Title:

Randomised Controlled Trial of Oral Fingolimod for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (FORCIDP Trial)

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Abstract

Background:

Fingolimod is approved for the treatment of relapsing–remitting multiple sclerosis and was effective in experimental autoimmune neuritis, a possible model for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We evaluated the efficacy of fingolimod in delaying disability progression in patients with CIDP who withdrew from currently effective treatments (intravenous immune globulin [IVIg] or corticosteroids).

Methods:

This double-blind, multicentre, parallel-group study was conducted in 48 neurology centres across Europe, Japan, and USA. Participants with CIDP receiving IVIg or corticosteroids were randomised to once-daily fingolimod 0·5 mg or placebo (1:1). Owing to the event-driven design, treatment duration was flexible and up to 3 years. Randomisation was done with an automated interactive voice response/web response system and was stratified by Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale scores. Previous IVIg treatment was discontinued after one final course just before randomisation, while corticosteroids were tapered off over 8 weeks after randomisation. The primary endpoint time-to-first confirmed worsening (≥1 point increase on the adjusted INCAT score versus baseline) was assessed using the Kaplan-Meier method in the full analysis set. The trial was registered with ClinicalTrials.gov (NCT01625182).

Findings:

Of 106 participants randomised, 54 (IVIg, n=41; corticosteroids, n=13) received fingolimod (mean (SD) age 54 (13) years, 69% male) and 52 (IVIg, n=41; corticosteroids, n=11) received placebo (age 55 (12) years, 58% male). The trial ended for futility as recommended by an independent data monitoring committee after an interim analysis when 44 confirmed worsenings had been observed. At the end of the study, the survival estimate of the percentage (95% confidence interval) of participants free from confirmed worsening was not significantly different between the fingolimod (42% [23%–60%]) and

placebo groups (43% [28%–59%]; p=0·91). Adverse events (AEs) occurred in 41 (75·9%) participants receiving fingolimod and 44 (84·6%) on placebo. Serious AEs occurred in 9 (16·7%) and 4 (7·7%), respectively. Headache, hypertension, and extremity pain were the most common AEs with fingolimod. Adverse events leading to study discontinuation occurred in seven (13%) participants on fingolimod and none on placebo.

Interpretation:

Fingolimod 0·5 mg once-daily was not better than placebo for the treatment of CIDP. Future trial designs should take account of the possibilities that if IVIg is stopped abruptly some patients relapse soon afterwards and others remain in remission.

Funding:

Novartis Pharma AG, Basel

Research in Context

Evidence before the study

International consensus guidelines recommend intravenous immune globulin (IVIg), corticosteroids, and plasma exchange as first-line treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), based on clinical experience and randomised controlled trials (RCT). Because of the side effects, expense, and limited efficacy of these treatments, alternative immunomodulatory agents are often used despite the lack of formal evidence of efficacy. On 24 May 2016, a Cochrane systematic review searched from January 1966 in MEDLINE and seven other databases for randomised controlled trials of immunomodulatory agents other than corticosteroids, intravenous immune globulin and plasma exchange in CIDP. The review identified 202 possibly relevant records but only four RCTs, one each of azathioprine and methotrexate and two of beta interferon: none showed significant benefit. We searched MEDLINE on March 1, 2018, with no restriction on language for any publications between May 2016 and Feb 2018. Limiting the search to clinical trials, we obtained 104 articles. Of these, one trial of subcutaneous immune globulin was the only additional randomised study not included in the systematic review cited. Fingolimod, a sphingosine 1-phosphate receptor modulator, has shown effectiveness in reducing neuro-inflammatory processes in multiple sclerosis and experimental autoimmune neuritis, a possible model of CIDP. The convenience of its oral administration and its well-established safety profile in multiple sclerosis provided the rationale for considering fingolimod as a treatment candidate for CIDP.

Added value of this study

This placebo controlled, double-blind, event-driven trial showed no evidence of efficacy of fingolimod in people with CIDP who had been taking corticosteroids or IVIg and withdrew from them. Twenty of 82 (24.4%) of participants previously on IVIg worsened within 45 days of its discontinuation. An estimated 40% of participants randomised to placebo were able to stop their treatment with corticosteroids or IVIg without relapsing on the adjusted INCAT scale.

Implications of all the available evidence

There is no evidence from RCTs that any immunomodulatory treatments other than corticosteroids, intravenous or subcutaneous immune globulin, and plasma exchange are

beneficial in CIDP. RCTs of new treatments in CIDP patients must overcome multiple methodological problems in this rare and heterogeneous disease with known effective treatments.

Background

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare and clinically heterogeneous disabling disease of the peripheral nervous system probably caused by autoimmune mechanisms.[1] The underlying pathology of active lesions is lymphocyte and macrophage infiltration of the peripheral nerves, with macrophage invasion and subsequent stripping of the myelin sheath resembling experimental autoimmune neuritis, an animal model of demyelination in the peripheral nervous system. There is evidence for clonal expansion of $CD8^+$ T cells.[2] Recommended first-line treatment options are corticosteroids, intravenous immune globulin (IVIg) and, if these fail, plasma exchange.[3] The side effects, expense, and limited efficacy of these treatments have led to the use of other immunosuppressive or immunomodulatory treatments, but randomised controlled trials (RCTs) of such agents have either not been carried out or the results have been negative.[4]

Fingolimod, a sphingosine 1-phosphate receptor modulator, reduced the rate of relapse, progression of clinical disability, and magnetic resonance imaging evidence of inflammatory lesion activity and tissue destruction in relapsing multiple sclerosis for which it is an approved treatment.[5,6] In this central nervous system inflammatory demyelinating disorder the major effect appears to be retention of autoreactive T cells in lymph nodes preventing their invasion of the brain and spinal cord. Fingolimod has multiple actions that suggested therapeutic potential in CIDP, including reduction of circulating naïve and central memory T cells and memory B cells, impairment of myeloid cell activation, and increase of regulatory B cells.[7,8] In healthy subjects, treatment with fingolimod induced a 58% reduction in circulating lymphocytes by Day 2 of treatment. Absolute lymphocyte nadir was observed between Days 3 to 7 (mean [SD] 0.4 (0.1) x 10^9/L), which corresponded to about 80% decrease from baseline counts.[9] The efficacy of

fingolimod demonstrated in the experimental autoimmune neuritis model further strengthened the case for testing it in CIDP.[10] This animal study, the rapid pharmacodynamic effect on lymphocytes, the beneficial effect in multiple sclerosis and known safety profile were the scientific basis for this trial in CIDP.

Methods

Study design

This was a double-blind, randomised, multicentre, placebo-controlled, parallel-group, event-driven study in patients with CIDP who were treated with IVIg and/or corticosteroids before study entry. Inclusion criteria required a documented history of relapsing or progressive clinical course upon interruption or reduction of treatment within 18 months prior to screening. Treatment-naïve patients were excluded for ethical reasons.

Following a screening period lasting up to 45 days, eligible participants were randomised (1:1) to receive oral fingolimod 0·5 mg daily or matching placebo and treated during a double-blind treatment period before a follow-up period of about 12 weeks (Supplementary **Figure 1**).

Owing to the event-driven study design, the number of participants to be randomised and the treatment duration for each participant were flexible and dependent on the rate of events in the entire study population. The maximal study duration for an individual was expected to be approximately 4·5 years.

The end of the study was to be declared when one of the following pre-determined criteria was met: 1. Futility criterion: study declared futile after 50 confirmed events because of the low probability of detecting benefit at the end of the study; 2. Worsening of the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale score in a minimal required number of events (111 confirmed events); 3. Failure to observe the minimal required number of events 4·5 years after the enrolment of the first participant.

Participants

Participants of either sex had to be at least 18 years of age and fulfil the clinical inclusion criteria for typical or atypical CIDP and the definite electrodiagnostic criteria for CIDP of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) Task Force First Revision.[11] Additional inclusion criteria were INCAT Disability Scale score of 1 to 9, receiving either IVIg (minimal dose equivalent to 0.4 g/kg every 4 weeks for a minimum of 12 weeks) or corticosteroids (minimal dose equivalent to prednisone 10 mg/day) prior to the screening visit, documented clinically meaningful deterioration confirmed by clinical examination, during therapy or upon interruption or reduction of therapy within 18 months, and being stable without a significant change in treatment for the 6 weeks before randomisation. If the INCAT score was zero at screening, it was required that the patient had a documented history of disability sufficient to require treatment within the past 2 years following reduction or interruption of treatment. The key exclusion criteria were other causes of chronic demyelinating neuropathy and treatment with plasma exchange within 2 months of randomisation, immunosuppressives within 6 months of randomisation, and chemotherapeutic agents with sustained effects or haematopoietic stem cell transplantation at any time (please refer to **Supplementary Table 1** for complete inclusion and exclusion criteria).

Randomisation, treatment allocation concealment, and blinding

Randomisation was performed via an interactive voice response system/interactive web response system that automated the random assignment of patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. Randomisation was stratified based on prior predominant treatment (IVIg or corticosteroids), INCAT Disability Scale score at the pre-randomisation visit (≤3 or >3), and region (Japan, or countries outside of Japan). Randomisation data were

confidential until the time of unblinding and were not accessible except to the independent data monitoring committee or for medical emergencies. The identity of the treatments was concealed by the use of study drugs with identical packaging, labelling, appearance and schedule of administration. Independent evaluating physicians undertook all efficacy assessments in order to maintain blinding. Participants were instructed not to discuss any adverse events or other symptoms they may have experienced with the independent evaluating physician assessing efficacy. A separate treating physician was responsible for patient care and management.

Study procedures

The trial was approved by independent ethics committees and health authorities at each of the participating institutions. Patients who agreed to take part in the trial signed an informed consent form and then entered a screening period during which they could continue being treated with IVIg and/or corticosteroids up to the randomisation visit.

Participants receiving IVIg had baseline assessments taken for efficacy parameters during a pre-randomisation visit the week before the start of their last IVIg cycle. They underwent randomisation, received their first trial medication on the day after the last IVIg infusion cycle, and then received no further IVIg treatment. Participants receiving oral corticosteroids had their baseline assessments taken at any time during the week before randomisation and, on the day of randomisation, began tapering their corticosteroid dose to zero over a maximum period of 8 weeks. While the study was ongoing, the protocol was amended to allow the inclusion of patients on pulse intravenous corticosteroids. For those participants, their first trial medication was on the day after the last pulse, and they did not taper the corticosteroid dose. Oral corticosteroid tapering was carried out at weekly intervals from the equivalent of prednisolone 60 mg daily to 50 mg (Week 1), 40 mg (Week 2), 30 mg (Week 3), 25 mg (Week 4), 20 mg (Week 5), 15 mg (Week 6), 10 mg (Week 7), and 5 mg (Week 8). Participants receiving a lower dose than 60 mg

daily started the reductions at an appropriate point according to this schedule. Participants receiving corticosteroids also received oral valacyclovir or acyclovir 400–500 mg twice daily from randomisation until 4 weeks after the last dose of corticosteroid tapering concomitant with the study drug.

In view of the known bradyarrhythmic effects of fingolimod at treatment initiation, participants remained under supervision in the clinic for at least six hours after the first dose of the study drug. They also underwent ambulatory Holter electrocardiogram monitoring for 24 hours. To avoid potential unblinding, an independent physician monitored participants during the first dose administration assessments. All participants had visits at Day 15 and at Months 1, 2 and 3, and then every 3 months until the end of the study.

At any time during the study, participants with perceived worsening of CIDP symptoms were assessed by an independent evaluating physician. If a worsening on the adjusted INCAT Disability Scale was confirmed (increase by 1 point or more from baseline), use of the study drug was discontinued for the participant and they either resumed their previous treatment or initiated new treatment as judged by the investigator. The adjusted INCAT Disability Scale is identical to the INCAT Disability Scale except for the exclusion of changes in upper limb function from 0 (normal) to 1 (minor symptoms or signs in one or both arms but not affecting any of the functions listed in the scale).[12] Participants completed a follow-up visit approximately 3 months after study drug discontinuation.

Outcome measures

The primary outcome was time-to-first confirmed worsening on the adjusted INCAT Disability Scale.[12] A confirmed worsening was defined as an increase of the adjusted INCAT Disability Scale score by 1 point or more from baseline. During the study unconfirmed worsening events were observed and defined as those worsening events, not confirmed on the INCAT Disability

Scale, leading to study drug discontinuation due to unsatisfactory therapeutic effect. The date of study drug discontinuation was used to calculate the time to unconfirmed worsening. The efficacy secondary outcomes were change in grip strength, measured with a Martin Vigorimeter[13] from baseline to Month 6/end of the study (whichever occurred first); change in Rasch-Built Overall Disability Scale (R-ODS)[14] from baseline to Month 6/End-of-Treatment (whichever occurred first); and safety and tolerability as assessed by serious and non-serious adverse events, haematology and biochemistry laboratory tests, vital signs, ECG, and pulmonary function tests. Exploratory outcomes were the change from baseline in Medical Research Council (MRC) sum score and the 36 Item Short-Form Health Survey (SF 36®) physical component summary.

Statistical analysis, sample size and futility analysis

All analyses were performed on the full analysis set. The primary outcome was time-to-first confirmed worsening. The survival distribution functions of time-to-first worsening were estimated within each treatment group by the Kaplan-Meier method, and compared using a stratified log-rank test, within eight strata formed as combinations of previous predominant treatment (IVIg or corticosteroids), baseline INCAT disability score (≤3 or >3), and region (Japan, or elsewhere). Furthermore, reduction in risk of time-to-first confirmed worsening was analysed using a Cox proportional hazards model with treatment and prior predominant treatment (IVIg or corticosteroids) as factors and baseline INCAT as a categorical covariate (INCAT score (≤3, >3). These analyses were pre-planned.

Subgroup analyses for the primary outcome were pre-planned (before the database lock and study unblinding) to better understand the futility outcome. Subgroups were defined based on history of previous predominant CIDP treatment (IVIg or corticosteroids), baseline INCAT Disability Scale score (<3, 3, >3), CIDP duration since diagnosis (<2, 2 to <5, ≥5 years), and

number of worsenings over the past 2 years prior to screening (0 to 1, 2, ≥3). For each subgroup analysis the survival estimates of event-free survival rate were presented for each treatment group and each subgroup category. The log-rank test (non-stratified) was used to test the difference between treatment groups for each subgroup category. The Cox proportional hazards model was performed by adding the treatment-by-subgroup variable interaction in the model. Based on the Cox model, the p-value for the interaction term and the hazard ratios of treatment effect for each subgroup category were presented.

Participants who prematurely discontinued from study drug for any reason were followed according to the planned assessment schedule. Events were counted regardless of whether they occurred on or off study drug.

Changes from baseline to Month 6/end of treatment in grip strength and R-ODS were analysed using analysis of covariance (ANCOVA) model adjusted for gender, previous predominant treatment (IVIg or corticosteroids) as factors, and with baseline INCAT Disability Scale score and the corresponding baseline value as covariates. The least squares mean of the change from baseline with its 95% confidence interval (CI) was reported by treatment.

An unblinded interim analysis was originally scheduled after 50 confirmed worsening events, approximately 45% of the maximal information needed for the trial, with the purpose of discontinuing the trial for futility, but not for efficacy. On the assumption of an exponential distribution for the time to the primary endpoint with one interim analysis scheduled after 50 events, 111 events would have been needed in order to detect a hazard ratio of 0·51 in a log-rank test at a one-sided alpha level of 0·025 with a power of 90%. The sample size calculations were based on the assumption that 6 months after randomisation, 50% of participants on placebo group and 30% in the fingolimod group would have had an event (approximately 40% blinded

event rate). The study was to be stopped for futility if the log-rank test resulted in a p value of ≥0·21 (corresponding to a hazard ratio ≥0·77). The planned timing of the interim analysis was chosen as a trade-off between the expected proportion of participants recruited at the time of the interim analysis and the probability of correctly stopping for futility. However, after almost three years of recruitment, the combination of low enrolment and lower confirmed event rate than anticipated presaged a substantial shortfall of the number of confirmed events observed by 4.5 years below the target of 111 required to support the planned power of the trial. Scheduling of the futility analysis was then revisited, in light of the reduced information thus anticipated over trial's planned full duration. A list of statistical scenarios projecting when the interim analysis could occur is presented in **Supplementary Table 2**. Following this assessment the futility analysis was conducted earlier than planned, at 44 rather than 50 confirmed events. The analysis was performed by an independent statistical team and the results of this interim analysis were reviewed by the independent data monitoring committee.

Role of funding source

The study sponsor participated in the design and conduct of the study, data collection, data management, data analysis and interpretation, and preparation, review, and approval of the manuscript. All authors had full access to all data in the study and take final responsibility for the decision to submit for publication. Institutions wishing to analyse data from the study can apply via www.clinicalstudydatarequest.com

Results

Out of 159 patients screened in 48 centres in 14 countries, 106 (67%) eligible subjects were randomised between 24 January 2013 and 10 March 2016; 53 (33%) failed the screening (**Figure 1**). Screen failure was most commonly due to exclusion criteria such as relevant medical history,

abnormal laboratory values, or positive serology markers for hepatitis. There were 54 participants randomised to the fingolimod group and 52 to the placebo group; **Table 1** shows their demographic variables and baseline characteristics. The groups were well matched for age, sex, and race. The mean (standard deviation, SD) age of the study participants was 54·5 (12·5) years, which is approximately 10–15 years older compared to patients in fingolimod trials in relapsing–remitting multiple sclerosis.[5,6]

The number of worsening events in the past two years, disability, grip strength, MRC sum score and SF 36® physical component summary score were comparable in both groups. Minor differences in disease duration, time since diagnosis, and previous predominant treatment (IVIg or corticosteroids) was noted between the two groups but no statistical test for significance was performed.

In March 2016, after just over 3 years since study start, the interim futility analysis was performed when 44 confirmed events had occurred. At this time, there had also been 12 unconfirmed worsening events. The interim futility analysis was performed after only 44 confirmed events rather than 50 as stipulated in the protocol because the slow recruitment meant that only 72 confirmed events were estimated to accrue at the planned end of the trial. The analysis was therefore performed when 60% of the estimated total information was available, considerably more than 55% of the intended total information on which the protocol futility analysis calculation had been based. The independent data monitoring committee recommended termination of the trial, as the primary outcome event rates for the two groups up to that point were too similar to support a reasonable probability of achieving statistical significance were the study continued. Thereupon investigators and participants were informed, the remaining

participant visits were conducted, and the database was completed and locked. Only then was the study unblinded.

There was no difference between the groups in the primary outcome (time to confirmed worsening): the percentage (95% confidence interval [CI]) of participants free from confirmed worsening was 60% (47·0%–73·5%) in the fingolimod group and also 60% (46·7%–73·9%) in the placebo group at Month 6 according to the Kaplan-Meier estimate (**Figure 2**). At the time that the study was closed for futility (end of the study), 42% (95% CI: 22·7, 60·3) of the fingolimod group and 43% (95% CI: 27·7, 58·7) of the placebo group had no confirmed worsening (p=0·91). Further analysis using Cox proportional hazards model indicated no risk reduction in time-to-first confirmed worsening over the course of the study (fingolimod vs. placebo, HR [95% CI]: 1·0 [0·6, 1·7]; p=0·98). The mean (SD) time on the study drug was 9·0 (10) months in the fingolimod group and 9·7 (9) months in the placebo group. Within the first 45 days from starting the study drug, 20 participants (11 on fingolimod; 9 on placebo) experienced their first confirmed worsening event. These participants had all been receiving IVIg as their previous CIDP treatment.

A pre-planned sensitivity analysis including both confirmed and unconfirmed CIDP worsening events was conducted before the interim futility analysis, final database lock and unblinding. The Kaplan-Meier estimate of the percentage (95% CI) of participants who did not experience confirmed or unconfirmed worsening at 6 months was 49·7 % (36·3%–63·1%) with fingolimod and 52·4% (38·6%–66·2%) with placebo (**Supplementary Figure 2**).

Additional analyses of subgroups (CIDP duration since diagnosis, baseline INCAT Disability Scale score, and number of worsening events over the two years before screening) likewise did not reveal any significant differences between the treatment groups (**Supplementary Table 3**).

We investigated whether the results at the end of the study were different in the subgroup previously receiving IVIg compared with the group previously receiving corticosteroids. In the previous IVIg subgroup, similar proportions of the fingolimod (18/41 [44%]) and the placebo participants (21/41 [51%]) had no confirmed worsening; the time to confirmed worsening was not significantly different between fingolimod and placebo participants (hazard ratio 1·28: 95% CI 0·70–2·34; p = 0·41). In the corticosteroid subgroup, more of the fingolimod treated participants (11/13 [85%]) had no confirmed worsening compared with the placebo participants (5/11 [45%]); in this subgroup, the time to confirmed worsening was longer in the fingolimod than the placebo participants (hazard ratio 0·26: 95% CI 0·05–1·29; p = 0·10). All the secondary and exploratory outcomes were similar between the treatments in the whole trial (**Table 2, Figure 3, and Supplementary Table 4**) and in the pre-determined subgroups.

More participants in the fingolimod group (9 [17%]) had serious adverse events than the placebo group (4 [8%]) and discontinued the study drug due to adverse events (7 [13%] compared with 0%, respectively). There were no deaths. Most participants had one or more adverse events (**Table 3**). However, adverse events in this cohort of participants with a mean age of greater than 54 years overall were not more common in the fingolimod than the placebo group. Headache, hypertension, and extremity pain were more common with fingolimod than placebo.

Discussion

In CIDP, randomised trials have shown the efficacy of IVIg and plasma exchange, and there is overwhelming observational evidence that corticosteroids are effective.[3] In this parallel group, randomised trial in patients with CIDP previously treated with corticosteroids or IVIg, fingolimod did not show significant benefit compared to placebo for the primary or any of the secondary or exploratory outcomes. Better results were observed in the subgroup of participants previously treated with corticosteroids. This might be related to the slow withdrawal of

corticosteroids in these participants compared with the abrupt cessation of treatment in those receiving IVIg but we are reluctant to draw conclusions from such small numbers.

The study inclusion criteria were designed to enrich the trial population with CIDP patients with active disease and exclude patients in remission. Current medical practice includes regular attempts at dose reduction of, or withdrawal from, ongoing treatment with IVIg or corticosteroids to assess whether treatment is still necessary or if the patient has reached remission. Because non-treatment is part of medical practice during drug withdrawal periods ("drug holidays"), this paradigm allows the use of a placebo-controlled parallel-group withdrawal design.

We identified challenges when testing fingolimod as a possible new treatment for CIDP. First was the low prevalence of CIDP, which made recruitment difficult. Recruitment was slow despite extending efforts to 48 centres in 14 countries. Second was the reluctance of investigators and patients to discontinue active and reportedly effective treatment with either corticosteroids or IVIg, in order to be randomised to a treatment of unknown efficacy or a placebo. Third, recruitment was limited to those on active treatment and excluded naïve patients, further limiting the pool of potential subjects. Given the existence of known efficacious treatments, it would have been unethical to test an unproven drug in untreated patients. Fourth, adding fingolimod to optimal existing treatment would have had a low power for detecting a treatment effect. Fifth is the difficulty of identifying participants who still need treatment to prevent deterioration.

Although the trial design aimed to recruit CIDP patients with active disease, approximately 40% of participants did not show a confirmed worsening event and approximately 50% did not show a confirmed or unconfirmed worsening event 18–27 months after the start of the study. These participants may be considered as having been in remission at the start of the study even though

the inclusion criteria required objective evidence of clinical worsening in the prior 18 months. Sixth is the marked clinical and pathological heterogeneity of CIDP such that some subgroups might respond poorly to standard treatments.[1,15]

Aiming for an even more focused recruitment of participants having better evidence of active disease may be a way forward. This could be achieved by having a screening phase in which participants undergo withdrawal from their existing treatment and only those who have a confirmed clinical relapse are randomised in the next phase of the study. This strategy was used in the PATH trial which compared subcutaneous immune globulin with placebo but, even then, 37% of the participants randomised to placebo did not relapse during the blinded placebo phase, despite having had confirmed worsening during the preceding unblinded withdrawal phase.[16] This strategy requires participants to endure two phases of treatment withdrawal, which makes entering a trial less attractive and recruitment consequently more difficult. Implementation of an extra phase withdrawing patients from IVIg and corticosteroids would require a uniform treatment strategy on how these patients who worsen will be treated and definition of recovery back to original baseline.

In the present trial, 20 participants receiving IVIg (24% of those receiving IVIg) experienced their first confirmed worsening event within the first six weeks of the trial indicating that indeed they had active disease. This might have interfered with detecting an efficacious effect of fingolimod in CIDP if it took longer than six weeks for an effect to be seen.

The combined effect of these two factors reduced the percentage of participants in whom a delayed treatment effect could be detected to about 40% (42/106 recruited). This would be consistent with either lack of efficacy of fingolimod 0·5 mg daily in these participants or a delayed onset of effect. From previous studies, we know that the pharmacological effects of

fingolimod are evident quickly, lowering heart rate within hours[17] and reducing lymphocyte counts within 2 weeks.[9] Whether fingolimod would have been efficacious in CIDP if the IVIg had not been withdrawn abruptly remains a subject of uncertainty and possible future study. Recent experimental evidence reduces enthusiasm for such a study. Intraperitoneal fingolimod did not produce benefit in CD86 knockout NOD mouse spontaneous autoimmune peripheral polyneuropathy, an alternative animal model for CIDP, contradicting a previous report that oral fingolimod was effective in the same model.[22,23] Fingolimod also reduced myelination in myelinating rat dorsal root ganglion cultures.[24]

The choice of the primary outcome measure was not likely to have been a decisive factor for the negative results in this trial since the secondary and exploratory outcomes all pointed in the same direction. In other trials, grip strength and R-ODS have been found to be more responsive than the adjusted INCAT scale and therefore might be considered as better primary outcomes in future trials.[14,18,19]

Since some patients with CIDP do not respond fully to corticosteroids, IVIg, or plasma exchange or have intolerable side effects from them, the search for alternative treatment options or add-on treatments should continue. Future trials could benefit from the lessons learnt from this trial. Better understanding of the pathogenesis of CIDP should allow for more rational choices of immunomodulatory treatments.

The adverse event profile of fingolimod has been well studied in multiple sclerosis.[20, 21] It includes transient bradycardia upon treatment initiation, elevated liver enzymes, lymphocytopenia and increased risk of infections (including opportunistic infections), macular oedema, and hypertension.[5,6, 20, 21] Serious adverse events and events leading to discontinuation of treatment were more common with fingolimod compared to placebo in this CIDP trial but adverse events were not more common in these participants (with a mean age of greater than 54

years); they were also in line with the known safety profile of fingolimod in multiple sclerosis patients.[5,6]

Authors' contributions

Richard Hughes contributed to the design, data analysis and interpretation, wrote the first draft and provided critical review.

Marinos Dalakas contributed to the design, data collection, data analysis and interpretation and provided critical review during the preparation of the manuscript.

Ingemar Merkies contributed to the design, data collection, data analysis and interpretation and provided critical review during the preparation of the manuscript.

Norman Latov contributed to the literature search, study design, data interpretation and critical review of the manuscript.

Jean-Marc Léger contributed to the study design, data collection, and review of the manuscript writing.

Eduardo Nobile-Orazio contributed to the study design, data collection, analysis and interpretation and critical review of the manuscript.

Gen Sobue contributed to the design, data collection, data analysis and interpretation and provided critical review during the preparation of the manuscript.

Angela Genge contributed to the design, data collection, data analysis and interpretation and provided critical review during the preparation of the manuscript.

David Cornblath contributed to the data analysis and interpretation and provided critical review during the preparation of the manuscript.

Martin Bernhard Merschhemke contributed to overall oversight of study conduct, data review, data analysis and data interpretation, as well as towards writing and reviewing this manuscript.

Carolyn Marie Ervin contributed to the study as the trial statistician assisting with data analysis, study design, data collection issues and manuscript preparations.

Catherine Agoropoulou, as the responsible clinical scientist on this study at Novartis Pharma AG have been an author of the protocol, oversaw the execution of the study and an author of the final study report and have been closely involved in the preparation and critical review of the manuscript describing the study results.

Hans-Peter Hartung contributed to the design, data collection, data analysis and interpretation and provided critical review during the preparation of the manuscript.

Declaration of interests

Richard Hughes has received compensation for consultancy from CSL Behring, LFB and Novartis.

Marinos Dalakas personal fees from THERAPTH LABORATORY, personal fees from BAXALTA, personal fees from OCTAPHARMA, grants and personal fees from NOVARTIS, personal fees from Hoffman La Roche, grants and personal fees from Dysimmune Diseases Foundation, personal fees from THERAPEUTIC ADVANCES IN NEUROLOGY, grants from GENZYME, grants from MERCK SERONO, grants from GENESIS, grants from CSL, outside the submitted work.

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Norman Latov reports personal fees from Novartis, during the conduct of the study. Outside the submitted work he has received grants and personal fees from Shire, consulting fees from Pfizer, stock ownership in Therapath, and book royalties from American Academy of Neurology.

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Tables and figures

Table 1. Demographic variables and baseline characteristics

Demographic variable	Fingolimod 0·5 mg N=54	Placebo N=52
Age, years	54 (13·3)	55 (11·7)
Sex, n (%)		
Male	37 (68·5)	30 (57·7)
Female	17 (31·5)	22 (42·3)
Race, n (%)		
Caucasian	50 (92·6)	47 (90·4)
African-American	0	2 (3·8)
Asian	4 (7·4)	3 (5·8)
Weight, kg	85 (17·8)[a]	82 (18·3)
Duration of CIDP since diagnosis, years	5·6 (5·7)	7·2 (6·5)
CIDP duration category, n (%)		
<2 years	15 (27·8)	8 (15·4)
2–<5 years	16 (29·6)	18 (34·6)
≥5 years	23 (42·6)	26 (50·0)
Number of worsenings in the last 2 years	3·6 (4·3)	3·5 (5·2)
INCAT score	2·7 (1·5)	2·7 (1·7)
Grip strength (kPa) - dominant hand	71 (25·7)[a]	71 (27·5)
Grip strength (kPa) - non-dominant hand	69 (28·3)[a]	70 (26·7)
RODS centile metric score	66 (17·7)	66 (16·9)
Baseline MRC sum score	55 (5·3)[a]	56 (5·5)
Baseline SF-36 physical component summary score	40 (9·2)	41 (8·8)
Previous treatment predominantly IVIg, n (%)	41 (75·9)	41 (78·8)
Previous treatment predominantly steroids, n (%)	13 (24·1)	11 (21·2)

Data represent Mean (SD) unless specified otherwise. [a]Missing value for one participant.
CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; INCAT = Inflammatory Neuropathy Cause and Treatment; IVIg = intravenous immune globulin; MRC = Medical Research Council; R-ODS = Rasch-Built Overall Disability Scale; SF-36 = 36-Item Short-Form Health Survey

Table 2. Secondary outcomes

Endpoints	Fingolimod 0·5 mg N=54	Placebo N=52
Secondary		
Change from baseline in grip strength up to Month 6/EOS[a]		
Dominant hand	n=53	n=50
Mean (SD)	−4·1 (20·0)	−4·8 (15·0)
Median (Min, Max)	−1·3 (−60·3, 36·0)	−4·3 (−43·7, 34·7)
LS Mean difference (95% CI)[b]	1·2 (−5·9, 8·2); p=0·73	
Non-dominant hand	n=53	n=50
Mean (SD)	−4·7 (19·9)	−7·4 (14·8)
Median (Min, Max)	−1·0 (−55·3, 38·3)	-4·7 (−52·7, 34·0)
LS Mean difference (95% CI)[b]	3·4 (−3·6, 10·4); p=0·33	
Change from baseline in R-ODS, up to Month 6/EOS	n=54	n=51
Mean (SD)	−6·5 (11·7)	−5·8 (10·2)
Median (Min, Max)	−3·0 (−35·0, 9·0)	−3·0 (−49·0, 10·0)
LS Mean difference (95% CI)[b]	−0·8 (−5·0, 3·4); p=0·70	

CI = confidence interval; EOS = end of the study; INCAT = Inflammatory Neuropathy Cause and Treatment; LS = least squares; Max = maximum; Min = minimum; R-ODS = Rasch-Built Overall Disability Scale

'n' is the number of participants with non-missing baseline and a given post baseline value.

[a]Visit refers to Month 6 or the EOS, whichever occurred first.

[b]Analysis of covariance (ANCOVA) model adjusted for gender, previous predominant treatment (intravenous immune globulin or steroids), baseline INCAT Disability Scale score, and corresponding parameter baseline value. The LS Mean values were estimated from the ANCOVA model.

Table 3. Participants with adverse events and serious adverse events

Preferred term	Fingolimod 0·5 mg N=54 n (%)	Placebo N=52 n (%)
Any AE	41 (75·9)	44 (84·6)
Headache	12 (22·2)	8 (15·4)
Hypertension	10 (18·5)	1 (1·9)
Pain in extremity	7 (13·0)	3 (5·8)
Nasopharyngitis	6 (11·1)	7 (13·5)
Paraesthesia	5 (9·3)	0
Back pain	4 (7·4)	3 (5·8)
Fall	4 (7·4)	1 (1·9)
Fatigue	4 (7·4)	6 (11·5)
Bronchitis	3 (5·6)	1 (1·9)
Diarrhoea	3 (5·6)	2 (3·8)
Dizziness	3 (5·6)	2 (3·8)
Gamma-glutamyl transferase increased	3 (5·6)	0
Urinary tract infection	3 (5·6)	1 (1·9)
Vertigo	3 (5·6)	3 (5·8)
Any SAE	9 (16.7)	4 (7.7)
Chronic inflammatory demyelinating polyradiculoneuropathy	2 (3.7)	1 (1.9)
Breast cancer	1 (1.9)	0
Retroperitoneal cancer	1 (1.9)	0
Guillain-Barré syndrome	1 (1.9)	0
Peripheral oedema	1 (1.9)	0
Vasculitis	1 (1.9)	0
Abdominal sepsis	1 (1.9)	0
Cellulitis	1 (1.9)	0
Bursitis	1 (1.9)	0
Cauda equina syndrome	0	1 (1.9)
Gastric cancer	0	1 (1.9)
Ankle fracture	0	1 (1.9)
Nephrolithiasis	0	1 (1.9)

Preferred terms are listed by descending frequency in the fingolimod group.

AE = adverse events; SAE = serious AE

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