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

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W. Ludo van der Pol	**argenx**, Biogen, Novartis Gene Therapies, Roche, Takeda
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Yessar Hussain	Nothing to declare
Inge Van de Walle **Emma Persson** **Iris Van Hoomissen**	Employees of **argenx**
Olivier Van de Steen	Consultant for **argenx**
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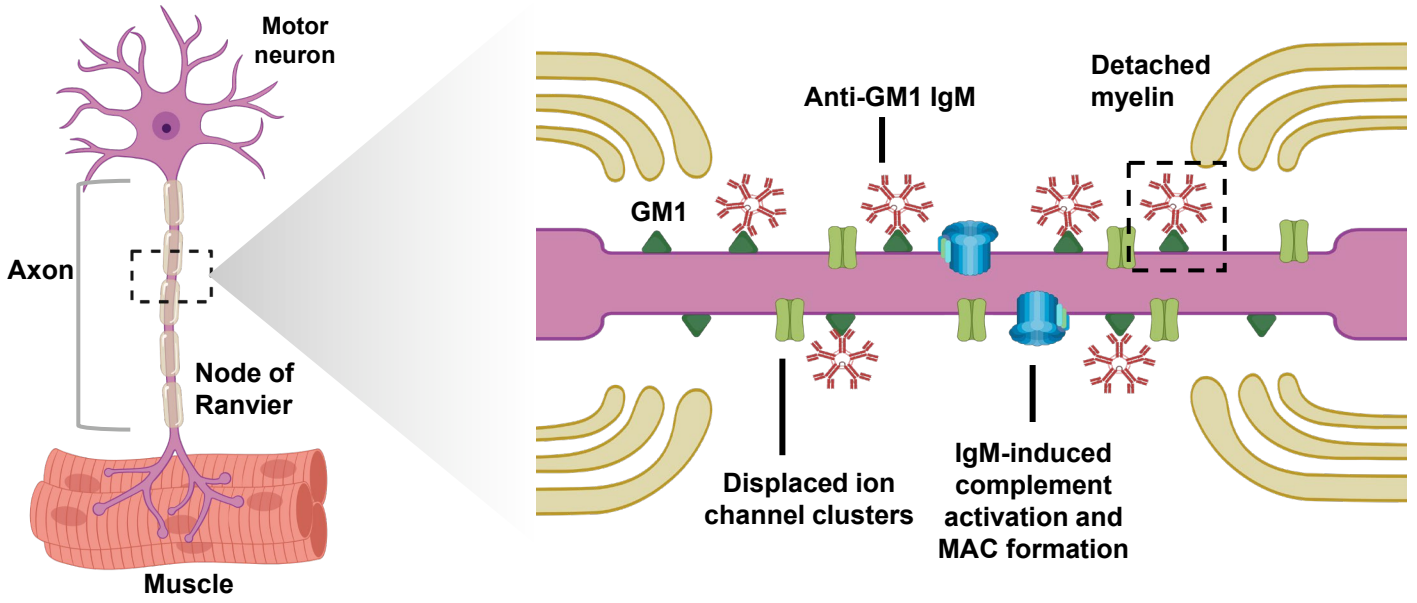
Empasiprubart is an investigational agent. Empasiprubart is not currently approved by the US Food and Drug Administration for any use, and its safety and efficacy have not been established

MMN: An immune-mediated neuropathy[1–3]

- 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]
- While **IVIg** is the **current standard of care** in MMN, patients typically **experience disease progression**[1,4]



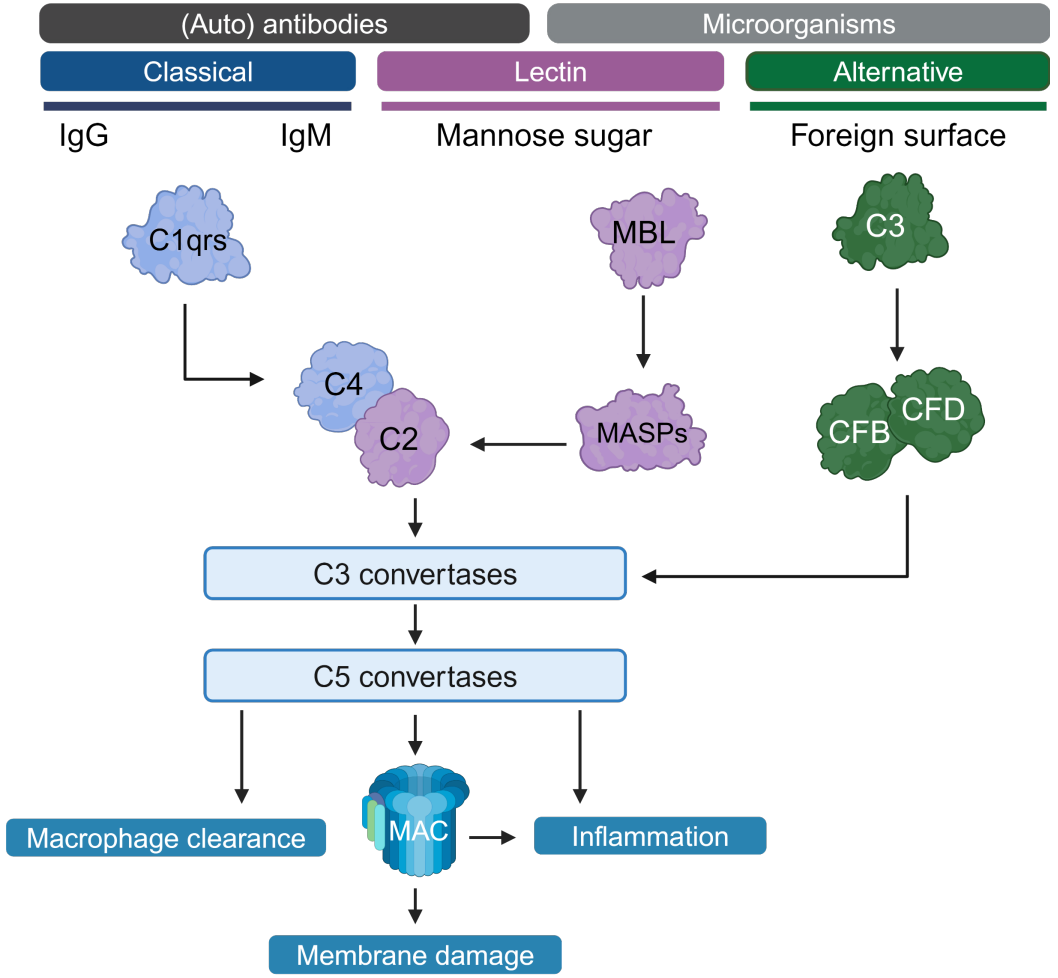
- In MMN, IgM autoantibodies can mediate the activation of the classical complement pathway, resulting in MAC deposition and axonal damage[3,5]
- IgM autoantibody-mediated complement activation was effectively inhibited by targeting C2 with empasiprubart in an *in vitro* model for MMN[1]

Figure created with BioRender.com, adapted from Vlam L, et al. *Nat Rev Neurol*. 2011;8:48–58.

GM1, monosialotetrahexosylganglioside; IgM, immunoglobulin M; IVIg, intravenous immunoglobulin; MAC, membrane attack complex; MMN, multifocal motor neuropathy.

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.** Herraets I, et al. *Neurology*. 2020;95:e1979–87. **5**. Sathe A, Cusick JK. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK555995/. Accessed June 2024.

C2 may be an optimal point of intervention within the complement cascade



- C2 is at the **crossroad of the classical and lectin** pathways[1]
- The **alternative pathway remains intact** (reduced infection risk)[1,2]
- Targeting C2, **upstream of C3 and C5,** inhibits **C3 and C5 effector functions**[2]
- **C2 is less abundant** in plasma than other complement factors[1]
- **C2 genetic deficiencies** are associated with a lower prevalence of autoimmune diseases (compared with C1 or C4 deficiencies)[1,3]

C, complement component; CF, complement factor; Ig, immunoglobulin; MAC, membrane attack complex; MASP, mannin-binding lectin serine protease; MBL, mannose-binding lectin.

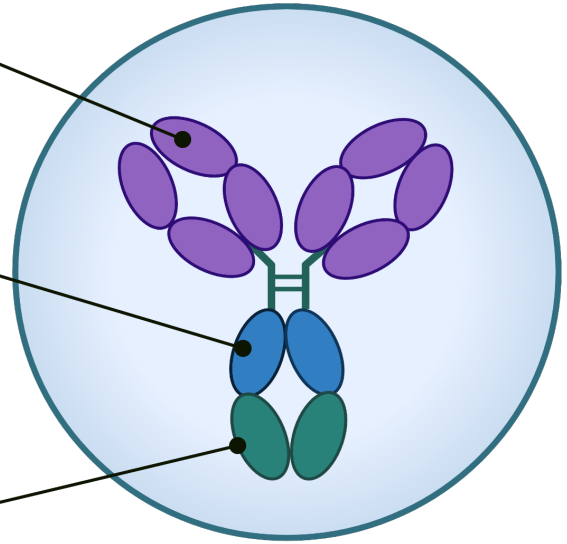
1. Van de Walle I, et al. *J Allergy Clin Immunol*. 2021;147:1420–9. **2**. Garred, P, et al. *Pharmacol Rev*. 2021;73:792–827. **3**. Coss SL, et al. *J Autoimmun*. 2023;137:102979.

Empasiprubart is a first-in-class, humanized, monoclonal antibody that specifically binds to C2[1,2]

Binds C2 in a pH- and Ca^{2+}-dependent manner[1]

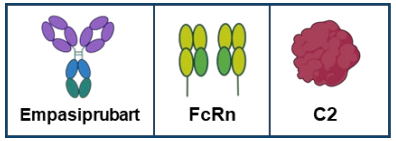
Decreased affinity for other Fc receptors to **avoid activating** IgG-dependent **effector functions**[1,2]

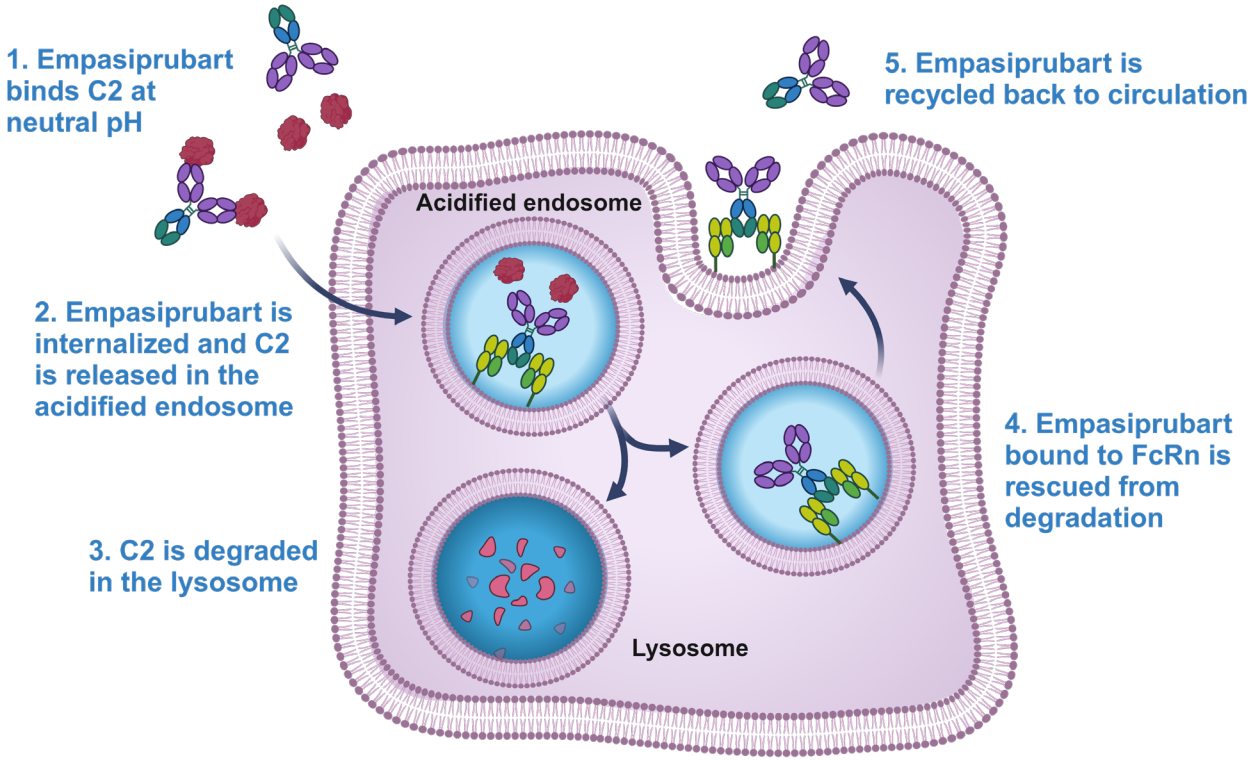
Engineered for a long half-life through **increased affinity** to FcRn at acidic pH[1,2]



Empasiprubart

Proposed MoA of Empasiprubart[1]





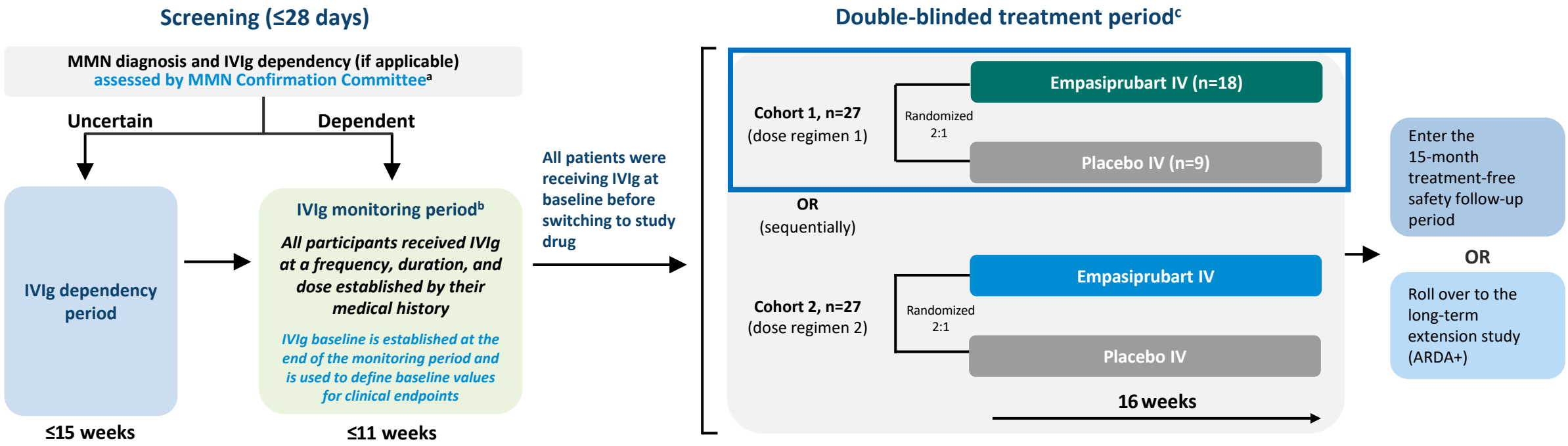
C2, complement component 2; Ca^{2+}, calcium ion; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; MoA, mechanism of action.

1. Van de Walle I, et al. *J Allergy Clin Immunol*. 2021;147:1420–9. **2**. Vaccaro C, et al. *Proc Natl Acad Sci*. 2006;103:18709–14.

ARDA: Phase 2, randomized, double-blinded, placebo-controlled, parallel-group trial in MMN[1,2]

arda Multifocal Motor Neuropathy Study

NCT05225675



Primary endpoint | Safety outcomes based on AE monitoring and other safety assessments (clinical laboratory tests)

Secondary and additional endpoints

- Time to first retreatment with IVIg
- Evaluation of efficacy measures
- Evaluation of productivity, treatment satisfaction, and QoL measures
- Evaluation of PK, PD, and immunogenicity

AE, adverse event; IV, intravenous; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; PD, pharmacodynamics; PK, pharmacokinetics; QoL, quality of life.

[a]Vaccinations were required. IVIg dependency parameters and vaccination requirements are summarized in the key inclusion criteria, full details provided at https://www.clinicaltrials.gov/study/NCT05225675. [b]The length of the monitoring period will depend 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. [c]Double-blinded treatment period will begin 7 days after final IVIg administration during the monitoring period. Participants will be retreated with IVIg if there is a clinically meaningful deterioration in muscle strength and/or motor function.

1. ClinicalTrials.gov identifier: NCT05225675. https://www.clinicaltrials.gov/study/NCT05225675. Accessed June 2024. **2**. van der Pol, WL, et al. Presented at NMSG Annual Scientific Meeting; September 22–24, 2023; Orlando, FL.

Baseline characteristics

	Empasiprubart (n=18)	Placebo (n=9)
Median age, y (Q1, Q3)	**54.5 (47.0, 61.0)**	**44.0 (42.0, 54.0)**
Sex, female, n (%)	7 (38.9)	4 (44.4)
Median time since diagnosis, y (Q1, Q3)	8.10 (5.39, 11.28)	9.99 (4.77, 11.29)
Median IVIg duration (years)[a] (Q1, Q3)	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)
Median IVIg dose, g/kg (Q1, Q3)	1.550 (1.000, 2.000)	1.300 (0.800, 1.500)
Median grip strength 3-day moving average, kPa (Q1, Q3)[b] **Most affected hand** **Less 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)**
Median mMRC-10 sum score (Q1, Q3)[b]	96.0 (87.0, 98.0)	95.0 (88.0, 96.0)
Median MMN-RODS Centile Metric Score (Q1, Q3)[b]	**59.0 (53.0, 67.0)**	**70.0 (60.0, 82.0)**
Median FSS (Q1, Q3)[b]	4.667 (3.222, 6.333)	4.222 (3.667, 4.556)
Median CAP-PRI (Q1, Q3)[b]	**13.0 (10.0, 19.0)**	**8.0 (6.0, 10.0)**

CAP-PRI, chronic acquired polyneuropathy patient-reported index; eCRF, electronic case report form; FSS, 9-item Fatigue Severity Scale; IVIg, intravenous immunoglobulin; kPa, kilopascal; MMN-RODS, Rasch-Built Overall Disability Scale for Multifocal Motor Neuropathy; mMRC-10, modified Medical Research Council-10; Q, quartile; y, years.

All baseline values were established at the initiation of the IVIg monitoring period unless otherwise specified. [a]The duration of IVIg ongoing at screening (in days) is defined as follows: screening date – starting date of last IVIg administration stable before screening +1. [b]Baseline values established following IVIg monitoring period and prior to initiation of the double-blinded treatment period.

Empasiprubart was generally well tolerated, with most AEs mild or moderate in severity

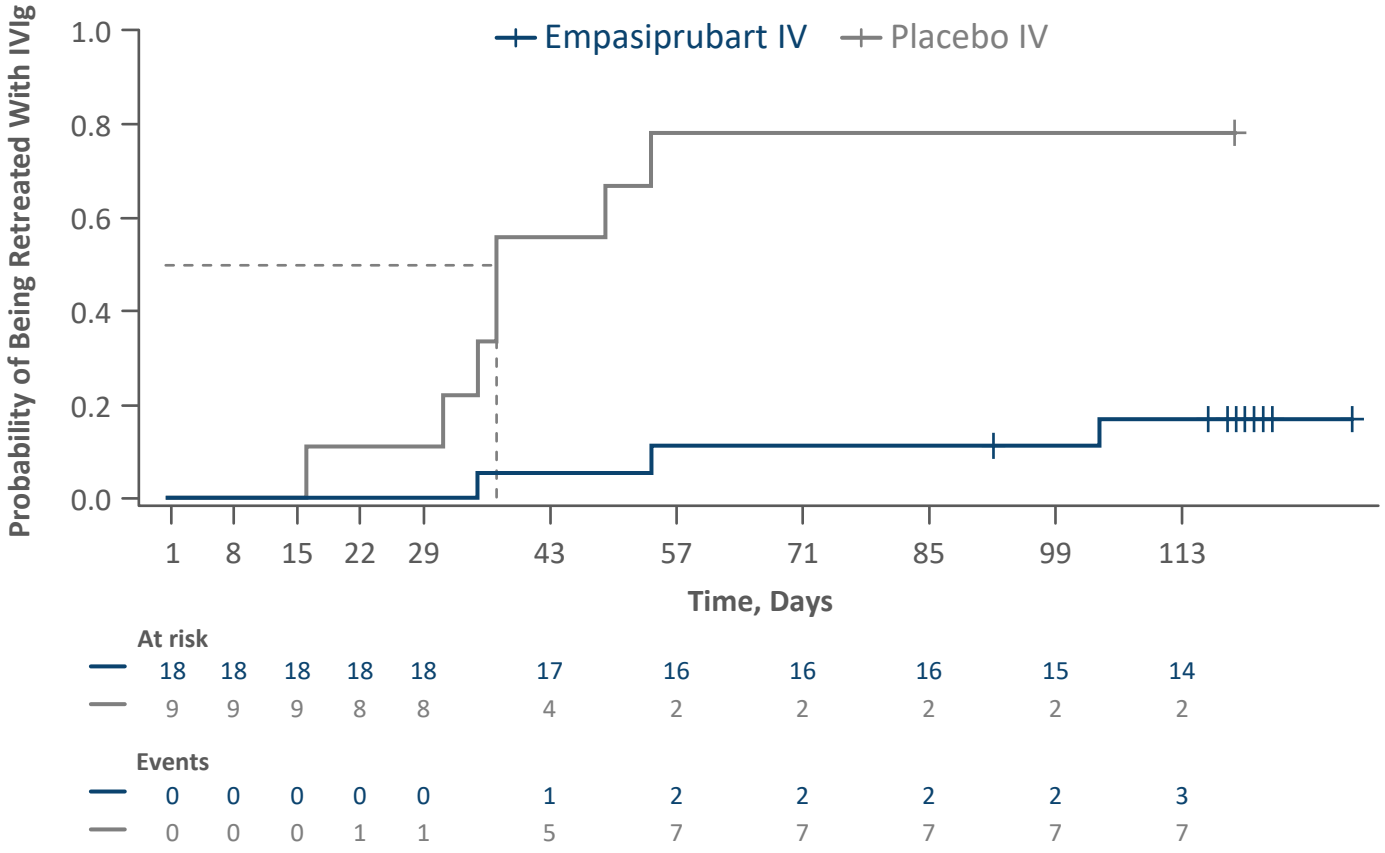
	Empasiprubart (n=18; PYFU=5.55)		Placebo (n=9; PYFU=2.62)	
	n (%)	Events	n (%)	Events
Participant with event				
Any AE[a]	14 (77.8)	33	5 (55.6)	14
Any SAE	2 (11.1)[b]	2	0 (0.0)	0
Procedure-related AEs	2 (11.1)	2	0 (0.0)	0
Discontinued due to AEs	1 (5.6)[c]	1	0 (0.0)	0
Any grade ≥3 AEs	2 (11.1)	2	0 (0.0)	0
AEs of special interest (severe infections)[d]	1 (5.6)[e]	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

AE, adverse event; PYFU, participants years of follow-up; SAE, serious adverse event.

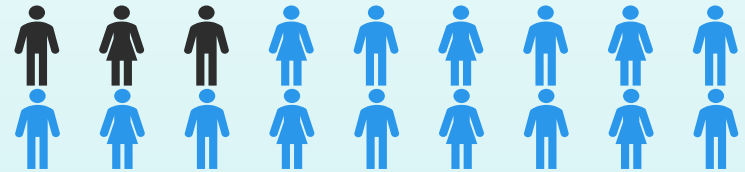
[a]AEs were predominantly mild or moderate in severity. [b]SAEs: Pneumonia grade 3 (not related) and acute coronary syndrome grade 4 (considered treatment-related by the investigators).[c]One patient discontinued due to grade 4 acute coronary syndrome. [d]AEs of special interest were defined as severe infection events (grade ≥3). [e]Severe infection: Pneumonia grade 3 (not related).

Empasiprubart reduced the risk of IVIg retreatment by 91% compared with placebo

Time to First Retreatment[a] With IVIg (days)



Participants retreated with IVIg:



Empasiprubart: 16.7% (**3 out of 18**)

Placebo: 77.8% (**7 out of 9**)

HR: 0.09 (95% CI: 0.02–0.44)

Participants were retreated with IVIg during the DBTP if there was a clinically meaningful deterioration in muscle strength and/or motor function, 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

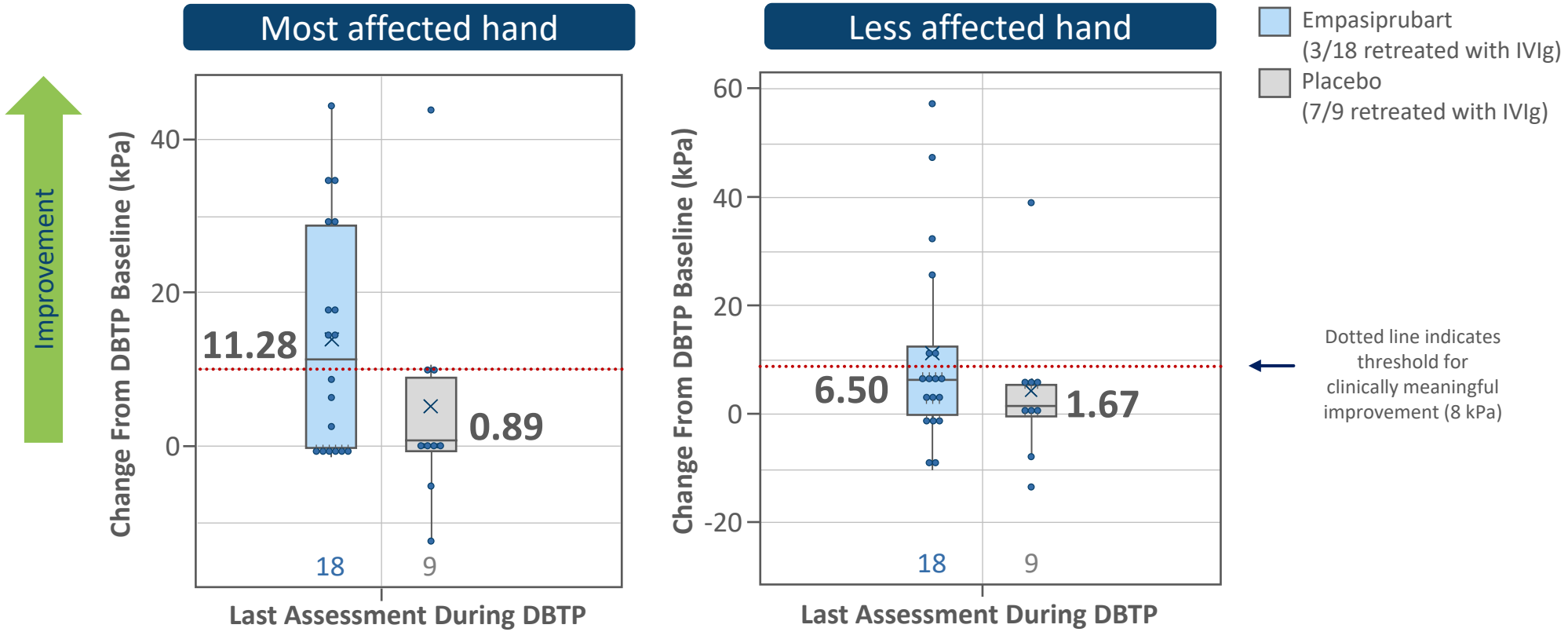
However, based on their clinical judgment, the investigator may have chosen to not retreat the participant with IVIg

CI, confidence interval; DBTP, double-blinded treatment period; HR, hazard ratio; IV, intravenous; IVIg, intravenous immunoglobulin; mMRC-10, modified Medical Research Council-10.

[a]Time to first treatment with IVIg is defined as the time from last IVIg administration before randomization (including unscheduled visits) up to the first IVIg retreatment during the DBTP.

Empasiprubart improved grip strength in both hands compared with placebo

Change From Baseline[a] Grip Strength 3-Day Moving Average (kPa)[b] by Treatment Group at Last Assessment During Treatment Period

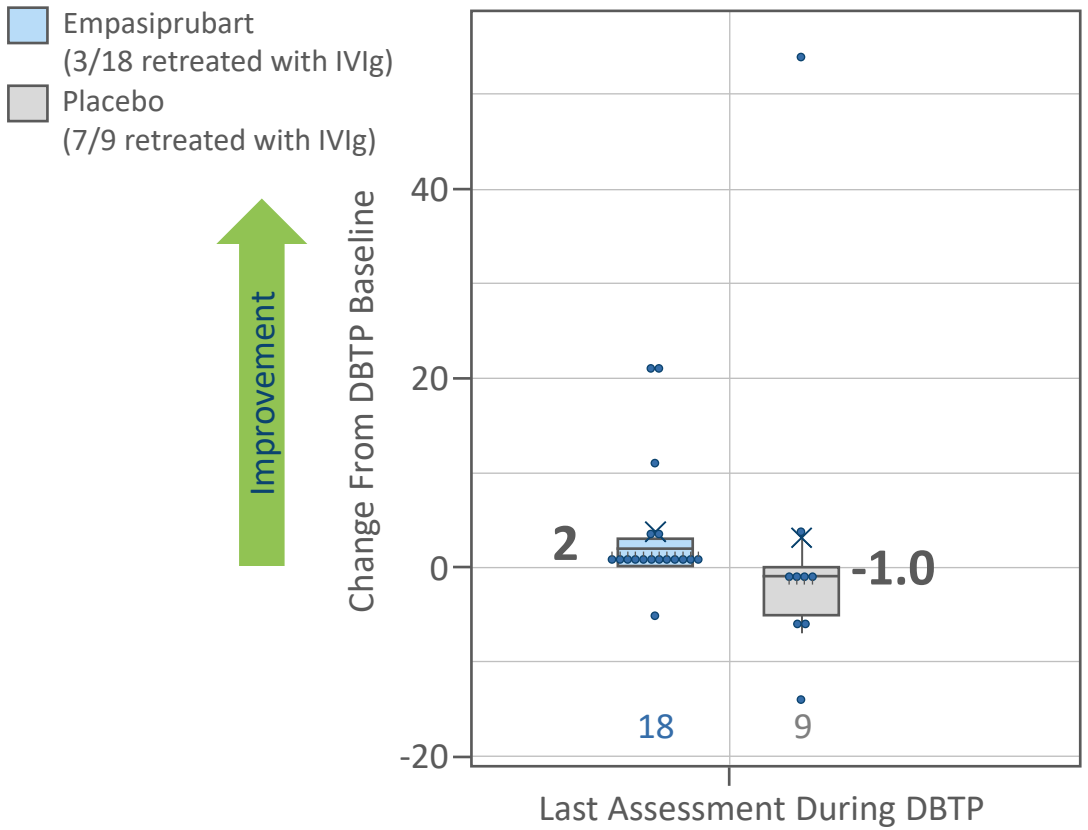


DBTP, double-blinded treatment period; IVIg, intravenous immunoglobulin; kPa, kilopascal.

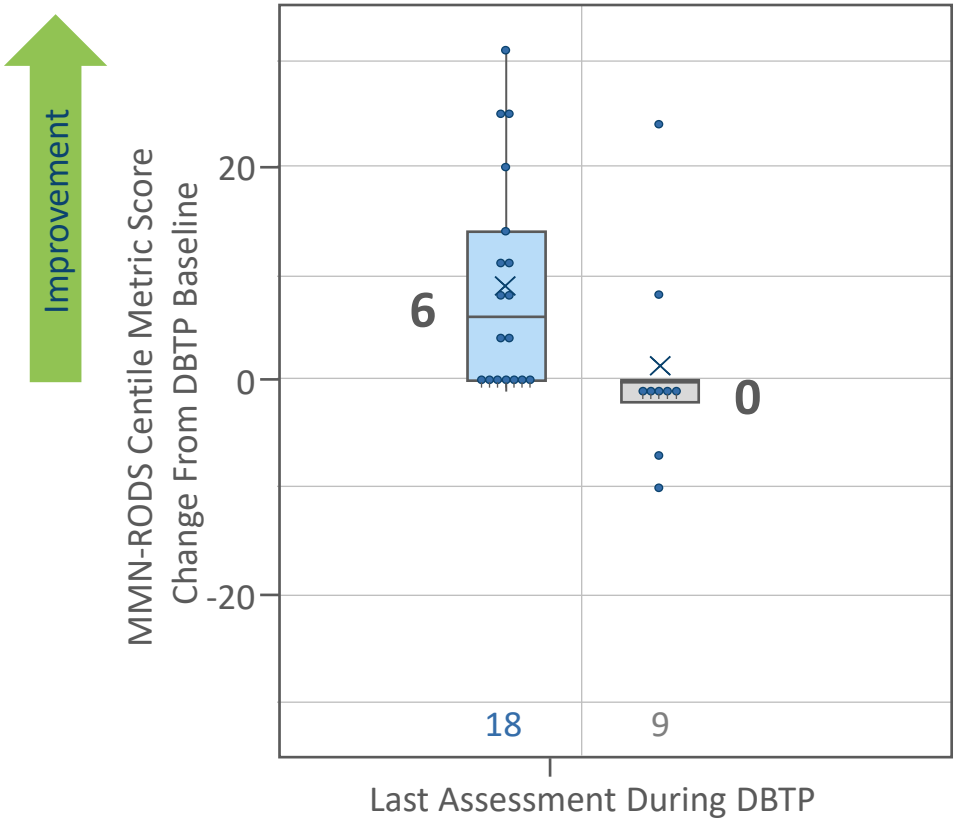
[a]Baseline values established following IVIg monitoring period and prior to initiation of the DBTP. [b]Grip strength 3-day moving average: A 3-day moving average is calculated using grip strength data from day −2, −1, and 0.

Empasiprubart improved muscle strength and disease-specific activity limitations compared with placebo

Change From Baseline[a] mMRC-10 Sum Score[b] by Treatment Group at Last Assessment During Treatment Period



Change From Baseline[a] MMN-RODS Score[c] by Treatment Group at Last Assessment During Treatment Period



DBTP, double-blinded treatment period; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MMN-RODS, Rasch-Built Overall Disability Scale for Multifocal Motor Neuropathy; mMRC-10, modified Medical Research Council-10; PRO, patient-reported outcome.

[a]Baseline values established following IVIg monitoring period and prior to initiation of the DBTP. [b]mMRC-10 sum score measures motor strength or weakness in a predetermined set of muscle groups; a decrease of ≥2 points indicates clinical deterioration. [c]The MMN-RODS is a disease-specific PRO instrument constructed specifically to capture activity limitations in patients with MMN. It consists of 25 items that are 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. For the analysis, the centile score was used (ie, ranging from 0 to 100).

Conclusions

ARDA is the largest interventional study conducted in MMN to date; we report data for the 27 participants who received empasiprubart (n=18) or placebo (n=9) in cohort 1 of the ARDA study

Empasiprubart was generally well tolerated, with most AEs being mild or moderate in severity

Compared with placebo, treatment with empasiprubart:

- Reduced the risk of IVIg retreatment by 91% (HR: 0.09 [95% CI: 0.02–0.44])
- Improved grip and muscle strength
- Improved activity/disability levels

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

AE, adverse event; CI, confidence interval; HR, hazard ratio; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy.