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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

[†]At the time of the study.

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(AEs) were more frequent with fSCIG 10% (79.0% of patients) than placebo (57.1%), but severe (1.6% vs 8.6%) and serious AEs (3.2% vs 7.1%) were less common.

Interpretation: fSCIG 10% more effectively prevented CIDP relapse than placebo, supporting its potential use as maintenance CIDP treatment.

KEYWORDS
ADVANCE-CIDP 1 randomized controlled trial, chronic inflammatory demyelinating polyradiculoneuropathy, efficacy, hyaluronidase-facilitated subcutaneous immunoglobulin 10%, safety

1 | INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare immune-mediated neurological disorder in which the immune system attacks the myelin sheath resulting in weakness, impaired sensation, pain, fatigue, and a significant impact on functional ability.[1–4] The European Academy of Neurology and Peripheral Nerve Society joint guidelines recommend systemic corticosteroids or intravenous immunoglobulin (IVIG) for first-line treatment of CIDP with disabling symptoms, both for induction and maintenance of response.[5] These guidelines also recommend subcutaneous immunoglobulin (SCIG) as an alternative maintenance therapy in IVIG-responsive patients with active disease.[5] In addition to the substantial physical, psychosocial, and economic burden associated with CIDP,[2,6] existing recommended treatments have limitations including tolerability issues and administration challenges.[7]

HyQvia, a facilitated subcutaneous immunoglobulin (fSCIG) therapy (Baxalta US Inc., a Takeda company) comprises a dual-vial unit of immunoglobulin G (IgG) 10% (GAMMAGARD LIQUID, Baxalta US Inc.; KIOVIG, Takeda Manufacturing Austria AG) and recombinant human hyaluronidase (rHuPH20). rHuPH20 depolymerizes hyaluronan in the extracellular matrix, transiently increasing the permeability of subcutaneous tissue to IgG. This allows high-volume IgG administration (equivalent to volumes administered intravenously) into the subcutaneous tissue over a short time. fSCIG 10% is approved in the EU as immunoglobulin replacement therapy for adults and children (aged 0–18 years) with primary or secondary immunodeficiency diseases,[8] and in the USA for the treatment of primary immunodeficiency diseases in adults and children aged 2 years and above.[9] fSCIG 10% combines the benefits of IVIG and SCIG, may have fewer systemic adverse reactions than IVIG,[10–12] and offers the opportunity for self-administration at home. Additionally, fSCIG 10% enables the administration of large infusion volumes with high infusion rates. Hence, for equivalent monthly doses, less frequent infusions and fewer infusion sites (up to three per infusion) are required for fSCIG 10% compared with conventional SCIG.[13]

Here we report results from the phase 3 placebo-controlled trial, ADVANCE-CIDP 1, which evaluated the efficacy, safety, and tolerability of fSCIG 10% as a maintenance therapy to prevent disease relapse leading to neuromuscular disability in patients with CIDP.

2 | MATERIALS AND METHODS

2.1 | Study design

ADVANCE-CIDP 1 was a phase 3, prospective, randomized, double-blind, multicenter, placebo-controlled study (NCT02549170) enrolling adults with CIDP from 54 sites in 21 countries conducted from December 15, 2015 to February 23, 2022 (details of sites and investigators are provided in Table S1). Following a screening and baseline period (≤8 weeks), the study comprised 2 "epochs" (Epochs 1 and 2; Figure S1), with the results of Epoch 1 presented here (hereafter referred to as ADVANCE-CIDP 1).

In ADVANCE-CIDP 1, patients were randomized 1:1 to fSCIG 10% or placebo (0.25% albumin solution together with rHuPH20), for a period of 6 months or until relapse or withdrawal from the study. fSCIG 10% was administered at the same dose as the patient's pre-randomization monthly equivalent IVIG dose, or matching infusion volume for those receiving placebo, and at the same interval as prior IVIG (maximum 4-weekly administration). Patients receiving placebo who did not experience relapse remained blinded to study treatment and were permitted to enter an ongoing, long-term, open-label extension study (ADVANCE-CIDP 3), during which all patients received fSCIG 10%. Further information regarding dosing, administration, and infusion rates is provided in Appendix S1, Table S2, and Appendix S2, respectively. Additional details of study blinding are provided in Appendix S3, and details of protocol amendments are given in Appendix S4.

2.2 | Patient population

Eligible patients were aged ≥ 18 years at screening with a documented diagnosis of definite or probable CIDP[14] (excluding focal atypical and pure sensory atypical CIDP) confirmed by a neurologist specializing/experienced in neuromuscular diseases, to ensure the true presence of CIDP. Diagnosis of CIDP was confirmed using electrodiagnostic criteria, adjudicated by an independent experienced reader blinded to treatment assignment (Dr Mary L. Vo, M.D., Weill Cornell Medicine, NY, USA). Patients were required to have previously responded to IgG treatment and were receiving a stable dose of IVIG treatment (equivalent to a cumulative monthly dose of 0.4–2.4 g/kg [inclusive] for ≥ 12 weeks before screening,

with a dosing interval of 2–6 weeks [inclusive]). In addition, patients had an adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score[15] of 0–7 (inclusive) and provided informed consent. Patients with a screening and/or baseline adjusted INCAT disability score of 0–1 were required to have a documented score of ≥2 prior to screening, with at least 2 score points taken from the lower extremities. No concomitant steroid use, steroid use within 8 weeks prior to screening, or use of other immunomodulatory or immunosuppressive treatments within 6 months prior to screening was permitted (full eligibility criteria are provided in Table S3).

2.3 | Study outcome measures

2.3.1 | Efficacy outcomes

The primary efficacy outcome was relapse rate, assessed by the proportion of patients experiencing worsening functional disability, defined as an increase of ≥1 point relative to baseline (i.e., pre-subcutaneous treatment) in 2 consecutive adjusted INCAT disability assessments obtained ≤7 days apart. INCAT disability scores were assessed at screening and baseline and at regular intervals afterwards prior to each infusion. Unscheduled INCAT assessments were performed at any time during the study if the investigator deemed there was worsening of CIDP symptoms. An adjusted INCAT assessment that was suggestive of relapse (increase of ≥1 point relative to baseline) triggered a second, confirmatory INCAT evaluation. The INCAT disability score is a validated instrument that assesses disability and functional deterioration.[15] Adjusted INCAT disability scores (used for assessment of the primary endpoint) were identical to INCAT disability scores (scored 0–10, with higher values indicating increasing inability to make purposeful movements), with the exception that upper extremity score changes from 0 to 1 (normal to minor symptoms) or from 1 to 0 were excluded.

Secondary efficacy outcomes included the proportion of patients experiencing functional worsening, time to relapse, and least-squares mean change from baseline in Rasch-built Overall Disability Scale (R-ODS) centile scores.[16] Functional worsening was a composite endpoint defined as the occurrence of at least 1 of the following: a ≥ 1-point increase relative to baseline in 2 consecutive adjusted INCAT disability scores; a ≥ 8 kPa decrease in hand grip strength (in the more affected hand) measured using the Vigorimeter (Martin), or a ≥ 4-point decrease in R-ODS raw summed scores. For hand grip strength and R-ODS scores, changes were relative to the baseline at withdrawal from fSCIG 10% treatment. The R-ODS score, used to assess activities of daily living, was a centile metric score with lower scores reflecting more severe limitations.[16] Aside from the composite endpoint, the other R-ODS score outcome used the centile score. Pre-infusion R-ODS scores were recorded at least once weekly throughout the study in electronic diaries (DIARYpro) provided to patients during screening. Manuals containing detailed instructions for use were provided to study sites and patients.

Tertiary efficacy outcomes included the change in adjusted INCAT disability score, hand grip strength score, and Medical Research Council (MRC) sum score at the end of the study compared with baseline. A maximum of three hand grip strength measurements were taken for each hand at each visit.

2.3.2 | Infusion characteristics

The DIARYpro tool was also used to capture data on the characteristics of infusions, namely mean and median monthly dose equivalents, mean duration of infusion per dose, dosing interval, and the number of sites used per infusion.

2.3.3 | Patient-reported outcomes

The impact of fSCIG 10% therapy on patients' health-related quality of life (HRQoL) and health status was assessed by change from baseline in the 36-Item Short-Form Health Survey (SF-36)[17] and EuroQoL-5 Dimensions (EQ-5D)[18] scores. Higher values reflect a more favorable health state for the SF-36 measure, whereas higher scores for individual questions on the EQ-5D scale indicate poorer HRQoL.[17,18] The EQ-5D also includes a visual analog scale (EQ-VAS) to indicate general health status, scored between 0 and 100 (higher scores indicate better health). SF-36 and EQ-5D scores were measured during the baseline period and at the final treatment visit.

Patient treatment satisfaction and treatment preference were evaluated using the self-administered abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM-9) and a non-validated treatment preference questionnaire, respectively. The TSQM-9 was used to assess effectiveness, convenience, and global satisfaction, with higher scores representing increased satisfaction.[19,20] The treatment preference questionnaire was used to assess patient preference for various attributes of fSCIG 10% therapy, such as ease of administration, frequency and duration of administration, and convenience. The TSQM-9 and treatment preference questionnaire were administered during the baseline period and at the final treatment visit for patients receiving fSCIG 10% or placebo.

2.3.4 | Safety outcomes

Safety outcomes included assessment of the number (percentage) of patients with any serious or nonserious adverse events (AEs), including both those causally related and regardless of causality, and the number (percentage) of temporally related AEs and systemic or local AEs associated with infusions. The number and proportion of infusions for which the infusion rate was reduced, interrupted, or stopped owing to intolerability or AEs was also evaluated, in addition to rates of all AEs and systemic and local AEs, expressed as the number of events per infusion, per patient, and per 1000 patient-years.

Development of binding and neutralizing anti-rHuPH20 antibodies was assessed using anti-rHuPH20 antibody (GCL-612) and anti-rHuPH20 neutralizing activity (MN14006) assays at baseline and 4- to 12-week intervals. Elevated anti-rHuPH20 antibody titers were defined as 2 consecutively recorded post-baseline titers of ≥1:160. Neutralizing antibodies were assessed following a binding antibody titer of ≥1:160. All AEs and related AEs in patients with titers ≥1:160 were summarized.

2.4 | Statistical analysis

2.4.1 | Sample size

It was originally planned in 2015 to randomize 174 patients 1:1 to fSCIG 10% or placebo to detect a difference in relapse rates of 18% with a power of ~80% at the two-sided 5% significance level. This was based on a 15% drop-out rate, and assumed relapse rates of 7% and 25% for fSCIG 10% and placebo, respectively.[21] Owing completely to external factors, such as the COVID-19 pandemic and slow recruitment, the trial was stopped on blinded data by the sponsor in 2022 with 138 patients randomized in the study (Appendix S4). This was supported by more recent scientific literature suggesting a larger treatment difference based on expected relapse rates of 10% and 39% for fSCIG 10% and placebo, respectively.[22,23] Prior to stopping, and under these modified assumptions, 120 randomized patients (i.e., 60 per group and assuming a 15% drop-out rate) were estimated to provide 90% power to detect a treatment difference of 29% at the two-sided 5% significance level.

2.4.2 | Analysis cohorts

The primary efficacy analysis was conducted in the modified intention-to-treat analysis set, which included all randomized patients who received any double-blind study medication. Analysis of additional efficacy and patient-reported outcomes was also performed in the modified intention-to-treat analysis set. The safety set included all patients who received any double-blind study medication, and was used for analysis of safety outcomes. The prespecified sensitivity per-protocol analysis for the primary endpoint included all randomized patients who received any double-blind study medication without major or critical protocol deviations during the study, which may have significantly affected the primary outcome measure.

2.4.3 | Methods of analysis

The primary efficacy analysis compared the relapse rates in the 2 treatment groups using a continuity-corrected χ^2 test conducted at the 5% level of statistical significance, with a missing relapse outcome imputed as no relapse. Estimated relapse rates in each treatment group and the difference in relapse rates between the treatment groups were determined, along with the 95% confidence intervals (CIs).[24,25] Several additional prespecified sensitivity analyses of the primary endpoint were also performed to assess the impact of imputing missing relapse data as "no relapse" and the requirement for a confirmatory INCAT assessment. Prespecified sensitivity analyses included comparisons of the relapse rates in: (1) the modified intent-to-treat (MITT) analysis set with missing or incomplete relapse data imputed as relapse; (2) a MITT observed cases analysis with missing relapse outcomes excluded; (3) the per protocol set with missing relapse outcomes imputed as no relapse; and (4) the MITT analysis set with missing relapse data imputed as no relapse, where relapse was alternatively defined as an increase in adjusted INCAT disability score of ≥1 point relative to the pre-subcutaneous treatment baseline score, but on a single INCAT assessment only. The fourth sensitivity analysis removed the requirement for the increase to be confirmed at a secondary confirmatory INCAT evaluation to classify a patient as having relapsed. All sensitivity analyses used similar statistical methods to the primary analysis. Two additional ad hoc sensitivity analyses of the primary endpoint were also performed to further assess the impact of missing relapse outcomes data: (1) a sensitivity analysis that imputed data for patients with a missing second confirmatory INCAT score in a setting of clinical deterioration as "relapse"; and (2) a multiple imputation analysis under the missing at random premise via multiple imputation chained equations.[26]

Time to relapse was compared between treatment groups using the generalized Wilcoxon (i.e., Gehan's) survival test,[27] with survival functions estimated using the Kaplan–Meier method. An ad hoc time to relapse analysis with missing relapse outcomes imputed as relapse was also performed. The change in R-ODS centile scores from baseline to end of treatment was analyzed using an analysis of covariance (ANCOVA) model to test the treatment effect, with baseline R-ODS score as a covariate. No adjustments for multiplicity were performed for any efficacy evaluation. Change from baseline in adjusted INCAT disability scores, hand grip strength scores, and MRC sum scores were summarized using descriptive statistics. No statistical testing was performed for tertiary efficacy outcomes. SF-36, EQ-5D, and TSQM-9 scores and treatment preference responses were all summarized using descriptive statistics. AEs were coded using the Medical Dictionary for Regulatory Activities version 24.1 and were summarized descriptively.

2.5 | Ethics statement

This study was conducted in accordance with the Code of Federal Regulations pertaining to clinical trials, the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and all applicable national and local regulations. All patients agreed to participate in the study by providing written informed consent.

3 | RESULTS

3.1 | Patient disposition, demographics, and baseline characteristics

Overall, 184 patients were screened and enrolled, of whom 138 were randomized (including 2 screen failures randomized in error), and

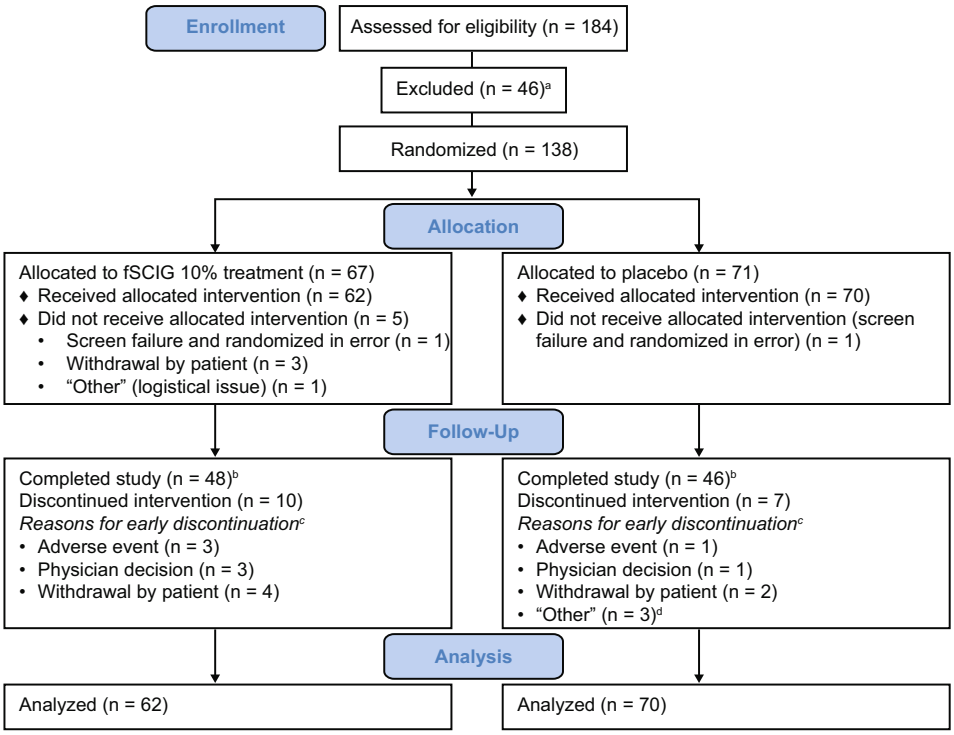

FIGURE 1 Study disposition. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; fSCIG, facilitated subcutaneous immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; IVIG, intravenous immunoglobulin. [a]Patients were excluded for not meeting inclusion criteria ($n = 21$) for the following reasons: did not meet diagnosis criteria ($n = 4$); did not meet prior treatment criteria ($n = 5$); did not meet INCAT disability score criteria ($n = 5$); unwilling/unable to comply with protocol requirements ($n = 7$). Patients were also excluded for meeting exclusion criteria ($n = 25$) for the following reasons: presence of disease potentially affecting assessment ($n = 2$); presence/history of exclusionary conditions/infections ($n = 14$); hypersensitivity/allergy to study treatments ($n = 3$); abnormal laboratory values ($n = 4$); treatment with corticosteroids within 8 weeks of screening ($n = 1$); condition judged to impede participation/pose patient risk/confound study results ($n = 1$). [b]Patients who relapsed and entered Epoch 2 were not included in the number of patients who completed Epoch 1 nor in the number of patients who discontinued early from Epoch 1. [c]CIDP relapse per protocol definition was recorded as the reason for early discontinuation under the following categories: fSCIG 10% treatment arm – physician decision ($n = 2$); placebo arm – physician decision ($n = 1$), withdrawal by patient ($n = 1$), "other" ($n = 3$). [d]2 patients relapsed per protocol definition and decided not to enroll in Epoch 2; 1 patient relapsed per protocol definition and did not enroll in Epoch 2 because of "sponsor decision: protocol deviation" (patients used IVIG outside of study).

132 were dosed with study medication (fSCIG 10%, $n = 62$; placebo, $n = 70$). In all, 17 patients (12.9%) prematurely discontinued the study (Figure 1). Patient demographics and baseline disease characteristics are presented in Table 1.

3.2 | Efficacy analysis

fSCIG 10%, when administered at the same dose and dosing interval as the patient's previous IVIG therapy, significantly reduced CIDP relapse compared with placebo (fSCIG 10% group relapse rate: 9.7% [95% CI 4.5%, 19.6%]; placebo group relapse rate: 31.4% [95% CI 21.8%, 43.0%]; $p = .0045$) with an estimated treatment difference of −21.8% (95% CI −34.5%, −7.9%; Table 2A). Prespecified sensitivity analyses supported the primary analysis, showing consistent reductions in relapse with fSCIG 10% therapy over placebo (Table 2A).

In total, eight patients had a missing relapse assessment (placebo [$n = 2$], fSCIG 10% [$n = 6$]; Table 2A). Of these, 6 had a missing confirmatory INCAT assessment. A conservative prespecified sensitivity analysis, where missing or incomplete relapse outcome data were imputed as relapse in the MITT population, showed a lower relapse rate with fSCIG 10% (19.4%) than with placebo (34.3%), resulting in an observed treatment difference of −14.9% (95% CI −29.0%, 0.33%; $p = .0842$). A prespecified sensitivity analysis, where a second confirmatory INCAT assessment was not required, demonstrated a significant difference in relapse rate between the fSCIG 10% (16.1%) and placebo (34.3%) groups ($p = .0292$). Other prespecified sensitivity analyses supported the findings of the primary analysis, showing consistent reductions in relapse with fSCIG 10% over placebo (Table 2A). The two additional ad hoc sensitivity analyses also supported the primary analysis. When missing relapse outcomes were imputed as relapse for patients who had a missing confirmatory INCAT assessment in a setting of clinical deterioration in the MITT population, the treatment difference between fSCIG 10% and placebo was statistically significant (−16.9% [95% CI: −30.30%, −2.40%; $p = .0373$]). The multiple imputation analysis with missing outcomes imputed

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)
Use of corticosteroids in the 6 months prior to screening, *n* (%)			
Yes	7 (10.0)	7 (11.3)	14 (10.6)
No	63 (90.0)	55 (88.7)	118 (89.4)
INCAT adjusted score, median (IQR)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
R-ODS centile metric score			
n	63	59	122
Median (IQR)	55.0 (46.0, 67.0)	61.0 (47.0, 73.0)	57.5 (46.0, 71.0)
Maximum hand grip strength (most affected hand; kPa)			
n	69	62	131
Median (IQR)	54.0 (38.0, 70.0)	54.0 (42.0, 70.0)	54.0 (40.0, 70.0)
Overall MRC sum score, median (IQR)	56.0 (50.0, 58.0)	57.0 (52.0, 60.0)	56.0 (52.0, 58.0)

Note: Data presented for the MITT analysis set. The MRC assessment included 6 muscles from each side of the body, and the sum score ranged from 0 (paralysis) to 60 (healthy strength). Adjusted INCAT disability scores (used for primary endpoint assessment) were identical to INCAT disability scores (scored 0–10, higher values indicating increasing inability to make purposeful movements), with the exception that upper extremity score changes from 0 to 1 (normal to minor symptoms) or from 1 to 0 were excluded.

Abbreviations: BMI, body mass index; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; fSCIG, facilitated subcutaneous immunoglobulin; INCAT, inflammatory neuropathy cause and treatment; IQR, interquartile range; max, maximum; min, minimum; MITT, modified intention-to-treat; MRC, Medical Research Council; R-ODS, Rasch-built overall disability scale; SD, standard deviation.

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	
Prespecified sensitivity analyses				
MITT set with missing relapse outcome data[b] imputed as relapse				
Relapse rate, *n*/*N* (%)	24/70 (34.3)	12/62 (19.4)	−14.90	.0842
95% CI	24.3, 46.0	11.4, 30.9	−29.0, 0.33	
MITT observed cases with missing relapse outcomes excluded				
Relapse rate, *n*/*N* (%)	22/68 (32.4)	6/56 (10.7)	−21.60	.008
95% CI	22.4, 44.2	5.0, 21.5	−34.8, −7.0	
PP set[c] with missing relapse outcomes imputed as no relapse				
Relapse rate, *n*/*N* (%)	14/59 (23.7)	3/50 (6.0)	−17.70	.0228
95% CI	14.7, 36.0	2.1, 16.2	−30.6, −4.1	
MITT set with no confirmatory INCAT requirement				
Relapse rate, *n*/*N* (%)	24/70 (34.3)	10/62 (16.1)	−18.20	.0292
95% CI	24.3, 46.0	9.0, 27.2	−31.8, −3.2	
MITT set with missing relapse outcomes in a setting of clinical deterioration imputed as relapse				
Relapse rate, *n*/*N* (%)	22/70 (31.4)	9/62 (14.5)	−16.9	.0373
95% CI	21.8, 43.0	7.8, 25.3	−30.3, −2.4	
MITT set with missing relapse outcomes imputed under the missing at random premise using multiple imputation by chained equations				
Relapse rate (%)	31.5	13.7	−17.8	
95% CI	21.8, 43.2	7.0, 25.2	−31.2, −2.8	

(B)

Outcome measure (MITT set)	Placebo ($n = 70$)	fSCIG 10% ($n = 62$)	Treatment difference	*p* value
Functional worsening, composite endpoint[d]				
Patients who worsened, *n* (%)	37 (54.4)	21 (37.5)	−16.9	.09
95% CI	42.66, 65.70	26.01, 50.59	−33.02, 0.69	
Met INCAT component criterion, *n* (%)	22 (32.4)	6 (10.7)		
Met grip strength component criterion, *n* (%)	17 (25.0)	8 (14.3)		
Met R-ODS score component criterion, *n* (%)	20 (29.4)	13 (23.2)		
Time to relapse (days)[e]				
Number of days (min, max)	20, 221[f]	7[f], 217[f]		.002[g]
Number of patients with relapse (%)	22 (31.4)	6 (9.7)		
Number of censored patients (%)	48 (68.6)	56 (90.3)		
Change from baseline in R-ODS centile score				
LS mean difference (standard error)	−6.1 (1.64)	−0.9 (1.69)		.03
Difference (fSCIG 10% – placebo) in LS mean (95% CI)			−5.2 (0.5, 9.9)	

Note: For the MITT set, missing outcomes data were imputed as no relapse. Adjusted INCAT disability scores (used for primary endpoint assessment) were identical to INCAT disability scores (scored 0–10, higher values indicating increasing inability to make purposeful movements), with the exception that upper extremity score changes from 0 to 1 (normal to minor symptoms) or from 1 to 0 were excluded.

Abbreviations: CI, confidence interval; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; fSCIG, facilitated subcutaneous immunoglobulin; INCAT, inflammatory neuropathy cause and treatment; LS, least-squares; MITT, modified intention-to-treat; MRC, Medical Research Council; PP, per protocol; R-ODS, Rasch-built overall disability scale; SD, standard deviation.

[a]The proportion of patients with functional worsening defined as ≥1 point increase relative to the baseline score in 2 consecutive adjusted INCAT disability scores. Relapse status was missing if a patient did not have a baseline INCAT score and at least 1 post-dose INCAT score, or had missing confirmatory INCAT score in the presence of an abnormal INCAT score within 7 days.

[b]Missing outcomes: Placebo ($n = 2$), fSCIG 10% ($n = 6$).

[c]Protocol deviations: Placebo ($n = 11$), fSCIG 10% ($n = 12$). Missing outcomes: placebo ($n = 2$), fSCIG 10% ($n = 2$).

[d]Functional worsening was defined as 1 or more of the following: an increase of ≥1 point relative to the baseline score in 2 consecutive adjusted INCAT disability scores OR who experienced CIDP worsening (defined as a ≥ 8 kPa decrease in hand grip strength in the more affected hand) OR a ≥ 4 point decrease in raw summed R-ODS score relative to the baseline score (at the time of withdrawal from the SC treatment period).

[e]Time to relapse was calculated as date of relapse − date of initial dose of study medication +1 day. Relapse was defined based on the primary efficacy endpoint. Median values are unavailable given the high censoring rate and that fewer than 50% of patients relapsed in either group.

[f]Indicates that time was censored.

[g]Based on the Wilcoxon survival test, which compares the overall survival times, rather than the percentage of patients relapsing.

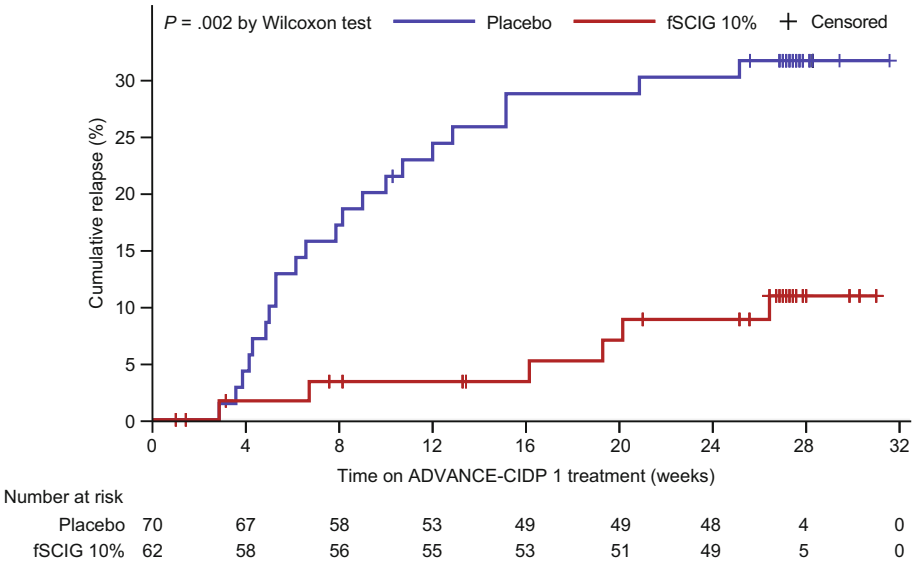

FIGURE 2 Kaplan–Meier curves for time to relapse. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; fSCIG, facilitated subcutaneous immunoglobulin; MITT, modified intention-to-treat. Curves estimated using the Kaplan–Meier method for the MITT population, with missing outcomes imputed as no relapse. Time to relapse was calculated as: date of relapse − date of initial dose of treatment +1. Patients who did not relapse were censored with time to censoring calculated as: date of discontinuation or completion−date of initial treatment +1. ADVANCE-CIDP 1 was a double-blind, placebo-controlled phase, in which patients were randomized 1:1 to receive either fSCIG 10% or placebo for a period of 6 months or until relapse.

under the missing at random premise using multiple imputation chained equations estimated a treatment difference of −17.8% in relapse rates between fSCIG 10% and placebo (95% CI: −31.24%, −2.80%), indicating a statistically significant (at the two-sided 5% level) lower relapse rate with fSCIG 10% than with placebo (as the CI did not contain zero).

The proportion of patients who experienced functional worsening (composite secondary efficacy endpoint) was 37.5% in the fSCIG 10% group and 54.4% in the placebo group, with a treatment difference of −16.9% (95% CI −33.02%, 0.69%; Table 2B). Probability of relapse was higher with placebo versus fSCIG 10% over time (Table 2B and Figure 2; $p = .002$), with the Kaplan–Meier curves separating early at approximately Week 4, consistent with the time taken for the last IVIG dose to lose effect prior to administration of the study treatment. The ad hoc time to relapse sensitivity analysis, where missing relapse outcomes were imputed as relapse, confirmed the original findings, demonstrating a significant difference in time to relapse between treatment groups favoring fSCIG 10% ($p = .023$; Figure S2). For R-ODS centile scores, the least-squares mean difference (standard error) at the end of the study for patients receiving placebo and fSCIG 10% was −6.1 (1.64) versus −0.9 (1.69), respectively (Table 2B), indicating less deterioration in the fSCIG 10% group. Results for tertiary efficacy endpoints are presented in Appendix S5 and Table S4.

3.3 | Infusion characteristics

The mean monthly dose equivalent (averaged per patient at 4.35 weeks/month) for patients receiving fSCIG 10% or placebo was 85.4 g or 84.8 g, respectively, equal to 1.1 g/kg for the fSCIG 10% group or 1.0 g/kg for the placebo group. For patients receiving fSCIG 10% or placebo, the median (range) monthly dose equivalent was 82.6 g (27–217 g) or 69.6 g (27–217 g), respectively. The mean (SD) duration of infusion per dose was 125.9 (49.3) minutes for patients receiving fSCIG 10% and 124.5 (56.4) minutes for those in the placebo group. Overall, most patients (87.9%) had a 4-week dosing interval, while 1.5% and 10.6% of patients were dosed every 2 or 3 weeks, respectively. The majority of patients (86.3%) received study treatment using 2 infusion sites per infusion, while 9.6% and 3.7% of patients used 1 or 3 infusion sites, respectively.

3.4 | Patient-reported outcomes

Patients receiving fSCIG 10% showed favorable changes from baseline in both SF-36 and EQ-5D scores compared with patients receiving placebo (Table 3). The fSCIG 10% group maintained their SF-36 score across most domains, with general health, bodily pain, physical functioning, and role limitation due to physical health domains showing improvements. By contrast, the placebo group showed a decline across most domains. When considering EQ-5D scores, patients receiving fSCIG 10% maintained scores in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression domains, whereas the placebo group showed slight worsening across all domains.

With respect to patient perceptions of study medication, at the end of treatment mean TSQM-9 global satisfaction scores were higher in the fSCIG 10% group (65.3) than in the placebo group (55.7). When considering the treatment preference questionnaire, both treatment groups demonstrated a favorable overall preference for their facilitated subcutaneous study treatment: in patients receiving fSCIG 10% and placebo, respectively, 66.7% and 70.6% of patients preferred it to their previous IVIG therapy, and 83.3% and 92.2%, respectively, responded that they would choose to continue receiving their allocated treatment at the end of the study (Table 3).

3.5 | Safety analysis

In total, 491 AEs were reported in 89 patients during the study (Table 4), with a rate of 0.39 events per infusion, 3.72 events per

TABLE 3 Patient-reported outcomes.

Outcome measure	Placebo ($n = 70$)	fSCIG 10% ($n = 62$)	Total ($N = 132$)
36-item short-form health survey			
Physical Component Summary score			
n	66	62	128
At baseline	39.5 (7.6)	41.6 (9.3)	40.5 (8.5)
n	58	57	115
At study end	38.5 (8.6)	43.0 (9.5)	40.8 (9.3)
n	58	57	115
Change from baseline	−0.8 (9.0)	1.1 (6.6)	0.1 (7.9)
Mental component summary score			
n	66	62	128
At baseline	49.0 (10.1)	50.7 (9.7)	49.8 (9.9)
n	58	57	115
At study end	47.2 (9.8)	49.8 (10.1)	48.5 (10.0)
n	58	57	115
Change from baseline	−2.4 (7.1)	−0.7 (9.2)	−1.6 (8.2)
EuroQoL-5 dimension			
Mobility score			
n	65	62	127
At baseline	1.9 (0.38)	1.8 (0.44)	1.8 (0.41)
n	61	57	118
At study end	2.0 (0.43)	1.7 (0.47)	1.8 (0.46)
n	59	57	116
Change from baseline	0.1 (0.53)	−0.1 (0.49)	0.0 (0.52)
Self-care score			
n	65	62	127
At baseline	1.5 (0.53)	1.5 (0.50)	1.5 (0.52)
n	61	57	118
At study end	1.6 (0.63)	1.3 (0.48)	1.5 (0.58)
n	59	57	116
Change from baseline	0.2 (0.53)	−0.1 (0.50)	0.0 (0.54)
Usual activities score			
n	65	62	127
At baseline	1.8 (0.53)	1.7 (0.49)	1.7 (0.51)
n	61	57	118
At study end	1.9 (0.51)	1.7 (0.58)	1.8 (0.55)
n	59	57	116
Change from baseline	0.1 (0.63)	0.0 (0.60)	0.1 (0.62)
Pain/discomfort score			
n	65	62	127
At baseline	1.7 (0.54)	1.6 (0.58)	1.7 (0.55)
n	61	57	118
At study end	1.8 (0.52)	1.6 (0.53)	1.7 (0.54)
n	59	57	116
Change from baseline	0.2 (0.67)	0.0 (0.55)	0.1 (0.62)
Anxiety/depression score			
n	65	62	127

TABLE 3 (Continued)

Outcome measure	Placebo ($n = 70$)	fSCIG 10% ($n = 62$)	Total ($N = 132$)
At baseline	1.5 (0.59)	1.4 (0.55)	1.4 (0.57)
n	61	57	118
At study end	1.6 (0.59)	1.3 (0.48)	1.5 (0.55)
n	59	57	116
Change from baseline	0.1 (0.57)	0.0 (0.40)	0.1 (0.49)
EuroQoL visual analog scale score			
n	65	62	127
At baseline	64.2 (17.90)	69.3 (18.77)	66.7 (18.43)
n	61	57	118
At study end	64.4 (19.45)	72.4 (16.48)	68.3 (18.45)
n	59	57	116
Change from baseline	0.6 (20.01)	3.1 (17.73)	1.8 (18.88)
Treatment satisfaction questionnaire for medication-9			
Global satisfaction score			
n	65	62	127
At baseline	71.4 (16.70)	71.2 (17.83)	71.3 (17.19)
n	61	57	118
At study end	55.7 (26.56)	65.3 (25.27)	60.4 (26.28)
Treatment preference questionnaire			
Treatment overall, *n* (%)			
n	51	54	105
Prefer study drug	36 (70.6)	36 (66.7)	72 (68.6)
No preference	8 (15.7)	10 (18.5)	18 (17.1)
Prefer previous treatment	5 (9.8)	6 (11.1)	11 (10.5)
Not applicable	2 (3.9)	2 (3.7)	4 (3.8)
Patient would choose to continue receiving study drug, *n* (%)			
n	51	54	105
Yes	47 (92.2)	45 (83.3)	92 (87.6)
No	4 (7.8)	9 (16.7)	13 (12.4)

Note: Data are mean (standard deviation) unless otherwise stated.
Abbreviation: fSCIG, facilitated subcutaneous immunoglobulin.

patient, and 8945.42 events per 1000 patient-years (Table S5). More patients receiving fSCIG 10% experienced AEs than those receiving placebo (79.0% vs. 57.1% [Table 4]). However, the majority of AEs in the fSCIG 10% group were mild or moderate, local, did not require suspension of infusions, and resolved without sequelae (Table S5). Causally related AEs occurred in 19 patients (27.1%) in the placebo group and 38 patients (61.3%) in the fSCIG 10% group. The most common (reported in >5% of patients) causally related AEs included headache and nausea, as well as local AEs including infusion site pain, erythema, pruritis, and edema. Overall, 7 patients (5.3%) reported serious AEs with a lower rate of occurrence in the fSCIG 10% group (3.2%) than in the placebo group (7.1%) (Table 4). In total, 1247 infusions were administered during the study, of which 72 (5.8%) were interrupted, stopped, or had the infusion rate reduced, with <1% of infusions affected by intolerability and/or AEs (Table S5).

One patient in the placebo group and 7 patients (11.3%) in the fSCIG 10% group developed positive (≥1:160) binding anti-rHuPH20 antibody titers. No local or systemic reactions could be attributed to anti-rHuPH20 antibodies. No patients with positive binding antibodies developed neutralizing antibodies. Details of AEs prior to and after detection of the first positive titer, and rates in patients with and without anti-rHuPH20 antibodies, are provided in Appendix S6.

4 | DISCUSSION

A major goal of maintenance treatment in CIDP is to prevent a relapse and thereby maintain neuromuscular function and quality of life. ADVANCE-CIDP 1 showed that fSCIG 10%, when administered at the same dose and interval as prior IVIG therapy, is more effective

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)
Events per 100 infusions	< 1	< 1	< 1
Any serious AE			
Cardiac disorders, no. of patients (%)	1 (1.4)	0 (0.0)	1 (0.8)
Arrhythmia	1 (1.4)	0 (0.0)	1 (0.8)
Infections and infestations, no. of patients (%)	0 (0.0)	1 (1.6)	1 (0.8)
Otitis media chronic	0 (0.0)	1 (1.6)	1 (0.8)
Nervous system disorders, no. of patients (%)	4 (5.7)	1 (1.6)	5 (3.8)
CIDP (relapse)	4 (5.7)	0 (0.0)	4 (3.0)
Cerebrovascular accident	0 (0.0)	1 (1.6)	1 (0.8)

Note: Table shows AEs reported in ≥5% of patients in any group, and all serious events. Events shown by system organ class and preferred term.
Abbreviations: AE, adverse event; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; fSCIG, facilitated subcutaneous immunoglobulin.
[a]Included for information.
[b]A serious AE was defined as meeting 1 or more of the following criteria: (1) the outcome was life-threatening/fatal (including fetal death); (2) the AE required inpatient hospitalization (regardless of length of stay) or resulted in prolongation of an existing hospitalization; (3) the AE resulted in persistent or significant disability/incapacity; or (4) the AE was a congenital anomaly/birth defect.

than placebo at preventing relapse of neuromuscular disability and functional deterioration in CIDP, with fSCIG 10% reducing the absolute risk of relapse by 22%. The efficacy of fSCIG 10% as a maintenance treatment was further supported by evidence that included: (1) predefined and ad hoc sensitivity analyses using simple and multiple imputations for missing relapse outcomes; (2) time to relapse analysis (predefined secondary endpoint); (3) use of an alternative relapse definition, where relapse was defined based on a single INCAT assessment (predefined sensitivity analysis); and (4) based on an alternative outcome metric for efficacy assessment using the R-ODS scale[28] (predefined secondary endpoint). Patients receiving fSCIG 10% experienced maintained or improved quality of life versus those receiving placebo, and both treatment groups expressed generally high satisfaction with treatment.

While the relapse rate of 9.7% on fSCIG 10% compared favorably with previously reported rates for IVIG (13%)[21] and conventional SCIG (19%–33%),[22,29] the effect size of 22% in ADVANCE-CIDP 1 was lower than that reported for IVIG (32%)[21] and conventional SCIG (23–37%).[21,22] The smaller effect size with fSCIG 10% was primarily driven by a lower placebo relapse rate in ADVANCE-CIDP 1 (31% vs 43–57% in published literature).[21,22,29] The IVIG-experienced patients enrolled in ADVANCE-CIDP 1 did not undergo a disease activation process through IVIG-dependency testing prior to randomization; only patients who had responded to IgG treatment in the past and who were on stable doses of IVIG for at least 12 weeks prior to screening were allowed to enter into the study. Hence, the ADVANCE-CIDP 1 population comprised patients with a higher probability of CIDP remission than other study populations, which could explain the lower fSCIG 10% and placebo relapse rates observed in ADVANCE-CIDP 1. Not including an IVIG-dependency test potentially better reflects a real-world clinical practice setting, which would be the clinical environment for fSCIG 10% use in this patient population.

The proportion of patients who experienced functional worsening based on the composite endpoint including adjusted INCAT scores, hand grip strength, or R-ODS score at the time of study completion or withdrawal relative to baseline was 37.5% for the fSCIG 10% group versus 54.4% of those receiving placebo (treatment difference − 16.9%, 95% CI −33.02%, 0.69%). Potential reasons for the treatment difference not reaching statistical significance could be the composite nature of this endpoint and/or limitations in threshold definitions for each component of the outcome. Evaluating mean change from treatment baseline using ANCOVA rather than difference in proportions is an appropriate approach and has been used for this purpose in other studies of CIDP.[22,30] In ADVANCE-CIDP 1, the least-squares mean treatment difference in R-ODS score showed statistically significant improvement in favor of fSCIG 10%, with a substantial difference observed between treatment groups that was larger than previously reported for conventional SCIG.[22] Grip strength and MRC score results also further supported findings for the primary and other secondary efficacy endpoints favoring fSCIG 10% over placebo.

Conventional SCIG treatment allows for delivery of a limited volume of immunoglobulin into the subcutaneous tissue (approximately 30–60 mL per infusion site), necessitating the use of multiple needlesticks, and frequent administration (usually weekly rather than monthly).[22,31] Conventional SCIG also has a bioavailability of approximately 65–69%,[32] thus requiring a higher monthly total IgG dose than IVIG. fSCIG 10% enables subcutaneous administration of large volumes of IgG (up to 600 mL [60 g] per infusion site) with a bioavailability >90% and IgG trough levels comparable to those achieved with IVIG,[33] thereby reducing the number of needle sticks, infusion duration, and infusion frequency. In contrast, and like conventional SCIG, fSCIG 10% does not require vascular access and may not require travel to infusion centers. In ADVANCE-CIDP 1, the mean monthly equivalent dose of fSCIG 10% was 1.1 g/kg (range 0.4–2.2 g/kg). The dosing schedule for most patients (88.7%) receiving fSCIG 10% was every 4 weeks, and the mean time to deliver fSCIG 10% in this group was 125.9 minutes. In ADVANCE-CIDP 1, systemic reactions such as hemodynamic alterations, hypersensitivity reactions, and flu-like symptoms, occurred infrequently, and rates of treatment-related systemic AEs were low. High patient satisfaction and a preference for facilitated subcutaneous therapy over IVIG in both treatment groups may indicate that infusion volumes delivered subcutaneously are well-tolerated. The majority of patients in the placebo group provided responses to the treatment satisfaction questionnaire at the end of study treatment; thus, the higher proportions observed in the placebo group can potentially be attributed to those patients that were likely to be in remission.

fSCIG 10% administration is a 2-step process using a subcutaneous needle/infusion set to infuse rHuPH20, followed by immunoglobulin 10%. rHuPH20 is a highly purified human hyaluronidase that modifies connective tissue permeability through the hydrolysis of hyaluronan, temporarily decreasing the viscosity of the extracellular matrix and promoting dispersion of infused fluids, facilitating their absorption.[34–36] ADVANCE-CIDP 1 examined the immunogenic potential of rHuPH20. A total of 8 patients developed non-neutralizing binding anti-rHuPH20 antibodies (≥1:160), which were not associated with an increased incidence of AEs, or local or systemic reactions. The lack of clinical relevance of binding anti-rHuPH20 antibodies in ADVANCE-CIDP 1 is consistent with an analysis of a study of fSCIG 10% for primary immunodeficiency diseases, as well as an extensive review of hyaluronidase-conjugated antibody therapeutics in a multitude of diseases.[37,38]

This study was affected by the COVID-19 pandemic and was closed to recruitment before the target sample size was achieved. This might have limited the characterization of the safety profile. However, the long-term safety profile of fSCIG 10% in CIDP is currently being explored in the ongoing ADVANCE-CIDP 3 trial, which is the longest extension study of its kind, with up to 6 years of follow-up data for some patients. Other recruitment challenges were common to other CIDP trials, such as low disease prevalence, competition for recruitment, patient unwillingness to discontinue existing treatments, and the reluctance of physicians and patients to receive placebo given the existence of efficacious therapies. Relapse status was missing for 8 patients overall, with more missing data in those receiving active treatment. However, prespecified sensitivity analyses evaluating the impact of missing data generally supported the primary analysis. In addition, although treatment preference for fSCIG 10% was high, this

finding may be biased given the clinical trial setting, and thus may limit the wider generalizability of this finding in real-world practice.

In conclusion, ADVANCE-CIDP 1 met its primary endpoint. It demonstrated that fSCIG 10%, used as a maintenance therapy in a patient population with stable CIDP receiving intravenous immunoglobulin treatment, was more effective than placebo in preventing relapse of neuromuscular disability. Both fSCIG 10% and placebo subcutaneous infusions were well tolerated and preferred by most patients over their previous intravenous treatment.

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CONFLICT OF INTEREST STATEMENT

V. Bril has acted as a consultant for Alnylam Pharmaceuticals, Akcea, Argenx, AstraZeneca-Alexion, CSL Behring, Grifols, Ionis Pharmaceuticals, Immunovant, Janssen, Momenta (J&J), NovoNordisk, Pfizer, Powell Mansfield Inc., Octapharma, Roche, Sanofi, Takeda, and UCB Pharma, and has received research support from Akcea, Argenx, AstraZeneca-Alexion, CSL Behring, Grifols, Ionis Pharmaceuticals, Immunovant, Momenta (J&J), Octapharma, Takeda, and UCB Pharma. R.D.M. Hadden has received payments for advisory board membership (Argenx, Janssen, Takeda); conference expenses (CSL Behring); speaker fees (Alnylam); and departmental payments (CSL Behring). T.H. Brannagan III has received honoraria for consulting from Argenx, CSL Behring, and Grifols, and institutional support in the form of clinical trial funding from Argenx, Sanofi, and Takeda. M. Bar has no potential conflicts of interest relevant to the current study. E. Chroni has received speaking honoraria and advisory board membership fees from Alexion-AstraZeneca, Argenx-Medison, Genesis Pharma, and ITF Hellas. K. Rejdak has received speaking honoraria and travel expenses for participation in scientific meetings, and participated in advisory boards for Bayer, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva Pharmaceuticals. A. Rivero has no potential conflicts of interest relevant to the current study. H. Andersen has received research support from CSL Behring, NMD Pharma, Sanofi Genzyme, speaker honoraria from Alexion, and served as consultant on advisory boards for Alexion, Amicus Pharmaceuticals, Lundbeck, Sanofi Genzyme, and UCB Pharma. N. Latov received consultancy fees from Alexion, Appelis, Argenx, Grifols, Immunovant, Ipsen, Pfizer, Sanofi, Takeda, and Therapath. T. Levine has served as a consultant for Alexion, FFF, and Immunovant. M. Pasnoor has served as consultant or medical adviser for Alexion, Argenx, Catalyst, CSL Behring, Immunovant, Janssen, Momenta, Takeda, Terumo BCT, and UCB Pharma. S. Sacconi has received payment for consultant activity for Biogen, Dyne Therapeutics, Fulcrum Therapeutics, LFB, Lupin, Sanofi Genzyme, Roche, and UCB Pharma, and has received research funding from Roche. N. Souayah has acted as a consultant to Takeda Pharmaceuticals Ltd for work outside of this manuscript. C. Anderson-Smits, K. Duff, E. Greco, S. Hasan, Z. Li, and H. Ay are employees of Takeda Development Center Americas, Inc. and are Takeda shareholders. L. Yel is a Takeda shareholder, and was an employee of Takeda Development Center Americas, Inc. at the time of the study.

DATA AVAILABILITY STATEMENT

The study is registered with the ClincialTrials.gov registry at https://clinicaltrials.gov/ct2/show/NCT02549170 (ClinicalTrials.gov identifier: NCT02549170). Information pertaining to this study and the associated study protocol may be found at ClinicalTrials.gov. The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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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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