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A Phase 1b Clinical Trial of CV-MG01, Acetylcholine Receptor Mimetic Peptides

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Myasterix Project

Clinical safety, immunogenicity and efficacy of a therapeutic vaccine that combines peptides mimicking antigen receptors on autoimmune B and T cells associated with myasthenia gravis

In answer to the European Union FP7 call:

«HEALTH.2013.1.3-3: Safety and efficacy of therapeutic vaccines»

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Background

All current therapies for myasthenia gravis are symptomatic or non specific

Non specific immunological treatments have limitations and side effects

A specific immunological treatment for MG is highly desirable

MG is an excellent model for the development of a disease specific immunological treatment

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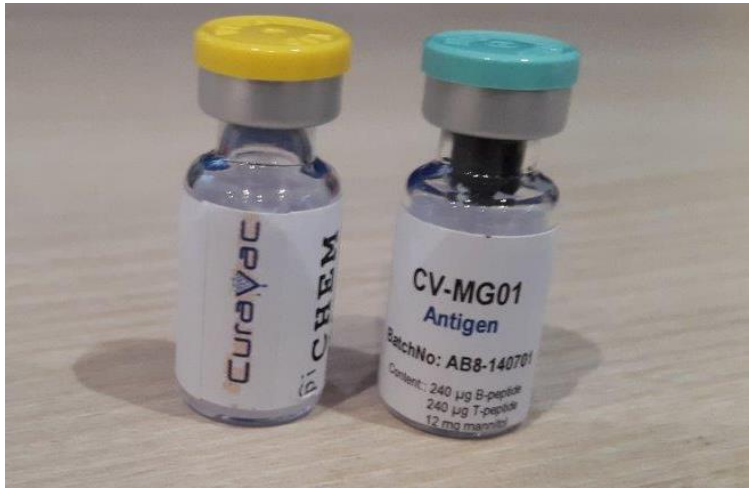
Product: CV-MG01

Peptide based on AChR α AA 61-76 >
ARM peptide RhCA 67-16 = B-peptide

Peptide based on AChR α AA 100-116 >
ARM peptide RhCA 611-001 = T-peptide



Coupled to CRM197
(detoxified DT, carrier protein used in Prevnar® or Menjugate ®)

With aluminum hydroxide as adjuvant in saline

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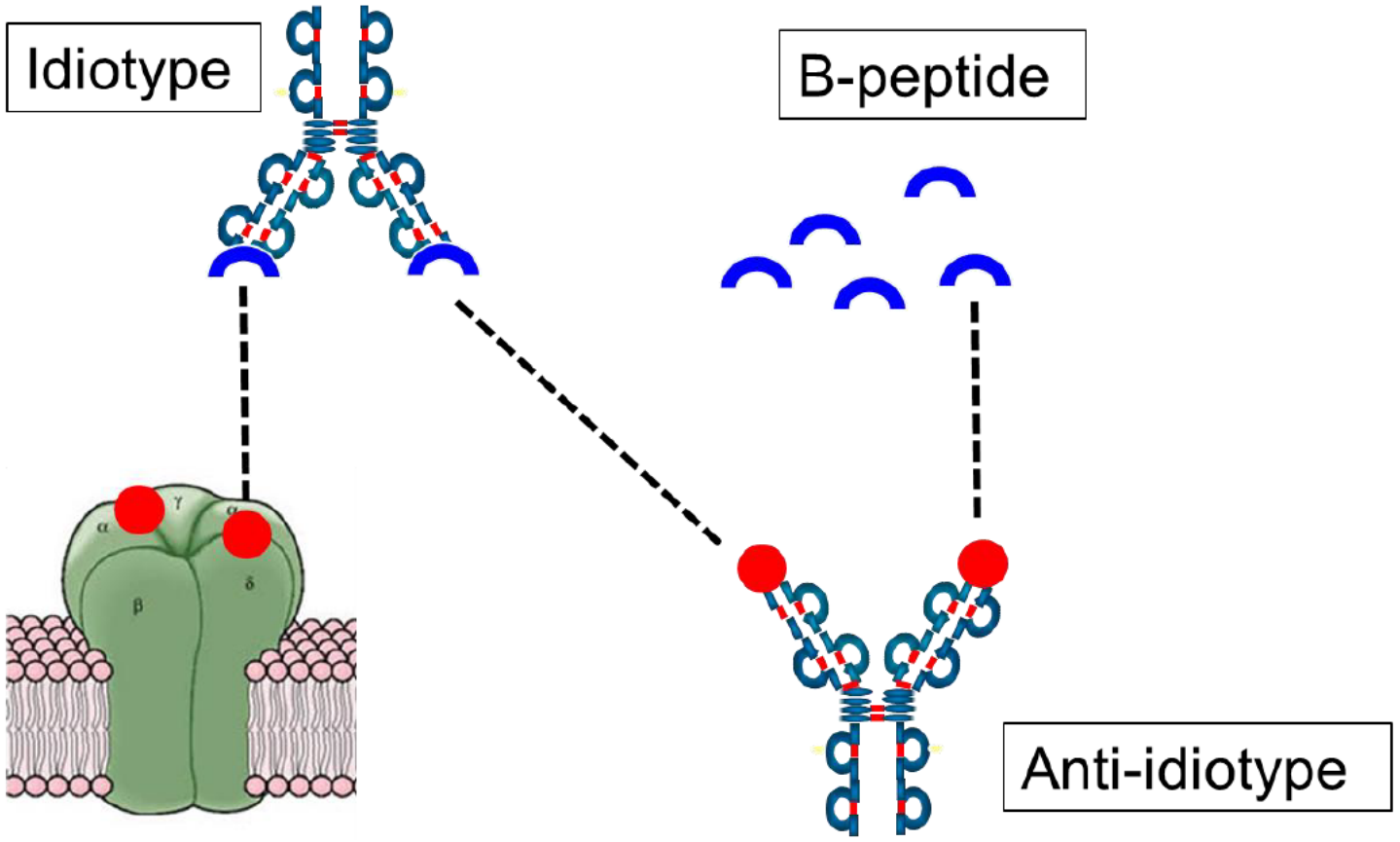
Mechanism of Action of the B-peptide

Figure 1. Anti-B-peptide antibodies are anti-idiotype antibodies of the anti-MIR-AChR antibodies, recognizing the 61-76 epitope on the alfa subunit of the AChR



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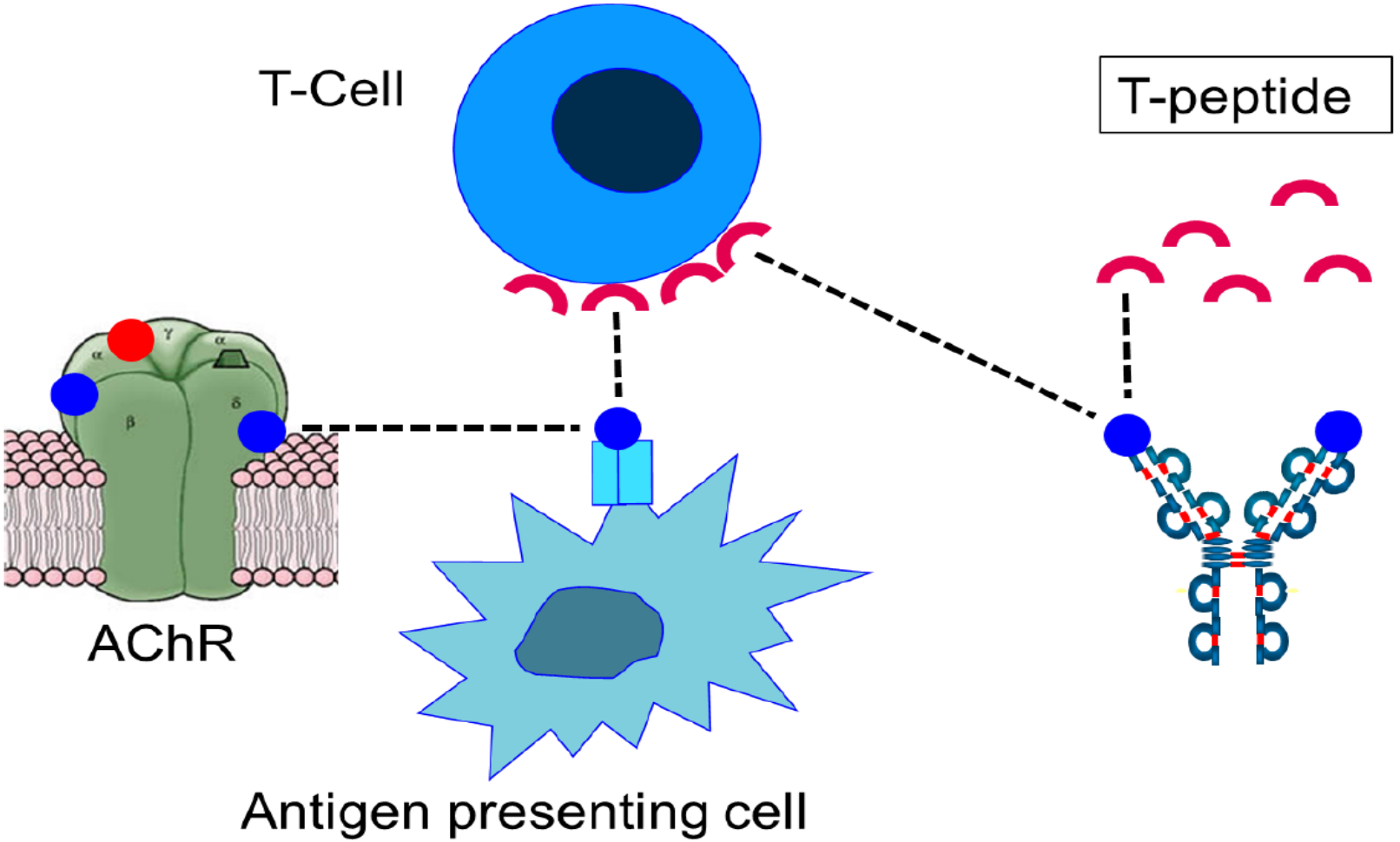
Mechanism of Action of the T-peptide

Figure 2. Anti-T-peptide antibodies bind to the T cell receptor of the T-cells recognizing the 100-116 peptide of the AChR alfasubunit.



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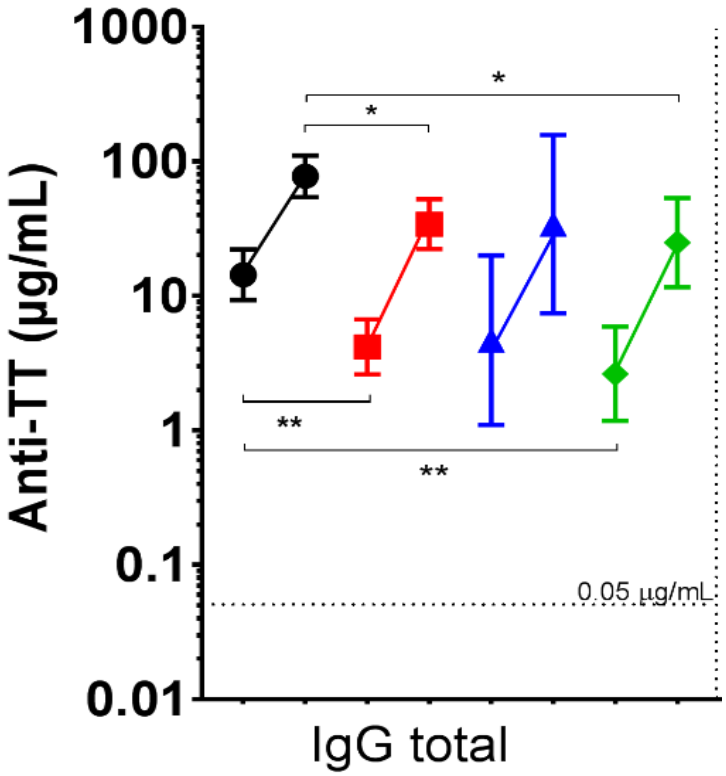
Preclinical & Preliminary Studies

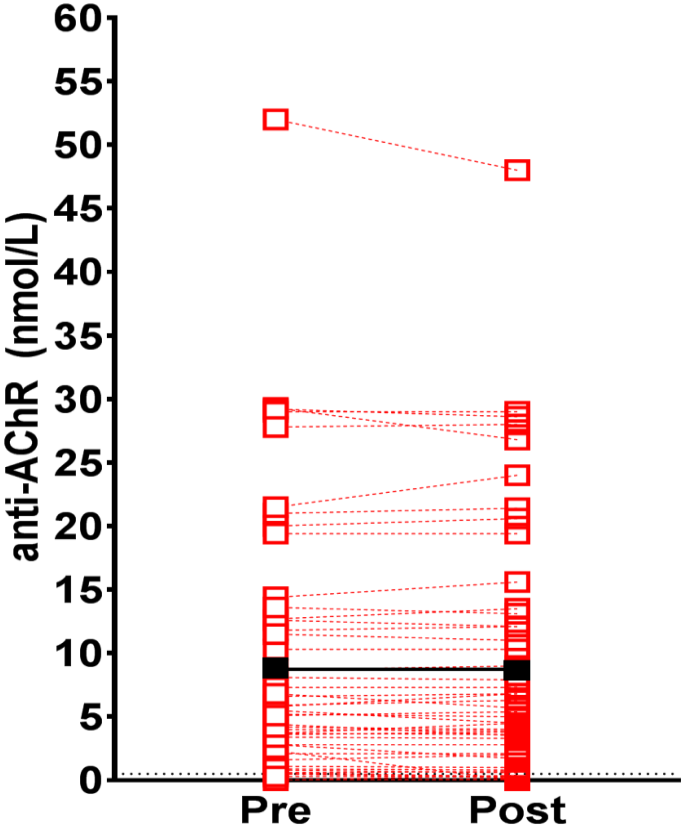
- Early work in vitro, on EAMG rats and on dogs
  - B-peptide, T-peptide and monoclonal antibodies against B- and T-peptide reduce incidence and severity of EAMG in rats
- Is vaccination possible and safe in MG patients?
  - Tetanus study (Strijbos et al, Leiden)
    - vaccination is possible even under immunosuppression
    - tetanus vaccination does not exacerbate MG
- Preparation of therapeutic vaccine for human use
  - Dose finding and GLP regulatory toxicology studies in rats
  - Database search for possible sequence alignment with Human proteome

Tetanus vaccination in MG patients

Anti-tetanus toxin Ab



Anti-AChR Ab



20 healthy controls (●), 50 patients with AChR MG (■), 6 patients with MuSK MG (▲) and 9 with LEMS (◆)

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Study Objectives

Primary objectives:

- To evaluate the **safety** and **tolerability** of CV-MG01 after subcutaneous injections in patients with MG.
- To assess the **immunogenic response** after subcutaneous injections of CV-MG01 on the plasma levels of $RhCA_{611\text{-}001}$ and $RhCA_{67\text{-}16}$ antibodies.

Secondary objectives:

- To perform a **preliminary** evaluation of **efficacy** using clinical scales and questionnaires
- To assess the effect of CV-MG01 subcutaneous injections on the **plasma level of AChR Ab**
- To explore changes in the humoral and cellular immune responses

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Main Inclusion / Exclusion Criteria

Patients with AChR+ MG between age 18 and 65

MGFA grade I, II or III

Stable disease and immunosuppressant treatment

No recent (< 3 m) plasma exchange or IVIG

No recent (< 1 year) thymectomy

No thymoma or other malignancy

No pregnancy

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Study design

3 or 4 cohorts of 8 patients

- double blind, 6 active + 2 placebo

SC injections at week 1, 5 and 13

- Overnight hospital stay after every injection

Biweekly follow-up until week 20

- QMG, MG composite, MG-ADL, QOL-15
- Safety lab, ECG, exploratory lab

Followed by an observational part for 2 years

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Participants

Recruitment period 1 year

24 patients from 6 different countries

18 female patients (24 - 61 y.) / 6 male patients (29 – 64 y.)

MGFA: mostly grade II (18)
QMG: median 8, range 2-19
MG-ADL: median 4, range 0-9

17 patients on steroids and/or immunosuppressants
7 patients only pyridostigmine or no treatment

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Study Progress

Cohort 1: low dose

Interim safety analysis

Cohort 2: high dose

Immunogenicity analysis

Cohort 3: high dose, ongoing

5 x 3 inj, 2 x 2 inj, 1 x 1 inj

Cohort 4: skipped

6 low dose
6 high dose
4 placebo

Immunogenicity and efficacy on 16 patients

Safety analysis on all 24 patients

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Interim Results: Safety

- No Serious Adverse Event
- Frequent local reactions at the injection site, of mild to moderate severity, with spontaneous resolution over days
- One episode of fever 6 hours after the 1st injection in cohort 3
- No significant changes of laboratory values or ECG
- No deterioration of MG during the study, despite fluctuations in some patients.
- One patient of cohort 1 was excluded for an episode of functional weakness several days after the 1st injection of low dose of placebo, with complete recovery within days
- No drop-out, no missed visit

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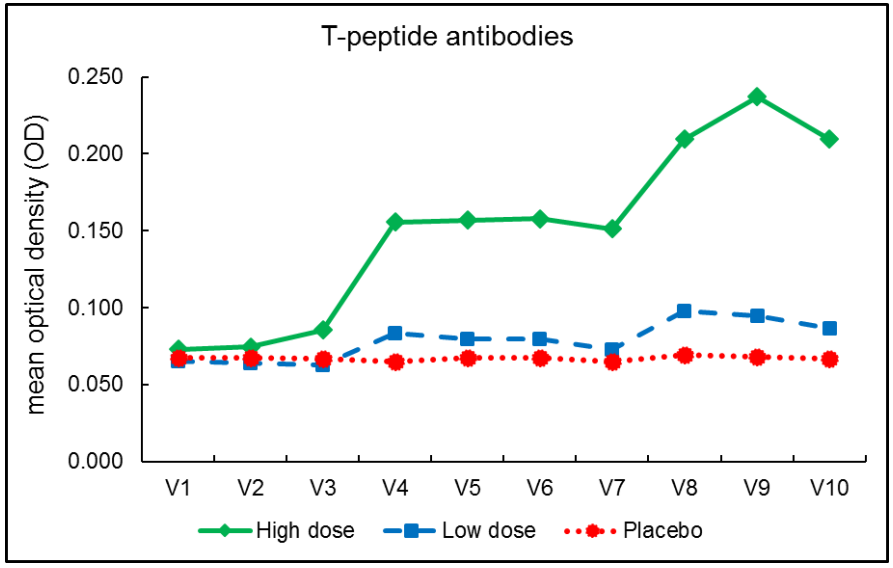
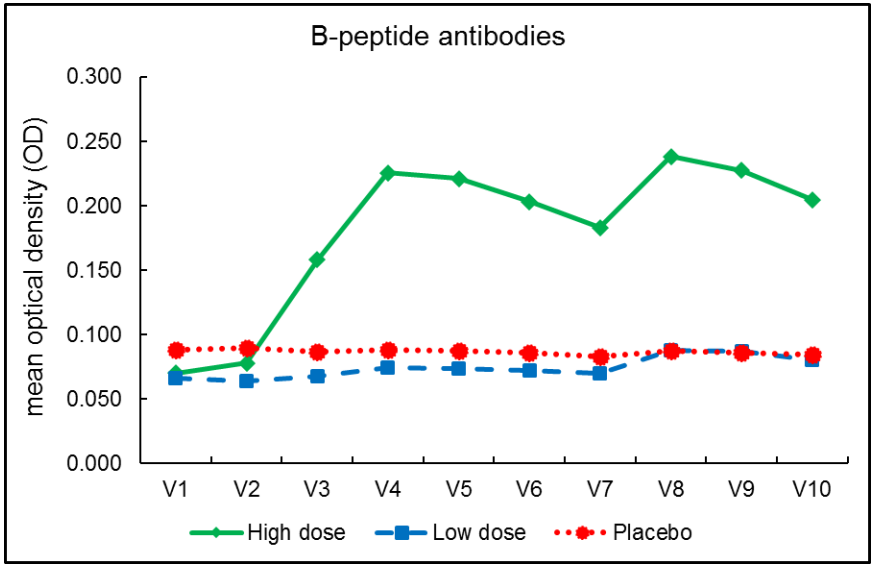
Interim Results: Immunogenicity

- Both peptides are immunogenic at high dose
- Immunogenicity higher at high dose than at low dose

→ high dose selected for cohort 3





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Interim Results: AChR-Ab

Stable level of AChR-Ab with the classic RIA until visit 10 (7 weeks after the 3th injection) in low dose, high dose and placebo

No increase in any patient

Additional tests of anti-MIR-Ab are ongoing

4-montly follow-up for 2 years in the observational study part

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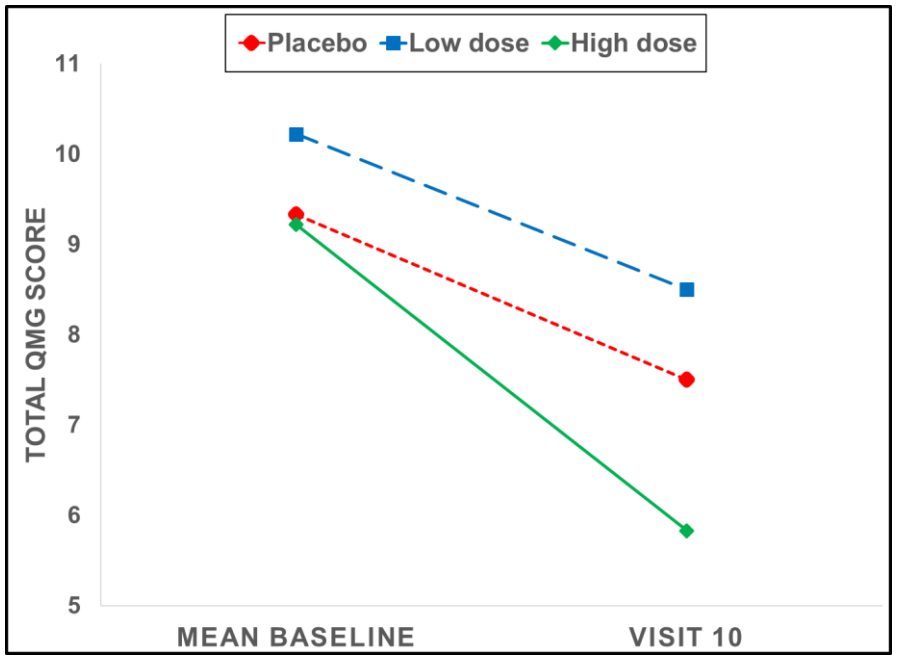
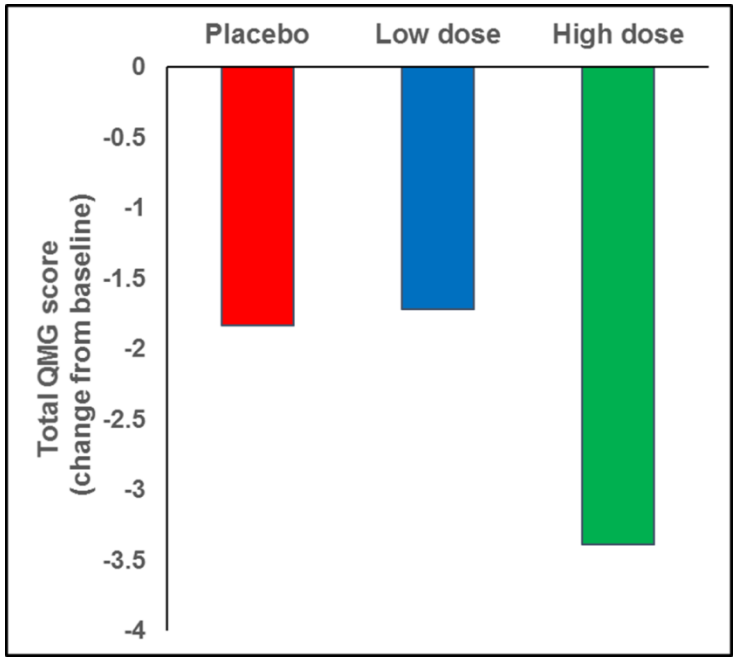
Interim Results: QMG

Larger improvement observed in the high dose group (high dose n=6; low dose n=6; placebo n=4)





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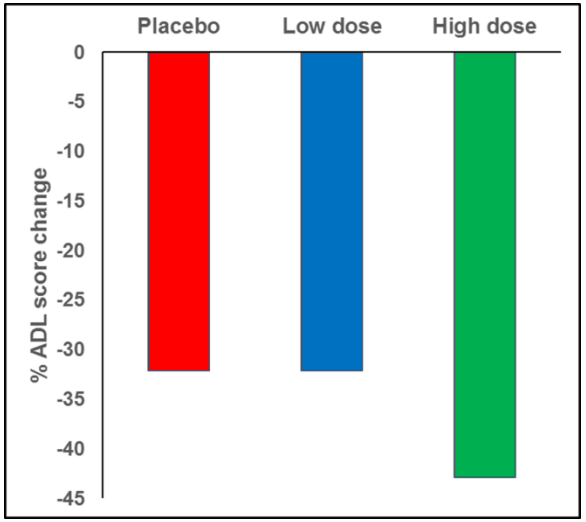
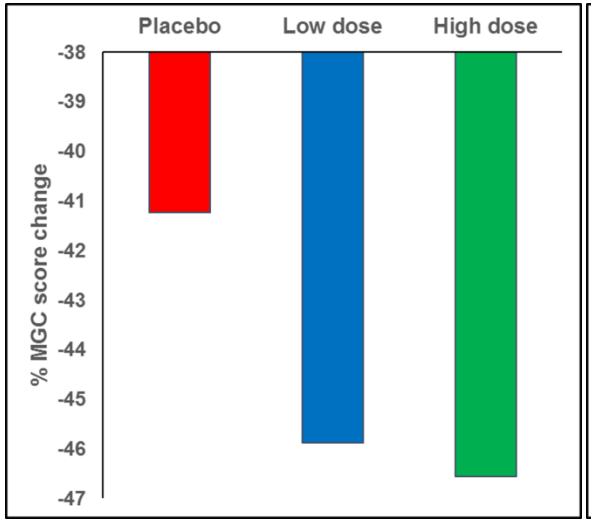
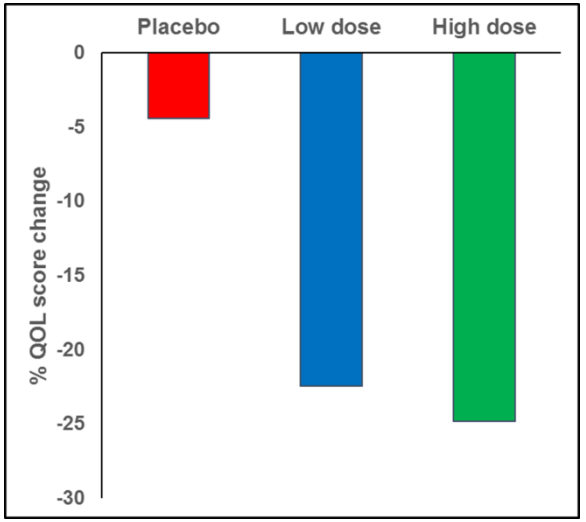
Interim Results: MG-ADL, MGC, QOL-15

MGC index and Quality of life markedly improved in low and high dose group (both n=6) vs. placebo group(n=4)







MG-ADL MG composite QOL-15

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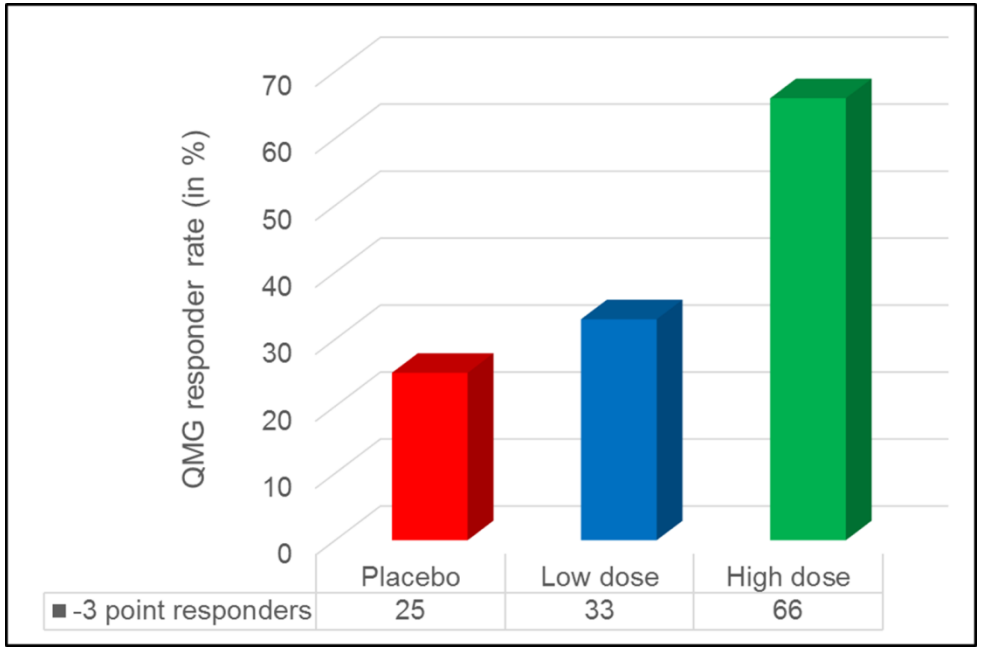
Interim Results: QMG 3-point reduction

Proportion of responders with a diminution of 3 or more QMG points in placebo (n=4), low dose (n=6), and high dose group (n=6)



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Conclusions

Phase 1b

Demonstration of Safety and Immunogenicity (primary objectives)

Preliminary Indication of Efficacy (secondary objective)

but number of patients too small to bring statistical significance

ongoing

Complete 3rd cohort (last visit September 2017)

2-year follow-up in observational part

Exploratory studies

MIR antibodies, functional tests on lymphocytes

Phase 2/3 (Clinical Trial Authorization filed).

High dose vs. placebo with the same injections schedule on 66 patients to bring statistically significant results.

Primary objective: Efficacy

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Thank You !

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