2024 MGFA Scientific Session

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Safety and efficacy of BCMA-directed mRNA CAR T-cell therapy in generalized myasthenia gravis

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COI Disclosures

- Consultant and/or on speaker bureaus for Alexion/AstraZeneca Rare Disease, Amgen, argenx, CSL Behring, Dianthus, ImmunAbs, Johnson & Johnson, and Takeda.
- 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

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

Cartesian THERAPEUTICS mRNA Cell Therapy

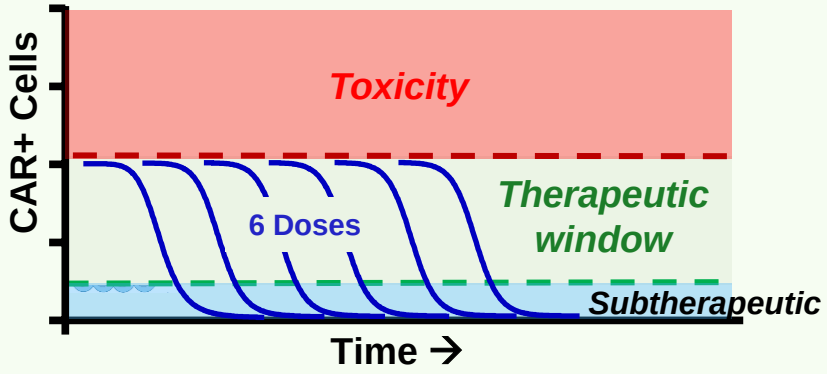
No Lymphodepleting Chemotherapy Required
No requirement for cell proliferation → no expected need for pre-treatment chemotherapy → no Grade 3-4 cytopenias

Administered Outpatient
Reduced patient burden and lower indirect cost

Delivered at Therapeutic Levels
Expectation for cells to be administered at therapeutic, but sub-toxic doses

Controllable PK/PD
mRNA does not replicate → predictable half-life with more controllable PK/PD defined by the dose

Transient Cell Modification
Does not carry risk of genomic integration



Conventional CAR T-Cell Therapy

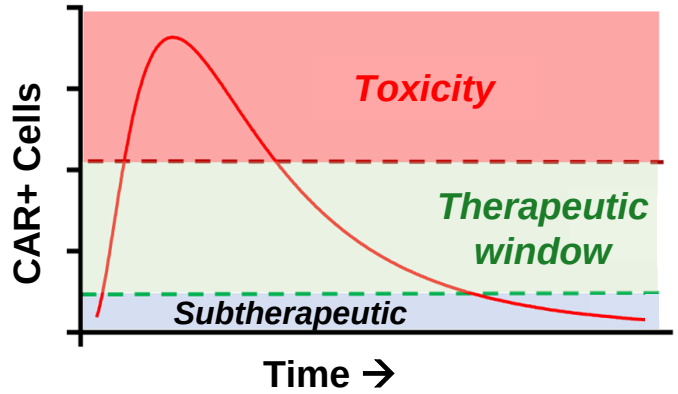
Requires Lymphodepleting Chemotherapy
Associated with high rates of toxicity, including cytokine release syndrome

Requires Inpatient Administration
High patient burden resulting in higher indirect costs

Administered at Subtherapeutic Levels
Cells proliferate rapidly beyond therapeutic window

Uncontrollable PK/PD
Effector function of cell therapy engineered with DNA amplifies exponentially with cell replication

Permanent Cell Modification
Associated with insertional mutagenesis leading to potential secondary malignancies



Descartes-08 is designed for dual action, precisely targeting two key BCMA+ cell populations involved in a spectrum of autoimmune diseases

Descartes-08 is designed to target BCMA, a surface antigen expressed on ***plasma cells/plasmablasts*** and ***plasmacytoid dendritic cells***

PLASMA CELLS (PCs) AND PLASMABLASTS

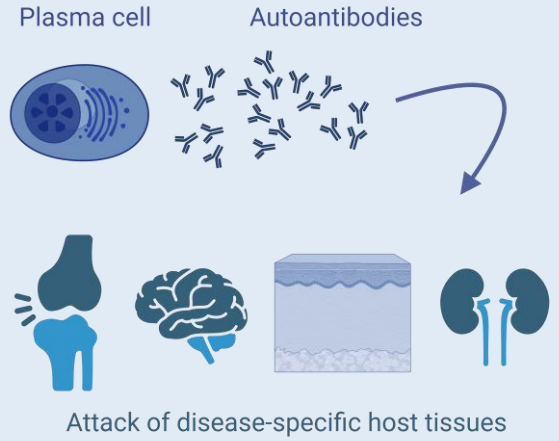
- PCs, plasmablasts and proliferating B cells targeted by Descartes-08 represent a small fraction of B cells
- These cells are entirely responsible for secreting pathogenic autoantibodies
- During autoimmunity, autoantibodies attack host tissue and drive inflammation

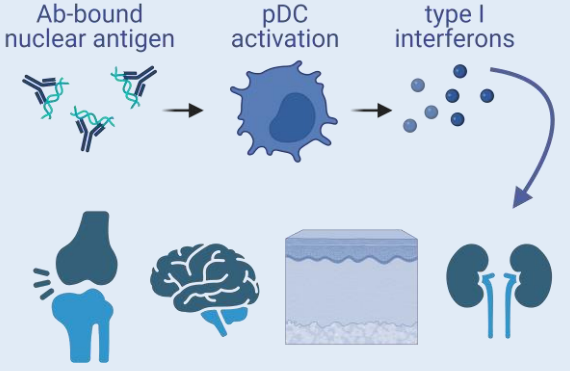
PLASMACYTOID DENDRITIC CELLS (pDCs)

- pDCs, which Descartes-08 is designed to target, are a rare subset of antigen-presenting cells
- These cells secrete high levels of cytokines (i.e., type I interferons) that cause inflammation and tissue damage during many human autoimmune diseases
- pDCs are increased in patients with autoimmunity (e.g., SLE) and interfere with optimal treatment

Several autoimmune disease segments involve pathogenic contributions from ***both PCs/plasmablasts*** and ***pDCs***, including rheumatology, nephrology, neurology, and others

Selectively deleting PCs/plasmablasts and pDCs, if successful, may create a differentiated cell therapy platform





BCMA, B cell maturation antigen

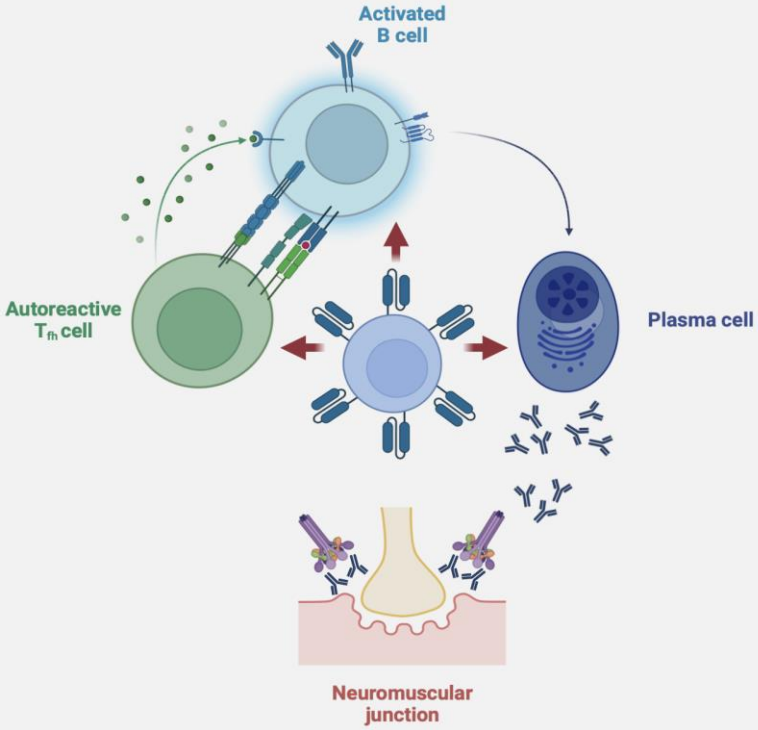
A. Merino-Vico et al, Eur. J. Immunol. 53, e2149675 (2023).
E. Schuh, A. Musumeci et al. J. Immunol. 198, 3081–3088 (2017).

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

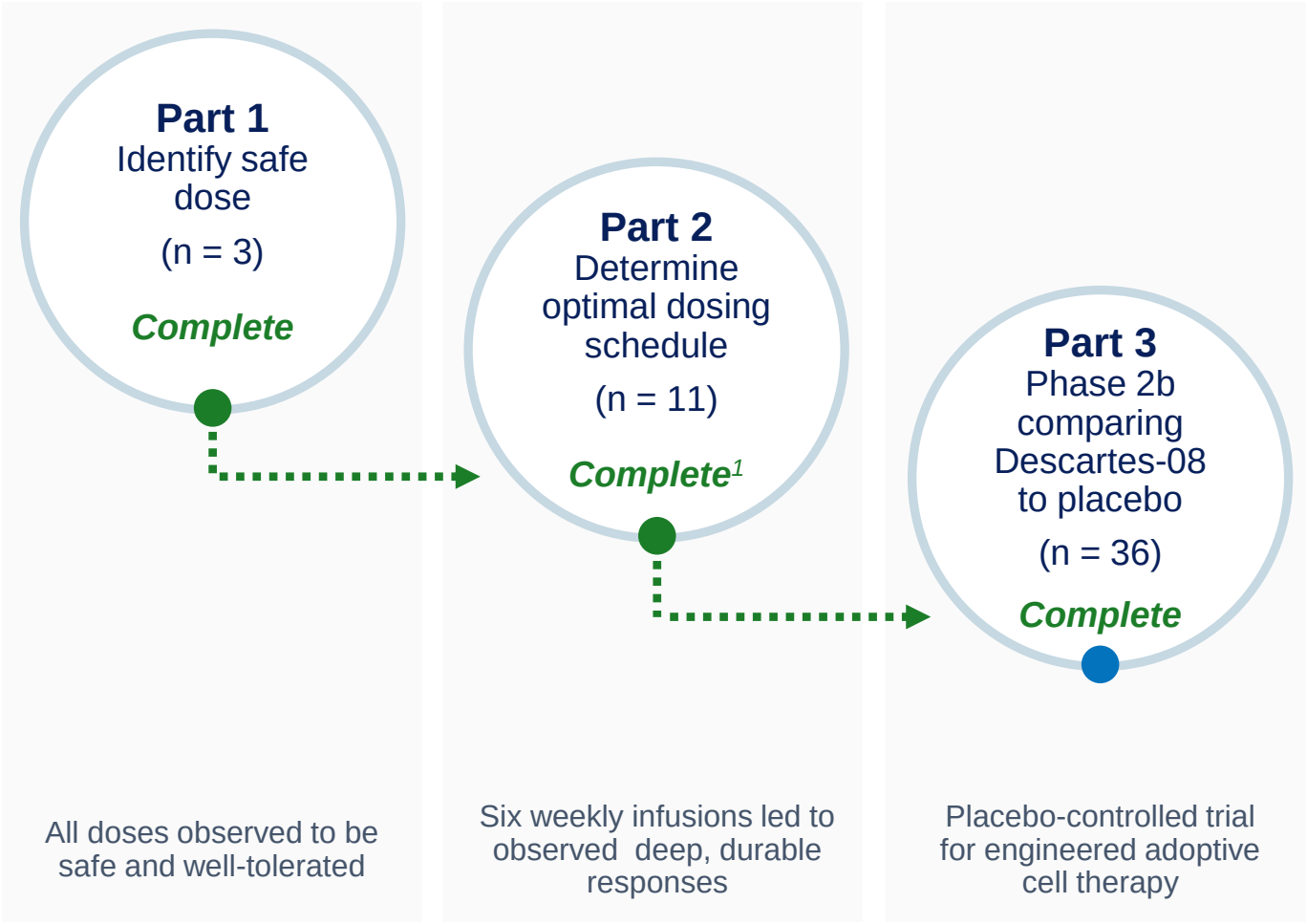
Typical lot processed for infusion within ~3 weeks

Granted U.S. FDA orphan and RMAT designations for generalized myasthenia gravis



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

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



Patient eligibility

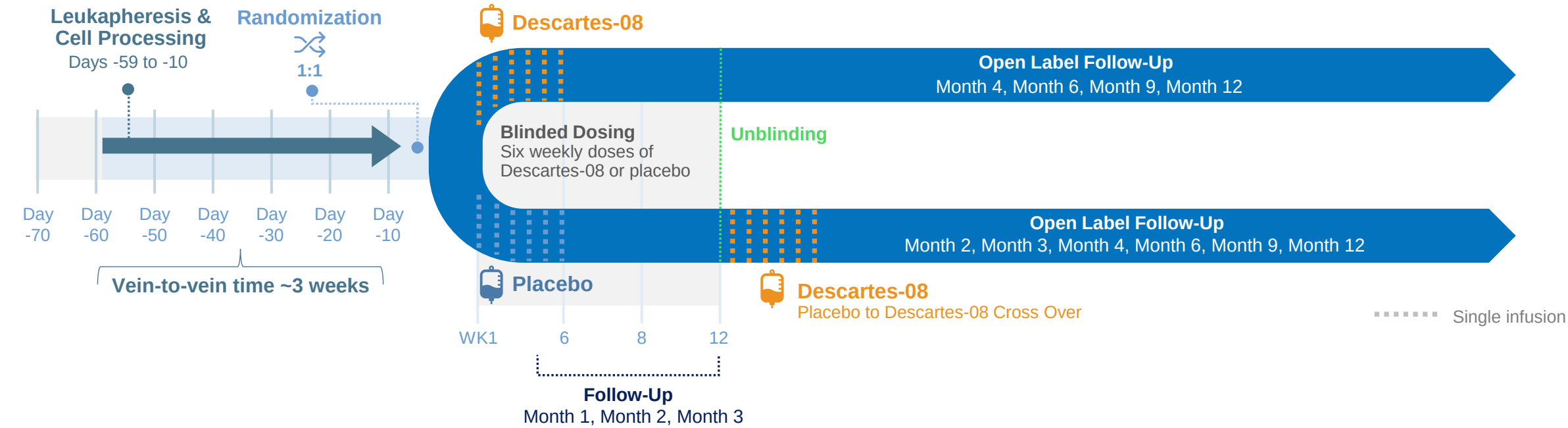
- Non-MuSK gMG
- MG-ADL ≥ 6
- MGFA Class II-IV
- Stable medication dosing ≥ 8 wks prior to infusion
- 4-week washout for biologics
- IVIg and plasma exchange not allowed after starting Descartes-08

Patients on immunosuppression or complement inhibitors expected to be able to continue their treatment while receiving Descartes-08

Cell manufacturing platform tolerates most standard immunosuppressive therapies

[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

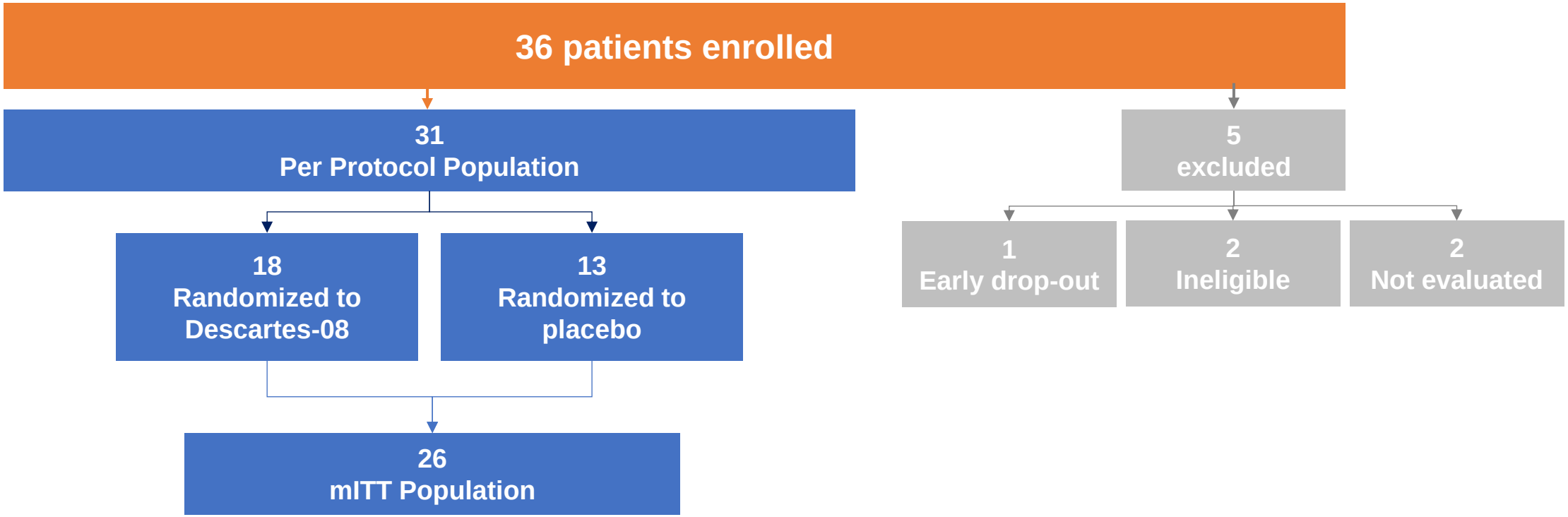
- Proportion of patients with MG Composite improvement of ≥5-points at Month 3, relative to placebo
- Predefined primary efficacy dataset

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

14 patients received Descartes-08 and 12 patients received placebo in the pre-specified primary efficacy dataset



- Modified ITT (mITT) population includes all participants enrolled at academic medical centers qualified for MG Composite assessment with at least one post-baseline follow-up.
- Safety dataset includes all participants at academic medical centers and community clinics who received at least one dose of Descartes-08 or placebo.

IND, Investigational New Drug Application
ITT, Intention to Treat

Baseline characteristics: highly symptomatic patient population with severe disease

		Descartes-08	Placebo	Total
	Mean age, years (SD)	56.7 (16.7)	60 (13.4)	58.2 (15.0)
	Female	10 (71%)	6 (50%)	16 (62%)
	Male	4 (29%)	6 (50%)	10 (38%)
Weight	**Mean weight, kg (SD)**	94.1 (20.7)	104.0 (26.6)	98.7 (23.7)
Race and ethnicity	White, non-Hispanic	12 (86%)	12 (100%)	24 (92%)
	Other	2 (14%)	0 (0%)	2 (8%)
MGFA class at screening	II	4 (29%)	3 (25%)	7 (27%)
	III	9 (64%)	9 (75%)	18 (69%)
	IV	1 (7%)	0 (0%)	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	Anti-AChR antibody	10 (71%)	9 (75%)	19 (73%)
	Anti-LRP4 antibody	1 (7%)	0 (0%)	1 (4%)
	Seronegative1	3 (21%)	3 (25%)	6 (23%)
Mean baseline scores (SD)	QMG	16.9 (7.2)	15.1 (4.0)	15.1 (4.0)
	MG-ADL	10.1 (2.9)	10.3 (3.2)	10.3 (3.2)
	MGC	16.1 (6.4)	16.1 (4.0)	16.1 (5.4)
	MG-QoL-15r	19.5 (7.7)	17.3 (4.7)	18.5 (6.5)

1 for AChR, MuSK, and LRP4 antibodies
MGC, MG Composite

Prior and ongoing treatments: heavily pre-treated patient population

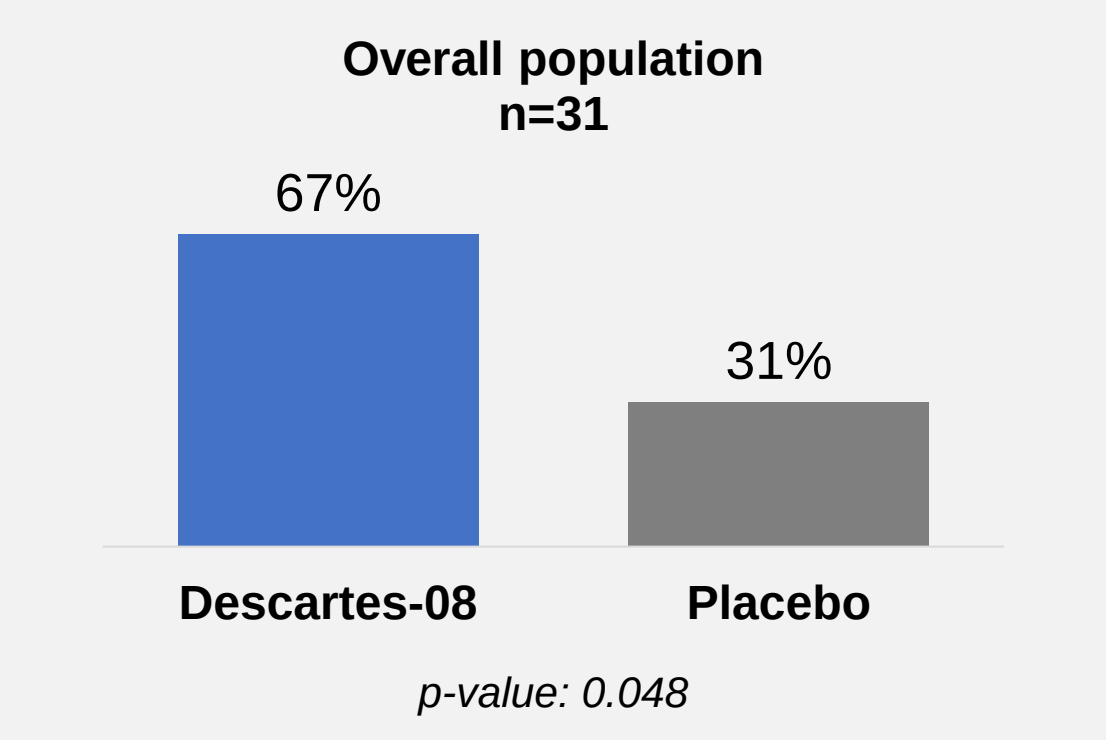
		Descartes-08	Placebo	Total	
Previous myasthenia gravis therapies (standard of care)	Pyridostigmine	9 (64%)	8 (67%)	17 (65%)	
	Prednisone	8 (57%)	6 (50%)	14 (54%)	
	Other immunosuppressants	8 (57%)	9 (75%)	17 (65%)	
	Complement inhibitor	3 (21%)	5 (42%)	8 (31%)	*
	FcRN antagonist	4 (29%)	5 (42%)	9 (35%)	
Previous intravenous immunoglobin		10 (71%)	10 (83%)	20 (77%)	
Previous plasma exchange		3 (21%)	6 (50%)	9 (35%)	
Diagnosis of thymoma*		0 (0%)	5 (42%)	5 (19%)	
Previous thymectomy		3 (21%)	7 (58%)	10 (38%)	*
Previous MG crisis requiring intubation		2 (14%)	0 (0%)	2 (8%)	
MG ongoing therapy	Pyridostigmine	9 (69%)	7 (58%)	16 (62%)	
	Prednisone	8 (57%)	4 (33%)	12 (46%)	*
	Azathioprine	5 (21%)	1 (8%)	4 (15%)	*
	Mycophenolate mofetil	2 (14%)	5 (41%)	7 (27%)	*
	Complement inhibitor	1 (7%)	2 (14%)	3 (12%)	*

*Imbalance

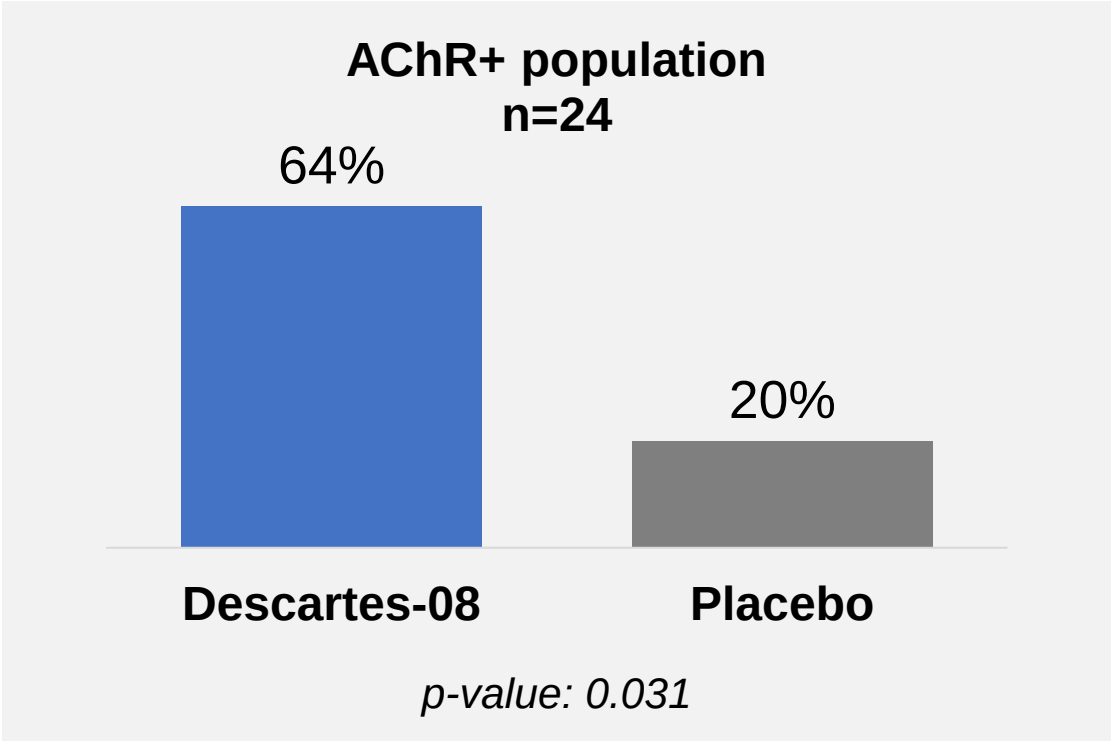
Trial met primary endpoint with statistical significance

- **Responders in pre-specified analysis observed to have ~3x greater improvements than clinically meaningful* in the AChR Ab+ patients**
- **Data support advancement to Phase 3**

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



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

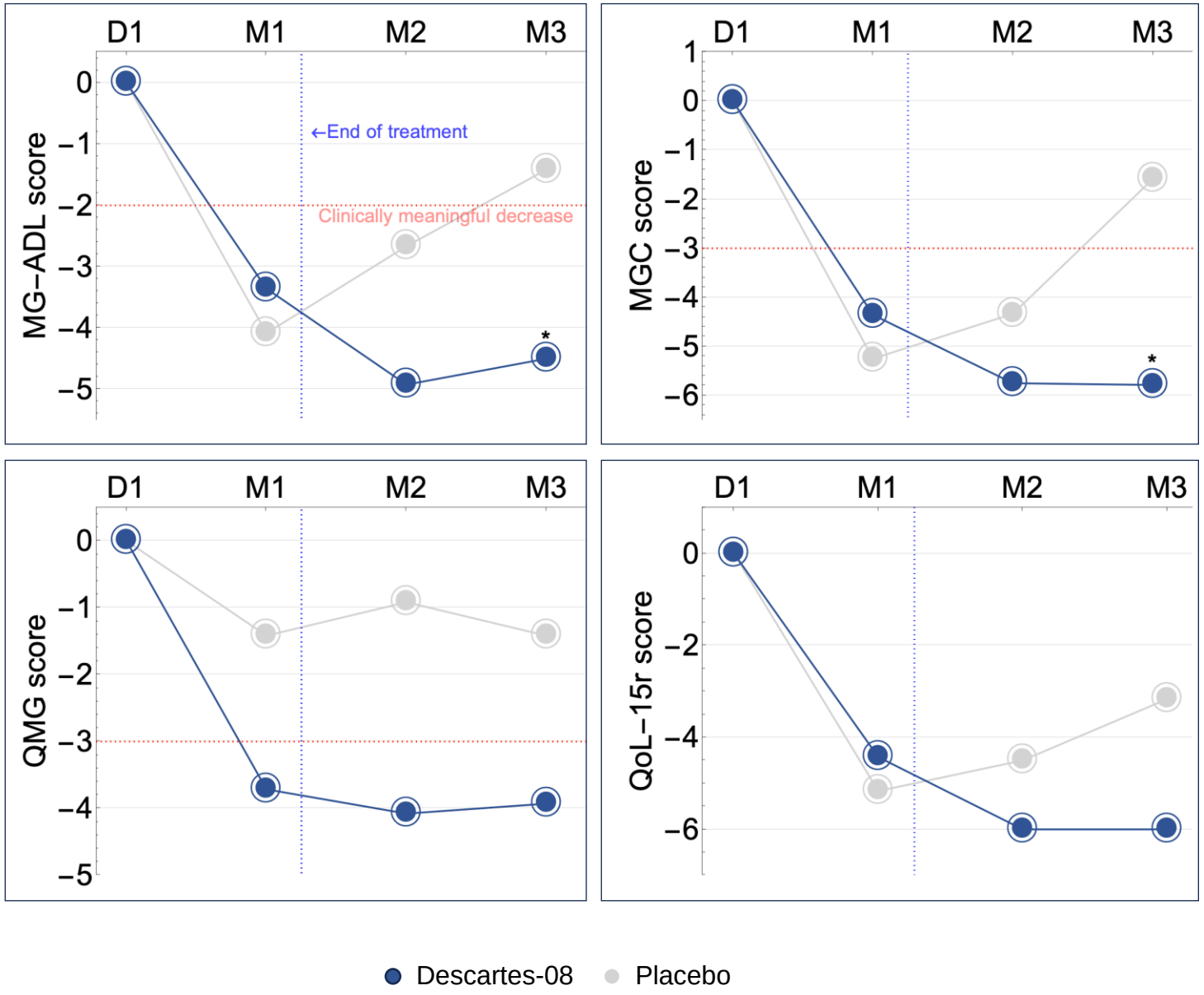


Per Protocol Responders: Descartes-08, n= 9/14; placebo, n=2/10

*Clinically meaningful response is a three-point reduction from baseline

In overall populaton, statistically significant improvements in MG-ADL and MGC were observed at month 3 in Descartes-08 vs. placebo treated patients

- **Non-responders (n=4)**
  - 1 LRP4+ MG non-responder at Month 3 onward
  - 1 non-responder at Month 3 onward
  - 1 responded during open label follow-up
  - 1 has not reached 1st open label follow-up
- **Placebo response generally in line with expectations**



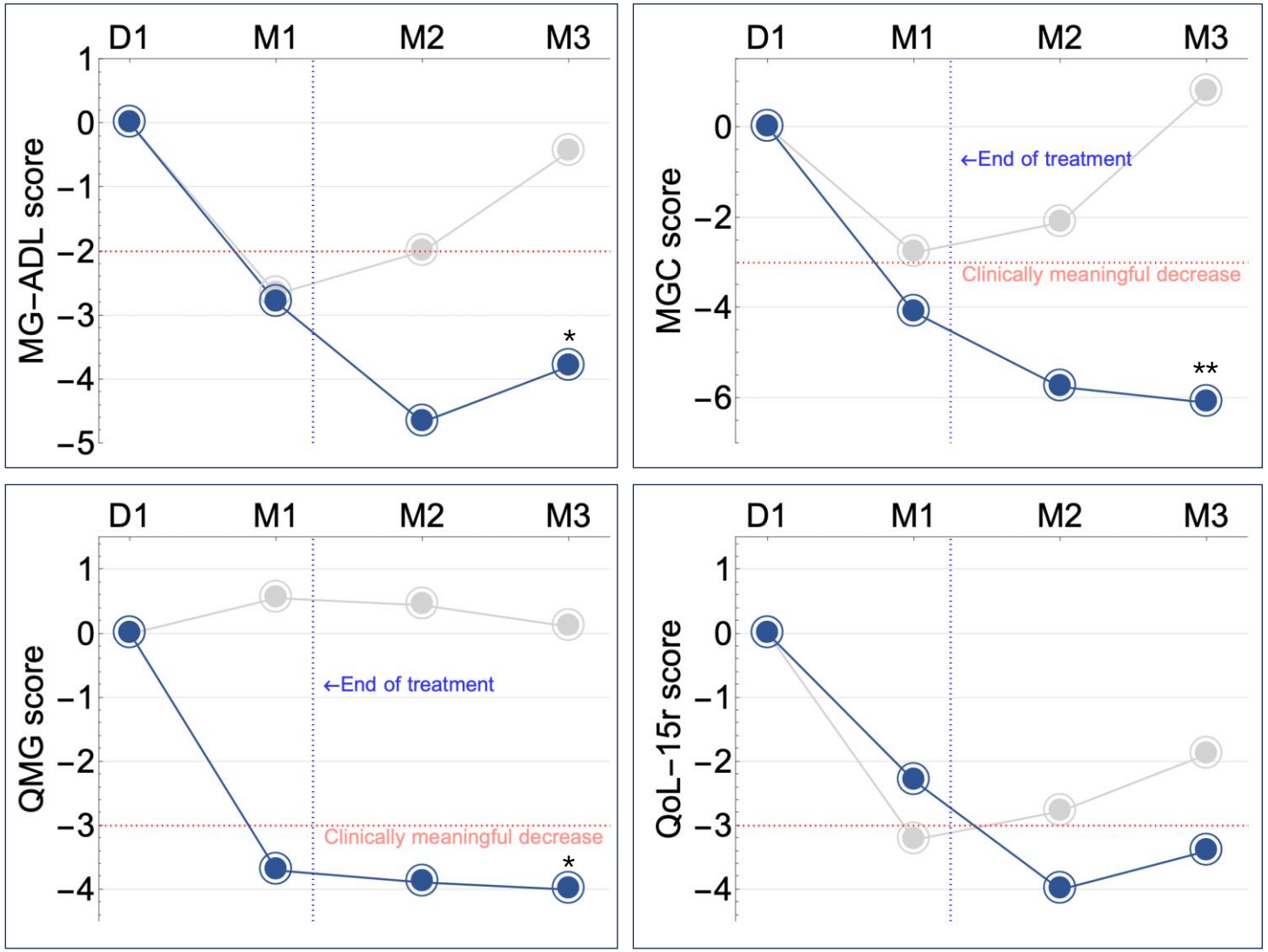
Mean decrease from Baseline in the prespecified mITT population (n=26)
- p<0.05 by Mann-Whitney U test at Month 3 in MGC and MG-ADL

LRP4+, low-density lipoprotein receptor-related protein 4

In AChR Ab+ patients, Descartes-08 demonstrated statistically significant improvements in MG-ADL, MGC, and QMG scores vs. placebo

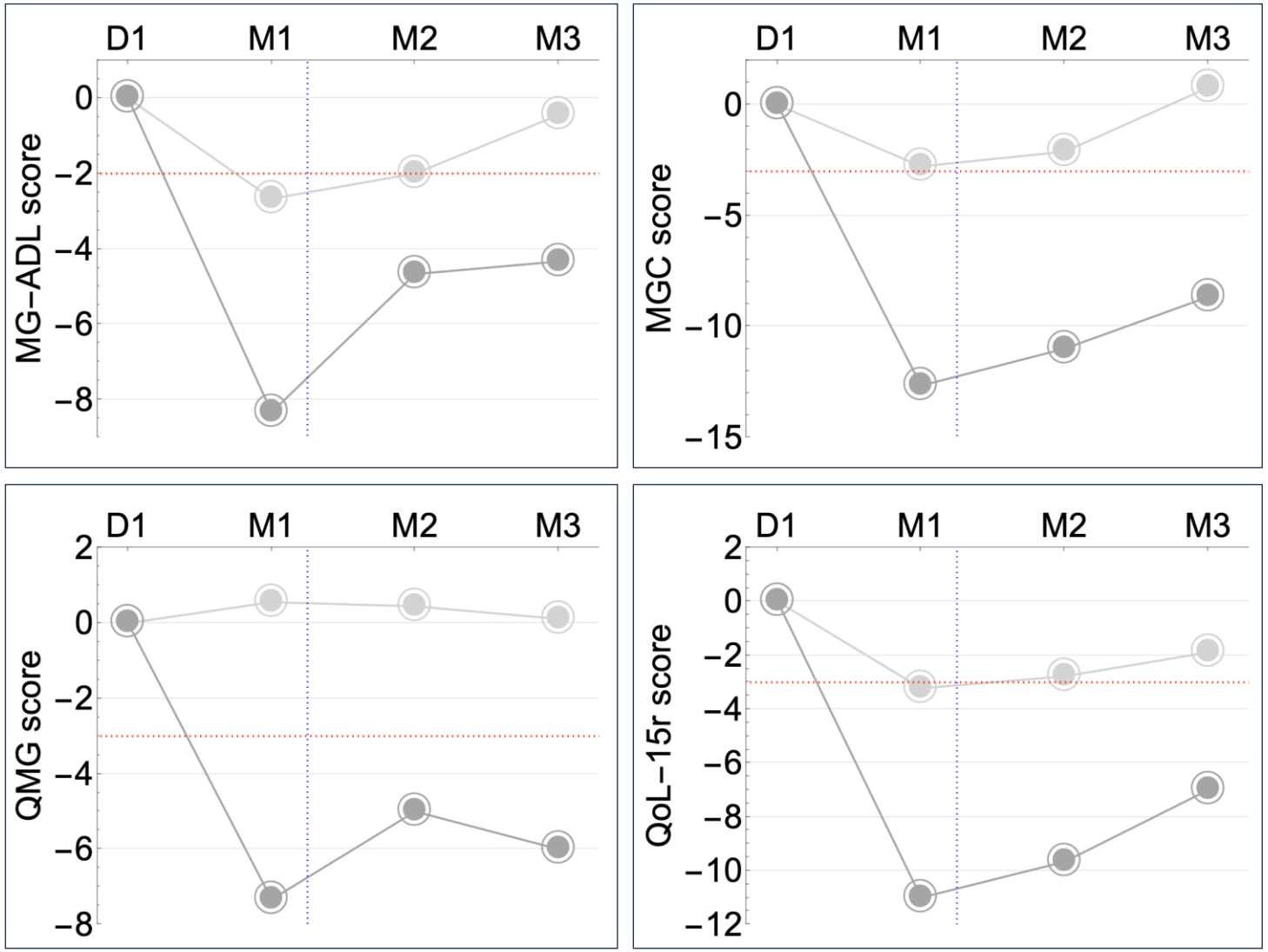
Statistically significant improvement in Descartes-08 compared to placebo at Month 3 seen across MGC (p=0.002), MG-ADL (p=0.012) and QMG (p=0.029).

Placebo responses in AChR Ab+ subjects were consistent with Phase 2/3 published literature.



Improvements from baseline in participants with AChR Ab⁺ MG receiving Descartes-08 (n=10) versus placebo (n=9).
* p<0.05, ** p<0.01 by Mann Whitney U test

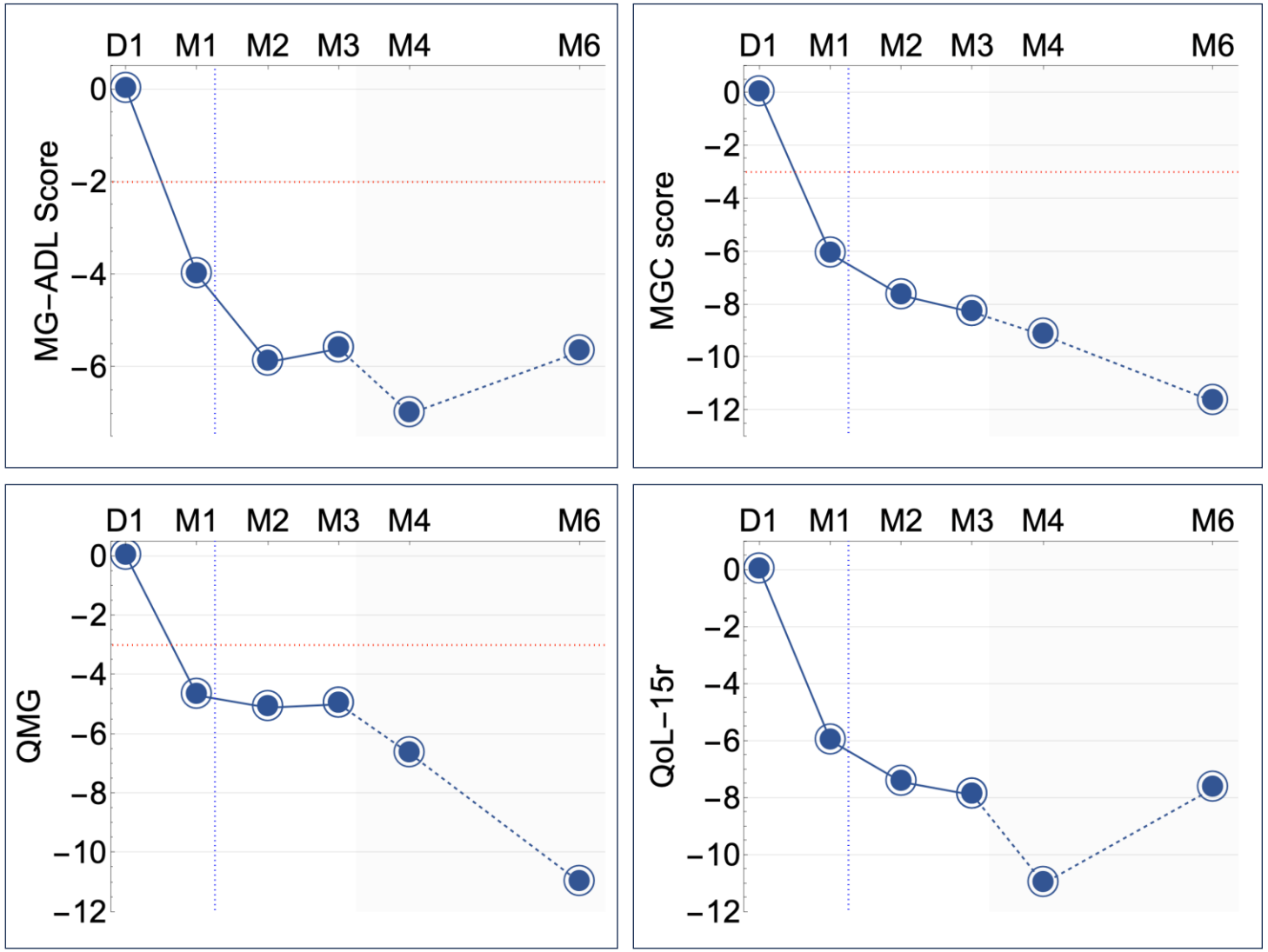
In the placebo treated group, score reductions in measures of disease activity was driven by responses in seronegative subjects



Mean change from baseline in AChR Ab+ (n=9) and seronegative (n=3) participants randomized to placebo (mITT population)

Deep and durable responses observed in Descartes-08 responders through Month 6

Results consistent with Phase 2a open-label trial findings



Mean decrease from Baseline in MGC Responders (participants who achieved a ≥5-point reduction in MGC at Month 3, n=10. Month 4 n=5, Month 6 n=3.

Observed safety results support outpatient administration and in line with Phase 2a observations

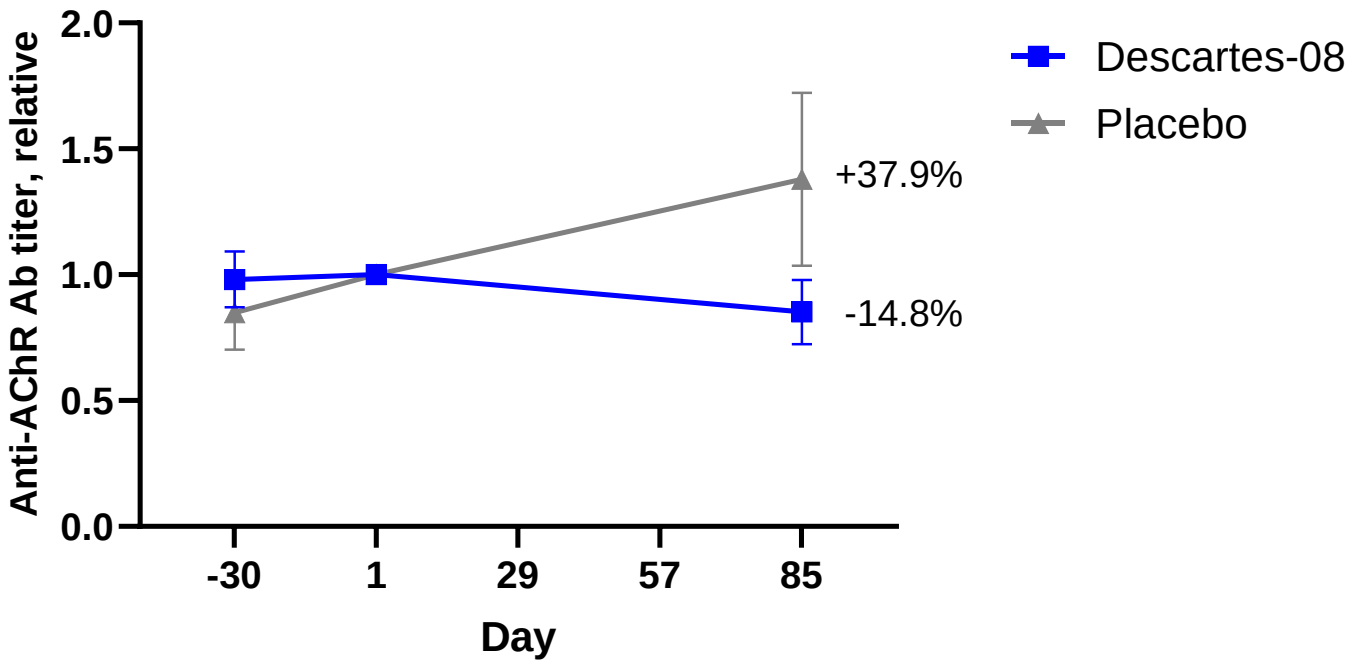
- No cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS)
- Most AEs were transient or mild

	Descartes-08 (n=19)			Placebo (n=17)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Headache	6 (32%)	4 (21%)		2 (12%)	3 (18%)	
Chills	7 (37%)	4 (21%)		1 (6%)		
Nausea	2 (11%)	5 (26%)		2 (12%)	2 (12%)	
Fever	6 (32%)	3 (17%)	1 (6%)	0 (0%)	0 (0%)	
Fatigue	5 (26%)	1 (5%)		1 (6%)		
Myalgia	3 (16%)	3 (16%)		1 (6%)		
Infusion related reaction	1 (5%)	2 (11%)	1 (6%)	1 (6%)		
Muscle weakness	1 (5%)	1 (5%)		1 (6%)		
Arthralgia	0 (0%)	1 (5%)		1 (6%)	1 (6%)	
Tachycardia	3 (16%)					
Herpes simplex reactivation	2 (11%)		1 (6%)			
Dysgeusia	3 (16%)					
Diarrhea	1 (5%)				1 (6%)	
Sweating	1 (5%)			1 (6%)		
Limb edema	1 (5%)	1 (5%)				
Flushing	2 (11%)					
Dyspnea	1 (5%)	1 (5%)				
Insomnia	2 (11%)					
Vomiting	2 (11%)					
Tremor	2 (11%)					

*

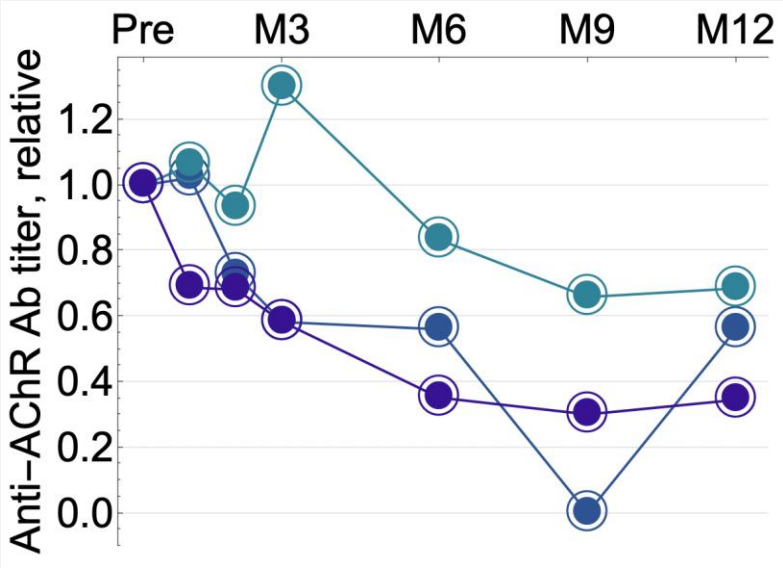
Safety dataset comprises all subjects who received at least one dose of Descartes-08 (n=19) or placebo (n=17)
All Grade 1–2 adverse events deemed possibly, probably or definitely related to the study drug with a cumulative incidence ≥10% and all Grade 3 adverse events deemed possibly, probably or definitely related to the study drug are reported. There were no Grade 4 adverse events.
AE, Adverse Event

Approximately 15% reduction in AChR antibody titer at Month 3 is in-line with Phase 2a data



Average reduction (±SEM) in AChR antibody in participants with baseline levels above LLOQ randomized to Descartes-08 (n=12) vs. Placebo (n=9)

Phase 2a data

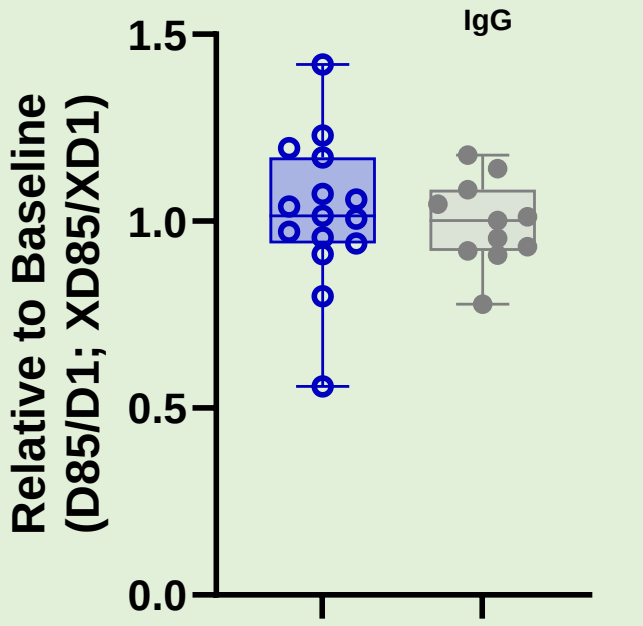


*

Individual Anti-AChR antibody titers in all participants receiving six once-weekly infusions in the Phase 2a trial with detectable baseline levels (n=3)

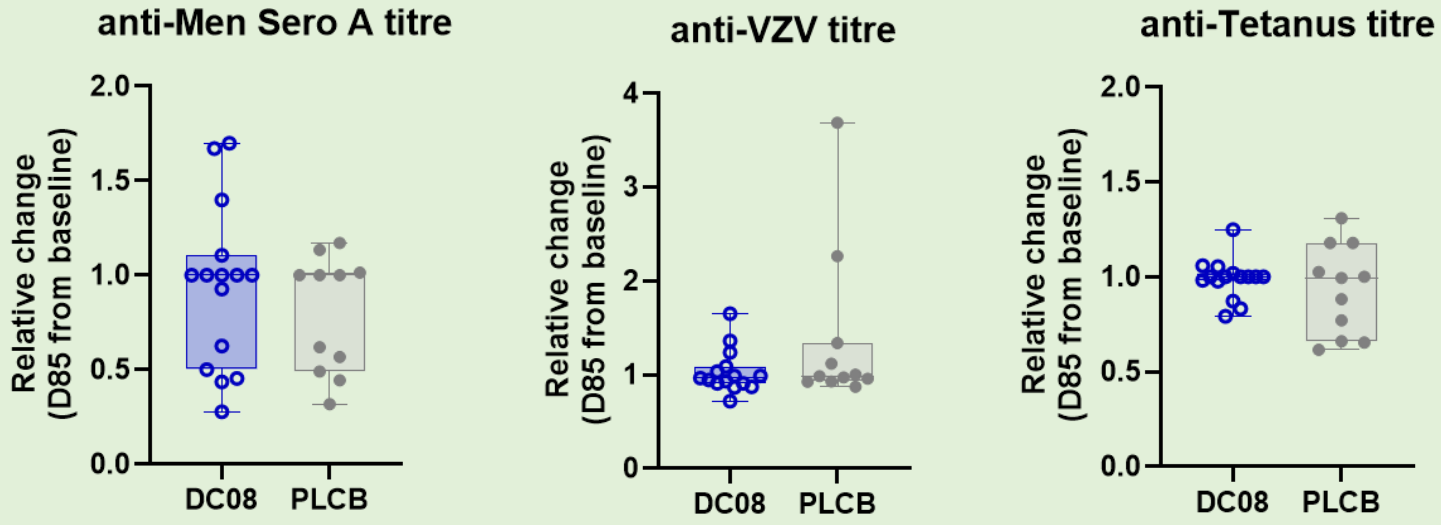
Descartes-08 does not deplete broader antibody repertoire or decrease vaccine titers for common viruses

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]



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)

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

Summary

Six once-weekly doses of Descartes-08 were associated with a significantly greater proportion of MGC responders than placebo at Month 3

Responses were greater than clinically meaningful and durable at last follow-up (up to 6 months)

Safety data supports outpatient administration with 1hr post-infusion monitoring

Average reduction in AChR+ antibody at 3 months was 14.8% in the Descartes-08 group, compared to 37.9% average increase in the placebo group

Descartes-08 was not associated with increased rates of infection, hypogammaglobulinemia or reduction of vaccine antibody titers

Safety and efficacy of Descartes-08 will be tested further in a Phase 3 randomized placebo-controlled trial

Thank you

Special thanks to patients, their caregivers and the entire MG-001 study team