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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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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

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1 | INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disease characterized by inflammation and demyelination of the peripheral nervous system, leading to the impairment of motor and sensory functions.¹ Clinical manifestations of CIDP typically include the development of symmetrical, proximal, and distal muscle weakness over a period of time that exceeds 2 months, and sensory impairment due to the involvement of large diameter sensory nerve fibers.^{2–4} The course of CIDP can be relapsing–remitting or progressive, but in either case, symptoms usually persist and worsen over time.^{3,5} CIDP causes accumulating disability that substantially impacts the activities of daily living. Fifty percent of patients are severely disabled at some point in their illness, and 47% stop working because of CIDP.^{6,7} The prevalence of CIDP ranges from 0.8 to 10.3 cases per 100 000 persons, with an incidence of 0.2 to 1.6 cases per 100 000 person-years.^{1,4}

CIDP is a chronic condition, and most patients require long-term treatment to maintain function. While standard-of-care (SOC) therapies exist, including intravenous/subcutaneous immunoglobulin (IVIg/SCIg), corticosteroids, and plasma exchange, there is still a significant unmet need in this disease. Not all patients with CIDP respond to these existing SOC and even when they respond, the response is often partial or transient.⁴ Approximately one-third of patients with CIDP do not respond to a first-line therapy,⁸ 10%–25% are resistant to all SOC therapies,⁹ and only 11% achieve long-term remission (>5 years) or cure.¹⁰ In addition, current SOC therapies are associated with considerable burden, significant side effects, and high costs. IVIg administration usually requires frequent, approximately once every 2–4 weekly visits to a hospital or an infusion center and can cause infusion reactions and serious adverse events (AEs), such as venous thrombosis, stroke and acute renal failure.^{11,12} Chronic use of corticosteroids is also associated with multiple serious AEs.¹³ Plasma exchange requires frequent hospital visits and is often associated with AEs related to venous access, thrombosis, allergy, or sepsis.^{14,15} Therefore, new treatment approaches for CIDP should address these unmet treatment needs.³

Conducting clinical trials in CIDP is challenging. First, CIDP is a rare disease, and enrollment in clinical trials for this condition can be difficult. Two recent phase 3 trials comprising 106 and 172 patients with CIDP, respectively, required 3–4 years to enroll.^{16,17} Second, the clinical and immunological heterogeneity of CIDP,³ with the lack of an objective biomarker, increases the risk of high variability in clinical trials. Last, the use of placebo as a control intervention, often required for an unequivocal demonstration of safety and efficacy of a new compound, may be ethically questionable in CIDP since SOC therapies are available. Because of these limitations, efficient and innovative trial designs are required to accelerate the development of new therapies to address the unmet needs of patients with CIDP.

Both cellular and humoral mechanisms have been proposed as causes of peripheral nerve damage in CIDP.¹⁸ Several lines of evidence support a prominent role of autoantibodies and complement

activation as drivers of demyelination in CIDP.¹⁹ Autoreactive antibodies may aberrantly target myelin, Schwann cell membranes, or node of Ranvier structures, leading to demyelination and axonal damage. Passive exposure to sera or purified immunoglobulin G (IgG) obtained from the patients with CIDP has been shown to trigger conduction block and demyelination in animals, supporting an important role of autoantibodies in the pathogenesis of CIDP.^{20–22} Furthermore, complement deposition on myelin in sural nerve biopsies from patients with CIDP^{23,24} as well as detection of increased complement activation (C3d) in the serum in active disease suggests that CIDP could be complement-mediated.²⁵ Moreover, complement inhibition in experimental autoimmune neuritis, an animal model that recapitulates the features of CIDP, has been shown to restore nerve function and suppress disease progression.^{26–28} The role of complement is further supported by the development of childhood-onset polyneuropathy that resembles CIDP in individuals with rare mutations in the complement regulator CD59 causing excessive activation of the complement system.²⁹ Lastly, in a recent study using a functional human-on-a-chip in vitro model, sera of patients with CIDP led to binding of autoantibodies to Schwann cells and motor neurons, C3b and C5b-9 deposition, and induction of neurophysiological dysfunction.³⁰ Altogether, the above-mentioned data provide a compelling rationale for targeting the complement system as a therapeutic strategy in CIDP.¹⁹

SAR445088, formerly known as BIVV020, is a humanized monoclonal antibody that targets active C1s protein, a C1 complex serine protease, responsible for activating the classical complement pathway (Figure 1). By selectively inhibiting the C1-complex, SAR445088 suppresses the downstream activation of complement system signaling cascades that could block key inflammatory mechanisms underlying demyelination and axonal damage in CIDP. Selective inhibition of the classical complement pathway allows the lectin and alternative pathways to remain intact and may offer a better safety profile than complement inhibitors targeting downstream components such as C5, especially with regards to the risk of infections with encapsulated bacteria (e.g., meningococcus).

In this paper, we describe the design of a phase 2, open-label, proof-of-concept (PoC) trial that leverages Bayesian statistics to efficiently test SAR445088 in patients with CIDP. The aim of this phase 2 trial is to determine the efficacy, safety, and tolerability of SAR445088 in a broad spectrum of CIDP patient groups including patients treated with SOC therapies, patients refractory to SOC therapies, and patients who are naïve to SOC therapies.

2 | MATERIALS AND METHODS

2.1 | Trial design

This trial (NCT04658472) is a global, phase 2, open-label, non-randomized trial evaluating SAR445088 across the three groups of patients with CIDP (Table 1):

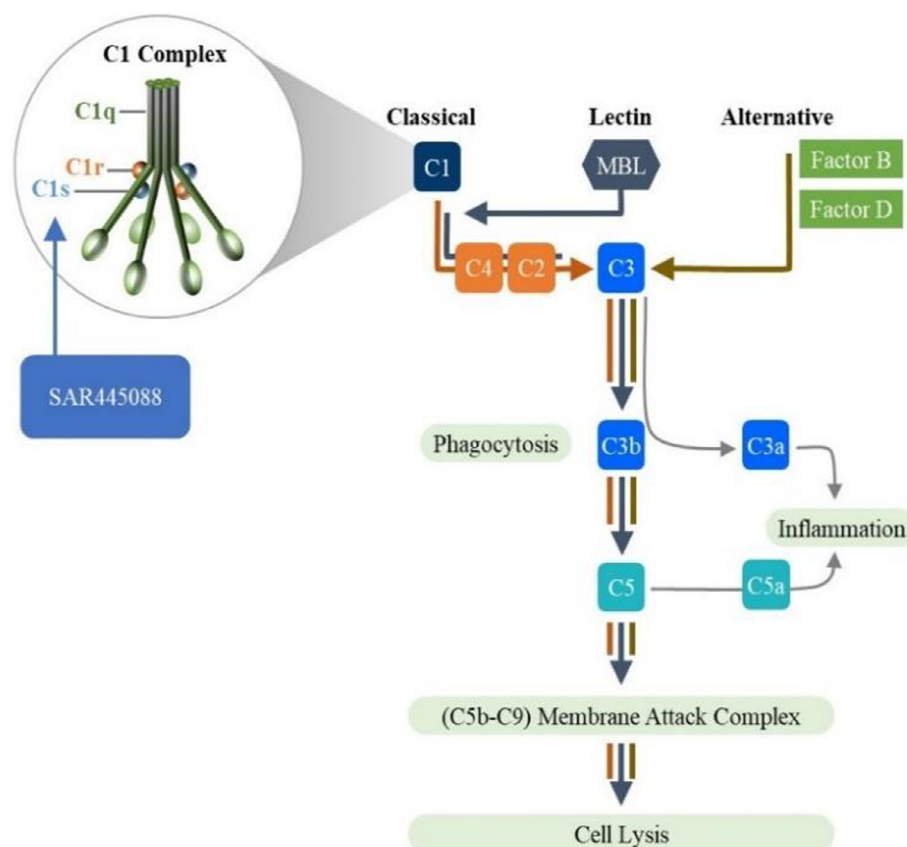


FIGURE 1 Proposed mechanism of action of SAR445088. SAR445088 is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds to the specific serine protease C1s, thus preventing the activation of downstream enzymatic cascade that leads to the activation of C3 convertase and formation of the membrane attack complex. Complement pathway activation also promotes macrophage recruitment, inflammation, and cell lysis. SAR445088 target is specific to C1s of the classical complement pathway, leaving the lectin and alternative pathways intact for host defense. MBL, mannose binding proteins.

- SOC-Treated: Patients treated with the SOC therapies, defined as either immunoglobulins or corticosteroids,
- SOC-Refractory: Patients refractory to SOC therapies, and
- SOC-Naïve: Patients naïve to SOC therapies.

A schematic diagram of the trial is provided in Figure 2. The trial consists of two parts (part A and part B). Part A is a 24-week initial treatment period to evaluate the efficacy and tolerability of SAR445088 across the three patient groups. Part B is a 52-week optional extension period to evaluate the long-term safety and durability of efficacy of SAR445088. The overall duration of the trial, from screening to the follow-up period, is approximately 104 weeks (Figure 2). The conduct of the study is overseen by the trial steering committee of neurologists with expertise in CIDP.

In part A, enrolled participants will receive SAR445088 for 24 weeks. In the SOC-Treated group, the remaining effect of SOC therapy and SAR445088 will overlap for the initial 12 weeks. Specifically, for participants on IVIg/SCIG/pulsed corticosteroids (IV methylprednisolone or oral dexamethasone), the Day 1 visit will be scheduled within 1 week after the last dose of these medications. In participants receiving daily oral corticosteroids, these medications will be tapered during the initial 12 weeks of part A. Participants who successfully complete part A without safety concerns and choose to roll over to the part B extension period, will receive an additional 52 weeks of treatment with SAR445088.

2.2 | Trial objectives

Primary, secondary, and exploratory objectives of this trial and their corresponding outcome measures are listed in Table 2.

2.2.1 | Primary objectives

The primary objective of part A is to determine the efficacy of SAR445088 across the three groups of patients with CIDP: SOC-Treated, SOC-Refractory, and SOC-Naïve. In part B, the primary objective is to determine the long-term safety and tolerability of SAR445088 in patients with CIDP.

2.2.2 | Secondary objectives

In part A, the secondary objectives are to determine safety, tolerability, and immunogenicity of SAR445088 across all patient groups and to evaluate the efficacy of SAR445088 with overlapping SOC therapy in the SOC-Treated group. In part B, the secondary objectives are to determine the long-term durability of efficacy and immunogenicity of SAR445088.

2.2.3 | Exploratory objectives

The exploratory objectives of the trial are to determine the effect of SAR445088 on additional efficacy outcomes, patient-reported

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 immunoglobulin (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)	

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulins; MRC-SS, Medical Research Council Sum Score; SCIG, subcutaneous immunoglobulins; SOC, standard of care.

^aClinically meaningful improvement (any of the following):

- ≥ 1 -point decrease in the adjusted INCAT score,
- ≥ 4 points increase in the I-RODS total score,
- ≥ 3 points increase in the MRC-SS,
- ≥ 8 kPa improvement in the mean grip strength (one hand), or
- an equivalent improvement.

^bClinically meaningful deterioration (any of the following):

- ≥ 1 -point increase in the adjusted INCAT score, decrease in the I-RODS total score ≥ 4 points,
- ≥ 3 points decrease in the MRC-SS,
- ≥ 8 kPa worsening in the mean grip strength (one hand), or
- an equivalent deterioration based on information from the medical records and at the principal investigator's judgment.

outcomes, physician's clinical global assessment, pharmacodynamic biomarkers, and pharmacokinetic parameters in patients with CIDP.

2.3 | Study population

2.3.1 | Inclusion criteria

Adults ≥ 18 years of age, with a definite or probable diagnosis of CIDP, as per the European Federation of Neurological Societies (EFNS)/the Peripheral Nerve Society (PNS) Task Force Guidelines, first revision (2010)³¹ are eligible for enrollment. Patients should belong to one of the three groups: SOC-Treated, SOC-Refractory, or SOC-Naïve (Table 1). All participants should have received vaccinations against encapsulated bacterial pathogens within 5 years of enrollment or initiated a minimum of 14 days prior to the first dose. The signed informed consent will be obtained before the study enrollment.

2.3.2 | Exclusion criteria

1. Patients with polyneuropathy of other causes (Table S1), pure sensory CIDP, and distal acquired demyelinating symmetric neuropathy (also known as distal CIDP)
2. Patients with evidence of immunoglobulin G subclass 4 (IgG4) autoantibodies against paranodal proteins (neurofascin-155 and contactin 1)
3. Prior treatment with plasma exchange, specific complement system inhibitors, rituximab, ocrelizumab, or highly immunosuppressive/chemotherapeutic medications

2.4 | Trial intervention

All eligible participants will enter the initial 24-week period of treatment with SAR445088. In the SOC-Treated group, for the initial 12-week overlap period (Week 1–12), participants will receive

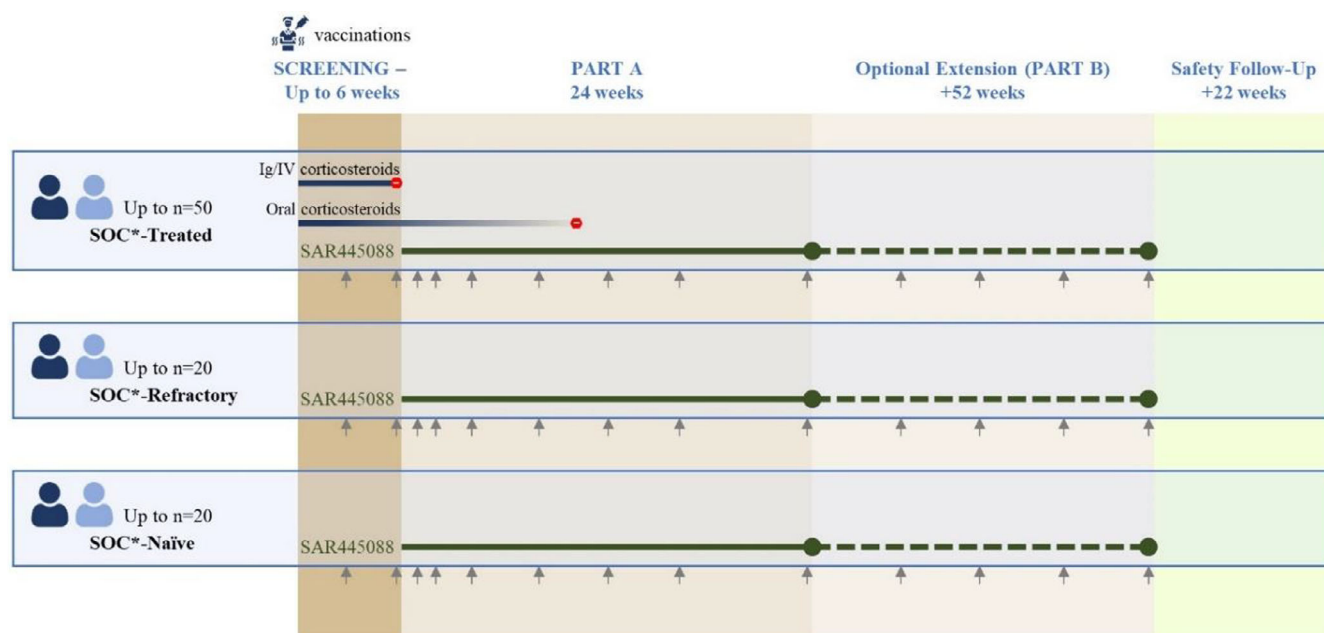


FIGURE 2 Trial design. *SOC, standard of care therapies, defined as immunoglobulin or corticosteroids; ↑ endpoint assessments (INCAT, I-RODS, MRC-SS, and grip strength); Ig, immunoglobulins; IV, intravenous; n, number of patients; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MRC-SS, Medical Research Council Sum Score; SOC, standard of care.

SAR445088, while SOC therapy will be discontinued or in the case of oral corticosteroids, tapered. These participants will then continue to receive SAR445088 for the next 12 weeks. In the SOC-Refractory and SOC-Naïve groups, only SAR445088 will be administered for the 24-week period. In part B, participants will continue to receive SAR445088 for an additional 52 weeks (Week 25–Week 76).

2.5 | Endpoints and outcome assessment

2.5.1 | Primary endpoints

In part A, the primary endpoint in the SOC-Treated group is the percentage of participants relapsing (defined as ≥ 1 -point increase in the adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability score relative to baseline) during the treatment period (Day 1 up to Week 24). In the SOC-Refractory and SOC-Naïve groups, the primary endpoint is the percentage of participants responding (≥ 1 -point decrease in the adjusted INCAT disability score relative to baseline) during the treatment period (Day 1 up to Week 24).

In part B, the primary endpoints include incidence, severity, seriousness, and relatedness of AEs during the treatment extension and follow-up periods (up to Week 98).

2.5.2 | Secondary endpoints

In part A, safety variables will be tabulated and summarized descriptively for overall participants and by CIDP group. In the SOC-Treated group, the percentage of participants showing improvement (defined

as ≥ 1 -point decrease in the adjusted INCAT disability score) will be evaluated to determine the efficacy with overlapping SOC therapies (up to 12 weeks).

In part B, secondary endpoints include the percentage of relapse-free participants in the SOC-Treated group and the percentage of participants maintaining a response in the SOC-Refractory and SOC-Naïve groups. Relapse-free is defined as no increase in the adjusted INCAT disability score of ≥ 2 points relative to that of Week 24.

2.5.3 | Exploratory endpoints

The exploratory endpoints for parts A and B are listed in Table 2.

2.6 | Concomitant medications

Systemic corticosteroids, systemic immunosuppressive agents, and systemic cytotoxic agents are prohibited, except for the SOC-Refractory group. For participants in the SOC-Refractory group, continuation of stable dose of immunosuppressants and low-dose oral corticosteroids (< 20 mg/day prednisone or equivalent) will be allowed.

2.7 | Statistical analysis

2.7.1 | Sample size

In anticipation of a screening failure rate of 30%, approximately 130 patients will be screened to enroll up to 90 participants in the

TABLE 2 Trial objectives and endpoints.

	Objectives	Study groups	Endpoints
Part A			
Primary	<ul style="list-style-type: none">Efficacy of SAR445088 across three CIDP sub-populations	SOC-Treated	<ul style="list-style-type: none">Percentage of participants relapsing after SOC therapy withdrawal and during the SAR445088 treatment period (up to Week 24)
		SOC-Refractory SOC-Naïve	<ul style="list-style-type: none">Percentage of participants responding during the SAR445088 treatment period (up to Week 24)
Secondary	<ul style="list-style-type: none">Safety and tolerability of SAR445088Immunogenicity of SAR445088	All groups	<ul style="list-style-type: none">Incidence, severity, seriousness, and relatedness of AEs during the treatment and follow-up periods (up to Week 46)Incidence and titer of anti-SAR445088 antibodies during the treatment and follow-up periods (up to Week 46)
Exploratory	<ul style="list-style-type: none">Efficacy of SAR445088 in the SOC-Treated group	SOC-Treated	<ul style="list-style-type: none">Percentage of participants improving during the overlap period (up to Week 12)
	<ul style="list-style-type: none">Efficacy of SAR445088 by additional measuresEffect of SAR445088 on patient-reported outcomes and physicians' clinical global assessment	All groups	<ul style="list-style-type: none">Change from baseline in the INCAT score, I-RODS, MRC-SS, and grip strength up to Week 24Change from baseline in quality-of-life (EQ-5D-5L score) and fatigue (R-FSS score) up to Week 24Change from baseline and score in patient's and physician's global impression of severity scores at Week 24
	<ul style="list-style-type: none">Effect of SAR445088 on PK/PD biomarkers		<ul style="list-style-type: none">Change from baseline in CH50, level of total C4, plasma NfL level, C_{max}, C_{min}, and AUC up to Week 24
Part B			
Primary	<ul style="list-style-type: none">Long-term safety and tolerability of SAR445088	All groups	<ul style="list-style-type: none">Incidence, severity, seriousness, and relatedness of AEs throughout the study period
Secondary	<ul style="list-style-type: none">Durability of efficacy during long-term treatment with SAR445088 in CIDP	All groups	<ul style="list-style-type: none">Percentage of participants with lasting efficacy during the treatment extension period (from Week 24 up to Week 76), i.e., relapse-free (SOC-Treated) or with sustained response (SOC-Refractory and SOC-Naïve), defined as no increase in the adjusted INCAT disability score ≥2 points)
Exploratory	<ul style="list-style-type: none">Long-term immunogenicity of SAR445088 in CIDP	All groups	<ul style="list-style-type: none">Incidence and titer of anti-SAR445088 antibodies throughout the study period
	<ul style="list-style-type: none">Long-term effect of SAR445088 on patient-reported outcome and physician's clinical global assessment		<ul style="list-style-type: none">Change from baseline in quality of life (EQ-5D-5L score) and fatigue (R-FSS score) during the entire treatment period (up to Week 76)Change from baseline and score in patient's and physician's global impression of severity score at the end of treatment in the extension period (Week 76)
	<ul style="list-style-type: none">Long-term effect of SAR445088 on PK/PD biomarkers		<ul style="list-style-type: none">Change from baseline in CH50, level of total C4, and other measures of complement activity, plasma NfL levels, C_{max}, C_{min}, and AUC during the entire treatment period (day 1 up to Week 76)
	<ul style="list-style-type: none">Durability of efficacy during long-term treatment with SAR445088 in CIDP, as determined by additional measures		<ul style="list-style-type: none">Change in the INCAT score, I-RODS score, MRC-SS, and grip strength (kilopascals) during the treatment extension period (from Week 24 up to Week 76)

Abbreviations: AEs, adverse events; AUC, area under curve; CIDP, chronic inflammatory demyelinating polyneuropathy; C_{max} , maximum (or peak) serum concentration; C_{min} , lowest serum concentration; EQ-5D-5L, EuroQol 5-Dimension, 5-Level Health Scale; 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; PD, pharmacodynamic; PK, pharmacokinetic; R-FSS, Modified Rasch-built Fatigue Severity Scale; SOC, standard of care.

trial. The SOC-Treated group includes up to 50 participants, which will have 80% power to detect a relapse rate of 23% with SAR445088 as compared with a placebo relapse rate of 40%, as noted in the PATH and FORCIDP trials.^{16,17} Both SOC-Refractory

and SOC-Naïve groups include up to 20 participants each, based on the Bayesian posterior probability analysis to detect a true response rate of $\geq 35\%$ in the SOC-Refractory group and $\geq 50\%$ in the SOC-Naïve group.

2.7.2 | Bayesian analysis

Bayesian statistics provides a formal mathematical method for combining prior knowledge with current information at the design stage, during the conduct of the trial, and at the analysis stage.³² Information from previous clinical trials can be used as prior knowledge to develop rules that can help interpret the results of a clinical trial. The Bayesian approach is particularly advantageous in early clinical development, as it can work with small sample sizes and can help predict future efficacy in phase 3 trials, which can ultimately support more efficient decision-making.

Data from this phase 2 study 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.^{17,33} The results from the ICE trial (54% response rate for the treatment group versus 21% response rate for the placebo group during the 24-week treatment period) was considered as the benchmark to inform the target efficacy and expected placebo effect in the SOC-Naïve and SOC-Refractory groups. The results from the PATH trial (33% relapse rate for the treatment group versus 63% for the placebo group during the 24-week treatment period) were considered as a benchmark to inform the target efficacy in the SOC-Treated group. For all three treatment groups, noninformative prior distributions were used to derive the posterior distribution of the efficacy parameters (relapse rate for the SOC-Treated group and response rates for the other two groups) based on Bayes' theorem. The decision will be based on the posterior distribution, which combines the information from the prior distribution and the observed data; the probability of the efficacy parameter passing a pre-specified threshold will be calculated to determine whether the accumulated information is adequate to proceed to a double-blind placebo-controlled trial.

2.8 | Efficacy and safety evaluation

For the primary efficacy endpoints, data will be presented as the percentage of participants with relapse (SOC-Treated group) and the percentage of participants who responded (SOC-Refractory and SOC-Naïve groups) during the treatment period. The 95% credible interval (CI) limits will be computed for the analysis. The incidence of AEs will be classified by severity, seriousness, and association with SAR445088.

3 | DISCUSSION

This open-label phase 2 PoC trial aims to assess the efficacy, safety, and tolerability of SAR445088 across the whole spectrum of patients with CIDP. After consideration of the practical issues observed in the previously published CIDP clinical trials, including patient recruitment, clinical variability, and statistical analysis, this innovative trial has been designed to provide an optimized solution to these challenges. The

inclusion of multiple patient groups and Bayesian statistics has not been routinely used in CIDP clinical trials. The present trial was designed to provide PoC of the efficacy and safety of SAR445088 and generate preliminary data to support future randomized controlled trials for CIDP. This innovative trial design may provide an efficient way to evaluate new candidate treatments across the CIDP spectrum and thus, aid the development of new therapies for this condition.

3.1 | Addressing feasibility/low recruitment rates

Recruitment difficulties are a major barrier to conducting efficient clinical trials in rare diseases because of low disease prevalence. This is particularly challenging in CIDP trials, as exemplified by the FOR-CIDP trial, where the planned recruitment period (3 years) had to be extended to 4.5 years because of very slow patient recruitment rate.¹⁶ To overcome this challenge, an open-label design was adopted in this trial, as it reduces the number of participants needed and removes uncertainty about being exposed to a placebo, making it more acceptable to patients and physicians. During the early discussions on the trial design and protocol development, expert leaders in the field as well as a panel of patients with CIDP expressed their preference for an open-label design, especially before efficacy is demonstrated. Some studies have identified the chance of receiving a placebo as detrimental for patients to join a clinical trial. For example, in a survey of 496 patients invited to participate in a clinical trial, 13 out of 57 patients declined because of the possibility of receiving a placebo.³⁴

3.2 | Addressing clinical heterogeneity

Because of the heterogeneity of CIDP clinical manifestations as well as treatment response to SOC therapies, it is important to include a wide patient population to evaluate the breadth of the efficacy of new therapies for CIDP. Hence, the present trial design covers three different patient groups to analyze the treatment response to SAR445088. In addition to SOC-Treated patients, SOC-Naïve patients and the target population in prior trials, this trial also includes SOC-Refractory patients, a group with a particular need for new treatment options and yet not the target of any treatment trials. In the absence of understanding of disease heterogeneity or adequate biomarkers to categorize, participants in this trial are grouped according to their response to SOC therapies.

3.3 | Addressing the lack of placebo-controlled groups

The use of a placebo in clinical trials of a disease with available SOC therapies raises ethical questions and reduces a patient's willingness to participate. The risks of withholding access to SOC therapies can

be mitigated by limiting exposure to the experimental drugs to a brief duration and providing rapid rescue therapy in case of worsening.^{16,35} However, this is challenging at an early stage of development, in the absence of any previous indication of efficacy. The use of a historical control group can compensate for the lack of placebo-control group, at least to some extent.³⁶ The Bayesian statistical analysis in this trial incorporates prior information/historical data into the trial conclusions, and the posterior distribution provides an overall summary of the available information.^{37,38} Given the relatively small sample sizes of the current trial, incorporation of the prior information will lead to better decision-making by means of the Bayesian approach as compared with the frequentist approach, which is solely based on the current trial data. In addition, the Bayesian posterior distribution gives complete information about the parameters of interest, which are more insightful than the point and interval estimates derived from the frequentist analysis.³⁹ With Bayesian statistics, periodic analysis can be conducted thus facilitating trial monitoring and potential early decision-making.

3.4 | Appropriateness of diagnostic criteria and outcome measurements

To ensure convenient comparisons against the historical control groups, well-established outcome measures are being used in this trial. Confirmation of CIDP diagnosis for eligibility will be based on the EFNS/PNS guidelines, 2010 first revision.³¹ These diagnostic criteria have been recently updated in the 2021 EAN/PNS guidelines,⁴⁰ after the start of this trial.

The primary efficacy measures (relapse/response) are based on the INCAT scale, which has been validated to evaluate disability in patients with CIDP and used in the large clinical trials for CIDP, including the ICE and PATH trials.^{17,33,41} Additional efficacy measures used in this trial, such as the Inflammatory Rasch-built Overall Disability Scale (I-RODS), the Medical Research Council sum score (MRC-SS), and grip strength, have also been validated and widely used in the CIDP trials.^{16,17,33,41}

3.5 | Rationale for testing SAR440588 in CIDP

Existing treatments for CIDP are inadequate, inconvenient, or expensive and leave a major need for better drugs. Emerging evidence implicates complement in CIDP pathogenesis.²⁵ There is, hence, a strong rationale for targeting the complement system as a new therapeutic approach in CIDP. The positive efficacy results with sutimlimab, a C1s inhibitor, in a complement-mediated disease (cold agglutinin disease)⁴² encourage further research on complement-targeted therapies.

This trial aims to determine the efficacy and safety of SAR445088, a C1s (C1 complex serine protease) inhibitor, in the treatment of CIDP. SAR445088 is the only novel therapeutic agent presently in clinical development for CIDP that specifically targets the classical complement pathway. SAR445088 may potentially block key inflammatory

mechanisms in CIDP, and inhibition of these key inflammatory mechanisms in CIDP by SAR445088 should lead to improved functional status and prevention of disease relapse or progression. The present trial, with three patient groups, will explore the efficacy and safety of SAR445088 across the clinical spectrum of CIDP, including SOC-Refractory patients. With a targeted mechanism of action, a relatively convenient dosage regimen, and a possibility of at-home treatment, SAR445088 has the potential to address the unmet needs in CIDP treatment and reduce the treatment burden in people with CIDP.

Although this study design addresses certain challenges associated with conducting clinical trials for a disease like CIDP, it is not short of limitations. The relevance of historical data may be affected by differences in baseline characteristics and the different use of concomitant treatments over the course of time, even though two of the benchmark trials used as historical data were published as recently as 2018.^{16,17} Also, the lack of randomization and blinding can potentially induce biases in the results. Despite these limitations, the Bayesian analysis provides a good trade-off at this exploratory stage of clinical development. The proposed design will generate critical decision information across the spectrum of patients with CIDP, and with a smaller sample size, will offer an attractive option to patients and physicians by optimizing the information gained with the smallest sample size possible.

This non-randomized trial will help establish a preliminary efficacy baseline of SAR445088, which will aid in assessing its feasibility and safety in the future phase 3 study. The innovative open-label trial design offers effective ways to overcome some major barriers to clinical research which might be adopted in other rare diseases.

3.6 | Trial status

Patient enrollment began in April 2021 and is still ongoing at the time of writing this manuscript. The trial is being conducted at approximately 30 sites across North America, Europe, and Asia. The protocol has been approved by the ethics committees of all the participating centers.

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CONFLICT OF INTEREST STATEMENT

Luis Querol received research grants from Instituto de Salud Carlos III—The Ministry of Economy and Innovation (Spain), the GBS-CIDP Foundation International, Novartis Pharma Spain, Roche, UCB, and Grifols. He provided expert testimony to Grifols, CSL Behring, Novartis, Sanofi, Merck, Annexon, Johnson & Johnson, Alexion, UCB, Takeda, and Roche. He is part of the Steering Committee for Sanofi and principal investigator for UCB's CIDP01 trial. Richard A. Lewis is a

consultant with CSL Behring, Grifols, Pfizer, Sanofi (Steering Committee), Argenx, Pharnext, Roche, Johnson & Johnson, Takeda, Boehringer Ingelheim (DSMB), and Momenta. He is also part scientific advisory boards Alnylam and Akcea and medical advisory board The GBS-CIDP Foundation International. Hans-Peter Hartung is a consultant with Sanofi and Octapharma. He has received fees for serving on Steering and Data Monitoring Committees from Biogen, BMS Celgene, GeNeuro, Merck, Novartis, Octapharma, Roche, and TG Therapeutics. Pieter van Doorn is a consultant with Hansa Biopharma, Immunic, Sanofi, Octapharma, Argenx, Hoffmann-la Roche and received grants from the Prinses Beatrix Spierfonds, Sanquin, and Grifols. Erik Wallstroem, Xiaodong Luo, Miguel Alonso-Alonso, and Nazem Atassi are employees of Sanofi and may hold shares and/or stock options in the company. Richard A. C. Hughes is a consultant with Hansa Biopharma, Immunic, and Sanofi.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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