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Empasiprubart (ARGX-117) in Multifocal Motor Neuropathy: Initial Safety and Efficacy Data of the Phase 2 ARDA Study

Luis Querol,[1,2] Chafic Karam,[3] W. Ludo van der Pol,[4] Stojan Peric,[5] Yessar Hussain,[6] Stephanie Cadour,[7] Inge Van de Walle,[7] Emma Persson,[7] Iris Van Hoomissen,[7] Oleksandr Mashchenko,[7] Miodrag Vujcic,[7] Olivier Van de Steen,[7] Jeffrey A. Allen[8]

[1]Hospital de la Santa Creu i Sant Pau, Neuromuscular Disorders Unit, Barcelona, Spain; [2]Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Madrid, Spain; [3]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht, The Netherlands; [5]University of Belgrade, Faculty of Medicine, Neurology Clinic, University Clinical Center of Serbia, Belgrade, Serbia; [6]Austin Neuromuscular Center, Austin, TX, USA; [7]argenx, Ghent, Belgium; [8]Department of Neurology, University of Minnesota, Minneapolis, MN, USA

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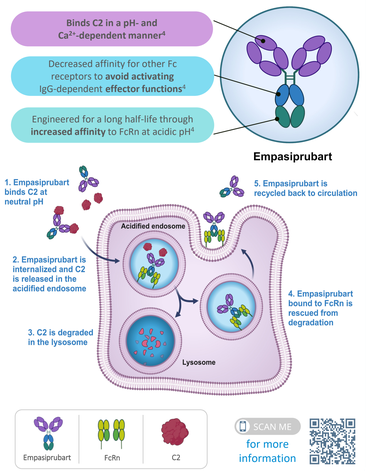
BACKGROUND

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



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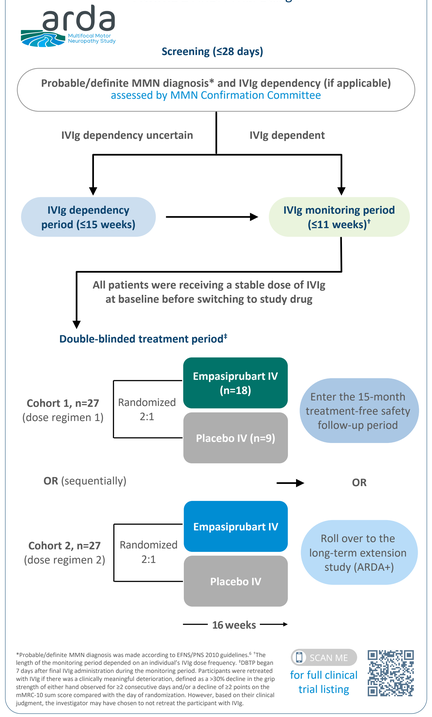
OBJECTIVE

- To assess the safety and efficacy of empasiprubart in ARDA (NCT05225675), a phase 2, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study in adults with MMN (**Figure 2**)

METHODS

FIGURE 2 ARDA Trial Design



*Probable/definite MMN diagnosis was made according to EFNS/PNS 2010 guidelines.[6] †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 retreat the participant with IVIg.

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RESULTS

Empasiprubart Was Generally Well Tolerated and Demonstrated Clinical Benefits Compared With Placebo

- 54 participants were enrolled; data from cohort 1 (n=27) are presented here
- Baseline characteristics were generally well balanced between the empasiprubart and placebo arms (**Table 1**)
- Most AEs were mild to moderate in severity (**Table 2**)
- A greater proportion of empasiprubart-treated participants reported their condition improved compared with placebo (**Figure 3**)
- Compared with placebo, empasiprubart:
  - Improved muscle strength, reduced fatigue severity, and improved health-related QoL and functional disability measures as reported by the participants (**Table 3**)
  - Reduced the risk of IVIg retreatment by 91% (**Figure 4**)
  - Improved grip strength in both hands (**Figure 5A**)
  - Improved disease-specific activity limitations associated with MMN (**Figure 5B**)

TABLE 1 Demographics and Baseline Disease Characteristics

	Empasiprubart (n=18)	Placebo (n=9)
Age, median (Q1, Q3), years	54.5 (47.0, 61.0)	44.0 (42.0, 54.0)
Sex, female, n (%)	7 (38.9)	4 (44.4)
Time since diagnosis, median (Q1, Q3), years	8.10 (5.39, 11.28)	9.99 (4.77, 11.29)
IVIg duration, median (Q1, Q3), years*	2.634 (0.764, 5.426)	1.892 (0.274, 3.211)
IVIg frequency issued from eCRF, n (%) Every 2 or 3 weeks Every 4 or 5 weeks	10 (55.6) 8 (44.4)	5 (55.6) 4 (44.4)
IVIg dose, median (Q1, Q3), g/kg	1.550 (1.000, 2.000)	1.300 (0.800, 1.500)
Grip strength 3-day moving average, median (Q1, Q3), kPa† Most affected hand Least affected hand	33.50 (14.44, 61.78) 56.92 (37.78, 74.00)	40.00 (23.11, 54.67) 64.00 (41.00, 69.00)
mMRC-10 sum score, median (Q1, Q3)†	96.0 (87.0, 98.0)	95.0 (88.0, 96.0)
MMN-RODS centile metric score, median (Q1, Q3)†	59.0 (53.0, 67.0)	70.0 (60.0, 82.0)
FSS score, median (Q1, Q3)†	4.67 (3.22, 6.33)	4.22 (3.67, 4.56)
CAP-PRI score, median, (Q1, Q3)†	13.0 (10.0, 19.0)	8.0 (6.0, 10.0)

*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 in median age, grip strength, MMN-RODS score, and CAP-PRI score between treatment arms, 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.

TABLE 2 Overview of Safety

	Empasiprubart (n=18; PYFU=5.55)		Placebo (n=9; PYFU=2.62)	
Participant with event	**n (%)**	**Events**	**n (%)**	**Events**
Any AE*	14 (77.8)	33	5 (55.6)	14
Any SAE	2 (11.1)†	2	0 (0.0)	0
Procedure-related AEs	2 (11.1)	2	0 (0.0)	0
Discontinued treatment due to AEs	1 (5.6)‡	1	0 (0.0)	0
Any grade ≥3 AEs	2 (11.1)	2	0 (0.0)	0
AEs of special interest§	1 (5.6)‖	1	0 (0.0)	0
Deaths	0 (0.0)	0	0 (0.0)	0
Most common AEs (≥2 participants in any group)				
Headache	5 (27.8)	6	1 (11.1)	1
Urinary tract infection	2 (11.1)	2	0 (0.0)	0

*AEs were predominantly mild or moderate in severity. †SAEs: Pneumonia grade 3 (not related) and acute coronary syndrome grade 4 (considered treatment-related by the investigators). ‡One patient discontinued treatment due to grade 4 acute coronary syndrome. §AEs of special interest were defined as severe infection events (grade ≥3). ‖Severe infection: Pneumonia grade 3 (not related).

TABLE 3 Change From Baseline in Strength and QoL Outcomes by Treatment Group at Last Assessment During DBTP

Change from baseline* at last assessment during DBTP, median (Q1, Q3)	Empasiprubart (n=18)†	Placebo (n=9)‡
Grip strength 3-day moving average, kPa§ Most affected hand Least affected hand	11.28 (0.00, 28.78) 6.50 (0.06, 12.61)	0.89 (−0.67, 9.00) 1.67 (−0.33, 5.44)
mMRC-10 sum score‖	2.0 (0.0, 3.0)	−1.0 (−5.0, 0.0)
MMN-RODS centile metric score¶	6.0 (0.0, 14.0)	0.0 (−2.0, 0.0)
FSS score**	−0.44 (−1.56, 0.0)	0.22 (0.11, 1.22)
CAP-PRI score††	−2.5 (−6.0, −1.0)	0 (−1.0, 2.0)

*Baseline values were established following IVIg monitoring period and prior to initiation of the DBTP. †Three out of 18 patients were retreated with IVIg during the DBTP. ‡Seven out of 9 patients were retreated with IVIg during the DBTP. §Grip strength was measured three times daily using the Martin vigorimeter, and a 3-day (Day −2, −1, and 0) moving average was generated. ‖The mMRC-10 sum score is a measure of motor strength or weakness in a predetermined set of muscle groups. Higher mMRC-10 scores indicate improvement. ¶MMN-RODS is a disease-specific 25-item instrument to capture activity limitations. Each item is scored 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty) for each item yielding a total score from 0 to 50. **The FSS consists of 9 items to measure the respondent's fatigue symptoms over the past week. The final score is an average of the 9 items and ranges from 0 to 7. Lower FSS scores indicate improvement. ††The CAP-PRI is a disease-specific QoL PRO. Lower CAP-PRI scores indicate improvement.

FIGURE 3 PGIC Score by Treatment Group at Last Assessment During DBTP

"How much has your condition (MMN) changed as compared to the time you received the first treatment in this trial?"

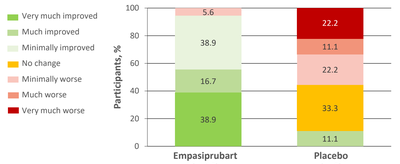
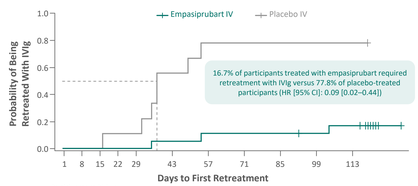
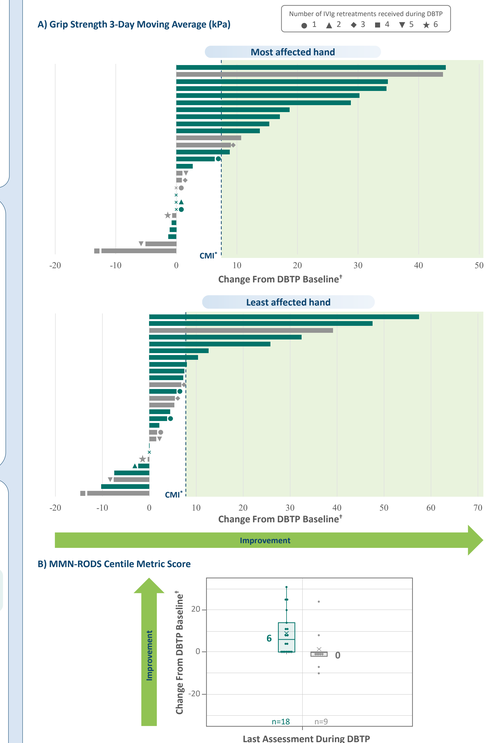


FIGURE 4 Time to First Retreatment* With IVIg



*Defined as the time from last IVIg administration before randomization (including unscheduled visits) up to first IVIg retreatment during the DBTP.

FIGURE 5 Change From Baseline in Grip Strength and MMN-RODS Centile Metric Score by Treatment Group at Last Assessment During DBTP



*Dotted line indicates the threshold for achieving CMI (≥8 kPa; participants achieving CMI are highlighted by the green box). †Baseline values were established following the IVIg monitoring period and prior to initiation of the DBTP.

KEY TAKEAWAYS

ARDA is the largest interventional study conducted in MMN to date; we report data for the 27 participants who received empasiprubart or placebo in cohort 1 of ARDA

Empasiprubart was generally well tolerated; most AEs were mild or moderate in severity

Compared with placebo, empasiprubart:

- Reduced IVIg retreatment risk by 91%
- Improved grip and muscle strength
- Improved disease-specific QoL and functional disability measures
- Improved self-reported condition

Early safety and efficacy results from ARDA cohort 1 support proof of concept of empasiprubart in MMN and pave the way for a phase 3 trial in this patient population

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ABBREVIATIONS

AE, adverse event; C2, complement component 2; Ca^{2+}, calcium ion; CAP-PRI, Chronic Acquired Polyneuropathy Patient-reported Index; CI, confidence interval; CMI, clinically meaningful improvement; 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; HR, hazard ratio; Ig, immunoglobulin; IV, intravenous; 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; PGIC, Patient Global Impression of Change; PNS, Peripheral Nerve Society; PRO, patient-reported outcome; PYFU, participant-years of follow-up; Q, quartile; QoL, quality of life; SAE, serious adverse event.

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