Empasiprubart Versus Intravenous Immunoglobulin in Multifocal Motor Neuropathy Phase 3 Study Design: EMPASSION

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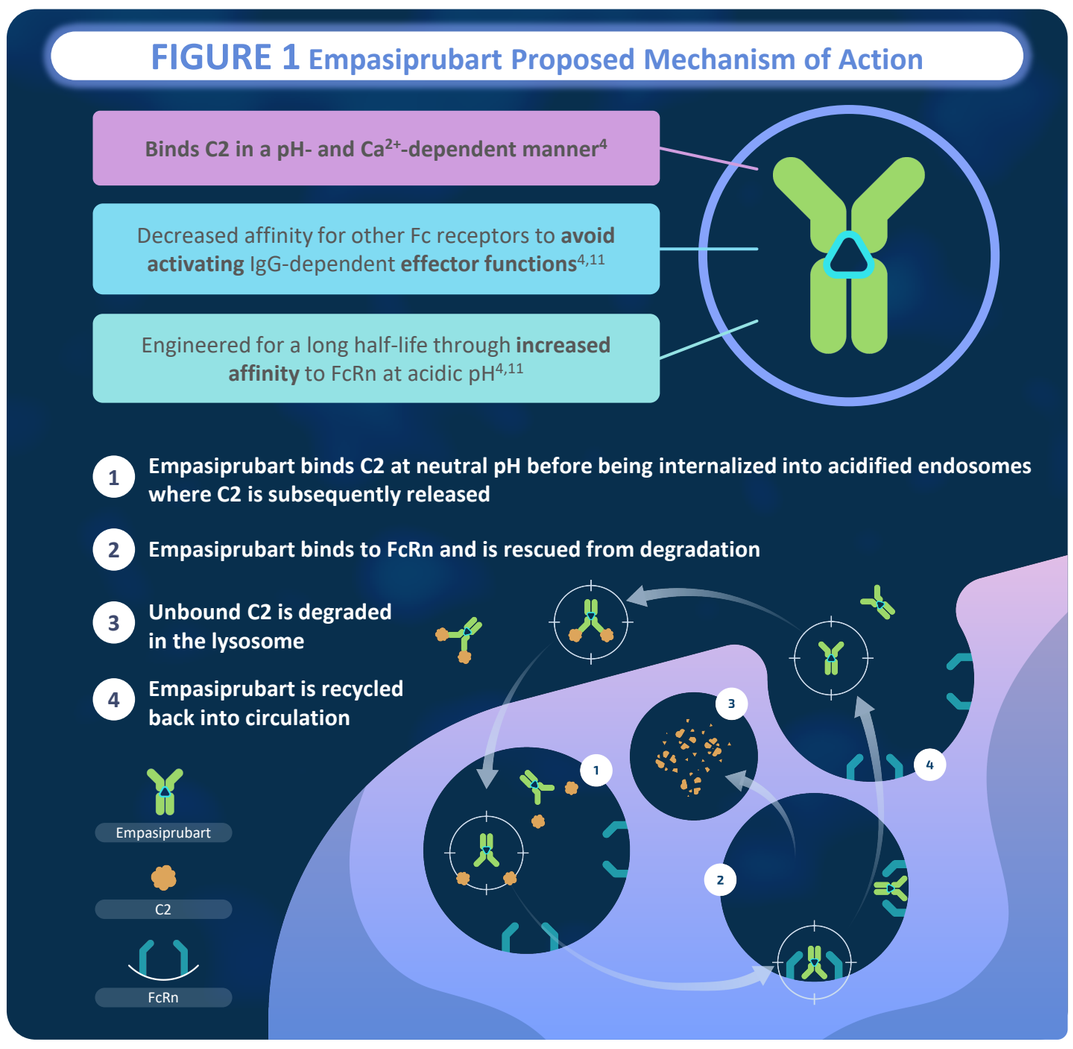
BACKGROUND

- MMN is a rare, immune-mediated, complement-driven chronic neuropathy leading to focal demyelination and axonal degeneration, and progressive, disabling, asymmetric limb weakness with absence of sensory loss[1–3]
- Anti-GM1 IgM antibody-mediated complement activation plays a central role in the pathogenesis of MMN[1–3]
- Complement component C2 is an optimal point of intervention within the complement cascade[4]
- Targeting C2 inhibits the classical and lectin complement pathways upstream of C3 and C5 while leaving the alternative pathway intact, leading to reduced infection risk[4,5]
- IVIg is the current standard of care in MMN; however:
  - ~90% of patients experience disease progression, despite maintenance treatment and dose increases[2,6]
  - IVIg requires frequent infusions which can last several hours or days, can be associated with adverse events, and may be subject to availability issues[4,7,8]
- There have been no new treatments for MMN since IVIg approval in 2012[9]

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

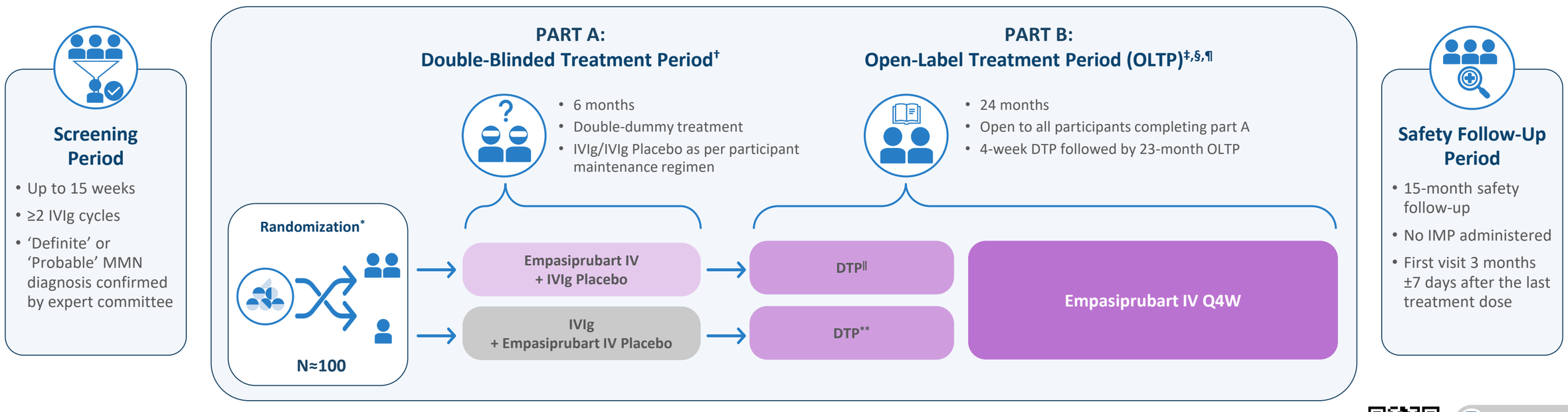
- Empasiprubart is a first-in-class, humanized, monoclonal antibody that specifically binds to C2[4] (**Figure 1**)
- IgM autoantibody-mediated complement activation was effectively inhibited by targeting C2 with empasiprubart in an *in vitro* model of MMN[1]
- In the phase 2 ARDA study, empasiprubart IV demonstrated clinical improvements across multiple efficacy parameters compared with placebo, was well tolerated with mostly mild or moderate AEs, and established proof of concept for the treatment of MMN patients with empasiprubart[10]
- The pivotal phase 3 EMPASSION study (NCT06742190) will evaluate the efficacy and safety of empasiprubart versus IVIg head-to-head in adult participants with MMN

FIGURE 1 Empasiprubart Proposed Mechanism of Action



STUDY DESIGN

FIGURE 2 EMPASSION: A Phase 3, Randomized, Double-Blinded, Double-Dummy Study Evaluating the Efficacy and Safety of Empasiprubart Versus IVIg in Adults With MMN (NCT06742190)



*Participants will be randomized 2:1 to receive empasiprubart IV/IVIg placebo or IVIg/empasiprubart placebo, respectively, in part A; randomization coincides with a scheduled IVIg infusion visit. †Participants will receive a loading dose on days 1 and 8, and maintenance dose Q4W from day 29. ‡Participants will receive treatment on day 169, day 176, and Q4W from day 197. §Part B of the study will remain open in all countries for a maximum of 2 years after completion of Part A of the study. Part B may end earlier than 2 years in countries where empasiprubart becomes available for MMN commercially or through a continued access program, whichever comes first. ¶Concomitant IVIg is not permitted during the OLTP; participants requiring IVIg will discontinue the open-label period and enter the safety follow-up period. ‖Participants will receive empasiprubart IV (maintenance dose) from day 169, empasiprubart placebo on day 176, and empasiprubart (maintenance dose) Q4W from day 197. **Participants will receive empasiprubart IV (loading dose) on days 169 and 176, and empasiprubart (maintenance dose) Q4W from day 197.

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For more information on EMPASSION

KEY ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Adults aged ≥18 years
- Confirmed diagnosis of definite/probable MMN according to the EFNS/PNS 2010 guidelines[12]
- Clinically meaningful response to IVIg in the past 5 years, as confirmed by expert committee
- Receiving IVIg (0.4–2.0 g/kg per cycle) once every 2, 3, 4, or 5 weeks with a minimum converted weekly dose of ≥0.125 g/kg
- Receiving a maintenance regimen of IVIg for ≥8 weeks (10 weeks if receiving IVIg Q5W) before screening and until baseline

EXCLUSION CRITERIA

- Presence of another known, confounding autoimmune disease/other medical condition
- Clinical signs/symptoms of neuropathies other than MMN
- History of malignancy, unless resolved with no recurrence at least 3 years before treatment administration
- Current participation in an interventional trial
- Receipt of any other IMP <12 weeks or <5 half-lives (whichever is longer) before screening

STUDY ENDPOINTS

1 PRIMARY ENDPOINT*

- Change from baseline in 25-Item MMN-RODS centile score

2 KEY SECONDARY ENDPOINTS*

- Change from baseline in grip strength (most affected hand)
- Change from baseline in mMRC-14 sum score
- Percentage change from baseline in time to complete 9-HPT (dominant hand)

3 OTHER SECONDARY ENDPOINTS

- Safety (incidence/severity of AEs)
- PK, PD, and immunogenicity of empasiprubart
- Efficacy measures to evaluate muscle strength and motor function (mMRC-10 and -14 sum score in the 2 most affected muscle groups), manual dexterity (9-HPT; non-dominant hand), health-related quality of life (EQ-5D-5L; RT-FSS), and patient-reported outcomes (CAP-PRI, PGI-C; PGI-S)

*Assessed at Week 24.

KEY TAKEAWAYS

Empasiprubart is a first-in-class, humanized, monoclonal antibody that specifically binds to C2[4]

The phase 2 ARDA study showed that empasiprubart IV was well tolerated, and improved muscle/grip strength as well as reduced the need for IVIg treatment[10]

The global, phase 3, EMPASSION study will evaluate the efficacy and safety of empasiprubart versus IVIg head-to-head in adult participants with MMN

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ABBREVIATIONS

AE, adverse event; C2, complement component 2; C3, complement component 3; C5, complement component 5; CAP-PRI, Chronic Acquired Polyneuropathy Patient-Reported Index; DTP, double-blind transition period; EFNS, European Federation of Neurological Societies; EQ-5D-5L, EuroQoL 5 Dimensions, 5 Levels; FcRn, neonatal Fc receptor; GM1, monosialotetrahexosylganglioside; HPT, Hole Peg test; Ig, immunoglobulin; IMP, investigational medicinal product; IV, intravenous; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MMN-RODS, Rasch-built Overall Disability Scale for MMN; mMRC, modified Medical Research Council; OLTP, open-label treatment period; PD, pharmacodynamics; PGI-C, Patients' Global Impression of Change; PGI-S, Patients' Global Impression of Severity; PK, pharmacokinetics; PNS, Peripheral Nerve Society; Q4W, every 4 weeks; Q5W, every 5 weeks; RT-FSS, Rasch-transformed Fatigue Severity Scale.

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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. **5.** Garred P, et al. *Pharmacol Rev*. 2021;73:792–827. **6.** Keddie S, et al. *Cochrane Database Syst Rev.* 2022;1:Cd004429. **7.** Champagne JN, et al. *Transfusion.* 2024:64:2286–95. **8.** GBS | CIDP Foundation International (2024) Voice of the Patient Meeting Report. Available at https://acrobat.adobe.com/id/urn:aaid:sc:US:cf63c325-eec7-4b65-aeb1-179ee3773ac8. Accessed May 8, 2025. **9.** Baxter International, Inc. (2012). Available at https://investor.baxter.com/investors/events-and-news/news/press-release-details/2012/Baxter-Announces-FDA-Approval-for-GAMMAGARD-LIQUID-as-a-Treatment-for-Multifocal-Motor-Neuropathy/default.aspx. Accessed May 8, 2025. **10.** Querol L, et al. Presented at ICNMD; October 25–29, 2024; Perth, Australia. **11.** Vaccaro C, et al. *Proc Natl Acad Sci.* 2006;103:18709–14. **12.** Joint Task Force of the EFNS and the PNS. *J Peripher Nerv Syst*. 2010;15:295–301.

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