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Empasiprubart (ARGX-117) in Multifocal Motor Neuropathy: Baseline Characteristics and MMN Confirmation Committee Outcomes of the Phase 2 ARDA Study

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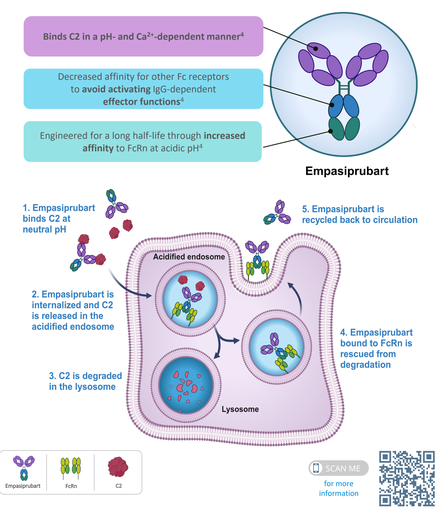
BACKGROUND

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

- MMN is a rare, immune-mediated, chronic neuropathy leading to axonal degeneration and progressive, disabling asymmetric limb weakness with absence of sensory loss[1–3]
- MMN is characterized by multifocal, persistent motor nerve conduction block[1,2]
- Anti-GM1 IgM antibody-mediated complement activation plays a central role in the pathogenesis of MMN[1–3]
  - Anti-GM1 IgM antibodies are found in ≥40% of MMN cases[2]
- C2 may be an optimal point of intervention within the complement cascade
  - C2 is at the crossroad of the classical and lectin pathways[4]
  - The alternative pathway remains intact (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 present updated baseline characteristics, demographics, and MMN confirmation committee (MCC) outcomes of participants from cohorts 1 and 2 in ARDA (NCT05225675), a phase 2, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study in adults with MMN

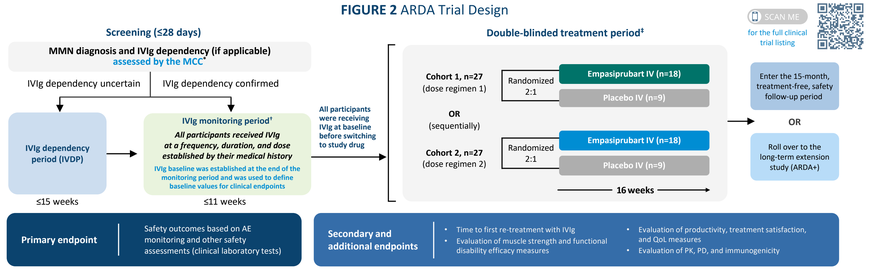
MCC Screening

- Participants were screened by the MCC to evaluate the diagnosis of MMN and assess IVIg dependency (**Figure 2**)
- The MCC was composed of an international panel of 4 neurologists experienced in the diagnosis and treatment of MMN
  - In the first phase (phase 1 MCC review), participant documentation was assessed to determine study eligibility
  - If there was diagnostic uncertainty during phase 1 MCC review, a second review was initiated (phase 2 MCC review)
- MMN was evaluated according to the clinical, electrophysiological, and supportive criteria from the EFNS/PNS 2010 guidelines[6]
- IVIg treatment dependency was evaluated using existing medical history data. Participants with unconfirmed IVIg dependency entered the IVDP (**Figure 2**)
  - During the IVDP, IVIg dependency was determined by assessing clinical outcomes following delayed IVIg administration

ARDA

- ARDA enrolled 54 adults with MCC-confirmed probable or definite MMN and proven IVIg dependency (**Figure 2**)

FIGURE 2 ARDA Trial Design

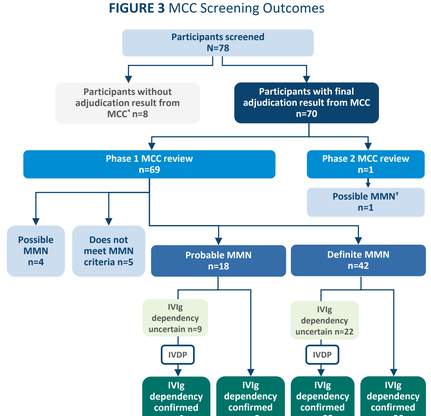


*Vaccinations were required. IVIg dependency parameters and vaccination requirements are summarized in the key inclusion criteria, the full details of which are provided at https://www.clinicaltrials.gov/study/NCT05225675. †The length of the monitoring period depended on an individual's IVIg dose frequency: dosed every 2 weeks–up to 35 days monitoring, dosed every 3 weeks–49 days monitoring, dosed every 4 weeks–63 days monitoring, dosed every 5 weeks–77 days monitoring. ‡DBTP began 7 days after final IVIg administration during the monitoring period. Participants were re-treated with IVIg if there was a clinically meaningful deterioration in muscle strength and/or motor function. Clinically meaningful deterioration was 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

- A total of 78 participants were screened (**Figure 3**)
- Of these, 70 were assessed by the MCC
  - 60 (86%) had probable or definite MMN per the EFNS/PNS 2010 criteria
  - Of these 60, most (70%) were classified as having definite MMN, while 30% were classified as having probable MMN
- Of the 60 participants with probable or definite MMN confirmed by the MCC
  - IVIg dependency was certain for 29 participants
  - IVIg dependency was initially uncertain for 31 participants but then confirmed by the MCC following IVDP
- Of the 60 participants with probable or definite MMN, 54 entered ARDA cohort 1 (n=27) or cohort 2 (n=27) and were randomized to empasiprubart IV or placebo; 6 participants were not randomized to ARDA following withdrawal of consent and/or not meeting inclusion criteria
- Baseline characteristics across cohorts were generally well balanced between the empasiprubart IV and placebo arms (**Table 1**)

FIGURE 3 MCC Screening Outcomes



*Participants who had already been screened and failed or who withdrew consent. †Not possible to make a diagnosis of MMN due to a lack of adequate NCS with CMAP durations and CMAP areas.

TABLE 1 Demographics and Baseline Disease Characteristics

	Cohort 1		Cohort 2	
	Empasiprubart IV (n=18)	Placebo IV (n=9)	Empasiprubart IV (n=18)	Placebo IV (n=9)
Age, median (Q1, Q3), years	54.5 (47.0, 61.0)	44.0 (42.0, 54.0)	55.5 (50.0, 59.0)	58.0 (55.0, 61.0)
Sex, female, n (%)	7 (38.9)	4 (44.4)	6 (33.3)	4 (44.4)
Region, n (%)				
North America*	5 (27.8)	4 (44.4)	2 (11.1)	4 (44.4)
Europe†	13 (72.2)	5 (55.6)	16 (88.9)	5 (55.6)
Time since diagnosis, median (Q1, Q3), years	8.10 (5.39, 11.28)	9.99 (4.77, 11.29)	10.14 (5.99, 13.30)	15.63 (8.24, 23.17)
IVIg duration, median (Q1, Q3), years‡	2.63 (0.76, 5.43)	1.89 (0.27, 3.21)	0.50 (0.27, 3.05)	1.80 (0.24, 9.99)
IVIg frequency issued from eCRF, n (%)				
Every 2 or 3 weeks	10 (55.6)	5 (55.6)	10 (55.6)	5 (55.6)
Every 4 or 5 weeks	8 (44.4)	4 (44.4)	8 (44.4)	4 (44.4)
IVIg dose, median (Q1, Q3), g/kg	1.55 (1.00, 2.00)	1.30 (0.80, 1.50)	1.00 (0.80, 1.21)	1.00 (0.62, 1.00)
Grip strength 3-day moving average, median (Q1, Q3), kPa§				
Most affected hand	33.50 (14.44, 61.78)	40.00 (23.11, 54.67)	31.11 (6.67, 52.56)	47.33 (40.78, 61.11)
Least affected hand	56.92 (37.78, 74.00)	64.00 (41.00, 69.00)	56.97 (22.00, 87.44)	57.78 (55.33, 74.89)
mMRC-10 sum score, median (Q1, Q3)§	96.0 (87.0, 98.0)	95.0 (88.0, 96.0)	93.5 (91.0, 95.0)	98.0 (89.0, 99.0)
MMN-RODS centile metric score, median (Q1, Q3)§	59.0 (53.0, 67.0)	70.0 (60.0, 82.0)	63.0 (58.0, 76.0)	66.0 (66.0, 76.0)
FSS score, median (Q1, Q3)§	4.67 (3.22, 6.33)	4.22 (3.67, 4.56)	3.83 (2.11, 5.56)	5.56 (5.11, 5.78)
CAP-PRI score, median (Q1, Q3)§	13.0 (10.0, 19.0)	8.0 (6.0, 10.0)	10.5 (5.0, 15.0)	12.0 (8.0, 12.0)

*US and Canada. †European Union, European Economic Area, European Free Trade Area, and the UK. ‡The duration of IVIg ongoing at screening is defined as follows: screening date – starting date of last IVIg administration stable before screening +1. §Baseline values established following IVIg monitoring period and prior to initiation of the DBTP. Slight imbalances were observed between treatment arms (cohort 1: median age, median IVIg duration, median MMN-RODS score, and median CAP-PRI score; cohort 2: median time since diagnosis, median IVIg duration, grip strength [most affected hand], and median FSS score), with lower disease-specific QoL and functional disability measures among participants in the empasiprubart arm compared with those in the placebo arm. All baseline values were established at the initiation of the IVIg monitoring period unless otherwise specified.

KEY TAKEAWAYS

ARDA, the largest interventional study conducted in MMN to date, used an MCC screening process to determine MMN diagnosis and IVIg dependency prior to first administration of study drug

70 participants were assessed by the MCC, which confirmed that 86% (n=60) had probable or definite MMN; 54 of these participants were randomized to ARDA to receive either the study drug or placebo

A considerable proportion of participants screened during the MCC review were diagnosed with possible or probable MMN rather than definite MMN. These uncertainties indicate a need for improved diagnostic markers and standardized diagnostic criteria for MMN

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ABBREVIATIONS

AE, adverse event; C2, complement component 2; Ca^{2+}, calcium ion; CAP-PRI, chronic acquired polyneuropathy patient-reported index; CMAP, compound muscle action potential; DBTP, double-blinded treatment period; eCRF, electronic case report form; EFNS, European Federation of Neurological Societies; FcRn, neonatal Fc receptor; FSS, 9-item Fatigue Severity Scale; GM1, monosialotetrahexosylganglioside; Ig, immunoglobulin; IV, intravenous; IVDP, IVIg dependency period; IVIg, intravenous immunoglobulin; kPa, kilopascal; MMN, multifocal motor neuropathy; MMN-RODS, Rasch-Built Overall Disability Scale for Multifocal Motor Neuropathy; mMRC-10, modified Medical Research Council-10; NCS, nerve conduction studies; PD, pharmacodynamics; PK, pharmacokinetics; PNS, Peripheral Nerve Society; Q, quartile; QoL, quality of life.

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REFERENCES

1. Budding K, et al. *Neurol Neuroimmunol Neuroinflamm*. 2021;9:e1107.
2. Yeh WZ, et al. *J Neurol Neurosurg Psychiatry.* 2020;91:140–8.
3. Vlam L, et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e119.
4. Van de Walle I, et al. *J Allergy Clin Immunol.* 2021;147:1420–9.e7.
5. Garred P, et al. *Pharmacol Rev.* 2021;73:792–827.
6. Joint Task Force of the EFNS and the PNS. *J Peripher Nerv Syst.* 2010;15:295–301.