Preliminary Efficacy and Safety Data from the Phase 2 Trial of Riliprubart (SAR445088), a Humanized Monoclonal Antibody Targeting Complement C1s, in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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- **Richard A. Lewis:** Consultant with CSL Behring, Grifols, Pfizer, Sanofi (Steering Committee), Argenx, Pharnext, Roche, Johnson & Johnson, Takeda, Boehringer Ingelheim (DSMB), and Momenta. He is also part of the scientific advisory boards Alnylam and Akcea and medical advisory board The GBS-CIDP Foundation International.
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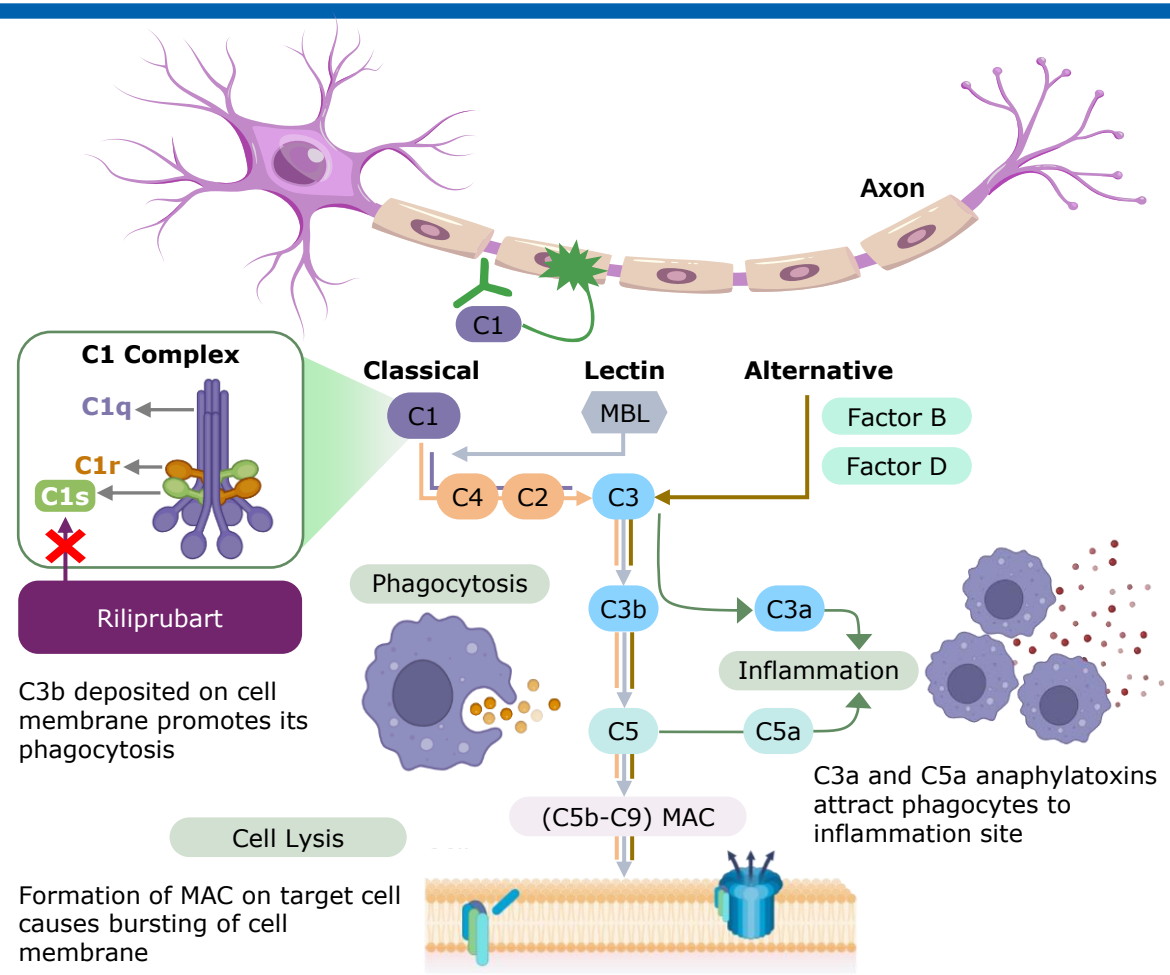
Riliprubart targets activated C1s in the classical complement pathway[1]

- **Significant unmet need in CIDP**: Standard of care therapies may have suboptimal efficacy, high administration burden, and undesirable side effects[2,3]
- Complement activation may contribute to demyelination and axonal damage in CIDP[4,5]
  - Genetic link: Mutations in **CD59,** a complement inhibitory protein, causes a **CIDP-like demyelinating neuropathy[6]**
  - Patient samples: Biopsy material shows **complement deposition** on myelin[7,8] and increased **complement activation** observed in the **blood[8]**
  - Experimental models: Complement inhibition **reduces inflammation** and **demyelination**[9,10]
- **Riliprubart is a first-in-class, humanized, IgG4 monoclonal antibody that selectively inhibits activated C1s in the classical complement pathway**



Objective: To report preliminary efficacy and safety results of riliprubart, a novel C1s inhibitor, across a broad spectrum of CIDP participants (SOC-Treated, SOC-Refractory and SOC-Naïve) in a global, multicentre, Phase 2 trial (NCT04658472)

1. Querol, et al. *J Peripher Nerv Syst*. 2023;28(2):276–285. 2. Gorson. *Neurol Disord.* 2012;5(6):359-73. 3. Bunschoten, et al. *Lancet Neurol*. 2019;18(8):784-94. 4. Dalakas. *Biochim Biophys Acta*. 2015;1852(4):658-66; 5. Köller, et al. *N Engl J Med*. 2005;352(13):1343-56; 6. Nevo, et al. *Blood.* 2013;121(1):129-35. 7. Dalakas and Engel. *Arch Neurol*. 1980;37(10):637-40; 8. Quast, et al. *Ann Clin Transl Neurol.* 2016;3(9):730-5; 9. Feasby, et al. *Brain Res*. 1987;419(1-2):97-103; 10. Vriesendorp, et al. *Acta Neuropathol*. 1998;95(3):297-30. C1, complement component 1, s subcomponent; CIDP, chronic inflammatory demyelinating polyneuropathy; MAC, membrane attack complex; MBL, mannose-binding lectin; SOC, standard-of-care.

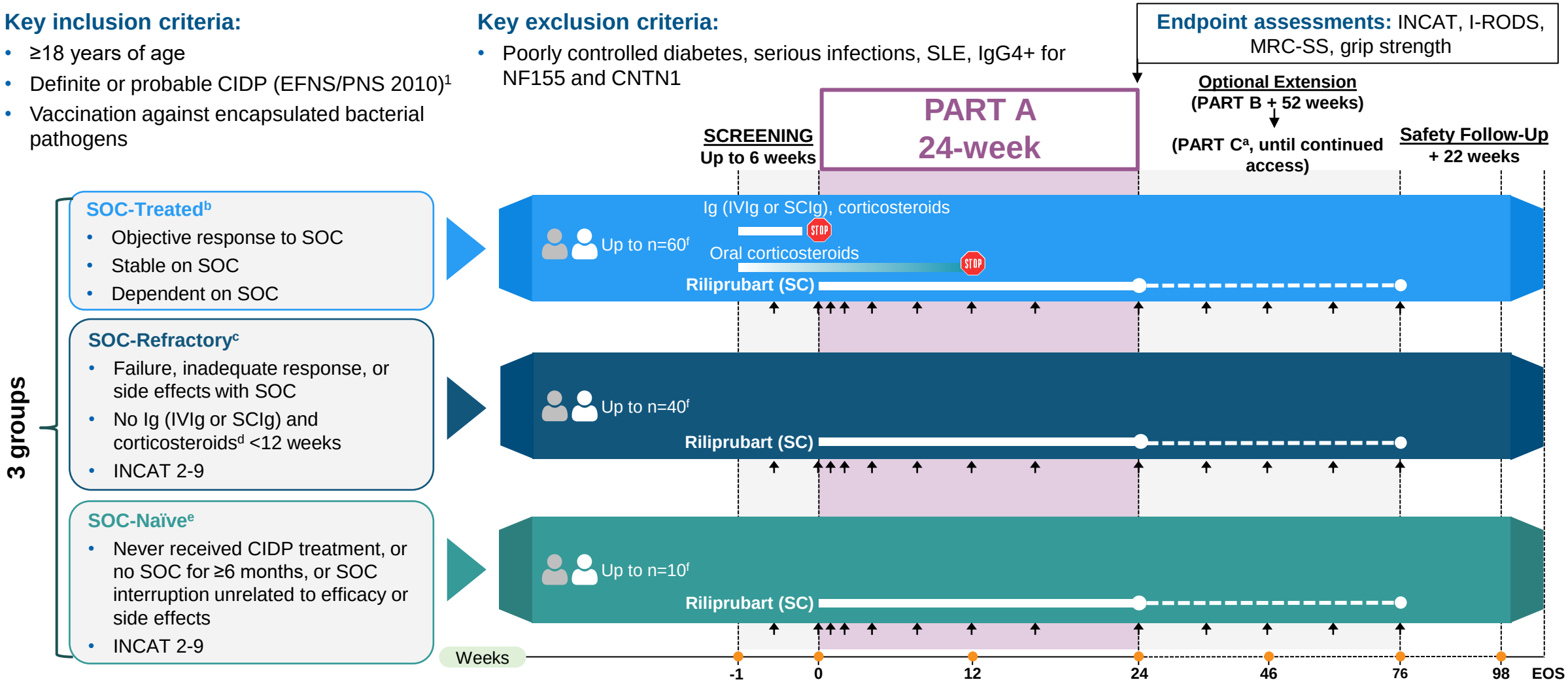
Phase 2 open-label trial in participants with CIDP across three subpopulations

Key inclusion criteria:

- ≥18 years of age
- Definite or probable CIDP (EFNS/PNS 2010)[1]
- Vaccination against encapsulated bacterial pathogens

Key exclusion criteria:

- Poorly controlled diabetes, serious infections, SLE, IgG4+ for NF155 and CNTN1



1. Van den Bergh, et al. *Eur J Neurol*. 2010;17(3):356-363.[a]Part C was added and estimated enrollment was updated for all study groups due to a protocol amendment after the trial design was published in: Querol, et al. *J Peripher Nerv Syst*. 2023;28(2):276-285. [b]Participants treated with SOC therapies (i.e., immunoglobulins or corticosteroids). [c]Participants refractory to SOC therapies. [d]Oral corticosteroids are allowed if on a stable dose of <20 mg/day of prednisone (or equivalent dose for other oral corticosteroids) for ≥3 months prior to screening. [e]Participants naïve to SOC therapies. [f]Enrollment is ongoing and number may change upon completion; the protocol was amended in 2023 to test the second dose and expand the sample size. CIDP, chronic inflammatory demyelinating polyneuropathy; CNTN1, contactin 1; EFNS, European Federation of Neurological Societies; EOS, end of study; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; MRC-SS, Medical Research Council Sum score; NF155, Neurofascin 155; PNS, Peripheral Nerve Society; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SLE, systemic lupus erythematosus; SOC, standard-of-care.

Primary endpoint based on pre-defined efficacy criteria for response and relapse[a]

Primary Efficacy Endpoint

- ***SOC-Treated***: % of participants with a *relapse (≥1 point increase in adjusted INCAT disability score)* after withdrawal of SOC and during the treatment period (up to 24 weeks)
- ***SOC-Refractory and SOC-Naïve***: % of participants with a *response (≥1 point decrease in adjusted INCAT disability score)* during the treatment period versus baseline (up to 24 weeks)

Key Secondary Endpoints

- **Safety and tolerability**
- **Immunogenicity**
- **Efficacy with overlapping SOC (SOC-Treated group) (up to 12 weeks)**

Key Exploratory Endpoints

- **Additional efficacy**
  - I-RODS, MRC-SS, grip strength
- **Pharmacodynamic biomarkers**
  - Complement and plasma NfL
  - PK parameters

Statistical analysis

- Data will be analyzed with Bayesian statistics with predefined efficacy criteria and placebo assumptions based on the historical data derived from published randomized, double-blind, placebo-controlled phase 3 clinical trials[1,2,3]
- Pre-specified interim analyses with defined criteria were conducted as of October 16, 2023[b]

1. Hughes, et al. *Lancet Neurol*. 2018;17(8):689-698. 2. van Schaik, et al. *Lancet Neurol*. 2018;17(1):35-46. 3. Querol, et al. *J Peripher Nerv Syst*. 2023;28(2):276-285. [a]Key endpoints for Part A are presented; Part B and Part C will examine long-term safety and efficacy durability. [b]Pre-defined interim analysis cut-off period included when first 50% of SOC-Treated enrolled participants completed Part A. Data cut-off was 16 May 2023 for SOC-Refractory and SOC-Treated participants and 16 Oct 2023 for SOC-Naïve participants for Part A at 24 weeks. INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MRC-SS, Medical Research Council Sum score; NfL, neurofilament light chain; PK, pharmacokinetics; SOC, standard-of-care.

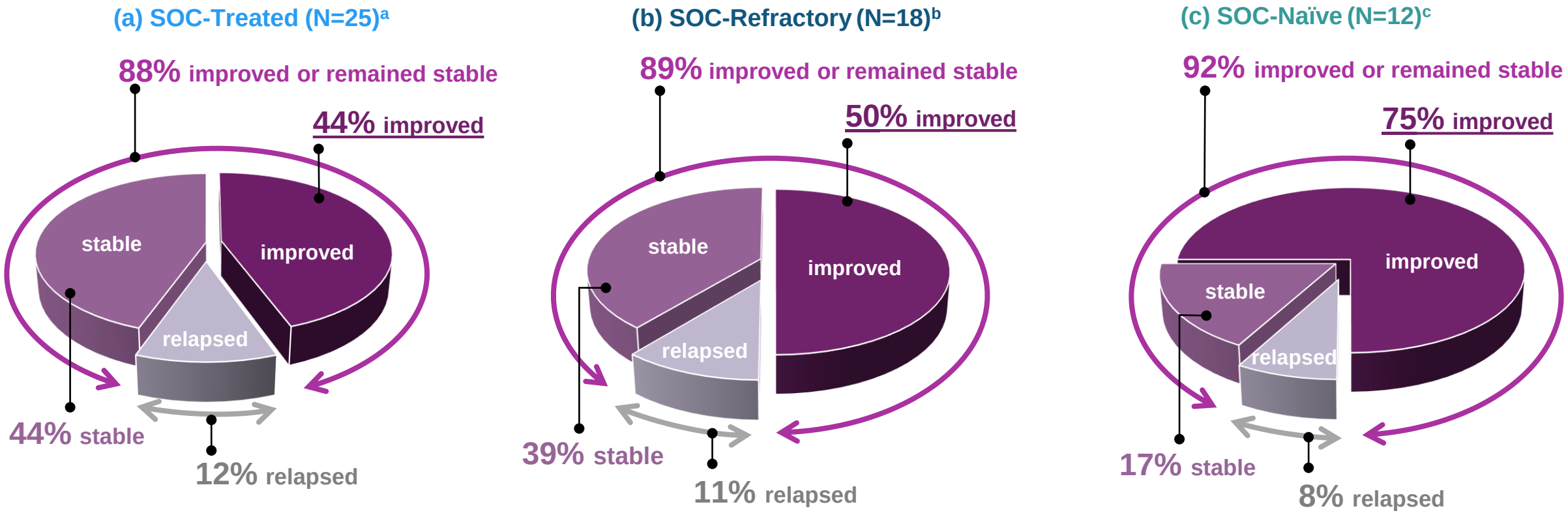
Baseline characteristics

As of Oct 16, 2023, 77 participants were enrolled and findings for 55 participants who completed the 24-week observation period are presented[a]

	SOC-Treated (N=25)	SOC-Refractory (N=18)	SOC-Naïve (N=12)
Age (years)			
Mean (SD)	58.2 (15.4)	63.9 (15.0)	59.1 (18.6)
Median (SEM)	64.0 (3.1)	67.0 (3.5)	65.0 (5.4)
Range	20-78	26-89	20-85
Male, n (%)	20 (80)	11 (61)	8 (67)
Typical CIDP diagnosis, n (%)	18 (72)	15 (83)	9 (75)
EFNS/PNS (2010 Task Force first revision) criteria[1], n (%)			
Definite	**24 (96)**	**18 (100)**	**11 (92)**
Probable	**1 (4)**	**0**	**1 (8)**
Time since diagnosis of CIDP (years), median (range)	7.9 (0.8-25.8)	4.5 (0.2-18.0)	1.6 (0.1-21.2)
Time since symptom onset (years), median (range)	9.0 (1.5-35.8)	5.6 (2.4-20.8)	8.3 (1.1-21.2)
INCAT Score, mean (SEM, range)	3.3 [(0.4) 1-9]	**5.4 [(0.4), 3-8]**	3.8 [(0.4), 2-6]
I-RODS, mean (SEM, range)	57.6 [(4.5), 0-100]	**40.5 [(3.7), 11-58]**	58.8 [(6.2), 35-88]
MRC-SS, mean (SEM, range)	52.1 [(1.7), 33-60]	**46.8 [(1.9), 30-60]**	52.9 [(1.8), 40-60]
Grip strength (kPa), mean (SEM, range)	66.6 [(8.4), 2-145]	**31.5 [(5.9), 0-79]**	52.8 [(6.7), 2-92]
CIDP prior medications (within past 24 months), n (%)			
Immunoglobulins	**22 (88)**	**15 (83)**	**6 (50)**
Corticosteroids	8 (32)	12 (66)	5 (42)
Immunosuppressants	1 (4)	8 (44)	0
Rituximab	1 (4)	3 (16)	1 (8)
Other medications	1 (4)	0	1 (8)

1. Van den Bergh, et al. *Eur J Neurol*. 2010;17(3):356-363. [a]Pre-defined interim analysis cut-off period included when first 50% of SOC-Treated enrolled participants completed Part A. Data cut-off was 16 May 2023 for SOC-Refractory and SOC-Treated participants and 16 Oct 2023 for SOC-Naïve participants for Part A at 24 weeks. CIDP, chronic inflammatory demyelinating polyneuropathy; EFNS, European Federation of Neurological Societies; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; kPa, kilopascals; MRC-SS, Medical Research Council Sum score; PNS, Peripheral Nerve Society; SD, standard deviation; SEM, standard error mean; SOC, standard-of-care.

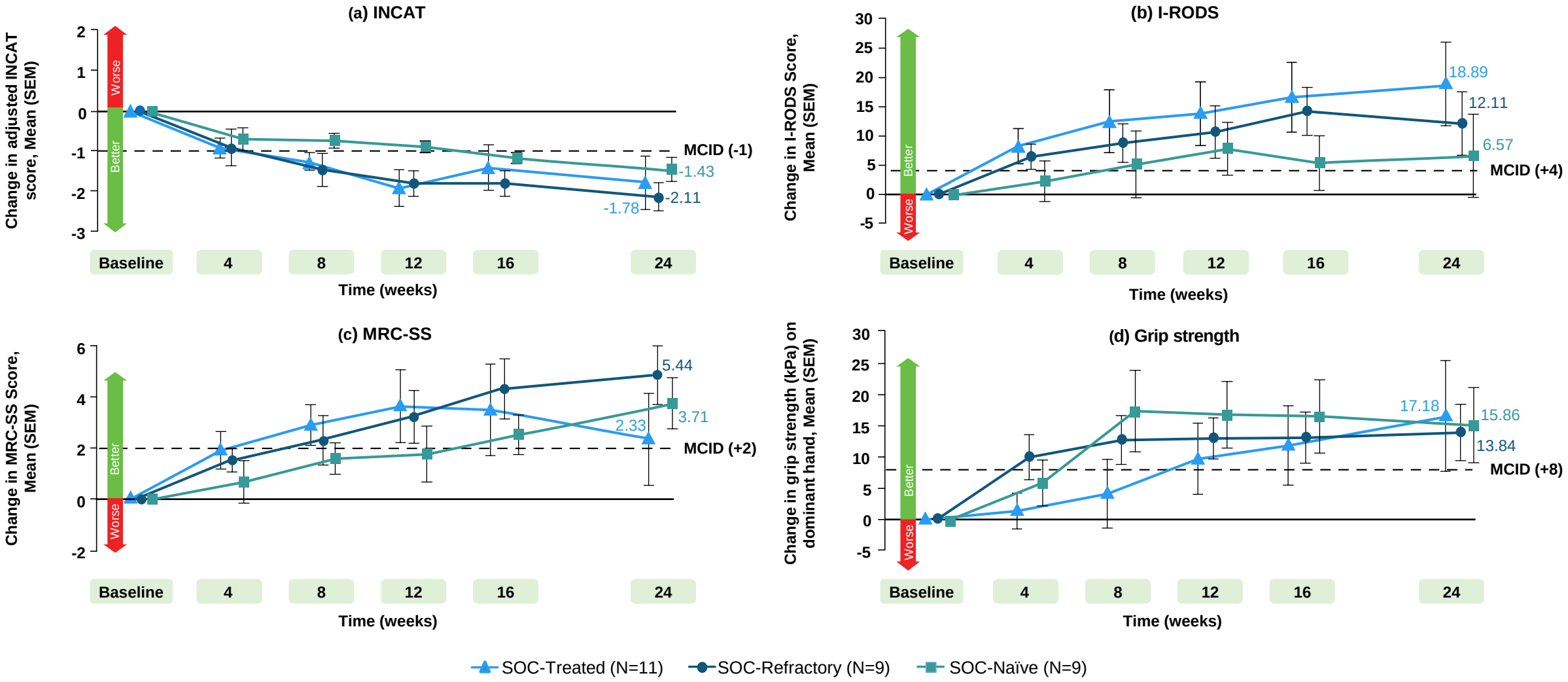
Majority of participants improved or remained stable on riliprubart at Week 24



In the SOC-Treated group, 44% of participants demonstrated improvement after switching from SOC (IVIg) to riliprubart Similarly, in the SOC-Refractory and SOC-Naïve groups, 50% and 75% of participants, respectively, showed improvement in response to riliprubart at Week 24

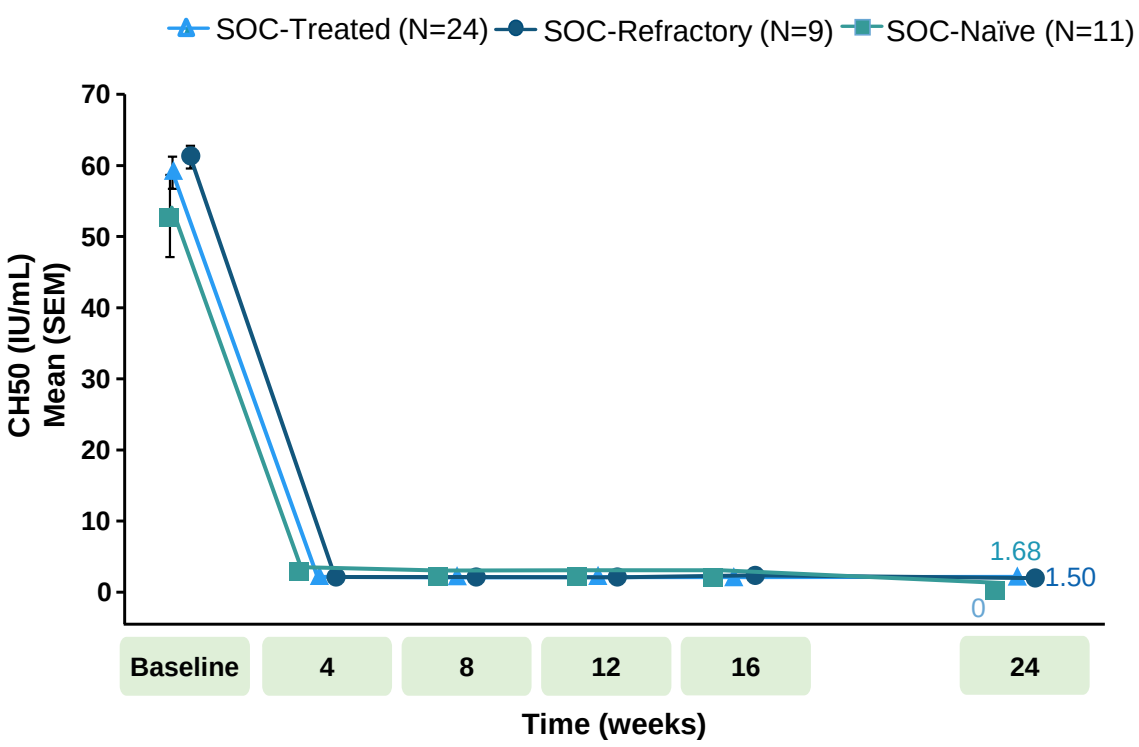
[a]% of participants with a relapse (≥1 point increase in adjusted INCAT disability score) after withdrawal of SOC and during the treatment period (up to 24 weeks). Out of 25 participants, 2 discontinuations unrelated to efficacy (death, visit schedule burden) were imputed as responses based on last observed data (12-week and 16-week). [b]% of participants with a response (≥1 point decrease in adjusted INCAT disability score) during the treatment period (up to 24 weeks). Out of 18 participants,14 completed 24 weeks, while 4 discontinued (due to pneumonia klebsiella, muscular weakness, death, visit schedule burden) were imputed as responses based on last observed data (4-week and 16-week). [C]% of participants with a response (≥1 point decrease in adjusted INCAT disability score) during the treatment period (up to 24 weeks). Out of 12 participants, 1 discontinuation unrelated to efficacy (COVID-19 stress) and 1 discontinuation related to lack of improvement at week 12 were imputed as responses based on last observed data (4-week and 16-week). CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; IVIg, intravenous immunoglobulin; SOC, standard-of-care.

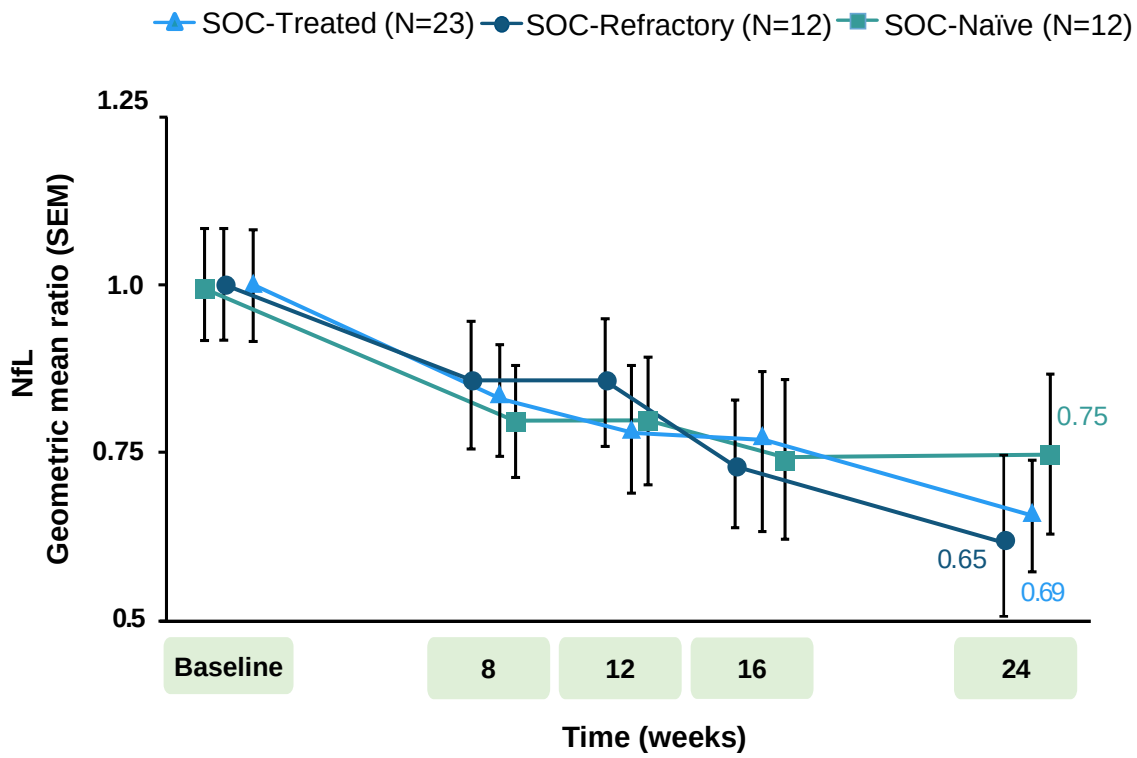
Responders on riliprubart show consistency across outcome measures and magnitude of effect around or beyond MCID thresholds[a]



[a]Responders data based on *post-hoc* definition, i.e., responder at 24 weeks OR discontinued before 24 weeks and last available INCAT shows a response. INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; kPa, kilopascals; MCID, minimal clinically important difference; MRC-SS, Medical Research Council Sum score; SEM, standard error of the mean; SOC, standard-of-care.

Riliprubart demonstrated inhibition of complement activity and reduced NfL levels from baseline





Strong and sustained reduction (CH50 ≤10 IU/mL) of complement activity was observed through Week 24

Trend for reduced NfL levels from baseline was observed across all subpopulations through Week 24

CH50, hemolytic complement; NfL, neurofilament light chain; SEM, standard error mean; SOC, standard-of-care.

Summary of adverse events by Week 24[a]

Participants, n (%)	SOC-Treated (N=25)	SOC-Refractory (N=18)	SOC-Naïve (N=12)
Any TEAE, n (%)[b]	15 (60)	13 (72)	9 (75)
Grade ≥3	1 (4)	3 (17)	1 (8)
TEAE (≥12% in any study group), n (%)			
Headache	3 (12)	2 (11)	2 (17)
Back pain	0	0	3 (25)
Fatigue	3 (12)	2 (11)	1 (8)
Injection site pruritus	0	0	2 (17)
COVID-19	3 (12)	0	0
Nasopharyngitis	1 (4)	3 (17)	1 (8)
Injection site erythema	3 (12)	0	0
TEAE leading to death[c], n (%)	1 (4)	1 (6)	0
Treatment emergent SAE, n (%)	1 (4)	2 (11)	1 (8)
TEAE leading to permanent treatment discontinuation, n (%)	0	2 (11)	0
Treatment emergent AESI[d], n (%)	2 (8)	1 (6)	0

[a]Predefined interim analysis cut-off period included when first 50% of SOC-Treated enrolled participants completed Part A. Data cut-off was 16 May 2023 for SOC-Refractory and SOC-Treated participants and 16 Oct 2023 for SOC-Naïve participants for Part A at 24 weeks. [b]By highest grade. [c]2 deaths were reported in participants with significant comorbidities (including past history of pulmonary embolism, cardiovascular diseases, and immobilization due to CIDP). [d]1 SOC-Refractory participant had infection with an encapsulated bacteria (Klebsiella pneumoniae) in the context of worsening of CIDP and dysphagia and 2 SOC-Treated participants had ALT increased >3 x upper limit of normal (ULN), both of which recovered spontaneously with no changes to treatment. AESI, adverse events of special interest; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; SAE, serious adverse event; SOC, standard-of-care; TEAE, treatment-emergent adverse event.

Conclusions

Riliprubart demonstrated **encouraging efficacy** across three subpopulations of participants with CIDP:

- **88%** SOC-Treated participants **improved or remained stable** after switching from SOC to riliprubart
  - **44%** improved while switching from SOC (IVIg) to riliprubart
- **50%** SOC-Refractory participants **improved** on riliprubart
- **75%** SOC-Naïve participants **improved** on riliprubart

Although this is an open-label study, the results exceeded the expected placebo response rate of ~11% (based on historical data[1]), and **clinically meaningful improvements** were observed consistently across **disability and impairment measures**

Strong **inhibition of complement activity** by riliprubart may indicate **decreased disease activity**, and reduced NfL levels may be associated with **less neuroaxonal damage** in CIDP

These results demonstrate proof of concept for C1s inhibition with riliprubart in CIDP

- An ongoing long-term extension (Part B) will continue to build on the efficacy and safety profile of riliprubart in CIDP, further supporting the development of riliprubart in two different Phase 3 trials that will target:
  - **Refractory participants** Mobilize Clinical Trial
  - Participants treated with **IVIg with residual disability** Vitalize Clinical Trial

1. Lewis, et al. *J Peripher Nerv Syst*. 2020;25(3):230-237. C1, complement component 1, s subcomponent; CIDP, chronic inflammatory demyelinating polyneuropathy; IVIg, intravenous immunoglobulin; NfL, neurofilament light chain; SOC, standard-of-care.