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# Efficacy, safety and tolerability of rozanolixizumab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a randomised, subject-blind, investigator-blind, placebo-controlled, phase 2a trial and open-label extension study

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## ABSTRACT

**Background** Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a peripheral nerve disorder characterised by weakness and sensory loss. We assessed the neonatal Fc receptor inhibitor rozanolixizumab for CIDP management.

**Methods** CIDP01 (NCT03861481) was a randomised, subject-blind, investigator-blind, placebo-controlled, phase 2a study. Adults with definite or probable CIDP receiving subcutaneous or intravenous immunoglobulin maintenance therapy were randomised 1:1 to 12 once-weekly subcutaneous infusions of rozanolixizumab 10 mg/kg or placebo, stratified according to previous immunoglobulin administration route. Investigators administering treatment and assessing efficacy, and patients, were blinded. The primary outcome was a change from baseline (CFB) to day 85 in inflammatory Rasch-built Overall Disability Scale (iRODS) score. Eligible patients who completed CIDP01 entered the open-label extension CIDP04 (NCT04051944).

**Results** In CIDP01, between 26 March 2019 and 31 March 2021, 34 patients were randomised to rozanolixizumab or placebo (17 (50%) each). No significant difference in CFB to day 85 in iRODS centile score was observed between rozanolixizumab (least squares mean 2.0 (SE 3.2)) and placebo (3.4 (2.6); difference −1.5 (90% CI −7.5 to 4.5)). Overall, 14 (82%) patients receiving rozanolixizumab and 13 (76%) receiving placebo experienced a treatment-emergent adverse event during the treatment period. Across CIDP01 and CIDP04, rozanolixizumab was well tolerated over up to 614 days; no clinically meaningful efficacy results were seen. No deaths occurred.

**Conclusions** Rozanolixizumab did not show efficacy in patients with CIDP in this study, although this could be due to a relatively high placebo stability rate. Rozanolixizumab was well tolerated over medium-to-long-term weekly use, with an acceptable safety profile.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is thought to be an autoantibody-mediated disease due to efficacy demonstrated by treatments such as plasma exchange or intravenous immunoglobulin. When CIDP01 was designed, there were no published phase 2 or 3 studies of a neonatal Fc receptor inhibitor for treatment of CIDP.

## INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare peripheral nerve disorder characterised by chronic and progressive weakness and sensation loss.[1 2] Cellular and humoral immune mechanisms are thought to be involved in CIDP pathogenesis[3 4] but are not fully elucidated, and their relative contribution in individual patients is probably diverse.[1 2] However, therapeutic response to plasma exchange, intravenous immunoglobulin (IVIg) and immunoadsorption suggests a role of autoantibodies in CIDP pathogenesis.[2 5 6] Immunoglobulin and complement deposition in sural nerve biopsies support autoantibody-mediated pathophysiology in certain patients.[7]

In some autoimmune diseases, pathogenic IgG antibodies are known to contribute significantly to disease progression.[8 9] However, no consistent antibody pattern has been established in CIDP and specific target antigens remain elusive.[10] While autoantibodies against nodal and paranodal antigens have been identified in approximately 10% of patients,[2 10] recent guidelines classify these patients within the autoimmune nodopathies category, distinct from CIDP.[11] Despite this knowledge gap, treatments such as IVIg and plasma exchange, which may affect IgG levels, are used to treat CIDP, particularly where corticosteroids are not tolerated or are no longer effective.[3 5 12 13]

The neonatal Fc receptor (FcRn) prolongs IgG half-life by preventing IgG degradation.[9] Targeted FcRn inhibition accelerates IgG destruction,

**WHAT THIS STUDY ADDS**

⇒ CIDP01 and its open-label extension study CIDP04 represent the longest exposure to rozanolixizumab in any patient population to date (up to 614 days). Rozanolixizumab did reduce immunoglobulin levels as expected, but it did not show efficacy in patients with CIDP; however, it was well tolerated over medium-term to long-term once-weekly use, with an acceptable safety profile.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The lack of efficacy demonstrated by rozanolixizumab is consistent with the hypothesis that multiple immunopathological mechanisms may exist in CIDP. However, the lack of efficacy could also be the result of the relatively high disease stability rate in the placebo group, which may have made it more difficult to identify a difference in efficacy between treatment groups. This stability rate could be the consequence of recruiting a low proportion of patients with active immunoglobulin-dependent disease or the use of an endpoint of disease deterioration, which has been shown to be associated with higher placebo response rates. Similar disease stability rates have been seen in other CIDP trials that required patients to have immunoglobulin-dependent disease, indicating that improved methods for identifying immunoglobulin dependency may be needed. A high stability rate in the placebo group should be accounted for in power calculations when designing future trials and further research into the pathophysiological mechanisms of CIDP is warranted.

including pathogenic IgG autoantibodies.[14] We hypothesised that reducing pathogenic IgG concentration via FcRn inhibition could benefit patients with CIDP with confirmed immunoglobulin dependency.[4 15 16] Rozanolixizumab is a humanised IgG4 monoclonal antibody targeting the FcRn IgG binding region to inhibit IgG salvage and recycling, shown to reduce IgG levels in healthy volunteers and patients with myasthenia gravis (MG) and immune thrombocytopaenia.[14 17] Here, we report results of a phase 2a study, CIDP01, and its open-label extension (OLE), CIDP04. These studies assessed the efficacy and safety of rozanolixizumab for CIDP in patients with active disease previously receiving immunoglobulin maintenance therapy.

## METHODS

### Study design and patients

CIDP01 (NCT03861481; 2016-002411-17) was a multicentre, randomised, subject-blind, investigator-blind, placebo-controlled, phase 2a trial of rozanolixizumab in patients with CIDP. Patients were recruited from 22 clinics and hospitals across Europe and the USA. CIDP04 (NCT04051944; 2018-004392-12) was a single-arm, OLE study assessing long-term efficacy and safety of rozanolixizumab in patients who completed CIDP01.

CIDP01 included adults with a definite or probable diagnosis of CIDP, with suspected therapeutic immunoglobulin dependency substantiated by clinical examination during therapy or on interruption/reduction of therapy within 18 months prior to screening and documented in the medical history (ie, that an attempted decrease/withdrawal of immunoglobulin resulted in a clinically relevant decrease in function), and on a stable dose of subcutaneous immunoglobulin (SCIg) or IVIg at a fixed interval for ≥4 months.

CIDP01 exclusion criteria included diabetes, IgM paraproteinaemia, IgM-mediated neuropathy, associated systemic diseases that may have caused neuropathy, an average IgG dose of <0.4 g/kg/month over the last 4 months and clinically relevant chronic or tuberculosis infection history. A complete list of eligibility criteria is provided in online supplemental material.

### Randomisation and blinding

In CIDP01, patients were randomised 1:1 to receive rozanolixizumab or placebo, stratified according to previous route of immunoglobulin administration (SCIg or IVIg; online supplemental figure 1). Blinding was specified in the protocol for patients, those administering treatment and those assessing efficacy. Unblinded personnel prepared treatments before passing to site investigators who administered treatments. Blinding was achieved by taping infusion lines. After investigators confirmed eligibility, the interactive response technology vendor assigned participants to groups using a randomisation schedule produced by the vendor. In CIDP04, all patients received open-label rozanolixizumab.

### Procedures

In CIDP01, patients received 12 once-weekly subcutaneous rozanolixizumab 10 mg/kg or placebo infusions during an 11-week treatment period (online supplemental figure 1), with dosage adjusted for bodyweight (online supplemental tables 1A,B). The 10 mg/kg dose could be reduced to 7 mg/kg for tolerability issues. Patients could then complete a 12-week observation period (with or without standard of care (SoC)) or enter the CIDP04 OLE directly. Patients who relapsed during the treatment or observation period, according to the inflammatory Rasch-built Overall Disability Scale (iRODS), adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale or maximum grip strength, could receive rescue medication, comprising SoC immunoglobulin treatment (eg, IVIg 2 g/kg) administered over a stabilisation period of 2–12 weeks. Once stabilised, patients could enter CIDP04 or continue receiving SoC treatment, with patients who relapsed during the treatment period only having the option to enter CIDP04 if they were originally assigned placebo. In CIDP04, patients received weekly subcutaneous infusions of rozanolixizumab 10 mg/kg or 7 mg/kg (depending on dose at completion of CIDP01) for 24 weeks and then an optional additional 52 weeks, followed by an 8-week observation period.

In CIDP01, the first dose was administered on the day of randomisation. Patients were required to be on maintenance immunoglobulin treatment (IVIg/SCIg), stopped before receipt of the first dose. The first dose administration timing was varied to ensure continuation of previous treatment. For patients on a 3–6-week IVIg regimen, randomisation occurred 1 week before the next planned IVIg dose. Those on a 2-week IVIg regimen continued their regular schedule for one further treatment before randomisation, occurring 1 week before the next planned IVIg dose. Patients on a weekly SCIg regimen continued their regular schedule for at least one further treatment before randomisation, occurring on the day of the planned SCIg dose.

### Outcomes

The primary outcome for CIDP01 was a change from baseline to week 13 (Day 85) in iRODS score (to analyse changes in activity and social participation limitation). Other efficacy outcomes for CIDP01 included CIDP relapse and time to CIDP relapse according to individual and combined assessments of

iRODS (minimum clinically important difference SE of ≤−1.96), adjusted INCAT disability scale (increase of ≥1 point) and maximum grip strength (decline of >14 kPa; cut-off chosen due to precedence in the literature as it has higher specificity than commonly used >8 kPa.[18 19]

Safety outcomes for CIDP01 included treatment-emergent adverse events (TEAEs), vital signs, abnormalities by physical and neurological examination, electrocardiograms, laboratory values, tuberculosis signs/symptoms and total protein, albumin and α-globulin and β-globulin concentrations. The primary outcome for CIDP04 was the occurrence of TEAEs.

Pharmacokinetic and pharmacodynamic outcomes were also assessed, such as serum neurofilament light (sNf-L) chain concentrations. A complete list of outcomes for CIDP01 and CIDP04 is provided in online supplemental material.

### Statistical analysis

For CIDP01, sample size calculation used a one-sided 5.0% t-test for comparison of rozanolixizumab and placebo, and an anticipated effect size index of 0.93. Based on this, a sample size of 15 in each group was required to provide 80% power to detect a statistically significant difference. If the effect size index was medium (0.52), the power decreased to 40%. It was assumed that 10% of randomised patients would not be eligible for inclusion in the efficacy analysis; hence, 34 patients were randomised.

The primary endpoint in CIDP01 was analysed on a logit transformed scale using mixed model for repeated measures. For ease of interpretation, iRODS scores were also analysed and reported on a centile metric scale. The model included treatment group, baseline iRODS score, route of administration of previous immunoglobulin therapy, assessment week and the treatment-by-week interaction as fixed-effect terms, with study patient as a random effect, using an unstructured covariance matrix. Kenward-Roger approximation was used to estimate denominator df. The same method was used to analyse change from baseline in adjusted INCAT and grip strength.

For individual and combined CIDP relapse, point estimates and corresponding two-sided 90% CIs for the difference between placebo and rozanolixizumab up to week 13 were reported. The CI was constructed using the asymptotic SE (asymptotic Wald confidence limits).

Time to CIDP relapse was calculated as time from starting treatment (day 1) to the occurrence of relapse and displayed using a Kaplan-Meier curve. HRs were calculated using the Cox proportional-hazards model. Patients who withdrew for any reason before week 13 or had missing data at week 13 were considered relapsed at the last available visit. Patients who did not experience a relapse while under observation and completed the treatment period were censored at week 13.

The primary outcome in CIDP01 was assessed in the full analysis set (all patients receiving ≥1 dose of treatment with baseline and at least one valid postbaseline iRODS measurement). Safety outcomes were assessed in the safety set (all patients receiving ≥1 dose of treatment). Because of the higher-than-expected disease stability rate in the placebo group, a post hoc analysis was done of baseline characteristics of patients whose disease relapsed vs those whose disease did not.

CIDP04 was an OLE study, therefore, no formal sample size calculation was performed. Baseline values when entering CIDP01 for all outcomes in patients who previously received rozanolixizumab in CIDP01 (rozanolixizumab/rozanolixizumab) were baseline values for analysis in CIDP04, whereas for patients who previously received placebo during CIDP01 (placebo/rozanolixizumab), baseline values were those when entering CIDP04. The primary outcome in CIDP04 (occurrence of TEAEs) was analysed in the safety set and efficacy outcomes in the full analysis set (as defined above). No statistical comparisons for any outcomes were performed between the rozanolixizumab/rozanolixizumab and placebo/rozanolixizumab groups.

A data-monitoring committee monitored safety data during the study. All analyses were performed by using SAS V.9.4 or higher.

## RESULTS

### CIDP01

Between 26 March 2019 and 31 March 2021, 34 patients were enrolled into CIDP01 (figure 1A). 21 (62%) patients completed the study, with 33 (97%) included in the full analysis set. Baseline characteristics were mostly balanced between treatment groups, although patients in the placebo group had a longer disease duration (table 1). Anti-myelin-associated glycoprotein antibodies were detected in two (12%) patients in the rozanolixizumab group after inclusion. Only one of these patients had IgM paraproteinaemia at study entry. Although enrolment of this patient constituted a protocol violation, they were included for data completeness.

In CIDP01, the primary efficacy endpoint of change from baseline to week 13 in iRODS score did not show a significant difference between rozanolixizumab (mean 4.1 (SD 9.8); least squares mean (LSM) 2.0 (SE 3.2)) and placebo (mean 3.9 (SD 8.9); LSM 3.4 (SE 2.6); LSM difference −1.5 (90% CI −7.5 to 4.5); table 2 and figure 2A). No significant differences were observed between groups for other efficacy outcomes (table 2, figures 2B,C and 3). A similar proportion of patients required rescue medication in the rozanolixizumab (5/16 (31%)) and placebo (5/17 (29%)) groups (difference in rate of patients taking rescue medication 0.02 (90% CI −0.25 to 0.28)). Time to rescue medication was similar between groups (HR 1.28 (90% CI 0.43 to 3.87)). No notable differences in Rasch-built, modified-interval Medical Research Council scale, fatigue or CIDP patient-reported outcome scores were observed between groups at any timepoint in CIDP01. Results for Patient Global Impression of Change and Patient Global Impression of Severity were similar for both groups.

Rozanolixizumab reduced IgG levels by >80% to a mean of approximately 2 g/L in CIDP01, with concentrations stabilising by around day 36 (online supplemental figure 2A,B); no notable differences were observed between IgG subclasses. Although high concentrations of sNf-L chain were reported in individual patients in both groups, no clinically meaningful trends were observed (online supplemental figure 3A).

The TEAE profile in CIDP01 was similar between rozanolixizumab and placebo (table 3). Incidence of treatment-emergent infections (three in each group) and headaches (six with rozanolixizumab vs five for placebo) was similar between groups during the treatment period. Most headaches occurred 1–3 days after rozanolixizumab treatment and all were mild. One (6%) headache occurred in each group during the observation period: the headache in the rozanolixizumab group was moderate, occurred 28 days after the last dose and was not treatment related. Two serious TEAEs occurred in the rozanolixizumab group during the treatment period; both were CIDP worsening (one moderate, one severe). Both patients required hospital admission and received immunoglobulin rescue therapy. The events were resolved, but both patients discontinued.

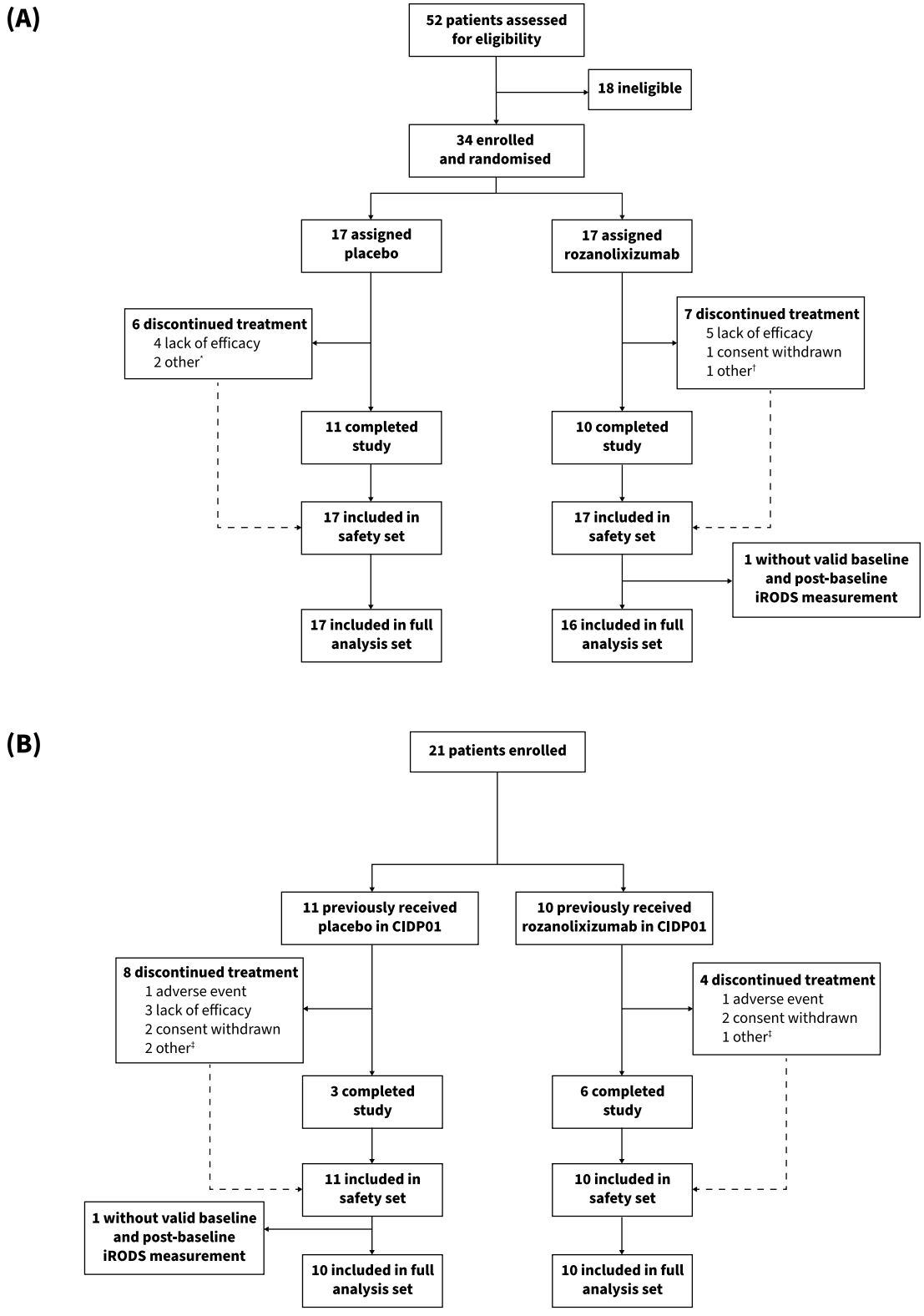


**Figure 1** CIDP01 and CIDP04 trial profiles. (A) CIDP01. (B) CIDP04. *One patient relapsed and one patient did not want to continue to CIDP04. †One COVID-19 pandemic circumstance. ‡Study ended once a managed access programme was in place, to allow patients in the optional second 52-week treatment period to continue receiving rozanolixizumab if wished. iRODS, inflammatory Rasch-built Overall Disability Scale.

No notable differences were observed between rozanolixizumab and placebo in vital signs, physical/neurological examination, ECG, laboratory values, tuberculosis signs and symptoms and total protein, albumin and α-globulin and β-globulin concentrations. During CIDP01, no dose reductions and no deaths occurred.

A post hoc analysis of baseline characteristics of patients with or without disease relapse (combined assessments) revealed no

**Table 1** CIDP01 baseline characteristics

| Characteristic | Placebo (n=17) | Rozanolixizumab (n=17) |
|---|---|---|
| Age (years), median (range) | 56.0 (38–66) | 58.0 (23–77) |
| Male, n (%) | 9 (53) | 9 (53) |
| Weight (kg), median (range) | 93.80 (51.2–117.1) | 85.00 (53.5–140.8) |
| Race, n (%) | | |
| Asian | 1 (6) | 0 |
| Black | 1 (6) | 1 (6) |
| White | 11 (65) | 15 (88) |
| Other/mixed | 4 (24) | 1 (6) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 1 (6) | 1 (6) |
| Not Hispanic or Latino | 13 (76) | 16 (94) |
| Missing | 3 (18) | 0 |
| Regions, n (%) | | |
| America | 5 (29) | 8 (47) |
| Europe | 12 (71) | 9 (53) |
| Duration of disease (years), median (range) | 5.79 (1.8–22.9) | 4.84 (0.9–49.0) |
| Disease severity at baseline, mean (SD) | | |
| iRODS centile metric score | 61.6 (17.9) | 58.6 (20.4) |
| Adjusted INCAT disability score | 2.8 (1.7) | 3.6 (1.8) |
| Clinician-assessed grip strength, maximum score | 77.35 (24.66) | 68.24 (32.48) |
| Patient-assessed grip strength, maximum score | 75.0 (26.9) | 76.0 (34.0) |
| CIDP medication at baseline, n (%) | | |
| Corticosteroids | 3 (18) | 3 (18) |
| Other immunosuppressants | 1 (6) | 2 (12) |
| Previous immunoglobulin treatment, n (%) | 17 (100) | 17 (100) |
| Subcutaneous | 3 (18) | 1 (6) |
| Intravenous | 14 (82) | 16 (94) |
| Previous immunoglobulin cycle type, n (%) | | |
| ≤1 week | 3 (18) | 2 (12) |
| 2 to <4 weeks | 5 (29) | 7 (4) |
| 4 to <6 weeks | 5 (29) | 8 (47) |
| ≥6 weeks | 4 (24) | 0 |
| CIDP phenotype, n (%) | | |
| Typical CIDP (definite/probable) | 16 (94) (13 (76)/3 (18)) | 16 (94) (15 (88)/1 (6))* |
| Atypical CIDP (definite/probable) | 1 (6) (1 (6)/0) | 1 (6) (1 (6)/0) |

*Two patients had anti-MAG antibodies (confirmed after inclusion), of whom only one had IgM paraproteinaemia at study entry.
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; iRODS, inflammatory Rasch-built Overall Disability Scale; MAG, myelin-associated glycoprotein.

notable differences between those who did and did not relapse in either group across any domains analysed (online supplemental table 2).

## CIDP04

All 21 patients who completed CIDP01 entered CIDP04 (figure 1B). At the end of CIDP04, four (19%) patients elected to continue rozanolixizumab in the managed access programme. Baseline characteristics were generally balanced between groups (online supplemental table 3). Exposure to rozanolixizumab was 1–527 days in CIDP04 in the placebo/rozanolixizumab group and 85–614 days in the rozanolixizumab/rozanolixizumab group (including CIDP01 and CIDP04), with a total of 17.5 patient-years of exposure across both groups.

During the CIDP04 treatment period, 19 (90%) patients experienced a TEAE; the most common were decreased blood IgG, headache and fatigue (table 4). Of eight patients who experienced decreased blood IgG, six experienced severe events (IgG <1 g/L), three of which were drug related. IgG values returned to normal ranges (7–16 g/L) after the final visit. Rozanolixizumab dose was reduced from 10 mg/kg to 7 mg/kg in four patients due to low IgG. All headaches were mild, with two drug related in the placebo/rozanolixizumab group. All fatigue events were mild or moderate.

During the treatment period, infections occurred in five (45%) patients in the placebo/rozanolixizumab group (four mild; one moderate) and two (20%) in the rozanolixizumab/rozanolixizumab group (one mild; one moderate). Rates of severe and drug-related TEAEs during the treatment period were similar between groups (table 4). One patient in the placebo/rozanolixizumab group and one in the rozanolixizumab/rozanolixizumab group experienced a serious TEAE leading to study discontinuation; neither was drug related. No deaths occurred (table 4).

No clinically meaningful changes over time in iRODS, adjusted INCAT disability score or clinician-assessed grip strength were observed during CIDP04. 10 (50%) patients relapsed based on combined assessments (6 (60%) patients in the placebo/

**Table 2** CIDP01 efficacy results

| Outcome | Placebo (n=17) | Rozanolixizumab (n=16) | Difference versus placebo |
|---|---|---|---|
| Change from baseline to week 13 (day 85), LSM (SE) or LSM difference versus placebo (90% CI) | | | |
| iRODS centile metric score | 3.4 (2.6) | 2.0 (3.2) | –1.5 (–7.5 to 4.5) |
| Adjusted INCAT disability score | –0.6 (0.2) | –1.0 (0.3) | –0.4 (–0.9 to 0.0) |
| Maximum grip strength (clinician assessed) | 13.27 (3.79) | 10.86 (4.41) | –2.41 (–11.09 to 6.28) |
| Maximum grip strength (patient assessed) | 8.1 (4.5) | 6.9 (5.4) | –1.2 (–12.0 to 9.5) |
| CIDP relapse up to week 13, n (%) or LSM difference versus placebo (90% CI)* | | | |
| Combined | 9 (53) | 8 (50) | –0.03 (–0.32 to 0.26) |
| iRODS | 6 (35) | 7 (44) | 0.09 (–0.20 to 0.36) |
| Adjusted INCAT disability score | 8 (47) | 7 (44) | –0.03 (–0.32 to 0.25) |
| Maximum grip strength | 7 (41) | 6 (38) | –0.04 (–0.32 to 0.24) |
| Time to CIDP relapse (days), HR (90% CI)* | | | |
| Combined | – | – | 0.97 (0.43 to 2.15) |
| iRODS | – | – | 1.36 (0.55 to 3.40) |
| Adjusted INCAT disability score | – | – | 0.96 (0.41 to 2.24) |
| Maximum grip strength | – | – | 1.04 (0.42 to 2.61) |

*Data presented are for patients worsening for each individual disability measure, with 'combined' referring to the patients who worsened according to any individual measure. A patient withdrawing from the study for any reason, having missing data or administered rescue medication before week 13 was considered relapsed.
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; iRODS, inflammatory Rasch-built Overall Disability Scale; LSM, least squares mean.

rozanolixizumab group and 4 (40%) in the rozanolixizumab/rozanolixizumab group).

Rozanolixizumab effectively and sustainably reduced mean total IgG levels by >70% in CIDP04 in both groups. Mean baseline IgG was 11.3 g/L (SD 2.2) in the placebo/rozanolixizumab group and 17.4 g/L (SD 1.9) in the rozanolixizumab/rozanolixizumab group. Transient fluctuations in immunological variables were observed over time; however, no clinically meaningful trends were observed. Similarly, although a slight upward trend was observed for sNf-L profiles, they were not clinically meaningful (online supplemental figure 3B). Treatment-induced anti-drug antibody-positive status was observed in six (55%) patients in the placebo/rozanolixizumab group and six (60%) in the rozanolixizumab/rozanolixizumab group. This finding did not appear to impact IgG response or cause TEAEs.

## DISCUSSION

In the phase 2a CIDP01 trial and OLE CIDP04, rozanolixizumab did not show efficacy in patients with CIDP. Rozanolixizumab was generally well tolerated, with an acceptable safety profile and no new safety findings over chronic weekly treatment lasting up to 614 days. To our knowledge, this is the longest exposure to an FcRn inhibitor in a clinical study to date.

FcRn inhibition reduces IgG levels, including pathogenic IgG autoantibodies.[14] Rozanolixizumab administration reduced IgG

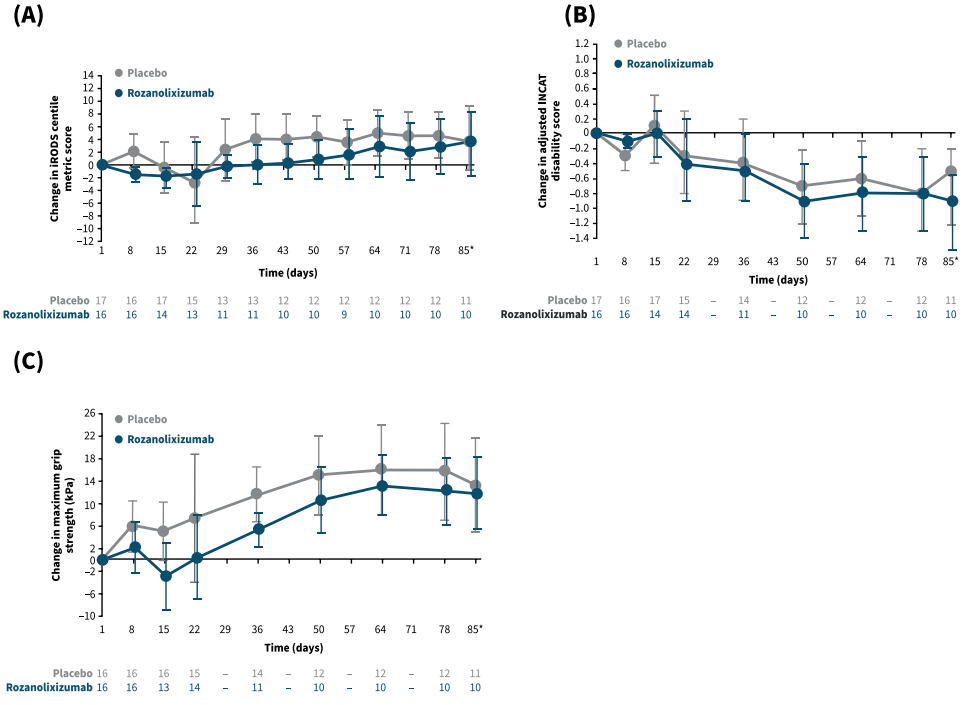


**Figure 2** CIDP01 mean change from baseline. (A) iRODS centile metric score. (B) Adjusted INCAT disability score. (C) Maximum grip strength. Error bars are 90% CI. *Denotes an observation visit (all other visits were treatment visits). INCAT, Inflammatory Neuropathy Cause and Treatment; iRODS, inflammatory Rasch-built Overall Disability Scale.

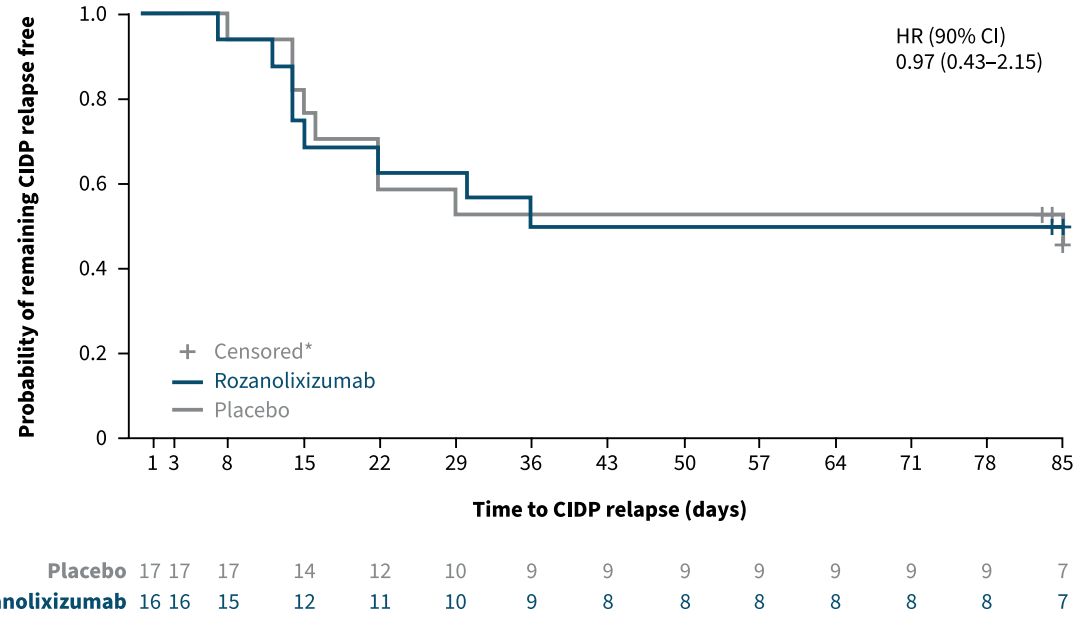


**Figure 3** Time to CIDP relapse (iRODS, adjusted INCAT disability scale and maximum grip strength combined assessments). *Patients who did not experience a relapse while under observation and completed the treatment period are censored at day 85. CIDP, chronic inflammatory demyelinating polyneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; iRODS, inflammatory Rasch-built Overall Disability Scale.

levels by >80% in CIDP01 and >70% in CIDP04. However, this reduction did not significantly affect CIDP efficacy outcomes, including iRODS, adjusted INCAT disability and maximum grip strength. Our hypotheses around this result centre on the nature of the immunopathological mechanisms responsible for CIDP, and trial design including recruitment.

Multiple immunopathological mechanisms may contribute to CIDP pathogenesis. The hypothesis that IgG has an important role is supported by plasma exchange, which may affect immunoglobulin levels including IgG, being effective in CIDP.[2 5 13] In a recent phase 3 study, rozanolixizumab was shown to be efficacious for MG,[20] a disease where the role of IgG autoantibodies is

**Table 3** CIDP01 TEAEs*

| | Treatment period | | Observation period | |
|---|---|---|---|---|
| TEAE | Placebo (n=17) | Rozanolixizumab (n=17) | Placebo (n=17) | Rozanolixizumab (n=17) |
| Any TEAE, n (%) | 13 (76) | 14 (82) | 4 (24) | 3 (18) |
| Headache | 5 (29) | 6 (35) | 1 (6) | 1 (6) |
| Arthralgia | 1 (6) | 3 (18) | 0 | 0 |
| CIDP worsening | 1 (6) | 3 (18) | 3 (18) | 3 (18) |
| Peripheral swelling | 1 (6) | 3 (18) | 0 | 0 |
| Infusion-site erythema | 0 | 3 (18) | 0 | 0 |
| Bacterial test positive | 0 | 2 (12) | 0 | 0 |
| Diarrhoea | 3 (18) | 2 (12) | 0 | 0 |
| Fatigue | 3 (18) | 1 (6) | 0 | 0 |
| Urinary tract infection | 3 (18) | 1 (6) | 1 (6) | 0 |
| Nausea | 2 (12) | 1 (6) | 0 | 0 |
| Administration-site pain | 2 (12) | 0 | 0 | 0 |
| Fall | 2 (12) | 0 | 0 | 0 |
| Hypothesia | 2 (12) | 0 | 0 | 0 |
| Rash | 2 (12) | 0 | 0 | 0 |
| Serious TEAE, n (%) | 0 | 2 (12) | 0 | 0 |
| Drug-related TEAE, n (%) | 5 (29) | 10 (59) | 1 (6) | 1 (6) |
| Severe TEAE, n (%) | 0 | 1 (6) | 2 (12) | 0 |
| Discontinuations due to TEAE, n (%)† | 2 (12) | 1 (6) | 3 (18) | 2 (12) |
| Deaths, n (%) | 0 | 0 | 0 | 0 |

*TEAEs occurring in two or more patients during the treatment period.
†TEAEs leading to discontinuation were CIDP worsening/relapse, muscle weakness and paraesthesia, all of which resolved. These patients are reported in the trial profile as withdrawing due to lack of efficacy or CIDP relapse (other).
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; TEAE, treatment-emergent adverse event.

**Table 4** CIDP04 TEAEs*

| TEAE | Treatment period | | Observation period | |
|---|---|---|---|---|
| | Placebo/rozanolixizumab (n=11) | Rozanolixizumab/rozanolixizumab (n=10) | Placebo/rozanolixizumab (n=11) | Rozanolixizumab/rozanolixizumab (n=10) |
| Any TEAE, n (%) | 9 (82) | 10 (100) | 7 (64) | 4 (40) |
| Blood IgG decreased | 4 (36) | 4 (40) | 0 | 1 (10) |
| Fatigue | 2 (18) | 3 (30) | 1 (9) | 0 |
| Headache | 4 (36) | 1 (10) | 0 | 0 |
| Nasopharyngitis | 2 (18) | 1 (10) | 0 | 1 (10) |
| Muscle strain | 1 (9) | 2 (20) | 0 | 0 |
| Joint swelling | 0 | 2 (20) | 1 (9) | 0 |
| Neuralgia | 0 | 2 (20) | 1 (9) | 0 |
| Constipation | 0 | 2 (20) | 0 | 0 |
| Fever | 2 (18) | 0 | 0 | 0 |
| Influenza | 2 (18) | 0 | 0 | 0 |
| Upper respiratory tract infection | 2 (18) | 0 | 0 | 0 |
| Fall | 0 | 2 (20) | 0 | 0 |
| Muscle spasms | 0 | 2 (20) | 0 | 0 |
| Muscular weakness | 1 (9) | 0 | 2 (18) | 0 |
| Sensory loss | 1 (9) | 0 | 2 (18) | 0 |
| Serious TEAE, n (%) | 1 (9) | 0 | 1 (9) | 2 (20) |
| Drug-related TEAE, n (%) | 6 (55) | 5 (50) | 0 | 0 |
| Severe TEAE, n (%) | 3 (27) | 4 (40) | 2 (18) | 4 (40) |
| Discontinuations due to TEAE, n (%)† | 1 (9) | 0 | 1 (9) | 1 (10) |
| Deaths, n (%) | 0 | 0 | 0 | 0 |

*TEAEs occurring in two or more patients during the treatment period.
†TEAEs leading to discontinuation were a serious TEAE of malignant melanoma in the placebo/rozanolixizumab group during the treatment period and a serious TEAE of CIDP relapse in the rozanolixizumab/rozanolixizumab group during the observation period, both of which resolved. These patients are reported in the trial profile as withdrawing due to an adverse event. One patient in the placebo/rozanolixizumab group experienced peripheral swelling (resolved) and muscular weakness (outcome unknown) during the observation period; this patient is reported in the trial profile as having withdrawn consent.
CIDP, chronic inflammatory demyelinating neuropathy; TEAE, treatment-emergent adverse event.

well established.[20 21] The fact that rozanolixizumab consistently lowered IgG levels in our study, yet did not provide benefit for a general CIDP population, supports the hypothesis that CIDP is not a purely IgG-mediated disease in all patients. Indeed, this study included one patient with IgM paraproteinaemia, a subtype not targeted by rozanolixizumab. Other cell types such as macrophages are also thought to play a role in CIDP pathogenesis.[7] Additionally, patients, who fulfil criteria for CIDP but have antibodies against nodal and paranodal proteins, demonstrate pathogenesis of neuropathy that appears distinct from classic CIDP.[11] Recent guidelines have proposed that these conditions are termed 'autoimmune nodopathies' and not considered CIDP variants.[11]

Recruitment of the correct population is challenging. No validated biomarkers exist for CIDP disease activity and immunoglobulin dependency is hard to establish, making identification of patients with CIDP difficult, particularly those with immunoglobulin-dependent CIDP.[22–24] In CIDP01, CIDP relapse according to the combined assessments of iRODS, adjusted INCAT disability and maximum grip strength showed that patients receiving placebo exhibited relatively stable disease, with only 53% relapsing during the double-blind period, suggesting that many of them did not have Ig-treatment-dependent active disease. We investigated the characteristics of patients who did and did not relapse in a post hoc analysis but did not observe any clear differences between groups.

Moreover, this placebo stability rate was higher than anticipated, making it harder to detect a difference between groups. Interestingly, other CIDP studies, published after CIDP01 was designed and using varying definitions of relapse, have seen comparable placebo stability rates. The FORCIDP trial of fingolimod reported a 43% stability rate in the placebo group, despite a longer period of observation than CIDP01.[25] In a non-inferiority trial of IVIg continuation versus withdrawal, 41% of patients who had IVIg withdrawn remained stable for 24 weeks compared with 58% of those who continued IVIg therapy.[23] Most telling were the placebo stability rates in the PATH trial assessing SCIg (37%) and the ADHERE trial assessing efgartigimod (46% at Week 24 of double-blind treatment), occurring despite only enrolling participants who demonstrated symptom worsening on prior treatment withdrawal and symptom improvement when put back on treatment (IVIg in PATH and efgartigimod in ADHERE) before starting double-blind treatment.[26–28] ADHERE found that efgartigimod had a significant benefit on relapse rates (26% for efgartigimod vs 54% for placebo after 24 weeks of double-blind treatment), indicating that FcRn inhibition can be effective in some patients with CIDP. Careful selection of the trial population by an expert panel and enrichment of the population to include patients in the double-blind phase who respond to the study drug (efgartigimod) after IVIg withdrawal are likely the main reasons explaining disparity of results between the ADHERE and CIDP01 trials, although drug-specific beneficial effects cannot be excluded.[26] High placebo stability rates could suggest that the patients in the CIDP01/04 studies did not have active disease. Nonetheless, even if high placebo response rates may have reduced the chances of finding a treatment effect, differences between the rozanolixizumab and placebo groups were not seen in any secondary outcome measures, including objective measures such as grip strength or sNf-L levels, suggesting that only a

subset of CIDP may have IgG as a key effector mechanism and respond favourably, a hypothesis that seems to be aligned with the findings of the ADHERE trial.

Lastly, a systematic review by the authors of the PATH trial showed that trials with an endpoint of deterioration (as in our study) had a placebo response of 43%, compared with only 11% for trials with an endpoint of improvement.[27] Overall, these findings suggest that the likely placebo stability rate should be considered carefully when designing future CIDP studies.

Further limitations of our study include the small sample size and relatively high proportion of patients taking concomitant corticosteroids or other immunosuppressants: just under one-third of patients were receiving these medications, which could have confounded the treatment effect. The studies also had a relatively high drop-out rate: approximately 40% of patients discontinued in CIDP01 and around 60% in CIDP04, with discontinuations in CIDP01 mainly driven by lack of efficacy.

When considered together, CIDP01 and CIDP04 represent, to our knowledge, the longest exposure to an FcRn inhibitor in a clinical study to date (up to 614 days), with chronic, weekly 10 mg/kg the highest dose of rozanolixizumab to have been studied. No dose reductions were required during CIDP01; however, the dose was decreased to 7 mg/kg in four (19%) patients in CIDP04 due to low IgG at least once during the study. Since the mechanism of action of rozanolixizumab is IgG lowering, this variable was monitored and did not appear to correlate with increased infection risk, with only five (19%) patients who received rozanolixizumab across CIDP01 and CIDP04 experiencing an infection.

In conclusion, this study provides important data on the medium-to-long-term safety profile of rozanolixizumab, with the 10 mg/kg dose well tolerated as a chronic, weekly treatment. Rozanolixizumab did not prevent CIDP disease progression or relapse in CIDP01 or CIDP04, but IgG lowering was consistent with previous studies.[20 29 30] Various factors, including heterogeneity of the disease and a low proportion of patients with active disease, could have influenced the negative results of our trial despite a potential benefit of IgG-lowering therapy in carefully selected patients with CIDP. These results should inform future trial design, including further research into the identification of pathophysiological phenotypes of CIDP (particularly the role of IgG autoantibodies), improving population selection methods by using available biomarker screening and accounting for a high placebo stability rate in power calculations.

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**Contributors** LQ and FE designed and conceptualised the study; drafted and revised the manuscript for content; major role in acquisition of data; interpretation of data. JDS, TD, TL, THR, MR, SS and AB drafted and revised the manuscript for content; major role in acquisition of data; interpretation of data. H-PH and A-OC drafted and revised the manuscript for content; interpretation of data. PK and UM designed and conceptualised study; drafted and revised the manuscript for content; interpretation of data. DM: statistical analysis and interpretation of data. LQ is responsible for the overall content as the guarantor.

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**Ethics approval** This study involves human participants and was approved by the following ethics committees for CIDP01: Belgium: Research Ethics Committee of the UZ/KU Leuven (S60639) Canada: The University Health Network Research Ethics Board (19-5563) Denmark: Biomedical Research Ethics of the Central Denmark Region, Committee I (no reference number provided) France: Comite De Protection Des Personnes Est I, Centre Hospitalier La Chartreuse (19.02.27.61025) Germany: Ethics Committee at the Medical School of the University of Düsseldorf (no reference number provided) Netherlands: Medisch Ethische Toetsingscommissie AMC (NL61913.018.19) Spain: Ethics Committee for Research with Medicinal Products of the Fundació de Gestió Sanitària Hospital de la Santa Creu i Sant Pau, Barcelona (19/058) UK: London—Westminster Research Ethics Committee (REC: 19/LO/0421; IRAS: 259113) USA: Advarra IRB (no reference number provided); CIDP04: Belgium: Research Ethics Committee of the UZ/KU Leuven (S62705) Denmark: Biomedical Research Ethics of the Central Denmark Region, Committee I (no reference number provided) France: Comite De Protection Des Personnes Est I, Centre Hospitalier La Chartreuse (1966) Germany: Ethics Committee at the Medical Faculty of the HHU Düsseldorf (no reference number provided) Netherlands: Medisch Ethische Toetsingscommissie AMC (2019_196) Spain: Ethics Committee for Research with Medicinal Products of the Fundació de Gestió Sanitària Hospital de la Santa Creu i Sant Pau, Barcelona (no reference number provided) UK: London - Westminster

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**Data availability statement** Data from this trial may be requested by qualified researchers 6 months after product approval in the USA and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymised individual patient-level data and redacted trial documents, which may include analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal. This plan may change if the risk of reidentifying trial participants is determined to be too high after the trial is completed; in this case and to protect participants, individual patient-level data would not be made available.



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