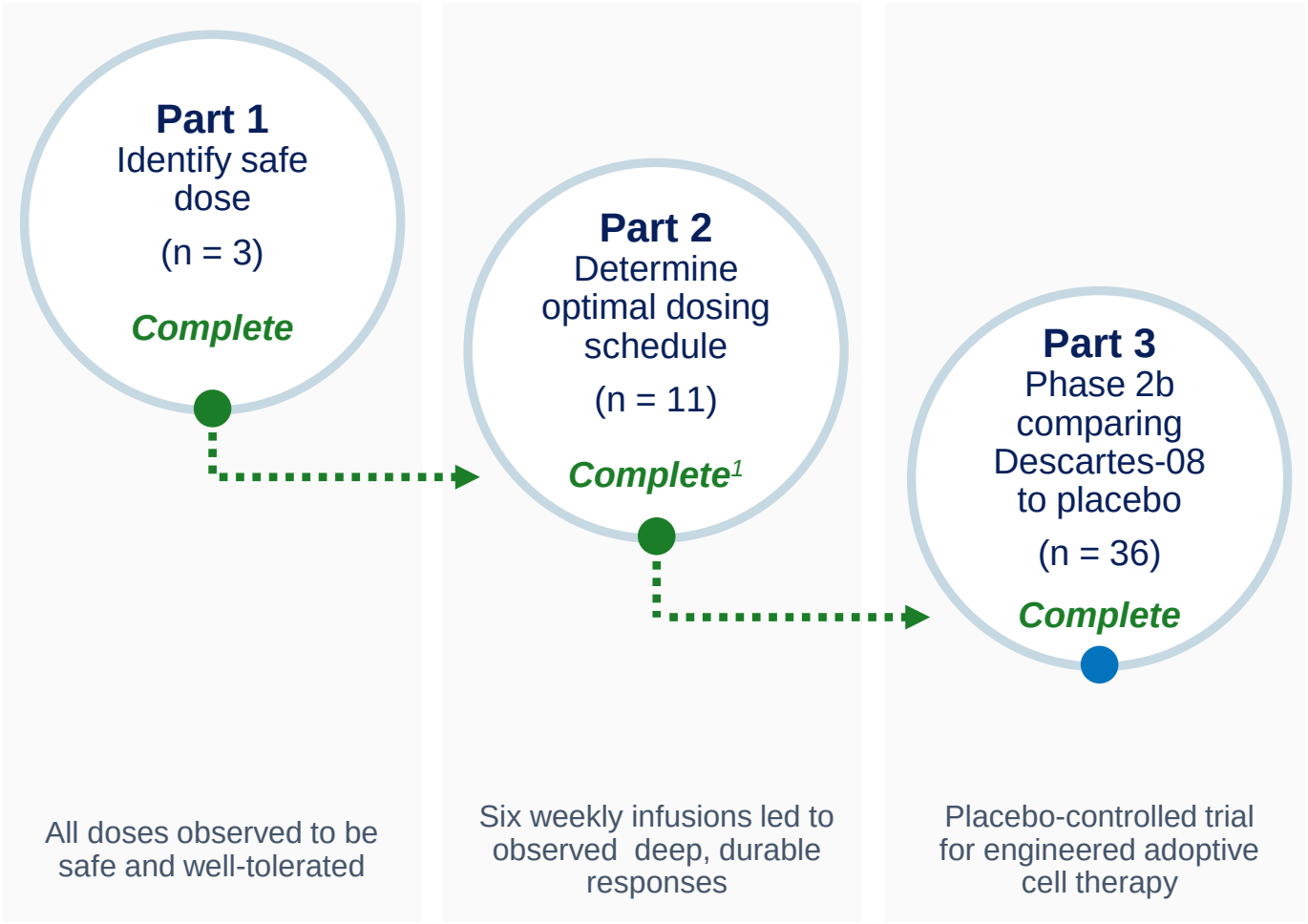
Administered at therapeutic doses without uncontrollable proliferation

mRNA does not replicate → predictable half-life

Transient Cell Modification

Does not carry risk of genomic integration

Phase 2 study of Descartes-08 in MG (NCT04146051)



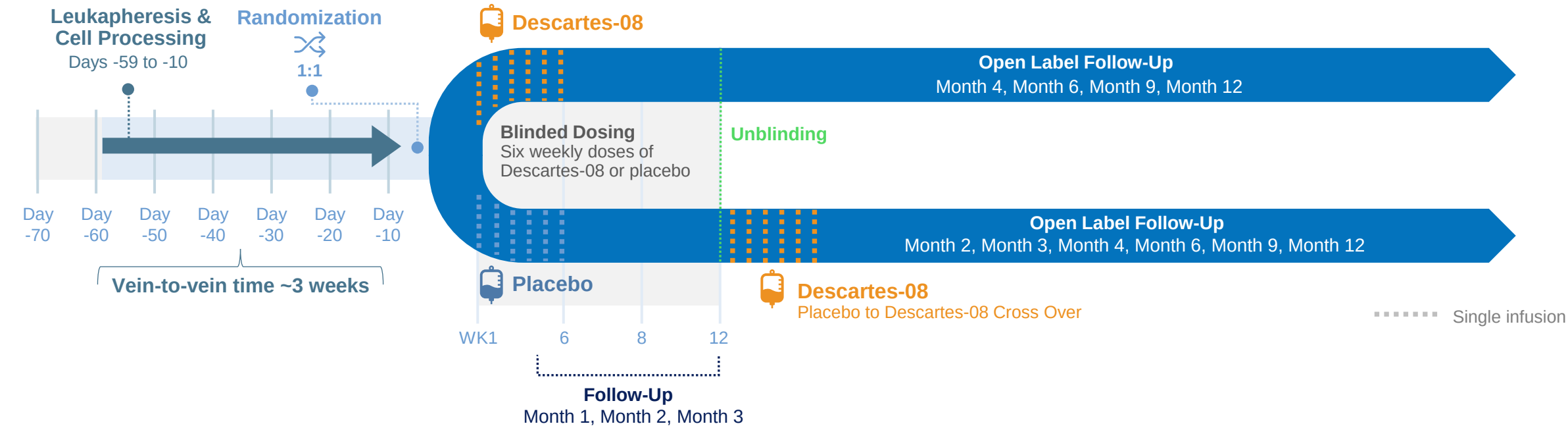
Patient eligibility

- Non-MuSK gMG
- MG-ADL ≥ 6
- MGFA Class II-IV
- Stable medication dosing ≥ 8 wks prior to infusion
- 4-week washout for certain biologics
- IVIg and plasma exchange not allowed after starting Descartes-08

Patients on MTX, MMF, AZA or complement inhibitors may continue their treatment while receiving Descartes-08

[1] Continues to enroll patients with MuSK MG and subjects who are otherwise not eligible for Part 3; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGFA, Myasthenia Gravis Foundation of America

Phase 2b trial: double-blind, placebo-controlled clinical trial of Descartes-08 in patients with myasthenia gravis



INCLUSION CRITERIA

- Non-MuSK-MG
- MGFA Class II-IV
- MG-ADL ≥6
- Severe disease despite stable doses of immunosuppressants

PRIMARY ENDPOINT

- Proportion of patients with MG Composite improvement of ≥5-points at Month 3, relative to placebo
- Predefined primary efficacy dataset

SECONDARY OBJECTIVES

- Safety and tolerability from predefined safety dataset
- Quantify clinical effect of Descartes-08 over 1 year
- QMG, MG QoL 15R, MG-ADL (change from baseline to Month 3)
- Effects of Descartes-08 versus placebo on MG scales (change from baseline to Month 3) in patients who cross over from placebo to Descartes-08

MGFA, Myasthenia Gravis Foundation of America
MG-ADL, Myasthenia Gravis Activities of Daily Living scale
MG QMG, Quantitative MG Scores
MG QoL 15R, MG Quality of Life 15-revised

Baseline characteristics

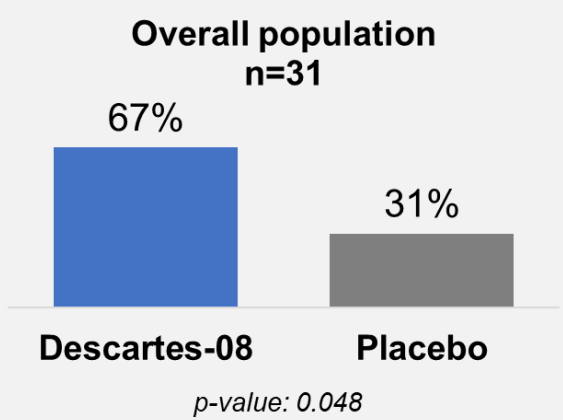
Highly symptomatic gMG patient population with severe disease

Characteristics		Descartes-08	Placebo	Total
Mean Age, Years (SD)		56.7 (16.7)	60 (13.4)	58.2 (15.0)
Sex, n (%)	Female	10 (71)	6 (50)	16 (62)
MGFA class at screening, n (%)	II III IV	4 (29) 9 (64) 1 (7)	3 (25) 9 (75) 0 (0)	7 (27) 18 (69) 1 (4)
Median age of disease onset	Years, (range)	55 (16-76)	50 (25-71)	51 (16-76)
Median duration of disease	Years, (range)	5 (2-23)	10 (4-26)	6 (2-26)
MG Antibody status , n (%)	Anti-AChR+ Anti-LRP4+ Seronegative[1]	10 (71) 1 (7) 3 (21)	9 (75) 0 (0) 3 (25)	19 (73) 1 (4) 6 (23)
Mean baseline scores (SD)	QMG MG-ADL MGC MG-QoL-15r	16.9 (7.2) 10.1 (2.9) 16.1 (6.4) 19.5 (7.7)	15.1 (4) 10.3 (3.2) 16.1 (4) 17.3 (4.7)	15.1 (4) 10.3 (3.2) 16.1 (5.4) 18.5 (6.5)
Previous myasthenia gravis therapies (standard of care), n (%)	Pyridostigmine Prednisone Other immunosuppressants Complement inhibitor FcRn antagonist	9 (64) 8 (57) 8 (57) 3 (21) 4 (29)	8 (67) 6 (50) 9 (75) 5 (42) 5 (42)	17 (65) 14 (54) 17 (65) 8 (31) ← 9 (35)
	Previous IVIG Previous plasma exchange Diagnosis of thymoma* Previous thymectomy Previous MG crisis requiring MV	10 (71) 3 (21) 0 (0) 3 (21) 2 (14)	10 (83) 6 (50) 5 (42) 7 (58) 0 (0)	20 (77) 9 (35) 5 (19) 10 (38) ← 2 (8)
MG ongoing therapy, n (%)	Pyridostigmine Prednisone Azathioprine Mycophenolate mofetil Complement inhibitor	9 (69) 8 (57) 5 (21) 2 (14) 1 (7)	7 (58) 4 (33) 1 (8) 5 (41) 2 (14)	16 (62) 12 (46) ← 4 (15) ← 7 (27) ← 3 (12) ←

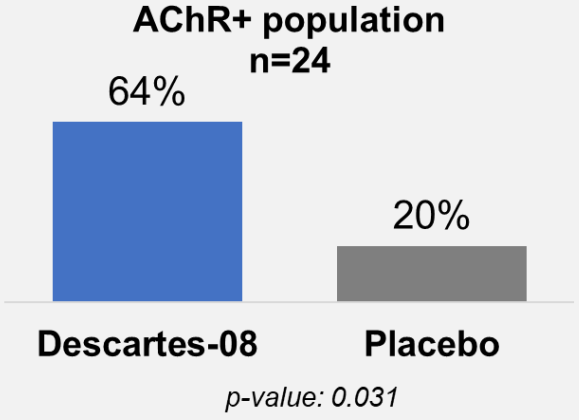
[1] for AChR, MuSK, and LRP4 antibodies; MGC=MG Composite; IVIG=intravenous immunoglobulin; MV=mechanical ventilation; ← for imbalance

Trial met primary endpoint with statistical significance

Proportion of MG Composite Responders (≥5-point reduction) at Month 3

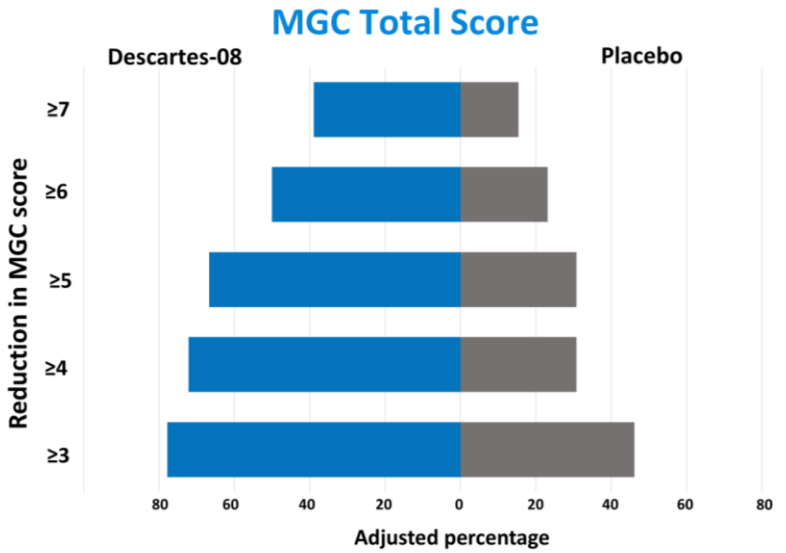


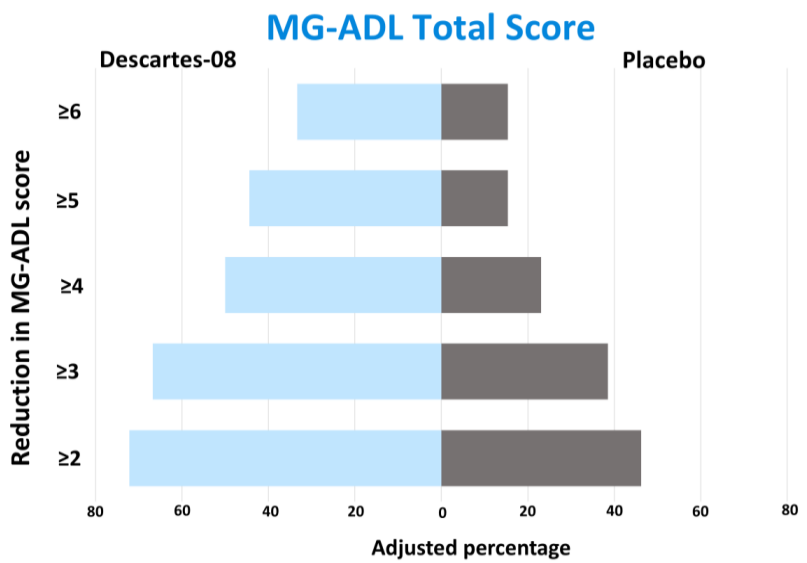
Per Protocol Responders: Descartes-08, n= 12/18; placebo, n=5/13



Per Protocol Responders: Descartes-08, n= 9/14; placebo, n=2/10

Minimum Point Improvement in MGC and MG-ADL at Month 3





Per Protocol Population

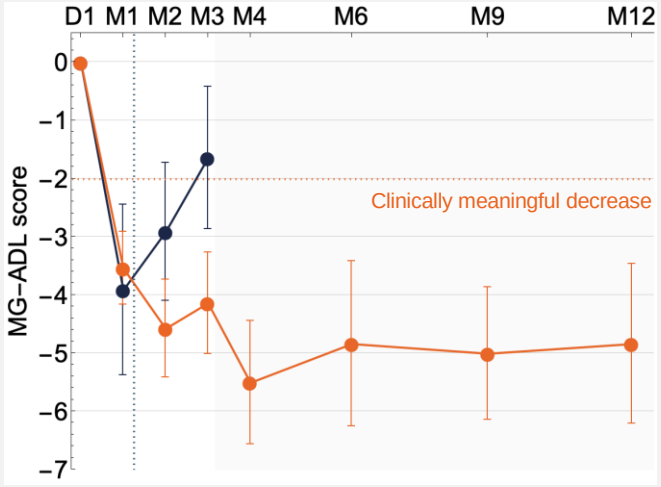
Descartes-08 treated participants sustained deep responses through month 12 after a single course of therapy

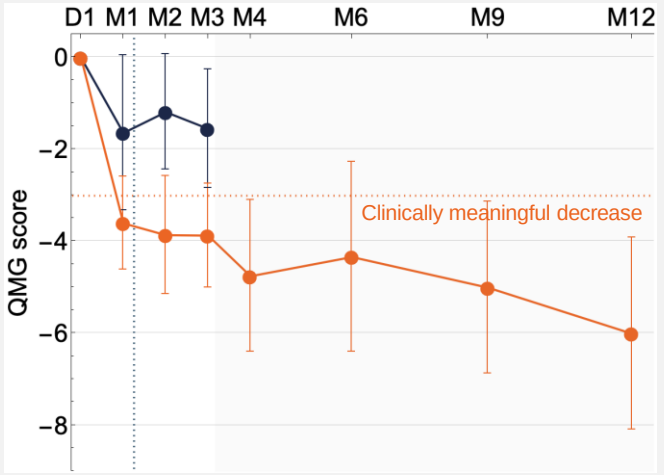
Deepest and most sustained responses seen in patients without prior biologics exposure

Primary Efficacy Dataset

- Average MG-ADL reduction of 5.5 (±1.1) points at Month 4, **sustained through Month 12 (4.8±1.4)**
- 33% of participants achieved minimum symptom expression at Month 6 and **sustained it through Month 12**

Month 3 (n=15), Month 4 to Month 12 (n=12*); **Three participants lost to follow-up*





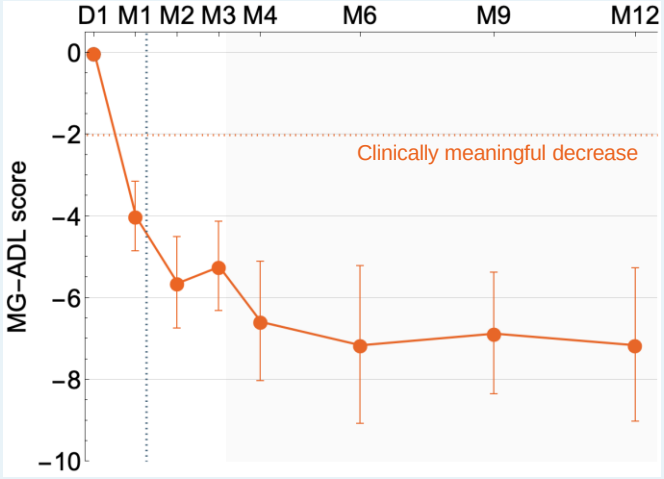
Descartes-08 Placebo

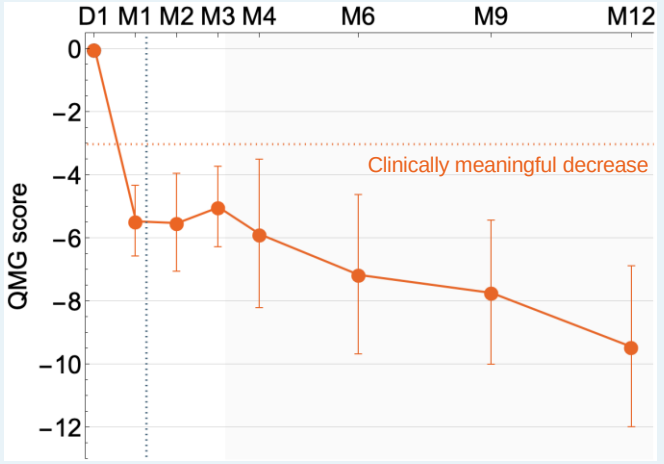
Primary Efficacy Dataset (No Prior Biologics*)

- Average MG-ADL reduction of 6.6 (±1.5) points at Month 4, **maintained through Month 12 (7.1±1.9)**
- 57% of participants achieved minimum symptom expression at Month 6 **and maintained it through Month 12**

*defined as no prior complement or FcRn inhibitors

Month 3 (n=9), Month 4 to Month 12 (n=7*); **Two participants lost to follow-up*





Descartes-08

Safety profile supports outpatient administration

- **Most AEs were transient or mild**
- **No cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS)**
- **No hypogammaglobulinemia or increased infections reported**

	Descartes-08 (n=20)			Placebo (n=16)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Headache	7 (35%)	4 (20%)		2 (13%)	3 (19%)	
Chills	8 (40%)	4 (20%)				
Nausea	3 (15%)	6 (30%)		1 (6%)	2 (13%)	
Fever	7 (35%)	4 (20%)	1 (5%)			
Fatigue	4 (20%)	1 (5%)		1 (6%)		
Myalgia	4 (20%)	2 (10%)				
Infusion related reaction	1 (5%)	2 (10%)	1 (5%)	1 (6%)		
Muscle weakness	1 (5%)	1 (5%)		1 (6%)		
Arthralgia	1 (5%)	1 (5%)			1 (6%)	
Tachycardia	3 (15%)					
Upper respiratory infection		1 (5%)			1 (6%)	
Herpes simplex reactivation	1 (5%)		1 (5%)			
Dysgeusia	3 (15%)					
Diarrhea	1 (5%)				1 (6%)	
Sweating	1 (5%)			1 (6%)		
Limb edema	1 (5%)	1 (5%)				
Flushing	2 (10%)					
Dyspnea	1 (5%)	1 (5%)				
Insomnia	2 (10%)					
Vomiting	2 (10%)	1 (5%)				
Tremor	2 (10%)					

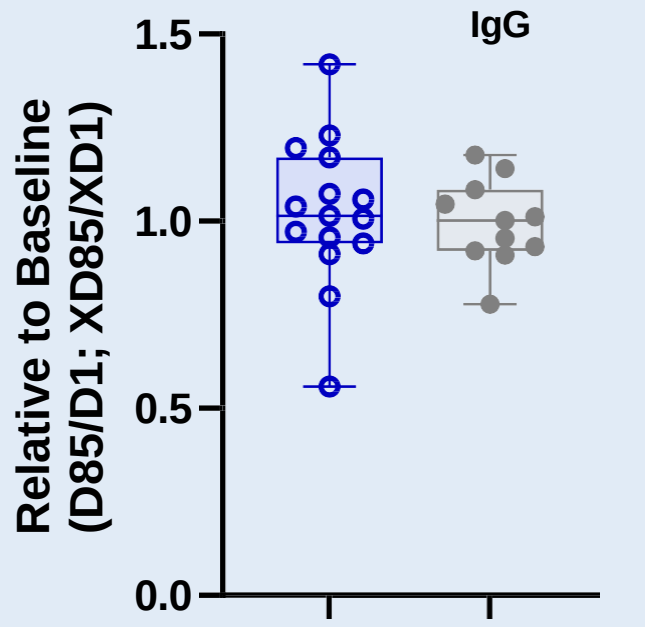
Safety dataset comprises all subjects who received at least one dose of Descartes-08 (n=20) or placebo (n=16).

All Grade 1–2 adverse events deemed possibly, probably or definitely related to the study drug with a cumulative incidence ≥10% and all Grade 3 adverse events deemed possibly, probably or definitely related to the study drug are reported. There were no Grade 4 adverse events

AE, Adverse event

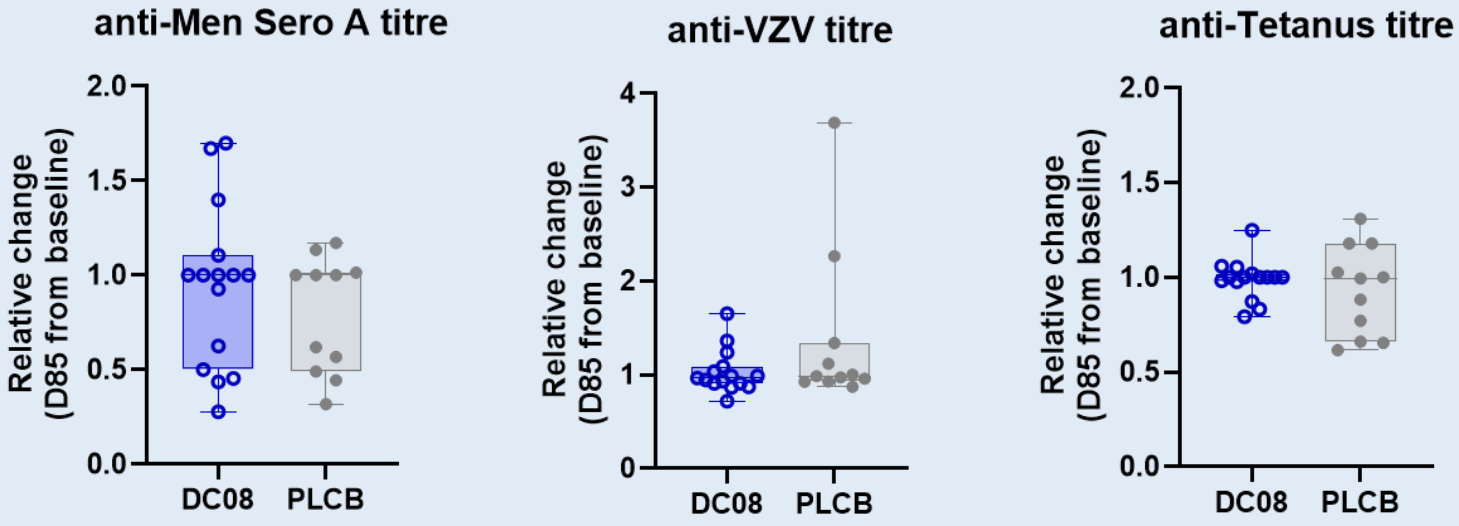
Descartes-08 observed not to deplete broader antibody repertoire or decrease vaccine titers for common viruses

No significance change in Ig at primary end point (D85) vs. Day 1[1]



Descartes-08 (DC08) Placebo (PLCB)

No significant change in common vaccine titers at primary end point (Day 85) relative to Day 1[2]



Similar results not shown: anti-Men Sero C, anti-Men Sero W135, anti-Men Sero Y, anti-Diphtheria, anti-Measels, anti-Mumps and anti-Rubella titers

Descartes-08 (DC08) Placebo (PLCB)

1. Data indicate change in Ig levels for each participant in the miTT group (n = 26) at Day 85 relative to Day 1. Data are individual values, median, range and IQR.
2. Data indicate change in vaccines titers for each participant in the mITT group (n=26) at Day 85 relative to Day 1. Data are individual values, median, range and IQR.

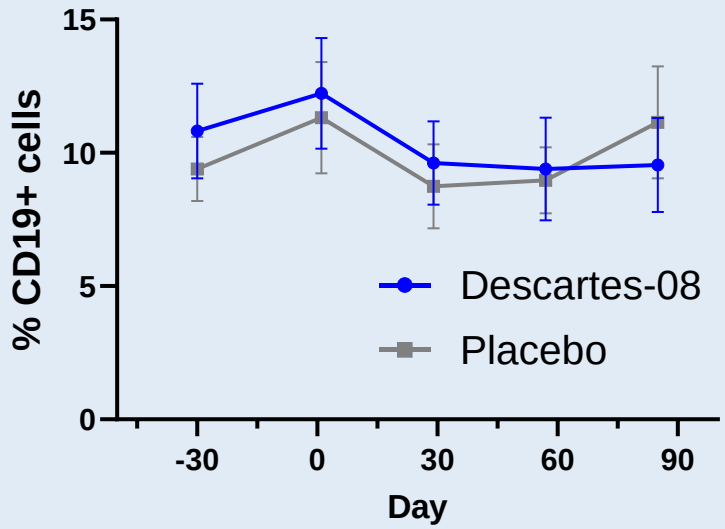
Ig, Immunoglobulin; VZV, Varicella zoster virus
mITT, Modified intent-to-treat

Descartes-08 observed not to impact circulating B Cell levels, but to reduce cytokine associated with MG clinical activity

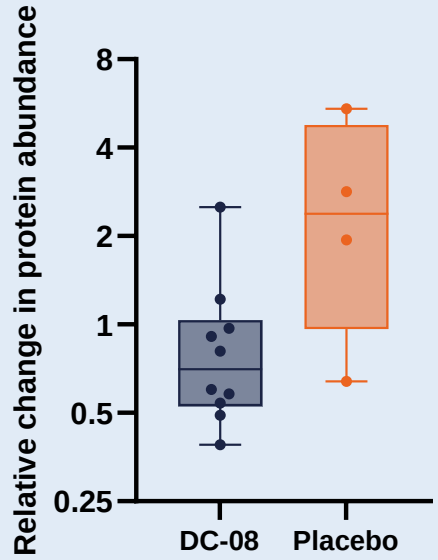
Descartes-08 does alter circulating B cell levels[1] relative to placebo

Descartes-08 reduces cytokine associated with MG activity (eg, IL-6)

Circulating B cells



IL-6



p-value = 0.01

DC-08: n=10; Placebo: n=4

Conclusions

- Six once-weekly doses of Descartes-08 were associated with a significantly greater proportion of MGC and MG-ADL responders than placebo at Month 3
- More profound improvement in symptoms seen in patients with MG with no prior biologics use
- Responses were greater than clinically meaningful and durable at last follow-up (up to 12 months)
- Safety data supports outpatient administration with 1hr post-infusion monitoring, approximately 50% of patients reported infusion related reactions, no ICANS or CRS
- Safety and efficacy of Descartes-08 will be tested further in the pivotal Phase 3 AURORA trial (NCT06799247)