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Empasiprubart in Multifocal Motor Neuropathy: Exploratory Analyses of the Phase 2 ARDA Study

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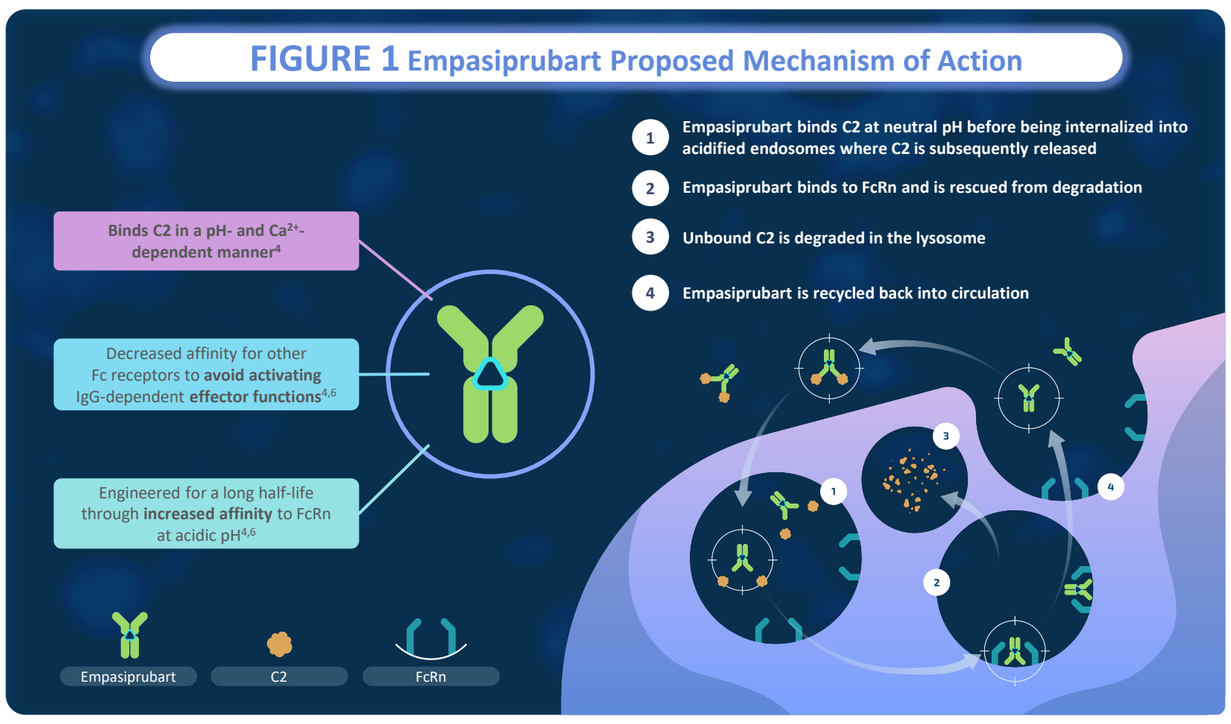
BACKGROUND

Empasiprubart Binds C2 and Blocks Activation of the Classical and Lectin Complement Pathways

- MMN is a rare, peripheral, immune-mediated, complement-driven chronic neuropathy characterized by progressive and disabling asymmetric limb weakness without sensory loss[1–3]
- MMN is caused by IgM autoantibodies, which can activate complement and induce motor nerve conduction block and axonal degeneration[1–3]
  - Anti-GM1 IgM antibodies are found in ≥40% of MMN cases (measured by INCAT ELISA)[2]
- C2 may be an optimal point of intervention within the complement cascade, as:
  - C2 is at the crossroads of the classical and lectin pathways[4] and does not impact the alternative pathway (reduced infection risk)[4,5]
  - Targeting C2 upstream of C3 and C5 inhibits C3 and C5 effector functions[5]
- Empasiprubart is a first-in-class, humanized, monoclonal antibody that specifically binds to C2[4] (**Figure 1**)
  - IgM autoantibody-mediated complement activation was effectively inhibited by targeting C2 with empasiprubart in an *in vitro* model of MMN[1]

FIGURE 1 Empasiprubart Proposed Mechanism of Action



OBJECTIVE AND METHODS

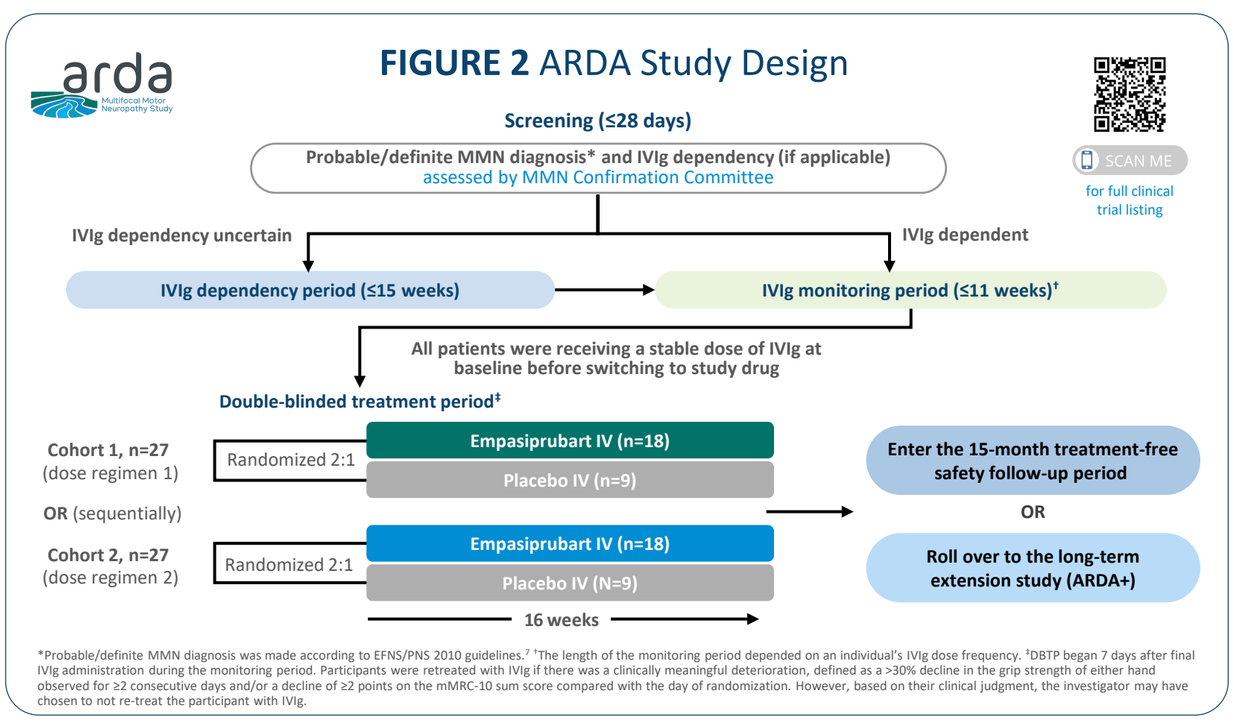
Objective

To investigate the effect of empasiprubart on anti-ganglioside GM1 status, the impact of this status on the empasiprubart treatment response, and the complement inhibitory effect of empasiprubart assessed by an *in vitro* iPSC motor neuron model in the phase 2 ARDA study (NCT05225675) in adults with MMN

Methods

- ARDA included 54 participants with probable/definite MMN, IVIg dependency, and stable IVIg dosing
- Participants were randomized (2:1) to receive empasiprubart or placebo (**Figure 2**)
- Blood samples were collected during the IVIg monitoring and double-blinded treatment periods to assess serum antiganglioside antibodies and changes in complement activity in an *in vitro* iPSC motor neuron model
- Treatment response was assessed using MMN-RODS, mMRC-10, and grip strength

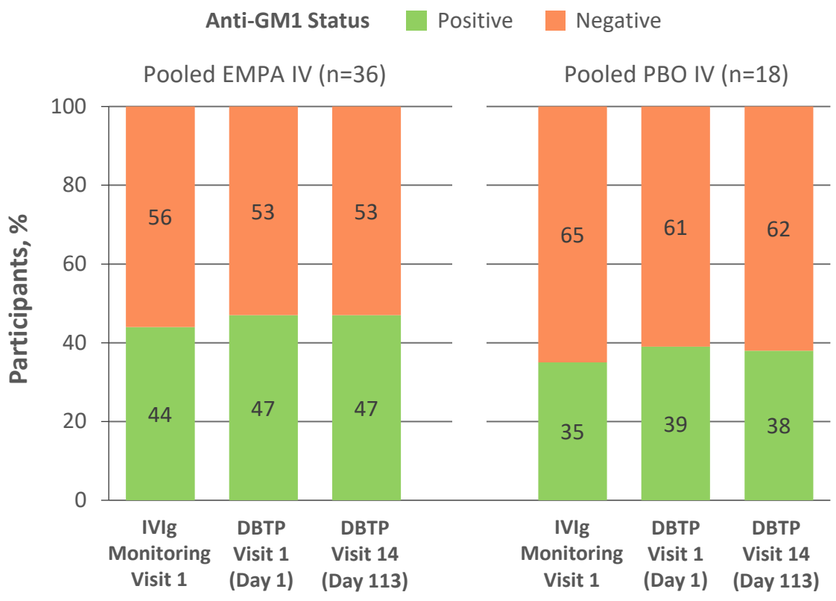
FIGURE 2 ARDA Study Design



*Probable/definite MMN diagnosis was made according to EFNS/PNS 2010 guidelines.[7] †The length of the monitoring period depended on an individual's IVIg dose frequency. ‡DBTP began 7 days after final IVIg administration during the monitoring period. Participants were retreated with IVIg if there was a clinically meaningful deterioration, defined as a >30% decline in the grip strength of either hand observed for ≥2 consecutive days and/or a decline of ≥2 points on the mMRC-10 sum score compared with the day of randomization. However, based on their clinical judgment, the investigator may have chosen to not re-treat the participant with IVIg.

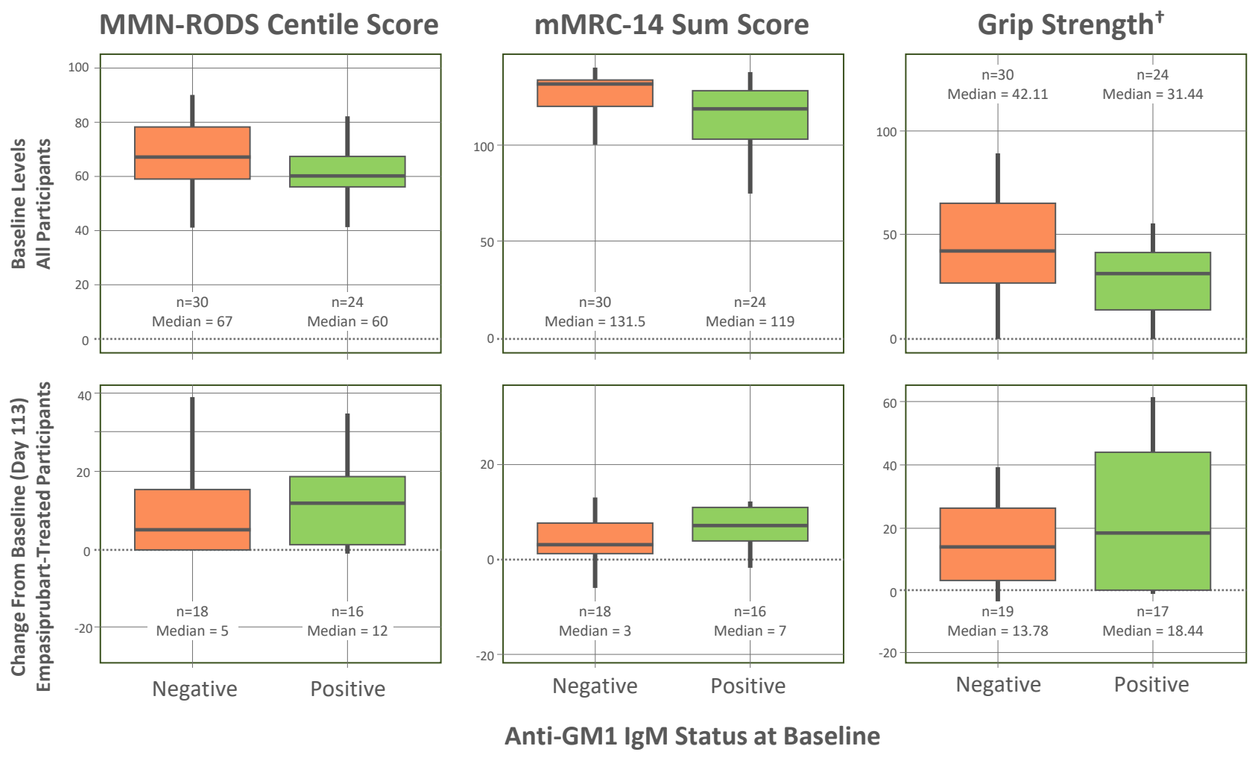
RESULTS

FIGURE 3 IgM Anti-GM1 Titers Over Time



- ~40% of participants had IgM antibodies against GM1, as detected by INCAT ELISA
- Anti-GM1 positivity/negativity remained stable over time and was unaffected by empasiprubart treatment

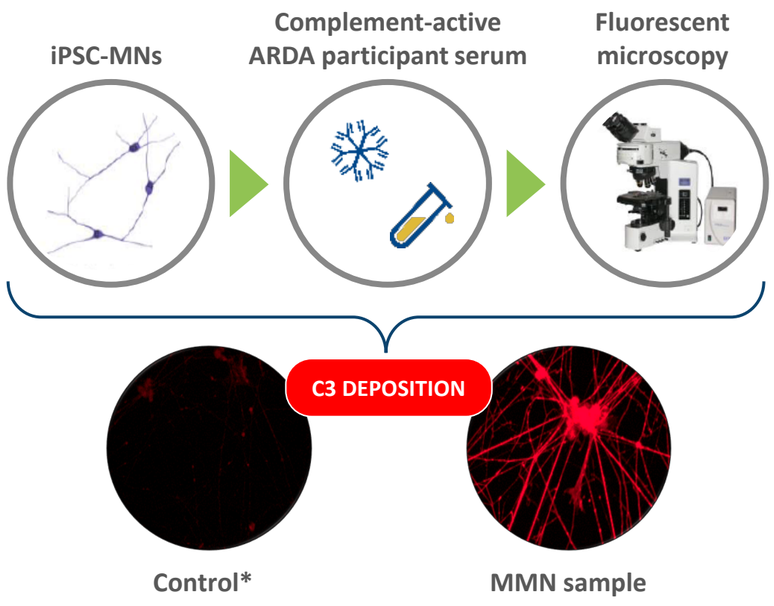
FIGURE 4 Baseline and Change From Baseline at Last Assessment* by Anti-GM1 Status



- Symptoms were slightly more severe at baseline in anti-GM1 positive participants
- Anti-GM1 status did not determine the response to empasiprubart treatment at Day 113

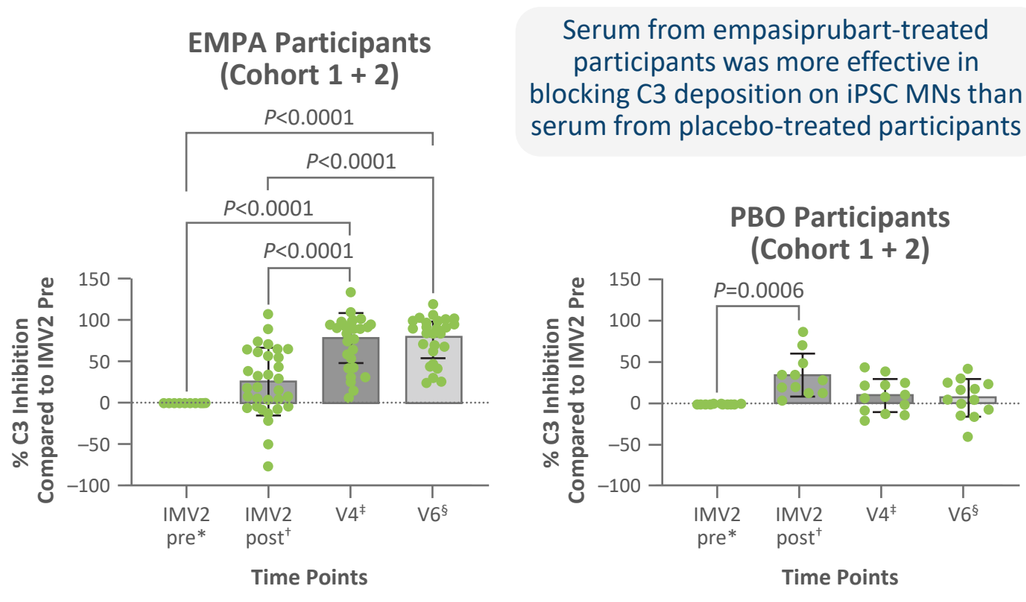
*Last assessment during the double-blinded treatment period. †3-day moving average; most affected hand.

FIGURE 5 *In Vitro* iPSC Motor Neuron Model



*Negative control sample was a complement active serum pre-incubated with 10 mM EDTA to correct for nonspecific background C3 fixation.

FIGURE 6 Inhibition of C3 Fixation



Serum from empasiprubart-treated participants was more effective in blocking C3 deposition on iPSC MNs than serum from placebo-treated participants

- >90% ARDA participant serum samples showed C3 complement deposition to iPSCs despite ~40% giving a positive anti-GM1 ELISA result
- Empasiprubart-treated participants demonstrated a decrease in C3 deposition, in alignment with positive clinical outcome in this treatment group
- A reduction in C3 fixation was linked with clinical improvement (grip strength, MMN-RODS, mMRC-14 sum score)

*IMV2 pre samples were taken prior to IVIg cycle 2 during the IVIg monitoring period. †IMV2 post samples were taken after IVIg cycle 2 during the IVIg monitoring period. ‡V4, visit 4 (Day 15); §V6, visit 6 (Day 29).

KEY TAKEAWAYS

ARDA is the largest interventional study conducted in MMN to date (N=54)

Anti-GM1 status remained stable over time and did not impact response to empasiprubart, suggesting empasiprubart may be effective regardless of anti-GM1 status

In an *in vitro* iPSC motor neuron model, empasiprubart provides potent complement inhibition, leading to improved outcomes over IVIg and supporting a complement-driven mechanism in MMN regardless of anti-GM1 status

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ABBREVIATIONS

C2, complement component 2; C3, complement component 3; C5, complement component 5; Ca^{2+}, calcium ion; DBTP, double-blind treatment period; EDTA, ethylenediaminetetraacetic acid; EFNS, European Federation of Neurological Societies; ELISA, enzyme-linked immunosorbent assay; EMPA, empasiprubart; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; GM1, monosialotetrahexosylganglioside; Ig, immunoglobulin; IMV, IVIg monitoring visit; INCAT, Inflammatory Neuropathy Cause and Treatment; iPSC, induced pluripotent stem cell; IV, intravenous; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MMN-RODS, Rasch-Built Overall Disability Scale for Multifocal Motor Neuropathy; MN, motor neuropathy; mMRC-10/14, modified Medical Research Council-10/14; PBO, placebo; PNS, Peripheral Nerve Society.

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