Safety and efficacy of leriglitazone for preventing disease progression in men with adrenomyeloneuropathy (ADVANCE): a randomised, double-blind, multi-centre, placebo-controlled phase 2–3 trial

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Summary

Background Adult patients with adrenoleukodystrophy have a poor prognosis owing to development of adrenomyeloneuropathy. Additionally, a large proportion of patients with adrenomyeloneuropathy develop life-threatening progressive cerebral adrenoleukodystrophy. Leriglitazone is a novel selective peroxisome proliferator-activated receptor gamma agonist that regulates expression of key genes that contribute to neuroinflammatory and neurodegenerative processes implicated in adrenoleukodystrophy disease progression. We aimed to assess the effect of leriglitazone on clinical, imaging, and biochemical markers of disease progression in adults with adrenomyeloneuropathy.

Methods ADVANCE was a 96-week, randomised, double-blind, placebo-controlled, phase 2–3 trial done at ten hospitals in France, Germany, Hungary, Italy, the Netherlands, Spain, the UK, and the USA. Ambulatory men aged 18–65 years with adrenomyeloneuropathy without gadolinium enhancing lesions suggestive of progressive cerebral adrenoleukodystrophy were randomly assigned (2:1 without stratification) to receive daily oral suspensions of leriglitazone (150 mg starting dose; between baseline and week 12, doses were increased or decreased to achieve plasma concentrations of 200 μg·h/mL [SD 20%]) or placebo by means of an interactive response system and a computer-generated sequence. Investigators and patients were masked to group assignment. The primary efficacy endpoint was change from baseline in the Six-Minute Walk Test distance at week 96, analysed in the full-analysis set by means of a mixed model for repeated measures with restricted maximum likelihood and baseline value as a covariate. Adverse events were also assessed in the full-analysis set. This study was registered with ClinicalTrials.gov, NCT03231878; the primary study is complete; patients had the option to continue treatment in an open-label extension, which is ongoing.

Findings Between Dec 8, 2017, and Oct 16, 2018, of 136 patients screened, 116 were randomly assigned; 62 [81%] of 77 patients receiving leriglitazone and 34 [87%] of 39 receiving placebo completed treatment. There was no between-group difference in the primary endpoint (mean [SD] change from baseline leriglitazone: –27·7 [41·4] m; placebo: –30·3 [60·5] m; least-squares mean difference –1·2 m; 95% CI –22·6 to 20·2; p=0·91). The most common treatment emergent adverse events in both the leriglitazone and placebo groups were weight gain (54 [70%] of 77 *vs* nine [23%] of 39 patients, respectively) and peripheral oedema (49 [64%] of 77 *vs* seven [18%] of 39). There were no deaths. Serious treatment-emergent adverse events occurred in 14 (18%) of 77 patients receiving leriglitazone and ten (26%) of 39 patients receiving placebo. The most common serious treatment emergent adverse event, clinically progressive cerebral adrenoleukodystrophy, occurred in six [5%] of 116 patients, all of whom were in the placebo group.

Interpretation The primary endpoint was not met, but leriglitazone was generally well tolerated and rates of adverse events were in line with the expected safety profile for this drug class. The finding that cerebral adrenoleukodystrophy, a life-threatening event for patients with adrenomyeloneuropathy, occurred only in patients in the placebo group supports further investigation of whether leriglitazone might slow the progression of cerebral adrenoleukodystrophy.

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Introduction

X-linked adrenoleukodystrophy is a rare inherited neurodegenerative disorder in which very long-chain fatty acids accumulate in plasma and tissues, particularly the brain, spinal cord, and adrenal glands.[1] Most adults with adrenoleukodystrophy develop a chronic myelopathic phenotype (adrenomyeloneuropathy), with onset usually in their late 20s. Adrenomyeloneuropathy is characterised by severe, ongoing axonal damage in the central and peripheral nervous systems, and it causes slowly

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See Online for appendix

Research in context

Evidence before this study

We searched the PubMed database from inception to Nov 1, 2022, using the terms ("adrenoleukodystrophy" OR "adrenomyeloneuropathy") AND ("treatment" OR "therapy" OR "drug") AND ("clinical trial" OR "trial" OR "randomised") AND ("patients" OR "subjects" OR "participants"). We screened search results to include only clinical study publications that reported functional disease outcomes in a patient population treated with disease-modifying drug therapies. We excluded trials of haemopoietic stem cell transplantation, gene therapy, or fatty acid supplementation. Previous studies have reported on disability, quality of life, and survival outcomes in patients treated with cyclophosphamide and steroids, lovastatin, intravenous immunoglobulin, and modified cobratoxin (one study each).

In a single-arm study of five children with cerebral adrenoleukodystrophy and substantial CNS involvement, cyclophosphamide and steroids had no effect on time to vegetative state (mean 1·35 years) or death (mean 2·4 years) compared with natural history data. In a randomised trial examining the effect of 12 months of high-dose intravenous immunoglobulin therapy in child and adolescent patients with adrenoleukodystrophy, both patients receiving standard care alone (n=6) and those also receiving intravenous immunoglobulin (n=6) had deterioration in EDSS scores. In a non-controlled pilot study of lovastatin in 12 patients with various adrenoleukodystrophy types, which primarily examined the effect of treatment on biochemical markers, no significant change in neurological or psychological function was established after 3–12 months of therapy. However, the authors cautioned that the variable nature of adrenoleukodystrophy clinical progression precludes conclusions about clinical efficacy of lovastatin in this small sample. Finally, in a randomised, double-blind, crossover trial in eight adults with adrenomyeloneuropathy, 3 months of treatment with modified cobratoxin did not improve ambulation, gait, quality of life, or EDSS score. However, this trial was not designed to detect long-term neuroprotective effects.

Added value of this study

Our literature review shows the absence of effective medical treatments in patients with adrenoleukodystrophy. To the best of our knowledge, ADVANCE is the first international, large, placebo-controlled, randomised multi-centre trial in patients with adrenoleukodystrophy aiming to address this urgent need.

Implications of all the available evidence

ADVANCE has examined a member of a novel drug class, peroxisome proliferator-activated receptor gamma agonists, for treatment of adults with adrenomyeloneuropathy. Although the primary endpoint was not met, this study provides some evidence that leriglitazone might reduce the occurrence of cerebral adrenoleukodystrophy. On the basis of body sway results, leriglitazone might also attenuate the progression of clinical symptoms resulting from chronic myelopathy. Future research should focus on further establishing whether leriglitazone might be neuroprotective in patients with adrenomyeloneuropathy and exploring its potential in other populations with adrenoleukodystrophy, including those with progressive cerebral adrenoleukodystrophy.

progressive spastic paraparesis, sensory ataxia, bowel and bladder dysfunction, and sometimes faecal incontinence.[1] Reduced postural stability can be detected as abnormal body sway amplitudes during quiet standing.[2–5] Gait is affected by spasticity, weakness, and impaired balance, resulting in increased risk of falls, limited walking distance, or loss of ambulation.[3,4] In addition to chronic neurodegeneration, acute inflammatory brain demyelination can occur (cerebral adrenoleukodystrophy), causing severe cognitive and motor deficits. Cerebral adrenoleukodystrophy can occur in both children and adults, including adults with adrenomyeloneuropathy:[1] an estimated 63% of men with adrenomyeloneuropathy will develop cerebral adrenoleukodystrophy in their lifetime.[2] Progression of cerebral adrenoleukodystrophy is associated with cognitive decline and rapid progression of disability, and it is a life-threatening event with a mean time from diagnosis of cerebral adrenoleukodystrophy to death of 3·1 years.[1,6] However, spontaneous halting of cerebral inflammation can occur in a minority of patients.[1,7]

Although a few drug therapies have been tested in small numbers of patients with adrenoleukodystrophy,[8–11] no effective disease-modifying medication is available. The only treatment available for cerebral adrenoleukodystrophy is haematopoietic stem cell transplantation. However, transplantation-based procedures are suitable for only a small proportion of patients, owing to the need to identify suitable donors and the mortality and morbidity associated with myeloablative procedures, particularly in adults, owing to their underlying myelopathy.[12–14]

Leriglitazone hydrochloride is a novel, neuroprotective brain-penetrant peroxisome proliferator-activated receptor gamma (PPARγ) full agonist, which acts simultaneously on several biological pathways activating or repressing genes relevant for neuroinflammatory and neurodegenerative diseases, including adrenoleukodystrophy. The main actions of leriglitazone include regulation of key genes that counteract oxidative stress; restoration of bioenergetics and adenosine triphosphate concentrations; preservation of myelination; stimulation of mitochondrial biogenesis through activation of the PPARγ/PPARγ-coactivator 1α pathway; and repression of the nuclear factor kappa B pathway, reducing inflammation and protecting the blood–brain barrier from the disruption that could initiate the progression of cerebral adrenoleukodystrophy.[15,16] In a phase 1 trial in healthy male volunteers, leriglitazone decreased plasma proinflammatory biomarker concentrations and increased adiponectin

concentrations, a biomarker for PPARγ engagement, in plasma and CSF.[17] Here, we report safety and efficacy results of leriglitazone treatment in men with adrenomyeloneuropathy.

Methods

Study design

ADVANCE was a 96-week, phase 2–3, randomised, double-blind, placebo-controlled study that took place at ten specialist referral centres experienced in adrenoleukodystrophy in France, Germany, Hungary, Italy, the Netherlands, Spain, the UK, and the USA. On completion of the 96-week study period, patients had the option to enter the open-label extension study.

The study was done in accordance with the Declaration of Helsinki and all participating sites obtained independent ethics committee or institutional review board approval (appendix p 2). There were five amendments to the protocol during the masking phase (appendix p 2). The complete study protocol is provided in the supplementary materials (appendix).

Participants

Men aged 18–65 years, with genetically confirmed adrenoleukodystrophy and clinical evidence of spinal cord involvement (adrenomyeloneuropathy), and an Expanded Disability Status Scale (EDSS) score of 2–6 were eligible to participate if they were able to walk for 6 min, with or without rest, using usual walking aids; were able to stand on a force plate with eyes closed and feet apart for at least 20 s; and had a normal brain MRI or type 1 to type 5 pattern MRI abnormality without gadolinium enhancement (ie, without evidence of progressive cerebral adrenoleukodystrophy).[18] Exclusion criteria were type 1 or 2 diabetes, clinically significant echocardiogram abnormalities, and clinically significant anaemia (haemoglobin <12·5 g/dL). Participants were recruited by treating physicians, through website advertising, and via patient organisations. All patients provided written informed consent at enrolment.

Randomisation and masking

Patients were enrolled into the study by principal investigators. Randomisation was done via secure, centralised, independent interactive response technology managed by Suvoda (Conshohocken, PA, USA). Once the patient had provided consent, investigational staff called the interactive response technology, and the system assigned identification numbers to randomly allocate patients to leriglitazone or placebo in a 2:1 ratio without stratification. Calls were placed to the interactive response technology at all subsequent in-clinic visits and a kit number was assigned to the patient. Suvoda had no further involvement in the conduct of the trial. To minimise unmasking, leriglitazone and the placebo suspensions were indistinguishable in appearance, taste, and packaging. An unmasked central laboratory pharmacokinetics expert established dose adjustments, where needed, to achieve target exposure. Dose adjustments of a similar range, recommended by the pharmacokinetics expert, were made in the placebo group to preserve masking.

Procedures

Study medication was administered orally, once daily in the morning for 96 weeks. Patients randomly assigned to leriglitazone started at a dose of 150 mg (10 mL); the placebo group received the same amount of matched placebo suspension. Until week 12, dosing was adjusted on an individual patient basis to achieve target plasma leriglitazone concentrations of 200 µg·h/mL (SD 20%). Dose adjustments were permitted after week 12 for safety or tolerability reasons, provided that expected exposure remained in the minimal efficacious range on the basis of preclinical data.[16] Patients attended the clinic at baseline and at weeks 4, 12, and 24, with additional telephone calls at weeks 3 and 10. Thereafter, patients alternated between a telephone call and clinic visit at 12-week intervals until week 96. Blood sampling for leriglitazone dosing adjustment was done at baseline and at weeks 4, 12, 24, 48, 72, and 96. Clinical rating scales of disease severity, dynamometry assessment, and biomarker blood sampling were done at baseline and weeks 24, 48, 72, and 96. Sampling of biomarkers in CSF was permitted as an optional assessment at baseline and week 96. MRI assessment of cerebral lesions was done at screening or baseline and at weeks 48 and 96. Adverse events were recorded at all in-clinic visits and telephone calls.

Participants could continue concomitant use of select therapies (those that were not expected to interfere with leriglitazone) for management of adrenoleukodystrophy symptoms, including Lorenzo's oil, and participation in physiotherapy or regular physical activity. The dose or regimen of these therapies and activities, as recorded in patient diaries, must have been stable for at least 6 months before screening and remained constant during the double-blind phase of the study.

Outcomes

The primary efficacy endpoint was the change from baseline to week 96 in total Six-Minute Walk Test (6MWT) distance, which in a previous trial in patients with adrenomyeloneuropathy showed a 60-m decline over 2 years.[19] Patients walked to the 30-m point on a flat walkway and returned, repeating this activity for the 6-min duration. Testing was done at each site by study investigators trained by an external vendor (Signant Health, Blue Bell, PA, USA) to maximise assessment consistency. A preplanned sensitivity analysis of 6MWT change from baseline adjusting for changes in bodyweight (weight-adjusted 6MWT) was done by means of the equation: 7·57×height (cm) – 5·02×age (years) – 1·76×weight (kg) – 309.[20]

The secondary endpoint of body sway amplitude (mm) was recorded with a portable plantar pressure system (Kistler Instruments, Hook, UK). Sway parameters (total average amplitude, and anteroposterior and mediolateral amplitudes) were measured in four different stances: eyes closed and feet apart (EC-FA), eyes closed and feet together (EC-FT), eyes open and feet apart (EO-FA), and eyes open and feet together (EO-FT). In the feet-apart stances, feet were placed approximately 25–35 cm apart.

Secondary endpoints also included scores from the Severity Score System for Progressive Myelopathy (SSPROM) ranging from 0 (total disability) to 100 (normal function),[21] the EDSS ranging from 0 to 10 (with higher scores representing greater degrees of disability) and its ambulation domain (EDSS ambulation),[22] the Clinician Global Impression–Severity (CGI-S), and the Clinician and Patient Global Impression–Improvement (CGI-I and PGI-I) scales. We did dynamometry using a handheld device (Lafayette Hand-Held Dynamometer Model 01165, Lafayette Instrument, Lafayette, IN, USA) to measure hip flexion strength bilaterally. We assessed quality of life with the following measures: the European Quality of Life 5-Dimensional 5-Level questionnaire (EQ-5D-5L), the Short Form Qualiveen (SF-Qualiveen)[23] measure of urinary continence, the International Index of Erectile Function (IIEF), and the 12-item Multiple Sclerosis Walking Scale (MSWS-12).

Progression of cerebral lesions on MRI was monitored as a secondary endpoint, assessed by means of both incidence of lesion progression and Loes scores.[24] Evaluations were done by two central readers masked to treatment assignment trained to identify cerebral adrenoleukodystrophy lesions. Discrepant ratings were adjudicated by a third reader.

We defined the incidence of adrenoleukodystrophy-related cerebral lesion progression as incidence of inflammatory lesions, growth of existing non-inflammatory lesions since screening or baseline, or occurrence of new non-inflammatory lesions after screening or baseline. The incidence of cerebral lesion progression was categorised as a binary variable (absent or present) at each study visit. All secondary endpoints were analysed as the change from baseline to week 96. Independently from the masked central reading, sites were instructed to report cases of clinically progressive cerebral adrenoleukodystrophy as serious adverse events, per their own assessment (combining radiological and clinical criteria).

We recorded concentrations of biomarkers indicative of disease progression and target engagement as exploratory endpoints throughout the study. Biomarkers assessed were adiponectin, neurofilament light chain, matrix metalloproteinase-9 (MMP-9), fatty acid binding protein 4 (FABP4), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-18 (IL-18), interleukin-1 receptor antagonist (IL-1Ra), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein-1 beta (MIP-1β).

The statistical analysis of the between-group difference in incidence of cerebral lesion progression and investigators' determination of progression to cerebral adrenoleukodystrophy was defined post hoc after the database lock. Changes in the use of walking aids were recorded prospectively and defined as a secondary post-hoc comparison. We monitored treatment-emergent adverse events (TEAEs) and serious TEAEs throughout the study.

Statistical analysis

The estimated minimum sample size was 60 for the leriglitazone group and 30 for the placebo group. The initial planned recruitment was 105 to account for an assumed 15% dropout rate. We based the sample size estimation on a 2:1 two-group *t* test (5% two-sided significance) at 80% power to detect a 45-m targeted effect size between treatment groups in the primary efficacy outcome, assuming a SD of 70 m. A 30-m change has been considered clinically relevant in a neuromuscular indication in Duchenne muscular dystrophy[25] and other respiratory, cardiovascular, and musculoskeletal disorders.

If a significant difference was observed in the primary endpoint in the full-analysis set, secondary efficacy endpoints were to be evaluated in the following predefined hierarchy: EC-FA total amplitude, PGI-I, SSPROM, SF-Qualiveen. In agreement with the US Food and Drug Administration, EC-FA total was selected as the key secondary endpoint because body sway is the most objective measure of myelopathy. The remaining hierarchical endpoints were included at the request of the US Food and Drug Administration to provide a balanced account of multiple aspects of disease symptomology; their position in the hierarchy does not reflect order of clinical importance.

The full-analysis and safety-analysis sets included all randomly assigned patients who received at least one dose of study medication. The per-protocol set included all patients in the full-analysis set without a major protocol deviation; the decision regarding which protocol deviations were relevant was made by the contract research organisation biostatistics group, in collaboration with the study sponsor, at the masked data review meeting on the basis of potential effect on the study outcomes. We analysed the primary and secondary continuous endpoints selected for hierarchical testing in the full-analysis set using a mixed model for repeated measures with restricted maximum likelihood and baseline values as covariates. Analyses of the remaining secondary continuous endpoints were done in the full-analysis set by means of an ANCOVA model with baseline values as covariates. Analyses of the categorical endpoints PGI-I, CGI-I, and CGI-S were done by means of the Wilcoxon rank sum test. Least-squares means, 95% CIs, and p values were calculated for the difference between the leriglitazone and placebo groups. Significance testing was done at the 5%, two-sided level. Binary outcomes (between-group

differences in incidence of lesion progression and progression to cerebral adrenoleukodystrophy) were analysed with a two-sided Fisher's exact test with Newcombe–Wilson score method to determine CIs and the specific statistical test was defined after database lock. Safety results were summarised for each treatment group and overall by system organ class and preferred term on basis of the Medical Dictionary for Regulatory Activities version 23.0. We did all analyses in SAS (version 9.3); see appendix p 2 for further details of the mixed model for repeated measures and database handling procedures. An independent data safety monitoring board reviewed safety data at regular intervals (18 times) throughout the study (see appendix p 2 for board membership).

Comparisons between treatment groups in absolute change and change from baseline biomarker concentrations were done by means of the geometric mean ratio with 90% CIs for analysis of variance. We did post-hoc analyses to establish the effect of disease duration on ambulation-related outcomes (6MWT and EDSS ambulation). Patients were stratified as up to 10 years since onset of myelopathy (early-stage disease) or greater than 10 years since onset (late-stage disease). We did sensitivity analyses of this effect using disease severity defined by the EDSS. A threshold of EDSS score greater than 5·5 for severe disease was selected on the basis of clinical relevance in multiple sclerosis.[26] The trial is registered with ClinicalTrials.gov, NCT03231878.

Role of the funding source

The sponsor was involved in study design, data collection, data analysis, data interpretation, and drafting and review of the manuscript.

Results

Between Dec 8, 2017, and Oct 16, 2018, of 136 patients screened, 116 were randomly assigned and included in the analysis sets (figure and appendix p 3). 62 (81%) of 77 patients in the leriglitazone group and 34 (87%) of 39 patients in the placebo group, completed treatment. Five patients had a study visit delay owing to the COVID-19 pandemic. The open-label extension of the study, which 88 patients have entered, is ongoing.

Baseline demographic characteristics were similar for patients in the leriglitazone and placebo groups, except for median years since onset of myelopathy, which was slightly longer in the placebo group (table 1). The mean adjusted dose of leriglitazone based on pharmacokinetic measurements was 11·8 (SD 2·9) mL. Concomitant use of Lorenzo's oil did not differ substantially between groups (leriglitazone eight [10%] of 77; placebo six [15%] of 39).

The total distance walked at baseline in the 6MWT was similar between treatment groups (table 1) and mean total distance walked decreased from baseline to week 96 in both groups (table 2). The least-squares mean difference between treatment groups was –1·2 m (95% CI –22·6 to 20·2; p=0·91) in the primary analysis and 6·5 m (–15·2 to 28·2; p=0·56) in the weight-adjusted sensitivity analysis (table 2). Because the primary endpoint did not meet significance, the preplanned hierarchical order of analyses of secondary endpoints did not apply and thus subsequent results are presented descriptively. Endpoints are presented in order of clinical relevance, as prespecified in the study protocol.

The least-squares mean difference between treatment groups was –1·0 for EC-FA total sway, –0·3 mm for EC-FA mediolateral sway and –3·8 mm for EC-FA anteroposterior sway, and was –2·4 for EC-FT total sway, –2·5 mm for EC-FT anteroposterior sway, and –5·6 mm for EC-FT mediolateral sway (appendix p 4). Eyes-open stances showed little change in both treatment groups (appendix p 4).

On the SSPROM and EDSS scores, there was some evidence to suggest that patients receiving placebo had a potentially greater increase in disability from baseline to week 96 than patients receiving leriglitazone (ie, decreased SSPROM score and increased EDSS score,

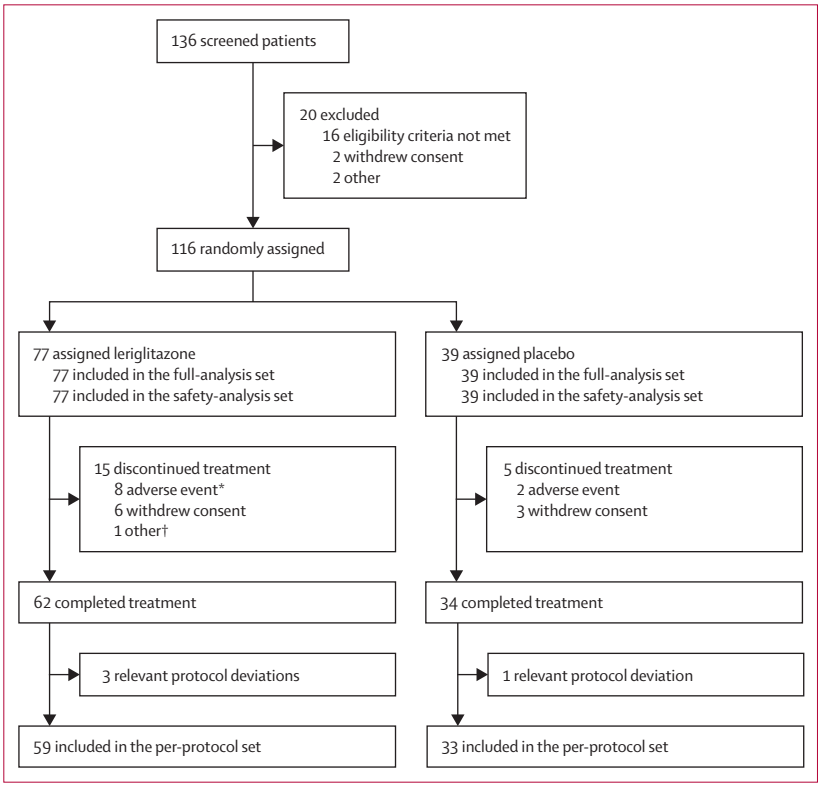

***Figure*: Trial profile**

The full-analysis and safety-analysis sets included all randomly assigned patients who received at least one dose of study medication. The per-protocol set included all patients in the full-analysis set who did not have a relevant major protocol deviation. The decision regarding which protocol deviations were relevant was made by the contract research organisation biostatistics group, in collaboration with the study sponsor at the masked data review meeting on the basis of potential effect on the study outcomes. *One patient had an adverse event leading to permanent withdrawal of study medication but completed the double-blind study. †No further information was provided.

	Leriglitazone group (n=77)	Placebo group (n=39)
Age, years	42 (34–50)	48 (36–53)
Race		
White	62 (81%)	30 (77%)
Other	1 (1%)	1 (3%)
Not collected	14 (18%)	8 (21%)
Ethnicity		
Not Hispanic or Latino	59 (77%)	29 (74%)
Hispanic or Latino	4 (5%)	2 (5%)
Not collected	14 (18%)	8 (21%)
Weight, kg	77·6 (12·7)	80·1 (13·5)
Body-mass index, kg/m²	23·8 (21·8–26·5)	24·1 (22·1–27·0)
Six-Minute Walk Test distance, m	375 (254–480)	369 (268–402)
Total body sway eyes closed and feet apart, mm	10·2 (8·0–12·9)	11·9 (9·4–14·5)
Severity Score System for Progressive Myelopathy	79·8 (6·6)	77·7 (6·7)
Expanded Disability Status Scale: ambulation	1·0 (1·0–6·0)	1·5 (1·0–6·0)
Expanded Disability Status Scale: step	4·0 (3·5–6·0)	4·0 (3·5–6·0)
Years of myelopathy		
n*	66	34
Years	10 (5–14)	12 (8–18)
>10 years since myelopathy onset, n	31 (47%)	19 (56%)
Loes score†		
n	76	38
Score >0, n	38 (50%)	22 (58%)

Data are median (IQR), n (%), or mean (SD). Data are shown for the full analysis set and safety analysis set, which both included all randomly assigned patients who received at least one dose of study medication. Selected secondary endpoints are shown to provide data on patients' level of disability and disease state at baseline. *Unknown for 16 patients. †Not done for two patients.

Table 1: **Demographic characteristics and primary and secondary endpoint assessments at baseline**

although the 95% CI for these differences between groups include 0). Change in EDSS ambulation from baseline was similar between the groups. There was no difference between groups in change from baseline to week 96 on CGI-S. Improvement at week 96 in the CGI-I was reported only for the leriglitazone group. The proportion of patients reporting an improvement in the PGI-I at week 96 was numerically higher in the leriglitazone group than in the placebo group. There were no meaningful changes in dynamometry or on the IIEF or MSWS-12 scales or in either group from baseline to week 96. On the EQ-5D-5L, there was some evidence to suggest a potentially greater decline with placebo than with leriglitazone. For the SF-Qualiveen, scores increased similarly for both groups from baseline to week 96 (table 2).

Between baseline and week 96, patients receiving placebo had a greater change in Loes score than patients receiving leriglitazone, and in a post-hoc analysis radiological progression of cerebral lesions occurred in a smaller proportion of patients receiving leriglitazone than of those receiving placebo (table 2).

With the exploratory plasma biomarkers, the mean change from baseline in adiponectin concentrations was higher at all timepoints in the leriglitazone group (appendix p 5). At week 96, the placebo group had higher mean plasma concentrations of NfL, MMP-9, and the inflammatory biomarkers IL-18, IL-1Ra, and MIP-1β, whereas concentrations of FABP4 were higher in the leriglitazone group. Mean plasma concentrations of IL-8 and MCP-1 were similar in the leriglitazone and placebo groups at week 96 (appendix pp 6–8). Plasma concentrations of IL-6 were below the lower limit of quantification (2·6 pg/mL) so these data are not reported. Only four patients consented to CSF sampling; CSF biomarkers are not presented owing to the small sample size.

Six patients, all in the placebo group, were independently reported by investigators at study sites to have a TEAE of clinically progressive cerebral adrenoleukodystrophy (table 2). Of these patients, at baseline three had a Loes score of 0 and three had a score greater than 0 (appendix p 9). Three of these patients received leriglitazone for at least 12 months in the open-label extension, and in all of them, lesion stabilisation was observed on treatment with leriglitazone (appendix p 9).

Post-hoc exclusion of patients with clinically progressive cerebral adrenoleukodystrophy did not have a relevant effect on myelopathy-specific outcomes compared with analysis of the full-analysis set (appendix p 10).

In addition to the planned analyses, we did post-hoc subgroup analyses examining the effect of disease duration. We found a potential between-group difference favouring leriglitazone in patients with early-stage disease on the secondary endpoint of EDSS ambulation, with similar results in the disease severity-based stratification (appendix p 11). During the study, one (1%) of 77 patients receiving leriglitazone and four (10%) of 39 patients receiving placebo required a switch to a higher category of walking aid (post-hoc analysis of proportion difference –0·09; 95% CI –0·22 to –0·01).

In the safety set, 112 (97%) of 116 patients had at least one treatment emergent adverse event. The proportion of patients with treatment emergent adverse events was slightly higher with leriglitazone (76 [99%] of 77 patients) than with the placebo (36 [92%] of 39 patients; table 3). Treatment emergent adverse events that were judged to be treatment related occurred in more patients in the leriglitazone group (71 [92%] of 77 patients) than in the placebo group (14 [36%] of 39 patients). All treatment-related treatment emergent adverse events were of mild or moderate severity. There were no deaths during the study.

The most frequently reported treatment emergent adverse events that were related to treatment (occurring in >10% of patients) in the leriglitazone group were

	Leriglitazone group (n=77)	Placebo group (n=39)	Least-squares mean difference (SE) or proportion difference	95% CI
Primary endpoint				
Six-Minute Walk Test, m	−27·7 (41·4)	−30·3 (60·5)	−1·2 (10·9)	−22·6 to 20·2
Weight-adjusted Six-Minute Walk Test, m*	−7·5 (44·6)	−18·4 (58·7)	6·5 (11·1)	−15·2 to 28·2
Secondary endpoints				
Body sway, mm				
Eyes closed, feet apart (1)	0·4 (3·7)	1·1 (4·4)	−1·0 (0·9)	−2·8 to 0·7
Eyes closed, feet together	−1·3 (4·6)	0·1 (5·4)	−2·4 (1·1)	−4·6 to −0·2
Eyes open, feet apart	0·3 (2·0)	0·5 (2·2)	−0·5 (0·5)	−1·4 to 0·5
Eyes open, feet together	0·2 (3·1)	0·2 (3·1)	0·0 (0·6)	−1·2 to 1·3
Overall disability, points				
Severity Score for Progressive Myelopathy (3)	−0·9 (5·0)	−3·3 (7·6)	2·3 (1·3)	−0·3 to 4·9
Expanded Disability Status Scale: step	0·27 (0·78)	0·50 (1·05)	−0·34 (0·19)	−0·72 to 0·05
Ambulation, points				
Expanded Disability Status Scale: ambulation	0·5 (1·45)	0·8 (2·40)	−0·5 (0·39)	−1·3 to 0·3
Global impressions, n (%)				
Clinical Global Impression—Severity worsening	20 (26%)	10 (26%)	0	−0·19 to 0·19
Clinical Global Impression—Improvement†	5 (7%)	0	0·06	−0·13 to 0·25
Patient Global Impression—Improvement (2)†	13 (17%)	2 (5%)	0·12	−0·08 to 0·30
Muscle strength				
Dynamometry, kg	2·3 (12·36)	2·6 (11·29)	0·6 (2·62)	−4·6 to 5·8
Quality of life				
European Quality of Life 5-Dimensional 5-Level questionnaire, index value	−0·01 (0·11)	−0·05 (0·16)	0·04 (0·03)	−0·01 to 0·09
Qualiveen short form, points (4)	0·14 (0·73)	0·19 (0·72)	−0·12 (0·14)	−0·40 to 0·16
International Index of Erectile Dysfunction, points	−2·6 (18·01)	0·8 (15·14)	−1·9 (3·52)	−8·9 to 5·1
Multiple Sclerosis Walking Scale, 12-item, points	4·6 (15·25)	4·9 (15·27)	−2·3 (3·29)	−8·9 to 4·2
Cerebral progression				
Loes score change‡	0·09 (0·37)	0·74 (1·90)	−0·58 (0·25)	−1·09 to −0·08
Post-hoc analyses				
Cerebral lesion progression on MRI, n§	3 (4%)	8 (21%)	−0·17	−0·32 to −0·05
Cerebral adrenoleukodystrophy cases reported by sites, n¶	0	6 (15%)	−0·15	−0·30 to −0·06

Data are mean (SD) unless otherwise stated. Data are for the full analysis set (N=116). Numbers in parentheses in the first column represent the position of secondary endpoints in the pre-specified statistical hierarchy; because the primary endpoint was not met, the hierarchical order of analyses of secondary endpoints did not apply and outcomes are presented according to clinical relevance as specified in the study protocol. On the Severity Score for Progressive Myelopathy, lower scores indicate greater levels of disability; on the Expanded Disability Status scale, greater scores indicate greater levels of disability. *Pre-planned sensitivity analysis of Six-Minute Walk Test adjusting for changes in body weight. †Analysed with p values based on Wilcoxon's rank sum test. ‡Analysed with ANCOVA (pre-specified secondary comparison). §Analysed with a two-sided Fisher's exact test (prespecified endpoint with statistical comparison defined post hoc). ¶Analysed with a two-sided Fisher's exact test (post-hoc comparison).

Table 2: **Change from baseline to week 96 in primary and secondary study endpoints and incidence of cerebral adrenoleukodystrophy**

weight gain (54 [70%] of 77), peripheral oedema (49 [64%] of 77), increased lacrimation (14 [18%] of 77), oedema (11 [14%] of 77), and eyelid oedema (seven [9%] of 77). The most frequently reported treatment emergent adverse events that were related to treatment in the placebo group were peripheral weight gain and oedema (nine [23%] of 39 and seven [18%] of 39). Mean (SD) change in bodyweight from baseline to week 96 was 5·8 (4·6) kg with leriglitazone and 1·3 (4·26) kg with placebo. No cardiac treatment emergent adverse events were reported in the placebo group and four were reported (with two events occurring in the same patient) in the leriglitazone group (three [4%] of 77 patients). These events were isolated palpitations or extrasystoles, with their severity assessed as mild (3/4) or moderate (1/4) and reversible without sequelae.

Serious treatment emergent adverse events were less frequent with leriglitazone (14 [18%] of 77 patients) than with placebo (ten [26%] of 39 patients). The most common serious treatment emergent adverse event was clinically progressive cerebral adrenoleukodystrophy, which occurred in six (15%) of 39 patients receiving placebo and no patients receiving leriglitazone. Only one serious treatment emergent adverse event in the leriglitazone group was considered related to treatment (an increase in hepatic enzymes in a patient subsequently

	Leriglitazone group (n=77)		Placebo group (n=39)	
	Patients, n	Events, n	Patients, n	Events, n
Adverse events overall				
Patients with ≥1 TEAE	76 (99%)	755	36 (92%)	262
Patients with ≥1 treatment-related TEAE	71 (92%)	270	14 (36%)	20
Patients with ≥1 TEAE leading to permanent withdrawal of study medication	9 (12%)	10	2 (5%)	2
Patients with ≥1 TEAE leading to temporary withdrawal of study medication	8 (10%)	11	1 (3%)	3
Patients with ≥1 TEAE leading to study medication dose adjustment	34 (44%)	74	2 (5%)	2
Most frequent adverse events of special interest (>10% of patients in any group)				
Weight increased	54 (70%)	63	9 (23%)	9
Oedema, peripheral	49 (64%)	81	7 (18%)	10
Lacrimation increased	14 (18%)	16	0	0
Oedema	11 (14%)	12	0	0
Eyelid oedema	7 (9%)	7	0	0
Serious adverse events				
Patients with ≥1 serious TEAE	14 (18%)	18	10 (26%)	15
Patients with ≥1 serious treatment-related TEAE	1 (1%)	1	0	0
Deaths	0	0	0	0
Serious TEAEs reported in ≥1 patients in either treatment group				
Clinically progressive cerebral adrenoleukodystrophy	0	0	6 (15%)	6
Acute adrenocortical insufficiency	1 (1%)	1	1 (3%)	2
Urinary tract infection	1 (1%)	1	1 (3%)	1
Fibula fracture	1 (1%)	1	1 (3%)	1
Ankle fracture	2 (3%)	2	0	0

Data are n (%) or number of events. TEAE=treatment-emergent adverse event.

Table 3: **Summary of adverse events (safety set)**

diagnosed with Gilbert's syndrome). Treatment emergent adverse events leading to permanent or temporary medication withdrawal or dose adjustment occurred in a greater proportion of patients in the leriglitazone group (nine [12%] of 77, eight [10%] of 77, and 34 [44%] of 77, respectively) than in the placebo group (two [5%] of 39, one [3%] of 39, and two [5%] of 39, respectively). The most common treatment emergent adverse events leading to dose adjustment were weight gain and peripheral oedema. No treatment emergent adverse events leading to dose adjustment were serious. Of the 15 patients receiving leriglitazone who withdrew from the study, 12 (80%) had late-stage disease, one (7%) had early-stage disease, and disease duration was unknown for two patients (13%). Of the five patients receiving placebo who withdrew from the study, one had late-stage disease, three had early-stage disease, and disease duration was unknown for one patient.

Discussion

In this phase 2–3, double-blind, placebo-controlled study of leriglitazone in patients with adrenomyeloneuropathy, there was no difference between treatment groups in the primary endpoint of change from baseline in distance walked on the 6MWT after 96 weeks of treatment. However, there were numerical differences between treatment groups in some secondary and post-hoc endpoints related to myelopathy and cerebral lesion progression. These components of adrenoleukodystrophy pathology are expected to be clinically relevant and were highlighted in a patient listening session as severely affecting day-to-day functioning.[27] The clinical relevance of the study results, determined on the basis of literature review, is illustrated in the appendix (p 12).

Although this study was not primarily designed to assess cerebral adrenoleukodystrophy progression, leriglitazone reduced progression in Loes score and, in a post-hoc analysis, the incidence of radiologically assessed cerebral lesion progression. Only patients in the placebo group developed clinically progressive cerebral adrenoleukodystrophy, on the basis of a comprehensive assessment by study investigators. Cerebral lesion progression occurred in patients with differing ages and degrees of disease severity at baseline. Three out of six patients who developed cerebral adrenoleukodystrophy had a Loes score of 0 at baseline; hence it is unlikely that baseline characteristics promoted the more frequent progression into cerebral adrenoleukodystrophy in the placebo group. With regard to change in Loes score, any difference in baseline values would have been accounted for in the ANCOVA model, which included baseline Loes values as a covariate. Brain MRI parameters and their evolution throughout the pathological cascade of cerebral adrenoleukodystrophy are considered predictors of rapidly progressive disease and death.[6,7] As such, if leriglitazone has an effect on cerebral lesions, it has the potential to protect against a life-threatening event in patients with adrenomyeloneuropathy.

The slowing of cerebral lesion progression is supported by exploratory biomarker data. Plasma concentrations of biomarkers indicating neuronal damage, neuroinflammation, and blood–brain barrier disruption were higher at week 96 in patients receiving placebo than those receiving leriglitazone, predominantly driven by those patients in the placebo group developing cerebral adrenoleukodystrophy. PPARγ target engagement of leriglitazone was indicated by increased adiponectin and FABP4 concentrations.[28]

Measures of ambulation and postural sway have been established as reliable indicators of myelopathy progression in patients with adrenomyeloneuropathy.[19] Patients with adrenomyeloneuropathy typically show body sway amplitudes of 5–10 mm greater than healthy controls.[4] Improvements of just 1–2 mm in body sway reflect a clinically meaningful change (appendix p 12). There were clinically relevant between-group differences of up to 5·6 mm in body sway parameters for all but EC-FA mediolateral sway, usually driven by reduced body sway from baseline to week 96 in patients receiving leriglitazone. Reduced impairment in eyes-closed conditions might

especially benefit patients because postural deficits in patients with adrenomyeloneuropathy can be particularly pronounced when visual cues are removed.[3] Consistent with treatment effects of preserved body sway, post-hoc analysis of walking aid use supported preserved ambulation; a smaller proportion of patients receiving leriglitazone increased their category of walking aid than patients receiving placebo. Consistent numerical effects were seen on overall neurological symptoms as determined by the SSPROM and EDSS, with between-group differences that were equivalent to approximately 2 years of adrenomyeloneuropathy symptom progression,[29] in addition to improvements in CGI-I and EQ-5D-5L scores.

Natural history data in patients with adrenomyeloneuropathy that were unavailable when this study was designed indicate that duration of myelopathy is a predictor of decline in various ambulation-related outcomes, including 6MWT (unpublished Marc Engelen). In post-hoc subgroup analyses, patients with early-stage disease (≤10 years of myelopathy symptoms) receiving leriglitazone had numerically less decline in 6MWT and less worsening in EDSS ambulation score at week 96 compared with placebo. Although the 2-year follow up in ADVANCE might be sufficient to detect a treatment effect on ambulation in patients in the early phase of the disease, a longer treatment duration or larger sample size might be required for patients with late-stage adrenomyeloneuropathy.

A favourable safety profile was observed during the study. Treatment emergent adverse events related to treatment were predominantly weight gain, peripheral oedema, and increased lacrimation. These events were generally mild to moderate and manageable with diuretics or dose reductions without the need for treatment discontinuation. The adverse event profile of leriglitazone in the adrenomyeloneuropathy population reflects the known class effects of PPARγ agonists and is consistent with the mechanism of action.[30] Reassuringly, despite the high rates of oedema and weight gain, no deterioration in renal or cardiac function was observed during 96 weeks of follow-up.

Some limitations of the study should be noted. Because the primary endpoint did not meet significance, hierarchical testing of secondary endpoints was not done so analyses of secondary endpoints cannot be considered confirmatory. Unmasking cannot be fully discounted owing to the class effects of leriglitazone on weight gain and oedema. These events occurred at greater rates with leriglitazone than with placebo. However, body sway, centrally read MRI, and biomarker concentration results were objective measures that would be minimally affected by unmasking. 6MWT is known to be influenced by different variables, especially weight gain. Although weight-adjusted analyses were done to account for this, the formula used to correct the distance walked is derived from healthy participants and patients with adrenomyeloneuropathy might be more negatively affected by weight gain.

Leriglitazone was generally well tolerated, and rates of adverse events were in line with the expected safety profile for this drug class. Although the primary endpoint was not met, leriglitazone showed evidence of beneficial effects on several study parameters. Participants in the leriglitazone group had lower incidence of cerebral lesion progression and, by implication from nominal results for body sway, possibly myelopathy progression. Post-hoc analyses suggest that leriglitazone might provide a beneficial effect on ambulation in patients with early-stage disease. The extension phase of the study might provide further evidence on the potential protective effects of leriglitazone in reducing incidence of progressive cerebral adrenoleukodystrophy and possible attenuation of myelopathy symptoms, and further studies could investigate whether leriglitazone might reduce disease progression in patients with progressive cerebral adrenoleukodystrophy. Cerebral adrenoleukodystrophy is life-threatening and adrenomyeloneuropathy is highly debilitating, and there is an unmet need for effective therapies. We believe that our findings show a favourable benefit–risk profile for leriglitazone, which might offer a promising therapy for patients with adrenomyeloneuropathy and cerebral adrenoleukodystrophy.

Contributors

All authors contributed to the drafting of this manuscript and approved the final submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AV, FM, GP, and WK had full access to and verified the data reported.

Declaration of interests

AF received grants or contracts from Minoryx Therapeutics, Autobahn Therapeutics, Poxel, SwanBio Therapeutics, and Affinia Therapeutics; has royalties or licences with Ashvattha Therapeutics; is coinventor of patent WO2017075580A1; and has been a member of a data safety monitoring board for Bluebird Bio. ES has received honoraria from Orphazyme and received payments to his institution from Minoryx Therapeutics for the conduct of this study. FE is the principal investigator of clinical trials for Bluebird Bio and Minoryx Therapeutics; has received consulting fees from Autobahn, Poxel, SwanBio Therapeutics, and Taysha Gene Therapies; has received payment from UpToDate; and has patents and stock or stock options with SwanBio Therapeutics. FM has received grants or contracts to her institution from Minoryx Therapeutics; and consulting fees from Minoryx Therapeutics and Poxel. ME has received grants or contracts from Autobahn Therapeutics, Bluebird Bio, the European Leukodystrophy Association, the Netherlands Organization for Scientific Research, Minoryx Therapeutics, and SwanBio Therapeutics; payments to his institution from Minoryx Therapeutics; consulting fees from Autobahn Therapeutics and Poxel; meeting honoraria and travel support from Minoryx Therapeutics; and has been an unpaid advisor for the United Leukodystrophy Foundation. WK has received grants or contracts from Bluebird Bio, Minoryx Therapeutics, and SwanBio Therapeutics; consulting fees from Alexion, Bristol Myers Squibb, Minoryx Therapeutics, Poxel, Pharmaelle, Roche, and Vigil; honoraria or travel support from Bayer, Biogen, and Minoryx Therapeutics; and has been an unpaid advisor for the European Leukodystrophy Association, Myelin Project Germany, and the United Leukodystrophy Foundation. ET is an employee of, has patents with, and has stock options in Minoryx Therapeutics and has received the Torres Quevedo grant issued to Minoryx Therapeutics. AV is an employee of and has stock options in Minoryx Therapeutics. AM, MP, SP, GP, PP, LR-P, MR, and AV are employees of, have patents with, and have stock options in Minoryx Therapeutics. MM is co-founder of and has patents with and

stock options in Minoryx Therapeutics. UM is a former employee of and has stock options in Minoryx Therapeutics. IM-U, JG, MJM, JS, and RL declare no competing interests.

Data sharing

The study sponsor, Minoryx Therapeutics, is committed to sharing access to patient-level data and supporting clinical documents with qualified external researchers. Individual anonymised participant data and relevant clinical study documents will first be made available between 12 and 24 months after publication. Data requests will be reviewed and approved by an independent review panel on the basis of scientific merit. All data will be anonymised, to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. A data-sharing agreement signed by the requesting researcher(s) is required before data access can be provided. Proposals should be submitted to SP (spascual@minoryx.com).

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