CIDP

AMBASSADOR PROGRAM

Emerging Therapies for CIDP

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Emerging Therapies for CIDP

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- Facilitated SCIG (recombinant hyaluronidase)
- Complement inhibitors
- FcRn antagonists
- CD20

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Hyaluronidase-Facilitated SCIG

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- Recombinant human hyaluronidase
  - Depolymerizes hyaluronan in the extracellular matrix (ECM)
  - Transiently increases permeability of SC tissue to Ig
  - Administered SC before IVIG 10%
- Used for several years for immunodeficiency
- Can be administered over ~2 hours q 3-4 weeks

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RESEARCH REPORT

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Hyaluronidase-facilitated subcutaneous immunoglobulin 10% as maintenance therapy for chronic inflammatory demyelinating polyradiculoneuropathy: The ADVANCE-CIDP 1 randomized controlled trial

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Abstract

Background and Aims: ADVANCE-CIDP 1 evaluated facilitated subcutaneous immunoglobulin (fSCIG; human immunoglobulin G 10% with recombinant human hyaluronidase) efficacy and safety in preventing chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) relapse.

Methods: ADVANCE-CIDP 1 was a phase 3, double-blind, placebo-controlled trial conducted at 54 sites in 21 countries. Eligible adults had definite or probable CIDP and adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability scores of 0–7 (inclusive), and received stable intravenous immunoglobulin (IVIG) for ≥12 weeks before screening. After stopping IVIG, patients were randomized 1:1 to fSCIG 10% or placebo for 6 months or until relapse/discontinuation. fSCIG 10% was administered at the same dose (or matching placebo volume) and interval as pre-randomization IVIG. The primary outcome was patient proportion experiencing CIDP relapse (≥1-point increase in adjusted INCAT score from pre-subcutaneous treatment baseline) in the modified intention-to-treat population. Secondary outcomes included time to relapse and safety endpoints.

Results: Overall, 132 patients (mean age 54.4 years, 56.1% male) received fSCIG 10% ($n = 62$) or placebo ($n = 70$). CIDP relapse was reduced with fSCIG 10% versus placebo ($n = 6$ [9.7%; 95% confidence interval 4.5%, 19.6%] vs $n = 22$ [31.4%; 21.8%, 43.0%], respectively; absolute difference: −21.8% [−34.5%, −7.9%], $p = .0045$). Relapse probability was higher with placebo versus fSCIG 10% over time ($p = .002$). Adverse events

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ADVANCE-CIDP Trial

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- Randomized, double-blind, placebo-controlled phase 3 clinical trial evaluating the efficacy and safety of facilitated subcutaneous immunoglobulin (fSCIG) 10% for maintenance treatment of CIDP
- 132 adults with CIDP randomized 1:1 to receive fSCIG 10% (n=62) or placebo (n=70) for 6 months or until relapse/discontinuation
- fSCIG 10% significantly reduced the proportion of patients experiencing CIDP relapse compared to placebo (9.7% vs 31.4%, p=0.0045)
- Time to relapse was significantly longer with fSCIG 10% versus placebo (p=0.002)

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ADVANCE-CIDP Trial

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- Subjects had probable or definite CIDP
- Stable on IVIg for > 12 weeks
- 0.4 – 2.4 g/kg per month, dosed q2-6 weeks

- Switched to fSCIg or placebo (albumin plus hyaluronidase)

- Primary outcome increase of ≥1 point INCAT

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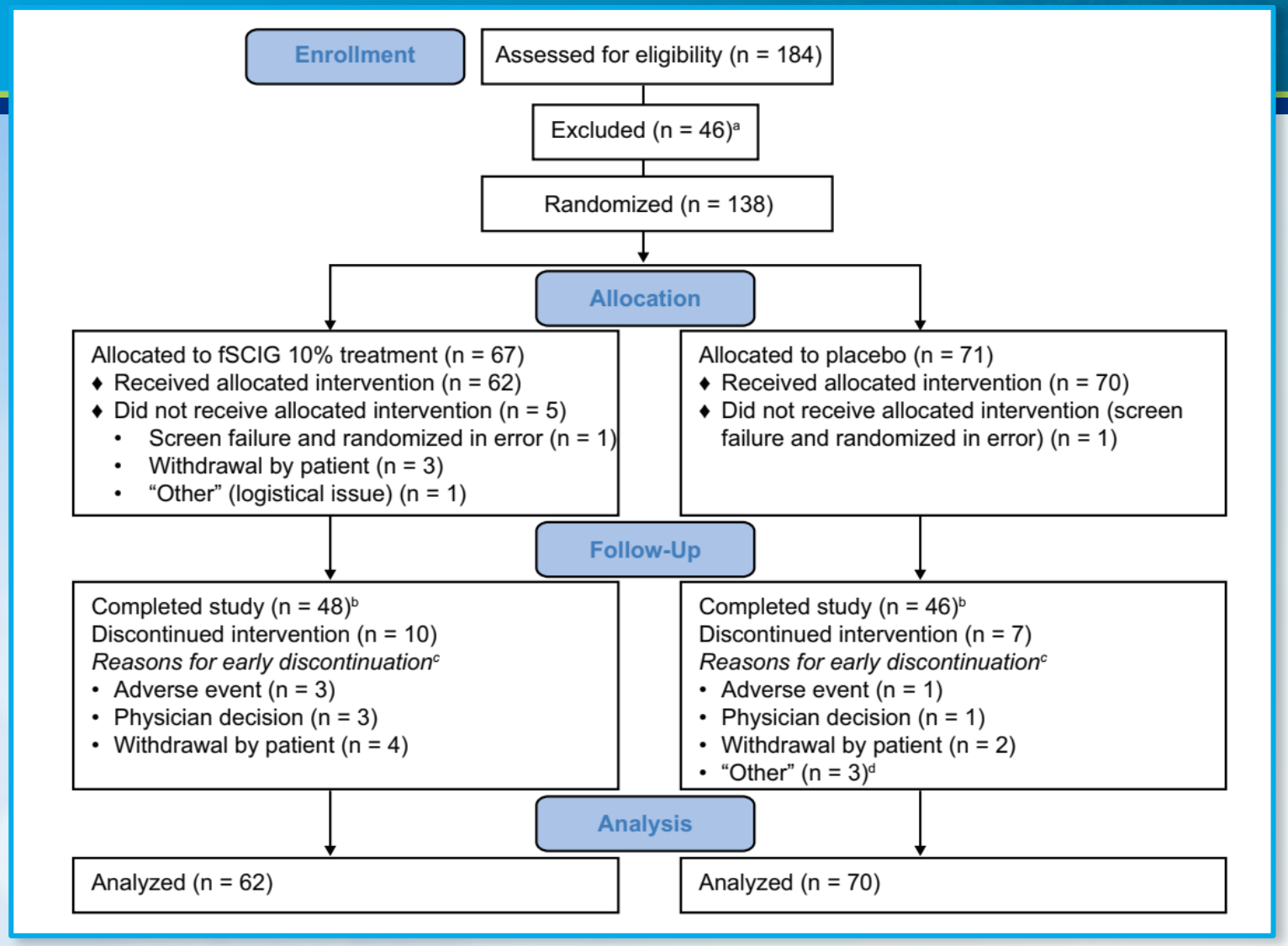

Enrollment
Assessed for eligibility (n = 184)
Excluded (n = 46)[a]
Randomized (n = 138)
Allocation
Allocated to fSCIG 10% treatment (n = 67)
♦ Received allocated intervention (n = 62)
♦ Did not receive allocated intervention (n = 5)
• Screen failure and randomized in error (n = 1)
• Withdrawal by patient (n = 3)
• "Other" (logistical issue) (n = 1)
Allocated to placebo (n = 71)
♦ Received allocated intervention (n = 70)
♦ Did not receive allocated intervention (screen failure and randomized in error) (n = 1)
Follow-Up
Completed study (n = 48)[b]
Discontinued intervention (n = 10)
Reasons for early discontinuation[c]
• Adverse event (n = 3)
• Physician decision (n = 3)
• Withdrawal by patient (n = 4)
Completed study (n = 46)[b]
Discontinued intervention (n = 7)
Reasons for early discontinuation[c]
• Adverse event (n = 1)
• Physician decision (n = 1)
• Withdrawal by patient (n = 2)
• "Other" (n = 3)[d]
Analysis
Analyzed (n = 62)
Analyzed (n = 70)

TABLE 1 Patient demographics and baseline disease characteristics.

Variable	Placebo ($n = 70$)	fSCIG 10% ($n = 62$)	Total ($N = 132$)
Age, years, mean (SD)	53.9 (13.4)	55.0 (14.3)	54.4 (13.8)
Sex, *n* (%)			
Male	38 (54.3)	36 (58.1)	74 (56.1)
Female	32 (45.7)	26 (41.9)	58 (43.9)
Race, *n* (%)			
White	64 (91.4)	58 (93.5)	122 (92.4)
American Indian or Alaskan Native	2 (2.9)	1 (1.6)	3 (2.3)
Multiple	0	1 (1.6)	1 (0.8)
Not reported	4 (5.7)	2 (3.2)	6 (4.5)
Ethnicity, *n* (%)			
Hispanic or Latino	14 (20.0)	9 (14.5)	23 (17.4)
Not Hispanic or Latino	46 (65.7)	47 (75.8)	93 (70.5)
Not reported	10 (14.3)	6 (9.7)	16 (12.1)
BMI, mean (SD), kg/m^2	28.3 (6.4)	27.6 (4.7)	28.0 (5.6)
Time since first symptoms of CIDP (years)			
n	69	62	131
Mean (SD)	5.1 (4.1)	6.5 (6.4)	5.8 (5.3)
Median (min, max)	4.0 (0.5, 18.2)	4.5 (0.2, 29.2)	4.1 (0.2, 29.2)
Time since first diagnosis of CIDP (years)			
n	70	61	131
Mean (SD)	3.8 (3.6)	4.5 (4.8)	4.1 (4.2)
Median (min, max)	2.4 (0.2, 13.6)	2.0 (0.2, 19.6)	2.3 (0.2, 19.6)
Age at first diagnosis of CIDP (years)			
n	70	61	131
Mean (SD)	50.1 (14.0)	50.5 (13.9)	50.3 (13.9)
Median (min, max)	50.0 (21, 76)	51.0 (18, 81)	50.0 (18, 81)
Dosing schedule, *n* (%)			
2 weeks	0	2 (3.2)	2 (1.5)
3 weeks	9 (12.9)	5 (8.1)	14 (10.6)
4 weeks	61 (87.1)	55 (88.7)	116 (87.9)

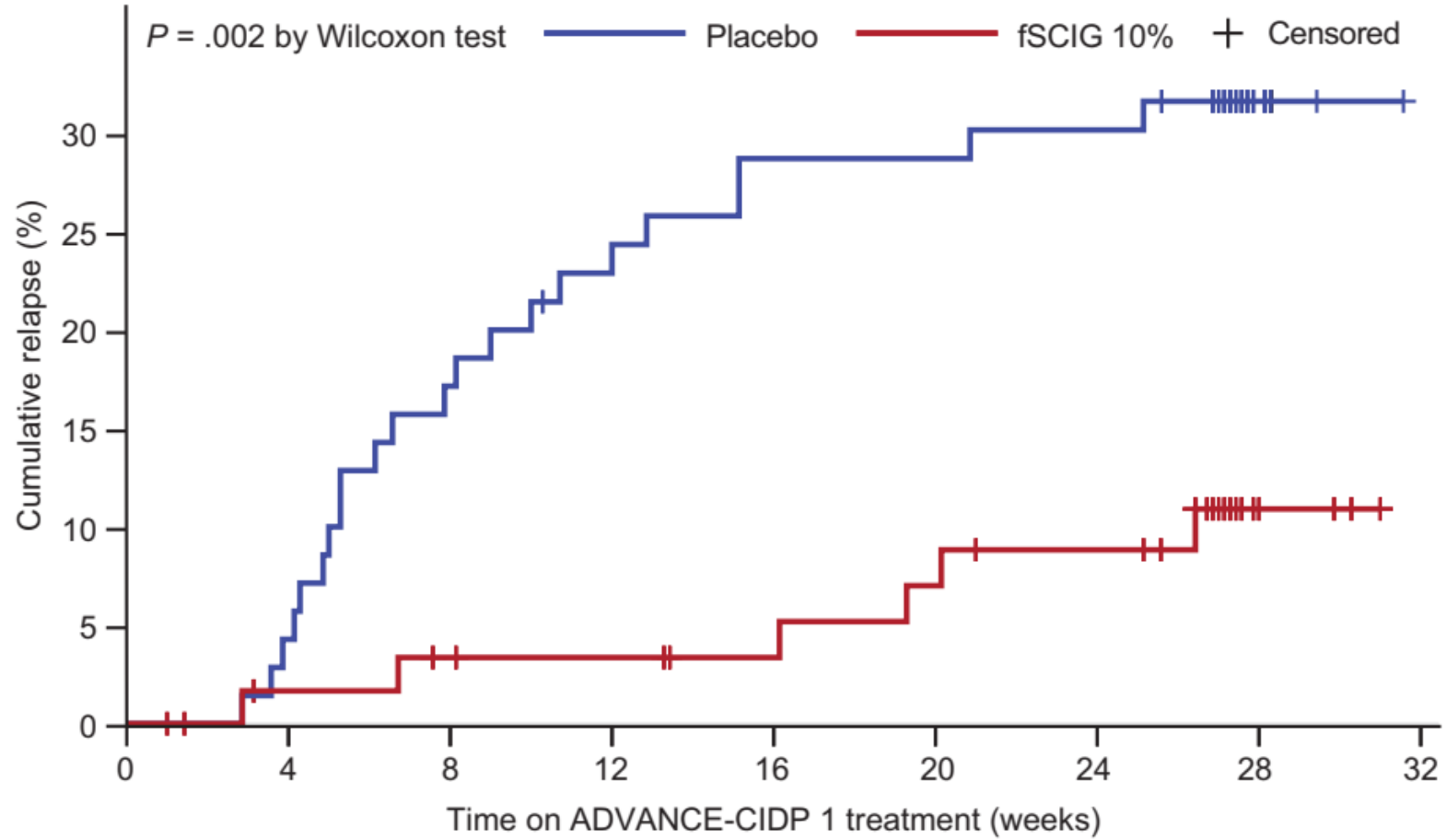
Infusion Details (fSCIG)

- Mean monthly dose 85.4 grams (1.1 g/kg)
- Mean duration of infusion 126 minutes
- Dosing interval 4 weeks in 88% (3 weeks in 10%)

TABLE 2 Primary efficacy endpoint and sensitivity analysis (A) and secondary efficacy endpoints (B).

(A)

Outcome measure	Placebo ($n = 70$)	fSCIG 10% ($n = 62$)	Absolute difference in percentage of relapse (%)	p value
Primary endpoint (MITT set)				
Relapse rate, n/N (%)[a]	22/70 (31.4)	6/62 (9.7)	−21.80	.0045
95% CI	21.8, 43.0	4.5, 19.6	−34.5, −7.9	



Number at risk

Placebo	70	67	58	53	49	49	48	4	0
fSCIG 10%	62	58	56	55	53	51	49	5	0

TABLE 4 Adverse events in the safety set.

Number of patients with AE (%)	Placebo ($n = 70$)	fSCIG 10% ($n = 62$)	Total ($N = 132$)
Any AE	40 (57.1)	49 (79.0)	89 (67.4)
Events per 100 infusions	23	57	39
Systemic AEs, events per 100 infusions	20	34	26
Gastrointestinal disorders, no. of patients (%)	14 (20.0)	12 (19.4)	26 (19.7)
Nausea	2 (2.9)	7 (11.3)	9 (6.8)
Diarrhea	5 (7.1)	0 (0.0)	5 (3.8)
Vomiting	4 (5.7)	1 (1.6)	5 (3.8)
General disorders and administration site conditions, no. of patients (%)	4 (5.7)	19 (30.6)	23 (17.4)
Fatigue	2 (2.9)	6 (9.7)	8 (6.1)
Pyrexia	1 (1.4)	7 (11.3)	8 (6.1)
Musculoskeletal and connective tissue disorders, no. of patients (%)	12 (17.1)	12 (19.4)	24 (18.2)
Back pain	2 (2.9)	4 (6.5)	6 (4.5)
Arthralgia	3 (4.3)	3 (4.8)	6 (4.5)
Nervous system disorders, no. of patients (%)	18 (25.7)	19 (30.6)	37 (28.0)
Headache	8 (11.4)	8 (12.9)	16 (12.1)
Dizziness	1 (1.4)	4 (6.5)	5 (3.8)
CIDP (relapse)[a]	4 (5.7)	0 (0.0)	4 (3.0)
Skin and subcutaneous tissue disorders, no. of patients (%)	4 (5.7)	8 (12.9)	12 (9.1)
Pruritis	1 (1.4)	5 (8.1)	6 (4.5)
Vascular disorders, no. of patients (%)	4 (5.7)	5 (8.1)	9 (6.8)
Hypertension	1 (1.4)	4 (6.5)	5 (3.8)
Local AEs, events per 100 infusions	3	24	13
General disorders and administration site conditions, no. of patients (%)	8 (11.4)	24 (38.7)	32 (24.2)
Injection/infusion site pain	4 (5.7)	10 (16.1)	14 (10.6)
Injection/infusion site erythema	0 (0.0)	13 (21.0)	13 (9.8)
Injection/infusion site pruritis	0 (0.0)	8 (12.9)	8 (6.1)
Injection/infusion site edema	1 (1.4)	2 (3.2)	3 (2.3)
Any serious AE[b]	5 (7.1)	2 (3.2)	7 (5.3)

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Injection/infusion site edema	1 (1.4)	2 (3.2)	3 (2.3)
Any serious AE[b]	5 (7.1)	2 (3.2)	7 (5.3)

Subject Preferences

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- Preferred study drug over IVIG: 70%
- Would choose to continue receiving study drug: 92%

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Considerations

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- Patients were not required to show deterioration if IVIG withdrawn
  - only 31% of placebo group relapsed
- fSCIG could provide IVIG doses in less than half the time at q 3-4 intervals without need for IV access

Complement

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Neurotherapeutics (2022) 19:864–873
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REVIEW

Check for updates

The Role of the Complement System in Chronic Inflammatory Demyelinating Polyneuropathy: Implications for Complement-Targeted Therapies

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Summary

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common, heterogeneous, immune-mediated neuropathy, characterized by predominant demyelination of motor and sensory nerves. CIDP follows a relapsing–remitting or a progressive course and causes substantial disability. The pathogenesis of CIDP involves a complex interplay of multiple aberrant immune responses, creating a pro-inflammatory environment, subsequently inflicting damage on the myelin sheath. Though the exact triggers are unclear, diverse immune mechanisms encompassing cellular and humoral pathways are implicated. The complement system appears to play a role in promoting macrophage-mediated demyelination. Complement deposition in sural nerve biopsies, as well as signs of increased complement activation in serum and CSF of patients with CIDP, suggest complement involvement in CIDP pathogenesis. Here, we present a comprehensive overview of the preclinical and clinical evidence supporting the potential role of the complement system in CIDP. This understanding furnishes a strong rationale for targeting the complement system to develop new therapies that could serve the unmet needs of patients affected by CIDP, particularly in those refractory to standard therapies.

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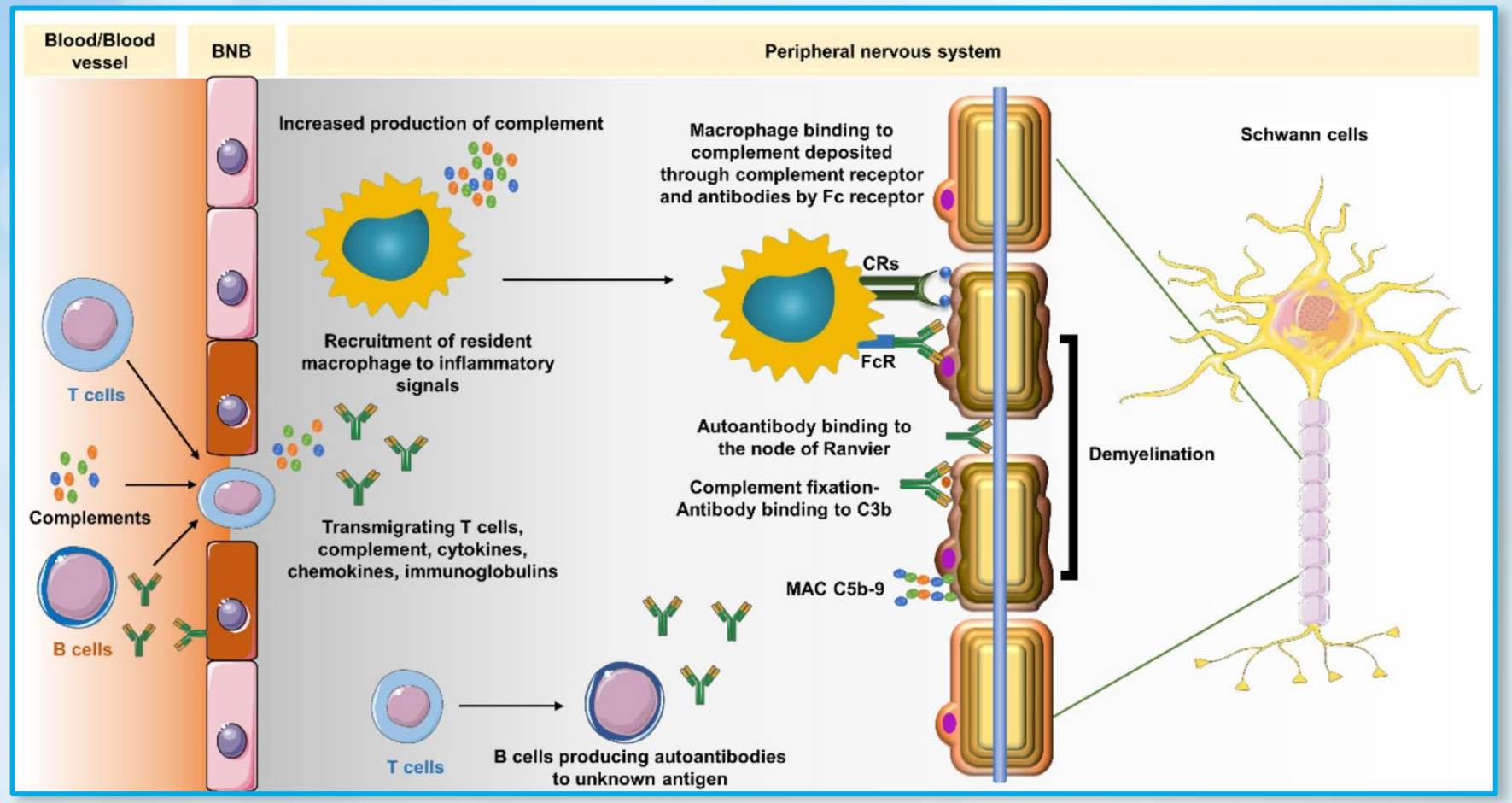
Blood/Blood vessel
BNB
Peripheral nervous system
Increased production of complement
Recruitment of resident macrophage to inflammatory signals
Transmigrating T cells, complement, cytokines, chemokines, immunoglobulins
T cells
Complements
B cells
T cells
B cells producing autoantibodies to unknown antigen
Macrophage binding to complement deposited through complement receptor and antibodies by Fc receptor
CRs
FcR
Autoantibody binding to the node of Ranvier
Complement fixation-Antibody binding to C3b
MAC C5b-9
Demyelination
Schwann cells

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RESEARCH PROTOCOL

WILEY

An innovative phase 2 proof-of-concept trial design to evaluate SAR445088, a monoclonal antibody targeting complement C1s in chronic inflammatory demyelinating polyneuropathy

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Funding information
Sanofi

Abstract

Background and Aims: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated disease of the peripheral nerves, with significant unmet treatment needs. Clinical trials in CIDP are challenging; thus, new trial designs are needed. We present design of an open-label phase 2 study (NCT04658472) evaluating efficacy and safety of SAR445088, a monoclonal antibody targeting complement C1s, in CIDP.

Methods: This phase 2, proof-of-concept, multicenter, open-label trial will evaluate the efficacy, and safety of SAR445088 in 90 patients with CIDP across three groups: (1) currently treated with standard-of-care (SOC) therapies, including immunoglobulin or corticosteroids (SOC-Treated); (2) refractory to SOC (SOC-Refractory); and (3) naïve to SOC (SOC-Naïve). Enrolled participants undergo a 24-week treatment period (part A), followed by an optional treatment extension for up to an additional 52 weeks (part B).

In part A, the primary endpoint for the SOC-Treated group is the percentage of participants with a relapse after switching from SOC to SAR445088. The primary endpoint for the SOC-Refractory and SOC-Naïve groups is the percentage of participants with a response, compared to baseline. Secondary endpoints include safety, tolerability, immunogenicity, and efficacy of SAR445088 during 12-week overlapping period (SOC-Treated). Part B evaluates long-term safety and durability of efficacy. Data analysis will be performed using Bayesian statistics (predefined efficacy thresholds) and historical data-based placebo assumptions to support program decision-making.

Interpretation: This innovative trial design based on patient groups and Bayesian statistics provides an efficient paradigm to evaluate new treatment candidates across the CIDP spectrum and can help accelerate development of new therapies.

KEYWORDS
Bayesian analysis, CIDP, complement classical pathway, complement C1s, SAR445088, trial design

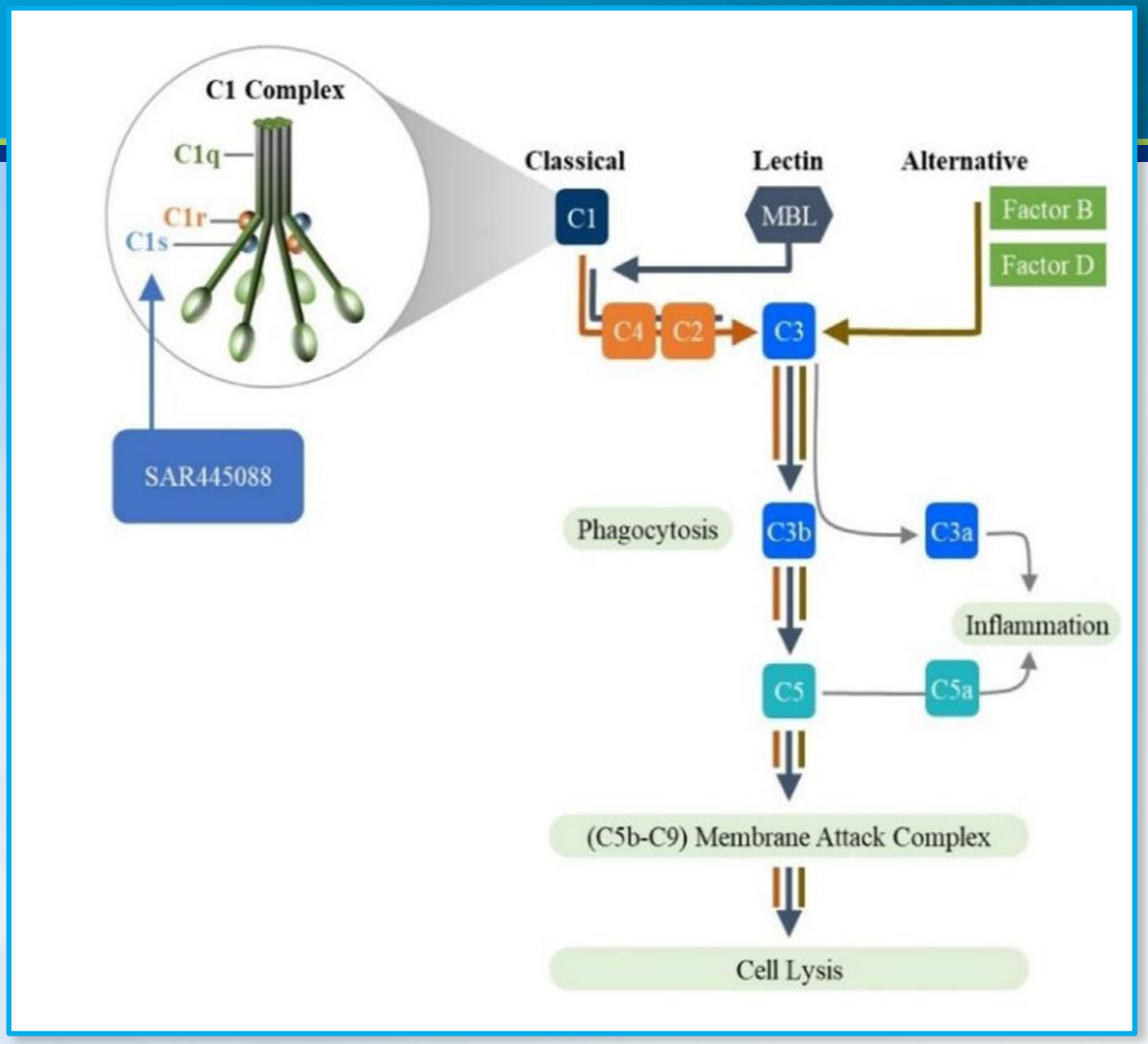
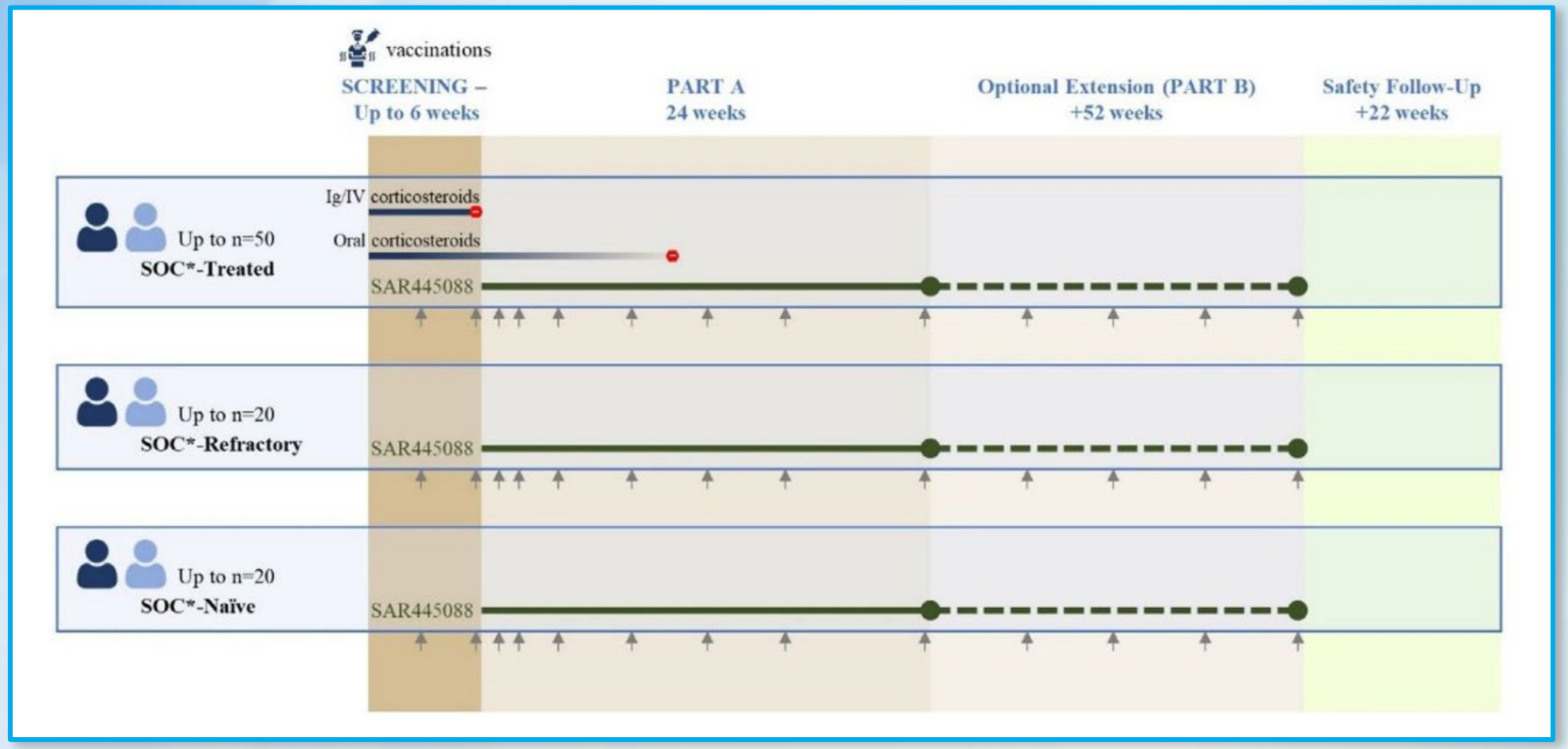
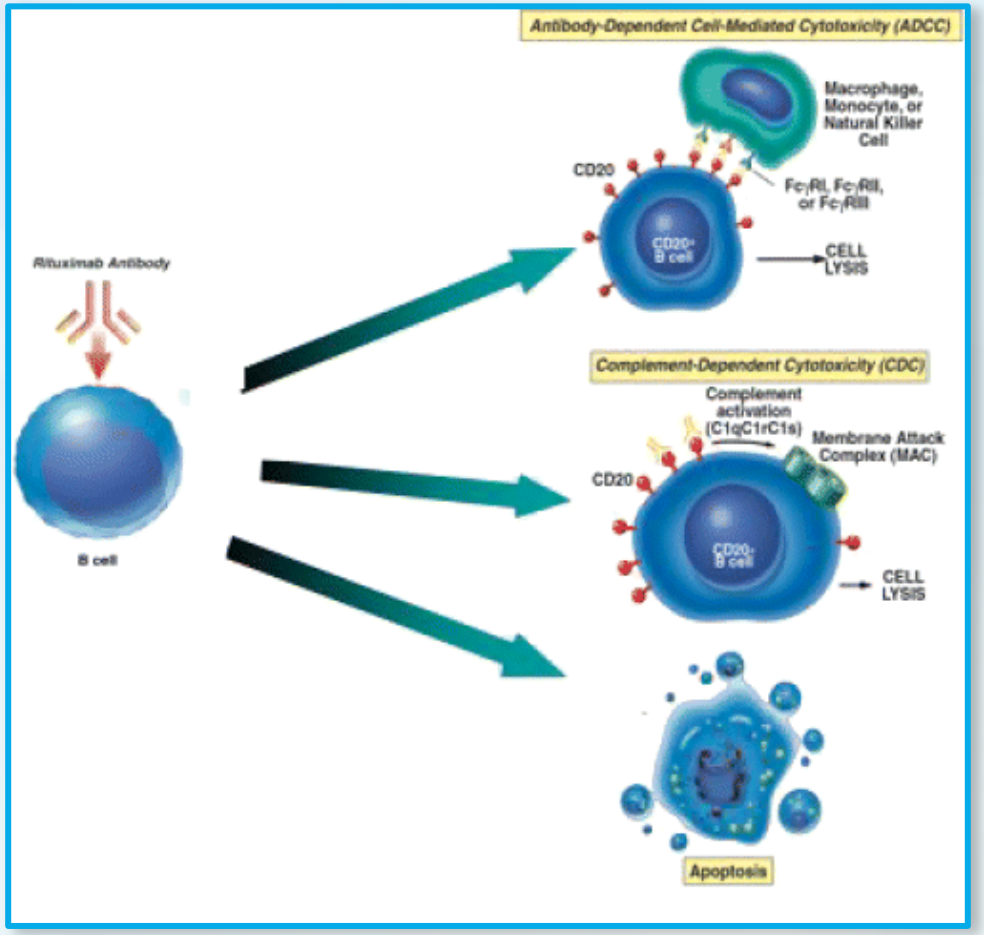

C1 Complex
C1q
C1r
C1s
SAR445088
Classical
Lectin
Alternative
C1
MBL
Factor B
Factor D
C4
C2
C3
Phagocytosis
C3b
C3a
Inflammation
C5
C5a
(C5b-C9) Membrane Attack Complex
Cell Lysis

TABLE 1 Patient groups.

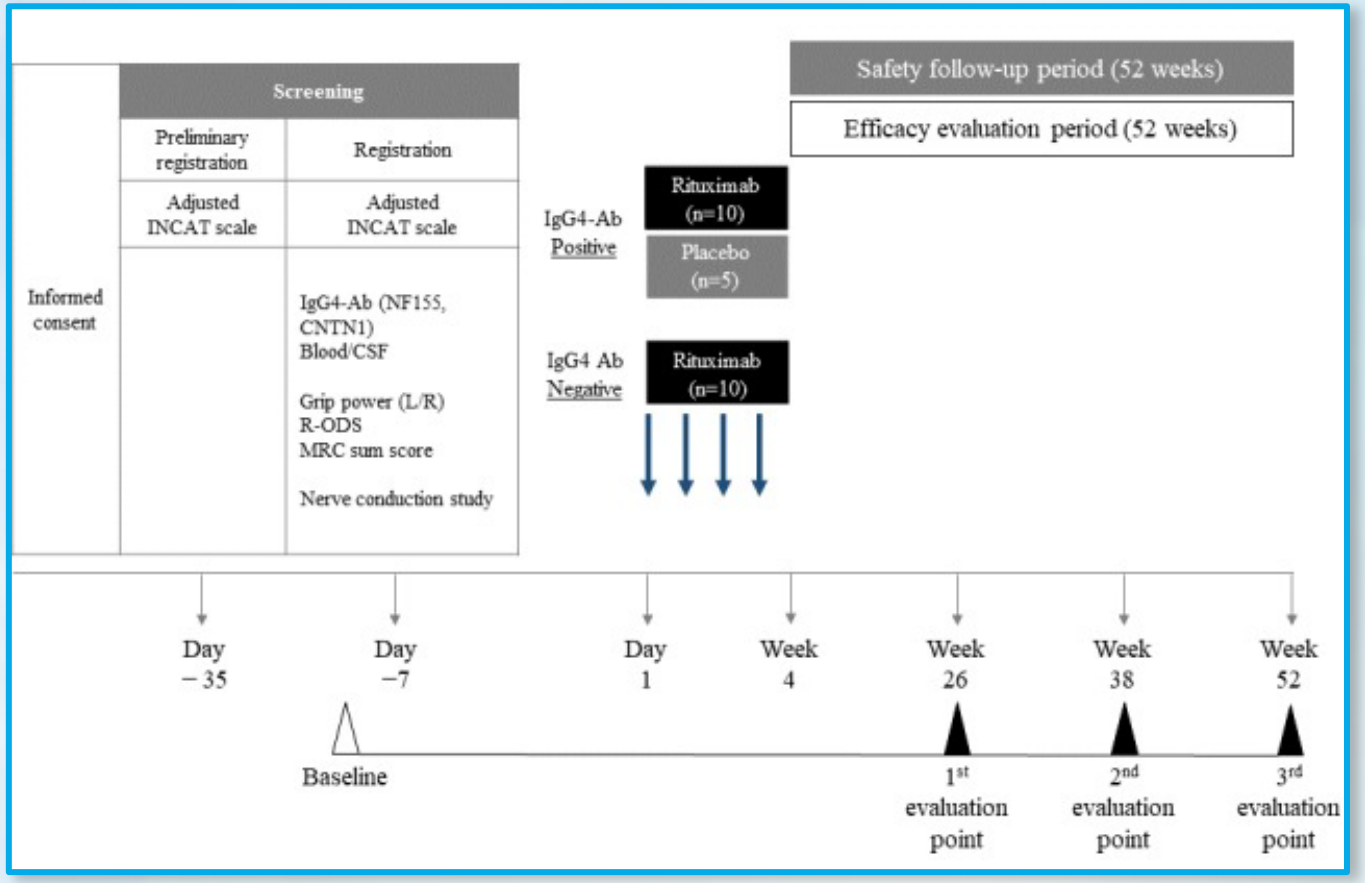
SOC-Treated All criteria (A to C) must be met	SOC-Refractory All criteria (A to D) must be met	SOC-Naïve All criteria (A to C) must be met
A. Objective response to SOC, with clinically meaningful improvement[a]	A. Failure or inadequate response to SOC therapy defined as no clinically meaningful improvement and persistent INCAT score ≥2 after treatment for a minimum of 12 weeks on SOC therapy prior to screening	A. No prior treatment for CIDP or have received IVIg/SCIg/corticosteroids but were stopped for reasons other than the lack of response or side effects
B. Must be on stable SOC therapy (no change of >10% in frequency/dose of immunoglobulins/corticosteroids within 8 weeks prior to screening, remaining on stable SOC therapy until the time of first SAR445088 dosing)	B. Not received immunoglobin (IVIg/SCIg) within 12 weeks prior to screening	B. Not treated with IVIg/SCIg/corticosteroids for at least 6 months prior to screening
C. Clinically meaningful deterioration[b] on interruption or dose reduction of SOC therapy within 24 months prior to screening	C. Certain immunosuppressant drugs (azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine) are allowed if taken for ≥6 months and at a stable dose for ≥3 months prior to screening	C. The INCAT score of 2–9 (a score of 2 should be exclusively from the leg disability component of INCAT)
	D. The INCAT score of 2–9 (a score of 2 should be exclusively from the leg disability component of INCAT)	


vaccinations
SCREENING –
Up to 6 weeks
PART A
24 weeks
Optional Extension (PART B)
+52 weeks
Safety Follow-Up
+22 weeks
Ig/IV corticosteroids
Oral corticosteroids
Up to n=50
SOC*-Treated
SAR445088
Up to n=20
SOC*-Refractory
SAR445088
Up to n=20
SOC*-Naïve
SAR445088

Anti-CD20 antibody



RECIPE Study



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FcRn antagonist

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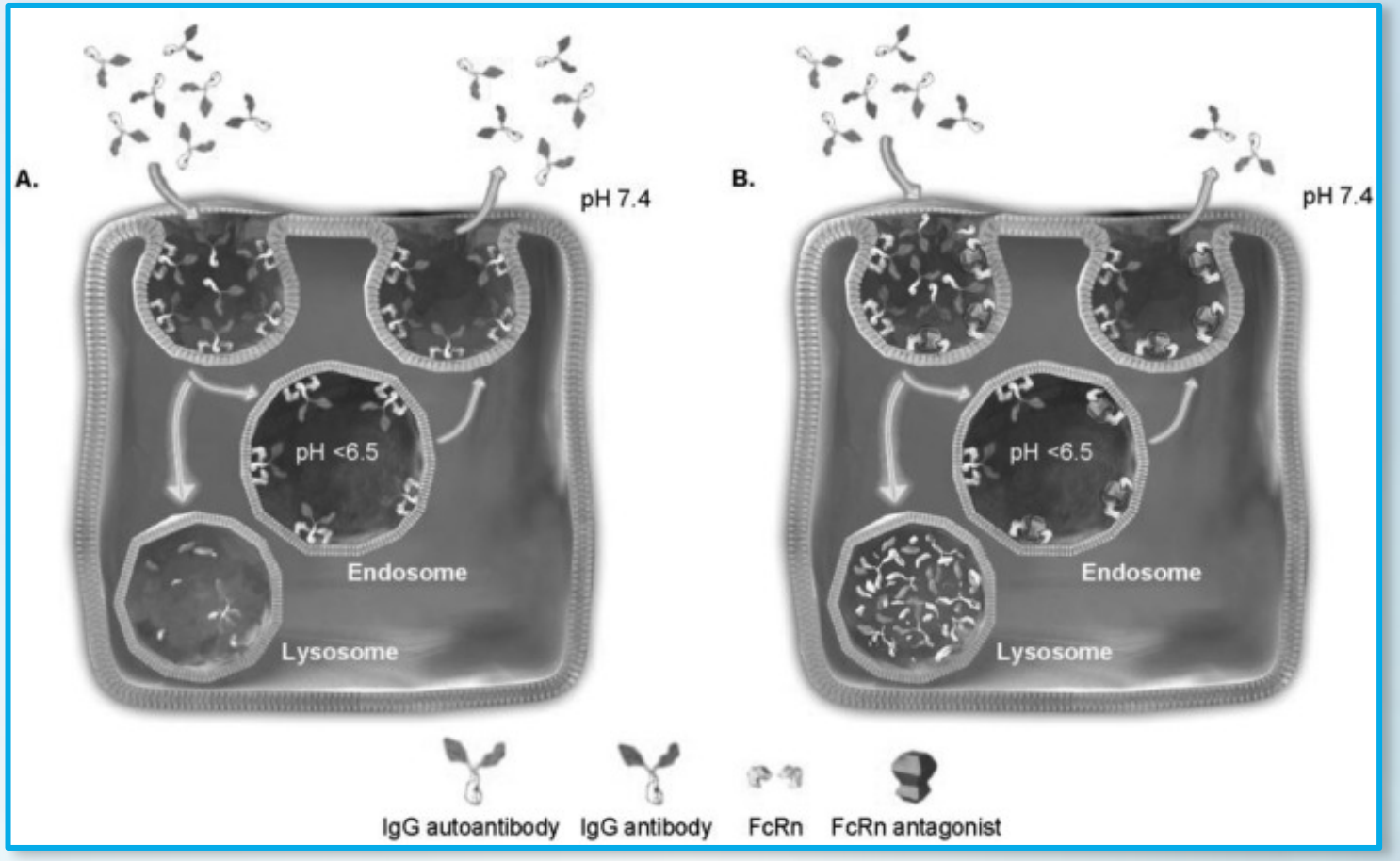
- Batoclimab
- Nipocalimab
- Rozanolixizumab
- Efgartigimod



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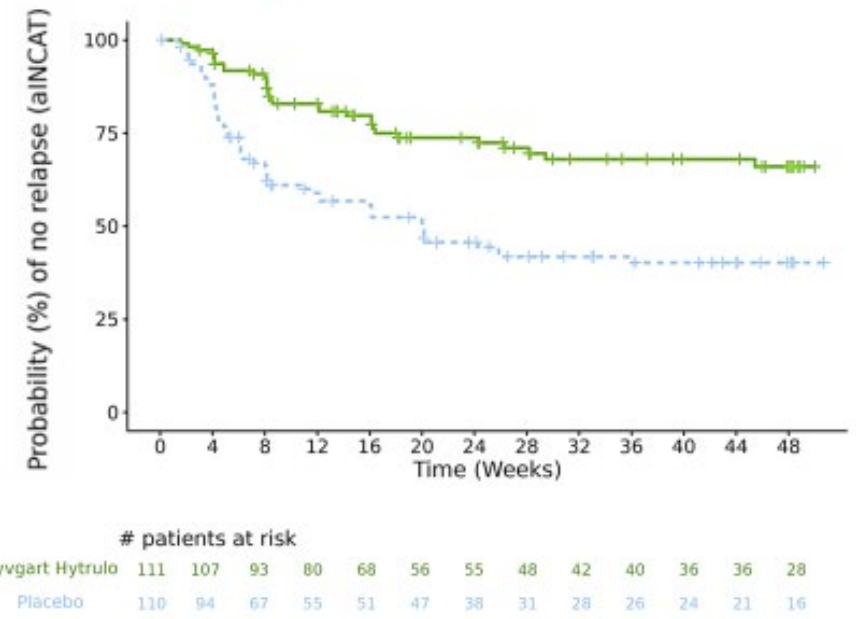
Baseline Characteristics

	STAGE A	STAGE B	
	VYVGART Hytrulo (N=322)	VYVGART Hytrulo (N=111)	Placebo (N=110)
Age - Mean years (SD)	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)
Females - n (%)	114 (35.4)	38 (34.2)	41 (37.3)
Time Since Diagnosis - Mean years (SD)	4.9 (6.1)	3.7 (4.4)	3.8 (4.7)
Atypical CIDP Diagnosis - n (%)	54 (16.8)	14 (12.6)	15 (13.6)
Adjusted INCAT Score - Mean (SD)	4.6 (1.67)	3.1 (1.5)	3.3 (1.6)
I-RODS - Mean (SD)	40.1 (14.7)	53.6 (17.9)	51.2 (15.3)
Grip Strength (in dominant hand) – Mean (SD) Non-dominant scores are similar	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)
Prior Treatment (within past six months) - n (%)			
Corticosteroids	63 (19.6)	24 (21.6)	23 (20.9)
Immunoglobulins (IVIg, SCIg)	165 (51.2)	48 (43.2)	48 (43.6)
Treatment naïve (not on active treatment within past six months)	94 (29.2)	39 (35.1)	39 (35.5)
CIDP Disease Activity Score (CDAS) - n (%)			
Stable active disease (CDAS: 2-4)	125 (38.8)	37 (33.3)	34 (30.9)
Unstable active disease (CDAS: 5)	197 (61.2)	74 (66.7)	76 (69.1)

Stage B: Relative Risk of Relapse Based on Time to First Adjusted INCAT Deterioration



Primary endpoint met

demonstrating a **61% lower risk of relapse** based on time to first adjusted INCAT deterioration with VYVGART Hytrulo compared to placebo

HR: 0.39
p = 0.000039

Clinical benefit observed across all efficacy scales and patient subgroups, regardless of prior therapy

Secondary Endpoints

Secondary Endpoints	Measure	VYVGART Hytrulo n (%)	Placebo n (%)	Hazard Ratio HR (95% CI)	P-value
Risk of CIDP Disease Progression	*Time to First I-RODS Deterioration of at least 4 points*	-	-	0.54 (0.35; 0.81)	0.0034
Improved Functional Level	*I-RODS Improvement of at least 4 points from Stage B Baseline*	50 (45.0)	40 (36.4)	-	0.2294
Adjusted INCAT Score	*Mean (SD) change from Stage B Baseline to Last Assessment*	0.1 (1.1) Median = 0.0	0.9 (2.0) Median = 1.0		
Adjusted I-RODS Score		0.8 (12.3)	-7.0 (19.1)		
Adjusted Mean Grip Strength (dominant hand)		2.1 (13.3)	-8.2 (20.7)		
Adjusted Mean Grip Strength (non-dominant hand)		2.0 (17.3)	-6.9 (21.3)		

Clinically meaningful measured improvement across efficacy scales

- VYVGART Hytrulo patients had **mean improvement of 7.7 points on I-RODS and 12.3kPa on mean grip strength** in Stage A, which was maintained in Stage B by treated patients and lost in placebo patients
- **Consistent trend** observed with mean grip strength

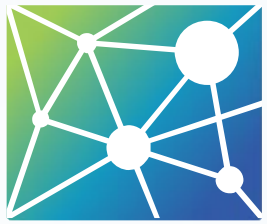
Favorable and Consistent Safety Profile

	STAGE A	STAGE B	
	VYVGART Hytrulo (N=322) n (%)	VYVGART Hytrulo (N=111) n (%)	Placebo (N=110) n (%)
Number of patients with an Adverse Event (AE)	204 (63.4)	71 (64)	62 (56.4)
Number of patients with AEs deemed related by investigator	101 (34.4)	27 (24.3)	22 (20.0)
Number of patients with a Serious Adverse Event (SAE)	21 (6.5)	6 (5.4)	6 (5.5)
Number of patients with SAEs deemed related by investigator	4 (1.2)	0	4 (3.6)
Injection Site Reaction (ISR)	62 (19.3)	16 (14.4)	7 (6.4)
Headache	16 (5.0)	4 (3.6)	2 (1.8)
Infections	44 (13.7)	35 (31.5)	37 (33.6)
COVID-19	*7 (2.2)*	*19 (17.1)*	*14 (12.7)*
Number of patients who discontinued due to AEs	22 (6.8)	3 (2.7)	1 (0.9)
Number of patients with malignancies*	1 (0.3)	2 (1.8)	0
Number of patients with fatal outcome**	2 (0.6)	0	1 (0.9)

Most adverse events were considered mild or moderate

No new safety signals identified with up to 60 weeks of weekly treatment

No increased infection rate with increased exposure



CIDP

AMBASSADOR PROGRAM

GRIFOLS

Clinical Neurological Society of America