
EBMT
EHA
6th European
CAR T-cell Meeting
Valencia, Spain
15-17
February
2024

mRNA CAR-T in Myasthenia Gravis

6th edition of the European CAR T-cell Meeting
February 26, 2024

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Howard Disclosures (26 February 2024)

Research Support (active & within 2 years)

- Ad Scientiam
- Alexion Pharmaceuticals
- argenx BV
- Cartesian Therapeutics
- CDC (The Centers for Disease Control & Prevention)
- Duke Research Institute
- NIH (NINDS, NIAMS, RDCRN-MGNet)
- NMD Pharma
- PCORI
- UCB Bioscience

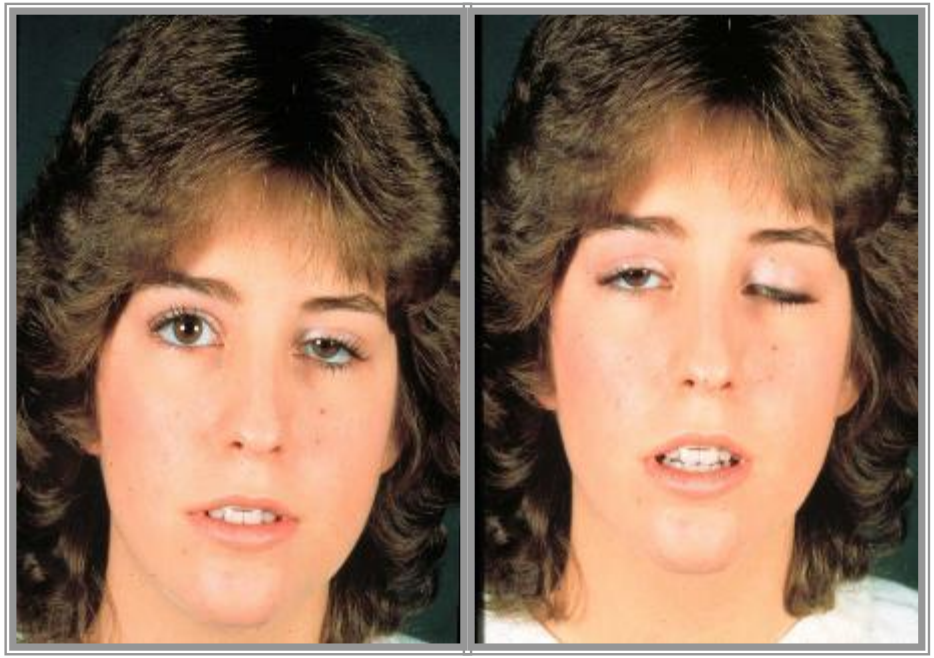
Consulting / Advisory Services (within 2 years)

- Alexion Pharmaceuticals
- argenx BV
- Avilar Therapeutics
- F. Hoffman LaRoche
- Horizon Therapeutics (now Amgen)
- Merck EMD Serono
- NMD Pharma
- Novartis Pharmaceuticals
- Regeneron Pharma
- Sanofi USA
- Seismic Therapeutics
- Toleranzia AB
- UCB Bioscience

Boards (*e.g.* Directors & Advisory) (active)

- Alexion gMG Scientific Advisory Board, (Chair)
- argenx gMG Collegium, (Chair)
- Horizon Therapeutics (now Amgen), Scientific Advisory Board, (Chair)
- UCB, Rare Disease Connect Neurology, Steering Committee

Myasthenia Gravis

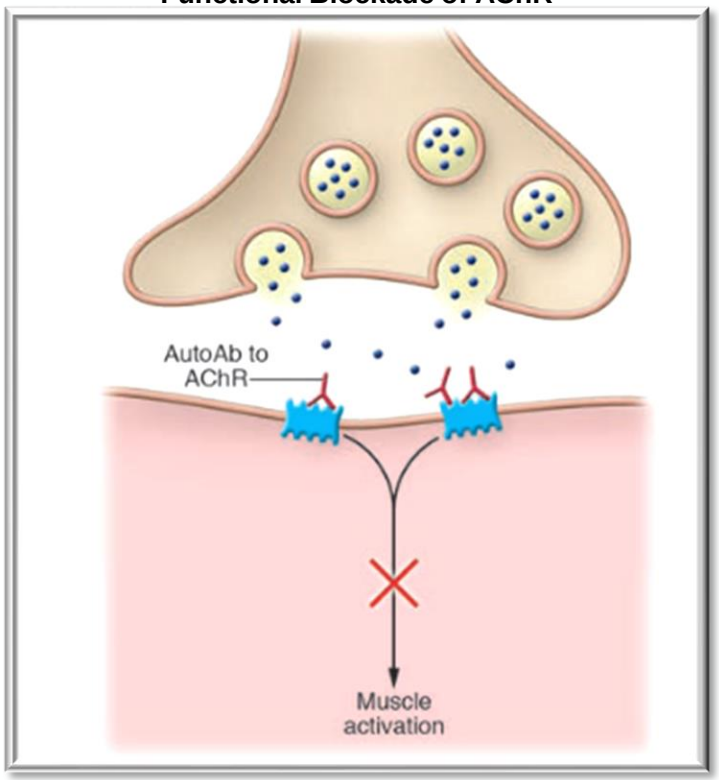


- Chronic, antibody dependent, complement mediate autoimmune neuromuscular disorder
- Characterized by variable fluctuating muscle weakness and exertional muscle fatigue
- Multiple effector antibodies targeting
  - acetylcholine receptor AChR,~83%),
  - muscle specific kinase (MuSK, ~8%),
  - lipoprotein receptor-related protein 4 (LRP-4, <1%)
- Seronegative population (~8%)

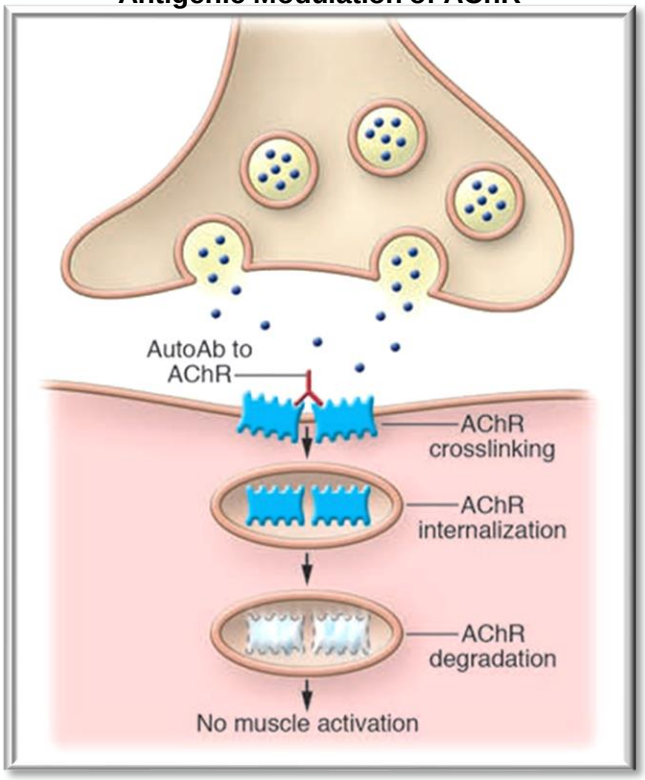
Neuromuscular Transmission

Mechanisms of Synaptic Block

Functional Blockade of AChR



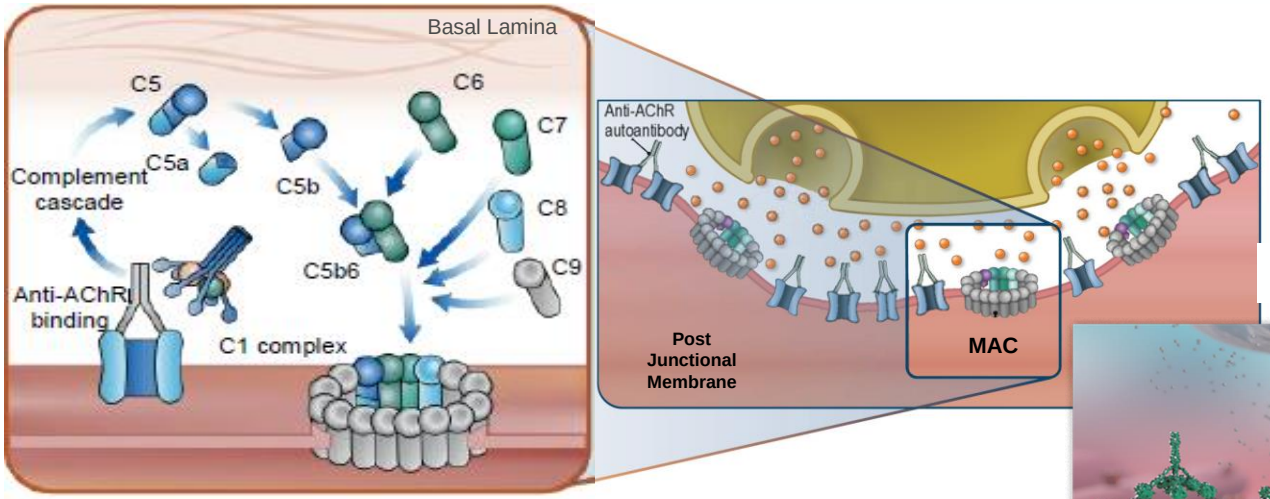
Antigenic Modulation of AChR

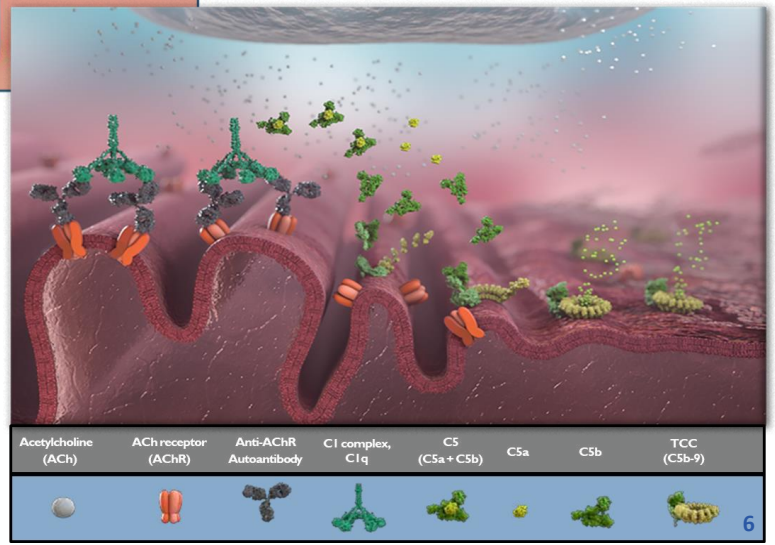


Conti-Fine, BM et al. *The Journal of Clinical Investigation,* (2006):116 (11) 2843-54. doi:10.1172/JCI29894

Myasthenia Gravis

Complement Activation



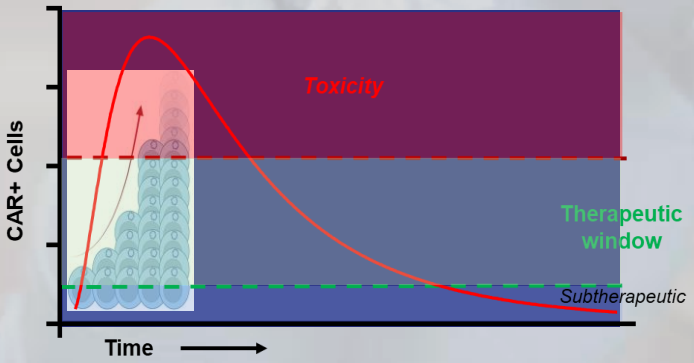


- Anti-AChR antibodies bind to the AChR and initiate the complement cascade via activation of the C1 complex
- The product of the complement cascade is the membrane attack complex (MAC / TCC)

Howard JF et al, Exp Opinion Invest Drugs, 2021 v30 p483

Conventional engineered cell therapy uses DNA, which can lead to toxicity and increased patient burden

- Effector function of cell therapy engineered with DNA amplifies exponentially with cell replication and frequently leads to uncontrollable PK/PD
- Cells administered at subtherapeutic levels quickly proliferate beyond therapeutic window



DNA transduced CAR-T associated with:

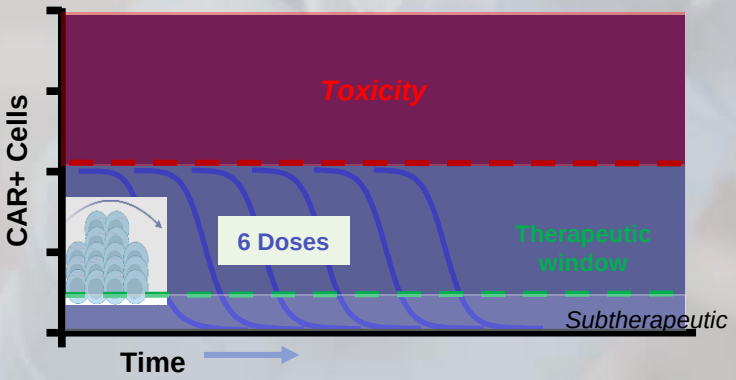
- Cytokine release syndrome (CRS)
- Neurotoxicity and parkinsonism
- Cytopenia (from pre-treatment chemo)
- Infections
- Secondary malignancies
- Death

DNA CAR-T cell therapy creates increased patient burden

- Patients receiving DNA CAR-T require inpatient administration and pre-treatment chemotherapy (lymphodepletion)
- Indirect costs high due to monitoring/treatment of toxicities

Cartesian's mRNA approach is designed to expand the reach of potent cell therapy products to address potential autoimmune indications

- mRNA does not replicate → predictable half-life with more controllable PK/PD defined by the dose
- No requirement for cell proliferation → no expected need for pre-treatment chemotherapy → no Grade 3-4 cytopenias



Expectation for cells to be administered at the **therapeutic but sub-toxic doses**

Descartes-08 has been **administered to 66 patients** with autoimmune diseases and cancer[1] with **no CRS, neurotoxicity, or infections** observed

Ability to treat in **outpatient setting** offers potential to be **administered in community clinics**

Potential for **safe re-dosing**

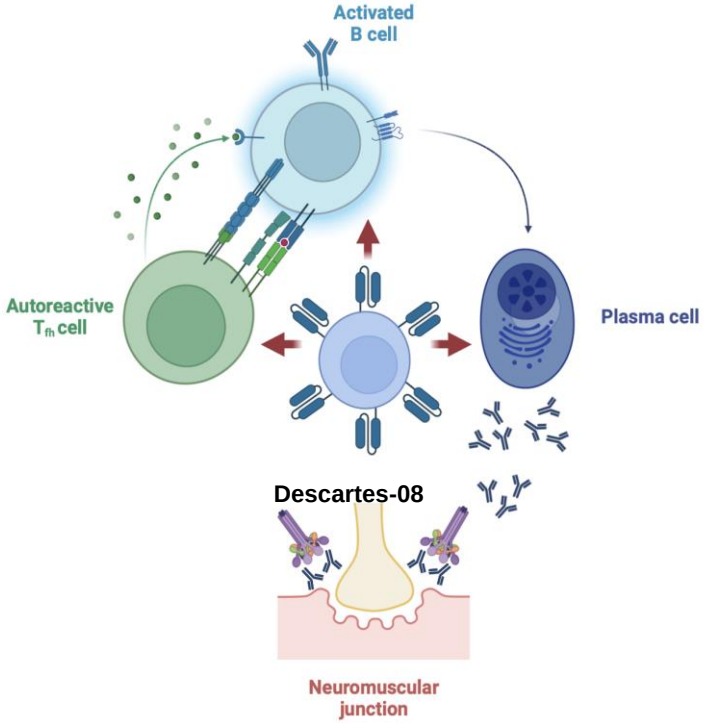
mRNA CAR-Ts have potential to **overcome challenges of DNA CAR-Ts**

- No expected need for hospitalization, lymphodepletion, toxicity management, and monitoring
- Produces multiple cycles from one apheresis
- Lower manufacturing costs

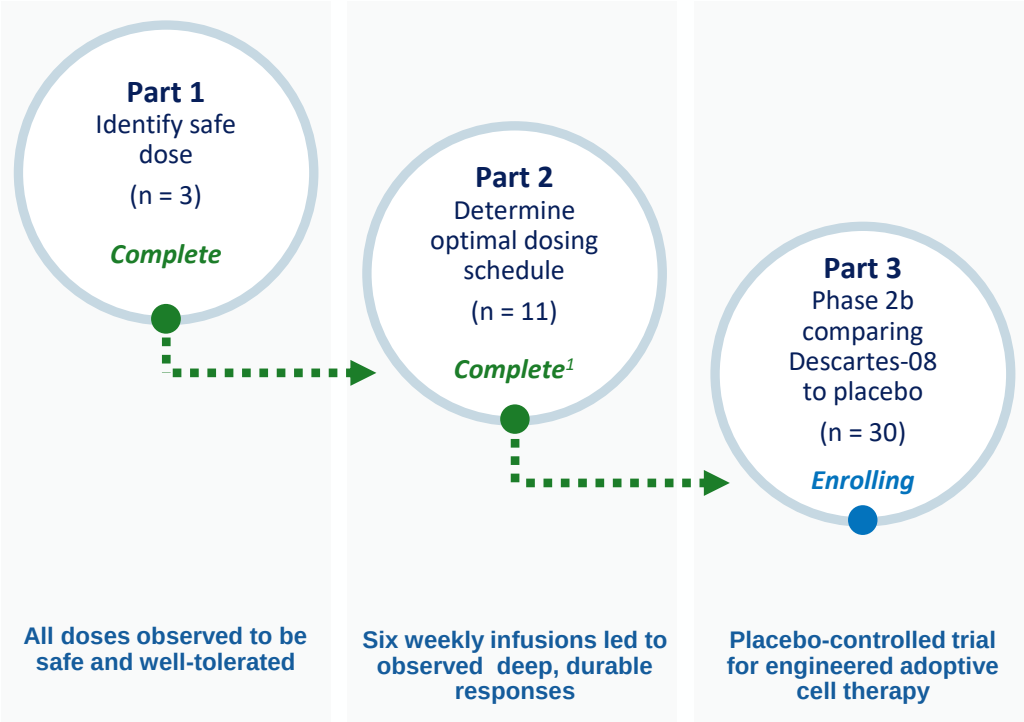
[1]All open-label patients treated with Descartes-08 as of Oct 30, 2023

Descartes-08
believed to be the first mRNA CAR-T in clinical development for autoimmune disease

- Engineered by transfection of autologous CD8+ T cells with mRNA encoding BCMA-directed CAR
- Typical lot **processed for infusion within ~3 weeks**
- Observed to **enhance killing and suppression of inflammatory cytokine secretion**
- **Phase 2a data** in myasthenia gravis underscores potential for deep and durable responses versus current agents
- Granted **U.S. FDA orphan designation** for generalized myasthenia gravis (2022)



MG-001 Descartes-08 (Phase 2; NCT04146051)



Patient eligibility

- MG-ADL ≥ 6
- MGFA Clinical 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

mRNA CAR-T

MG-001 Descartes-08, Part 2 (NCT04146051)

Phase 1b/2a Open Label

Key Inclusion/Exclusion Criteria

- MGFA Clinical Class II-IV
- MG-ADL ≥ 6
- AChR Ab+ or AChR Ab–
- Stable SOC

Primary endpoint

- Type and frequency of AEs at the MTD administered at 3 different schedules

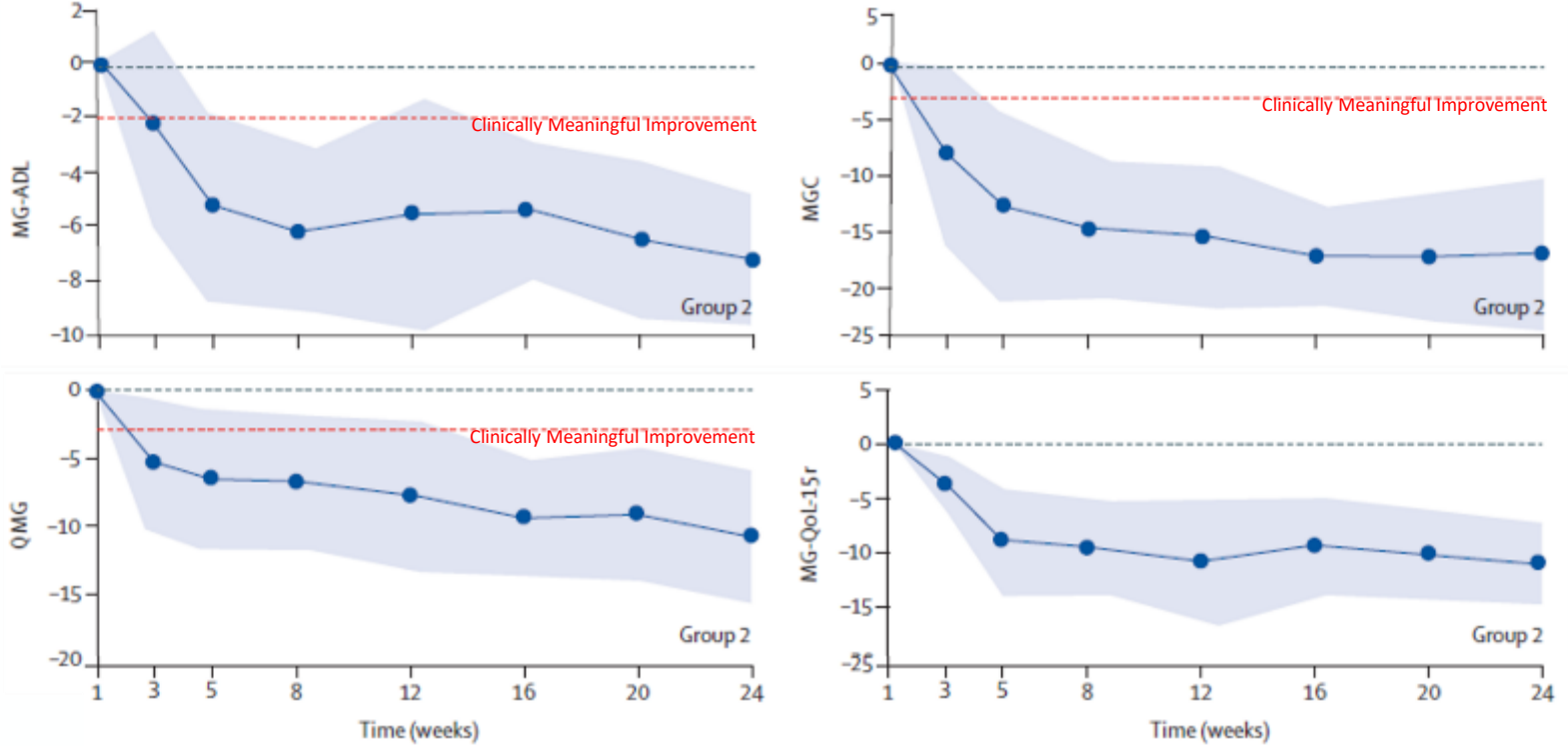
Secondary endpoints

- Multiple MG outcome measures, ie MG-ADL, MG-QMG, MG-Composite Scores

Abbreviations: AChR: acetylcholine receptor; ADL: Activities of Daily Living; AEs: adverse events; CAR: chimeric antigen receptor; MG: myasthenia gravis; MGFA: Myasthenia Gravis Foundation of America, MTD: Maximum Tolerated Dose; SOC: Standard of Care; QMG: Quantified MG Score

MG-001 Descartes-08

Group 2; n=7



Data are mean score improvement (point) and 95% Confidence Interval (light blue shading).

Granit V etal. Lancet Neurol 2023 v22 p578

NCT04146051

Descartes-08 was observed to be safe and well-tolerated in MG

THE LANCET Neurology

Volume 22, Issue 7, July 2023, Pages 578-590

KEY OBSERVATIONS:

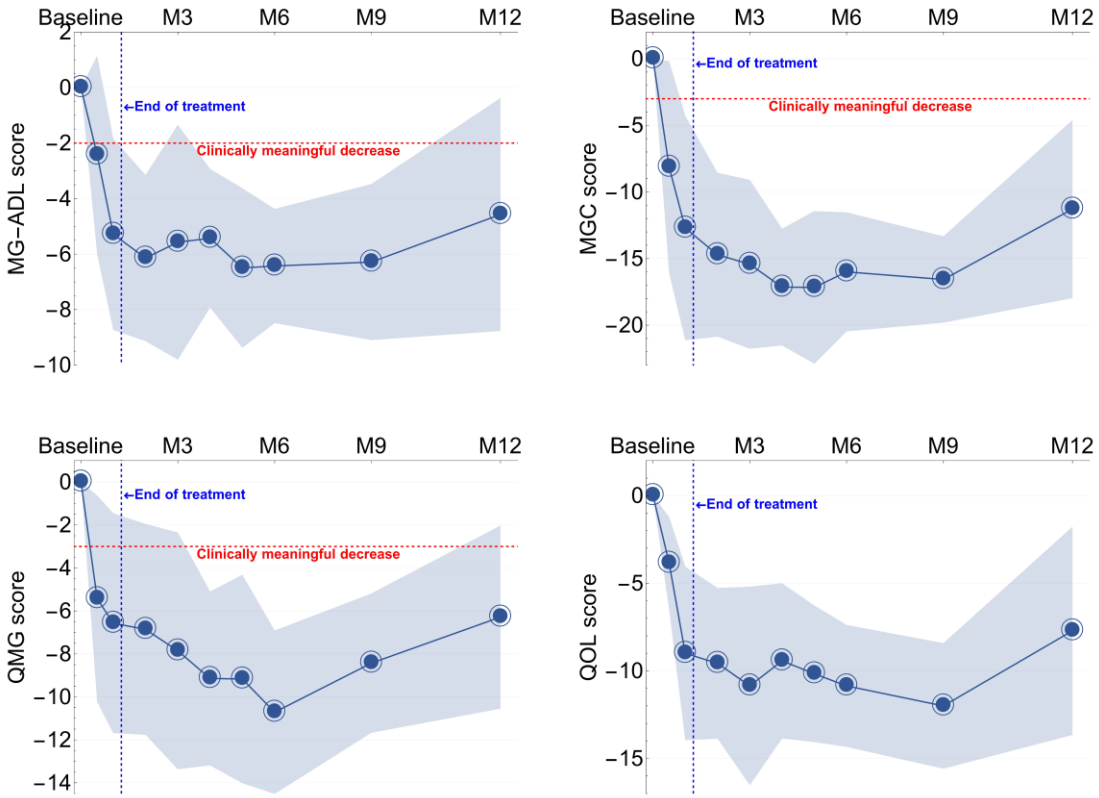
- No dose-limiting toxicities
- No cytokine release syndrome
- No neurotoxicity
- No pre-treatment chemotherapy and related cytopenia
- Outpatient treatment

	Grade*	Part 1 (n=3)	Part 2: all groups (n=11)	Part 2: group 1 (n=3)	Part 2: group 2 (n=7)	Part 2: group 3 (n=1)
Hand numbness	2	1 (33%)	0	0	0	0
Headache	1	1 (33%)	5 (45%)	1 (33%)	3 (43%)	1 (100%)
Muscle soreness	1	1 (33%)	1 (9%)	0	1 (14%)	0
Nausea	1	1 (33%)	4 (36%)	2 (67%)	2 (29%)	0
Rash	3	0	1 (9%)	1 (33%)	0	0
Itchy throat	1	0	2 (18%)	0	1 (14%)	1 (100%)
Vomiting	1	0	3 (27%)	2 (67%)	1 (14%)	0
Weakness	1	0	2 (18%)	2 (67%)	0	0
Line infiltration	1	0	1 (9%)	1 (33%)	0	0
Fever	1	0	4 (36%)	1 (33%)	3 (43%)	0
Shortness of breath[1]	1	0	2 (18%)	1 (33%)	1 (14%)	0
Chills	1	0	2 (18%)	1 (33%)	1 (14%)	0
Diarrhoea	1	0	1 (9%)	1 (33%)	1 (14%)	0
Gum inflammation	1	0	1 (9%)	0	1 (14%)	0
Teeth sensitivity	1	0	1 (9%)	0	1 (14%)	0
Night sweats	1	0	1 (9%)	0	1 (14%)	0
Restless leg	1	0	1 (9%)	0	1 (14%)	0
Light-headedness	1	0	1 (9%)	0	1 (14%)	0

*There were no adverse events of grade 3 or higher reported in part 1, and no grade 2 or grade 4 events reported in part 2, where grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening.
[1]Not associated with hypoxia

Descartes-08 observed to induce deep and durable clinical improvement in MG

- **Notable magnitude and duration of response** across all 4 standard MG severity scales
- Responses appear **to *deepen after completing treatment*** at Week 6
- **Positive** twelve-month follow-up data from Phase 2a study reinforce prior findings published in *Lancet Neurology*



Manuscript submitted for peer review; pre-print available at medRxiv.org
Efficacy dataset includes all MG patients completing the 6-dose once-weekly regimen (n=7). Data are mean score improvement (point) and 95% Confidence Interval (light blue shading). Note that QOL scale does not have an agreed-upon threshold for clinically meaningful disease improvement; MG-ADL, MGC and QMG scales are validated, quantitated, standardized instruments of disease severity and have been acceptable endpoints for registration studies.

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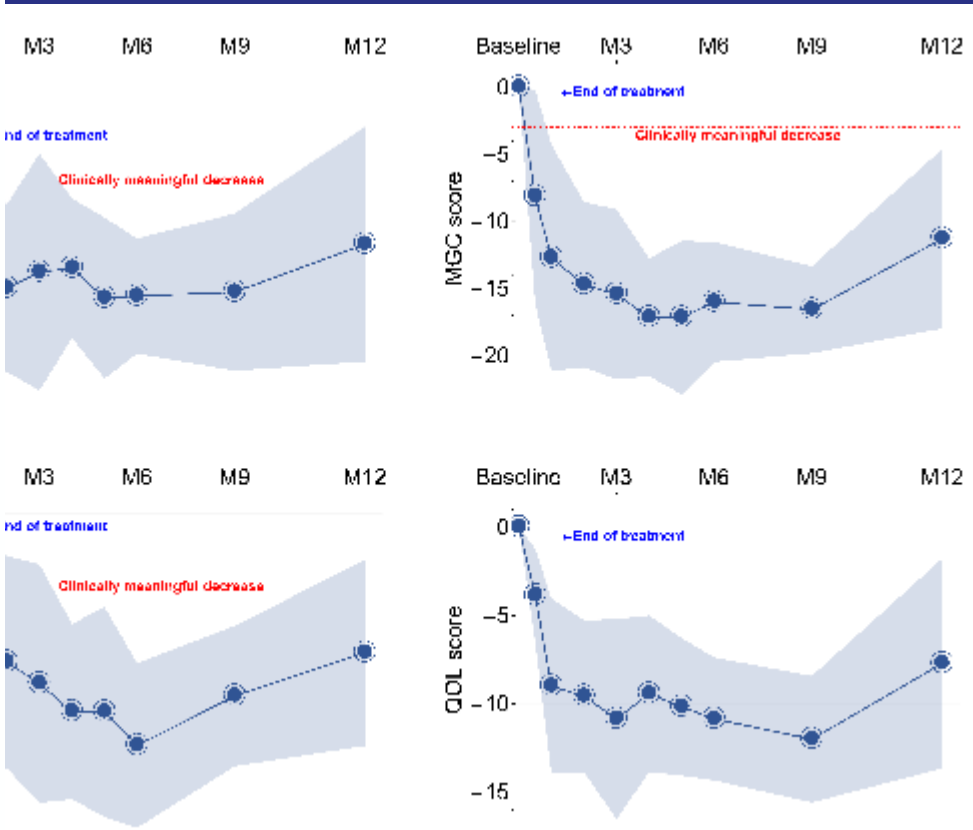

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MG-001 Descartes-08

Measures of Disease Severity at Week 12

	All participants who completed treatment in part 2 (n=9)	By treatment group		By myasthenia gravis type		
		Group 1 (n=2)	Group 2 (n=7)	AChR antibody-positive (n=6)	MuSK antibody-positive (n=2)	Seronegative (n=1)
Mean score change (95% CI)*						
MG-ADL	−5·9 (−9 to −2·8)	−6, −8	−6 (−15 to 3)	−6 (−11 to −1)	−3, −4	−8
QMG	−7 (−11 to −3)	−5, −3	−8 (−20 to 4)	−5 (−10 to 0)	−9, −5	−17
MGC	−14 (−19 to −9)	−7, −11	−15 (−29 to −1)	−14 (−21 to −7)	−14, −7	−22
MG-QoL-15r	−9 (−15 to −3)	−8, 4	−11 (−23 to 1)	−8 (−17 to 1)	−10, −6	−14
Number of participants with improvement (%)						
MG-ADL decrease ≥2 points	8 (89%)	2 (100%)	6 (86%)	5 (83%)	2 (100%)	1 (100%)
MGC decrease ≥3 points	9 (100%)	2 (100%)	7 (100%)	6 (100%)	2 (100%)	1 (100%)
QMG decrease ≥3 points†	8 (89%)	2 (100%)	6 (86%)	5 (83%)	2 (100%)	1 (100%)
MG-ADL decrease ≥6 points‡	5 (56%)	2 (100%)	3 (43%)	4 (67%)	0	1 (100%)

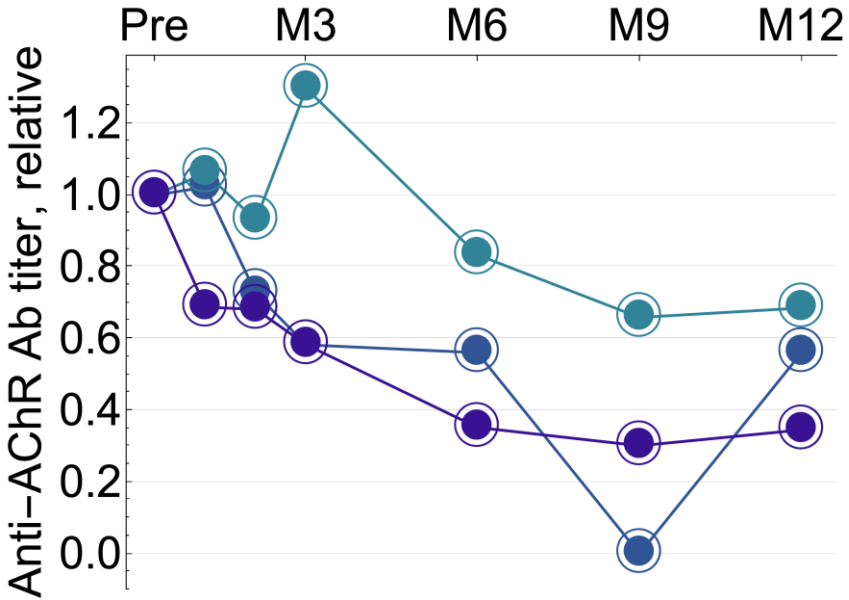
Data are for participants in groups 1 and 2 of part 2 who completed all six infusions and 12-week follow-up. One group 1 participant withdrew from the study before the first assessment after treatment. Clinical efficacy outcomes for the single group 3 participant are shown in figure 1. AChR=acetylcholine receptor. *Individual values are presented for groups of ≤2 participants. †All participants who had the prespecified ≥2-point improvement in QMG also had a ≥3-point improvement. ‡Post-hoc analysis of depth of response.

***Table 3*: Measures of disease severity at week 12**

Granit V etal. Lancet Neurol 2023 v22 p578

MG-001 Descartes-08

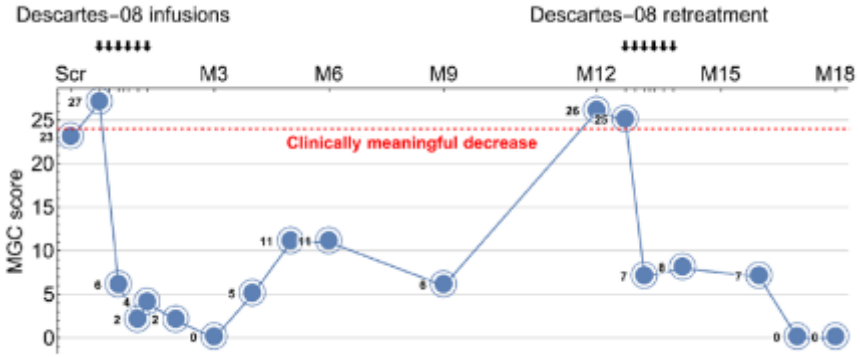
Lasting reductions in autoantibody titers are consistent with the observed clinical responses and mechanism of action



Manuscript submitted for peer review; pre-print available at medRxiv.org.
Anti-AChR Antibody titers of all participants who received six once-weekly infusions and had detectable levels at baseline (n=3), measured in a CLIA-certified lab. Lines represent individual participants.

MG-001 Descartes-08

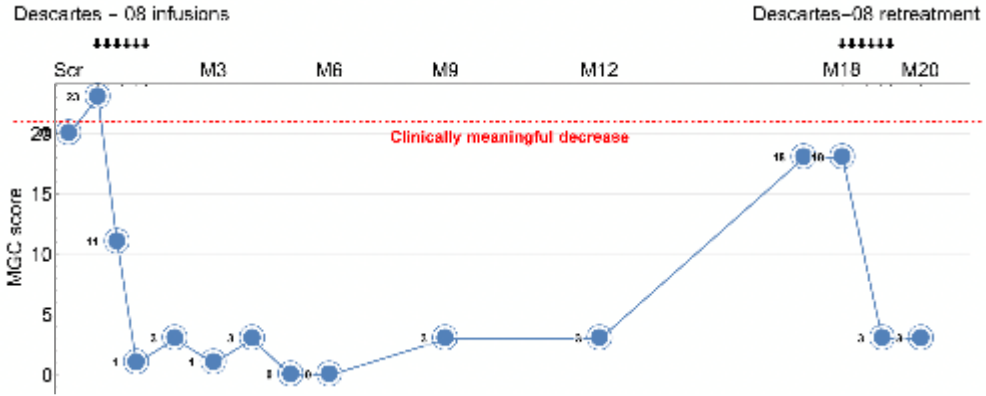
Retreated patients experienced rapid improvement in clinical scores which was ongoing at last follow-up (Month 18 and Month 20)



Retreatment patient 1

Experienced worsening of symptoms to baseline at Month 12

AChR-Ab pos, Failed AZA, Ecu, Pred, Thymex



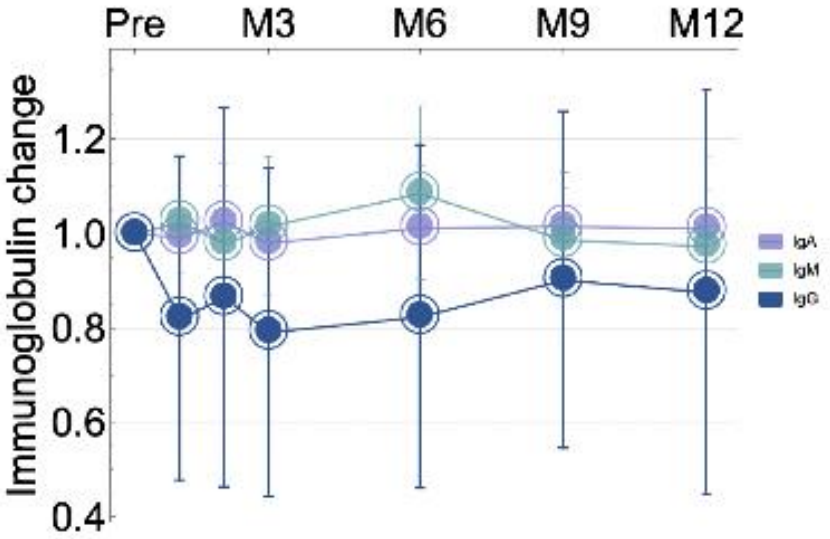
Retreatment patient 2

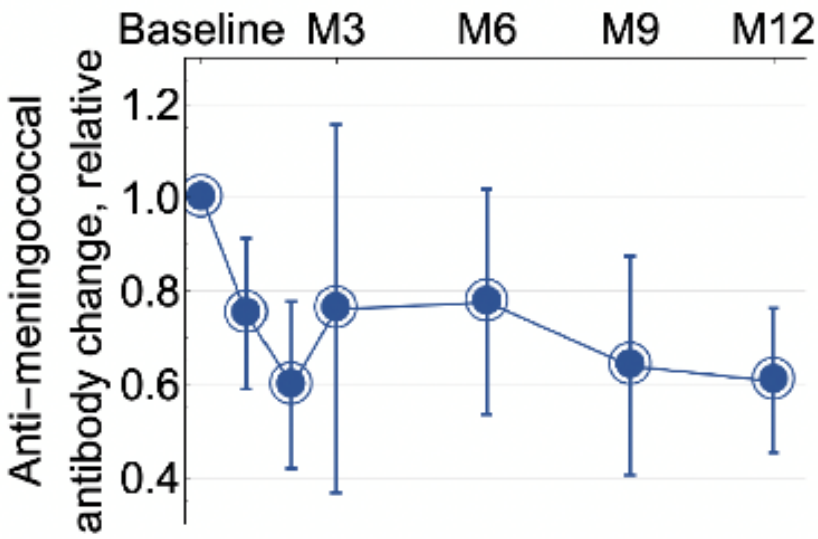
Experienced worsening of symptoms approximately 18 months after initial round of therapy

Seroneg, Failed Pred, MMF

MG-001 Descartes-08

Changes in anti-meningococcal antibody titers and total immunoglobulin levels over 12 months





Manuscript submitted for peer review; pre-print available at medRxiv.org.
Quantitative immunoglobulin levels and anti-meningococcal antibody titers of all participants who received six once-weekly infusions (n=7), measured in a CLIA-certified lab. Lines represent mean levels relative to pre-treatment (“Pre”). Error bars represent 95% Confidence Interval.

Descartes-08 in MG

Phase 2b randomized, placebo-controlled study

Plan to treat ~30 patients

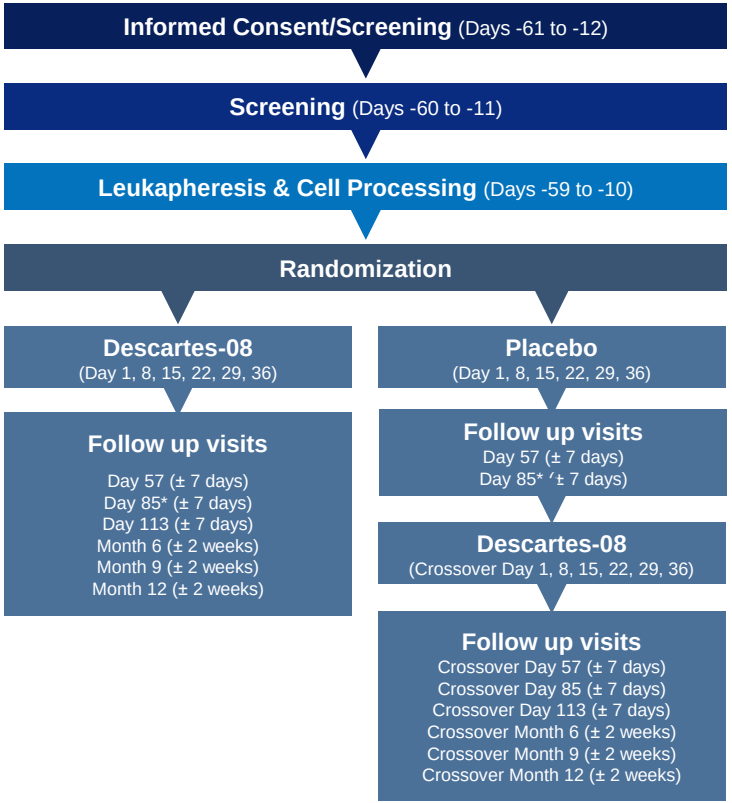
PRIMARY ENDPOINT

- Proportion of **MG Composite** responders (**≥5-point** reduction) at Day 85

SECONDARY OBJECTIVES

- Safety and tolerability
- Quantify clinical effect of Descartes-08 over 1 year
- QMG, MG QoL 15R, MG ADL, and MG PIS (change from baseline to Day 85)
- Compare effect of Descartes-08 versus placebo on MG scales (change from baseline to Day 85) in patients who cross over from placebo to Descartes-08

Enrollment underway, with top-line results expected in mid-2024



MG QMG, Quantitative MG Scores
MG QOL15R, MG Quality of Life 15-revised

MG ADL, MG Activities of Daily Living
MG PIS, MG Post-intervention Status

Summary

- mRNA CAR-Ts have potential to overcome the multiple challenges of DNA CAR-Ts
  - Ability to treat in outpatient setting
  - No lymphodepletion
  - Produces multiple cycles from one apheresis
  - Limited adverse event profile with no CRS, ICANS or severe infection to date
- Expectation for cells to be administered at therapeutic but sub-toxic doses
- Potential for safe re-dosing

Thank You!

Any questions?

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