



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 May 2024
EMA/CHMP/301934/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nezglial

International non-proprietary name: leriglitzone

Procedure No. EMEA/H/C/005757/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

6MWT	Six-minute walk test
ABCD	ATP-binding cassette transporter of subfamily D
AE	Adverse event
AESI	Adverse event of special interest
ADR	Adverse drug reaction
ALD	Adrenoleukodystrophy
ALDP	ALD protein
ALP	Alkaline phosphatase
AMN	Adrenomyeloneuropathy
AMPK	Adenosine monophosphate activated protein kinase
ANOVA	Analysis of variance
AP	Anteroposterior
APD	Action potential duration
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
BBB	Blood-brain barrier
BID	Twice daily
BMI	Body mass index
BMT	Bone marrow transplantation
BNP	Brain natriuretic peptide
BRM	Blinded review meeting
BSA	Bovine serum albumin
CA	Cerotinic acid
cALD	Cerebral demyelinating form of ALD
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
GIS	Gadolinium Intensity Score
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
CMC	Carboxymethylcellulose

CNS	Central nervous system
CPK	Creatine phosphokinase
CSF	Cerebrospinal fluid
CSR	Clinical study report
DDI	Drug-drug interaction
DKO	Double knock-out
DMSO	Dimethyl sulfoxide
DTT	Dithiothreitol
EAE	Experimental autoimmune encephalitis
EAN	Experimental autoimmune neuritis
EDSS	Expanded disability status scale
ECFA	Eyes closed / feet apart
ECFT	Eyes closed / feet together
ECG	Electrocardiogram
EC50	Half-maximal effective concentration
ED50	Median effective dose
ELISA	Enzyme-linked immunosorbent assay
ELOVL1; 3	Elongation of very long chain fatty acids protein 1; protein 3
EMA	European Medicines Agency
ER	Endoplasmic reticulum
EQ-5D-5L	European Quality of Life 5 Dimensions
EU	European Union
FA	Fractional anisotropy
Fabp4	Fatty acid binding protein 4
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fibre density and cross section
FRDA	Friedreich's ataxia
Gd	Gadolinium
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
GVHD	Graft-versus host disease
hERG	Human ether-à-go-go-related gene
HLT	Higher level term
HSCT	Haematopoietic stem cell transplantation
ICH	International Council for Harmonization of Technical Requirements

IC50	Half-maximal inhibitory concentration
IIEF	International Index of Erectile Function
IL	Interleukin
IP	Intraperitoneal
IT	Intrathecal
IV	Intravenous
IND	Investigational new drug
JVP	Jugular venus pressure
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LPS	Lipopolysaccharide
LS	Least square
MAA	Marketing authorisation application
MAO	Monoamine oxidase
MAD	Multiple ascending dose
MCP-1	Monocyte chemoattractant protein 1
Minoryx	Minoryx Therapeutics S.L.
MIP-1 β	Macrophage inflammatory protein-1 β
ML	Mediolateral
MMP-9	Matrix metalloproteinase 9
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MRM	Multiple reaction monitoring
mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
MSWS-12	Multiple sclerosis walking scale
MTR	Magnetisation transfer ratio
NfL	Neurofilament light chain protein
NF- κ B	Nuclear factor-kappa beta
NOAEL	No-observed-adverse-effects level
Nrf1	Nuclear respiratory factor 1
NYHA	New York Heart Association
OLE	Open-label extension
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PGC-1	Peroxisome proliferator-activated receptor gamma-coactivator 1

PGI-I	Patient Global Impressions - Improvement
PK	Pharmacokinetic(s)
PPAR γ	Peroxisome proliferator-activated receptor gamma
PPRE	PPAR γ regulatory element
PSM	Pre-submission meeting
PT	Preferred term
QoL	Quality of Life
qPCR	Quantitative polymerase chain reaction
QTc	Corrected QT interval
Qualiveen-SF	Qualiveen short form quality of life questionnaire for urinary disorders
RD	Radial diffusivity
Rpm	Revolutions per minute
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Single-dose / standard deviation
SE	Standard error
SEM	Standard error of the mean
SmPC	Summary of product characteristics
SOC	System organ class
SOD2	Superoxide dismutase 2
SSPROM	Severity score system for progressive myelopathy
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNF- α	Tumour necrosis factor alpha
TUG	Timed up-and-go
UK	United Kingdom
US	United States
VLCFA	Very-long-chain fatty acids
w/w	Weight/weight
λ_{em}	Emission wavelength
λ_{ex}	Excitation wavelength

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Minoryx Therapeutics S.L. submitted on 29 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Nezglyal, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 September 2020.

Nezglyal, was designated as an orphan medicinal product EU/3/16/1770 on 18 November 2016 in the following condition: the treatment of adrenoleukodystrophy (ALD).

The applicant applied initially for the following indication for the treatment of cerebral progression and myelopathy in male patients with adrenoleukodystrophy (ALD).

Over the course of the assessment, in the last round of the procedure, the applicant proposed the following updated indication:

For the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0115/2022 on the agreement of a paediatric investigation plan (PIP) and granting of waiver for subsets of the paediatric population and condition.

At the time of submission of the application, the PIP P/0115/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance leriglitazone contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Furthermore, the applicant also requested leriglitazone to be considered as a new active substance in comparison to pioglitazone previously authorised in the European Union as Actos, as the applicant claimed that leriglitazone differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
13 October 2016	EMA/H/SA/2862/2/2016/SME/I	<i>Dr Marion Haberkamp, Dr Andre Elferink</i>
13 October 2016	EMA/H/SA/2862/1/FU/1/2016/SME/III	<i>Dr Marion Haberkamp, Dr Andre Elferink</i>

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Drug substance specifications and new active substance status considerations
- Non-clinical evidence generation strategy
- Clinical pharmacology programme
- Phase 3 development plans: single pivotal study, study design, placebo control, patient population, treatment duration, target exposure levels, efficacy endpoints, statistical analysis plan including interim analyses.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Maria Concepcion Prieto Yerro

The application was received by the EMA on	29 July 2022
The procedure started on	18 August 2022

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 June 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 September 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 November 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	12 December 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Nezglyal on	25 January 2024
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	25 January 2024

1.8. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Karin Janssen van Doorn Co-Rapporteur: Ewa Balkowiec Iskra

The applicant submitted written notice to the EMA, to request a re-examination of Nezglyal CHMP opinion of 25 January 2024, on	8 February 2024
The CHMP appointed Karin Janssen van Doorn as Rapporteur and Ewa Balkowiec Iskra as Co-Rapporteur on	15 March 2024
The applicant submitted the detailed grounds for the re-examination on	29 March 2024
The re-examination procedure started on	30 March 2024
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP and PRAC members on	26 April 2024

The CHMP Co-Rapporteur's assessment report was circulated to all CHMP and PRAC members on	26 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the detailed grounds for re-examination to all CHMP and PRAC members on	13 May 2024
SAG/Expert group/ Working Party experts (as appropriate) were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG/Expert group/ Working Party (as appropriate) as presented in the minutes of this meeting	15 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice on	16 May 2024
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	28 May 2024
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the conditional marketing authorisation on	28 May 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Adrenoleukodystrophy (ALD) is a chromosome X-linked rare inherited neurodegenerative disorder that affects the brain, nerves and adrenal glands. ALD causes severe axonal damage in central and peripheral nervous system, resulting in a chronic progressive myelopathic and neuropathic adrenomyeloneuropathy (AMN) in adulthood. In addition to chronic neurodegeneration, acute inflammatory brain demyelination can appear, either in childhood or in adults, which is known as cerebral adrenoleukodystrophy (cALD), leading to rapid death or vegetative state.

2.1.2. Epidemiology and risk factors, screening tools/prevention

ALD has an estimated birth incidence of 1 in 20,000 worldwide (male and female) (Orphanet Report Series, 2020), and neither ethnicity nor country of birth is thought to have any impact on this (Raymond et al., 2018). The estimated prevalence is 0.35 per 10,000 people in the EU (EU/3/16/1770).

Childhood cALD occurs in 31-35% of ALD patients with onset typically between age 2 and 12 years of age. Recent literature reports that the majority of adult ALD men, i.e., up to 60%, will develop cALD over time, in addition to their myelopathy (50% in an observation period of 15.1 years in Suzuki et al., 2005; 63% with a mean of 10 years from myelopathy symptoms onset in de Beer et al., 2014).

Adults and boys undergo lifelong MRI surveillance due to the risk of cALD conversion and live with the constant fear and anxiety of developing cALD (Patients listening session, 7 May 2021). There is currently no test or biomarker that can predict cALD onset in ALD patients.

Because ALD is a chromosome X-linked disease, women have been classically considered asymptomatic carriers. However, more recent studies have reported that most women became symptomatic with an onset of myelopathy during their fifth decade of life with a prominent sensory ataxia resulting in rates of decline in body sway that are comparable to males (Engelen et al., 2014; Horn et al., 2015; Keller et al., 2021). Women rarely develop cALD.

2.1.3. Aetiology and pathogenesis

ALD is caused by mutations of the ABCD1 gene that result in loss of function of the encoded ALD protein (ALDP), an ABCD transporter located in the peroxisomal membrane. Deficiency of the ALDP impairs peroxisomal β - oxidation of very long-chain fatty acids (VLCFAs) leading to its accumulation in plasma and tissues, particularly the brain, spinal cord, and adrenal glands (Contreras et al., 1994; Ofman et al., 2010; van Roermund et al., 2008). Additionally, mutations in the ABCD1 gene also cause changes in adhesion molecules and tight junctions in the brain endothelium, which in turn promote an increase in blood-brain barrier (BBB) permeability independently of VLCFA accumulation (Musolino et al., 2015).

2.1.4. Clinical presentation, diagnosis and prognosis

Adrenomyeloneuropathy (AMN)

Most ALD male patients reaching adulthood develop AMN, with onset usually in the late 20s, with slowly progressive spastic paraparesis and sensory ataxia (Engelen et al., 2012).

There are two neurophysiological systems typically affected in AMN patients: the corticospinal tract and the dorsal column. Degeneration of these systems impair proprioception, resulting in reduced ambulation and postural stability, respectively. Gait in ALD is affected by spasticity, weakness and impaired balance resulting in tripping and falling, limited walking distance or loss of ambulation (Zackowski et al., 2006; van Ballegoij et al., 2020; Godbole et al., 2021). The myelopathy also causes urinary and sometimes faecal incontinence (Engelen et al., 2012). The day-to-day functioning of these young patients is severely impacted by balance and ambulation dysfunction and general disability, resulting in assistive walking device and ultimately wheelchair use (Turk et al., 2020).

Cerebral adrenoleukodystrophy (cALD)

The greatest risk to ALD patients is the development of the fast progressing and finally fatal cALD, which is defined as appearance of progressive cerebral white matter lesions. These are initially indicative of oligodendrocyte degeneration and frequently progress with inflammation leading to disruption of the BBB. These lesions precede a rapid cognitive decline with loss of voluntary movements, inability to swallow, loss of communication, cortical blindness and total incontinence and death with a mean survival of only 3 years approximately (2.3 years in van Geel et al., 2001; 3.4 years in de Beer et al., 2014; 2.6 years in Koehler et al. (manuscript under preparation)), meaning that appearance of cALD is an end-of-life event.

In contrast to AMN, which occurs only in adults, cALD can appear during childhood and adulthood. No differences have been reported in the mechanisms related to the disease start or disease progression when comparing childhood and adult cerebral forms.

A diagnosis of ALD can be made by demonstration of increased levels of VLCFA in plasma. This is the most frequently used diagnostic technique. It is reliable for the diagnosis of affected males at any age, but false-negative results occur in approximately 15% of women heterozygous for X-ALD. Mutation analysis is the most reliable technique for heterozygote identification and is now available on a service

basis (Moser et al., 2000). New-born screening for ALD is not implemented in most European countries (<https://www.technologynetworks.com/diagnostics/blog/a-landscape-assessment-of-newborn-screening-in-europe-359964>).

2.1.5. Management

There is currently no pharmacological treatment approved for patients with ALD. On 20 May 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Skysona (elivaldogene autotemcel), intended for the treatment of early cALD in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen-matched sibling haematopoietic stem cell donor is not available. However, shortly after approval, the marketing authorisation holder, Bluebird bio, submitted an application to withdraw Skysona from the European market. The withdrawal became effective on 18 Nov 2021.

Therapies designed to either reduce hyperlipidaemia (bezafibrate, lovastatin) (Engelen et al., 2012a; Engelen et al., 2010; Moraes et al., 2013) or lower dietary VLCFA intake (Moser et al., 1992) failed to slow myelopathy in ALD patients. Dietary supplementation with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) can normalise plasma VLCFA levels but clinical studies have shown that this does not prevent disease progression (van Geel et al., 1999). This apparent disconnect between reduced plasma VLCFA levels and functional outcome could result from the pathogenic cascade having already been triggered by the time of VLCFA increase.

If childhood cALD is detected in the early stages before major neurological disability appears, accumulated experience supports the use of hematopoietic stem cell transplantation (HSCT) to arrest inflammatory demyelination. The procedure is, however, associated with serious and sometimes fatal complications, including those due to myeloablative conditioning, infection, graft-versus host disease (GVHD), and graft failure or rejection (Raymond et al., 2019). Since HSCT needs to be performed in early stages of the disease, and requires finding appropriate donors, this option is only available for a portion of paediatric cALD patients. Even if HSCT is successful, the transplanted patients can still develop myelopathy in adulthood indicating that HSCT only stabilises the inflammatory component of cALD.

In the current standard of care, adult patients with cALD are only offered the option for HSCT if myelopathy and their overall clinical condition are not too advanced, their lesions are not affecting certain brain regions and there aren't other relevant comorbidities. Importantly, there is no marker to predict when or where brain lesions may appear, hence all adult ALD patients are at risk of developing cerebral lesions that cannot be treated by HSCT. Even if HSCT is being performed, these patients bear a substantial risk of post-transplant complications and further neurocognitive decline and ultimately of death.

2.2. About the product

Leriglitazone is a full and selective peroxisome proliferator-activated receptor gamma (PPAR γ) agonist. PPAR γ agonists activate key genes that counteract oxidative stress, stimulate mitochondrial biogenesis and decrease inflammation, preventing axonal degeneration and neuroinflammation (Corona and Duchon, 2016). Nezgylal oral suspension contains leriglitazone (also known as M4, M-IV and MIN-102 as hydrochloride), one of the active metabolites of pioglitazone.

Pioglitazone (Actos) is a PPAR γ agonist that is currently in use for treatment of type 2 diabetes mellitus (Chiarelli and Marzio, 2008). It has been pharmacologically validated in motor dysfunction ALD

preclinical models, i.e., single Abcd1 and double Abcd1/Abcd2 knockout mice and neuroinflammatory models that resemble features of the cerebral form of ALD (Ramkalawan et al., 2012; Hunter et al., 2008; Feinstein et al., 2002). However, translation into clinical efficacy has not been successful due to limited BBB penetration leading to insufficient target exposure to pioglitazone within the central nervous system (CNS) in humans.

Leriglitazone is thought to penetrate the BBB and to prevent ALD progression by counteracting the downstream effects of the VLCFA accumulation due to ABCD1 deficiency, which include mitochondrial dysfunction and depolarisation, oxidative stress, inflammation, and bioenergetic failure, which ultimately leads to axonal degeneration in ALD patients.

In non-clinical studies, leriglitazone demonstrated high oral bioavailability in both rodents and non-rodent species and has a nonclinical toxicological profile in line with the drug class, without additional unexpected adverse effects. Importantly, contrary to pioglitazone, leriglitazone can reach the required CNS exposure in humans, so it is uniquely suited to achieve the objective of treating cerebral progression and myelopathy in ALD patients.

The initial claimed indication of leriglitazone was “the treatment of cerebral progression and myelopathy in male patients with adrenoleukodystrophy (ALD)”. After initial assessment, the claimed indication has been revised to “the treatment of ambulatory adrenoleukodystrophy (ALD) in adult male patients with early stage myeloneuropathy, and paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)”. After the D195 assessment, the claimed indication was further revised to “the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)”.

Leriglitazone is an oral suspension and should be administered with a syringe. The proposed posology is a starting dose of 10 mL once daily. After 1 month from initiation of treatment the dose should be increased to 12 mL to achieve a target leriglitazone plasma exposure of 200 µg·h/mL (±20%) at steady state.

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive according to the applicant based on the pivotal study and available clinical data. Results are provided from ADVANCE (MT-2-01), NEXUS (MT-2-02) and compassionate use with more than 160 ALD patients treated with leriglitazone, from which more than 60 have cALD.
- It is likely that the applicant will be able to provide comprehensive data. Interim data in boys to be complemented by ongoing NEXUS confirmatory long-term clinical data. In addition, CALYX is a randomised controlled study in adult patients with cALD assessing overall survival (OS), with anticipated CSR finalisation up to 2027. Additional studies are ongoing and planned to provide further confirmation of efficacy and extend the safety data.
- Unmet medical needs will be addressed, as there is currently no pharmacological treatment approved for patients with ALD and ALD is a rare, serious, life-threatening disease. No treatments available for AMN, neither to treat myeloneuropathy progression nor incidence of cALD in adult patients. For cALD (adult and paediatric) need for less invasive alternatives than HSCT.
- The benefits to public health of the immediate availability outweigh the risks inherent in the

fact that additional data are still required, as there is no pharmacological treatment approved in ALD and patients with cALD are rapidly deteriorating.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as an oral suspension containing 13.66 mg of leriglitazone as active substance.

Other ingredients are: sorbitol (E420), microcrystalline cellulose (E460), carmellose sodium (E466), saccharin sodium (E954), sodium benzoate (E211), sodium citrate (E331), citric acid monohydrate (E330), strawberry flavour, citric acid monohydrate 0.2M solution, and purified water.

The product is available in a hydrolytic class III amber glass bottle with a white polyethylene child-resistant cap.

The pack includes a polyethylene oral dosing syringe of 12 mL graduated every 0.5 mL.

2.4.2. Active Substance

General information

The chemical name of the active substance is 5-[[4-[2-[5-(1-Hydroxyethyl)-2-pyridinyl]ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride (1:1) corresponding to the molecular formula $C_{19}H_{20}N_2O_4S.HCl$. It has a relative molecular mass of 408.90 g/mol and the following structure:

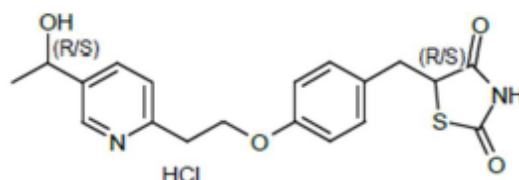


Figure 1: Active Substance Structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis, Fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance spectroscopy (NMR), ultraviolet-visible absorption spectrophotometry (UV-VIS), accurate mass determination by high performance liquid chromatography-mass spectrometry (HPLC-MS).

The solid-state properties of the active substance were measured by powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SCXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

The active substance is a slightly hygroscopic white to off-white powder, practically insoluble in acetonitrile, slightly soluble in ethanol, sparingly soluble in methanol. In acidic aqueous solutions, it is slightly soluble, while at pH 7 and pH 8 it is insoluble.

The active substance is a racemic mixture of four stereoisomers.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

The active substance is synthesised in 6 main steps using well defined starting materials with acceptable specifications.

Starting material was initially not accepted since its specification and control strategy was considered deficient. Therefore, the CHMP requested as a major objection (MO) further information. After the responses from the applicant, all issues related to specification and control strategy of the proposed starting material were considered resolved, therefore the proposed starting material was accepted.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Potential, structurally related organic impurities have been provided along with structures, origin, control and levels observed

The control strategy of residual solvents used in active substance synthesis is summarised and considered acceptable. The risk assessment on elemental impurities content is not provided, instead control of seven elemental impurities (Class 1 and 2a) is included in the specification of active substance with acceptance criteria set according to ICH Q3D, option 1 for oral route. Carry-over of several reagents is sufficiently addressed.

The information provided on the evaluation of potentially genotoxic impurities was not considered to be sufficient. Therefore, the CHMP, requested as a major objection (MO) that the control strategy for potentially genotoxic impurities be discussed and implemented in line with the ICH M7 guideline.

The information provided by the applicant on the evaluation of potentially genotoxic impurities was considered sufficient. All the structures considered in mutagenicity assessment, along with the results of the *in silico* evaluation and the relevant ICH M7 classification, are provided. All potential impurities including reagents, intermediates, starting materials and potential impurities arising from starting material synthesis are included. The control strategy for potentially genotoxic impurities was discussed and implemented in line with the ICH M7 guideline. For all compounds, the risk associated with their carry over to the final active substance was demonstrated to be negligible and the relevant control strategy adequate for assuring the quality and safety of the active substance. Therefore, the issue was considered resolved.

A nitrosamines risk evaluation was performed taking into account the requirements of ICH M7, EMA, EU and FDA guidelines and covers all possible sources. The risk was determined to be very low and no analytical testing was requested.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Specification

The active substance specification includes tests for appearance (visual), identification (IR, HPLC), polymorphic form (XRPD), equivalent purity (water and solvent free) (titration), assay (HPLC), related substances (HPLC), stereoisomers (HPLC), residual solvents (GC-HS), water content (Ph. Eur.), elemental impurities (ICP-OES/MS), residue on ignition, sulphated ash (Ph. Eur.), microbial tests (Ph. Eur.), and particle size distribution (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (16 batches, including pilot and commercial batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 pilot scale batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \text{ RH} \pm 5\% \text{ RH}$) and for up to 6 months under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \text{ RH} \pm 5\% \text{ RH}$) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, specified impurities, unspecified impurities and total impurities, water content, stereoisomers, particle size distribution, microbiological quality, and polymorphic form. The analytical methods used were the same as for release and are stability indicating.

Based on the presented stability results, the active substance is stable under long term and accelerated conditions.

Forced degradation studies and studies at stressed conditions have been also performed on one batch, considering the effects of photo-degradation, temperature/humidity, oxidation, and different pHs.

The active substance showed no degradation under the ICH Q1B applied light stress conditions. It is not negatively impacted by light stress condition according to ICH requirement.

The active substance showed (almost) no degradation under the other stressed conditions like temperature/humidity, hydrogen peroxide and acidic stress conditions.

Taking into consideration the results of the stability studies, the active substance does not require any special storage conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period without storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as a white, homogeneous oral suspension containing 13.66. mg/ml of leriglitazone as active substance.

The aim of the pharmaceutical development was to develop an immediate release oral dosage form as oral suspension in multidose packaging allowing flexible dosing. The oral suspension is contained in a glass bottle capped with child resistant closures supplemented with a oral syringe. The bottle is filled with 100 ml of oral suspension.

The suitability of the pharmaceutical form and composition for use in paediatric patients is considered sufficiently justified in accordance with guideline EMA/CHMP/QWP/805880/2012.

The properties of the active substance and the choice of the excipients have been satisfactorily described. The studies used to investigate the compatibility between the active substance and the excipients selected for the formulation of the finished product are provided.

The active substance does not show hygroscopicity, has a defined melting point and a defined crystal form. The particle size distribution is consistent batch to batch. Both polymorphic form and particle size distribution are controlled in the active substance specification.

A variation in the polymorph form in the finished product may represent a potential impact in certain finished product attributes, especially in its dissolution rate and extent, and in sedimentation tendency. However, these finished product attributes have demonstrated to remain unaltered in the oral suspension, both at release and during stability studies (accelerated and long-term conditions). The Quality Target Product Profile (QTPP) has been established for the finished product. Based on QTPP together with product knowledge from early clinical studies, critical quality attributes (CQAs) related to the product which have an impact on quality, safety, or efficacy have been identified and defined

Formulations used in clinical phase 1 and clinical phase 2/3/registration studies differs. An EU Phase I clinical study utilised a non-flavoured formulation with minimum excipients to achieve immediate solubility, suspension, and stability. The final formulation used in the clinical phase 2/3 and proposed for commercialisation was developed to support the QTPP for conventional immediate-release oral suspension by removing of polysorbate as an excipient and improved the characteristics for patient acceptability by addition of sweetening and flavouring agents. The excipients chosen for development of the finished product are common excipients used in suspension dosage forms. The relationship between excipient characteristics and finished product CQAs has been demonstrated through risk assessment and discussed in detail to justify the selected concentrations and grades.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. requirements except the flavour and the citric acid monohydrate for which in house specifications are used. There are no novel excipients used in the finished product formulation.

The formulation development included studies to investigate viscosity, pH, optimisation of organoleptic characteristics, dissolution, particle size stability, preservative efficacy, homogeneity, syringe dosage test, and impact of thermal cycling.

Initially, a 10 ml syringe was proposed requiring repeated withdrawal of suspension to reach the maximum 12 ml dose. Therefore, the proposed 10 ml syringe was not considered appropriate for patients, especially the elderly, and can lead to the risk for dosing errors. From a safety perspective, particularly overdosing is anticipated to lead to increased safety risks, especially since the target dose is already considered too high in >40% of patients (i.e., with the need for dose reductions due to adverse events). Therefore, the CHMP requested as MO to select syringe allowing appropriate dosing within proposed dosage range. To ensure the proposed dosing regimen (1.5 ml to 12 ml), a 12 ml oral syringe with 0.5 mL graduation scale was selected and the MO was considered resolved. Dosing accuracy within the proposed dosage range has been demonstrated as per Ph. Eur. 2.9.27.

Dissolution limit acceptance criteria in the finished product specification have been provided based on dissolution data obtained from batches used in the clinical and stability studies. the initially proposed description of the dissolution method development was considered insufficient, therefore, the CHMP requested as MO, to justify the choice of dissolution method, to consider tightening the dissolution limit acceptance criteria, and to demonstrate the discriminatory power of the dissolution method. All the issues were addressed satisfactory by the applicant, and the MO was considered resolved. Based on development studies, a medium was selected for routine quality control since in all other media, dissolution was not complete. The following dissolution conditions for routine analysis have been defined.

The experiments performing deliberate variations of composition of the formulation and of attributes of active substance (change in particle size) to show discriminatory power of the method showed that these modifications had an impact on the dissolution profiles, showing a decrease in dissolution rate. However, dissolution results were within the proposed specification limit for routine control. A complete and fast dissolution of leriglitazone was observed and in accordance with EMA *Reflection paper on dissolution specification for generic solid oral immediate release products with systemic action*, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes in the formulation, material specifications and/or manufacturing parameters and the method is considered adequate without further justification of the discriminatory power.

Manufacturing process development has been described and is based on assessment of the CQAs, and process by FMEA as well as product and process knowledge. No design space is proposed. The control strategy is based on fixed production parameter settings, in process controls and product testing after bulk manufacture and after filling/packaging. With the exception of the manufacturing process scale-up, the manufacturing process of the finished product remained unchanged throughout the product development.

Suitability of proposed packaging and dosing materials was demonstrated by thermal cycling studies, compatibility studies (including migration/interaction studies, stability) and a glass delamination study. In relation to the oral syringe provided with the finished product, a copy of the EC Certificate was provided demonstrating conformity with Directive 93/42/EEC.

An extractable study was performed to investigate the extractable profile of the bottle caps in organic solvents (polar and apolar) and aqueous media. Extractables were only detected in the apolar organic extract. Many compounds were detected above the toxicological threshold but only one of these was also found in stressed samples of the finished product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 4 main steps: preparation of suspension, mixing, filling and packaging. The process is considered to be a standard manufacturing process.

As it is a standard manufacturing process, no validation data is provided. A process validation protocol is included and considered acceptable. Based on the information provided to date, it can be inferred that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The in-process controls are adequate for this type of manufacturing process. No holding time is proposed during manufacturing.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), sediment (visual), identification of active substance (HPLC, UV), identification of sodium benzoate (HPLC, UV), assay of the active substance (HPLC), assay of sodium benzoate (HPLC), related substances (HPLC), total impurities (HPLC), stereoisomers (HPLC), dissolution (Ph. Eur.), pH (Ph. Eur.), viscosity (Ph. Eur.), uniformity of mass of delivered doses (Ph. Eur.), deliverable volume (USP), and microbial content (Ph. Eur.)

Based on an evaluation of the release and stability data from clinical and registration batches manufactured to date, three specified impurities have been identified as potential related substances of the active substance.

Individual specified and unspecified impurities are limited to $\leq 0.2\%$ corresponding to the identification and qualification threshold for impurities in a finished product with a maximum daily dose ≤ 2 g/day. In accordance with ICH Q3B, the proposed limits are appropriate and justified.

The limit for total impurities is specified in line with the currently available release and stability data.

Impurity levels at batch release from representative batches were provided. Impurities were below quantitation limits, and unspecified impurities were present at levels $\leq 0.1\%$. These results showed that the finished product is highly pure with respect to related substances. Furthermore, in stability studies, the specified, and unspecified individual impurity levels remained at or below 0.2%.

The elemental impurities risk assessment was performed in line with ICH Q3D(R1) Guideline for Elemental Impurities according to component-based approach, using data collected from suppliers and evaluation of contribution of utilities (including water), manufacturing equipment and the container closure system. According to the product assessment, there is no level of elemental impurities above control thresholds, therefore testing of elemental impurities is not required in the specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was initially performed, however, the CHMP considered that that provided risk assessment did not cover all potential sources listed in the updated EMA Q&A document (EMA/409815/2020 Rev.11), therefore, relevant finished product factors should be considered carefully by the applicant. Risk factors related to the potential reaction of amine containing impurities with potential nitrite sources should be expanded on, and the absence of risk robustly justified, and requested as MO that the relevant Article 5(3) nitrosamines declaration template following this review in line with published guidance should be provided. The applicant was also reminded of the need to provide results of confirmatory testing in the event that a risk of nitrosamine presence is identified. An updated risk assessment was provided and the issue was considered resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch results have been provided for various batches including development, clinical and stability batches, all manufactured according to the proposed commercial formulation. Results comply to the specifications valid at the time of testing. For final formulation batches manufactured with API from the proposed manufacturer, results are presented confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of finished product up to production scale used in clinical and stability studies, stored under long term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $60\% \text{ RH} \pm 5\% \text{ RH}$) and for up to 6 months under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \text{ RH} \pm 5\% \text{ RH}$) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, sediment, leriglitazone assay, sodium benzoate assay, related substances, total impurities, stereoisomers, dissolution, pH, viscosity, uniformity of mass of delivered doses, and microbial content. The analytical procedures used are stability indicating.

The finished product is physically, chemically, and microbiologically stable under long term and accelerated conditions.

In order to demonstrate the stability of the product after the first opening, an in-use stability study was performed on two leriglitazone oral suspension batches. The test simulated the use of the product in practice taking into consideration the use of the graduated oral dosing syringe. The results demonstrated that there is no risk regarding microbiological contamination or physical and chemical degradation of the finished product for a maximum of 66 days at 25°C.

A photostability study was conducted according to ICH Q1B Photostability Testing of New Drug Substances and Products guideline on one batch. The results demonstrated that light exposure has no impact on the physical and chemical characteristics of the finished product.

An accelerated degradation study was performed on one batch to identify the likely degradation products of the finished product. The degradation testing included the effect of temperature, photolysis, oxidation as well as the effect of acidic or alkaline conditions. The accelerated degradation study performed shows that the product is sensitive to alkaline treatment, generating several impurities peaks, slightly sensitive to oxidative, acid and light stress conditions and relatively stable to heat.

Based on available stability data, the proposed shelf-life without special storage conditions is acceptable. After the first opening, the in-use shelf life is 66 days stored below 25°C.

Post approval change management protocol

The applicant proposes to introduce alternative starting material via Post Approval Change Management Protocol (PACMP).

The proposed addition is considered feasible. The documentation that will be submitted in the proposed Post Approval Change version of the dossier is clearly indicated and considered sufficient. A commitment is included to update the approved protocol, if this becomes invalid, due to significant changes to the proposed test methods/acceptance criteria or a significant body of new knowledge or new regulatory requirements.

With respect to the reporting of the implementation of the change to the relevant competent authorities using the existing variation procedures, a Type IA / IAIN variation (implemented prior to notification) is proposed. The updated version of the dossier sections affected by the changes will be submitted, including comparative analytical batch data of active substance manufactured from starting material from both the current and proposed manufacturers, as evidence of the quality equivalence. The applicant's proposal to classify the variations as Type IA is considered acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation, 5 major objections were raised by the CHMP in relation to starting materials, evaluation of potentially genotoxic impurities of the active substance, choice of syringe to allow appropriate dosing, dissolution method development, and risk assessment of nitrosamines. The responses from the applicant to the MOs were considered satisfactory and all the issues were considered to be resolved, as explained above.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be adequate. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Leriglitazone is a full and selective peroxisome proliferator-activated receptor gamma (PPAR γ) agonist. Agonism of PPAR γ is aimed to induce neuroprotective and restorative effects in animal models of ALD by activating key genes that counteract oxidative stress, mitochondrial dysfunction and inflammation, thus preventing axonal degeneration and neuroinflammation, which are downstream effects of ALDP deficiency.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

First, the potency at the PPAR γ receptor binding was demonstrated along with the potential to interact with a series of primary and secondary targets. *In vitro* studies were performed to demonstrate the neuroprotective and/or anti-inflammatory effects of leriglitazone in spinal cord motor neurons, astrocytes and microglia exposed to VLCFA and other stimuli. VLCFA with 22 or more carbon atoms, and predominantly cerotinic acid (C26:0), accumulate in ALD patients and VLCFAs have been reported to cause (oxidative) toxicity by mechanisms involving either alterations in mitochondrial physiology or changes in intracellular Ca²⁺ homeostasis. *In vivo*, the effects of leriglitazone were studied in mouse models of adrenomyeloneuropathy (AMN) and neuroinflammatory models such as experimental autoimmune encephalitis (EAE) and demyelination and demyelination-remyelination in order support the utility of leriglitazone in the treatment of AMN and cerebral adrenoleukodystrophy (cALD).

In vitro

Binding studies showed that leriglitazone was equipotent as an agonist at the human and rodent PPAR γ receptors. Therefore, the rat is a pharmacologically relevant species, supporting also the selection of

the rat as a toxicologically relevant species. No binding data for the dog PPAR γ receptor were presented. Major metabolite M3 and leriglitazone diastereomers exhibited comparable potencies as leriglitazone. Leriglitazone displayed a 5-fold higher EC₅₀ for PPAR γ compared to pioglitazone but the total transactivation was higher with leriglitazone. Leriglitazone nor M3 demonstrated agonist activity at PPAR α or PPAR δ receptors.

In vitro assays suggest that leriglitazone may protect spinal cord motor neurons, astrocytes and oligodendrocytes from VLCFA-induced toxicity, representing cellular changes typically observed with ALD. PPAR γ is known to modulate key genes that counteract oxidative stress, stimulate mitochondrial biogenesis and correct mitochondrial function. In this context, experiments were performed in VLCFA models, demonstrating leriglitazone-mediated protective effects regarding mitochondrial functionality in motor neurons, as evident by a reduction of oxidative damage and mitochondrial loss.

In a model mimicking the blood-brain-barrier (BBB), leriglitazone improved neuronal survival and neuronal network and abolished the activation of microglial cells in inflammatory/VLCFA toxicity conditions, suggesting that leriglitazone crosses the BBB and provides neuroprotection when there is no BBB disruption. In conditions where the endothelial cells (HBMECs) were ABCD1-silenced, the BBB integrity was mildly impaired in inflammatory/VLCFA toxicity conditions and protective effects on neurons, astrocytes and microglia were still evident. Of note, it appears that leriglitazone passes the BBB *in vitro*, but at lower levels than when endothelial cells were ABCD1-silenced. In a monocyte (THP-1 cells) adhesion experiment leriglitazone decreased BBB permeability in inflammatory conditions. This was demonstrated by an attenuation of ABCD1-related brain endothelial dysfunction by decreasing monocyte adhesion to endothelial cells. The same was apparently shown for PBMC adhesion, but these data were not submitted.

Regarding inflammation, in a monocyte cell line and in monocyte-derived macrophages from ALD patients, leriglitazone decreased proinflammatory skewing in inflammatory conditions. Notably, a variable, subject dependent induction of PPAR γ target gene FABP-4 was observed in these patient cells upon leriglitazone treatment.

In LPS-activated microglia, leriglitazone improved phagocytosis of myelin debris particles. Additionally submitted *in vitro* studies showed that leriglitazone promoted the maturation of oligodendrocyte progenitor cells, protected the integrity of the neurite network of central neurons and myelin wraps upon LPS and cuprizone injury (demyelinating models), and protected sensory neurons neurites and peripheral myelin in a model of peripheral neuropathy. Overall, a comprehensive package of *in vitro* experiments relevant for the mode of action of leriglitazone in ALD was provided. Results on the mode of action suggest that leriglitazone may protect motor neuron, oligodendrocyte and astrocyte survival upon VLCFA-induced toxicity possibly via reducing oxidative stress. Leriglitazone may also promote remyelination and reduce (neuro)inflammation and initial BBB disruption in cALD development.

In vivo

Abcd1 knockout (KO) mice treated with leriglitazone demonstrated an increase in adiponectin plasma levels (biomarker for PPAR γ engagement), expression levels of genes involved in anti-oxidant mechanisms and mitochondrial biogenesis, FABP-4 (PPAR γ activation) and a reduction of Nf κ B-dependent pro-inflammatory markers. While biomarkers for inflammation are considered relevant for the evaluation of leriglitazone's pharmacodynamic effects in ALD, changes in adiponectin and FABP-4 are not related to the pathophysiology of ALD and only reflect PPAR γ engagement. In line with other PPAR γ agonists and data in *Abcd1* KO mice, leriglitazone normalised biomarkers of inflammation (Monocyte chemoattractant protein-1 (MCP-1), Eotaxin-1, SCF and IL-1 α) and mitochondrial function (PGC1 α and Nrf1) following treatment for 4 months in double knockout (DKO) *Abcd1/Abcd2* mice. In addition, a reduction of axonal degeneration and microglia activation was shown in spinal cord tissue, potentially related to the observed dose-dependent improvement in motor performance. The motor

performance results provide support that leriglitazone can have a functional effect on parameters of clinical relevance for AMN.

Since *Abcd1* KO and *Abcd1/Abcd2* DKO mouse models present a milder neuroinflammatory phenotype than observed in cALD patients, *in vivo* models of neuroinflammation (EAE and EAN) were used to further support the proof of concept of leriglitazone for the treatment of cALD. Leriglitazone dose-dependently reduced clinical signs of neuroinflammation in the EAE model. In the rat EAN study, leriglitazone showed minor ameliorating effects on disease severity suggesting minimal effects of leriglitazone on demyelinating neuropathy in this model. PPAR γ engagement in the CNS was confirmed by a dose-related increase in CSF adiponectin levels following leriglitazone treatment.

Demyelination or remyelination upon leriglitazone treatment was evaluated in the cuprizone mouse model. Strong demyelination was detected in the corpus callosum of cuprizone-treated animals. Leriglitazone (125 mg/kg) treatment resulted in a tendency to preserve the oligodendrocyte population and demyelination. A higher proportion of axons appeared myelinated after treatment with leriglitazone compared to cuprizone injury alone.

Overall, various *in vivo* disease models representing hallmarks of ALD and AMN showed that leriglitazone is able to induce PPAR γ engagement, modulate biomarkers of inflammation and mitochondrial function, reduce neuroinflammation, improve motor performance and mildly ameliorate demyelination *in vivo*.

2.5.2.2. Secondary pharmacodynamic studies

The selectivity of leriglitazone was evaluated in binding screens of receptors, ion channels, and enzyme. Leriglitazone (at 10 μ M) had no meaningful (more than 50%) binding affinity for any of the 55 tested targets.

Another screen was performed to evaluate the potential inhibition of monoamine oxidase (MAO)-A and MAO-B enzyme activity. For MAO-B, leriglitazone inhibited the receptor with an IC₅₀ of 0.7 μ M, compared to 0.15 μ M for pioglitazone. The enantiomers of leriglitazone had a comparable inhibition. Neither of the compounds showed activity on MAO-A. The CNS leriglitazone concentrations reached at clinical doses are 500 nM-900 nM, which is around the IC₅₀ (705 nM and 822 nM) but below the IC₈₀ for MAO-B (2.3-4.7 μ M).

2.5.2.3. Safety pharmacology programme

The safety pharmacology package comprised GLP-compliant cardiovascular (dogs) and CNS (rats) safety studies and a non-GLP respiratory safety (rats) study. *In vitro* studies comprised a GLP-compliant hERG inhibition assay and a Purkinje fibre assay to evaluate potential effects on cardiac action potential. No stand-alone studies were performed concerning renal function/urinary parameters, but these were evaluated in the general toxicity studies.

Leriglitazone nor pioglitazone had adverse pharmacologically driven effects on neurobehaviour or on body temperature at any dose level in rats. Leriglitazone induced a dose-dependent, reversible increase in peak inspiratory flow at 30 minutes post dose at all dose levels, lasting up to 120 minutes at the top dose of 150 mg/kg. This was accompanied by a reversible decrease in inspiratory time at 50 and 150 mg/kg. At the highest dose, the airway resistance index was significantly higher at 180 and 240 minutes post dose. No respiratory effects were observed in repeated dose toxicity studies.

In a GLP-compliant *in vitro* hERG inhibition study, no significant hERG inhibition was observed at concentrations up to 30 μ M, which is approximately 25-fold the highest anticipated unbound clinical

exposure (C_{max}: 1.16 µM). Leriglitazone significantly inhibited potassium ion current at 100 µM (32.1%) and 300 µM (43.6%), but the IC₅₀ exceeded 300 µM, more than 250-fold the highest anticipated unbound clinical exposure. Thus, leriglitazone has a low potency as hERG channel blocker at clinically relevant concentrations. Leriglitazone had an effect on Action Potential Duration at 50% of repolarisation (APD₅₀) at concentrations approximately 25-fold the clinical C_{max}. Decrease in the plateau of APD₅₀ suggests a possible inhibition of calcium currents. When comparing these characteristics to a reference compounds database (TDPscreen™), leriglitazone was classified as group "C", having no risk to cause Torsade de Pointes and/or QT prolongation in clinical use.

In a GLP-compliant cardiovascular telemetry dog study, there were no effects on blood pressure, body temperature, QRS complex, QTc and ST segment at doses up to 50 mg/kg. A decrease in the normal heart rate (HR) reduction at night was observed. This effect was accompanied with a shortening of cardiac conduction times (PQ and PR intervals) and ventricular repolarisation duration (QT and QT shift). These findings were attributed to a disruption of the HR nycthemeral cycle. However, differences in HR were still apparent during daytime. No abnormalities on HR and ECG were observed during the repeated-dose dog studies of up to 9 months duration, where doses of up to 10 mg/kg/day (around clinical exposures) were administered, but it should be noted that the safety margins are not certain (see toxicokinetics assessment).

Although M3 metabolite is present at >10%, given that it is found at higher exposure levels in non-clinical species than in humans, no dedicated assessment in terms of safety pharmacology has been conducted.

Overall, *in vitro* studies suggest a low risk for QT prolongation at the proposed clinical exposures. There were no apparent effects of leriglitazone on CNS, respiratory and cardiovascular safety *in vivo*.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted. Considering that leriglitazone is contraindicated in patients with type 1 or type 2 diabetes or with (history of) cardiac failure, no drug interactions are anticipated.

2.5.3. Pharmacokinetics

Leriglitazone pharmacokinetic profile was characterised following intravenous (iv) and oral administration to mouse, rat and dog. Toxicokinetic profiles were characterised in rats and dogs following daily oral dosing for a total duration of up to 6- and 9-months. Exposure in pregnant rats and rabbits and juvenile rats was assessed in EFD and juvenile toxicity studies. In addition, distribution of leriglitazone to the brain, spinal cord and cerebral spinal fluid (CSF) were characterised. PK of both leriglitazone itself and the major metabolite M3 were investigated.

Methods of analysis

The LC-MS/MS methods for rabbit, rat and dog plasma were correctly validated, following the principles of GLP. For rat plasma, pioglitazone, leriglitazone and metabolite M3 were all validated. The LLOQ was 25.0 ng/mL for pioglitazone and 50 ng/mL for leriglitazone and M3. The upper limit of quantification (ULOQ) was established at 25,000 ng/mL for pioglitazone and 50,000 ng/mL for leriglitazone and M3. A second LC-MS/MS method had a lower quantification range, with an LLOQ of 30 ng/mL for leriglitazone and 20 ng/mL for M3 in rat plasma.

For rabbit plasma the LLOQ was 100 ng/mL for leriglitzazone and 10.0 ng/mL for M3. The ULOQs were 100,000 ng/mL and 10,000 ng/mL for leriglitzazone and M3 respectively. For dog plasma the ranges were established at 20.0 ng/mL to 20,000 ng/mL for leriglitzazone and 10.0-10,000 ng/mL for M3.

The non-validated methods were used for LC-MS/MS analysis of the samples collected from rat and mouse brain and CSF samples. These methods were based on protein precipitation with acetonitrile and collection of supernatant. The LLOQ ranges for leriglitzazone were 0.99 to 6.02 ng/mL in plasma and 0.99 to 3.01 ng/mL in CSF, brain, and spinal cord; the LLOQ for M3 was 1.0 ng/mL both in plasma and brain.

The validation of the methods was done according to the established guidelines. A different LC-MS/MS method was developed and validated for each of the pre-clinical species and the ranges differ. Yet, for the analysis of the samples all the ranges are appropriate. For some high concentration samples extra dilution is needed for the concentration to fall within the linear range of the method.

Absorption

An extensive package of non-clinical PK and TK studies was provided by the applicant. Single-dose pharmacokinetics were established in mice, rats and dogs. In some of these studies both leriglitzazone and the metabolite M3 were studied. Repeat-dose kinetics were established in mice, rats, dogs and rabbits. Also pregnant (rats and rabbits) and juvenile animals (rats) were studied.

Overall, leriglitzazone was absorbed quickly in all species with T_{max} ranging from 1-4 hours. The half-life was established at approx. 2 hours in mice, 2-6 hours in rats, 5-16 hours in dogs, 24 hours in humans. Within these ranges the lower half-life was usually measured with the lowest dose and the higher ones with the higher doses. In general, at lower doses, 3-12 mg/kg, the C_{max} and AUC values increase approximately dose-proportional. At higher doses, 30-50 mg/kg, the AUC increases more than dose-proportional after single-dose administration. This higher AUC value may be the consequence of the increased half-life. The clearance of leriglitzazone was established at 2.63 mL/min/kg in rats. The volume of distribution (V_d) was 0.73 L/kg for leriglitzazone and 0.47 L/kg for M3. In the single-dose rat study (CBN0001), C_{max} and AUC_{last} to M3 were nearly as high as C_{max} and AUC_{last} for leriglitzazone. T_{max} was 1 or 2 hours for leriglitzazone and 1 hour for M3. Following a single dose of pioglitazone, the C_{max} for pioglitazone >>> leriglitzazone > M3. Systemic exposure (AUC_{last}) to these analytes was also ranked in that order. T_{max} for pioglitazone was 2 or 4 hours, and for both M3 and leriglitzazone, T_{max} was notably longer at 8 hours. In mice the V_d of leriglitzazone was slightly higher at 1.26 L/kg, indicating a more extensive tissue distribution in mice compared to rats. The clearance was 11.79 mL/min/kg. Metabolite M3 exhibited a low systemic plasma clearance (20.65 mL/min/kg, normal liver blood flow in mice = 90 mL/min/kg) with a half-life of 2 hours, similar to leriglitzazone. The V_{ss} of M3 was 2.73 L/kg, the C_{max} was 1,305 ng/mL the AUC was 3,147 ng·h/mL. The AUC is approx. 50% of the AUC of leriglitzazone. In dogs the leriglitzazone V_d was lower, 0.5 L/kg and the clearance was 0.8 mL/min/kg. Three studies assessed the PK of M3 after single-doses of leriglitzazone. The AUC and C_{max} values of M3 were approx. 10-15% of the values measured for leriglitzazone across the three studies. T_{max} of M3 was within 30 minutes of dosing leriglitzazone.

Repeat-dose studies for leriglitzazone revealed a few noteworthy characteristics. There was no evidence of accumulation following repeated administration in any species, dose levels and study duration. Also, no substantial sex differences were observed in any of the studied animal species and dosing regimens. The pharmacokinetic profile of pregnant animals did not differ from the data obtained from non-pregnant adult animals. PK differences were observed between juvenile (age 22 days and 90 days) and adult animals after repeat-dosing. AUC in the high-dose (50 mg/kg) group was approx. 1.5x lower in juvenile rats compared to adults. AUC at other dose levels (12.5 and 25 mg/kg) were similar.

One repeat-dose study was performed in rats that also measured M3. The M3 C_{max} and AUC₀₋₂₄ also increased with dose, with sub-proportional increases in C_{max} and broadly dose proportional increases in AUC₀₋₂₄. The leriglitazone/M3 AUC₀₋₂₄ ratio was fairly constant across dose levels between 0.75 and 1.18 except in the case of females at the maximum dose tested (50 mg/kg), where the ratio ranged between 1.30 and 1.37. In dogs, three repeat-dose studies also assessed the PK of M3, that all showed a similar profile. Mean C_{max} and AUC_{0-24h} values for leriglitazone and M3 increased in an approximately dose proportional manner across the dose range and did not appear to change following repeated administration. Systemic exposure (AUC_{0-24h}) to M3 was lower than that observed for leriglitazone. The metabolite ratio of leriglitazone:M3 did not appear to change with increasing dose or time. In pregnant rabbits, the M3 profile was comparable to that seen in other species. The metabolite ratio of leriglitazone:M3 was consistent across the dose levels, the AUC and C_{max} <10% of the leriglitazone AUC and C_{max}.

The oral bioavailability was also established in all species, except the rabbit. In mice the bioavailability was 85%, in rats 86% and in dogs 90%. The bioavailability of M3 was 93% in rats. The bioavailability of leriglitazone is very comparable across the non-clinical species, however, an exact value for bioavailability of leriglitazone in humans is not available.

Two pairs of diastereoisomers (E1 and E2) were reported, which showed different predominant forms in rodent and non-rodent species. A ratio of E1/E2 >1 was noted in rodent species (3 and 2 for mice and rats), while a ratio <1 was observed in dogs and humans. The applicant reported a similar efficacy at the PPAR gamma receptor, so no differences are expected in the non-clinical studies.

Distribution

Plasma protein binding was assessed *in vitro* with a method based on rapid equilibrium dialysis and LC/MS/MS analysis, in plasma from all pre-clinical species (mice, rat, dogs and rabbits) and humans. Some substantial interspecies differences were observed. In the studied range (1, 10 and 100 µM) the free fraction was 2.9-4.3% in humans and 4.9-5.2% in rats, indicating no concentration dependency in the studied range in these species. In rabbit, dogs and mice however, some indication for a concentration-dependent plasma protein was observed. For rabbits, the free fractions were 4.1, 4.9 and 6.9% at 1, 10 and 100 µM respectively. For dogs, these values were 9.4, 10.6 and 14.3% and for mice it was 33.6, 32.7 and 36.1%. The differences in protein binding between animal species is substantial, especially the free fractions in dogs and mice compared rats and humans. Protein binding of the leriglitazone metabolite M3 at 0.5 and 5 µM in human, dog, rat, mouse, and rabbit plasma was evaluated using an equilibrium dialysis-based method and LC/MS/MS analysis. A similar pattern was seen in free fraction for this metabolite, with the lowest free fraction in humans (1.9 and 1.8% in 0.5 and 5 µM, respectively) and the highest free fraction in mice (4.9 and 7.9% in 0.5 and 5 µM, respectively).

Furthermore, a method based on rapid equilibrium dialysis and LC/MS/MS analysis was used to assess free fractions of leriglitazone in rodent brains. The unbound fraction of leriglitazone in rat brain at 5 µM concentration was about 13.6% and in mouse brain about 9.1%.

Distribution was studied in Sprague Dawley rats and partially pigmented Long Evans rats (n=6 per group) after a single oral administration of 18 mg/kg radiolabelled leriglitazone. Absorption from the gastrointestinal (GI) tract was rapid with greatest radioactive concentrations observed for the majority of tissues between 1 and 2 hours post-dose. Greatest radioactive concentrations were generally observed in blood and tissues associated with elimination (GI tract, urinary bladder, liver and kidney) but also in lung, spinal nerves, pituitary and adrenal glands. Radioactivity in tissues generally declined by 8 hours post-dose, however, the pattern of distribution remained the same, with high concentrations measured in contents of the GI tract and urinary bladder. In partially pigmented rats radioactivity was observed in melanin containing structures (uvea tract, pigmented skin), with

concentrations in pigmented skin consistently greater than that observed in non-pigmented skin indicating some affinity of the test material for melanin. Concentrations in melanin containing tissues declined steadily with time however, which suggests a reversible interaction rather than the strong binding associated with high affinity.

No placental transfer studies of leriglitazone have been conducted and none are planned. Since the indication of leriglitazone only includes male patients, this is acceptable.

Several studies were performed in mice and rats to elucidate the distribution of leriglitazone to the brain and the spinal fluid. Following a single IV administration of leriglitazone to C57BL/6 mice at 1 mg/kg, leriglitazone exhibited a brain-to-plasma exposure (AUClast) ratio of 0.12. After a single oral administration of leriglitazone to C57BL/6 mice at 4.5 mg/kg, brain concentrations were detectable until 8 hours post-dose. The Tmax in brain was 0.50 hours with a brain-to-plasma exposure (AUClast) ratio of 0.12. Following a single oral administration of leriglitazone to C57BL/6 mice at 25 mg/kg, brain concentrations were observed at 1 and 6 hours. Brain-to-plasma concentration ratios were 0.10 and 0.60 at 1 and 6 hours, respectively. In SD rats, the brain-to-plasma ratios at 1 hour post-dose were found to be 0.17 and 0.10 following 2 mg/kg IV and 10 mg/kg oral administration, respectively. Following a single oral administration (17 mg/kg) in male Sprague Dawley rats, CSF concentrations were observed until 8 hours with Tmax at 0.50 hours post-dose and CSF-to-plasma concentration ratio across the time point ranged from 0.009 to 0.023. Spinal cord-to-plasma concentration ratio across the time point ranged from 0.061 to 0.176. Brain concentrations were observed until 8 hours with Tmax at 2.00 h and brain-to-plasma concentration ratios across the time points ranged from 0.059 to 0.118.

Given the therapeutic indication of leriglitazone, distribution to the brain and CSF is essential for a pharmaceutical effect. The mentioned studies appropriately demonstrate the distribution of leriglitazone to these tissues. However, only 470 nM and 736 nM unbound concentrations are reached in brain and CSF of rats respectively. In mice, following the findings in studies DRF 00084-14 and DRC 00158-15 (see non-clinical Pharmacodynamics section of this report) the maximum concentrations reached in the mouse brain following PO administration of 62.5 mg/kg b.i.d. (the highest tested dose) is 9.1 µM. Taken into account the free fraction of leriglitazone in mouse brain was 9.1%, the free concentration in mouse brain comes to 0.83 µM (827 nM). In toxicity studies in rats, at 178 days, the Cmax at the highest dose was 83,600 ng/mL. The highest Cmax was measured in the 24-day study at 127,000 ng/mL. 10% of this concentration would theoretically reach the brain after oral administration, so 8,360 ng/mL and 12,700 ng/mL. Of these concentrations only 13.6% is available as free fraction of leriglitazone. This would result in unbound concentrations in the rat brain, at the highest dose used in the repeated-dose studies, of 2.78 µM and 4.22 µM respectively.

In cALD the integrity of the blood-brain-barrier is affected, initially localised, but larger parts may become affected. The applicant performed a study in Middle Cerebral Artery Occlusion (MCAO) mice to demonstrate the distribution of leriglitazone in mice with a damaged blood-brain-barrier function. The model did not reveal different brain distribution in MCAO mice compared to naïve animals. A similar experiment in rats following a single PO administration of leriglitazone did not show substantially higher brain:plasma ratio compared to naïve animals either. Since the MCAO model is a stroke model, these results are of limited value for the assessment of brain distribution in cALD patients. Yet, there seems to be no strong evidence for risks associated purely with substantial increases of leriglitazone in the brain following local blood-brain-barrier disruption.

Metabolism

In human hepatocytes, leriglitazone is mainly metabolised via alcohol degeneration to M3. Other metabolites were found at very low concentrations (<1%). Studies in human liver microsomes indicate that M-3 is formed mainly via CYP2C8, with a minor role for CYP3A. Since M3 is pharmacologically

active and may contribute to the safety profile, it should also be investigated *in vitro* which CYPs and other enzymes are responsible for the metabolism of M3.

In vivo metabolism of leriglitazone was investigated in rats, dogs and humans (although it is noted that the pivotal mass balance study in humans is still awaited and therefore the human data mentioned below still have to be confirmed, see also clinical assessment). The parent compound was the major component in plasma of all investigated species (50-69% in rats, 86-87% in dogs and 70-74% in humans). The most important metabolic pathway is alcoholic dehydrogenation (25-31% in rats, 7-11% in dogs and 21-25% in humans), resulting in the formation of major metabolite M3 (corresponding to M7 in rats and dogs). In total, 27 metabolites were found in human plasma, corresponding well to the metabolites found in animal species. Except for the major metabolite M3, all other metabolites in plasma were below 2% of total drug related circulating material. In human urine, 32 metabolites were found. Leriglitazone and M3 were found in urine at concentrations about 1% of the total LC/MS peak. Metabolites M17 and M21 were the most abundant in urine (12.1 to 27.8%).

In a mass balance study in rats, 5 different compounds were detected in plasma, 14 in urine, 8 in faeces and 13 in bile. M3 and M424 (a sulphate of Metabolite M344) represented more than 10% of total sample radioactivity in plasma, whereas a sulphate of leriglitazone and metabolite M372 represented more than 10% of the total administered radioactivity in bile and faeces.

Excretion

Hepatic uptake and biliary secretion of leriglitazone was evaluated using sandwich culture hepatocytes (human). The "*in vitro*" biliary clearance at 10 and 1 μ M was 0.0003 and 0.0008 μ L/min/mg protein respectively.

In a mass balance study, male bile duct cannulated and non-cannulated rats were orally administered 18 mg/kg leriglitazone. The majority of leriglitazone was excreted within 24 hours (87% in non-cannulated rats and 99% in cannulated rats). In non-cannulated rats, 68% was excreted via faeces (over 168h). In cannulated rats, the majority (74% in the first 48h) was excreted via the biliary route. This indicates enterohepatic exposure. In cannulated and non-cannulated rats, 22 and 32%, respectively, was excreted via urine.

It is unknown whether leriglitazone or its major metabolite M3 are excreted in milk.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

2.5.4.2. Repeat dose toxicity

Toxicity of leriglitazone was investigated in rats up to 6 months and dogs up to 9 months. In the three- and one-month rat studies, additional pioglitazone treatment groups were included for comparison. Overall, the toxicological effects observed for leriglitazone were in accordance with those expected for PPAR γ agonists and observed in the pioglitazone groups.

Margins of exposure (MoE) are expressed as estimates and based on unbound leriglitazone (as protein binding differs between species) and on the 200 μ g.h/ml AUC for humans that is mentioned in the SPC.

Haematopoietic system

In both rats and dogs, effects on the haematopoietic system as reductions of red cell mass were observed after administration of leriglitazone. This impact on red cell parameters has been described

as a class effect of PPAR γ agonists occurring secondary to oedema as haemodilution. These effects occurred at a MoE just above the clinical exposure in rats (2-5 to 5-fold), and around clinical exposure in dogs. Anaemia has been observed in the clinic.

As a class, PPAR agonists have been associated with anaemias due to the reduction of marrow mass after infiltration of the marrow cavity with fat cells. Although there was no indication of this from the histopathology, subtle differences can be difficult to detect due to the inherent variation seen in laboratory rats.

Cardiovascular system

Increased heart weight was seen in rats and dogs at doses which were below the clinical exposure. In rats, myocarditis and brown fat in the aorta with macrovesicular change was also seen, and in dogs hypertrophy/hyperplasia of mesothelial cell in the heart was observed. The heart weight remained increased after a recovery period. Cardiac hypertrophy is a known class effect of PPAR γ agonists, and as such cardiac failure is categorised as an important potential risk for humans.

Liver

Increased liver weight was seen in rats (MoE about 2.5 to 5-fold) and dogs (around clinical exposure) with some liver enzyme increases only in the dog. As effects on liver enzymes have also been observed in the clinic and considered a class effect, liver injury is considered an important potential risk.

Adipose tissue

Proliferation of adipose tissue (increased deposition of white and brown fat and fatty infiltration of tissues) is a known class effect of PPAR γ agonists. In the current study fat deposits and adipose changes were observed in skin, epididymis, ovaries, mammary gland, mesenteric tissue, aorta and hibernating gland, in both the groups treated with leriglitzzone and pioglitazone. These changes occurred at exposures below the clinical exposure, with brown fat deposits in the aorta occurring at the lowest dose.

Reproductive organs

In rats, several effects on reproductive organs were observed. Follicular cysts and increased atresia with decrease corpora lutea, and a disruption of oestrous cycle was observed in 3-month study, in both leriglitzzone and pioglitazone treatment groups. Additionally ovarian atrophy was evident after 6 months of dosing. These effects point to early onset of reproductive senescence in females. The effects on the adrenal gland are also likely related to a disturbance in sex hormones. Decreased corpora lutea were also seen on dogs. Most effects occurred at exposures below clinical exposure. Importantly, no effects on fertility were seen in a dedicated fertility study (see section 3.2.4.4.).

Pituitary gland

Increased weight, vacuolation of cells and diffuse hyperplasia was seen in the pituitary gland, only in rats. Vacuolation in the pars distalis of the pituitary was typically seen after gonadectomy or after treatment with anti-androgens. Increased pituitary weight was evident after 3-month dosing with pioglitazone, whereas 6 months of dosing was required to induce this effect for leriglitzzone. This suggests the effect on the pituitary gland is less severe for leriglitzzone as compared to pioglitazone. Effect occurred at exposures just above the clinical exposures in males and females (MoE around 2.5 to 5-fold). Since these exposure margins are low, it could be clinically relevant as leriglitzzone could have an effect on the hypothalamic-pituitary-adrenal (HPA) axis.

2.5.4.3. Genotoxicity

Leriglitazone was negative for genotoxic potential in the bacterial mutagenesis assay, and after 3-hour treatment in the mouse lymphoma mutagenesis assay. However, increased mutation frequency was seen in mouse lymphoma cells after 24-hour treatment. In light of this positive result, the *in vitro* tests were followed up by two *in vivo* studies, in line with recommendations in guideline ICH S2 (R2). Both *in vivo* rat studies were negative after sufficient exposure of the animals, and therefore it is concluded that leriglitazone has low genotoxic potential. It should be noted that the positive results in the mouse lymphoma assay can be viewed as a class effect of PPAR γ agonists, and is likely due to formation of Reactive Oxygen Species.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were performed.

2.5.4.5. Reproductive and developmental toxicity

Leriglitazone has no effect on fertility in male and female rats when dose up to 50 mg/kg/day (MOE: around 2.5 to 3-fold). In embryo-fetal development studies in rats and rabbits decreased fetal weight was observed at the high dose in both species at exposures at (rabbit) or below (rat) the clinical exposure. These findings are however not relevant for the current patient population of males only. No post-natal development toxicity study was conducted. Considering the indication, this is agreed.

Juvenile toxicity

Rats were dosed for 10 weeks starting at post-natal day 22, in a juvenile toxicity study. No effects other than dose observed in adult animals were seen, apart from reduced bone density of the vertebrae which was not statistically significant. The effect, albeit slight, was observed at clinically relevant doses. There is a plausible mode of action for the effect of PPAR γ agonists on BMD, where promotion of adipocyte differentiation is at the expense of osteoblast formation and thus reduced bone formation as a result. Since the indication applied for includes children, possible detrimental effects on growing bones are of particular concern.

2.5.4.6. Toxicokinetic data

Exposure to M3 was only sufficient in rats, not in dogs. For toxicology assessment, this is sufficient.

Margins of exposure for the toxicology studies are expressed as estimates and based on unbound leriglitazone (as protein binding differs between species) and on the 200 $\mu\text{g}\cdot\text{h}/\text{ml}$ AUC for humans that is mentioned in the proposed SmPC.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of Main Study Results

Substance (INN/Invented Name): Leriglitazone			
CAS-number (if available): 146062-46-6			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	D_{ow} : -0.97 (pH 1) K_{ow} : 2.21 (pH 5.5) D_{ow} : -0.57 (pH 9.9)	Potential PBT (N)
Phase I			
Calculation	Value	Unit	Conclusion

PEC _{surfacewater, refined}	0.00329	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Conclusions on studies for leriglitazone

PEC_{surfacewater} is below the action limit of 0.01 µg/L and leriglitazone is not a PBT substance as log K_{ow} does not exceed 4.5.

Therefore, leriglitazone is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics

In vitro binding studies showed that leriglitazone was equipotent as an agonist at the human and rodent PPAR γ receptors supporting the selection of the rat as a toxicologically relevant species. No binding data are presented for dog PPAR γ receptors, the non-rodent species used in toxicology studies. However, dogs treated with leriglitazone presented exaggerated pharmacology-related toxicity effects known for PPAR γ agonists. In addition, dogs have a similar metabolic profile as humans. Therefore, the dog is a relevant non-rodent species for toxicological assessment.

In vitro data on the mode of action suggest that leriglitazone may protect spinal cord motor neurons, astrocytes, and oligodendrocytes from VLCFA-induced toxicity, possibly via reducing oxidative stress. Leriglitazone may also promote remyelination and reduce (neuro)inflammation and initial BBB disruption in cALD development. However, discrepancies were observed between different *in vitro* studies regarding the protection of leriglitazone against different VLCFAs, as well as differences between susceptibility of cell types. The applicant argues that the milder effects towards protection with leriglitazone treatment upon C24:0 (lignoceric acid) injury compared to C26:0 injury (cerotinic acid) are due to stronger increase in ROS generation and cell death upon C26:0 injury compared to C24:0 injury. In addition, C26:0 is implicated in peroxisomal diseases and predominantly accumulates in patients with ALD. Regarding different vulnerabilities per cell type, the applicant explains that VLCFA accumulation exerts different effects depending on the brain cell type and brain tissue origin. Oligodendrocytes are more susceptible to VLCFA exposure compared to neurons and astrocytes, and oligodendrocyte loss could occur in cALD due to demyelinating lesions. Further, the applicant suggests that differences could be explained by the origin of the primary cultures. Only a tendency towards protection was observed in astrocytes derived from forebrain, while stronger effects were seen in astrocytes derived from spinal cord and from full brain primary cortical culture in an *in vitro* model mimicking the BBB.

In general, the applicant presented some data that is reported as statistically significant, which is in contrast to the results in the study reports. Upon request for clarification, the applicant indicates that discrepancies between statistically significant data in the summary and study reports are due to different statistical methods applied and the different (fewer) number of conditions used in some graphs. The main aim for showing different graphs was to standardise the data obtained across different contract research organisations following the same statistics rules and methods. The justification is considered sufficient. The conclusions do not change with the use of different statistics.

In the first round, there was much uncertainty whether leriglitazone exerts the observed neuroprotective effects via PPAR γ agonism. The concentration range of leriglitazone that provided *in vitro* protection in neurons, astrocytes, microglia and oligodendrocytes against VLCFAs (10 – 500 nM) is much lower than the calculated EC₅₀ of 12.5 µM for activation of the rodent PPAR γ receptor and it

was not considered likely that PPAR γ activation was possible with the concentrations in the brain reached in the animal studies at levels which would exert a noticeable effect. The applicant provided new studies supporting that in both ALD and Parkinson's disease *in vitro* models, the MoA of leriglitazone is driven by agonism of PPAR γ , since in the presence of a PPAR γ antagonist, the neuroprotective effects were reduced. Specific inhibitors of MAO-B inhibition did not affect the neuroprotective effects of leriglitazone. Finally, the expression of PPAR γ and PPAR γ engagement markers (FABP4, adiponectin) after treatment with leriglitazone was abolished with the PPAR γ antagonist.

In addition, the applicant states that since the repertoire of cofactors available for recruitment to the PPAR γ -RXR complex varies among cell types, the extent of PPAR γ responses is assay-dependent. Consequently, EC₅₀ values are greatly dependent on the actual co-activator, reporter genes and cell type used. Therefore, it was argued that *in vitro* PPAR γ agonism assays are only valid to characterise the relative potency among different compounds rather than providing a true estimate of their potency relative to other cellular targets. This can be agreed. As the true potency remains unknown, comparing the effective concentrations in the functional *in vitro* assays with the levels of leriglitazone that are reaching the brain is in this case of higher importance. Although varying widely among the *in vitro* assays, neuroprotective concentrations of leriglitazone *in vitro* seem to be approximately in the range of the free leriglitazone concentrations in the brain in the rodent PD studies. It should be noted that the free leriglitazone concentrations in CSF in humans were only measured in a few patients.

The applicant also proposes that efficient MAO-B inhibition requires exposure in the CNS about 10 times higher than that achieved with leriglitazone in ALD patients. It was suggested that the MAO-B receptor must be inhibited by at least 80%-90%, but since this was based on other compounds with other indications this may be different for effects on ALD. The clinically achieved CNS concentrations are 500-900 nM and *in vitro* studies showed MAO-B IC₅₀ values at 705 nM and 822 nM and IC₈₀ values at 2.3-4.7 μ M. The clinically achieved values are between the IC₅₀ and IC₈₀ values, but the clinical relevance of this partial MAO-B inhibition remains unknown. Therefore, a contribution of partial MAO-B inhibition to the clinical effect of leriglitazone cannot be ruled out.

Overall, studies in various disease models representing hallmarks of ALD and AMN showed that leriglitazone is able to induce PPAR γ engagement, modulate biomarkers of inflammation and mitochondrial function, reduce neuroinflammation, resulting in improved motor performance *in vivo* and mildly ameliorated demyelination. Although a minor contribution of MAO-B inhibition cannot be completely excluded and needs to be further substantiated, the overall non-clinical evidence suggests that leriglitazone most likely acts via activation of the PPAR γ receptor. Although agonism of PPAR γ counteracted the downstream effects of ALDP deficiency, such as mitochondrial dysfunction, oxidative stress and inflammation and bioenergetic failure, these are all general concepts, suggesting a non-specific mode of action.

Regarding secondary pharmacodynamics, the selectivity of leriglitazone was evaluated in binding screens of receptors, ion channels, and enzymes. Leriglitazone (at 10 μ M) had no meaningful (more than 50%) binding affinity for any of the 55 tested targets in a binding screen of receptors, ion channels and enzymes. Another screen was performed to evaluate the potential inhibition of monoamine oxidase (MAO)-A and MAO-B enzyme activity. For MAO-B, leriglitazone inhibited the receptor with an IC₅₀ of 0.7 μ M, compared to 0.15 μ M for pioglitazone. The enantiomers of leriglitazone had a comparable inhibition.

With regard to safety pharmacology, *in vitro* studies suggest a low risk for QT prolongation at the proposed clinical exposures. There were no apparent effects of leriglitazone on CNS, respiratory and cardiovascular safety *in vivo*.

Pharmacokinetics

Distribution of leriglitazone was proven to be extensive in NC animal studies and included brain and spinal fluid distribution, which are necessary for a pharmacological effect. In order to study the distribution of leriglitazone in animals with blood-brain-barrier damage (as is, to some extent, the case in cALD patients), a study was performed in a Middle Cerebral Artery Occlusion (MCAO) mouse model and a MCAO rat model. In the MCAO model BBB disruption is caused in one half of the brain of mice and rats by occlusion of the ipsilateral site of the brain for 60 minutes followed by reperfusion, resulting in stroke-like symptoms and BBB damage. No difference in leriglitazone concentration is observed between ipsilateral and contralateral parts of the brain, which may have very different explanations. Firstly, the occlusion may not have resulted in substantial BBB damage, and therefore no difference is observed. Secondly, the BBB may be damaged resulting in higher inflow of leriglitazone into the brain, but if transporter function is not affected (BCRP and PGP) the efflux may still be intact and non-saturated, resulting in similar concentrations in both parts of the brain. However, with induction of ischemia and the resulting damage, it seems unlikely the transporter function is still completely intact. In the rat stroke model only total brain concentrations were presented, which showed no substantial differences compared to the brain concentrations of leriglitazone and M3 in naïve animals.

Another observation in the mice study data provided by the applicant is the three-fold difference in plasma and brain concentrations between the MCAO-mice and the naïve animals. The mean leriglitazone plasma concentration is three-fold increased, however, the mean M3 concentration in plasma is similar to the concentration in naïve animals. In the brain both leriglitazone and M3 are increased in MCAO-mice compared to naïve animals. No sufficient explanation is provided by the applicant as to why there is such a substantial difference between those two groups of animals. Therefore, the presented *in vivo* study results do not provide additional insight into the severeness of BBB disruption in cALD patients and the consequences for leriglitazone concentrations. Yet, it is acknowledged that the precise nature of BBB disruption in cALD is not fully elucidated and therefore it is very difficult to assess the distribution of leriglitazone in these patients. Also, sufficient exposure margins were achieved at the high doses in the preclinical *in vivo* toxicity studies.

Toxicology

There are some uncertainties relating to the non-clinical studies performed with leriglitazone. Margins of exposure (MoE) are expressed as estimates and based on unbound leriglitazone (as protein binding differs between species) and on the 200 µg.h/ml AUC for humans that is mentioned in the SmPC.

Overall, the toxicological effects observed for leriglitazone were in accordance with those expected for PPAR γ agonists and observed in the pioglitazone groups. However, some differences were observed. Although proliferation of adipose tissue (increased deposition of white and brown fat and fatty infiltration of tissues) is a known class effect of PPAR γ agonists, the location of the fat deposits in the rat appears different to those previously reported for pioglitazone (bone marrow, spleen, and parotid gland). In the current study fat deposits and adipose changes were observed in skin, epididymis, ovaries, mammary gland, mesenteric tissue, aorta and hibernating gland, in both the groups treated with leriglitazone and pioglitazone. These changes occurred at exposures below the clinical exposure, with brown fat deposits in the aorta occurring at the lowest dose. The applicant has indicated that the original studies with pioglitazone were conducted 30 years ago, and hence the rats used are not equivalent anymore, which could explain the difference. Also, more recent studies with pioglitazone show similar fat deposits to the current studies. The clinical relevance is likely to be low, since long term clinical experience with glitazones indicate little concern for human risk with regard to fatty acid deposits. Effects on the pituitary gland in the form of increased weight, vacuolation of cells and diffuse hyperplasia have not been previously described for pioglitazone. No such effect has been reported in

dogs, and therefore seems to be rat specific. In ALD patients the HPA axis is clinically monitored and adrenal insufficiency is treated with corticosteroid replacement therapy. Further, so far no adverse effects on the HPA-axis have been reported, after many years of chronic pioglitazone use. It is therefore concluded that a risk for patients is low.

Leriglitazone was negative for genotoxic potential in the bacterial mutagenesis assay, and after 3-hour treatment in the mouse lymphoma mutagenesis assay. However, increased mutation frequency was seen in mouse lymphoma cells after 24-hour treatment. In light of this positive result, the *in vitro* tests were followed up by two *in vivo* studies, in line with recommendations in guideline ICH S2 (R2). The Comet assay is considered an appropriate *in vivo* follow-up assay, since the mouse lymphoma assay appears to indicate a clastogenic effect. Overall, the weight of evidence indicates that leriglitazone has no genotoxic potential.

The role of PPAR γ agonist in tumorigenesis is unclear. While most carcinogenicity studies performed with PPAR γ agonist show an increase in tumour formation, other studies show a protective effect.

Previous rodent studies with other PPAR γ agonist or dual PPAR α/γ agonist have revealed tumours in the bladder, liver, liposarcomas, hemangiosarcomas, and sarcomatous tumours at multiple sites (muscle, skin, stomach, uterus and renal tubules). For these types of tumours research has provided insight into possible mechanisms of action, which are likely to be rodent specific. Of concern for leriglitazone in particular are proliferative changes in the pituitary gland, mammary tissue and reproductive tract. These changes are likely due to a disturbance of normal endocrine homeostasis and related to disturbance of the HPA axis. Although it is not known at this time whether this could lead to the formation of tumours in rodents or in humans, it can also not be excluded. Up to now, conflicting evidence from clinical studies on the risk of bladder tumours have been reported, but for other types of tumours there is no evidence of an increased risk for humans. To further investigate the carcinogenic potential of leriglitazone, the applicant has initiated a 2-year rat carcinogenicity study. For now, a risk of tumour formation in patients cannot be ruled out and will be monitored carefully. This safety issue is part of the benefit/risk analysis.

Embryofetal development toxicity studies were performed in pregnant rats and rabbits and leriglitazone showed to be not teratogenic at any tested dose (highest doses above the target clinical exposure) and that foetal growth was reduced after treatment with leriglitazone at the high dose but there were no effects on foetal morphology (external, visceral, or skeletal) at any dose. Adverse effects on female fertility and early embryonic development were limited to the maximum dose of 50 mg/kg/day, as demonstrated by fewer live embryos on Day 13 of gestation due to a reduction in the mean number of corpora lutea and slight increases in the extent of pre- and post-implantation loss. No adverse effects for male fertility and male mediated effects on early embryonic development were observed at any dose evaluated. No post-natal development toxicity study was conducted.

In a juvenile toxicity study on rats, reduced bone density of the vertebra was seen. It is concluded that the effects on BMD seen in juvenile rats could be relevant for humans, and in particular the pediatric population. This is based on a lack of safety margin in the animal study, a known association between bone fractures and use of PPAR γ agonists from clinical data, increased bone fractures in the leriglitazone arm of the clinical trial, and a plausible mode of action. The effects on bone in the juvenile study are described in the proposed SmPC section 5.3 and the RMP.

2.5.7. Conclusion on the non-clinical aspects

Assessment of the non-clinical dossier of leriglitazone revealed no major objections to marketing authorisation. Not all other concerns could be completely resolved, as these issues concerned topics

that could not be fully elucidated on a scientific level. These issues are not further pursued as they did not have a major impact on the benefit/risk assessment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

study	study aim	dose of leriglitzazone
MT-1-01 (n = 33)	To determine safety, tolerability, PK profile, CSF concentration and food effects of leriglitzazone, and explore effects on biomarkers in healthy adult males	<u>Part A:</u> single dose of 27.32 mg, 81.96 mg, or 245.88 mg under fasted conditions and 81.96 mg or 245.88 mg under fed conditions <u>Part B:</u> multiple dose of 122.94 mg or 245.88 mg once daily for 8 days under fasted conditions <u>Part C:</u> multiple dose of 122.94 mg or 245.88 mg once daily for 8 days under fed conditions
MT-1-03 (n = 12)	To determine absorption, metabolism and excretion and absolute bioavailability in humans of leriglitzazone	<u>Part A:</u> a single oral dose of 180 mg [¹⁴ C]-leriglitzazone hydrochloride as an oral suspension containing 3.7 MBq of radioactivity on Day 1. <u>Part B:</u> 180 mg leriglitzazone hydrochloride as an oral suspension, followed by a 15-minute iv infusion of approximately 100 µg [¹⁴ C]-leriglitzazone hydrochloride containing 0.1 MBq of radioactivity administered 1.5 hours after the oral dose administration on Day 1
MT-2-01 (n = 116)	To determine efficacy and safety in adult male AMN patients with dosing based on PK	initial dose was 136.6 mg once daily; dosages for individual patients were modified after V2 (Week 12) to achieve the desired plasma exposure of 200 µg × h/mL. The average doses were 163 ± 41 mg and 161 ± 40 mg at week 4 and week 12, respectively
MT-2-02 (n = 16, at data cut-off, 11/2022)	To evaluate whether leriglitzazone can arrest disease progression	As specified by PK specialist to achieve desired plasma exposure of 170 µg × h/mL.
MT-2-03 (n = 39)	To determine efficacy and safety in male and female patients aged ≥12 and ≤60 years with FRDA	initial doses were 2.0 mg/kg once daily in patients aged ≥12 to 17 years, 118.39 mg once daily in adult females and 136.6 mg once daily in adult males; dosages for individual patients were modified at V1 (week 4) to achieve the desired plasma exposure of 170 µg × h/mL for each patient

Furthermore, the following clinical studies will be conducted as post-authorisation measure (PAM):

- a food effect study for the commercial formulation.

- a DDI study with leriglitzazone as victim of strong CYP2C8 and 3A4 inhibitors and inducers.
- A DDI study with leriglitzazone as perpetrator of substrates for the transporters BCRP, OATP1B1 and OATP1B3.

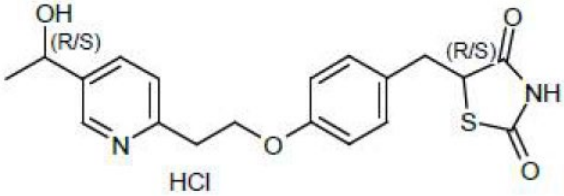
2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of leriglitzazone and its active metabolite M3 were investigated in five clinical studies; two studies in healthy male volunteers (full sampling), one study in male patients with AMN (sparse sampling), one study in male and female patients with Friedreich's Ataxia (sparse sampling) and one study in boys aged ≥ 2 and ≤ 12 years with cALD (sparse sampling) (see tabular overview of clinical trials above). Furthermore, *in vitro* studies were conducted to investigate the plasma protein binding, metabolism, enzyme identification, transporters substrate, DDIs as perpetrator via inhibition and induction of leriglitzazone and M3. M3 has similar pharmacological activity as leriglitzazone and may contribute to the overall efficacy and safety of Nezgylal.

Leriglitzazone is formulated as oral suspension with each mL containing 13.66 mg of leriglitzazone equivalent to 15 mg of leriglitzazone hydrochloride. The recommended starting dose in adults is 10 mL once daily leading to a dose of 136.6 mg leriglitzazone. After 1 month from initiation of treatment, the dose should be increased in adults to 12 mL once daily (163.92 mg leriglitzazone) to achieve a target leriglitzazone plasma AUC of $200 \mu\text{g} \times \text{h/mL}$ ($\pm 20\%$) at steady state. The fixed dose regimen is considered not suitable for paediatric patients by the applicant due to variability in patient weight and BMI due to their growth. Therefore, paediatric patients are recommended to be dosed based on age, height and body weight, which targets an exposure of approximately $170 \mu\text{g} \times \text{h/mL}$ ($\pm 20\%$) at steady state.

Figure 2. Key General Physicochemical Properties of Leriglitzazone

	Molecular formula: $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ Molecular weight: 372.44 g/mol $\text{pK}_a = 4.97$ (base) and 6.42 (acid) Partition Coefficient (n-octanol/water): 2.47 Solubility in aqueous solutions (mg/mL) 2.1 mg/mL at pH 2 0.8 mg/mL at pH 4 <0.1 mg/mL at pH 7 Stereochemistry: Leriglitzazone is a mixture of 4 stereoisomers corresponding to two pairs of diastereomers, E1 and E2. The two isomers present in E1 have the same configuration at C2 (chiral centre in the ethyl side chain) and a different configuration at C5 (chiral centre in the glitazone). The same is true for the two isomers present in E2.
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Population pharmacokinetic analysis

Aim: The population pharmacokinetic analysis aimed to develop a population pharmacokinetic model that jointly describes the concentrations of leriglitzazone and its major metabolite M3 and to simulate the

concentration-time curve and plasma exposure, in terms of AUC, in children, adolescents and adults using different dosing schemes.

Data: The analysis dataset consisted of 156 subjects who received leriglitzazone. A total of 2 subjects (1 in MT-2-01 and 1 in MT-1-03) had no valid pharmacokinetic samples and were therefore excluded. Leriglitzazone and M3 observations were included in the analysis. Subjects included in the analysis had a mean age of 34.2 years (ranging from 4 to 66), a mean bodyweight of 70.5 kg (ranging from 18.4 to 137.8 kg) and a mean body mass index of 23.3 kg/m² (ranging from 14.3 to 36.6 kg/m²). Subjects were predominantly male (n=145, 92.9%) and Caucasian (n=127, 81.4%).

Method: Non-linear mixed-effects methodology was used to develop the population pharmacokinetic analysis. NONMEM (version 7.5.0) and the first-order conditional estimation with interaction algorithm was used for estimation of model parameters. PsN (version 5.0.0) was used for running visual predictive checks, sampling importance resampling and stepwise covariate modelling. Campsis version 1.3.1 and RxODE (version 1.1.5) was used for model simulations. The population pharmacokinetic model was based on a previous population pharmacokinetic model, developed on studies MT-1-01, MT-2-01, and MT-2-03). This model was a 2-compartment disposition model with first-order absorption and first-order elimination. Covariate effects were included on the first-order absorption rate constant and relative bioavailability (food effect), allometric scaling on clearance and volume of distribution parameters (fixed exponents), relative bioavailability (body mass index) and clearance (age and sex). Inter-occasion and inter-subject variability was included on clearance and clearance, volume of distribution of peripheral compartment, relative bioavailability, and the absorption rate constant. The previously developed model was rerun on the updated dataset and additional adjustments were made if necessary. Additionally, potential differences between formulations and the influence of food were (re-)evaluated as covariates. After finalising the parent model, a joint parent-metabolite model was fit to the data, where pharmacokinetic parameters of the parent (leriglitzazone) were fixed to the final estimates. For the joint parent-metabolite model, a similar approach as described by Lindauer *et al.* was used, in which pre-systemic and systemic formation of metabolite was assumed. Apart from including allometric scaling on clearance of the metabolite, no additional covariates were explored. Standard goodness-of-fit plots were used to assess models during model development. Additional criteria were successful minimisation and covariance step in NONMEM and a condition number below 1000.

Model development: Re-running the previous model on the updated dataset resulted in failed convergence of the minimisation, which was attributed to the IV data obtained in MT-1-03. These data were therefore excluded as they were not considered relevant to characterise the pharmacokinetic profile of leriglitzazone after oral dosing. No significant formulation effects were found on the absorption rate or relative bioavailability. Time-varying bodyweight and BMI improved the objective function value significantly (delta OFV: -6.7). An additional study effect (MT-1-03) on the absorption rate constant also significantly improved the overall model fit (delta OFV: -49).

Final model: The final parent only model remained a two-compartment disposition model with first-order absorption and elimination. Food was identified as a significant covariate, leading in a about 84% lower Ka and an about 4% less bioavailability. A small effect of age on CL was observed, while CL in females was about 19% lower. In addition, BMI was also identified as a significant covariate.

As the model was mainly used to quantify the pharmacokinetics in paediatrics, prediction-corrected visual predictive checks for study MT-2-02 showed acceptable performance of the model.

Simulations: Simulations were conducted to evaluate different dosing regimens in paediatrics, adolescents and adults. For this, virtual populations were used, which were based on covariate distributions observed in: 1. MT-2-01, Lorenzo's Oil study by Kennedy Krieger Institute (KKI, unpublished) and Amsterdam Medical Centre natural history study (Huffnagel *et al.*, 2019, and

Ballegoij et al., 2020). Individual AUCs were calculated from the simulated pharmacokinetic parameters; relative bioavailability (F) and clearance (CL).

Physiology-based pharmacokinetic analyses

The applicant developed a PBPK model to predict the PK of leriglitazone in paediatric patients and to predict CYP and transporter mediated DDIs. The model was based on *in vitro* and *in vivo* data (full sampling in healthy volunteers and sparse sampling in patients aged 4 to 66 years). The PBPK model is insufficiently qualified to waive clinical DDI studies and no qualification was shown for paediatric patients. The applicant proposes to use the PBPK model prospectively to assess the effect of renal and hepatic impairment, the effect of CYP2C8 genotypes on the PK and the effect of DDIs on the PK of leriglitazone before conducting clinical studies. This is acceptable.

Exposure-response modelling

No dose finding study was performed. Only one dose was investigated in the clinical studies in patients. The exposure was comparable for the different individuals with limited inter-individual variability in C_{min} ; ranging from 3.84 to 5.22 µg/mL. Based on the data, there was no exposure-efficacy relationship for the C_{min} of leriglitazone. M3 was not included since the penetration into the brain is very limited (CSF/plasma ratio was 0.004 for M3).

There was a correlation between the C_{min} and the two safety issues investigated (weight gain and oedema), but this was mainly attributed to differences between the placebo and active treatment groups. Therefore, there is no quantified exposure-safety relationship.

The rationale for using a concentration-targeted approach in study MT-2-01 in AMN patients is based solely on non-clinical findings. These findings cannot be confirmed in the currently conducted clinical trials. It therefore remains unclear whether the selected posology can be considered optimal.

Analytical methods

During the clinical development program, leriglitazone and M3 concentrations were determined in plasma, urine and CSF. Furthermore, a method to determine plasma concentrations of both leriglitazone diastereoisomers E1 and E2 was also provided.

Leriglitazone/M3 in serum: Validation of a bioanalytical method for determination of leriglitazone and M3 in serum was initially conducted in method validation report. This method formed the basis for determination of leriglitazone and M3 concentrations in studies MT-1-01, MT-2-01 MT-2-03. This method was subsequently adapted to another HPLC system and re-validated to comply with latest guidelines. This new bioanalytical method formed the basis for determination of leriglitazone and M3 concentrations in studies MT-2-02 and MT-1-03. A cross-validation between methods has been performed. In short, plasma samples were initially analysed for leriglitazone and the main metabolite, M3, using LC-MS/MS. EDTA was used as anticoagulant and hydroxytioglitazone-d5 and ketopioglitazone-d4 were used as internal standards. Sample processing is performed by protein precipitation. All validation samples were analysed after 1 freeze-thaw cycle. Separation between potential metabolites and interfering endogenous compounds is achieved by HPLC. A mass spectrometer is used for detection in positive ion mode. Long-term stability was confirmed up to 246 days at -20°C and at -70°C for both analytes. This method was subsequently adapted to a new method where separation between potential metabolites and interfering endogenous compounds is achieved by UPLC. Remaining conditions were similar between both methods. Cross-validation results demonstrated that the obtained mean accuracy by the different methods was within 15% (leriglitazone: 6.9%, M3: 5.7%). Both methods were validated for selectivity (endogenous compounds and concomitant medication), within- and between accuracy and precision, matrix effect, stability (stock solution, autosampler, bench-top, freeze/thaw [up to 5 times at -20 °C and -70 °C], long-term [up to 246 days at -20 °C and -70 °C]) and carry-over. In some studies, significant carry-over was

observed, but samples were analysed in order of the pharmacokinetic profile. Additionally, sample results were sufficiently high to exclude relevant carry-over effects. Bioanalytical reports were provided for all studies.

Leriglitazone diastereoisomers: Leriglitazone has two chiral centres (C2 and C5 position). A bioanalytical method using a LC-MS/MS method for the determination of stereoisomers of leriglitazone was therefore developed. The quantitative determination of E1 and E2, each a mixture of two enantiomers of leriglitazone in human EDTA plasma samples was conducted. No full method validation was conducted, only determination of linearity, accuracy and precision (one run), matrix effect, dilution, selectivity, carry-over and matrix variability was performed. In addition, an attempt was made to measure the four different stereoisomers in MT-2-01 (ADVANCE). The method was qualified or scientifically validated. This method was considered not fully validated, because it was not possible to obtain the four stable diastereoisomers used as reference, due to their instability and easy interconversion.

Leriglitazone/M3 in urine: A LC-MS/MS method for detecting leriglitazone and M3 in human urine samples was developed. Sample processing is performed by liquid-liquid extraction. Separation between potential metabolites and interfering endogenous compounds is achieved by HPLC. A mass spectrometer is used for detection in positive ion mode.

Leriglitazone/M3 in CSF: Leriglitazone and M3 were analysed in CSF in studies MT-1-01 and MT-2-01. CSF samples were analysed for leriglitazone and the main metabolite, M3, using LC-MS/MS. Hydroxytioglitazone-d5 and ketoprogitazone-d4 were used as internal standards. Sample processing is performed by dilution. All validation samples were analysed after 1 freeze-thaw cycle. Separation between potential metabolites and interfering endogenous compounds is achieved by HPLC.

Permeability

The *in vitro* permeability of leriglitazone was investigated in Caco-2 cells in the presence of P glycoprotein and BCRP inhibitors. Leriglitazone appears to be a highly permeable compound. The absolute oral bioavailability was >90%, indicating high absorption. Therefore, leriglitazone can be considered a BCS Class II compound (poor solubility – high permeability).

Absorption

The pharmacokinetics of leriglitazone are currently based on data from two studies in healthy volunteers over a dose range of 27.32 to 245.88 mg following a single dose and over a dose range of 122.94 to 245.88 mg following once daily dosing for 8 days. Both leriglitazone and M3 showed rapid absorption with a t_{max} around 1.5 hour. The absolute oral bioavailability of leriglitazone is ~91%. The C_{max} and AUC of leriglitazone and M3 increase dose proportional over a single dose range of 27.32 to 245.88 mg leriglitazone. Approximate steady state was reached by 5 days. An accumulation of ~1.7-fold for C_{max} and AUC occurs for leriglitazone and M3 following once daily dosing. No time-dependency in the pharmacokinetics of leriglitazone was detected in healthy volunteers that were dosed up to 8 days. Variability in the pharmacokinetics was relatively low in healthy volunteer (9 to 29%), which could be explained by the relatively homogeneous population.

No clinical study was conducted investigating if the two oral suspensions used in the clinical studies were bioequivalent. The population pharmacokinetic model indicated that the formulation used in study MT-1-03 (commercial formulation) had a 80% reduction in the absorption rate constant. Study MT-2-01 also used the commercial formulation, but only sparse data were collected. Potential differences in the pharmacokinetics between formulations cannot be excluded. A new food effect study would be conducted as PAM.

Administration of leriglitzazone after a high-fat meal only delays the absorption of leriglitzazone. The $t_{\max}$ was observed at 3 to 4 hours under fed conditions compared to 0.9 to 1.5 hours under fasted conditions for leriglitzazone and 4 to 5 hours under fed conditions compared to 0.6 to 1.5 hours under fasted conditions for M3. Therefore, in the clinical studies in patients, it was recommended that leriglitzazone could be administered without regard of food. This is also the recommendation in the SmPC. No data on the food effect is however available for the commercial formulation, which is needed to assess the impact on the relative bioavailability (and AUC) and absorption rate constant (and $C_{\max}$).

Distribution

The plasma protein binding of leriglitzazone ranged from 95.7 to 97.0% over a concentration range of 1 to 100 μM (372 to 37244 ng/mL) and was concentration independent. The plasma protein binding of M3 ranged from 98.1 to 98.2% over a concentration range of 0.5 to 5 μM (185-1852 ng/mL) and was concentration independent. The provided *in vitro* data at 1 μM indicate that leriglitzazone and M3 do not distribute into erythrocytes (ratio was 0.725 for leriglitzazone and 0.786 for M3) to a significant extent. Together with the *ex vivo* data, these results indicate that leriglitzazone and M3 most likely do not distribute to erythrocytes to a significant extent over the clinical concentration range.

Based on study MT-1-01 (Part A) and the absolute oral bioavailability, the volume of distribution is ~ 24.4 L (~ 0.30 L/kg when correcting for the average body weight of 81.3 kg in study MT-1-01). The estimated apparent volume of distribution was 0.3 L/kg using the PopPK analysis which corresponds with the *in vivo* observed volume of distribution. The distribution of leriglitzazone to the cerebrospinal fluid was investigated since the brain is the side of action. The analysis is based on samples taken 4 hours post-dose in 6 subjects from the study in healthy volunteers. The CSF-to-plasma ratio is approximately 0.022 for leriglitzazone and 0.004 for M3. However, the CSF-to-plasma ratio was only determined at 4 hours post-dose. It is unknown if the CSF-to-plasma ratio is different at other time points.

Metabolism

The metabolism of leriglitzazone was low in human liver microsomes ($<10\%$ metabolised after 1 hour) and moderate in human hepatocytes ($\sim 25\%$ metabolised after 2 hours). *In vitro* studies with human liver microsomes and CYP-selective inhibitors and human recombinant CYP enzymes identified CYP2C8 and 3A as the main CYP enzymes involved in the metabolism of leriglitzazone. The metabolism of leriglitzazone by recombinant human CYP2C8 followed Michaelis-Menten kinetics well; the K_m value was 34.0 μM and the $V_{\max}$ 2.27 pmol/min/pmol CYP based on M3 formation, and 13.7 μM and 1.60 pmol/min/pmol CYP based on leriglitzazone depletion. The metabolism of leriglitzazone by recombinant CYP3A4 did not saturate and the kinetic parameters for this enzyme could not be determined. The fraction metabolised by CYP2C8 is estimated to be 70 to 84%.

Metabolite profiling was evaluated in plasma and urine samples from the study in healthy volunteers. In the 0-48 h plasma sample, 63% of the radioactivity was leriglitzazone and 25% was M3. A total of 12% was unidentified radioactivity. No further metabolites were identified in plasma. In a pooled urine sample from 0-168 h, 11 metabolite peaks were observed. Only 0.4% of the administered dose was eliminated as leriglitzazone and $<0.02\%$ as M3. Several direct glucuronide metabolites were detected in urine with a total of 27% of the radioactivity, but the individual glucuronide metabolites were $<15\%$ of the radioactivity. In contrast, 27% of the radioactivity originated from a -CH₄+O metabolite. Since 77% of the administered leriglitzazone is eliminated via urine, this metabolite is 21% of the total radioactivity. Since the metabolite compromises $<25\%$ of the total radioactivity no further investigation is warranted. In a pooled faeces sample from 0-168 h, 4 metabolite peaks were observed. A total of 27% is excreted as parent compound of which 9% is unabsorbed material and

18% is absorbed leriglitzazone. Only 2.8% is excreted as M3. A +SO₃ metabolite was the major metabolite in faeces with a total of 30% of the radioactivity. A total of 24% is eliminated via faeces, thus the +SO₃ metabolite is only 7% of the total radioactivity.

In vitro data indicated that leriglitzazone is metabolised to M3 and that M3 can be back-metabolised to leriglitzazone by carbonyl reductase and aldo-keto reductase. Following a 2 h incubation with human hepatocytes, 40% of M3 remained and 10 metabolites were observed. These metabolites were not observed *in vivo*. It is unclear if this is due to the investigated sampling period, sample preparation (some glucuronide metabolites are unstable and can be deconjugated if samples are not directly acidified) or the metabolites are not formed at all *in vivo* because M3 is metabolised back to leriglitzazone and then metabolised via an alternative pathway into another metabolite. Therefore there remains uncertainty on the elimination of M3 *in vivo*.

Transporters

Leriglitzazone is a substrate of P-glycoprotein and BCRP, but not a substrate of OATP1B1 and 1B3. In addition, leriglitzazone is not a substrate of the blood-brain barrier influx transporters OATP1A2 and 2B1. M3 is a substrate of BCRP and OATP1B1. M3 was not a substrate of P-glycoprotein and OATP1B3. In addition, M3 is not a substrate of the blood-brain barrier influx transporters OATP1A2 and 2B1. Leriglitzazone and M3 are not substrates of the transporters OATP1A2 and OATP2B1 in the blood-brain-barrier, indicating that leriglitzazone and M3 are not actively transported into the brain, but actively excreted from the brain by P-glycoprotein and BCRP.

Excretion

Following a single [¹⁴C]-labelled 136.6 mg leriglitzazone dose, radioactivity is mainly excreted in urine (77%) and to a more limited extent via faeces (24% of which 9% is non-absorbed material). The elimination half-life of leriglitzazone and M3 is ~22 h.

Inter-conversion

Leriglitzazone is a mixture of four stereoisomers corresponding to two pairs of diastereomers, E1 and E2. The two isomers present in E1 have the same configuration at C2 (chiral centre in the ethyl side chain) and a different configuration at C5 (chiral centre in the glitazone) and, in E2, the same configuration at C5 and a different configuration at C2.

The ratio between E1 and E2 diastereoisomer pair concentrations in humans is dominated by E2. Geometric mean E1/E2 ratios ranged from 0.1 to 0.3 and did not show any trend with dose administered, fasted or fed status, or time point of the samples. No consequences are expected for efficacy as both E1 and E2 display similar affinity for the PPAR gamma receptor. Regarding the C5 diastereoisomers, it is known to equilibrate rapidly *in vivo* after oral administration.

Pharmacokinetics in patients

The target population are male patients with adrenoleukodystrophy, including adrenomyeloneuropathy and cerebral adrenoleukodystrophy. The disease leads to changes in adhesion molecules and tight junctions in the brain endothelium, which in turn promote an increase in blood-brain-barrier permeability. The applicant investigated the PK of leriglitzazone and M3 in adult patients with adrenomyeloneuropathy, and in paediatric patients with cerebral adrenoleukodystrophy (cALD).

The estimation of pharmacokinetic parameters in adult patients with adrenomyeloneuropathy from sparse sampling using PopPK modelling assumes that the pharmacokinetic profile is similar in shape as the pharmacokinetic profile in healthy volunteers. Only at week 12 in study MT-2-01, samples were collected at 2, 4, and 6 hours post-dose that could be informative for potential shape changes. However, these samples were not used in the dose titration algorithm in study MT-2-01. An algorithm was used to estimate the AUC in patients based solely on the trough concentrations.

The exposure in paediatric study MT-2-02 was deemed comparable to the exposure observed in study MT-2-01 in adults at Week 12 (C_{min} was 5.22 µg/mL for leriglitzazone and 2.03 µg/mL for M3; AUC was 186 µg × h/mL for leriglitzazone and not provided for M3).

The applicant has proposed a different posology for paediatric patients than investigated in study MT-2-02. Therefore, estimated paediatric exposure may be different with the new posology than paediatric exposures that were studied. The new posology adjusts the paediatric dose based on bodyweight, height and age (age categories (2-5, 6-11 and 12-17 years)). The new posology in paediatric and adolescent patients is based on dosing simulations that aimed to target an AUC of 170 µg × h/mL ±20%. Simulations showed that applying the SmPC recommended doses, resulted in an acceptable exposure. It should however be noted that the target exposure in paediatrics is lower than for adult patients (170 versus 200 µg × h/mL). The target exposures were derived from non-clinical studies and have not been clinically validated. Therefore, it is unknown whether these target exposures can be considered optimal. Additionally, the youngest patient included in the population pharmacokinetic analysis was 4 years of age. Allometric scaling was the main factor explaining differences between paediatric patients and adult patients. The applicant is applying for a paediatric indication down to 2 years of age. The plasma exposure can be expected to be reasonably well extrapolated with bodyweight up to the age of 2. Nonetheless, there are no data to confirm this extrapolation exercise in paediatrics <4 years of age.

No clear time-dependent trends in the pharmacokinetics were observed for both leriglitzazone and the metabolite M3 in adult patients with adrenomyeloneuropathy. No results regarding the dose proportionality in patients with adrenomyeloneuropathy have been provided. No deviations from dose proportionality were reported in the PopPK analysis, which was partially based on sparse pharmacokinetic samples in patients with adrenomyeloneuropathy.

In adult patients with adrenomyeloneuropathy (n=2), the CSF-to-plasma ratio for leriglitzazone ranged from 0.016 to 0.029 which appears similar to that observed in healthy volunteers (i.e., 0.022). Leriglitzazone may be actively excreted from the brain by P-glycoprotein and BCRP, inhibitors of these transporters may result in an increase of leriglitzazone concentration in the brain which may have an effect on the efficacy and safety.

The predicted leriglitzazone C_{max} and AUC at Week 12 in patients with an average dose of 147 ± 36 mg leriglitzazone appear comparable with the leriglitzazone C_{max} and AUC in healthy volunteers, but lower for M3 C_{max} (no AUC was predicted). This could be due to all individual dosages in the patients, but could also indicate a lower exposure to M3 in patients.

Pharmacokinetics in special populations

Overall, technically speaking, the intrinsic factors have been reasonably studied using the PopPK model. A major limitation to the investigation of intrinsic factors is however that the current PK data does not allow to detect effects of several intrinsic factors (age, race, renal and hepatic impairment) as a majority of the data is either from healthy volunteers (with a homogenous distribution of covariates) or based on very sparse data.

Renal impairment. The impact of impaired renal function on the leriglitzazone PK is expected not to be clinically significant. Based on the results of the mass balance study, approximately 80% of the leriglitzazone dose was excreted in urine, with only a limited fraction as unchanged drug or M3 metabolite. Therefore, it can be agreed with the applicant that there is a limited risk of significant accumulation of leriglitzazone or M3 in patients with mild and moderate renal impairment. Severe renal impairment may affect the hepatic function and may therefore have an effect on the PK of leriglitzazone

and M3. Efforts should be made to collect data in patients with impaired kidney function in future clinical trials.

Hepatic impairment. Results of the mass balance study indicate that hepatic function plays a prominent role in the pharmacokinetics of leriglitzazone. Leriglitzazone is extensively metabolised and partially excreted via bile acids. Leriglitzazone may not be used in patients with hepatic impairment.

Body weight. The PopPK analysis assumes a large impact of bodyweight on the pharmacokinetics of leriglitzazone as a consequence of the allometric scaling. This could have large implications for the optimal dose of patients at the extremes of the bodyweight distribution in patients. Nonetheless, no exposure-response relationship has been quantified. Therefore, the potential clinical impact of the influence of bodyweight on the pharmacokinetics is unknown.

Age. No data is available in elderly patients. Only one patient of 66 years was included in the PopPK analysis. Therefore, no recommendations can be made in patients >65 years. For paediatric patients with Friedreich's Ataxia, plasma exposure appeared to decrease with age after correction for bodyweight based on PopPK. This effect is presumably not clinically relevant for patients older than 12 years.

Genetic polymorphism. Leriglitzazone appears mainly metabolised by CYP2C8 and 3A. Therefore genetic polymorphisms in CYP2C8, 3A4 and 3A5 may affect the PK of leriglitzazone and its metabolite M3. Currently, the effect of genetic polymorphisms on the PK of leriglitzazone and M3 is unknown. The applicant will conduct a planned DDI study with genotype profiling and if possible, effect of gene polymorphisms will be further evaluated. The results of the effect of genetic polymorphisms on the PK of leriglitzazone and M3 are awaited.

DDI with leriglitzazone and M3 as perpetrator

The concentrations used to determine if leriglitzazone and M3 are an *in vitro* inhibitor or inducers at clinically relevant concentrations were based on the EMA guideline and draft ICH M12 guideline.

Leriglitzazone. At maximal intestinal concentration, leriglitzazone is not an inhibitor of CYP3A4 and P-glycoprotein. The *in vitro* results for BCRP are contradicting and an IC₅₀ value could not be calculated and the inhibition does not seem to be concentration dependent. Maximum inhibition was observed at a concentration of 125 µM (68.5% inhibition). Therefore, leriglitzazone could be an inhibitor of BCRP at maximal intestinal concentration. At maximal portal vein concentrations, leriglitzazone is an inhibitor of OATP1B1 and 1B3. At maximal systemic concentration, leriglitzazone is an inhibitor of the transporters OATP1B1, and OCT1. Leriglitzazone is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A and the transporters P-glycoprotein, BCRP, OATP1B3, OAT1, OAT3, and MATE1. Leriglitzazone is not a time-dependent inhibitor of CYPs and OATP1B1 and 1B3. Leriglitzazone is most likely not an inducer of CYPs and transporters via AhR, but may be an inducer via CAR and PXR (induction observed at concentrations of 50 µM and more). Thus, leriglitzazone could be an inhibitor of the transporters BCRP (maximal intestinal concentration), OAT1B1 (maximal portal vein and systemic concentration) OATB13 (maximal portal vein concentration) and OCT1 (maximal systemic concentration) in clinical practise.

M3. At maximal systemic concentrations, M3 may be an inhibitor of BCRP. At maximal systemic concentrations, M3 is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A and the transporters P-glycoprotein, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and MATE1. M3 is not a time-dependent inhibitor of CYPs. M3 is most likely not an inducer of CYPs and transporters via AhR, CAR and PXR. Thus, M3 could be an inhibitor of BCRP (maximal systemic concentration) in clinical practise.

Based on the outcome of these *in vitro* results, the applicant was planning a DDI study investigating leriglitzazone and M3 as perpetrator on the PK of substrates of BCRP, OATP1B1 and OATP1B3. Currently, no sensitive substrate for OCT1 is available and therefore no clinical DDI study can be

conducted. The proposal from the applicant was that the transporter DDI study could be submitted as post-approval commitment in case of positive outcome.

DDI with leriglitzazone and M3 as victim

Leriglitzazone is mainly metabolised by CYP2C8 and 3A4. Leriglitzazone is a substrate of P-glycoprotein and BCRP. Thus, inhibitors of CYP2C8, CYP3A4, P-glycoprotein, and BCRP and inducers of CAR/PXR (increase in CYP2C8 and 3A4 activity) may have a clinically relevant effect on the PK of leriglitzazone. The applicant is planning a clinical DDI study with leriglitzazone as victim of strong CYP2C8 and 3A4 inhibitors and inducers in which on both the pharmacokinetics of leriglitzazone and M3 will be investigated. Furthermore, leriglitzazone may be actively excreted from the brain by P-glycoprotein and BCRP, inhibitors of these transporters may result in an increase of leriglitzazone concentration in the brain. Currently, it cannot be concluded that increases in brain concentration of leriglitzazone could result in an increase in safety issues.

The effect of increase in gastric pH on the PK of leriglitzazone and M3 was not specifically studied, and only a small number of patients were treated with co-medication to increase their gastric pH (n=9). In these limited number of patients, no effect was observed on the C_{min} . Therefore, the effect of increase in gastric pH is most likely limited.

Conclusion

The PK of leriglitzazone and its pharmacologically active metabolite M3 were investigated in five clinical studies; two studies in healthy male volunteers (full sampling), one study in male patients with AMN (sparse sampling), one study in male and female patients with Friedreich's Ataxia (sparse sampling) and one study in boys aged ≥ 2 and ≤ 12 years with cALD (sparse sampling). There are uncertainties regarding the effect of food on the commercial formulation and DDIs.

2.6.2.2. Pharmacodynamics

Mechanism of action

Leriglitzazone is a full and selective peroxisome proliferator-activated receptor gamma (PPAR γ) agonist. PPAR γ agonists activate key genes that counteract oxidative stress, stimulate mitochondrial biogenesis and decrease inflammation, preventing axonal degeneration and neuroinflammation (Corona and Duchon, 2016). Neziglyal oral suspension contains leriglitzazone (also known as M4, M-IV and MIN-102 as hydrochloride), one of the active metabolites of pioglitazone. PPAR γ agonists induce neuroprotective and restorative effects in several preclinical models of neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson's disease, Friedreich's ataxia (FRDA) and Alzheimer's disease (AD), as well as in ALD.

In nonclinical studies, leriglitzazone demonstrated high oral bioavailability in both rodents and non-rodent species and has a nonclinical toxicological profile in line with the drug class, without additional unexpected adverse effects.

Primary and Secondary pharmacology

The PD of leriglitzazone was investigated in healthy male volunteers (Study MT-1-01) and in adult male patients in the pivotal study MT-02-1.

Study MT-1-01

Study MT-1-01 was a PK study in 33 healthy male volunteers, with three parts. Part A included a single oral administration of leriglitazone (N=9; dose 30, 90 and 270mg). Part B (N=18; dose 135 and 270mg) and C (N=6; dose 135 and 270mg)) included single and multipole oral administration of leriglitazone.

Adiponectine was included as a marker for PPAR γ engagement. PFABP-4 was included as a marker of PPAR γ activation in the CNS. C-reactive protein (CRP), cytokines (Interleukin [IL]-6 and IL-8) and chemokines (monocyte chemotactic protein [MCP]-1 and C-X-C motif chemokine 10 [CXCL10]-interferon γ -induced protein [IP10]) were evaluated as biomarkers for inflammation, see Table 2, Table 3 and Table 4.

Table 2. Mean Plasma Concentrations of Adiponectin and FABP-4 in MAD Part of Study MT 1 01

Biomarker	135 mg			270 mg		
	Day 1 (Baseline)	Day 8	Change from Baseline	Day 1 (Baseline)	Day 8	Change from Baseline
	Mean	Mean	(%) Mean	Mean	Mean	(%) Mean
Adiponectin ($\mu\text{g/mL}$)	4.53	13.9	+207	5.01	22.7	+353
FABP-4 (ng/mL)	8.84	15.6	+76	9.28	16.7	+80

Abbreviations: CSF = Cerebrospinal fluid; FABP-4 = Fatty acid binding protein 4; MAD = Multiple ascending dose; ND = Not determined; QD = Daily; SAD = Single ascending dose.

Table 3. Mean CSF Concentrations of Adiponectin and FABP-4 in MAD Part of Study MT 1 01

Biomarker	135 mg			270 mg		
	Day 1 (Baseline)	Day 8	Change from Baseline	Day 1 (Baseline)	Day 8	Change from Baseline
	Mean	Mean	(%) Mean	Mean	Mean	(%) Mean
Adiponectin ($\mu\text{g/mL}$)	6.0	9.4	+57	5.8	9.8	+69
FABP-4 (ng/mL)	0.74	0.76	+2	0.75	1.18	+59

Abbreviations: CSF = Cerebrospinal fluid; FABP-4 = Fatty acid binding protein 4; MAD = Multiple ascending dose; ND = Not determined; QD = Daily; SAD = Single ascending dose.

Table 4. Change from Baseline (%) of Inflammatory Biomarkers in CSF in MAD Part of Study MT 1 01

Biomarkers	135 mg			270 mg		
	Day 1 (Baseline)	Day 8	Change from Baseline	Day 1 (Baseline)	Day 8	Change from Baseline
	Mean	Mean	(%) Mean	Mean	Mean	(%) Mean
IL-8 (pg/mL)	36.3	33.7	-7.2	45.7	33.7	-26.3
IL-6 (pg/mL)	4.19	2.96	-29.3	7.52	1.27	-83.2
MCP-1 (pg/mL)	591	458	-22.5	799	476	-40.4
CXCL10-IP10 (pg/mL)	897	849	-5.3	560	473	-15.5

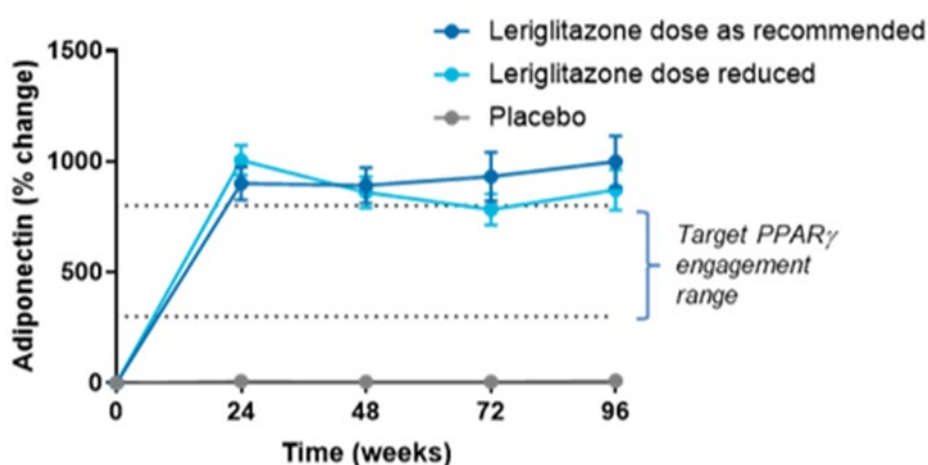
Abbreviations: IL = Interleukin; MAD = Multiple ascending dose; MCP-1 = Monocyte chemotactic protein; CXCL10-IP10 = C-X-C motif chemokine 10, also known as interferon γ -induced protein.

Study MT-2-01

Study MT-2-01 was a Phase II/III, randomised, double-blind, placebo-controlled study in 116 adult male AMN subjects. The dose of leriglitzazone was individually adjusted in each patient to achieve a target exposure of 200 $\mu\text{g}\cdot\text{h}/\text{mL}$, as translated from animal efficacy studies. This study included a substudy in which adiponectin and FABP4 were measured as biomarkers of PPAR γ engagement in plasma. In CSF, adiponectin was measured.

For all patients in the active treatment arm, there was a clear increase in adiponectin levels in plasma at all the timepoints, see Figure 3.

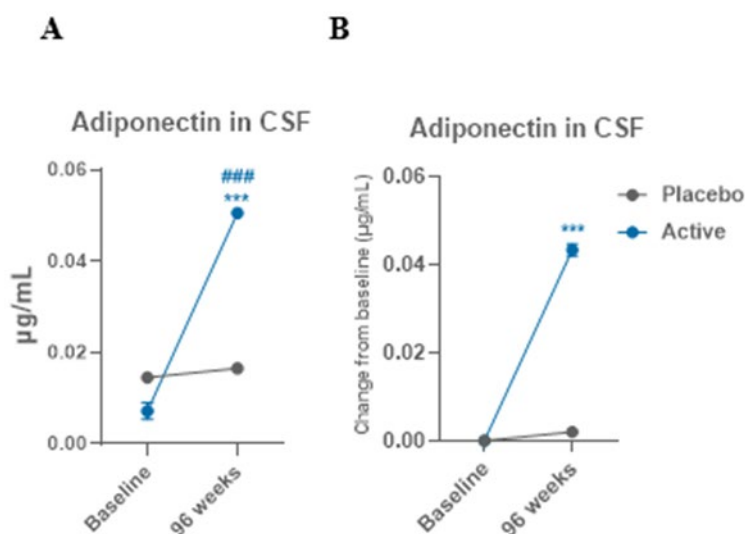
Figure 3. Increase in Adiponectin Levels in Plasma in Treated Patients (% Change vs Baseline)



Time course for adiponectin (ng/mL) in plasma represented as mean % change from baseline $\pm$ SEM. Subgroup "Leriglitzazone dose as recommended" includes all active subjects to whom the investigator prescribed the same dose ($\pm 10\%$) as the dose recommended by the PK expert for at least 50% of days between V2 and V6. Subgroup "Leriglitzazone dose reduced" includes all active subjects to whom the investigator prescribed a dose that was $>10\%$ to $\leq 50\%$ lower than the dose recommended by the PK expert for at least 50% of days between V2 and V6.

In CSF samples, the mean adiponectin concentration and change from baseline to week 96 was increased significantly from baseline to week 96 in the active arm but not in the placebo ($n=2$ per treatment arm), see Figure 4.

Figure 4. Concentration of Adiponectin ($\mu\text{g/mL}$) in CSF Represented as Absolute Values (A) and Change from Baseline at Week 96 (B)

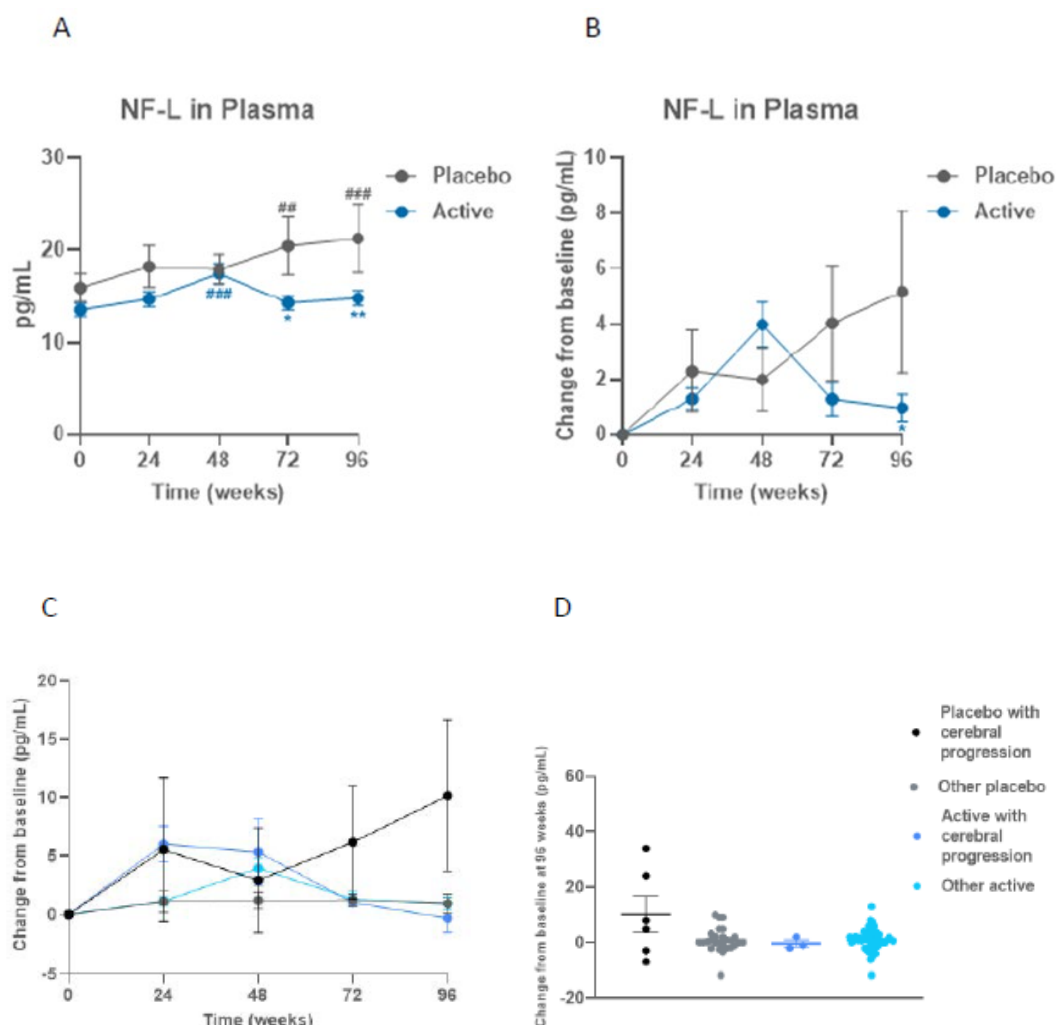


n=2 per treatment arm. Data analysed by ANOVA RM model: Treatment arm, Visit, Interaction as fixed effects, Subject as random effect. ***, $P < 0.001$ (active compared to placebo) and ###, $p < 0.001$ (96 weeks compared to baseline).

In study MT-2-01, the following biochemical biomarkers in plasma were, in addition, measured as exploratory endpoints: neurofilament light chain (NfL), interleukin-8 (IL-8), and Macrophage Inflammatory Protein beta (MIP-1beta). In CSF the following additional markers were measured: monocyte chemotactic protein 1, IL-8, and interleukin-6 (IL-6).

Figure 5 displays the NfL concentration in plasma for placebo and leriglitzazone in study MT-2-01. An increase in plasma NfL concentration in the placebo arm (Figure 5A and 5B), mostly driven by those patients reported with cerebral lesion progression (Figure 5C). Plasma NfL levels increased at 96 weeks in patients with cerebral lesion progression in the placebo arm (mean change of baseline at week 96 of 10.17 pg/mL) but did not increase in the active arm (Figure 5D). In the Open Label Extension (OLE), NfL levels from placebo patients that showed cerebral lesion progression decreased after crossing over to active.

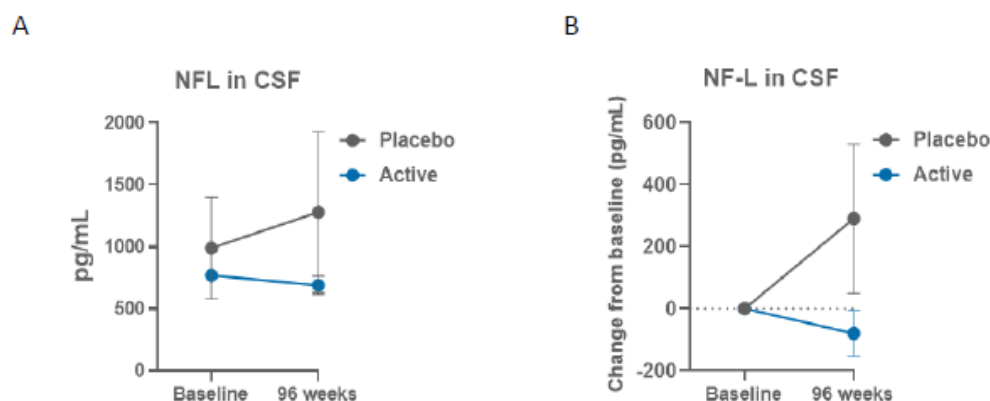
Figure 5. Time Course for NfL (pg/mL) in Plasma in the MT-2-01 Study



NfL concentration (pg/mL) in plasma, (A) absolute values and (B) change from baseline for placebo and active patients at all analysed timepoints. Change from baseline by subgroups according to incidence of cerebral lesion progression, (C) timecourse and (D) change from baseline to week 96. Represented as mean $\pm$ SEM. "Cerebral lesion progression" groups based on central reading criteria as detailed. Supporting listings and descriptive tables showing results by incidence of cerebral lesion progression are reported separately in MT-2-01 statistical report PD additional TFLs v1.0. * used for comparing active versus placebo, # used for comparing each timepoint to baseline. *, $p < 0.05$; **/###, $p < 0.01$; ###, $p < 0.001$.

In CSF, NfL was evaluated in 4 patients and NfL tended to increase in the placebo while showed a trend to decrease in the patient on leriglitazone, see figure below.

Figure 6. (A) Absolute Values and (B) Change from Baseline to Week 96 for NF-L (pg/mL) in CSF. Mean $\pm$ SEM.



Relationship between plasma concentration and effect

A minimum efficacious exposure level was established for plasma AUC (100-130 $\mu\text{g}\cdot\text{h}/\text{mL}$) based on nonclinical efficacy in mice and rat models relevant to AMN and cALD (Rodriguez-Pascau et al., 2021).

In Study MT-1-01 in healthy volunteers, similar concentrations of leriglitzazone were reached in plasma and CSF after oral administration. Adiponectin changes were confirmed with a dose- and concentration-dependent increase of 200% at the dose levels of 135 mg and a 350% at 270 mg, supporting PPAR γ engagement (Rodriguez-Pascau et al., 2021).

No exposure – adverse event relationship was established. A safety margin of 1.14 was obtained with the chronic rat toxicology NOAEL for a target clinical exposure for leriglitzazone of 200 $\mu\text{g}\cdot\text{h}/\text{mL}$.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The PK of leriglitzazone and its pharmacologically active metabolite M3 were investigated in five clinical studies; two studies in healthy male volunteers (full sampling), one study in male patients with AMN (sparse sampling), one study in male and female patients with Friedreich's Ataxia (sparse sampling) and one ongoing study in boys aged ≥ 2 and ≤ 12 years with cALD (sparse sampling). There are uncertainties regarding the effect of food on the commercial formulation and DDIs.

Pharmacodynamics

Leriglitzazone's mode of action seems a-specific: agonism of PPAR γ in the CNS is thought to counteract the downstream effects of ALDP deficiency, i.e., mitochondrial dysfunction and depolarisation, oxidative stress, inflammation and bioenergetic failure. The general mode of action presumably also triggered the evaluation of leriglitzazone in a variety of other neurodegenerative diseases: amyotrophic lateral sclerosis (ALS), Parkinson's disease, Friedreich's ataxia (FRDA) and Alzheimer's disease (AD).

Target engagement of leriglitzazone on biomarkers in plasma and CSF as indicators of PPAR γ receptor engagement is confirmed. However, these biomarkers are not biomarkers of ALD pathophysiology. This was confirmed by the applicant. Non-clinically, a minor contribution of MAO-B inhibition cannot be completely excluded, though, the overall non-clinical evidence suggests that leriglitzazone most likely acts via activation of the PPAR γ receptor (please refer to the non-clinical aspects in this report). Leriglitzazone in CSF was measured in healthy volunteers and in two patients with ALD randomised to leriglitzazone. For these, limited data are provided for CSF, this hampers the interpretation.

Biomarkers of inflammation, e.g. MCP-1 and IL-6, decreased after leriglitazone administration, however additional data shows that they were not successful in predicting ALD disease course. And are thus of limited support for the PD of leriglitazone.

Neurofilament light chain (NfL) is a biomarker for axonal damage. The exploratory analyses seem to indicate that at week 96 the change in NfL concentration in plasma for patients on leriglitazone remained around their baseline value. For placebo an increase in NfL was observed. From the additional analyses it seems that patients who developed cerebral progression have a larger increase in NfL plasma concentration and this seems to explain the increase in NfL in plasma in the placebo group. Though an effect on this biomarker translates not into a clinical benefit.

MMP-9 is included as a biomarker of blood brain barrier dysfunction. This marker is not formally validated. Thus, the data for this marker are considered exploratory and do not allow for conclusion on the validity of MMP-9 as surrogate for clinical benefit.

No pharmacodynamic drug-drug interactions studies have been conducted. Though Drug-Drug Interaction (DDI) studies would have been considered important in light of the negative opinion this is no longer of relevance.

The minimum efficacious exposure level was based on non-clinical data indicating at a certain adiponectin target range. An adiponectin target range implying a minimal efficacy level was based on a non-clinical mouse model. Adiponectin was exclusively used to monitor PPAR γ engagement and therewith leriglitazone agonism activity. Adiponectin is not related to ALD pathophysiology. No exposure-response model was provided, which questions the adequacy of the target dose. For study MT-2-01 in adults males with AMN, the target plasma exposure was set at 200 $\mu\text{g}\cdot\text{h}/\text{mL}\pm 20\%$. However, no *in vitro-in vivo* relationship has been established to confirm the clinical relevance of the exposure target.

No exposure – adverse event relationship has been established. A safety margin of 1.14 was obtained with the chronic rat toxicology NOAEL for a target clinical exposure for leriglitazone of 200 $\mu\text{g}\cdot\text{h}/\text{mL}$. This is considered a small safety margin, especially considering the uncertainties regarding safety in relation to exposure.

2.6.4. Conclusions on clinical pharmacology

No formal dose finding study in patients with ALD was conducted to support the dosing regimen evaluated in the single pivotal study MT-2-01. The rationale for the concentration-targeted approach was based on non-clinical findings. Target engagement of leriglitazone on biomarkers in plasma and CSF, as indicators of PPAR γ receptor engagement, is confirmed. However, these biomarkers are not specific for ALD pathophysiology. In addition, no exposure-response and exposure-safety relationship has been established.

2.6.5. Clinical efficacy

Table below provides the clinical studies for efficacy of leriglitazone in ALD submitted in the MAA. In support of the sought indication, the applicant submitted one pivotal study MT-2-01 (Part 1). This was a phase 2/3, randomised, double-blind, placebo-controlled study in 116 adult male adrenomyeloneuropathy (AMN) patients who received leriglitazone or placebo. This study will provide the main evidence for the efficacy of leriglitazone in the amended claimed indication of "treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)".

Currently, the open-label extension (OLE) of study MT-2-01 is finalised in patients who completed the double-blind period of study MT-2-01 (N=88). In the OLE all patients received leriglitzazone. The objective was to evaluate the long-term safety and efficacy of leriglitzazone on myelopathy and cerebral progression (144 weeks). This MAA contains safety data (cut-off date 03 January 2023) and efficacy data from one year follow up for cerebral progression.

In addition, an open-label study (MT-2-02) in boys (aged 2-12 years) with cerebral ALD (cALD) is ongoing. The aim of this study is to evaluate if leriglitzazone can arrest cerebral progression in paediatrics with cALD. Inclusion is completed (N=23) and top-line results of the pre-defined interim assessment are provided (N=11). Also, a study in 39 patients with Friedreich's ataxia (MT-2-03) is completed. This study was a Phase IIa double-blind, placebo-controlled study in male and female (14 adolescents and 25 adults) with Friedreich's Ataxia with 48 weeks of treatment. 39 patients (26 leriglitzazone, 13 placebo) were included.

Table 5. Clinical studies in Marketing Authorisation Application

Study ID	Diagnosis Incl. criteria	Design	Study Posology	Subjects by arm entered/ compl.	Primary and (key) secondary endpoints
No. of study centres / locations	Age (median; range)	Study Objective			
Study period/status		Duration			
MT-2-01 part 1 (ADVANCE) 10 (FR, DE, HU, IT, ES, NL, UK, US) 08-12-2017 – 16-10-2020 Completed	Adult males with ALD Genetic confirmed 43.5 years (19-66)	Phase 2/3 RD (2:1) DB PC Efficacy, safety and PK 96 weeks	Starting dose: leriglitzazone 150mg 1dd Titrated to plasma exposure of 200 µg·h/mL	116 total: 77 leriglitzazone 39 placebo 96 completed: 62 leriglitzazone 34 placebo	Primary: Δ from BL in 6MWT at Week 96 Key secondary: Δ from BL at Week 96 in: total Body sway PGI-I SSPROM Qualiveen-SF Secondary: EDSS CGI-I Loes severity score
MT-2-01 part 2 Completed	Adult males with ALD Genetic confirmed	OLE of MT-2-01 part 1 Long-term efficacy and safety 144 weeks	Starting dose: leriglitzazone 150mg 1dd Titrated to plasma exposure of 200 µg·h/mL	88 total	Primary: Safety endpoints Efficacy endpoints assessing: Cerebral lesion progression Myelopathy
MT-2-02 (NEXUS) 4 planned Ongoing; planned end date June 2024	Boys (aged 2-12 years) with cALD Genetic confirmed*	Phase 2 Open-label, uncontrolled Efficacy, safety and PK Up to 96 weeks	Starting dose: leriglitzazone 2.6mg/kg (2-5 year); 2.4mg/kg (6-11 year); 2.2mg/kg (12 year); 1dd	13 total	Co-Primary: Arrest of disease progression of cALD at Week 24 and 96 (MRI) Secondary: Effects on other imaging and biochemical parameters

			Titrated to plasma exposure of 170 µg·h/mL		
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2.6.5.1. Dose response studies

The target exposure for Study MT-2-01 in AMN patients was selected based on non-clinical studies (200 µg·h/mL ±20%) with the intention to provide maximal efficacy to AMN patients while remaining in the same range of the NOAEL dose level determined in rodent's studies. A variability margin of ±20% around the target exposure was initially set without prior knowledge, considering that an AUC 20% below the target would still be above the minimum efficacious exposure of 100 µg·h/mL.

The dose to achieve target exposure was selected based on the pharmacokinetic findings of the Phase I, Study MT-1-01, which showed that plasma levels of leriglitazone increased linearly with dose and there was no change in clearance with either dose or time. In order to achieve the target plasma exposure of 200 µg·h/mL in a 24-hour dose interval at steady state, a concentration-control approach was used by measuring C_{min}.

2.6.5.2. Main study

MT-2-01 (Part 1)

Methods

Study MT-2-01 is a phase 2/3, randomised, double-blind, placebo-controlled study that investigated the efficacy and safety of leriglitazone in 116 adult male patients with adrenomyeloneuropathy (AMN).

Figure 7 provides a presentation of the study design. The study consisted of a 28-day screening period, after which the patients were randomised to placebo or leriglitazone (2:1). Patients were titrated in week 0-12 of the double-blind period. The total duration of the double-blind period was 96 weeks. After the double-blind period eligible patients who completed part 1 could enrol in the open-label extension (OLE) phase of the study (i.e. part 2). The OLE is currently completed.

Figure 7. Study Design – MT-2-01



Study Participants

The main inclusion criteria were:

- Male patients aged ≥ 18 to ≤ 65 years. For patients in France only: male patients aged ≥ 18 to ≤ 60 years.
- Diagnosis of ALD based on genetic testing.
- Clinical evidence of spinal cord involvement, with an EDSS score between 2 and 6.
- Ability to walk for 6 minutes, without or with rest, with usual walking aids (e.g., leg braces, cane, or crutch).
- Ability to stand on a force plate with eyes closed and with feet apart for a minimum of 20 seconds.
- Either a normal brain MRI or a type-1 through type-5 pattern MRI abnormality in which the abnormality did not show presence of inflammation. Note: MRI was not required at V-1 if an MRI was obtained within the 6 months before the first day of screening.

The main exclusion criteria were:

- Any other chronic neurological disease with signs of spastic paraplegia, such as hereditary spastic paraplegia, multiple sclerosis, etc.
- Presence of inflammatory (gadolinium [Gd]-enhancing) MRI lesions or any abnormality other than those mentioned in the inclusion criteria.
- Known type 1 or type 2 diabetes.
- Previous or current history of congestive heart failure.
- Reduced left-ventricular ejection fraction, or other clinically significant cardiac abnormalities on echocardiogram that in the investigator's opinion could predispose the patient to volume overload or its attendant consequences.

Treatments

Patients were randomised to leriglitazone or placebo in a 2:1 ratio. The proposed starting dose was 150 mg leriglitazone administered once daily, corresponding to a volume of 10 mL of leriglitazone or placebo oral suspension. Dosing was adjusted on an individual patient basis, based on PK data obtained up to 12 weeks after first dose, to achieve leriglitazone target plasma exposure of 200 $\mu\text{g}\cdot\text{h}/\text{mL}$. Dose adjustments were made for safety/tolerability reasons.

Objectives

The primary efficacy objective of the study was to evaluate the efficacy of MIN-102 on the progression of adrenomyeloneuropathy (AMN) in male patients as determined by the change from baseline in 6-minute walk test (6MWT) compared with placebo after 96 weeks of treatment.

The secondary efficacy objectives of the study were to evaluate the effects of MIN-102 after 96 weeks of treatment on 1) Change from baseline in body sway amplitude (in 4 states: eyes closed/feet apart, eyes open/feet apart, eyes closed/feet together, eyes open/feet together); 2) Comprehensive clinical

rating scales (Severity Score System for Progressive Myelopathy [SSPROM] and Expanded Disability Status Scale [EDSS]); 3) Clinician and patient global impression of symptom severity and change; 4) Muscle strength; 5) Quality of life; 6) Incidence of progression of cerebral lesions; and 7) Loes severity score.

The exploratory objectives of the study were to evaluate the effects of MIN-102 on various biochemical markers in plasma, spinal cord (through magnetic resonance spectroscopy [MRS]) and cerebrospinal fluid (CSF), and brain and spinal cord imaging parameters.

The safety objective of the study was to evaluate the safety and tolerability of MIN-102.

Outcomes/endpoints

Primary endpoint:

1. Change from Baseline to Week 96 in total walking distance in the 6MWT.

Key Secondary endpoints:

2. Change from Baseline to Week 96 in Sway amplitude - total (mm) of body sway in the condition: eyes closed/feet apart
3. Change from Baseline to Week 96 in PGI-I
4. Change from Baseline to Week 96 in Final score of the SSPROM
5. Change from Baseline to Week 96 in Overall score of the Qualiveen Short Form Quality of Life Questionnaire for Urinary Disorders (Qualiveen-SF)

Most important secondary endpoints:

6. Change from Baseline to Week 96 in Sway amplitude - total (mm) of body sway in the conditions: eyes open/feet apart, eyes closed/feet together, eyes open/feet together and "Sway average amplitude – A-P" and "Sway average amplitude – M-L" in each of the 4 conditions
7. Change from Baseline to Week 96 in EDSS ambulation score
8. Change from Baseline to Week 96 in CGI-I
9. Change from Baseline to Week 96 in EDSS step score
10. Change from Baseline to Week 96 in Clinical Global Impression – Severity of Illness scale (CGI-S)
11. Incidence of progression of cerebral lesions in cerebral MRI from Baseline to Week 96
12. Loes severity scores on the MRI from Baseline to Week 96

Most important exploratory endpoints:

13. Spinal cord MRI, assessed at 1 site in the Netherlands
14. Biochemical markers in the brain (through MRS), assessed at 1 site in France
15. MRI exploratory parameters in the brain and spinal cord, assessed at 1 site in France
16. Biomarkers in plasma
17. Biomarkers in CSF, assessed at 1 site in the Netherlands

The primary endpoint was the change from baseline to week 96 in total walking distance in the **six-minute walk test** (6MWT). The 6MWT evaluates functional capacity by measuring the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in 6 minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.

Body sway is a sensitive, reliable method to assess postural stability. This measure is clinically relevant in AMN where the degeneration of the dorsal columns in the spinal cord impairs the patient's ability to control posture and maintain balance. This method measures the excursions of the centre of pressure caused by the natural sway of a subject while the subject is standing on a forceplate. Body sway assessment is done in a fixed sequence of different conditions (eyes closed - feet apart, eyes open - feet apart, eyes closed - feet together, eyes open - feet together) where different parameters are recorded (total amplitude, AP amplitude, and ML amplitude). Total sway amplitude indicates the average excursions of the centre of pressure, while AP and ML amplitudes indicate the excursions across these respective trajectories.

The **Patient Global Impression Scale for Improvement** (PGI-I) is a tool for assessing improvement as judged by the patient. It is a 1 to 7-point weighted scale, ranging from "very much improved" (1) to "very much worse" (7).

The **SSPROM18** is a scale covering 5 domains ranging from 0 (total disability) to 100 (normal) designed to assess progressive myelopathies. The domains covered by SSPROM are: patient-reported motor disability, examined motor disability, spasticity and hyperreflexia, sensory loss, and patient information on sphincter dysfunction. All items are weighted, so that the contributions of each system are as follows: motor disability (30%), strength (20%), sensory loss (20%), tonus (10%) and sphincter function (20%). The scores in all of these domains are added to obtain a final score (0 to 100) (SSPROM) with lower scores indicating a higher degree of impairment.

The **Qualiveen-SF** evaluates urinary-specific quality of life in patients with neurological disorders. The Qualiveen-SF overall score ranges from 0 (not at all affected by the problem) to 4 (extremely affected by the problem). The Qualiveen-SF scores were combined into a single score by summing the 4 individual domains (based on 2 questions each) and dividing the sum by 4.

The Kurtzke EDSS is a widely utilised method of quantifying disability and monitoring changes in the level of disability over time. It is based on a standard neurological examination. **EDSS step** is a measure originally designed to assess disability in multiple sclerosis but is also used in ALD. The EDSS "step" seems to be the "original" EDSS. It determines the overall neurological disability defined as "steps" ranging from 0 (no disability) to 10 (death) in 0.5-unit increments. These steps are defined as a composite from scoring on 8 domains: visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral functions and ambulation. The ambulation domain rates the degree of impairment of walking and is also often used as stand-alone endpoint known as **EDSS ambulation**. It ranges from 0 (unrestricted) to 12 (essentially restricted to bed or chair or perambulated in wheelchair).

The **Clinical Global Impression Scale for Improvement** (CGI-I) is a tool for assessing total overall improvement as judged by the investigator that considers whether or not the improvement is entirely due to the study medication treatment. It is a 1 to 7-point weighted scale, ranging from "very much improved" (1) to "very much worse" (7).

The **Patient Global Impression Scale for Improvement** (PGI-I) is a tool for assessing improvement as judged by the patient. It is a 1 to 7-point weighted scale, ranging from "very much improved" (1) to "very much worse" (7).

The **Loes severity score** is a 34-point severity scale for brain MRI findings and is based on the location and extent of white matter abnormalities involvement and on the presence of either focal or

global atrophy. Nine brain regions are scored (total score 0 = normal to 34 = most severe), a total score of ≥ 1 is considered abnormal by the authors (Loes et al., 2003).

Progression of cerebral lesions was defined as (i) incidence of inflammatory lesions, or (ii) increase in size of existing noninflammatory lesions since Screening or Baseline, or (iii) occurrence of new noninflammatory lesions after Screening or Baseline. Incidence of progression of cerebral lesions was categorised as 0 if lesions were absent at the respective visit and 1 if lesions were present.

Sample size

The sample size calculation for the single pivotal trial was based on the total distance walked on the six-minute walk test (6MWT). A two-sample t-test with a 5% two-sided significance level will have 80% power to detect a difference between both treatment arms of 45 meters (m) on the 6MWT assuming a common standard deviation (SD) of 70 meters when groups of 60 and 30 patients are included, respectively, for MIN-102 and placebo, i.e., a total sample size of 90 patients. In total, to account for dropouts assumed to be around 15%, 105 patients (70 for MIN-102 and 35 for placebo) should be randomised.

Randomisation and blinding (masking)

Patients were randomised through Interactive Response Technology (IRT) to MIN-102 or placebo using a 2:1 randomisation ratio. Randomisation was not stratified.

The following controls were employed to maintain the double-blind status of the study:

- The oral suspension containing active drug or placebo were indistinguishable in appearance and taste.
- The packaging and labelling of the bottles containing active drug or placebo were identical.
- Dosing was adjusted on an individual-patient basis, based on pharmacokinetic data obtained until 12 weeks after first dose, to achieve the required MIN-102 exposure level. Dose adjustment will be decided by an unblinded pharmacokinetic expert not involved in any other study activities; the pharmacokinetics expert will communicate any dose change required to the investigator.
- In order to preserve the blind, random dose adjustments will be made for patients receiving placebo. The unblinded pharmacokinetic expert adjusted the dose for placebo patients on a random basis, taking into account the distribution of dose adjustments in the active treatment group.

Randomisation data will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding of the allocated treatment of all patients after locking the database upon completion of the double-blind part of the study. Only after the study is completed and the data verified and locked will the randomisation codes be made available for data analysis.

Breaking the code at the investigative site in case of an emergency immediately disqualifies the patient from further participation in the study.

Statistical methods

Two statistical analyses plans were written for the placebo-controlled part of the single pivotal study:

- The main SAP version 2.0 dated 4 November 2020 (version 1.0 dated 11 May 2018).

- An additional SAP containing post-hoc analyses version 2.0 dated 8 March 2021 (version 1.0 dated 29 January 2021).

Analysis populations

The Full Analysis Set (FAS) consists of all randomised patients with at least one intake of study medication. The FAS will be used for all efficacy analyses. Patients will be analysed as randomised (intention-to-treat). The Per Protocol Set (PPS) will include all subjects in the FAS without a major protocol deviation as determined during the blinded review meeting. The statistical analysis will be repeated based on the PPS population.

Main SAP

The main SAP specifies the following analyses:

Primary analysis

The primary efficacy endpoint is the absolute change (in meters) from baseline after 96 weeks of treatment in the six-minute walk test (6MWT). Analysis of the primary endpoint will be performed using an MMRM model. MMRM Least Squares Means Estimates and 95% confidence intervals will be given for each treatment group and for the difference between treatment groups. Nominal p-values will be presented for these comparisons. A two-sided significant level of 5% will be used for the primary analysis. No interim analyses were planned.

Prespecified imputation methods for 6MWT include: a) imputation of first week follow-up for missing baseline measurements and imputation of missing baseline measurements using linear extrapolation based on average change in the treatment arm and the subject's first follow-up measurement; b) imputation of worst score on the scale for missing due to death or patient being unable to perform the 6MWT and c) correction of the 6MWT result to adjust for a change in walking aid and d) multiple imputation for missingness for other reasons including refusal of patient to take the test under a MAR assumption. Prespecified methods to correct the 6MWT scores to account for an increase in walking aid under c) use the expected decline based on subjects in the treatment group who did not change their walking aid for imputation.

Several sensitivity analyses are planned for the primary endpoint, including:

No imputation or correction at all, except for missing data under b).

An analysis where missing data under d) are assumed missing not a random (MNAR), i.e. that patients in the active treatment group who discontinue early will have the same evolution after treatment is stopped as patients in the placebo group (who are not exposed to treatment by definition). Patients who discontinue treatment early in the placebo group are assumed to behave as the placebo patients that remain in the study.

Replacing all missing values under c) and d) by the overall mean and i) with and ii) without a correction for change in walking aid.

Excluding observed week 96 data if visit is more than 10 weeks late and imputing the excluded week 96 data using the multiple imputation under d).

Key secondary endpoints

A hierarchical testing procedure will be used where only if the primary endpoint is significant at the 5% level the four key secondary endpoints will be tested sequentially in the following order:

Sway amplitude - total (mm) of Body Sway in the condition: eyes closed/feet apart

Patient Global Impression scale for Improvement (PGI-I)

The final score of the Severity Score System for Progressive Myelopathy (SSPROM)

The overall score of the Qualiveen Short Form quality of life questionnaire for urinary disorders (Qualiveen-SF)

The key secondary endpoints of body sway in the condition eyes closed/feet apart, the final severity score as assessed using SSPROM scale and the overall score on the Qualiveen-SF quality of life questionnaire will also be assessed using the same MMRM as used for the primary endpoint. The key secondary endpoint of PGI-C will be compared between treatment groups using the Wilcoxon Rank Sum test.

Secondary endpoints

The secondary endpoints that are continuous will use an ANCOVA model for statistical analysis and report least squares means for the change from baseline to week 96. This concerns the sway amplitude in the other three conditions, the EDSS ambulation score, the EDSS Step of the Kurtzke Expanded Disability Status Scale, EQ-5D-5L score, the worst of the right or left leg of the Dynamometry measurement, the Multiple Sclerosis Walking Scale (MSWS-12) score, the International Index of Erectile Function questionnaire (IIEF) total score and the Loes severity scores on the MRI. CGI-I and CGI-S will be compared using the Wilcoxon rank sum test. Summary statistics will be provided for incidence proportion of progression of cerebral lesions in each treatment arm (no statistical test was mentioned in the main SAP for comparing treatment arms on this outcome).

Exploratory endpoints

One of the exploratory endpoints is an O'Brien composite score. The sum of ranks of the change from baseline in the six-minute walk test and of the change from baseline in Body Sway (Sway amplitude - total (mm) of Body Sway in the condition: eyes closed/feet apart) will be combined in a composite variable at 48 and 96 weeks following the O'Brien procedure (O'Brien 1984). The ranking will be done using the multiply imputed data from the MAR analyses of the respective endpoint. Summary statistics (mean difference in sum of ranks, standard error and 95% CI) from the multiply imputed data will be calculated using Rubin's rules.

Additional SAP containing post-hoc analyses

Random-slope models were added for primary and key secondary endpoints to supplement the MMRM analyses, since random-slope models might statistically be more efficient and have a direct clinical interpretation in terms of progression slopes. Least Squares Means Estimates and 95% confidence intervals will be given for the slope in each treatment group and for their difference. Furthermore, p-values will be presented testing the null hypothesis of no difference in slopes between both treatment groups. MMRM and random slopes analysis are also introduced for Body Sway amplitude in the eyes closed/feet together condition.

The incidence proportions of progression of cerebral lesions (secondary endpoint) will be reported with 95% Clopper-Pearson confidence intervals and compared between treatment groups using a 2-sided Fisher's exact test.

The incidence proportion of a need for a higher-degree walking aid for the assessment of 6MWT is introduced as a new endpoint. The incidence proportion will be reported by treatment group with 95% Clopper-Pearson confidence intervals and compared between treatment groups using a 2-sided Fisher's exact test.

Also two new O'Brien composite endpoints are introduced in this SAP: i) A composite endpoint comprising 6MWT (function) and body sway (balance) to reflect the disease pathology in the two most relevant neurophysiological systems. For this purpose the sum of ranks of the change from baseline in

6MWT (with body weight adjustment) and Body Sway (eyes closed / feet together condition). For body sway, ADVANCE results indicate that eyes closed / feet together is the condition that might be more sensitive to change in line with a recent AMN natural history publication (van Ballegoij, 2020) and ii) A composite endpoint of balance, function and neurological disability that combines sum of ranks of the change from baseline in 6MWT (with adjustment for body weight), Body Sway (eyes closed / feet together) and SSPROM will be combined in a composite variable at 96 weeks. SSPROM was preferred for the analyses over EDSS as more disease specific and hence with more sensitivity to change in AMN patients.

Identification of markers predictive for the treatment effect

To identify markers predictive for treatment effects, the MMRM models as well as the random-slope models described will be extended to include selected baseline variables (one at a time) and explore their interaction with the treatment effect, i.e. if there are differences between treatment group means at specific time points in the MMRM model or the difference in treatment group slopes in the random-slope model. The analyses will be performed for change in 6MWT at 96 weeks adjusted for weight change as well as (key) secondary endpoint of the body Sway amplitude in eyes closed / feet together condition, the Severity Score System for Progressive Myelopathy (SSPROM), Expanded Disability Status Scale (EDSS), both step and ambulation, LOES score, EuroQol 5-dimensions questionnaire (EQ-5D-5L) and CGI-I because $p < 0.1$ for these outcomes. Candidates for predictive baseline variables considered in these analyses include age, baseline measurements indicating AMN disease severity such as deviation from predicted 6MWT value (based on the equation of Enright et al., 1998), Body Sway, SSPROM and EDSS, and disease duration/time from onset of myelopathy symptoms. P-values will be presented for the interaction between the baseline variables and the treatment effect. Subgroup analyses might be performed by searching for optimal thresholds for baseline variables with statistically significant interactions (two-sided $p \leq 0.05$) with the treatment effect by maximizing the difference in treatment effects for the subgroups with values of the baseline variable below or above the threshold. In addition, subgroups could be investigated with regard to cerebral lesion progression and LOES score.

Results

Participant flow

Patient disposition is presented in Table 6. All 116 randomised patients received at least 1 dose of study medication and were included in the safety set and in the full analysis set. Major protocol deviations leading to exclusion from the per-protocol set were reported for 24 patients, thus the per-protocol set included 92 patients (79.3% of the randomised patients); 33 patients (84.6%) in the placebo group and 59 patients (76.6%) in the leriglitazone group. Seventy-six (76) of the 77 patients (98.7%) in the leriglitazone group had at least 1 measured post-dose PK concentration in plasma or CSF and were included in the pharmacokinetic set.

Of the 116 randomised patients, 96 patients (82.8%) completed the double-blind treatment period and 20 patients (17.2%) prematurely discontinued from treatment. The most frequent reasons for premature treatment discontinuation were AEs, reported for 2 patients (5.1%) in the placebo group and 8 patients (10.4%) in the leriglitazone group, and withdrawal of consent, reported for 3 patients (7.7%) in the placebo group and 6 patients (7.8%) in the MIN-102 group. For 1 patient in the leriglitazone group, the reason was reported as "other" without further information. placebo group and 6 patients (7.8%) in the MIN-102 group. For 1 patient in the leriglitazone group, the reason was

reported as “other” without further information. MIN-102 group. For 1 patient in the leriglitzone group, the reason was reported as “other” without further information.

Table 6. Patient Disposition (Screened Set) Study MT-2-01 Part 1

Category	Placebo n (%)	MIN-102 n (%)	Overall n (%)
Screened set			136
Patients rescreened	0	0	0
Patients randomized	39	77	116
Safety set	39 (100)	77 (100)	116 (100)
Full analysis set	39 (100)	77 (100)	116 (100)
Per protocol set	33 (84.6)	59 (76.6)	92 (79.3)
Pharmacokinetic set	0	76 (98.7)	76 (65.5)
Completed treatment	34 (87.2)	62 (80.5)	96 (82.8)
Discontinued from treatment	5 (12.8)	15 (19.5)	20 (17.2)
Adverse event	2 (5.1)	8 (10.4) ^a	10 (8.6)
Withdrawal of consent	3 (7.7)	6 (7.8)	9 (7.8)
Non-compliance with the study treatment	0	0	0
Lost to follow-up	0	0	0
Investigator decision	0	0	0
Death	0	0	0
Protocol violation	0	0	0
Sponsor decision	0	0	0
Patient did not tolerate lowest dose	0	0	0
Other	0	1 (1.3)	1 (0.9)
Completed the study	34 (87.2)	62 (80.5)	96 (82.8)
Discontinued from the study	5 (12.8)	15 (19.5)	20 (17.2)
Adverse event	2 (5.1)	8 (10.4) ^a	10 (8.6)
Withdrawal of consent	3 (7.7)	6 (7.8)	9 (7.8)
Non-compliance with the study treatment	0	0	0
Lost to follow-up	0	0	0
Investigator decision	0	0	0
Death	0	0	0
Protocol violation	0	0	0
Sponsor decision	0	0	0
Other	0	1 (1.3)	1 (0.9)

Abbreviations: n, number of patients in category. Percentages are calculated based on the number of randomised patients. a One patient had an AE leading to permanent withdrawal of study medication, but completed the double-blind study.

Recruitment

Study period: 8 December 2017 till 16 October 2020.

The study was conducted at 10 sites in France, Germany, Hungary, Italy, Spain, the Netherlands, the United Kingdom, and the United States.

Conduct of the study

Major protocol amendments

In protocol amendment 1 version 2.0 (5 October 2017), the method to be used for replacing missing values at Week 96 for the primary efficacy endpoint was changed from the last value carried forward method to the method described in the SAP.

For France (protocol amendment 1, version 2.1; 24 October 2017), The following amendments were implemented:

- The upper age limit was lowered to 60 years due to a concern over higher risk of bladder cancer in patients older than 60 years.
- Additional exclusion criteria were added to exclude patients with an increased bladder cancer risk.
- Procedures to be followed in case of appearance of bladder cell abnormalities during treatment were added.

In protocol amendment 2 version 3.3 (4 July 2018) amendments were made for the US. The following amendments were implemented:

- A new section on conduct of echocardiograms in case of in case of peripheral oedema to detect risk of cardiac failure due to fluid overload.
- Exclusion criterion 17 specifying a value of BNP of >150 pg/mL at Screening was added to exclude patients with a risk of cardiac failure with a sufficient safety margin and BNP was added to the safety laboratory panel.
- Dose-adjustment guidance was updated to provide more detailed instructions on the steps for dose adjustments following the PK expert's recommendations and dose reductions in case of safety/tolerability issues.
- Added phone contacts between scheduled on-site visits and to remind patients to monitor their weight to protect patients against risk of cardiac failure due to fluid overload.

In protocol amendment 4 version 5.4 (9 April 2020) amendments were made for the US. The following amendments were made:

- Updated the definition of MRI cerebral lesions to indicate that progression of cerebral disease does not only encompass conversion to inflammatory lesions, but also growth of pre-existing non-inflammatory lesions and incidence of new non-inflammatory lesions.
- Specified that the Loes severity score would also be analysed as an endpoint.

Baseline data

Table 7 describes the demographics of the included patients.

Table 7. Patient Demographic Characteristics and Primary and Key Secondary Endpoint Assessment at Baseline, Safety Set

Category	Placebo (N=39)	Leriglitazone (N=77)	Overall (N=116)
Age, years			
Mean (SD)	44.6 (11.14)	42.6 (11.15)	43.3 (11.14)
Male sex, n (%)	39 (100%)	77 (100%)	116 (100%)
Race, n (%)			
White	30 (76.9%)	62 (80.5%)	92 (79.3%)
Other	1 (2.6%)	1 (1.3%)	2 (1.7%)
Not collected (France)	8 (20.5%)	14 (18.2%)	22 (19.0%)
Ethnicity, n (%)			
Not Hispanic or Latino	29 (74.4%)	59 (76.6%)	88 (75.9%)
Hispanic or Latino	2 (5.1%)	4 (5.2%)	6 (5.2%)
Not collected (France)	8 (20.5%)	14 (18.2%)	22 (19.0%)
Weight, kg			
Mean (SD)	80.11 (13.533)	77.56 (12.737)	78.42 (13.007)
BMI (kg/m²)			
Mean (SD)	24.817 (4.0852)	24.340 (3.4784)	24.501 (3.6827)
Years of myelopathy			
n	34	66	100
Mean (SD)	12.8 (6.24)	10.6 (6.26)	11.3 (6.32)
>10 years since myelopathy onset, n (%)	19 (55.9%)	31 (46.9%)	50 (50 %)
Clinical tests and scales			
6MWT distance, Mean (SD), m	354.0 (106.45)	370.0 (137.34)	364.6 (127.54)
Total body sway EC-FA, Mean (SD) (mm)	12.4 (5.52)	11.2 (4.84)	11.6 (5.09)
SSPROM, Mean (SD)	77.7 (6.67)	79.8 (6.55)	79.1 (6.64)
EDSS ambulation, Mean (SD)	3.1 (2.68)	2.8 (2.80)	2.9 (2.75)
EDSS step, Mean (SD)	4.69 (1.18)	4.4 (1.37)	4.5 (1.31)
Cerebral involvement			
Patients with <u>Loes</u> score > 0, n (%)	22 (57.9%)	38 (50%)	60 (52.63%)
Patients with <u>Loes</u> score = 0, n (%)	16 (42.1%)	38 (50%)	54 (47.37%)
<u>Loes</u> score, Mean (SD)	2.408 (4.417)	1.375 (2.288)	1.719 (3.178)

Abbreviations: 6MWT=Six-Minute Walk Test. BMI=body mass index. EC-FA=eyes closed/feet apart. EDSS=Expanded Disability Status Scale. SD=standard deviation. SSPROM=Severity Score System for Progressive Myelopathy; n, number of patients in category; N, total number of patients

Concomitant medications

Concomitant medications were reported for 114 of the 116 patients (98.3%) of the safety set overall. By ATC level 2, the most common concomitant medications were corticosteroids for systemic use (65.5%), followed by analgesics (50.9%), urologicals (48.3%), muscle relaxants (36.2%), anti-

inflammatory and antirheumatic products (32.8%), and antibacterials for systemic use (31.9%). The frequency of concomitant medications was similar in the 2 treatment groups for many of the frequently used concomitant medications. Larger differences ($\geq 15\%$) were noted for muscle relaxants (placebo: 6.2%, leriglitazone: 31.2%), and diuretics (placebo: 2.6%, leriglitazone: 20.8%).

Numbers analysed

Full Analysis Set: All patients in the safety set, i.e., all randomised patients with at least 1 intake of study medication were included in the full analysis set. Patients in this set were used for all efficacy analyses. Patients were analysed as randomised (intention-to-treat). Placebo: N=39 and leriglitazone: N=77.

Per Protocol Set: The per protocol set included all patients in the FAS without a major protocol deviation as determined during the BRM. Placebo: N=33/39 and leriglitazone: N=59/77.

Outcomes and estimation

Primary endpoint

The primary endpoint was the change on the Six-minute walk test (6MWT) at week 96. Results show that there was no difference in decline between leriglitazone and placebo ($p=0.914$). After adjustment for body weight also no difference between leriglitazone and placebo was observed ($p=0.556$), see table below.

Table 8. Change From Baseline to Week 96 in Total Distance Walked in 6 Minutes (Meters) - MMRM (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	39	77
Mean (SD)	354.000 (106.4546)	369.987 (137.3378)
Week 96		
n	33	55
Mean (SD)	311.755 (125.7101)	341.418 (148.7578)
Change from Baseline to Week 96		
n	33	55
Mean (SD)	-30.306 (60.4669)	-27.655 (41.4256)
MMRM model		
Absolute change from Baseline to Week 96		
n	39	77
LS means (SE)	-31.840 (8.7488)	-33.022 (6.6561)
95% CI	-48.9913, -14.6896	-46.0769, -19.9673
MIN-102 – Placebo		
LS means difference (SE)		-1.182 (10.9198)
95% CI		-22.5906, 20.2274
P-value		0.914

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; n, number of patients in a category; N, total number of patients; SD, standard deviation; SE, standard error. Baseline was defined as the last value recorded before first intake of double-blind study treatment. Change from Baseline was calculated as post-baseline value – baseline value. The MMRM model included baseline distance walked in 6 minutes as a covariate. As this imputation was partly done by multiple imputation, these imputed values cannot be presented in the descriptive statistics of this table, only in the MMRM model.

Table 9. Change from Baseline to Week 96 in Total Distance Walked in 6 Minutes (m), (A) Observed Values (B) Adjusted by Weight, Full Analysis Set

Absolute change from Baseline to Week 96	Full Analysis Set	
	Placebo (N=39)	Leriglitazone (N=77)
A. Observed values		
n	39	77
LS means (SE)	-31.8 (8.7)	-33 (6.7)
LS means difference (SE)	-1.2 (10.9)	
95% CI	-22.6, 20.2	
p-value	0.914	
B. Adjusted by weight – Sensitivity analysis		
n	39	77
LS means (SE)	-19.9 (8.9)	-13.4 (6.7)
LS means difference (SE)	6.5 (11.1)	
95% CI	-15.2, 28.2	
p-value	0.556	

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model repeated measures; n, number of patients in category; N, total number of patients; SD, standard deviation; SE, standard error. Baseline was defined as the last value recorded prior to first intake of double-blind study treatment. Change from Baseline was calculated as post-baseline value - baseline value. The MMRM model included baseline distance walked in 6 minutes as a covariate. Values imputed if missing, or if the patient needed a change to higher category of walking aid or became unable to perform the test.

Key secondary endpoints

Assessor's note: As the results on the primary endpoint did not meet statistical significance, results on the key secondary endpoint cannot be claimed being significant given the closed test procedure. Results of key secondary endpoints presented are purely descriptive and p-values are nominal.

Sway amplitude

Body sway total amplitude (mm): eyes closed/feet apart was a key secondary endpoint in this study, see Table 10.

Table 10. Change From Baseline to Week 96 in Total Body Sway Amplitude (mm), Eyes Closed/Feet Apart – Key Secondary Endpoint – MMRM (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	39	76
Mean (SD)	12.365 (5.5186)	11.219 (4.8430)
Week 96		
n	31	53
Mean (SD)	13.580 (5.2940)	11.585 (5.1026)
Change from Baseline to Week 96		
n	31	52
Mean (SD)	1.080 (4.3762)	0.408 (3.6679)
MMRM model		
Absolute change from Baseline to Week 96		
n	39	77
LS means (SE)	1.344 (0.6810)	0.296 (0.5158)
95% CI	0.0087, 2.6799	-0.7166, 1.3079
MIN-102 – Placebo		
LS means difference (SE)		-1.049 (0.8804)
95% CI		-2.7761, 0.6789
P-value		0.234

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; n, number of patients in category; N, total number of patients; SD, standard deviation; SE, standard error. Baseline was defined as the last value recorded before first intake of double-blind study treatment. Change from Baseline was calculated as post-baseline value - baseline value. The MMRM model included baseline total sway amplitude (eyes closed/feet apart) as a covariate. Missing values were imputed as detailed. As this imputation was partly done by multiple imputation, these imputed values cannot be presented in the descriptive statistics of this table, only in the MMRM model.

Patient Global Impression – Improvement Scale (PGI-I)

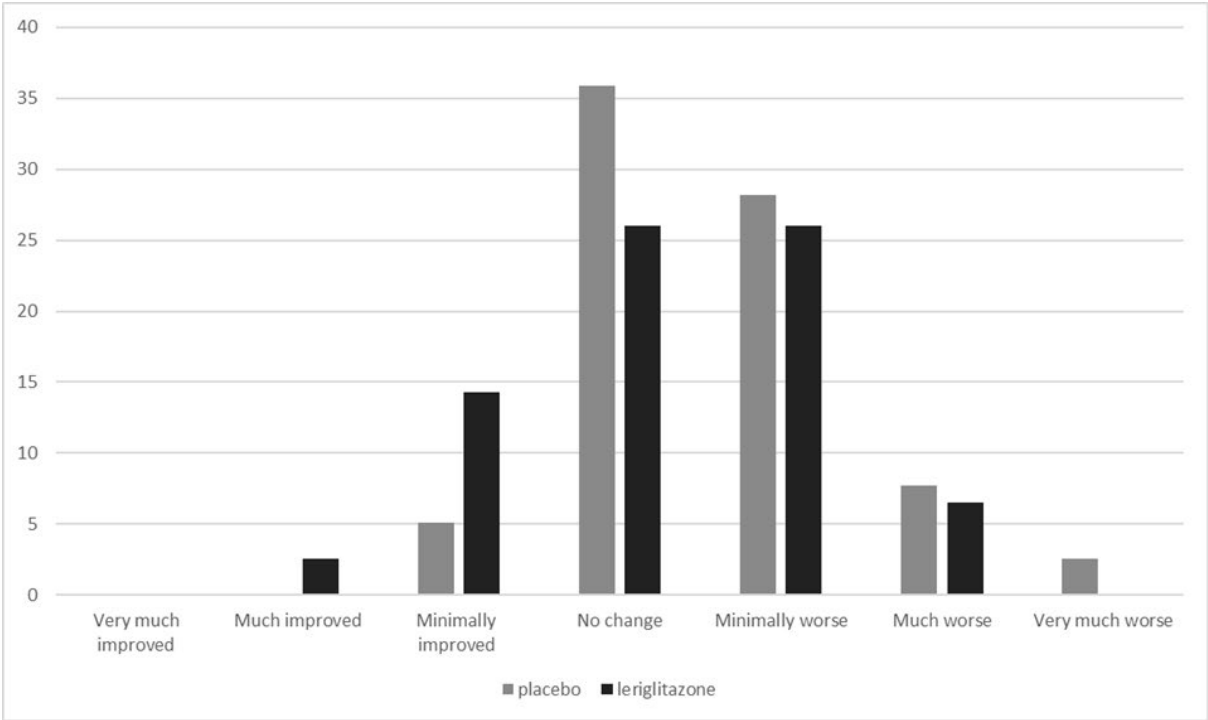
The Patient Global Impression – Improvement Scale (PGI-I) was a key secondary endpoint in this study, see Table 11 and Figure 8.

Table 11. Patient Global Impression – Improvement Scale at Week 96

PGI-I at Week 96	Full Analysis Set	
	Placebo (N=39)	Leriglitazone (N=77)
	Rating, n (%)	
Very much improved	0	0
Much improved	0	2 (2.6)
Minimally improved	2 (5.1)	11 (14.3)
No change	14 (35.9)	20 (26.0)
Minimally worse	11 (28.2)	20 (26.0)
Much worse	3 (7.7)	5 (6.5)
Very much worse	1 (2.6)	0
p-value Wilcoxon rank sum test		0.221

Abbreviations: n, number of patients in a category; N, total number of patients. Percentages calculated based on N. The PGI-I scale score ranges from 1 (very much improved) to 7 (very much worse).

Figure 8. Patient Global Impression – Improvement Scale (PGI-I)



Y-axis is % of patients, X-axis represents the seven categories of the Global Impression-Improvement Scale.

Final score of the SSPROM

The final score on the SSPROM was a key secondary outcome, see Table 12.

Table 12. Change From Baseline to Week 96 in SSPROM Total Score – Key Secondary Endpoint – MMRM (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	39	77
Mean (SD)	77.67 (6.669)	79.81 (6.546)
Week 96		
n	33	55
Mean (SD)	73.30 (10.020)	78.84 (8.919)
Change from Baseline to Week 96		
n	33	55
Mean (SD)	-3.27 (7.607)	-0.93 (4.970)
MMRM model		
Absolute change from Baseline to Week 96		
n	39	77
LS means (SE)	-3.235 (1.0702)	-0.920 (0.8065)
95% CI	-5.3336, -1.1373	-2.5019, 0.6618
MIN-102 – Placebo		
LS means difference (SE)		2.315 (1.3368)
95% CI		-0.3057, 4.9365
P-value		0.083

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; n, number of patients in category; N, total number of patients; SD, standard deviation; SE, standard error; SSPROM, Severity Score System for Progressive Myelopathy.

The SSPROM is a scale covering 5 domains, ranging from 0 (total disability) to 100 (normal). Baseline was defined as the last value recorded before first intake of double-blind study treatment. Change from Baseline was calculated as post-baseline value – baseline value.

Overall score of the Qualiveen Short Form Quality of Life Questionnaire for Urinary Disorders (Qualiveen-SF). The overall score of the Qualiveen-SF was a key secondary endpoint, see Table 13.

Table 13. Change From Baseline to Week 96 in Qualiveen-SF Overall Score – Key Secondary Endpoint – MMRM (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	39	77
Mean (SD)	1.493 (1.0272)	1.194 (0.9273)
Week 96		
n	33	62
Mean (SD)	1.612 (1.0220)	1.345 (1.0120)
Change from Baseline to Week 96		
n	33	62
Mean (SD)	0.189 (0.7175)	0.139 (0.7260)
MMRM model		
Absolute change from Baseline to Week 96		
n	39	77
LS means (SE)	0.221 (0.1174)	0.101 (0.0838)
95% CI	-0.0092, 0.4511	-0.0638, 0.2648
MIN-102 – Placebo		
LS means difference (SE)		-0.120 (0.1439)
95% CI		-0.4025, 0.1617
P-value		0.403

Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures; n, number of patients in category; N, total number of patients; Qualiveen-SF, Qualiveen Short Form Quality of Life Questionnaire for Urinary Disorders; SD, standard deviation; SE, standard error. The Qualiveen-SF overall score ranges from 0 (not at all) to 4 (extremely). Baseline was defined as the last value recorded before first intake of double-blind study treatment. Change from Baseline was calculated as post-baseline value – baseline value. The MMRM model included baseline Qualiveen-SF overall score as a covariate. Missing values were imputed as detailed. As this imputation was partly done by multiple imputation, these imputed values cannot be presented in the descriptive statistics of this table, only in the MMRM model.

Most important other secondary endpoints

EDSS step score

The LS mean change (SE) from baseline at week 96 for EDSS step score was 0.57 (0.15) for placebo and 0.23 (0.12) for leriglitzzone. The LS mean difference was -0.34; 95% CI -0.72, 0.05; p=0.085), see Table 14.

Table 14. Change From Baseline to Week 96 in EDSS Ambulation Score – Further Secondary Endpoint – ANCOVA (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	39	77
Mean (SD)	4.69 (1.184)	4.40 (1.368)
Week 96		
n	33	55
Mean (SD)	5.32 (1.178)	4.55 (1.457)
Change from Baseline to Week 96		
n	33	55
Mean (SD)	0.50 (1.046)	0.27 (0.781)
ANCOVA		
Absolute change from Baseline to Week 96		
n	33	55
LS means (SE)	0.567 (0.1507)	0.232 (0.1161)
95% CI	0.2676, 0.8667	0.0016, 0.4633
MIN-102 – Placebo		
LS means difference (SE)		-0.335 (0.1920)
95% CI		-0.7164, 0.0471
P-value		0.085

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EDSS, Expanded Disability Status Scale; LS, least squares; n, number of patients in category; N, total number of patients; SD, standard deviation; SE, standard error. The EDSS score ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. Baseline was defined as the last value recorded before first intake of double-blind study treatment. Change from Baseline was calculated as visit value - baseline value. The ANCOVA included baseline EDSS step score as a covariate.

MRI-based endpoints – cerebral lesion progression

Based on central radiological readers, a total of 11 patients showed cerebral lesion progression (as per the pre-specified criteria): 8 patients (20.5%) in the placebo group, compared with 3 patients (3.9%) in the leriglitazone group, see Table 15.

Table 15. Incidence of Progression of Cerebral Lesions – Further Secondary Endpoint (Full Analysis Set)

Variable Timepoint	Placebo (N=39)	MIN-102 (N=77)
Presence of cerebral lesions, n (%)		
Baseline	1 (2.6)	1 (1.3)
Incidence of progression of cerebral lesions, n (%)		
Week 48	7 (17.9)	1 (1.3)
Week 96	1 (2.6)	2 (2.6)
Total	8 (20.5)	3 (3.9)

Abbreviations: n, number of patients in a category; N, total number of patients. Percentages were calculated based on N. Baseline was defined as the last value recorded before first intake of double-blind study treatment. Incidence of progression of cerebral lesions was defined as (1) incidence of inflammatory lesions; (2) increase in size of existing noninflammatory lesions since Screening or Baseline; or (3) occurrence of new noninflammatory lesions after Screening or Baseline.

Incidence of progression of cerebral lesions is displayed by new incidence at each timepoint: Patients were only counted once even if they met the progression of cerebral lesions criteria more than once during the study. Two patients had existing inflammatory lesions at Baseline and were not considered in the post-baseline descriptive statistics.

Incidence of progression to cALD

Based on the clinical picture and the radiological changes, threatening physicians made diagnosis of a SAE of clinically progressive cerebral adrenoleukodystrophy. Six patients on placebo and none on leriglitazone were reported to have a SAE of clinically progressive cALD.

Loes severity scores on the MRI

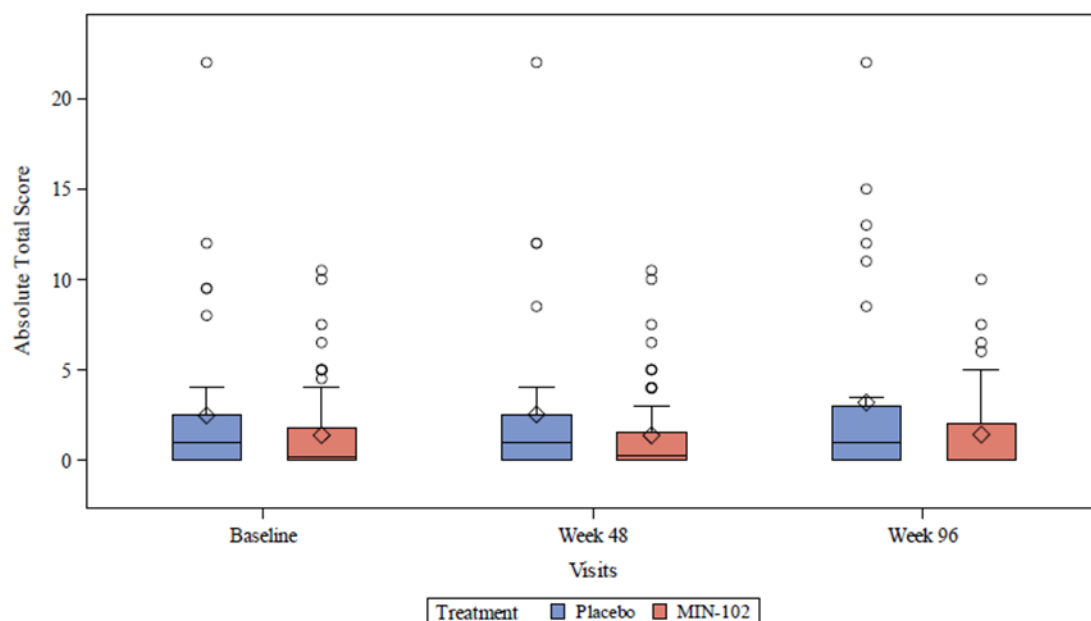
Table 16 shows the change from baseline to week 96 for cerebral MRI Loes score. The patients in the placebo group showed a higher mean (SE) increase in Loes score (0.696 [0.202]) when compared with patients treated with leriglitazone (0.114 [0.151]). Figure 9 displays the boxplots for the Loes severity scores at baseline, week 48 and 96.

Table 16. Change From Baseline to Week 96 in Cerebral MRI Loes Scores – Further Secondary Endpoint – ANCOVA (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	38	76
Mean (SD)	2.408 (4.4172)	1.375 (2.2875)
Week 96		
n	35	61
Mean (SD)	3.186 (5.2189)	1.418 (2.2327)
Change from Baseline to Week 96		
n	34	60
Mean (SD)	0.735 (1.8959)	0.092 (0.3652)
ANCOVA		
Absolute change from Baseline to Week 96		
n	34	60
LS means (SE)	0.696 (0.2021)	0.114 (0.1515)
95% CI	0.2948, 1.0977	-0.1871, 0.4147
MIN-102 – Placebo		
LS means difference (SE)		-0.582 (0.2544)
95% CI		-1.0877, -0.0772
P-value		0.024

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; MRI, magnetic resonance imaging; n, number of patients in category; N, total number of patients; SD, standard deviation; SE, standard error. Loes scores range from 0 to 34. Baseline was defined as the last value recorded before first intake of double-blind study treatment. Change from Baseline was calculated as post-baseline value – baseline value. The ANCOVA model included baseline Loes score as a covariate.

Figure 9. Boxplot of Loes Severity Scores at Baseline, Week 48 and Week 96



- The symbol in the box interior represents the group mean, the horizontal line in the box interior represents the group median. The vertical lines (whiskers) extend from the box to the lower and upper fences and reflect the Interquartile Range (IQR = Q3 – Q1)

In addition, the applicant was requested to present the data on the Loes score as median and IQR with corresponding Hodges-Lehman estimates for location shift. The reason was that the Loes data were highly skewed and therefore the means are highly influenced by the extreme values i.e., not interpretable, see Table 17.

Table 17. Descriptive Statistics of the Loes and the Hodges-Lehmann Estimator of Location Shift and its Respective Cis for Comparison

	Placebo (N=39)	Leriglitazone (N=77)	Overall (N=116)
Loes: Change from Baseline to Week 96			
n	34	60	94
Mean (SD)	0.74 (1.90)	0.09 (0.37)	0.32 (1.21)
Median (Q1-Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
Min, Max	0, 8.5	-0.25, 2	-0.25, 8.5
Hodges-Lehmann Estimate of treatment difference	0.00		
95% CI	0.00,0.00		
p-value	0.1053		

Ancillary analyses

The sensitivity analysis of the primary endpoint adjusting for weight change is discussed under the primary endpoint above. Subgroup analyses were not prespecified but conducted post-hoc.

The following subgroup analyses for efficacy were provided: disease duration and disease severity. For disease duration recent findings in an AMN natural history cohort were taken into account. Therefore, the same cut-off as in the analysis of Natural History data (≤ 10 years since onset of myelopathy symptoms, or above) were used.

Subgroup analyses were conducted examining the impact of disease duration in study outcomes. 6MWT and EDSS ambulation showed a difference between subgroups, see Table 18.

Table 18. Change from Baseline to Week 96 in the Entire Population and in Subgroups Stratified by Disease Duration in Ambulation-related Outcomes

6MWT (m)	Leriglitazone		Placebo		LS means difference (SE)	95% CI	p-value
	n	LS Means	n	LS Means			
All	77	-33	39	-31.8	-1.2 (10.9)	-22.6, 20.2	0.914
≤ 10 years of myelopathy	35	-24.4	15	-62.7	38.3 (21.9)	-4.7, 81.3	0.080
> 10 years of myelopathy	31	-43.7	19	-22.3	-21.5 (15.0.96)	-50.8, 7.9	0.151
EDSS ambulation							
All	55	0.42	33	0.94	-0.52 (0.39)	-1.30, 0.26	0.191
≤ 10 years of myelopathy	30	0.21	10	2.08	-1.87 (0.56)	-3.01, -0.74	0.002
> 10 years of myelopathy	17	0.42	19	0.15	0.27 (0.61)	-0.98, 1.51	0.666
EDSS Step*							
All	55	0.23	33	0.57	-0.34 (0.19)	-0.72, 0.05	0.085
≤ 10 years of myelopathy	30	0.10	10	0.76	-0.66 (0.32)	-1.31, -0.01	0.047
> 10 years of myelopathy	17	0.24	19	0.28	-0.04 (0.24)	-0.54, 0.46	0.868

6MWT analysed by MMRM. For EDSS ambulation, descriptive statistics based on ANCOVA 6MWT=Six-Minute Walk Test. ANCOVA=analysis of covariance. EDSS=Expanded Disability Status Scale. LS=least-squares. MMRM=mixed model for repeated measures. SE=standard error. * Effect mostly driven by EDSS ambulation Source: MT-2-01 posthoc.

Subgroup analysis stratifying by disease severity on EDSS ambulation was performed for the endpoints that showed differences when stratifying by disease duration i.e., 6MWT, EDSS step and EDSS ambulation, see Table 19.

Table 19. Change from Baseline to Week 96 in Ambulation-related Outcomes in the Entire Population and in Subgroups Stratified by Disease Severity

	Leriglitazone		Placebo		LS means difference (SE)	95% CI	p-value
6MWT (m)	n	LS Means	n	LS Means			
All	77	-33	39	-31.8	-1.2 (10.9)	-22.6, 20.2	0.914
EDSS ≤5.5	49	-31.9	24	-37.6	5.7 (15.8)	-25.4, 36.7	0.721
EDSS >5.5	28	-32.5	15	-21.9	-10.7 (14.8)	-39.6, 18.2	0.469
EDSS ambulation							
All	55	0.42	33	0.94	-0.52 (0.39)	-1.30, 0.26	0.191
EDSS ≤5.5	36	0.69	18	1.85	-1.16 (0.54)	-2.24, -0.09	0.035
EDSS >5.5	19	0.11	14	-0.51	0.62 (0.56)	-0.53, 1.78	0.279
EDSS Step*							
All	55	0.23	33	0.57	-0.34 (0.19)	-0.72, 0.05	0.085
EDSS ≤5.5	36	0.37	19	0.88	-0.51 (0.32)	-1.15, 0.13	0.116
EDSS >5.5	19	0.03	14	0.07	-0.05 (0.11)	-0.27, 0.18	0.691

6MWT analysed by MMRM. For EDSS ambulation, descriptive statistics based on ANCOVA 6MWT=Six-Minute Walk Test. ANCOVA=analysis of covariance. EDSS=Expanded Disability Status Scale. LS=least-squares. MMRM=mixed model for repeated measures. SE=standard error. * Effect mostly driven by EDSS ambulation. Source: MT-2-01 posthoc.

• Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 20. Summary of Efficacy for Trial MT-2-01

Title: A randomized, double-blind, placebo-controlled, multinational, multicentre study with open-label treatment extension to assess the effect of MIN-102 on the progression of adrenomyeloneuropathy in male patients with X-linked adrenoleukodystrophy			
Study identifier	MT-2-01 EudraCT number: 2017-000748-16		
Design	A phase 2/3, randomised, double-blind, placebo-controlled, multicentre, 2 parallel-group study in male patients with the AMN phenotype of adrenoleukodystrophy (ALD) to assess the efficacy and safety of leriglitazone (company code MIN-102) treatment.		
	Duration of main phase:		96 weeks (FPFV: 8Dec2017 / LPLV: 28Oct2020)
	Duration of Run-in phase: Duration of Extension phase:		Not applicable +144 weeks (FPFV: 31Oct2019 (ongoing))
Hypothesis	Superiority		
Treatments groups	Leriglitazone		Dose was titrated to 200 µg·h/mL (±20%) 96 weeks, N=77 randomised
	Placebo		96 weeks, N=39 randomised
Endpoints and definitions	Primary endpoint	6MWT	Change from Baseline to Week 96 in total walking distance in the 6MWT [meters]
	Key secondary endpoint	Body sway total score	Change from Baseline to Week 96 in total body sway, eyes closed, feet apart (EC-FA) [mm]
	Key secondary	PGI-I	Change from Baseline to Week 96 in Patient Global Impression

	endpoint		
	Key secondary endpoint	SSPROM	Change from Baseline to Week 96 in SSPROM
	Key secondary endpoint	Qualiveen-SF	Change from Baseline to Week 96 in Qualiveen-SF
	Secondary endpoint	EDSS ambulation	Change from Baseline to Week 96 in EDSS ambulation score
	Secondary endpoint	Loes score	Change from Baseline to Week 96 in Loes score
Database lock	11-Nov-2020		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	All analyses were performed in the Full Analysis Set (FAS), following the intent-to-treat criteria. All analyses correspond to the change from baseline to week 96.		
Descriptive statistics and estimate variability	Treatment group	placebo	leriglitzazone
	Number of subjects	39	77
	6MWT (LS Mean) 95% confidence interval	-31.8 (-48.99;-14.69)	-33 (-46.08;-19.97)
	Body sway total score (LS Mean) 95% confidence interval	1.33 (0.01;2.68)	0.30 (-0.72;1.31)
	PGI-I (distribution)	Very much improved: 0% Much improved: 0% Minimally improved: 5.1% No change: 35.9% Minimally worse: 28.2% Much worse: 7.7% Very much worse: 2.6%	Very much improved: 0% Much improved: 2.6% Minimally improved 14.3% No change: 26% Minimally worse: 26% Much worse: 6.5% Very much worse: 0%
	SSPROM (LS Mean (SE))	-3.24 (1.07)	-0.92 (0.81)
	Qualiveen-SF 95% confidence interval	0.22 (-0.009;0.451)	0.10 (-0.064;0.265)
	EDSS step	0.56 (0.27;0.87)	0.23 (0.002;0.46)
	Loes score	0.70 (0.29;1.1)	0.11 (-0.19;0.41)
	Effect estimate per comparison	Primary endpoint:	Comparison groups
Difference from placebo (SE)			-1.18 (10.9)
95% confidence interval			-22.59;20.23
P-value			0.914
Key secondary endpoints:		Comparison groups	Leriglitzazone vs Placebo
		Difference from placebo (SE)	-1.05 (0.9)
		95% confidence interval	-2.78;0.68
		P-value	0.234
Body sway total score			
PGI-I		Comparison groups	Leriglitzazone vs Placebo

	SSPROM	P-value Wilcoxon rank sum test	0.221
		Comparison groups	Leriglitazone vs Placebo
		Difference from placebo (SE)	2.32 (1.4)
		95% confidence interval	-0.31;4.94
	Qualiveen-SF	P-value	0.083
		Comparison groups	Leriglitazone vs Placebo
		Difference from placebo (SE)	-0.12 (0.14)
		95% confidence interval	-0.40;0.16
	Secondary endpoints: EDSS step	P-value	0.40
		Comparison groups	Leriglitazone vs Placebo
		Difference from placebo (SE)	-0.34 (0.19)
		95% confidence interval	-0.72;0.047
	Loes score	P-value	0.09
		Comparison groups	Leriglitazone vs Placebo
		Difference from placebo (SE)	-0.58 (0.25)
		95% confidence interval	-1.09;-0.08
		P-value	0.024

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Open Label Extension Study MT-2-01

Ninety-six (96) patients completed the double-blind treatment phase (Part 1), and 88 patients (92%) continued in the ongoing OLE, Study MT-2-01 OLE (Part 2). Data concerning the incidence of cerebral progression and cALD incidence for the 3-year follow-up have been provided.

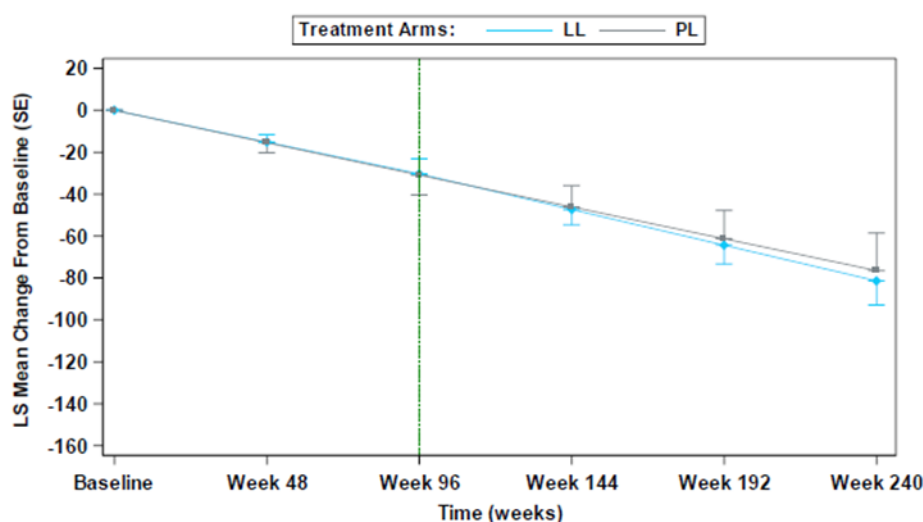
33/39 (85%) patients from placebo during the DB entered the OLE and were switched to leriglitazone treatment. 13/33 (39%) of these patients originally randomised to placebo completed 3 years of OLE leriglitazone treatment. The main reasons for discontinuation during the OLE were: adverse events (33.3%), withdrawal of consent (9.1%) and inability to tolerate the lowest dose (6.1%).

Of the patients who were on leriglitazone during the DB, 55/77 (71%) continued on leriglitazone in the OLE and of these 35/55 (64%) patients completed 3 years of OLE treatment. The main reasons for discontinuation during the OLE were: adverse events (9.1%), withdrawal of consent (9.1%) and inability to tolerate the lowest dose (3.6%).

For the primary endpoint, the 6MWT, there is no differences between treatment arms in the double-blind phase of the study and also not in the OLE, see Figure 10.

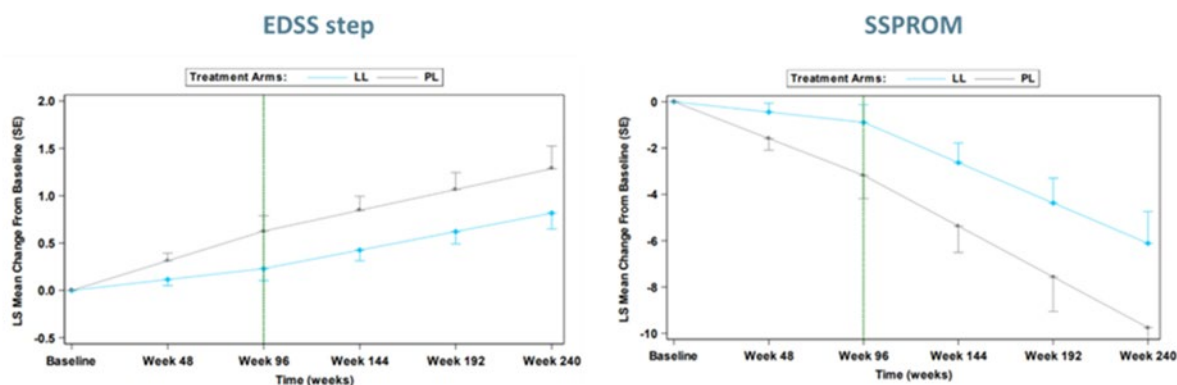
Figure 10. Change from Baseline in Total Distance (meters) Walked at 6 Minutes: Annualised Mean Change (6-minute Walk Test) (Full Analysis Set)

All patients



During the OLE the lines of progression of the two groups seems to run in parallel on the EDSS step and SSPROM.

Figure 11: Change from Baseline EDSS Step and SSPROM: Annualised Mean Change (Full Analysis Set)



During the 3 years in the OLE, 7 additional patients showed cerebral lesion progression according to the central readers. Two of these were originally randomised in the DB to placebo and 5 to leriglitazone.

During the 3 years in the OLE, 2 patients were reported to have a SAE of clinically progressive cerebral adrenoleukodystrophy by their threatening physician. One patient was randomised in the DB to placebo and the other one to leriglitazone.

NEXUS study in boys with cALD

NEXUS is a 96-week, open-label, multicentre study of once-daily oral leriglitazone included boys 2–12 years old with cALD with or without gadolinium-enhancing lesions. The primary endpoint is the proportion of patients with clinically and radiologically arrested disease at week 96 (success criteria: one-sided 95% confidence interval [CI] > 10%). The applicant provided data from the pre-defined 24-

week interim assessment. Secondary endpoints include change from baseline in neurological function score (NFS) and Loes score (LS).

Data for the pre-planned interim analysis at Week 24 are provided. From the study synopsis – as provided by the applicant- it turns out that at Week 24, 18 patients were suited for evaluation. Of these 18 evaluable patients, 8 (44.4%) patients met the “arrested disease” criteria (95% CI: 24.4,-100).

At week 24, 10 patients remained stable concerning Loes score and 8 had an increased score. Of the 10 stable patients at week 24, 3 showed progression after week 24. None of the patients developed major function disabilities (MFD). Though, 3 patients had a NFS of 1 at baseline and 2 of them at week 24, one of these patients had a NFS of 0 at week 24. Two patients progressed from baseline 0 to 1 on the NFS at week 24. Until now, 10 boys underwent hematopoietic stem cell transplantation (HSCT).

Friedreich’s ataxia (MT-2-03)

This study was a Phase IIa double-blind, placebo-controlled study in male and female (14 adolescents and 25 adults) with Friedreich’s ataxia with 48 weeks of treatment. 39 (26 leriglitazone, 13 placebo) patients were included. The applicant considered that the PK and safety data are supportive for the current MAA. Though, the efficacy results are of interest as well as there is no a priori reason, given the general mechanism of action, that leriglitazone might not be effective in Friedreich’s ataxia.

The primary objective was to evaluate the effect of 48 weeks treatment with leriglitazone compared to placebo on cervical spinal cord area as assessed by morphometric MRI measurements. Amongst the secondary endpoints were the Scale for the Assessment and Rating of Ataxia (SARA) and patient and clinicians reported outcomes. On these outcomes no differences were found between placebo and leriglitazone in change from baseline at week 48.

2.6.6. Discussion on clinical efficacy

The claimed indication for leriglitazone was amended twice during the procedure. The indication initially claimed by the applicant was for the treatment of cerebral progression and myelopathy in male patients with adrenoleukodystrophy (ALD). This was amended during the evaluation procedure for the treatment of ambulatory adrenoleukodystrophy (ALD) in adult male patients with early stage myeloneuropathy, and paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD). The latest proposed indication was for the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD). Each applied indication was reviewed based on all available data, as provided by the applicant, all along the assessment of the procedure which included also an oral explanation.

Mode of action and pharmacodynamics

The applicant assumed that mitochondrial dysfunction and depolarisation, oxidative stress, inflammation and bioenergetic failure were counteracted by the agonistic activity of leriglitazone on PPAR γ in the CNS. Considering this mechanism of action, a delay in disease progression or, in the best case, stabilisation of the disease might have been expected. The minimum efficacious exposure level was based on the adiponectin response in a mouse model. This indeed indicates PPAR γ engagement. However, as adiponectin response is not related to the ALD pathophysiology, the underlying assumption that this response also may predict (clinical) response in ALD was not demonstrated at the time of the opinion. From the non-clinical data, it appeared that leriglitazone has a high affinity for monoamine oxidase (MAO) B enzyme inhibition. Though the overall non-clinical evidence suggests that the mode of action of leriglitazone is driven by PPAR γ agonism, a contribution of MAO-B to the

leriglitzazone-mediated effects cannot be ruled based on the presented documentation (see non-clinical part). MAO-B inhibition was not measured clinically.

In addition, several points with regard to the PD were clarified over the course of procedure.

For biomarkers of inflammation like IL-6 and MCP-1, which were considered more relevant for the PD evaluation of leriglitzazone in ALD than adiponectin and FABP-4, additional data showed that they were not successful in predicting ALD disease course. Hence these are of limited support for the PD of leriglitzazone in ALD.

In addition, neurofilament light chain (NfL) is a known and important potential biomarker for axonal damage and as such a potential more plausible biomarker of ALD disease activity. The exploratory data seem to indicate that the change in NfL concentration in plasma for patients on leriglitzazone remained around baseline value, while for placebo the NfL plasma values increased. A priori, this marker was more plausible related to a possible effect in ALD.

For NfL, a correlation is claimed between plasma NfL and radiological findings (lesion volume). However, the data are limited and difficult to interpret. In the scatterplot the regression line is driven by some influential points but most points in the scatter plot cluster. The graphics depicted high variability in NfL basal concentrations and NfL patterns during both placebo phase and active treatment, between patients who developed cALD. Additionally, for most patients in leriglitzazone group, apparently also in those who developed cALD, NfL in plasma was rather stable or had smaller changes at the end of the study. More important, NfL changes did not translate into a clinical benefit.

MMP-9 is included as a biomarker of blood brain barrier dysfunction though not formally validated. As for MMP-9, plasma levels were initially reduced with respect to baseline levels in patients on leriglitzazone including those switched from placebo suggesting a protective effect. The increase in plasma level experienced beyond week 96 may question the duration of the PD effect. There is insufficient evidence that this exploratory biomarker could, even potentially, be predictive for clinical benefit.

In the clinical studies, leriglitzazone in CSF was measured in healthy volunteers and in two patients with ALD randomised to leriglitzazone. For these, limited data are provided for CSF. This hampers the interpretation whether sufficient amounts of leriglitzazone enters the CNS and whether leriglitzazone levels are larger in ALD considering that the BBB may be damaged.

Dose finding

No formal dose finding study in patients with ALD to support the dosing regimen evaluated in the single pivotal study MT-2-01 was conducted. A target exposure level was defined, based on the intention to provide maximal efficacy while remaining in the same range of the NOAEL dose level as determined in the rodent studies. It cannot be excluded that a higher dose could have been efficacious. It is unclear on what the dosing regimen was based on, though it is assumed that this was based on safety.

Design and conduct of clinical studies

Pivotal study

Study MT-2-01 (Part 1) is the main study for efficacy of leriglitzazone in the claimed indication of “the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)”. This study was a phase 2/3, randomised, double-blind, placebo-controlled study of 96 weeks in 116 adult male patients with adrenomyeloneuropathy (AMN) who received leriglitzazone or placebo. The 144-week open-label extension (OLE; Part 2) is completed. In

addition, limited data of ongoing study MT-2-02 in boys aged 2-12 years old with cALD are submitted as supportive data.

In scientific advice, in general the design of pivotal study MT-2-01 was considered acceptable. However, there were doubts that a study duration of 24 months may not be sensitive enough to detect a treatment effect as the natural course of AMN is insufficiently known. Therefore, building safeguards without compromising its methodological integrity into the design was recommended. This recommendation was not followed by the applicant.

Study participants <-> Target population

Patients with a diagnosis of ALD with genetic confirmation are included. For inclusion, patients were required to have either a normal brain MRI or a type-1 through type-5 pattern MRI abnormality in which the abnormality did not show presence of inflammation. In addition, patients with gadolinium-enhancing lesions were excluded from the main study as this would be indicative for cALD. According to the applicant, the Loes score is not related to the MRI patterns since the patterns are a classification based on the anatomic location of the lesion and the Loes score is a scoring scale based on the extent of the lesions. Though, according to Loes (2003), MRI abnormality pattern in combination with age and initial MRI severity score influences the MRI progression.

The initial claimed indication was first amended by the applicant during the evaluation procedure to: "the treatment of ambulatory adrenoleukodystrophy (ALD) in adult male patients with early stage myeloneuropathy, and paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)". In an additional subgroup analysis the impact of disease duration (≤ 10 years vs > 10 years of myelopathy) and EDSS score ($EDSS \leq 5.5$ versus $EDSS > 5.5$) was evaluated in support of an early-stage myelopathy indication. One may wonder whether these cut-off points are adequate i.e., a duration of myelopathy of 10 years and an EDSS of 5.5 hardly indicates early-stage disease. This proposed revision of the indication was not substantiated by data.

Consequently, the claimed indication was further changed by the applicant and restricted to: "the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)". However, the target population of the claimed new indication was not included in the pivotal study. See also discussion below.

Endpoints

The primary endpoint is the 6MWT. The 6MWT is used in different clinical settings ranging from cardiac surgery to Duchenne muscular dystrophy. Key secondary endpoints are body sway, patient global impression – improvement (PGI-I), SSPROM and Qualiveen-SF. Relevant secondary endpoints are the EDSS and the Loes score. Together, the proposed endpoints seem to cover the domains typically affected in patients with ALD. During the scientific advice it was indicated that unpublished data indicated that the 6MWT and Body Sway in the condition "eyes closed, feet apart" are variables sensitive to change over 24 months that could help isolating treatment effect in the proposed study MT-2-01. For the Loes score another cut-off for an abnormal score was chosen than originally proposed by the authors (Loes, 2003). The applicant justified that a cut-off of 0.5 is used in the current standard of treatment for HSCT and this is accepted.

In an exploratory MRI sub study in France and the Netherlands brain and spinal cord diffusion tensor imaging (DTI) was conducted to detect changes to the integrity of the white matter. In France additional analysis to characterise metabolic alterations, fibre density, changes in myelin content and atrophy were conducted.

Sample size

The sample size calculation based on a clinically relevant difference of 45 meters on the six-minute walk test (6MWT) is reproducible. The source of the estimate for the standard deviation of 70 meters was derived from data of the male participants in a previous clinical trial.

Randomisation and blinding

In line with CHMP scientific advice, unequal allocation using 2:1 randomisation was used. The relatively small sample size may have led to treatment groups differing on important baseline factors. Some imbalances were indeed found for disease duration with placebo patients having longer disease duration at baseline and related to this, slightly worse clinical score at baseline.

The applicant has implemented several procedures for masking and blinding. First, blood samples were collected also in the placebo group in order to maintain the blind. Though, subjects in the placebo-controlled part of the trial may have been able to guess their assignment through clinical symptoms and side effects of leriglitazone (oedema, weight gain) which were clearly more often present under leriglitazone than under placebo. It cannot be ruled out that there was at least some awareness among participants and investigators regarding the received treatment, which in turn may have impacted on the measured outcomes such as 6MWT.

Statistical methods

A mixed model for repeated measurements (MMRM) was used for primary endpoint and most of key secondary endpoints. The description of the precise model is brief with important information missing, e.g. the fixed part used for the analysis, the dependent variable and whether an adjustment for baseline was performed. The applicant has provided additional information about the settings used in the MMRM analysis and further explained that MMRM models for all four primary and key secondary endpoints used the change from baseline as the endpoint and included the baseline value as a covariate. This is accepted.

Type I error was controlled over primary and key secondary endpoints using a hierarchical testing approach. Estimands were defined with strategies to deal with intercurrent events such as the subject no longer being able to perform the 6MWT or no longer being alive (through a composite strategy) and a change in walking aid (through a hypothetical strategy). Missing data after early discontinuation of treatment is imputed using the observed data in the arm to which patients were randomised. These strategies are generally considered acceptable. Early discontinuation of treatment is preferably dealt with using a reference-based imputation, but this was included as a sensitivity analysis.

Even though statistical principles for the post-hoc analyses in an additional SAP were specified before performing these post-hoc analyses, the planned analyses could still be informed by the results of the analyses that were part of the main SAP. The majority of post-hoc analyses focus on endpoints that show larger treatment effects in the analyses performed as part of the main SAP, such as the body sway endpoint with eyes closed/feet together which was not a key secondary endpoint. The results of post-hoc analyses are therefore only considered exploratory/supportive.

Conduct of the study

Overall the study was reasonably well performed, but several issues needed clarification by the applicant:

- 14.7% of the major protocol violations that concerned the informed consent were not further clarified. The applicant explained that all patients gave informed consent at study entrance and reconsent concerned a protocol amendment during the study.

- Clarification was requested on the reasons and impact of protocol amendments. The applicant declared that protocol amendments were not informed by safety results available at that time and that there was no possible impact on the blinding of patients/investigators because of these amendments. It is agreed with the applicant that most of the amendments had no impact on the blinding. Clarifications were acceptable.

Efficacy data and additional analyses

Completion

87.2% of patients on placebo and 80.5% on leriglitazone completed the study. Reasons for discontinuation were adverse events: N=2 (5.1%) for placebo and N=8 (10.4%) for leriglitazone; withdrew consent N=3 (7.7%) for placebo and N=6 (7.8%) for leriglitazone. Overall, relative more subjects in the active group withdraw from treatment and adverse events were the main reason for that. However, differences are small. Therefore it is considered unlikely that this difference impacted the results.

Treatment effects

There was no difference in change from baseline at week 96 in 6MWT between leriglitazone and placebo; -1.2 meter (95%CI: -22.6; 20.2, $p=0.91$). The magnitude of this difference and is corresponding p-value suggest a treatment failure rather than a study failure.

Weight gain is a known class effect of PPAR γ compounds and it might have affected the ability to walk and body sway. Therefore, the applicant performed a pre-specified analysis adjusting the analysis of the primary endpoint for body weight. In this analysis also, no difference between placebo and leriglitazone were observed; (6.5 meter (95%CI: -15.2; 28.2 $p=0.56$).

From a methodological point of view, since the results on the primary endpoint did not meet statistical significance, results on the key secondary endpoint cannot be claimed as being significant, given the closed test procedure. Even disregarding this, no difference in change from baseline at week 96 between placebo and leriglitazone was observed in key secondary endpoints (body sway total amplitude in eyes closed/feet apart condition, PGI-I, SSPROM total score, Qualiveen-SF overall score) or other secondary endpoints (EDSS ambulation, EDSS step score, Clinician-based Assessment of Global Improvement and European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) index).

Sensitivity analyses conducted over the primary endpoint did not change this picture. As stated earlier, in an additional subgroup analysis the impact of disease duration (≤ 10 years vs >10 years of myelopathy) and EDSS score (EDSS ≤ 5.5 versus EDSS >5.5) was evaluated, in support of an early-stage myelopathy indication which was further amended by the applicant during the evaluation procedure. The cut-offs were based in a natural history data (see below).

Indeed, the 6MWT and EDSS-ambulation might be more sensitive to detect a delay in progression in subjects that are more ambulatory. However, the 6MWT and EDSS are numerically clearly worse under active treatment as compared to placebo in the late stage (less ambulatory) group, and this is rather unexpected. It would have been expected that there is no difference and certainly that there is no change in direction of the effect. This in turn, challenges the credibility of a hard distinction between early and late stage let alone the sharp cut-off point of 10 years.

Moreover, one of the main inclusion criteria in study MT-2-01 was the ability to walk for 6 minutes, without or with rest, with usual walking aids (e.g., leg braces, cane, or crutch). Hence all subjects still had sufficient ambulatory function that can be maintained for 6 minutes. Note that at baseline the mean 6MWT distance was 364.6 meter (SD 127.5). So even in the worst performers an effect could

have been detected although the absolute effect may be smaller. So the observed effect that the 6MWT is clearly numerically worse under active treatment as compared to placebo is not plausible.

Furthermore, in the other post-hoc subgroup analysis, early and late stage was defined on the EDSS (score ≤ 5.5 score versus a score > 5.5). A EDSS score of 5.5 is defined as a disability severe enough to preclude full daily activities but with an ability to walk without aid or rest for 100 m. A score of 5.0 is defined as disability severe enough to impair full daily activities but ability to work a full day without special provisions and able to walk without aid or rest for 200 m. Over these subgroups no difference in performance was observed between leriglitazone and placebo on 6MWT performance and EDSS-step score. There was a difference in the EDSS < 5.5 subgroup in the change in EDSS-ambulation score in favour of leriglitazone ($p=0.035$). The conclusion is that different but overlapping definitions for early and late-stage disease do not show the same effects over the endpoints, i.e., there is no consistency.

With respect to the natural history data, the applicant had access to the natural study data of the four functional measures collected (6MWT, SSPROM, EDDS and TUG). Indeed, the worsening in 6MWT and SSPROM over 2 years is larger in the < 10 years subgroup as compared to the > 10 years subgroup. However, for in the > 10 years subgroup the worsening in 6MWT and SSPROM is still substantial, i.e., substantial enough to pick up a treatment effect. For the EDSS this argument does not apply, since the decline in late AMN was not substantial. For the SSPROM, a key secondary endpoint in study MT-2-01 and also collected in the Natural history study, results for the < 10 years subgroup are presented. No difference between leriglitazone and placebo was found: 3.1 (95% CI: -1.7;7.8, p -value:0.21). It should be noted that, for the SSPROM the results of the > 10 years subgroup are not provided.

Overall the justification of the two subgroup analysis is poor. More important, the analysis is post-hoc and results are inconsistent over the endpoints and two subgroups. No conclusion can be drawn on the efficacy of leriglitazone in early AMN or a better efficacy compared to the overall AMN population. This would require a confirmatory study.

Two MRI-based endpoints were evaluated: cerebral lesion progression and Loes score. Two patients with existing inflammatory lesions (one in the placebo arm and one in the leriglitazone arm) at baseline were excluded from the post-baseline descriptive statistics. The progression of cerebral lesions was based on the judgement of independent readers, while the treating physicians made diagnosis of a SAE of clinically progressive cerebral adrenoleukodystrophy based on the clinical picture and the radiological changes. According to the applicant, the progression of cerebral lesions is associated with the development of progressive cALD with a major impact on life expectancy. In the double-blind phase, less patients on leriglitazone had cerebral lesion progression as judged by the central readers compared to placebo (3 vs. 8 patients). Six out of 39 patients on placebo had, according to the treating physicians, a diagnosis of cALD (15.4%) while in the leriglitazone arm it was 0 out of 77 patients. These results should be seen in the context of different severity of the groups, with placebo patients having longer disease duration and worse MRI scores and clinical score at baseline.

The applicant was requested to present the data on the Loes score as median and IQR with corresponding Hoghes-Lehman estimates for location shift. The reason was that the Loes data were highly skewed and therefore the means are highly influenced by the extreme values i.e., not interpretable. Patients in the placebo group had a higher Loes score at baseline as compared to patients in the leriglitazone group. More important, there is hardly a shift over time in Loes score in both groups as compared to their baseline. The difference over time just reflects that the baseline difference are persisting over week 48 and week 96. Hence, no conclusions can be drawn on the effect of leriglitazone based on the Loes score. As important, the correlation between changes in Loes score and other MRI indexes and clinical outcome could not be substantiated. Instead, the applicant refers to

the MRI sub-study of ADVANCE where the relationship between clinical outcome and MRI indexes was explored. Results are presented selectively and were not considered satisfactory.

At the end of the double-blind phase of the pivotal study, 19.5% of the originally 77 patients randomised to receive leriglitazone did not complete the double blind phase, 45.5% of the patients randomised to leriglitazone received the recommended dose and 33.8% of patients randomised to leriglitazone had a reduced dose. The full dose group was defined as the same dose as, or not lower than 10% of the PK-recommended dose for $\geq 50\%$ of days between week 12 and week 96. The reduced dose group was defined as a dose between 10% and 50% ($>10\%$ and $\leq 50\%$) lower than the PK-recommended dose for $\geq 50\%$ of days between week 12 and week 96. The main reasons for dose adjustments were adverse events i.e. oedema and weight gain. Additional subgroup analyses for dose taken (full or reduced) were submitted. All options were discussed and did not come to any efficacy outcomes. Overall, there is no clear pattern in support of the idea that a reduced dose resulted in a different effect size. This is not surprising, considering the overall effect size.

Open-label extension of the pivotal study

After the double-blind phase, patients could continue in the open-label extension (OLE). Data for three years are available. Compared to patients on placebo in the DB-phase, less patients from the leriglitazone arm entered the OLE (71 vs. 85%). During the OLE, 1/3 of patients who remained on leriglitazone discontinued, in comparison to around 2/3 of patients who switched from placebo to leriglitazone in the OLE. The drop-out during the OLE suggest that patients do not perceive the leriglitazone treatment as being efficacious. If efficacious, a larger portion of patients continuing leriglitazone treatment would have been expected.

For the primary endpoint, the 6MWT, there are no differences between treatment patients who switched from placebo to leriglitazone and patients who remained on leriglitazone in the OLE. Also, on the EDSS step, the patients who switched from placebo to leriglitazone do not have a catch-up effect, instead the lines of progression of the two groups seems to run in parallel. Especially the EDSS is a sensitive scale for spinal cord lesions, and to a lesser extend for cerebral lesions. On the SSPROM, patients who switched from placebo to leriglitazone progress in the same manner, while the patients remaining on leriglitazone seem to have a kink towards more progression in the OLE. The results on body sway conditions are patchy and inconsistent.

During the 3 years in the OLE, 7 additional patients showed cerebral lesion progression according to the central readers. Two of these were originally randomised to placebo and 5 to leriglitazone in the double-blind phase. During the 3 years in the OLE, 2 patients were reported to have a SAE of clinically progressive cerebral adrenoleukodystrophy by their treating physician. One patient was randomised to placebo and the other one to leriglitazone, in the double-blind phase. There is no association between radiologic scores and clinical outcomes, i.e. functional outcomes. The additional 3-year follow-up data do not change the previous conclusion that the efficacy of leriglitazone in ALD is not established.

Concomitant medication

The concomitant medication used in both groups is balanced. However, more patients in the placebo group used muscle relaxants compared to patients in the leriglitazone group. In the leriglitazone group more anti-inflammatory, antirheumatic and diuretic medicinal products were used. The applicant explained that both anti-inflammatory/antirheumatic medication and muscle relaxants were used as required. The additional data show that more patients on leriglitazone than on placebo started botulinum toxin for spasticity during the main study. This could be seen as an indication of lack of efficacy of leriglitazone. The data points which might have been impacted by the use of botulinum toxin were excluded from analysis, which is acceptable.

Supportive studies

The 24-week interim analysis data of the open label, single arm NEXUS study (96 weeks) in boys with cALD, aged 2-12 years was submitted. The number of subjects is limited and the duration of 24 weeks does not allow for a conclusion. It is not possible to disentangle whether the arrest/stability <24 weeks reflects a treatment effect or the plateau phase in the natural course of the cALD. Moreover, at 24 week it is unclear whether the claimed arrest is permanent. A 24-week study duration in an open label setting without control is has limited sensitivity to demonstrate a treatment effect. These data are not sufficient on their own to conclude on efficacy.

Moreover, a 48-week Phase IIa double-blind, placebo-controlled study in 39 male and female patients with Friedreich’s ataxia (MT-2-03) is completed. No clear effect of leriglitazone in the treatment of Friedreich’s Ataxia could be established. This study is of no relevance for establishing efficacy in the sought indication but would have supported the proof of principle.

In summary, the efficacy of leriglitazone in the treatment of (c)ALD is not established.

2.6.7. Conclusions on the clinical efficacy

Based on the data presented, the CHMP is of the opinion that efficacy has not been shown in a satisfactory manner.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety assessment of leriglitazone is mainly based on one pivotal phase II/III study, Study MT-2-01, which included 116 adult male patients diagnosed with ALD. The study consists of a placebo-controlled main phase and an open label extension (OLE) phase. The open-label phase was still ongoing at the initial cut-off date for this report (15 April 2022).

On the initial cut-off date (15 April 2022), the safety database contained 110 unique ALD patients treated with leriglitazone, of which 65 were still in the study. At the time, 91 patients had been exposed to leriglitazone for ≥ 1 year, 63 patients for ≥ 2 years, and 51 patients for ≥ 3 years. At the cut-off date of 03 January 2023, 57 patients were still in the study. At study finalisation (last patient last observation 20 June 2023), 50 patients had completed the OLE study.

The focus of safety assessment in this report will be on the 96-week double-blind phase of MT-2-01. The characteristics of Study MT-2-01 are presented in Table 21.

*Table 21. Clinical Study Contributing to the Safety Evaluation**

Study number and status	Study Design	Subject Population	Dose & Route of Administration	Number of Subjects Treated	Safety assessment
MT-2-01 Part 1 (main phase) Completed	Phase 2/3, multicenter, randomised, double-blind, placebo-	Adult male subjects aged 18 to ≤ 65* diagnosed with ALD	Leriglitazone starting dose 150 mg QD, oral. Individually adjusted to reach plasma	116 patients (77 leriglitazone; 39 placebo)	Safety was assessed by (S)AEs, vital signs, 12-lead ECGs, and clinical laboratory tests (incl. hematology, blood

	controlled 96-week study		exposure of 200 µg·h/mL		chemistry, urinalysis, cytology)
MT-2-01 Part 2 (OLE phase) Completed	Open-label, long-term follow-up to main phase (up to 144 weeks)	Subjects who completed MT-2-01 main phase	Leriglitzazone starting dose 150 mg QD, oral. Individually adjusted to reach plasma exposure of 200 µg·h/mL.	88 patients (all leriglitzazone)	Long-term safety of leriglitzazone (see also above).

* ≤60 years at French site. Abbreviations: (S)AE = (serious) adverse event; ALD = adrenoleukodystrophy; cALD=cerebral x-linked adrenoleukodystrophy; AMN = adrenomyeloneuropathy; ECG = electrocardiogram; MAD = multiple ascending dose; N/A = not applicable; OLE = open label extension; PBPK = physiologically based pharmacokinetic; PK = pharmacokinetic; SAD = single ascending dose; QD = daily.

The applicant additionally presents safety findings with leriglitzazone use in paediatric patients with cerebral ALD (cALD) (Study MT-2-02, ongoing) and patients with Friedreich's ataxia (MT-2-03), as well as safety findings from the phase I SAD and MAD study (MT-1-01) with healthy volunteers.

Exposure to Study Medication (MT-2-01: Main Phase)

A total of 96 of 116 subjects (82.8%) completed the full 96-week treatment period, including 62 of 77 patients in the leriglitzazone group, and 34 of 39 patients in the placebo group (see Table 22). A total of 20 subjects prematurely discontinued treatment (n = 15 [19.5%] leriglitzazone group; n = 5 [12.8%] placebo group). The most frequent reasons for premature treatment discontinuation were adverse events (AEs) (10.4% with leriglitzazone vs. 5.1% with placebo).

Table 22. Patient Disposition (Safety Set)

Category	Placebo n (%)	Leriglitzazone n (%)	Overall n (%)
Patients randomized	39	77	116
Completed treatment	34 (87.2)	62 (80.5)	96 (82.8)
Discontinued from treatment	5 (12.8)	15 (19.5)	20 (17.2)
Adverse event	2 (5.1)	8 (10.4) ^a	10 (8.6)
Withdrawal of consent	3 (7.7)	6 (7.8)	9 (7.8)
Other	0	1 (1.3)	1 (0.9)
Completed the study	34 (87.2)	62 (80.5)	96 (82.8)

Exposure to Study Medication (MT-2-01: OLE Phase)

A total of 88 subjects accepted to participate in the OLE phase, which started immediately after the day of last treatment in the main phase. Of these 88 participants, 55 had completed leriglitzazone treatment, and 33 had completed placebo treatment.

In the OLE phase, 23 patients discontinued treatment prematurely (n=10 from previous leriglitzazone group; n=13 from previous placebo group). The most frequent reason for treatment discontinuation were AEs (n=13 from previous placebo group; n=7 from previous leriglitzazone group).

Demographics and baseline characteristics

Baseline characteristics (e.g. concomitant medications) and demographics (e.g., age, ethnicity, height, weight, and BMI) are in general balanced between the treatment groups. Some imbalances exist in concomitant diseases hypercholesterolaemia, seasonal allergy, musculoskeletal disorders, and nervous system disorders.

2.6.8.2. Adverse events

Overall, 112 of 116 subjects (96.6%) experienced at least 1 treatment-emergent adverse event (AE), 85 of 116 subjects (73.3%) experienced at least 1 treatment-related AE, and one patient (1.3%) in the leriglitzazone group reported a serious treatment-related AE.

AEs leading to permanent or temporary withdrawal from study medication, and AEs leading to dose adjustments were all more frequent in the leriglitzazone group (11.7%, 10.4%, and 44.2%, respectively) than in the placebo group (5.1%, 2.6%, and 5.1%, respectively).

An overview of all treatment-emergent AEs occurring in MT-2-01 is presented in Table 23.

Table 23. Overview of Adverse Events in Study MT-2-01 (Main Phase)

Category	Placebo (N=39) n (%)	Leriglitzazone (N=77) n (%)	Overall (N=116) n (%)
Patients with:			
≥1 treatment-emergent AE	36 (92.3)	76 (98.7)	112 (96.6)
≥1 ADR ^a	14 (35.9)	71 (92.2)	85 (73.3)
≥ 1 serious treatment-emergent (TE)AE	10 (25.6)	14 (18.2)	24 (20.7)
≥ 1 severe TEAE	8 (20.5%)	9 (11.7%)	17 (14.7%)
≥ 1 serious treatment-related AE ^a	0	1 (1.3)	1 (0.9)
≥ 1 severe treatment-related AE ^a (Grade ≥3)	0	0	0
≥ 1 AE leading to permanent withdrawal	2 (5.1)	9 (11.7)	11 (9.5)
≥ 1 AE leading to temporary withdrawal	1 (2.6)	8 (10.4)	9 (7.8)
≥ 1 TEAE leading to dose adjustment	2 (5.1)	34 (44.2)	36 (31.0)
a TEAE leading to death	0	0	0

Table 9 (summary of clinical safety), adjusted by the assessor. (a)related to study drug as assessed by the investigator. Abbreviations: #AE, number of adverse events; n, number of patients in category; N, total number of patients; TEAE, treatment emergent adverse event. Percentages are calculated based on N.

Common treatment-emergent adverse events

The most frequently reported treatment-emergent AEs in the leriglitzazone group included weight increased (70.1%), peripheral oedema (63.6%), and increased lacrimation (18.2%).

Common treatment-emergent AEs (≥5% of subjects in any treatment group) observed during the 96-week placebo-controlled main phase are presented in Table 24.

Table 24. Treatment-Emergent Adverse Events (>5% of Patients in Any Treatment Group) by SOC and PT in Study MT-2-01 (Main Phase)

SOC PT	Placebo (N=39)		Leriglitazone (N=77)		Overall (N=116)	
	n (%)	# AEs	n (%)	# AEs	n (%)	# AEs
Patients with at least 1 TEAE	36 (92.3)	262	76 (98.7)	755	112 (96.6)	1017
Blood and lymphatic system disorders	2 (5.1)	2	18 (23.4)	25	20 (17.2)	27
Anaemia	1 (2.6)	1	10 (13.0)	10	11 (9.5)	11
Congenital, familial and genetic disorders	6 (15.4)	6	0	0	6 (5.2)	6
Adrenoleukodystrophy*	6 (15.4)	6	0	0	6 (5.2)	6
Endocrine disorders	4 (10.3)	7	4 (5.2)	5	8 (6.9)	12
Adrenocortical insufficiency acute	4 (10.3)	7	2 (2.6)	3	6 (5.2)	10
Eye disorders	0	0	30 (39.0)	39	30 (25.9)	39
Eyelid oedema	0	0	7 (9.1)	7	7 (6.0)	7
Lacrimation increased	0	0	14 (18.2)	16	14 (12.1)	16
Gastrointestinal disorders	12 (30.8)	17	33 (42.9)	59	45 (38.8)	76
Constipation	1 (2.6)	1	7 (9.1)	7	8 (6.9)	8
Diarrhoea	3 (7.7)	3	10 (13.0)	12	13 (11.2)	15
Nausea	1 (2.6)	2	6 (7.8)	8	7 (6.0)	10
Vomiting	3 (7.7)	3	5 (6.5)	5	8 (6.9)	8
General disorders and administration site conditions	16 (41.0)	24	65 (84.4)	134	81 (69.8)	158
Fatigue	4 (10.3)	4	11 (14.3)	13	15 (12.9)	17
Oedema	0	0	11 (14.3)	12	11 (9.5)	12

Table 25. Treatment-Emergent Adverse Events (>5% of Patients in Any Treatment Group) by SOC and PT in Study MT-2-01 (Main Phase) (continued)

SOC PT	Placebo (N=39)		Leriglitazone (N=77)		Overall (N=116)	
	n (%)	# AEs	n (%)	# AEs	n (%)	# AEs
Oedema peripheral	7 (17.9)	10	49 (63.6)	81	56 (48.3)	91
Infections and infestations	18 (46.2)	44	38 (49.4)	93	56 (48.3)	137
Gastroenteritis	3 (7.7)	3	4 (5.2)	6	7 (6.0)	9
Influenza	1 (2.6)	2	8 (10.4)	11	9 (7.8)	13
Nasopharyngitis	2 (5.1)	3	17 (22.1)	36	19 (16.4)	39
Urinary tract infection	8 (20.5)	21	7 (9.1)	10	15 (12.9)	31
Injury, poisoning and procedural complications	10 (25.6)	22	26 (33.8)	54	36 (31.0)	76
Fall	6 (15.4)	9	10 (13.0)	16	16 (13.8)	25
Investigations	16 (41.0)	29	64 (83.1)	119	80 (69.0)	148
Blood creatine phosphokinase increased	2 (5.1)	2	6 (7.8)	6	8 (6.9)	8
Urine cytology abnormal	5 (12.8)	6	8 (10.4)	9	13 (11.2)	15
Weight increased	9 (23.1)	9	54 (70.1)	63	63 (54.3)	72
Metabolism and nutrition disorders	4 (10.3)	5	14 (18.2)	18	18 (15.5)	23
Increased appetite	1 (2.6)	1	6 (7.8)	6	7 (6.0)	7
Musculoskeletal and connective tissue disorders	14 (35.9)	32	32 (41.6)	69	46 (39.7)	101
Arthralgia	2 (5.1)	2	4 (5.2)	5	6 (5.2)	7
Back pain	4 (10.3)	5	12 (15.6)	14	16 (13.8)	19
Muscle spasms	3 (7.7)	3	4 (5.2)	4	7 (6.0)	7
Pain in extremity	3 (7.7)	5	12 (15.6)	15	15 (12.9)	20
Nervous system disorders	17 (43.6)	27	31 (40.3)	40	48 (41.4)	67
Headache	5 (12.8)	9	9 (11.7)	14	14 (12.1)	23
Paraesthesia	3 (7.7)	3	3 (3.9)	3	6 (5.2)	6
Renal and urinary disorders	5 (12.8)	7	15 (19.5)	24	20 (17.2)	31
Nocturia	0	0	7 (9.1)	7	7 (6.0)	7

*Adrenoleukodystrophy as reported PT was used for encoding events related to progression of cALD.
Abbreviations: #AE, number of adverse events; n, number of patients in category; N, total number of patients; PT, preferred term; SOC, system organ class; TEAE, treatment emergent adverse event.
Percentages are calculated based on N.

AEs considered treatment-related were more frequent in the leriglitazone group (92.2%) than in the placebo group (35.9%). The most frequently reported AEs considered treatment-related (>10%) by PT in the leriglitazone group compared to placebo were weight increased (64.9% vs. 15.4%, respectively), oedema peripheral (62.3% vs. 15.4%, respectively), lacrimation increased (15.6% vs. 0%, respectively), and oedema (11.7% vs. 0%, respectively).

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

A total of 24 patients (20.7%) reported at least one serious AE in the 96-week placebo-controlled main phase of Study MT-2-01. The frequency of serious AEs was lower in the leriglitazone group (14 patients [18.2%]) than in the placebo group (10 patients [25.6%]). All serious AEs reported during the placebo-controlled main phase are presented in Table 26.

Table 26. Serious Treatment-Emergent Adverse Events (MT-2-01 Main Phase)

SOC PT	Placebo (N=39)		Leriglitazone (N=77)		Overall (N=116)	
	n (%)	#AEs	n (%)	#AEs	n (%)	#AEs
Patients with at least 1 serious TEAE	10 (25.6)	15	14 (18.2)	18	24 (20.7)	33
Cardiac disorders	0	0	1 (1.3)	1	1 (0.9)	1
Coronary artery occlusion	0	0	1 (1.3)	1	1 (0.9)	1
Congenital, familial and genetic disorders	6 (15.4)	6	0	0	6 (5.2)	6
Adrenoleukodystrophy	6 (15.4)	6	0	0	6 (5.2)	6
Endocrine disorders	1 (2.6)	1	1 (1.3)	1	2 (1.7)	2
Adrenocortical insufficiency acute	1 (2.6)	1	1 (1.3)	1	2 (1.7)	2
Gastrointestinal disorders	0	0	1 (1.3)	1	1 (0.9)	1
Colitis	0	0	1 (1.3)	1	1 (0.9)	1
Immune system disorders	0	0	1 (1.3)	1	1 (0.9)	1
Anaphylactic shock	0	0	1 (1.3)	1	1 (0.9)	1
Infections and infestations	2 (5.1)	3	3 (3.9)	4	5 (4.3)	7
Abscess limb	1 (2.6)	1	0	0	1 (0.9)	1
Cellulitis	1 (2.6)	1	0	0	1 (0.9)	1
Gastroenteritis	0	0	1 (1.3)	1	1 (0.9)	1
Gastroenteritis norovirus	0	0	1 (1.3)	1	1 (0.9)	1
Pneumonia	0	0	1 (1.3)	1	1 (0.9)	1
Urinary tract infection	1 (2.6)	1	1 (1.3)	1	2 (1.7)	2
Injury, poisoning and procedural complications	1 (2.6)	2	3 (3.9)	3	4 (3.4)	5
Ankle fracture	0	0	2 (2.6)	2	2 (1.7)	2
Fibular fracture	1 (2.6)	1	1 (1.3)	1	2 (1.7)	2
Tibia fracture	1 (2.6)	1	0	0	1 (0.9)	1
Investigations	0	0	2 (2.6)	2	2 (1.7)	2
Hepatic enzyme increased	0	0	1 (1.3)	1	1 (0.9)	1
Magnetic resonance imaging abnormal	0	0	1 (1.3)	1	1 (0.9)	1
Musculoskeletal and connective tissue disorders	0	0	2 (2.6)	2	2 (1.7)	2
Arthritis reactive	0	0	1 (1.3)	1	1 (0.9)	1
Pain in extremity	0	0	1 (1.3)	1	1 (0.9)	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.6)	2	2 (2.6)	2	3 (2.6)	4
Basal cell carcinoma	1 (2.6)	2	0	0	1 (0.9)	2
Chronic lymphocytic leukaemia	0	0	1 (1.3)	1	1 (0.9)	1
Renal hamartoma	0	0	1 (1.3)	1	1 (0.9)	1
Nervous system disorders	0	0	1 (1.3)	1	1 (0.9)	1
Loss of consciousness	0	0	1 (1.3)	1	1 (0.9)	1
Psychiatric disorders	1 (2.6)	1	0	0	1 (0.9)	1
Adjustment disorder with depressed mood	1 (2.6)	1	0	0	1 (0.9)	1

Abbreviations: #AE, number of adverse events; n, number of patients in category; N, total number of patients; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment emergent adverse event. Descriptions of adverse events were coded using MedDRA Version 23.0. Percentages are calculated based on N. Patients with multiple TEAEs within the same system organ class and/or preferred term were only counted once within the respective frequencies.

Serious events reported in more than one patient in a treatment group were ankle fracture (n=2 in leriglitzazone group) and adrenoleukodystrophy (n=6 in placebo group). Only one serious event was considered related to leriglitzazone, i.e., hepatic enzymes increased.

Deaths

One death was reported in the OLE phase of MT-2-01. No deaths were reported in the other clinical studies, i.e., MT-1-01 and MT-2-01 (Main Phase), MT-2-02 (cALD) and MT-2-03 (Friedreich's Ataxia), until cut-off date on 03 January 2023.

The fatal case concerned a 60-year-old patient who had transitioned from placebo to leriglitzazone, and was around 1.5 years into OLE before he deceased. His death was considered due to disease progression and not related to leriglitzazone. The patient had had cerebral lesion progression for two years and had deteriorating disease status at the time of death.

Adverse Events of Special Interest (AESIs)

Adverse events of special interest (AESIs) were defined post-hoc and were based on the safety profile of other PPAR γ agonists (e.g. pioglitazone). The AESIs concerned: Oedema, weight gain and lacrimation, cardiovascular events, endocrine events, hepatic safety, urine cytology, haematological events, bone fractures, and muscle enzymes.

Oedema and weight gain

The most frequently reported AEs in the leriglitzazone group were increased weight (70.1%), which was considered treatment-related in 64.9% of the patients, and peripheral oedema (63.6%), which was considered treatment-related in 62.3% of the patients. Overall, 89.6% of leriglitzazone-treated patients experienced a form of oedema.

AESIs in Study MT-2-01 (Main phase) related to oedema and weight gain are reported in Table 27.

Table 27. AESIs: Oedema, Weight Gain and Lacrimation (Study MT-2-01, Main Phase)

PT	Placebo (N=39)		~~Leriglitzazone~~ (N=77)		Overall (N=116)	
	n (%)	# AEs	n (%)	# AEs	n (%)	# AEs
Oedema	0	0	11 (14.3)	12	11 (9.5)	12
Oedema peripheral	7 (17.9)	10	49 (63.6)	81	56 (48.3)	91
Face oedema	0	0	2 (2.6)	2	2 (1.7)	2
Swelling face	0	0	3 (3.9)	3	3 (2.6)	3
Localised oedema	0	0	1 (1.3)	1	1 (0.9)	1
Peripheral swelling	1 (2.6)	1	4 (5.2)	4	5 (4.3)	5
Weight increased	9 (23.1)	9	54 (70.1)	63	63 (54.3)	72
Lacrimation increased	0	0	14 (18.2)	16	14 (12.1)	16

In addition, a case of ascites, a form of central oedema, was reported during the OLE phase, for which a causal role of leriglitzazone could not be ruled out.

The mean increase in weight from baseline to Week 96 was 5.8 kg for the leriglitzazone group versus 1.3 kg in the placebo group.

Weight change from baseline to Week 96 is presented in the table below.

Table 28 Weight Change from Baseline to Week 96

Change from baseline to Week 96	Placebo (n = 35)	Leriglitzazone (n = 61)
Mean kg (SD)	1.3 (4.3)	5.8 (4.6)
Median	0.0	5.9
Q1 - Q3	-1.5 to 4.0	3.0 to 8.8
Min - Max	-5.5 to 14.0	-5.0 to 14.6

Table created by the assessor. Abbreviations: SD, standard deviation.

The oedema-related events did not require additional treatment measures, or led to a dose reduction and/or (in case of oedema) prescription of diuretics. During the study, dose adjustments in 32 patients on leriglitzazone (41.6%) and 2 patients on placebo (5.1%) were made due to weight gain or oedema. In the first 24 weeks of treatment, 22 patients on leriglitzazone and 2 patients on placebo received dose adjustments. Within 24 to 48 weeks of treatment, the doses of 10 patients on leriglitzazone were adjusted; and within 48 to 72 weeks of treatment, 5 patients on leriglitzazone received an adjusted dose.

Sixteen (20.8%) patients in the leriglitzazone group used diuretics, and one patient (2.6%) in the placebo group. None of the patients in both groups prematurely discontinued treatment because of an inability to tolerate the lowest possible dose after dose reduction.

Cardiovascular events

Cardiac events occurred in 6 patients (7.8%) in the leriglitzazone group and 2 patients (5.1%) in the placebo group. Palpitations (3.9%) and tachycardia (2.6%) were the most frequently observed cardiovascular AEs, and only reported in the leriglitzazone group. Coronary artery occlusion was the only serious AE. All events were reversible on the short term. Palpitations and extrasystoles were considered related to leriglitzazone treatment in 2 patients (2.6%) and 1 patient (1.3%), respectively.

Cardiac events are reported in Table 29.

Table 29. AESIs: Cardiac Events (Study MT-2-01, Main Phase)

PT	Placebo (N=39)		Leriglitzazone (N=77)		Overall (N=116)	
	n (%)	# AEs	n (%)	# AEs	n (%)	# AEs
Angina pectoris	1 (2.6)	1	0	0	1 (0.9)	1
Aortic valve stenosis	0	0	1 (1.3)	1	1 (0.9)	1
Atrioventricular block first degree	0	0	1 (1.3)	1	1 (0.9)	1
Bundle branch block left	1 (2.6)	1	0	0	1 (0.9)	1
Coronary artery occlusion	0	0	1 (1.3)	1	1 (0.9)	1
Extrasystoles	0	0	1 (1.3)	1	1 (0.9)	1
Palpitations	0	0	3 (3.9)	5	3 (2.6)	5
Pericardial effusion	0	0	1 (1.3)	1	1 (0.9)	1
Tachycardia	0	0	2 (2.6)	2	2 (1.7)	2

In addition, increased B-type natriuretic peptide (BNP) was reported as treatment-related AE in 2 patients (2.6%) in the leriglitzazone group (only); and increased jugular venous pressure (JVP) was reported as treatment-related AE once (1.3%) with leriglitzazone.

During OLE phase, there was one case of atrial dilatation under leriglitzazone treatment in a 12-year-old patient with Friedreich's ataxia, which was considered related to leriglitzazone.

Endocrine events

One endocrine event, acute adrenocortical insufficiency, was reported during the study, and more frequently with placebo (n=4; 10.3%) than with leriglitzazone (n=2; 2.6%).

Hepatic safety

Hepatic events were reports in 4 patients (5.2%) in the leriglitzazone group and in one patient (2.6%) in the control group. One serious TEAE 'increased hepatic enzymes' was considered related to leriglitzazone and was reported with seriousness criterion "important medical event". Increases in both ALT and AST were reported in 3 (3.9%) leriglitzazone-treated patients. In all cases, the increases were Grade 1 according to CTCAE ($<3.0 \times \text{ULN}$) and the values normalised within 60 days with no action taken regarding the study medication.

In addition, one leriglitzazone-related event of hepatomegaly was reported. Liver injury (as PT) was not reported.

Urine cytology

Abnormal cytology findings were comparable between leriglitzazone and placebo group (10.4% vs. 12.8%, respectively). However, cytology findings suspicious of urothelial carcinoma (SHG and LHG, in the Paris Classification) were also reported. Follow-up with abdominal CT scan and cystoscopy revealed no urothelial malignancies.

Haematological events

Anaemia was reported most frequently in the leriglitzazone group (leriglitzazone: 10 patients [13.0%], placebo: 1 patient [2.6%]), followed by macrocytosis (5.2% in the leriglitzazone group), decreased haemoglobin, leukopenia, and pancytopenia (each 3.9% in the leriglitzazone group), versus no such findings in the placebo group. The other haematological events were reported in 1 or 2 patients overall.

The 3 events of pancytopenia occurred within the first 12 weeks of treatment when decreases in red and white cell lines and platelets were observed. In all cases, the levels remained within grade 1 (mild) according to the CTCAE 5-grades scale.

Most haematological adverse events were considered related to leriglitzazone treatment: i.e., anaemia (most cases, including iron deficiency anaemia), leukopenia (1 case), and all cases of lymphopenia, macrocytosis, neutropenia, haemoglobin decreased, haematocrit decreased and red blood cell count decreased. For pancytopenia, in 2 cases the relationship with leriglitzazone treatment was judged as not assessable and in one case as related.

The events were generally mild, recovered during the study and no actions regarding treatment had to be taken.

Changes in haematological parameters from baseline over the 96-week treatment period were generally small and assessed as not clinically significant by investigators.

Haematological events are presented in Table 30.

Table 30. AESIs: Haematological Events (Study MT-2-01, Main Phase)

PT	Placebo (N=39)		Leriglitazone (N=77)		Overall (N=116)	
	n (%)	# AEs	n (%)	# AEs	n (%)	# AEs
Anaemia	1 (2.6)	1	10 (13.0)	10	11 (9.5)	11
Anaemia macrocytic	0	0	1 (1.3)	1	1 (0.9)	1
Iron deficiency anaemia	0	0	1 (1.3)	1	1 (0.9)	1
Leukopenia	0	0	3 (3.9)	3	3 (2.6)	3
Lymphopenia	1 (2.6)	1	1 (1.3)	1	2 (1.7)	2
Macrocytosis	0	0	4 (5.2)	4	4 (3.4)	4
Neutropenia	0	0	1 (1.3)	2	1 (0.9)	2
Pancytopenia	0	0	3 (3.9)	3	3 (2.6)	3
Haemoglobin decreased	0	0	3 (3.9)	4	3 (2.6)	4
Haematocrit decreased	0	0	1 (1.3)	1	1 (0.9)	1
Red blood cell count decreased	0	0	2 (2.6)	2	2 (1.7)	2

Bone fractures

Fractures occurred in 9 patients, *i.e.*, in 2 (5.1%) patients on placebo and in 7 (9.1%) patients on leriglitazone treatment. All events were considered not related to the study medication. Four of 10 events (n=2 placebo; n=2 leriglitazone) were reported as serious events due to hospitalisation. For 3 of 7 events in the leriglitazone group, fall was described as the cause of the event. The other 4 events concerned foot bone fissure, vertebral collapse, costal cartilage fracture, and ankle fracture.

The percentage of patients on corticosteroids, which are associated with an increased risk of osteoporosis, was comparable in the treatment groups (placebo: 66.7%, leriglitazone: 64.9%).

Bone fractures were also reported in 8 patients during OLE phase.

Muscle enzymes

More patients in the leriglitazone group compared to placebo (7.8% vs. 5.1%) experienced increased levels of CPK. Half of the cases in the leriglitazone group were considered related to leriglitazone treatment. All cases were mild in severity, non-serious and without sequelae.

Apart from the AESIs defined by the applicant, glycaemic events were also to be expected based on the knowledge on PPAR γ agonists and their effect on glucose metabolism. However, no glycaemic events including hypoglycaemia, were reported in any of the clinical studies with leriglitazone.

2.6.8.4. Laboratory findings

Clinical laboratory findings

Apart from the clinical laboratory findings discussed under the respective AESIs, there were no notable changes from baseline in other parameters in either treatment group over time, and no notable differences between the treatment groups. The majority of patients had laboratory values that remained within normal ranges over the course of the study.

Vital signs

There were no clinically relevant changes from baseline over time, or differences between the treatment groups, in systolic and diastolic blood pressure or pulse rate.

ECG

Compared with placebo, patients in the leriglitzazone group showed a greater mean (SD) increase over time (from baseline to week 96) in QTc interval (assessed using the worst record of QTcF and QTcB). By Week 48, 4 patients (5.2%) in the leriglitzazone group had developed a QTc interval > 450 msec and ≤ 480 msec.

Physical examination

Physical examination findings were normal throughout the study in both treatment groups. Abnormal findings were more frequent in leriglitzazone-treated patients compared to placebo, and mostly concerned the extremities with the presence of peripheral oedema.

2.6.8.5. *In vitro* biomarker test for patient selection for safety

Not applicable.

2.6.8.6. *Safety in special populations*

Intrinsic and extrinsic factors

Safety of leriglitzazone with respect to intrinsic factors (e.g., age, gender) and extrinsic factors (e.g., smoking, diet) has not been evaluated in clinical studies. Paediatric patients (< 18 years of age) and elderly patients (> 65 years of age) were not included in the pivotal clinical trial.

Patients with cardiac failure or history of cardiac failure (NYHA stages I to IV) were excluded from clinical studies with leriglitzazone.

Use in pregnancy and lactation

Pregnancy, lactation and reproductive potential in women of childbearing age have not been evaluated in clinical studies with leriglitzazone.

The available results of the repeated-dose studies conducted in adult and juvenile rats suggest no findings of concern for male patients regarding reproductive organs.

Overdose, drug abuse, withdrawal and rebound

No cases of overdose have occurred with leriglitzazone. Leriglitzazone is not expected to have abuse potential. No effects of withdrawal or rebound have been observed in clinical studies with leriglitzazone.

Effects on ability to drive or operate machinery or impairment of mental ability

It is expected that leriglitzazone will have no or negligible influence on the ability to drive and use machines. Patients who experience visual disturbance should be cautious when driving or using machines.

2.6.8.7. *Immunological events*

No information was provided.

2.6.8.8. *Safety related to drug-drug interactions and other interactions*

Drug interactions with leriglitzazone have not been evaluated in clinical studies.

The major route of elimination after oral administration of leriglitzazone is via hepatic metabolism, with CYP2C8 and CYP3A being the key oxidative enzymes involved. Clinical DDI studies are planned to evaluate the potential risk of a drug interaction between leriglitzazone and inhibitors/inducers of CYP2C8 and CYP3A4.

2.6.8.9. Discontinuation due to adverse events

Dose adjustments due to AEs

Adverse events more frequently led to dose adjustments in leriglitzazone-treated patients (44.2%) compared to controls (5.1%). Most often, these AEs concerned oedema and weight gain.

Temporary and permanent discontinuation due to AEs

Adverse event that led to temporary and permanent withdrawal from study medication were more frequent in the leriglitzazone group (10.4% and 11.7%, respectively) than in the placebo group (2.6% and 5.1%, respectively).

Temporary discontinuation (n=8 with leriglitzazone, n=1 with placebo) was most often due to single, serious events (e.g., gastroenteritis norovirus, renal hematoma, increased hepatic enzymes, coronary artery occlusion, pneumonia, colitis, and reactive arthritis). These events were considered not related to leriglitzazone by the applicant and usually resolved within a month.

Permanent discontinuation (n=9 with leriglitzazone, n=2 with placebo) was due to non-serious events in the leriglitzazone group, most often oedema or weight gain (5 out of 9 patients). Other events were disrupted sleep and/or fatigue, increased lacrimation, or increased nocturia. The two placebo-treated patients withdrew due to serious events of adrenoleukodystrophy.

In the OLE phase, 39% of patients from previous placebo group, and 12.7% of patients from previous leriglitzazone group stopped prematurely with the study due to adverse events.

2.6.8.10. Post marketing experience

Not applicable. The product is not marketed anywhere.

2.6.9. Discussion on clinical safety

Safety assessment of leriglitzazone is mainly based on the double-blind phase of the single pivotal Study MT-2-01. Supportive safety data in boys aged 2-12 years with cALD and patients with Friedreich's ataxia are also discussed.

At the initial cut-off date, a total of 110 patients with ALD were exposed to leriglitzazone, of which 91 for at least one year and 51 for at least 3 years. Not all patients were exposed to the target dose for an extended period of time; in the double-blind phase, over 44% of patients received dose reductions due to adverse events. Based on additional analyses provided by the applicant, it was confirmed that dose reductions did not help stabilise or resolve the main adverse events oedema and weight gain. As the risk minimisation measures were not effective this should be clearly mentioned in the SmPC.

In line with this, there were concerns for overdosing and associated safety risks with the use of a 10 mL dosing syringe, which requires repeated withdrawal of suspension. Therefore, the applicant changed the co-packaged medical device to a 12 mL dosing syringe during the evaluation procedure, in line with the proposed posology.

A total of 96 of 116 patients completed the double-blind main phase, although not all patients had the

full 96 weeks of exposure to leriglitzazone (e.g., one outlier missed 5 months of exposure). Drop-out rate during the main phase was higher in the leriglitzazone group compared to placebo (19.5% vs. 12.8% respectively), and adverse events were the main reason for study discontinuation (10.4% vs. 5.1%, respectively). Reasons for withdrawal of consent during double-blind phase and reasons why patients in the active treatment arm (11.3%) did not want to enter OLE phase to continue treatment could not be provided.

Overall, 98.7% of the leriglitzazone-treated patients experienced at least 1 AE, compared to 92.3% in the placebo group. Treatment-related AEs were more frequent in the leriglitzazone group compared to placebo (92.2% vs. 35.9%). The most common adverse events ($\geq 5\%$) that were reported more frequently with leriglitzazone treatment ($> 10\%$ difference with placebo) were weight increased (70.1% vs. 23.1%), oedema peripheral (63.6% vs. 17.9%), nasopharyngitis (22.1% vs. 5.1%), lacrimation increased (18.2% vs. 0%), oedema (14.3% vs. 0%), and anaemia (13.0% vs. 2.6%). Thus, adverse events are dominated by oedema and weight gain, which were (amongst others) post-hoc identified as adverse events of special interest (AESI) based on safety profile of other PPAR γ agonists (see also below). Most adverse events were reported as mild to moderate and non-serious. Severe and serious events occurred more frequently in the placebo group (20.5% and 25.6%, respectively) compared to the leriglitzazone group (10.4% and 18.2%, respectively), and were generally considered isolated cases (occurring in 1 or 2 subjects). One life-threatening event of anaphylactic shock (Grade 4) occurred in the leriglitzazone group, but was not considered related to leriglitzazone. One death occurred during OLE phase due to natural disease progression. The applicant has, as requested, updated the ADR table of the SmPC to include all events that were assessed as at least possibly related to leriglitzazone.

AESIs

Oedema (81.8%) and/or weight gain (70.3%) occurred in the majority of patients treated with leriglitzazone. Oedema most often occurred peripherally, but also more local and central forms (ascites) were observed. Macular oedema, observed with other thiazolidinediones, was not actively monitored. Mean weight gain was 5.8 kg (Q1-Q3: 3.0.-8.8 kg) over two years, with 25% of patients showing weight gain > 8.8 kg, which is considered a large increase. In contrast, with pioglitazone, oedema was reported in 6-9% of patients and weight gain in 1-10% of patients, with a mean 2-3 kg weight increase over one year. Thus, the percentage of patients experiencing oedema/weight gain with leriglitzazone is much higher and the effect more pronounced compared to patients treated with pioglitazone. Oedema and weight gain were initially said to be manageable, either with dose adjustments (41.6%) and/or with diuretics (20.8%). There were no predefined criteria to start an intervention for these events; it was left to the investigator's discretion. However, at the end of the study, not all events had resolved and mean weight continued to increase up to week 96, suggesting that oedema and/or weight gain was not halted or reversed during the course of the study. Additional analyses confirmed that the use of diuretics and/or dose reductions, in fact, did not help resolve weight gain and oedema, or prevent recurrence of oedema. No risk factors could be identified for the development of these events. During the evaluation procedure and in line with the additional data provided, the initially proposed SmPC recommendations for oedema and/or weight gain were completely removed. No recommendations can be made to mitigate leriglitzazone-related oedema.

Almost a fifth of patients (18.2%) experienced increased lacrimation. The event is not listed for other PPAR γ agonists. It is hypothesised that PPAR γ activation, through inhibition of NO production, may suppress inflammatory cytokines and increase tear production. Thus, increased lacrimation is not considered related to oedema or oedema-associated events.

A high percentage of patients experienced fluid retention, but in general there were no signs of venous engorgement in the studied AMN population, or a pattern of cardiovascular events. However, leriglitzazone-related volume overload (including hepatomegaly) was observed incidentally. It is not

possible to determine whether such volume overload would specifically precipitate cardiac events in patients with cardiac risk factors (e.g., refer to the Friedreich's ataxia patient with atrial dilatation). In addition, the longer-term consequences of unresolved oedema and associated risk of volume overload in the population not at cardiac risk remain unknown. Four leriglitzazone-treated patients (5.2%) developed (borderline) QTc interval prolongation (>450 msec), but a possible role of leriglitzazone is unclear.

More leriglitzazone-treated patients than controls showed abnormal liver function tests (5.2% versus 2.6%, respectively), with one serious case attributed to leriglitzazone use. In addition, one leriglitzazone-related case of hepatomegaly was reported. During OLE phase, one case of increased liver enzymes (GGT) was related to leriglitzazone. Liver injury (as PT) was not reported.

One patient in each treatment group had urine cytology results suspicious of high-grade urothelial carcinoma, which is balanced. No malignancies were confirmed. Both patients were monitored throughout the extension part of the study with no new abnormal cytology results, until they discontinued the study.

PPAR γ agonists are classified as probable human carcinogens with carcinogenic potential existing beyond the site of the bladder. Carcinogenicity appears to be mediated by exaggerated pharmacologic effects observed as tissue hyperplasia. In non-clinical studies with leriglitzazone multiple hyperplastic changes were observed, in line with other PPAR γ agonists. Hence, also for leriglitzazone a carcinogenic risk for humans cannot be excluded. So far, there is no clinical evidence of carcinogenicity under leriglitzazone. Obviously, the duration of the clinical studies is relatively short to detect these events. To further investigate the carcinogenic risk of leriglitzazone on longer term, the applicant proposed an extended post-authorisation safety study (PASS) of 5 years, with inclusion of patients from the initial pivotal study.

The most frequently reported haematological events observed with leriglitzazone use were anaemias (15.6%), macrocytosis (5.2%) and cytopenias (leukopenia, lymphopenia, neutropenia, pancytopenia; all 1.3%-3.9%). Mostly, these events were not observed in controls. Based on the knowledge of PPAR γ agonist pioglitazone, these haematological events were initially hypothesised to be secondary events to haemodilution. However, cytopenias due to haemodilution would be exceptional. After additional analyses, the applicant confirmed that there was no evidence that cytopenias were due to haemodilution effects, although the exact mechanism by which they occur is not understood. Bone marrow suppressive effects could play a role.

There is a higher incidence of bone fractures with leriglitzazone treatment compared to controls (9.1% versus 5.1%). In OLE phase, similar high percentages of bone fractures under leriglitzazone have been reported so far (9.0% in previous placebo, 9.0% in previous leriglitzazone). The incidence of falls was similar across groups. Bone fracture is listed for other PPAR γ agonists. Although it has been mainly observed in females, there are also reports on fracture in males. PPAR γ is considered to have a role in bone metabolism, for example by inhibiting osteoblast formation and inducing osteocyte apoptosis, thus reducing bone formation. A causal role of leriglitzazone is therefore considered likely. This concern is especially relevant in a patient population that already has balance problems, which poses a higher risk for falls, and thus fracture. For the paediatric population, effects on bone density could be particularly detrimental.

No effect of leriglitzazone on glucose metabolism was observed. It should be noted that patients with diabetes (i.e., the population for which pioglitazone is indicated) were excluded from study participation.

Safety in special populations

The safety of leriglitazone with respect to intrinsic factors (e.g., age, gender) has not been evaluated in clinical studies. Given the inclusion criteria for the pivotal study (including age $\leq$ 65 years), there is a lack of safety data in the elderly.

Since the applicant applied for an indication including paediatric patients, safety in paediatric patients should be substantiated. However, only preliminary findings in children with cALD (MT-2-02) were available at the time of the opinion, which do not allow for safety conclusions for the paediatric population. Moreover, the applicant did not adequately justify the extrapolation of safety findings from adults to children.

Patients with (a history of) cardiac failure or with cardiac risk factors (reduced LVEF, or other clinically relevant cardiac abnormalities on echocardiogram, or baseline BNP levels of >150 pg/mL) were excluded from study participation. It cannot be ruled out that fluid retention may specifically lead to volume overload and related cardiac events in patients with cardiac failure or at cardiac risk. However, data on safe use of leriglitazone in these patients are lacking. The applicant proposed to exclude patients with (a history of) cardiac failure from leriglitazone treatment. With regard to leriglitazone use in patients with cardiac risk factors, appropriate risk minimisation measures were proposed to be included in the SmPC.

Furthermore, patients with chronic kidney disease (stage $\geq$ 3) and patients with moderate or severe hepatic impairment (Child-Pugh B or C) were excluded from study participation. The impact of decreased hepatic function on the PK of leriglitazone is unknown. Due to the metabolism and elimination routes of leriglitazone, use in subjects with moderate to severe renal impairment and patients with hepatic impairment is not recommended in the proposed SmPC.

The current lack of drug-drug interaction (DDI) data does not allow for adequate SmPC dosing instructions for combined use with CYP2C8 and CYP3A4 inhibitors/inducers, or other relevant co-medications. This could pose a safety risk, especially in cases where co-administration leads to increased exposure to leriglitazone and thus increased safety issues can be expected. It was agreed that an SmPC warning could have been accepted, pending the results of the DDI studies.

Discontinuation due to adverse events

Temporary and permanent withdrawal from study medication due to adverse events was more frequently observed in the leriglitazone group (10.4% and 11.7%, respectively) compared to placebo (2.6% and 5.1%, respectively). Temporary withdrawal of study medication in both groups was most often due to single, serious events, and not considered related to study medication. Permanent withdrawal in the leriglitazone group was due to non-serious events, most often (peripheral) oedema or increased weight (5 out of 9 subjects; 56%). During OLE phase, 39.4% of patients previous on placebo and 12.7% of patients previous on leriglitazone prematurely withdrew from the study due to adverse events most often oedema-related. This questions patients' willingness to bear the adverse events, even in light of their debilitating disease.

2.6.10. Conclusions on the clinical safety

Safety is dominated by a high incidence and magnitude of oedema and weight gain. The events led to dose reductions in almost half of all patients treated with leriglitazone. Withdrawal of treatment, often due to adverse events, is considered high and this could be a reflection of the tolerability of the product. The actions taken in response to oedema or weight gain (dose reductions and/or diuretics), which were not based on predefined criteria, actually did not halt or reverse these events. Thus, oedema and weight gain-related events could in fact not be managed. No risk factors for these events

were identified. Furthermore, also based on non-clinical studies with leriglitzone, concerns regarding the carcinogenic potential of leriglitzone remain at the time of the opinion, especially considering the anticipated long-term use of the product. Safety in special patient populations (e.g., elderly, patients with renal or hepatic impairment, patient at cardiac risk) was not properly evaluated. The proposed SmPC dosing instructions, warnings, and/or recommendations could have been accepted as measures to mitigate risks. Furthermore, safety in children was not substantiated, although the applicant applied for an indication including paediatric patients.

Taken together, the safety profile of leriglitzone at the recommended dose is unfavourable, especially with regard to oedema/weight gain. Appropriate mitigation measures for oedema/weight gain cannot be established. Clinical consequences on the long term (e.g., volume overload) and/or in specific patient groups, such as those already at cardiac risk, are unknown.

2.7. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance system

The CHMP and PRAC, having considered the data submitted by the applicant, were of the opinion that, due to the concerns identified with this application, as above outlined, the pharmacovigilance system summary cannot be agreed at this stage.

2.9. Periodic Safety Update Reports submission requirements

Not applicable

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Adrenoleukodystrophy (ALD) is a chromosome X-linked rare inherited neurodegenerative disorder that affects the brain, nerves and adrenal glands. ALD causes severe axonal damage in the central and peripheral nervous system, resulting in a chronic progressive myelopathic and neuropathic adrenomyeloneuropathy (AMN) in adulthood. In addition to chronic neurodegeneration, acute inflammatory brain demyelination can appear, either in childhood or in adults, which is known as cerebral adrenoleukodystrophy (cALD), progressing to rapid death or vegetative state.

Childhood cALD occurs in 31-35% of ALD patients with onset typically between age 2 and 12 years of age. The majority of adult ALD, i.e., up to 60%, will develop cALD over time, in addition to their myelopathy. ALD has an estimated birth incidence of 1 in 20,000 worldwide (male and female) (Orphanet Report Series, 2020). The estimated prevalence is 0.35 per 10,000 people in the EU (EU/3/16/1770).

3.1.2. Available therapies and unmet medical need

There is currently no pharmacological treatment approved for patients with ALD. Skysona (elivaldogene autotemcel), intended for the treatment of early cALD in patients less than 18 years of age was approved in 2021. However, shortly after approval, it was withdrawn from the European market by the MAH.

Therapies designed to either reduce hyperlipidaemia (bezafibrate, lovastatin) or lower dietary VLCFA intake failed to slow myelopathy in ALD patients. Dietary supplementation with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) can normalise plasma VLCFA levels, but clinical studies have shown that this does not prevent disease progression.

If childhood cALD is detected at an early stage before major neurological disability appears, accumulated experience supports the use of haematopoietic stem cell transplantation (HSCT) to arrest the inflammatory demyelination. Adult patients with cALD are offered HSCT if myelopathy and their overall clinical condition is not too advanced, their lesions are not affecting certain brain regions yet and there are no other relevant comorbidities.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is Study MT-2-01 (Part 1), which was a phase 2/3, randomised, double-blind, placebo-controlled study in adult male AMN patients who received leriglitazone or placebo. The study consisted of a 28-day screening period, after which the patients were randomised to placebo or leriglitazone. A total of 116 patients were randomised to leriglitazone (N=77) or placebo (N=39). Leriglitazone dose was titrated in week 0-12 of the double-blind period based on a target plasma exposure of leriglitazone of 200 µg·h/mL. Dose adjustments were allowed for safety/tolerability reasons.

The total duration of the double-blind period was 96 weeks. The 144-week open-label extension where 88 patients received leriglitazone (OLE; Part 2) is currently completed. In general, the study design was in accordance to the CHMP scientific advice, except for the comments on the total duration of the

study. There were doubts that a study duration of 24 months would be sensitive enough to detect a treatment effect as the natural course of AMN is insufficiently known. The recommendation to implement safeguards into the design without compromising its methodological integrity was, however, not followed.

Male patients ≥ 18 to ≤ 65 years of age were eligible to enrol into the study if they had a genetic confirmation of ALD and clinical evidence of spinal cord involvement.

The primary endpoint was the change from baseline to Week 96 in total walking distance in the 6-minute walk test (6MWT).

The key secondary endpoints were sway amplitude - total (mm) of body sway in the condition: eyes closed/feet apart, the Patient Global Impression Scale for Improvement (PGI-I), the total score on the Severity Score System for Progressive Myelopathy (SSPROM) and the overall score of the Qualiveen Short Form Quality of Life Questionnaire for Urinary Disorders (Qualiveen-SF). Other important secondary endpoints were the EDSS step and the Loes severity score.

3.2. Favourable effects

There was no difference in change from baseline at week 96 in the primary endpoint (6MWT) between leriglitazone and placebo. The least square mean change in 6MWT at week 96 was -31.8 m for placebo and -33.0 m for leriglitazone. The Least Square Mean difference was -1.2 m (CI_{95%} -22.6 ; 20.2 , $p=0.91$). Results of the sensitivity analyses were in line with the results of the primary analysis.

Also for the key secondary endpoints no differences between placebo and leriglitazone were observed after 96 weeks of treatment. For the body sway total score (eyes closed/feet apart) the difference in mean change was -1.05 mm (CI_{95%}: -2.78; 0.68) between placebo and leriglitazone ($p=0.23$). In PGI-I there was no difference in patients' impression of improvement between placebo and leriglitazone ($p=0.22$). In SSPROM the difference in mean change was 2.32 (95%CI: -0.31;4.94) between placebo and leriglitazone ($p=0.083$). For the Qualiveen-SF score the difference in mean change was -0.12 (95%CI: -0.40;0.16) between placebo and leriglitazone ($p=0.40$).

For the EDSS step the difference in mean change was -0.34 (95%CI: -0.72, 0.05) between placebo and leriglitazone ($p=0.09$). For the Loes severity score the difference in median change was -0 (Hodges-Lehmann Estimate of treatment difference; 95%CI: 0.0, 0.0) between placebo and leriglitazone ($p=0.11$). Six patients on placebo in the DB phase of the main study and one in the OLE-phase progressed to cALD, which was the newly sought target indication.

3.3. Uncertainties and limitations about favourable effects

Mode of action

Leriglitazone seems to have a general mode of action, not specific to (c)ALD. The applicant assumed that mitochondrial dysfunction and depolarisation, oxidative stress, inflammation and bioenergetic failure, hypothesised to contribute to the development and progression of ALD, is counteracted by PPAR γ . PPAR γ engagement of leriglitazone on molecular level is confirmed, however the relationship between PPAR γ receptor engagement and the pathophysiology/progression of ALD has not been demonstrated. From the non-clinical data it appears that leriglitazone has a high affinity for monoamine oxidase (MAO)-B enzyme inhibition. Though the overall non-clinical data indicate that the mode of action of leriglitazone is most likely to be driven by PPAR γ agonism, a minor contribution of MAO-B to the leriglitazone-mediated effects cannot be ruled out based on the presented

documentation (see non-clinical part). No relationship between leriglitazone's mechanism of action or the biomarker data and clinical progression of ALD was shown.

Dose finding

No formal dose finding study in patients with ALD was conducted to support the dosing regimen evaluated in the single pivotal study MT-2-01. A target exposure level was defined, based on the intention to provide maximal efficacy while remaining in the same range of the NOAEL dose level as determined in the rodent studies. It cannot be excluded that a higher dose could have been efficacious.

The dose was based on target exposure level (100-130 µg•h/mL). However, dose reduction in order to better control for oedema and weight gain occurred frequently. At the end of the study 45.5% of patients received the recommended dose and 33.8% a reduced dose. Dose reductions apparently did not result in a different effect size. 19.5% of the randomised patients to leriglitazone did not complete the double-blind phase.

Exposure

The target population are male patients with cALD. The disease leads to changes in adhesion molecules and tight junctions in the brain endothelium, which in turn promote an increase in blood-brain-barrier permeability. The main metabolite of leriglitazone, M3, is pharmacologically active, but only passes the blood-brain barrier to a very limited extent (<1%). When the blood-barrier is intact, M3 does not contribute to the efficacy, but can contribute to the safety. Furthermore, when the disease progresses the blood-brain barrier may be affected and M3 may be able to pass the blood-brain barrier to a similar extent as leriglitazone. Therefore, characterisation of the variability in the pharmacokinetic behaviour of M3 and leriglitazone + M3 is of importance. The applicant investigated the PK of leriglitazone and M3 in adult patients with AMN, but not in patients with cALD. In paediatric patients, ontogeny of metabolic enzymes may affect the PK of leriglitazone and M3. Only very limited data is available in paediatric patients aged 3 years and older. No PK data is available in younger children. Therefore, there is very limited data on the exposure in paediatric patients and no data on the exposure in patients with cALD supporting the last proposed indication.

Efficacy

The primary endpoint was not met. Almost no difference in effect was shown between the study arms. Thus, no efficacy of leriglitazone in the treatment of ALD was established.

No difference in change from baseline at week 96 between placebo and leriglitazone was observed in key secondary endpoints i.e., body sway total amplitude in eyes closed/feet apart condition, PGI-I, SSPROM total score and Qualiveen-SF overall score). Of the other secondary endpoints, only for the Loes severity score had a nominal $p=0.024$. For this score the analyses were conducted over the means, even though the medians are preferred because of the skewed distribution. Additional analysis based on median change, IQR and with corresponding Hoghes-Lehman estimates, showed that there is hardly a shift over time in Loes score in both groups. The difference over time just reflects that the baseline difference persists over week 48 and week 96.

In addition, the provided additional analyses with different cut-off scores of >0.5 or ≥ 1 for an 'abnormal' total Loes score at baseline indicate that patients on placebo were more advanced in terms of cerebral involvement. Furthermore, questions were raised about the results on cerebral progression in the context of the different severity of the groups, with placebo patients having longer disease duration and worse clinical score at baseline.

Sensitivity analyses conducted over the primary endpoint did not change the picture. Moreover, stratification by disease duration showed overall opposite results. Within the group of patients <10 years of myelopathy, less change from baseline was observed for leriglitazone compared to placebo.

While for patients with >10 years of myelopathy, patients on leriglitzazone showed more change from baseline than the patients on placebo. Moreover, a subgroup analysis of another definition but overlapping definition of early and late-stage disease (EDSS based) showed inconsistent results.

Study participants <-> Target population

The study population does not reflect the target population proposed in the indication, i.e., “the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD)”. The study population in the main study is restricted to ALD patients in the 18 - 65 years age range and, no subjects with cerebral ALD at baseline were included. Some patients were assessed as having cALD during DB or during the open-label extension. For paediatrics with cALD a pre-specified interim analysis for a small sample of patients is provided. However, this does not allow for any conclusion on the efficacy of leriglitzazone in a paediatric cALD population. Furthermore, extrapolation between adults and paediatrics and from ALD to cALD is not straightforward, due to e.g. a lack of PK data, anticipated differences in leriglitzazone plasma and brain exposure, and lack of an exposure-efficacy relation.

Post-hoc analyses

Even though statistical principles for the post-hoc analyses in the additional SAP were specified prior to performing these, the planned analyses could still be informed by the results of the analyses that were part of the main SAP introducing data driven choices. The results of post-hoc analyses are therefore considered exploratory/supportive.

3.4. Unfavourable effects

The safety of leriglitzazone has been evaluated in 110 adult male patients with ALD, who were exposed to leriglitzazone for at least two weeks to the target plasma exposure of 200 µg·h/mL, or a lower exposure down to 100 µg·h/mL (in case of dose modifications). Most of the safety assessment relies on the 77 patients that were exposed to leriglitzazone in the placebo-controlled phase of the pivotal study. Supportive safety data comes from studies in boys with cALD and patient with Friedreich’s Ataxia.

Almost all patients on leriglitzazone experienced an event related to the treatment (92.2%). Serious adverse events occurred in 18.2% of patients on leriglitzazone versus in 25.6% of patients on placebo. Mostly, these were single events observed in 1 or 2 patients, with the exception of adrenoleukodystrophy, reported in 6 (15.4%) patients in the placebo group only, referring to cALD progression. Per SOC, serious events were relatively balanced across the groups. One life-threatening event of anaphylactic shock occurred in the leriglitzazone group, but this was not considered treatment related. One death was reported during clinical studies with leriglitzazone.

The safety profile of leriglitzazone is dominated by oedema and weight gain; ‘oedema peripheral’ and ‘weight increased’ were reported most frequently and in the majority of patients treated with leriglitzazone (63.6% and 70.1%, resp.). Taking into account all reports (‘Preferred Terms’) of oedema, the incidence of oedema under leriglitzazone is 81.8%. A case of central oedema (ascites, during OLE) was also observed. Mean weight increase from baseline to Week 96 was 5.8 kg (Q1-Q3: 3.0-8.8) on leriglitzazone versus 1.3 kg (Q1-Q3: -1.5 – 4.0) on placebo. Oedema and weight gain were reported as non-serious and mild to moderate in nature. Nevertheless, a total of 41.6% of leriglitzazone-treated patients received dose reductions and 20.8% of patients received diuretics due to the occurrence of oedema and/or weight gain. In addition, 6.5% of patients on leriglitzazone permanently withdrew from the study due to these events.

With regard to the other post-hoc defined AESIs, cardiovascular events (most often palpitations and tachycardia) occurred in 7.8% of patients on leriglitzazone versus 5.1% of patients on placebo. Among

cardiovascular events were a case of increased jugular venous pressure and a case of atrial dilatation (MT-2-03, Friedreich's Ataxia). Hepatic events were reported in 5.2% of patients on leriglitazone versus 2.6% on placebo and mostly concerned increased ALT/AST levels; one case of leriglitazone-related hepatomegaly was reported. Abnormal urine cytology suspicious of urothelial carcinoma was observed, but no malignancies were confirmed. Haematological events most frequently comprised anaemia (15.6% on leriglitazone vs. 2.6% on placebo), but also cytopenia were observed (1.3% - 3.9%) on leriglitazone only. Bone fractures occurred in 9.1% of patients on leriglitazone versus 5.1% of patients on placebo.

In general, adverse events more frequently led to dose adjustments in leriglitazone-treated patients (44.2%) compared to placebo (5.1%). Similarly, adverse events that led to temporary and permanent withdrawal from study medication were more frequent in the leriglitazone group (10.4% and 11.7%, resp.) than in the placebo group (2.6% and 5.1%, resp.).

3.5. Uncertainties and limitations about unfavourable effects

Dosing

Almost half of all ALD patients treated with leriglitazone (44%) received dose reductions due to adverse events at some point during the pivotal study. Most dose reductions occurred due to oedema and/or weight gain, but they did not impact the course of the events.

Oedema and weight gain

The manageability of oedema and weight gain is a concern that could not be taken away. Oedema and weight gain occurred in the majority of leriglitazone-treated patients (81.8% and 70.1%, respectively), which was much more compared to controls (17.9% and 23.1%, respectively). The events could neither be stabilised nor reversed by dose adjustments and/or diuretics. Mean weight continued to increase up to the end of the double-blind phase and half of all patients still had oedema at the end of the double-blind phase, irrespective of receiving treatment or not. The provided patchy data indicate that oedema and weight gain show a variable pattern, are generally of long duration, and cannot be mitigated. No risk factors could be identified for the development of these events. There are no adequate treatment options to manage oedema, apart from complete withdrawal of leriglitazone, e.g., in case of intolerability or concerns of volume overload.

Carcinogenic potential

No bladder malignancies were reported in the study. However, PPAR γ compounds have been classified as 'probable human carcinogens', with carcinogenicity potentially existing beyond the site of the bladder. Carcinogenicity appears to be mediated by exaggerated pharmacologic effects observed as tissue hyperplasia. Hyperplastic changes were seen in the 6-month repeated dose toxicity study in rats under leriglitazone (i.e., subcutaneous sarcoma, pituitary gland, mammary tissue, uterus). A carcinogenic potential of chronic leriglitazone use cannot be excluded. The applicant proposed to evaluate this further in a post-authorisation safety study (PASS) as a post-marketing commitment. In the context of the negative opinion this is no longer of relevance.

Cardiac risk

Although the applicant confirmed that there were no signs of venous engorgement in the studied AMN population, i.e., in patients without cardiac risk factors, there is some evidence of leriglitazone-related volume overload (including hepatomegaly). By the time of the CHMP opinion, it was not possible to determine whether volume overload would specifically precipitate cardiac events in patients with cardiac risk factors (e.g., refer to the Friedreich's ataxia patient with atrial dilatation). In addition, the

longer-term consequences of unresolved oedema and associated risk of volume overload in the population not at cardiac risk are also not known.

Bone metabolism

Based on non-clinical and clinical data, a role of leriglitazone on bone density and associated adverse events (i.e., bone fractures) is considered likely. PPAR γ agonists were previously identified as having a role in bone metabolism, e.g., by inhibiting osteoblast formation and inducing osteocyte apoptosis, thereby reducing bone formation and contributing to the adverse effects on the bone. Effects of leriglitazone on bone metabolism are of particular concern for the paediatric population, as it may negatively affect bone growth.

Study discontinuation

Study discontinuation in the double-blind phase occurred more frequently in patients treated with leriglitazone than with placebo, often due to adverse events. However, reasons for study withdrawal were not always available. There are also no data on why 11.3% of patients on leriglitazone in the double-blind phase did not choose to enter the OLE phase to continue treatment. In addition, in the OLE phase, 39.4% patients from previous placebo who were switched to leriglitazone dropped out due to adverse events, most often oedema-related events. This percentage is much higher than drop-out due to AEs in the double-blind phase under leriglitazone. The increased drop-out rate due to AEs suggests that patients are not willing to adhere to leriglitazone treatment, also on the longer term.

Special populations

The safety of leriglitazone with respect to intrinsic factors (e.g., age) and extrinsic factors (e.g., hepatic impairment, renal impairment, patients at cardiac risk) has not been evaluated in the clinical studies. It remains uncertain how these in- and extrinsic factors impact the PK and safety of leriglitazone. The proposed product information dosing instructions, warnings, and/or recommendations could have been accepted as measures to mitigate risks.

Although the last indication claimed by the applicant was for the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral ALD (cALD), safety in children and adults with cALD was not sufficiently demonstrated at the time of the CHMP opinion.

Drug interaction studies

Clinical drug interaction data are lacking and the planned DDI studies do not sufficiently cover drug interactions expected to be of clinical relevance. This does not allow for adequate dosing instructions in case of co-administration with other medicinal products. This could pose a safety risk, especially in cases where co-administration leads to increased exposure to leriglitazone and thus to increased safety issues.

Table 31. Effects Table MT-2-01: A Randomised, Double-Blind, Placebo-Controlled, Multinational, Multicentre Study with Open-Label Treatment Extension to Assess the Effect of MIN-102 on the Progression of Adrenomyeloneuropathy in Male Patients with X-Linked Adrenoleukodystrophy. Cut-Off Date 15 April 2022

Effect	Short Description	Unit	Placebo	Leriglitazone	Uncertainties/ Strength of evidence	References
Favourable Effects						
6MWT	Δ from baseline at week 96 (mean (SE))	Meter	-31.8 (8.7)	-33 (6.7)	Unc: Primary endpoint, no difference between placebo and treatment: -1.2 (95%CI; -22.6, 20.2), p=0.914.	MT-2-01, Part 1
Body sway	Δ in mean total body sway amplitude at week 96	Millimeter	1.344	0.296	Unc: Key secondary endpoint. No difference between placebo and treatment: -1.05 (95%CI; -2.776, 0.679); p=0.234	MT-2-01, Part 1
PGI -I	Patient Global impression at week 96 Categories; 1 =very much improved to 7 =very much worse	N (%)	Very much improved: 0 Much improved: 0 Minimally improved: 2 (5.1) No change: 14 (35.9) Minimally worse: 11 (28.8) Much worse: 3 (7.7) Very much worse: 1 (2.6)	Very much improved: 0 Much improved: 2 (2.6) Minimally improved: 11 (14.3) No change: 20 (26.0) Minimally worse: 20 (26.0) Much worse: 5 (6.5) Very much worse: 0	Unc: Key secondary endpoint. No difference between placebo and treatment: p-value Wilcoxon rank sum test 0.221	MT-2-01, Part 1
SSPROM	Final score, Δ in mean (SE) score at week 96	0-100 points	-3.235 (1.1)	-0.920 (0.81)	Unc: Key secondary endpoint. No difference between placebo and treatment: 2.32 (95%CI; -0.306, 4.937); p=0.083	MT-2-01, Part 1

Qualiveen-SF	Δ from baseline at week 96 (mean (SE))	0-4* points	0.22 (0.12)	0.10 (0.08)	Unc: No difference between placebo and treatment: -0.12 (95%CI; -0.306, 4.937); p=0.083	MT-2-01, Part 1
EDSS step	Δ in mean (SE) score at week 96	0-10* points	0.56 (0.15)	0.23 (0.12)	Unc: No difference between placebo and treatment: -0.34 (95% CI; -0.40; 0.16; p=0.40	MT-2-01, Part 1
Loes Score	Δ in median score at week 96	0-34* points	0 (0)	0 (0)	Unc: No difference between placebo and treatment: 0.00 (95% CI; 0.0, 0.0); p=0.11	Applicant's response

Unfavourable Effects

Oedema	Incidence of any form of oedema	%	17.9	81.8%	Unc: How it can be resolved. Long-term consequences (e.g., volume overload). Consequences in patients at cardiac risk.	MT-2-01, Part 1
						MT-2-01, Part 1
Weight increased	Incidence of weight increased	%	23.1	70.1	Unc: How it can be reversed or stopped	MT-2-01, Part 1
Weight increased	Mean (IQR)	kg	1.3 (-1.5 - 4.0)	5.8 (3.0 - 8.8)		

6MWT = Six-Minute Walk Test, EDSS = Expanded Disability Status Scale, PGI-I = Patient Global Impression Scale for Improvement, SE= standard error, SSPROM = Severity Score System for Progressive Myelopathy, Qualiveen-SF = Overall score of the Qualiveen Short Form Quality of Life Questionnaire for Urinary Disorders

*Higher values means worsening

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Importance of favourable effects and the associated uncertainties

Uncertainties remain regarding the extent to which the mechanism of action of leriglitzazone is specific for ALD as well as the relationship between this mechanism of action and clinical progression of ALD.

The rationale for the chosen dosing regimen is based on the non-clinical studies, i.e. a combination of non-clinical safety and adiponectin response. An efficacy-exposure relation has not been established, which questions the adequacy of the target dose. No formal dose-finding study in patients with ALD to support the dosing regimen evaluated in the single pivotal study MT-2-01 was performed. The rationale for the chosen dosing regimen is unclear. The lack of knowledge on a potential effective dose range does not allow a position statement whether the reduced doses, which were frequently administered, are potentially efficacious.

In case of a single pivotal trial, the data have to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency (points to consider on application with 1. Meta-analysis, 2. One pivotal study, EMA; PMP/EWP/2330/99). The single pivotal study in support of this application was reasonably well-designed and well-conducted randomised controlled study. However, the primary and key secondary endpoints were not met. Hence, the data do not show that leriglitzazone is efficacious in the treatment of ALD or cALD, let alone that they are compelling.

The study population and target population do not converge.

In support of an early-stage myelopathy indication, in two subgroups analysis, the impact of disease duration (≤ 10 years vs >10 years of myelopathy) and EDSS score ($EDSS \leq 5.5$ versus $EDSS >5.5$) was evaluated. The cut-off criteria were based on natural history data but it is questionable whether these cut-off points adequately demarcate early and late-stage AMD. The evidence for a differential treatment effect is considered poor, from a methodological perspective the analyses were post-hoc, i.e., data-driven decisions cannot be excluded. From a clinical perspective, the different but overlapping definitions for early and late-stage disease do not show the same effects over the endpoints, i.e., there is no consistency. Most importantly, the 6MWT and EDSS-ambulation might be more sensitive to detecting a delay in progression in subjects that are more ambulatory. However, subjects were selected based on their ability to walk for 6 minutes, hence all subjects still had sufficient ambulatory function that could be maintained for 6 minutes. So even in the worst performers an effect could have been detected although the absolute effect may be smaller. The observed effect in the opposite direction (i.e., performing worse instead of better on leriglitzazone) is not plausible.

No conclusion can be drawn on efficacy or a better efficacy of leriglitzazone in the post-hoc subgroup analysis in early AMN. This would require a confirmatory study.

There are very limited data on the paediatric cALD population and adults with cALD were excluded at baseline. Interim open-label study data covering a short duration in a limited number of paediatric patients with cALD does not allow for any conclusion on the efficacy of leriglitzazone in a paediatric cALD population. Similarly, a limited number of adults with ALD were assessed as having progression to cALD in the pivotal study, and no conclusions on efficacy in the adult cALD population can be drawn.

Extrapolation between children and adults and from ALD to cALD is not straightforward, e.g. due to a lack of PK data, anticipated differences in leriglitzazone plasma and brain exposure, and lack of an

exposure-efficacy relation. There are only very limited data on the exposure in paediatric patients aged 4 years and older from study MT-2-02 (where only sparse samples were obtained). This is important since the ontogeny of metabolic enzymes in paediatric patients may affect the PK of leriglitzazone and its metabolite M3. Furthermore, data are lacking in adult patients with cerebral ALD that could support the last claimed indication. In these patients, changes in the blood-brain-barrier, which characterise this disease, or concomitant administration with P-glycoprotein and BCRP inhibitors may affect the exposure of leriglitzazone in the brain which in turn may have an effect on the efficacy and safety. Hence, as there are very limited data available, no conclusion can be drawn regarding the extrapolation of the study results in adults to children.

Importance of unfavourable effects and the associated uncertainties

Adverse events (mostly oedema and weight gain) led to dose reductions in almost half of the ALD patients treated with leriglitzazone. Withdrawal of treatment, often due to adverse events, is considered high and can be a reflection of the tolerability of the product. It could be argued that from a safety perspective, the proposed target dose is already too high. This may not be surprising, considering that the target dose was set at a tight safety margin of the NOAEL.

Leriglitzazone treatment is associated with oedema and weight gain in the majority of ALD patients. There were no predefined criteria to treat these events in the pivotal study. The actions taken in response to oedema and weight gain (dose reductions and/or diuretics) did not stabilise or reverse the events. Thus, oedema-related events are not manageable. No risk factors were identified for the occurrence of these events.

Although no malignancies were related to leriglitzazone treatment, concerns regarding the carcinogenic potential of leriglitzazone remain, especially since long-term use of the product would be anticipated. Hyperplastic changes, observed in non-clinical studies with leriglitzazone, and malignancies are anticipated to be observed only in long-term follow-up studies or post-marketing, as was the case with bladder cancer upon pioglitazone.

There are uncertainties on the safe use and dosing of leriglitzazone in special patient populations (e.g., patients with hepatic impairment) and patients taking concomitant medications that inhibit CYP2C8 and 3A4), since safety and PK data are scarce or lacking. This may pose safety risks, especially in case of increased plasma exposure to leriglitzazone. The proposed SmPC dosing instructions, warnings, and/or recommendations can be accepted as measures to mitigate risks. In addition, specific safety concerns may apply, e.g., effects on bone growth in children. Safety data in patients with cerebral ALD (cALD) are limited and do not allow for conclusions.

Altogether, the safety profile of leriglitzazone at the recommended dose appears unfavourable, especially regarding oedema/weight gain. Appropriate mitigation measures for oedema/weight gain cannot be identified. Clinical consequences in the long term (e.g., volume overload) and/or in specific patient groups, such as those already at cardiac risk, are unknown.

3.6.2. Balance of benefits and risks

The unmet need for a treatment of (c)ALD is acknowledged. Currently no approved medical treatments are available in the EU.

A single pivotal trial was conducted in male adults with ALD. The data indicate that leriglitzazone is not efficacious in the treatment of ALD. Also, the dosing regimen has no clear substantiation from a PK and efficacy perspective, and appears too high from a safety perspective. No appropriate mitigation measures could be determined for the oedema/weight gain. Moreover, the last requested indication, which is restricted to paediatric and adult male patients with cALD, does not correspond with the

studied population of adult male ALD patients. The provided data of paediatric patients and adults with cALD does not allow for conclusions.

Thus, the efficacy of leriglitzzone has not been shown in ALD or cALD and there are concerns with respect to safety. The applied indication is not substantiated by the submitted data.

3.6.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating life-threatening disease.

Over the course of the assessment, while amending the applied indication, the applicant requested a conditional marketing authorisation (CMA) for the treatment of ambulatory adrenoleukodystrophy (ALD) in adult male patients with early stage myeloneuropathy, and paediatric and adult ALD male patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD). In the very last stage of the assessment, the applicant proposed to restrict the indication for CMA to the treatment of paediatric and adult ALD male patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD).

The CHMP considers that the product cannot be recommended for a conditional marketing authorisation since there is a lack of demonstration that the required criteria are met:

- 1) The benefit-risk is considered negative (see benefit-risk discussion). There are uncertainties regarding the mode of action, the posology, the limited efficacy and safety data and the extrapolation. Neither in the population of male adults with ALD, nor in subpopulations of adults with early myeloneuropathy or paediatric patients from 2 years of age and adults with cALD a positive benefit-risk balance of leriglitzzone could be established. Efficacy on the primary and key secondary endpoints has not been met. The pivotal study in AMN is a failed study and efficacy has not been demonstrated in (early) AMN. Patients with cALD were not included in the pivotal study. Given that the efficacy has not been demonstrated, the high incidence of oedema and weight gain, which cannot be mitigated by appropriate mitigation measures, is not acceptable;
- 2) The negative benefit-risk precludes fulfilling the condition of generating comprehensive data post-authorisation. The NEXUS study had initially been proposed as a specific obligation (SOB), should the conditional marketing authorisation have been accepted. This open-label study includes boys aged 2-12 years with cALD, and only partly covers the sought indication. In addition, there were doubts whether efficacy claims could have been made upon completion of this study, given the study design and interim results (see efficacy discussion). Moreover, the CALYX study was initially proposed as an SOB. This is a double-blind placebo-controlled study of 36 months in adult patients with cALD. Enrolment has been initiated and the final study report is expected 3Q 2027. The design of CALYX seems more appropriate than NEXUS for part of the sought indication of cALD. However, the same issues regarding a single pivotal study and extrapolation to paediatric patients would apply;
- 3) The unmet medical need in ALD and cALD is acknowledged;
- 4) Since efficacy has not been established and there are concerns and uncertainties with regard to the safety of the product, a benefit to public health of immediate availability does not outweigh the risks inherent to the fact that additional data are still required (see B/R discussion).

3.7. Conclusions

The overall benefit/risk balance of Nezglyal is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Nezglyal in the treatment of paediatric and adult male ALD patients aged 2 years and older with cerebral adrenoleukodystrophy (cALD), the CHMP considers by consensus that safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product.

The CHMP considers that:

- Efficacy with regard to the primary and key secondary endpoints was not established in the single pivotal trial with ALD patients. The pivotal study is a failed study.
- No relationship between leriglitzzone's mechanism of action, or the biomarker data, and clinical progression of adrenoleukodystrophy (ALD) could be established. No exposure-response relation has been established.
- The limited data on patients with cerebral ALD (cALD) do not allow for conclusions on efficacy, nor do they overrule the negative results from the pivotal trial.
- No appropriate mitigation measures could be determined for the very commonly reported adverse events oedema/weight gain in the pivotal trial.
- A positive benefit-risk balance of leriglitzzone was not established in either the population of male adults with ALD, nor in post-hoc defined subpopulations of adults with early myeloneuropathy, or in paediatrics from 2 years of age or adults with cALD.
- Taking into account the negative benefit-risk balance of Nezglyal, the unlikelihood that the applicant will be able to provide comprehensive data post authorisation and the fact that the benefit to public health of the medicinal product's immediate availability on the market would not outweigh the risks inherent to the fact that additional data are still required, a conditional marketing authorisation cannot be granted.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

New active substance

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP is of the view that leriglitzzone is not to be qualified as a new active substance. The detailed position of the CHMP is reflected in the respective Appendix.

5. Re-examination of the CHMP opinion of 25 January 2024

Following the CHMP conclusion that Nezglyal was not approvable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal and a revised indication, i.e. "treatment of

male ALD patients aged 2 years and older with brain lesions to delay progression of cerebral adrenoleukodystrophy (cALD)".

The applicant did not submit a specific ground for re-examination in relation to the following ground for refusal: "A positive benefit-risk balance of leriglitazone was neither established in the population of male adults with ALD, nor in post-hoc defined subpopulations of adults with early myeloneuropathy, or in paediatrics from 2 years of age or adults with cALD". In view of the revised indication requested by the applicant as part of the re-examination procedure, the grounds for re-examination submitted by the applicant in relation to refusal grounds #1 and #3, and their assessment there (see section 5.1 below), the CHMP considered it is not necessary to maintain the above-mentioned ground for refusal.

Additional considerations were submitted by the applicant during the course of the re-examination procedure. The present assessment report discusses the scientific evidence and scientific arguments submitted by the applicant. Moreover, the applicant submitted within the re-examination procedure submission comments on 13 specific sections from the CHMP assessment report adopted on 25 January 2024 and from the Joint Assessment Reports generated during the initial assessment procedure. The applicant's comments have been taken into account in the re-examination of the CHMP opinion of 25 January 2024.

5.1. Detailed grounds for re-examination submitted by the applicant

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the SAG-N. As a response to the grounds for refusal, the applicant provided further analyses in writing and during an oral explanation on 28 May 2024.

5.1.1. Ground #1

Refusal Ground 1:

Efficacy with regard to the primary and key secondary endpoints was not established in the single pivotal trial with ALD patients. The pivotal study is a failed study.

Applicant's Grounds for re-examination:

It is agreed that the study with respect to the primary endpoint is a failed study. But claiming "... a failed study" as ground for refusal without discussing that data were submitted showing a positive response to treatment on all cALD related endpoints, is not understood at all. This ground for refusal appears to be based on misunderstandings regarding the disease cALD, the indication requested, and/or the relevant patient population within the pivotal trial. During the review, the applicant narrowed its application to seek approval in cALD. In light of the best available scientific information, only the cALD subgroup in ADVANCE should be considered:

- ADVANCE enrolled patients with AMN, which is an ALD phenotype that presents independently of cALD.
- AMN-related endpoints including the primary endpoint from ADVANCE are not relevant in the targeted cALD indication.
- 27% of the AMN patients in ADVANCE had also cALD, i.e., non-enhancing lesions, at baseline.
- All ADVANCE endpoints related to lesion progression favour leriglitazone over placebo (both in FAS and in patients with cALD).

In conclusion, for cALD, the pivotal study is not a failed study. In view of the above, the applicant does not believe that Refusal Ground 1 can be supported by the evidence presented to the CHMP.

Assessment of the applicant's grounds for re-examination

The most recently proposed indication during the evaluation process of this dossier is "Nezgylal is indicated for the treatment of male ALD patients aged 2 years and older with brain lesions to delay progression of cerebral adrenoleukodystrophy (cALD)".

Completed ADVANCE (MT-2-01) study was a placebo-controlled study primarily designed to evaluate the effect of leriglitazone on AMN progression in adult male ALD patients.

Therefore, the pre-specified primary endpoint (Change from Baseline to Week 96 in total walking distance in the 6MWT) and key secondary endpoints (Change from Baseline to Week 96 in: Sway amplitude; PGI-I; SSPROM; Qualiveen-SF) of the completed ADVANCE ALD trial are not appropriate for examining the most recently proposed paediatric and adult cALD indication, nevertheless, two of the secondary endpoints (Incidence of progression of cerebral lesions in cerebral MRI from Baseline to Week 96; Loes severity score on the MRI from Baseline to Week 96) are relevant for cALD subpopulation.

Patients suffering from cALD can have gadolinium enhancing (Gd-positive) cerebral lesions or non-Gd-enhancing (Gd-negative) cerebral lesions at MRI. However, in the ADVANCE study cALD patients with presence of inflammatory (Gd-enhancing) MRI cerebral lesions or any abnormality other than those mentioned in the inclusion criteria were excluded, furthermore only adult patients were included.

The applicant states that 27% (31/114) of the adult AMN ALD patients in ADVANCE had also cALD, i.e., non-Gd-enhancing lesions at cerebral MRI, at baseline. However, the presence of this cALD sub-group of the ALD study population is not apparent from the demographics tables in the Clinical Study Report (CSR) of MT-2-01 study i.e. ADVANCE (Table below) nor from the statistical analysis plan submitted with the initial application, for efficacy within cALD sub-group of the ALD study population. The Table 'Medical History/Concomitant Diseases' from initial documentation seems to contain only one patient with "Cerebral lesions without contrast enhancement" i.e. cALD.

Table 32. Demographic and Baseline Characteristics (Safety Set)

Category	Placebo (N=39) n (%)	MIN-102 (N=77) n (%)	Overall (N=116) n (%)
Age (years)			
n	39	77	116
Mean (SD)	44.6 (11.14)	42.6 (11.15)	43.3 (11.14)
Median	48.0	42.0	43.5
Min, max	23, 62	19, 66	19, 66
Race, n (%)			
White	30 (76.9)	62 (80.5)	92 (79.3)
Other	1 (2.6)	1 (1.3)	2 (1.7)
Not collected (France)	8 (20.5)	14 (18.2)	22 (19.0)
Ethnicity, n (%)			
Not Hispanic or Latino	29 (74.4)	59 (76.6)	88 (75.9)
Hispanic or Latino	2 (5.1)	4 (5.2)	6 (5.2)
Not collected (France)	8 (20.5)	14 (18.2)	22 (19.0)
Height (cm)			
n	39	77	116
Mean (SD)	179.7 (7.22)	178.4 (6.70)	178.8 (6.87)
Median	180.0	178.0	179.0
Min, max	161, 199	165, 197	161, 199
Weight (kg)			
n	39	77	116
Mean (SD)	80.11 (13.533)	77.56 (12.737)	78.42 (13.007)
Median	79.50	76.00	77.35
Min, max	52.0, 118.2	50.0, 137.8	50.0, 137.8
BMI (kg/m ²)			
n	39	77	116
Mean (SD)	24.817 (4.0852)	24.340 (3.4784)	24.501 (3.6827)
Median	24.131	23.837	23.991
Min, max	18.64, 35.88	17.30, 36.61	17.30, 36.61
Years of myelopathy			
n	34	66	100
Mean (SD)	12.8 (6.24)	10.6 (6.26)	11.3 (6.32)
Median	12.0	10.0	10.5
Min, max	3, 23	0, 30	0, 30

Abbreviations: BMI, body mass index; max, maximum; min, minimum; n, number of patients in a category; N, total number of patients; SD, standard deviation.

Percentages were calculated based on N.

Years of myelopathy indicates years elapsed since onset of myelopathy symptoms.

The applicant submitted at the re-examination the following Table 33, showing that 27% (n=31) (or 28% for n=33 with the 2 Gd+ cALD patients) of the adult patients in the ADVANCE trial had cALD at baseline (N=19 for leriglitazone and N=14 for placebo). Two patients with Gadolinium-enhancing (Gd+) brain lesions at MRI fulfilling the pre-defined exclusion criteria were enrolled (1 in leriglitazone, 1 in placebo) and hence were considered protocol deviations in ADVANCE study.

Table 33. ADVANCE: Diagnosis of Progressive cALD in Patients with or without cALD at Baseline (MRI based, Central Readers)

	No visible lesions		With non-enhancing brain lesions (cALD)	
	Leriglitazone N=58	Placebo N=25	Leriglitazone N=19	Placebo N=14
n	0	3	3	5
%	0	12	16	36

Progression of cerebral lesions by MRI defined as:

1. Appearance of Gd+ lesions, or
2. Growth of existing Gd- lesions, or
3. Appearance of new Gd- lesions

Abbreviations: cALD – cerebral adrenoleukodystrophy; N – number of patients; n – number of patients diagnosed with progressive cALD

Loes scores (gold-standard scoring system to evaluate radiological progression of cALD) >0 were recorded at baseline both in the placebo and the treated groups of ALD patients (initial application CSR Table 34 and D180 Figure 12 below) as pre-defined secondary endpoint in the ADVANCE.

Table 34. Change from Baseline to Week 96 in Cerebral MRI Loes Scores – Further Secondary Endpoint – ANCOVA (Full Analysis Set)

Timepoint Statistic	Placebo (N=39)	MIN-102 (N=77)
Baseline		
n	38	76
Mean (SD)	2.408 (4.4172)	1.375 (2.2875)
Week 96		
n	35	61
Mean (SD)	3.186 (5.2189)	1.418 (2.2327)
Change from Baseline to Week 96		
n	34	60
Mean (SD)	0.735 (1.8959)	0.092 (0.3652)
ANCOVA		
Absolute change from Baseline to Week 96		
n	34	60
LS means (SE)	0.696 (0.2021)	0.114 (0.1515)
95% CI	0.2948, 1.0977	-0.1871, 0.4147
MIN-102 – Placebo		
LS means difference (SE)		-0.582 (0.2544)
95% CI		-1.0877, -0.0772
P-value		0.024

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; MRI, magnetic resonance imaging; n, number of patients in category; N, total number of patients; SD, standard deviation; SE, standard error.

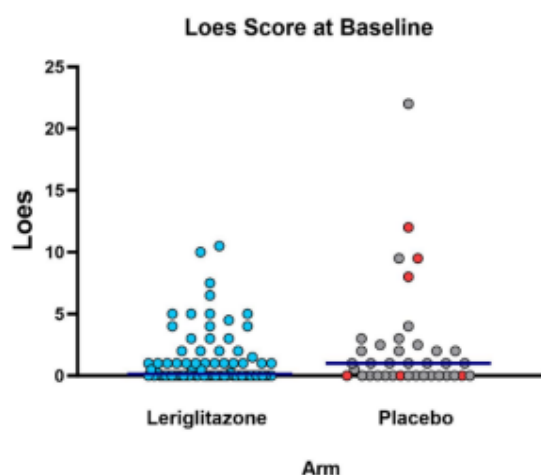
Loes scores range from 0 to 34.

Baseline was defined as the last value recorded before first intake of double-blind study treatment.

Change from Baseline was calculated as post-baseline value – baseline value.

The ANCOVA model included baseline Loes score as a covariate.

Figure 12. Baseline Loes Score for All Patients Randomised in ADVANCE



It should be noted that cerebral forms of ALD (cALD) begin most commonly in childhood; adolescent and adult onset occurs only occasionally (Moser, 1997). However, in the completed ADVANCE study, only male adult (ALD) patients aged ≥ 18 to ≤ 65 years are included, while included cALD patients were having only cerebral MRI lesions without Gd enhancement (and Gd+ cALD patients were excluded).

An open-label study (NEXUS) in paediatric patients with cALD to assess the effects of leriglitazone on disease progression prior to HSCT in males aged ≥ 2 and ≤ 12 years with cerebral MRI lesions with or without Gd enhancement at baseline is ongoing and interim results from this study were provided. See also assessment to ground #3 below.

ADVANCE Study results:

In new analyses and subgroup analyses on existing data of the completed ADVANCE ALD trial (in adults), the applicant presented:

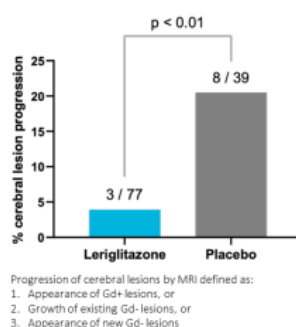
ADVANCE secondary endpoints related to cerebral lesion progression (Incidence of progression of cerebral lesions in cerebral MRI; Loes severity scores on MRI) favour leriglitazone over placebo in overall ALD FAS population (N=116) as well as in the ALD subgroups of patients with cALD (N=33) and ALD patients with no visible MRI lesions (N=83). It should also be noted that FAS (full analysis set) analysis includes the 2 enrolled cALD patients with Gd-enhancing (Gd+) brain lesions at MRI fulfilling the exclusion criteria for the ADVANCE study (1 in leriglitazone, 1 in placebo group); these patients were protocol deviations and, according to the applicant, were excluded from the secondary endpoint analysis "cerebral lesion progression", however still included in the "Loes" analysis as part of the FAS.

- Incidence of progression of cerebral lesions in cerebral MRI:

ALD population FAS: Incidence: 3.9% (N=3/77) Active / 20.5% (N=8/39) placebo (proportion difference of -0.17, Newcombe-Wilson CI of proportion difference -0.32 to -0.05; $p=0.007$, two-sided Fisher's exact test).

The applicant explained that central readers reported all patients showing radiological changes even if such changes were small. This differs from the standard of care criteria used by treating physicians to diagnose progressive cALD, which requires clinically meaningful changes in the MRI. Therefore radiological changes were reported in 11 patients. Out of these 11, six were diagnosed with progressive cALD (Figure 13).

Figure 13. ADVANCE: Cerebral Lesion Progression Reported by Central Readers



ALD patients with no visible MRI lesions subgroup (N=83): 0% Active (N=0)/ 12% placebo (N=3)

cALD subgroup (N=33; including 2 patients with Gd+): 16% Active (N=3)/ 36% placebo (N=5)

No statistics were provided for the cALD subgroup-analyses of Incidence of progression of cerebral lesions in cerebral MRI.

- Loes severity scores:

ALD population FAS: Active LS means change was 0.114 (95% CI: -0.1871, 0.4147)/placebo LS means change was 0.696 (95% CI: 0.2948, 1.0977). LS means difference between the treatment groups was -0.582 (95% CI: -1.0877, -0.0772), P=0.024

ALD patients with no visible MRI lesions subgroup: no raw data provided

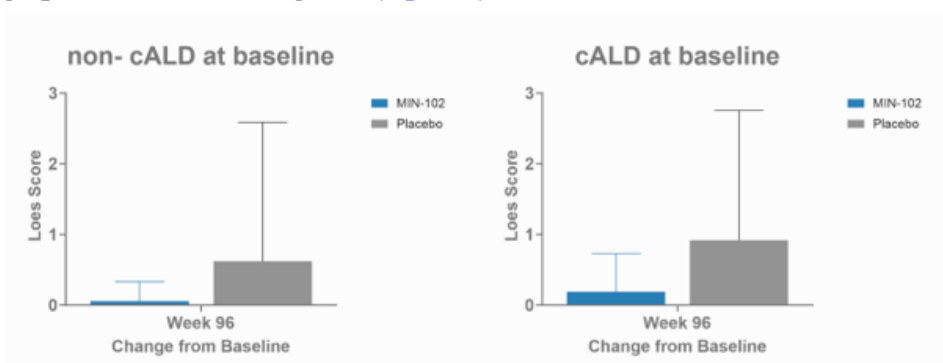
cALD subgroup: no raw data provided

No raw data or statistics were provided for Loes score by baseline cALD sub-groups, only histogram Figure 14 in Re-examination document and the applicant stated that Loes increase tends (no statistics) to be larger:

Figure 14. ADVANCE: Patients with No Visible Lesions + with Non-enhancing Brain Lesions (cALD): Loes Score – Mean Change from Baseline

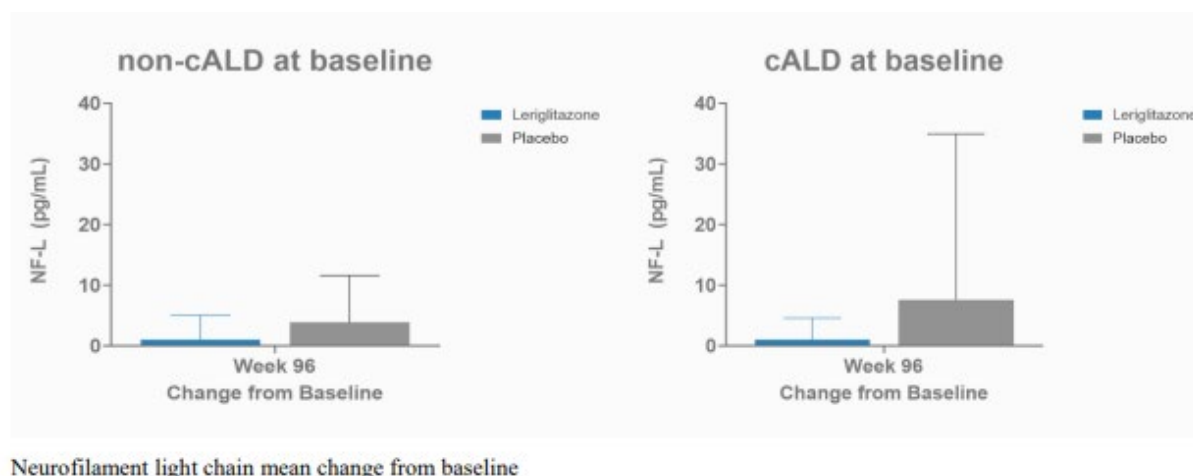
In both sub-groups, the Loes score increase was larger in the placebo arm driven by patients showing progression.

Moreover, Loes increase tends to be larger in the group of patients with non-enhancing brain lesions, i.e., cALD, at baseline, consistent with the increased risk of showing cerebral lesion progression once lesions are present (Figure 11).



The applicant provided Figure 15 stating that NfL, a disease non-specific biomarker (exploratory endpoint), increase tends (no statistics) to be larger in the placebo patients with non-enhancing brain lesions cALD at baseline:

Figure 15. ADVANCE: Patients with No Visual Lesions + with Non-Enhancing Brain Lesions (cALD): Neurofilament Light Chain (NFL) Mean Change From Baseline



None of the evaluated secondary endpoints related to a functional status or quality of life (EDSS, CGI-I, PGI-I, CGI-S, EQ-5D-5L) showed statistically significant differences between the treatment and the placebo groups in ALD patients. Moreover, CGI-S, CGI-I, PGI-I, EDSS, QoL are not disease-specific. No statistical analysis was provided for these parameters in the subgroups of patients with cALD at baseline and patients with no visible lesions on MRI at baseline.

Currently, the applicant focuses on the patients with cALD but this includes only 27% of patients of the completed pivotal ADVANCE trial.

Furthermore the primary endpoint, is the most important measure of any clinical trial on which all statistical analyses are based, should be specified in the protocol, along with the rationale for its selection, and should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial (ICH E9 Statistical principles for clinical trials; CPMP/ICH/363/96). The primary endpoint which was chosen for the investigation of AMN has no relevance for cALD, and did not show a significant result ($P=0.914$). There was no pre-specified relevant primary efficacy clinical outcome-measure for cALD in the completed ADVANCE ALD study. In addition, the key secondary endpoints were focused on the ALD population.

Overall and although some potential signal is suggested by the applicant for the 2 secondary endpoints, 'incidence of progression of cerebral lesions in cerebral MRI' and 'Loes severity scores' in the ALD population, since the primary study endpoint was not met, these secondary endpoints should be interpreted with caution. Nominally significant p-values of these secondary endpoints are informative only and are not considered sufficient to support an indication in the absence of the primary endpoint met, in the ALD population. No such statistical analyses were provided for the post hoc defined subgroup of baseline cALD patients, but these would not be considered sufficient either, also considering the post hoc nature of these analyses (ICH E9 Statistical principles for clinical trials; CPMP/ICH/363/96). In conclusion, the data provided from the ADVANCE study do not allow to conclude positively on efficacy in support of the most recently proposed cALD indication.

In support of the most recently claimed cALD indication, a dedicated pivotal trial including all relevant cALD age-groups and all relevant MRI presentations (Gd- and Gd+) should have been conducted with primary and secondary endpoints relevant for the claimed cALD indication.

Also, the majority of the SAG-N experts (see below section 5.2 on the SAG-N consultation) were not fully convinced that the current data are sufficient to conclude on a positive benefit in cALD due to the

prespecified design of the trial aiming to evaluate treatment effects in patients with myelopathy, the formal failure of the pivotal study (i.e. pivotal trial did not meet the specified primary endpoint) and the fact that results supporting a potential effect on patients with cALD were post-hoc derived and hence, not considered confirmatory but rather exploratory or hypothesis generating. However, a couple of these experts noted that even if not conclusive, available data do suggest that there could be a signal for some benefit in the treatment of cALD. The majority of the SAG-N experts thus view the ADVANCE study as a formally failed study in which post hoc data analyses provided results that could only serve to support further investigation of the product in the subgroup of cALD patients.

In conclusion, because of the primary endpoint failure, the available data provided by this study based on secondary endpoints only, are not considered sufficiently robust to support a positive B/R balance in cALD.

Point not resolved, the ground for refusal is maintained: "Efficacy with regard to the primary and key secondary endpoints was not established in the single pivotal trial with ALD patients. The pivotal study is a failed study."

5.1.2. Ground #2

Refusal Ground 2:

No relationship between leriglitazone's mechanism of action, or the biomarker data, and clinical progression of adrenoleukodystrophy (ALD) could be established. No exposure response relation has been established.

Applicant's Grounds for re-examination:

This statement is incorrect:

- It is a matter of fact that radiological outcomes correlate with clinical outcome - nobody in the field would question this.
- In terms of clinical outcomes, the CHMP is claiming "no effect" while looking into the ADVANCE (FAS) population, where, by definition, such an effect cannot be expected.
- The interpretation is totally different when it is focused on the cALD population in ADVANCE where the correlation between markers and clinical improvement has clearly been shown.
- An exposure-response relationship has been established in the context of dose finding and when establishing the dose applied in ADVANCE

This has been confirmed by the findings to date with NEXUS. Delaying disease progression and death in cALD establishes a sufficient link with the clinical benefit of leriglitazone. The relation between MOA (or biomarker) and efficacy is therefore of secondary interest and claiming that this information is not available has no impact on the benefit/risk. The applicant has presented an extensive overview from the literature on the correlation between biomarkers and clinical progression in patients with cALD, in both untreated patients and patients treated with HSCT or ex-vivo gene therapy (see also Mussolino Expert Report, D180 Response to MO on biomarkers and Oral Explanation). The applicant has also presented an integrated overview of leriglitazone's MoA, biomarker data and preclinical and clinical results. This information was originally provided on Day 120 alongside an overview of the pathophysiology of cALD, an overview on the biochemical and imaging biomarkers that are altered in each case, and an outlook on the clinical progression. This figure was also included on in the D180 Responses to the MO on Benefit-Risk, and was complemented in Appendix 2. Since the EMA D195 JAR reiterated the D120 and D180 statements without mentioning the above, the applicant cannot escape

the conclusion that the CHMP has not yet duly considered the additional information provided, in particular with its Day 180 responses. In view of the above, the applicant believes that Refusal Ground 2 is not compatible with the evidence submitted. At any rate, Refusal Ground 2 appears premature, since the full extent of the applicant's responses need to be reviewed by the CHMP.

Assessment of the applicant's grounds for re-examination

The applicant has presented their integrated view on leriglitazone's proposed mechanism of action, pathophysiology, biochemical and radiological markers.

Multiple potential pathophysiological effects of leriglitazone are proposed in ALD and cALD, and changes in a large number of biochemical biomarkers correlated with these potential pathophysiological effects (such as an effect on oxidative stress) are suggested by the company based on literature data. MRI is a diagnostic tool in cALD. Loes et al (2003) have shown that analysis of MRI patterns aids prediction of progression in X-ALD.

However, an exposure response relationship has not been established, and it is not totally agreed that the relationship between proposed mechanism of action on PPAR γ receptor (or inflammatory biomarkers) and clinical efficacy in cALD is only of secondary interest because this can add more credibility to the findings in the cALD subgroup as biological plausibility and the ability to find replication are key elements to evaluate the credibility of a subgroup finding (according to the guideline Investigation of subgroups in confirmatory clinical trials EMA/CHMP/539146/2013).

In the completed ADVANCE study double-blind phase, 11.7% of patients permanently withdrew from study medication due to AEs and over 44% of patients on leriglitazone received dose reductions (treatment suspension) due to adverse events, and were therefore not exposed to the proposed targeted daily dose in 12 mL of oral suspension for proposed extended period of time (high dose continuous chronic use). These temporarily dosing reductions (Table 35 below, and in initial documentation) raise concerns for overdosing in the currently proposed daily dose in cALD and associated safety risks (among others the important medical events listed in the Nezglyal proposed SmPC occurring frequently: leukopenia, neutropenia, pancytopenia; while bladder cancer is expected to be observed only in long-term follow-up studies or post-marketing, as it is the case for pioglitazone which exposes patients to several times lower doses of its metabolite leriglitazone compared to Nezglyal as discussed by the applicant).

Table 35. Dose Adjustment (Safety Net)

Category	MIN-102 (N=77) n (%)
Overall	
Dose as recommended	41 (53.2)
Dose reduced	33 (42.9)
Week 4	
Dose as recommended	74 (96.1)
Dose reduced	2 (2.6)
Week 12	
Dose as recommended	57 (74.0)
Dose reduced	19 (24.7)
Week 24	
Dose as recommended	57 (74.0)
Dose reduced	13 (16.9)
Week 48	
Dose as recommended	45 (58.4)
Dose reduced	24 (31.2)
Week 72	
Dose as recommended	36 (46.8)
Dose reduced	27 (35.1)
Week 96	
Dose as recommended	35 (45.5)
Dose reduced	26 (33.8)

Abbreviations: n, number of patients in category; N, total number of patients.

Percentages were calculated based on N.

Overall dose as recommended: all patients randomized to MIN-102 who took the most recent dose recommended by the PK expert ($\pm 10\%$) for $\geq 50\%$ of days between Week 12 and Week 96.

Overall dose reduced: all patients randomized to MIN-102 who took a dose between 10% and 50% ($>10\%$ and $\leq 50\%$) lower than the PK recommended dose for $\geq 50\%$ of days Week 12 and Week 96.

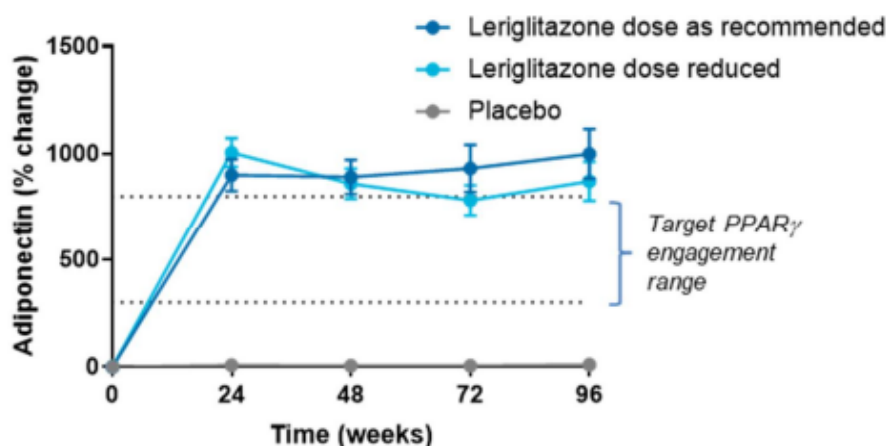
Dose as recommended per visit: all patients randomized to MIN-102 to whom the investigator prescribed the same dose ($\pm 10\%$) as the dose recommended by the PK expert over at least 5 days before the corresponding visit.

Dose reduced per visit: all patients randomized to MIN-102 to whom the investigator prescribed a dose that was $>10\%$ to $\leq 50\%$ lower than the dose recommended by the PK expert over at least 5 days before the corresponding visit.

At Week 4, the initial dose (10 mL) was considered as the 'last dose recommended by the PK expert' for the purpose of the subgroups.

No dose finding study was performed. The rationale for using a concentration-targeted approach in study MT-2-01 in AMN patients is based on non-clinical findings and phase 1 data. The applicant makes an assumption that the observation of a higher effect on inflammation biomarkers with a higher concentration at the tested dose range in the phase 1 study would support the notion of going to the highest possible dose in a devastating disease such as cALD which is mostly driven by neuroinflammation. These findings cannot be confirmed in the currently conducted clinical trials. It is uncertain whether the current dosing is the most optimal for the concerned cALD indication, which is a prerequisite for MA approval, and whether lower leriglitazone levels, could be efficacious as well with reduced need for treatment/exposure suspensions. For example, in the initial application the company has presented data showing that substantial leriglitazone dose reduction (" $>10\%$ to $\geq 50\%$ lower" "for at least 50% of the days between V2 and V6") has not lead to the substantial change in the adiponectin levels in plasma, which was measured as a biomarker of PPAR γ engagement in plasma (Figure 16).

Figure 16. Increase in Adiponectin Levels in Plasma in Treated Patients (% Change vs Baseline)



Time course for adiponectin (ng/mL) in plasma represented as mean % change from baseline $\pm$ SEM.

Subgroup "Leriglitzzone dose as recommended" includes all active subjects to whom the investigator prescribed the same dose ($\pm 10\%$) as the dose recommended by the PK expert for at least 50% of days between V2 and V6.

Subgroup "Leriglitzzone dose reduced" includes all active subjects to whom the investigator prescribed a dose that was $>10\%$ to $\leq 50\%$ lower than the dose recommended by the PK expert for at least 50% of days between V2 and V6.

It was stated that the dose of leriglitzzone was individually adjusted in each patient to achieve a target exposure of $200 \mu\text{g}\cdot\text{h/mL}$, as translated from animal efficacy studies. Therefore it is not clear whether in practice the product should be dosed based on a drug concentration measurement in each patient.

An exposure response relationship has not been established.

In the completed pivotal randomised controlled ADVANCE study in ALD, the primary endpoint (6MWT) failed. Although the secondary efficacy endpoints incidence of progression of cerebral lesions and Loes severity score on the MRI were prespecified for the initial trial in ALD population, they were not prespecified for cALD and, consequently, no reliable efficacy data were generated in baseline cALD patients in the ADVANCE study. It follows that the ADVANCE study cannot generate data to establish the relationship between leriglitzzone's mechanism of action, or the biomarker data, and clinical progression of cerebral adrenoleukodystrophy (cALD). No exposure response data were generated to establish the dose exposure response (DER) relationship in ADVANCE.

The open-label NEXUS study in 20 paediatric cALD patients 2-12 years of age, to assess the effects of leriglitzzone treatment on disease cerebral progression prior to human stem cell transplant, that includes clinical secondary endpoints and a composite clinical-MRI primary endpoint, is still ongoing. The preliminary, interim data in a small patient sample make it difficult to draw efficacy conclusions based on this study. The NEXUS study has, at present, not generated data that could support a relationship between the product's MOA and the observed clinical progression.

Overall SAG-N experts agreed that the mechanism of action of leriglitzzone for the treatment of ALD is unclear. The observed MRI stabilisation is -in the view of the experts- clearly deviating from the expected natural course of the cALD phenotype, and thus, the results on MRI findings are perceived as relevant from a clinical perspective. These data add further to the hypothesis generating post hoc analyses that were performed on the ADVANCE study data. Since no clear effect of leriglitzzone on clinical progression of ALD or cALD has been demonstrated up to now, which would have to be reflected in a statistically significant and clinically relevant pre-specified primary study endpoint outcome, no relationship with MOA or biomarker data can be established either at present.

Point not resolved, the ground for refusal is maintained: "No relationship between leriglitzzone's mechanism of action, or the biomarker data, and clinical progression of adrenoleukodystrophy (ALD)

could be established. No exposure response relation has been established.”

5.1.3. Ground #3

Refusal Ground 3:

The limited data on patients with cerebral ALD (cALD) do neither allow for conclusions on efficacy, nor overrule the negative results from the pivotal trial.

Applicant's Grounds for re-examination:

It is agreed, the available data is limited – per se. However, considering the ultra-rare nature of the disease (less than 0,4/10.000 in the EU), the number of patients treated is significant.

To date, more than 100 patients with cALD have been treated:

- 31 patients with non-enhancing brain lesions (ADVANCE)
- 23 paediatric patients with non-enhancing brain lesions and progressive cALD (NEXUS)
- Approximately 60 adult and paediatric patients with non-enhancing brain lesions or progressive cALD under compassionate use.

Therefore, within this context, it is not appropriate to conclude that the database is limited. If the CHMP statement on cALD patient data being “limited” is based on the CHMP’s perception that there were no cALD patients in the ADVANCE trial, that perception is factually incorrect as noted above. Furthermore, the data presented from the NEXUS study in paediatric cALD does not appear to have been taken into account by the CHMP. The NEXUS study in paediatric cALD has been entirely disregarded by the CHMP. This ongoing study that included patients with non-enhancing and with enhancing lesions has already met its primary endpoint of disease arrest and is considered a positive study. Taken together, the three data sets of cALD patients allow for conclusions on efficacy, as explained in more detail in Section 5. The conclusion that the data cannot be used to overrule the negative results from the first study is incorrect. a) the cALD population within ADVANCE has shown delay in progression following treatment, and these results are not negative, but positive; and b) The primary endpoint in ADVANCE (6MWT) is not relevant for assessing cALD. The applicant concludes that Refusal Ground 3 cannot be based on the evidence submitted, and does not constitute a valid ground for refusal. In addition, there is a clear precedent from other marketing authorisations that have been granted in previous years based on very comparable patient populations to cALD, in the orphan disease space, with high unmet medical need. The data provided for leriglitzone are in line, if not exceeding, with what has been provided for these precedents, where overall a positive benefit/risk could be concluded based on a restricted ultra-rare patient population, on missed primary endpoints and historical controls were established (see Appendix C).

Assessment of the applicant's grounds for re-examination

The applicant agrees that the available data in cALD is limited. Although it is indeed acknowledged that the rare nature of the disease must be taken into account, still the scattered available data do not allow to conclude that efficacy (and therefore a positive benefit/risk balance) has been demonstrated in cALD. See also below ground 5.

Data from ADVANCE study:

The applicant states that 27% (31/114) of the AMN patients in ADVANCE had also cALD, i.e., non-enhancing brain lesions (Gd-) at MRI, at baseline. However the presence of this baseline cALD sub-

group of the study ALD population was not apparent from the demographics table (see Table 32 from assessment to ground #1 above) nor from the statistical analysis plan initially submitted with the initial application. The baseline cALD subgroup was not prespecified, no statistical analysis was foreseen and no statistical efficacy analyses on the cALD subgroup have been submitted.

From the baseline characteristics of cALD patients by treatment arms submitted as part of the re-examination (Table 36), placebo arm seems to have had higher variability in baseline Loes score and in NfL disease non-specific exploratory biomarker.

Table 36. Baseline Characteristics for Patients with "No Visible Lesions" and Patients "with cALD" in ADVANCE

		No visible lesions		cALD patients	
		Leriglitazone N=58	Placebo N=25	Leriglitazone N=19	Placebo N=14
Age (years)	n	58	25	19	14
	Mean (SD)	43.67 (11.55)	48.88 (9.59)	39.53 (9.42)	37.07 (9.85)
	Median (Q1, Q3)	43.00 (35.00, 52.00)	50.00 (44.00, 56.00)	40.00 (32.00, 47.00)	35.00 (30.00, 46.00)
	Min, Max	19.0, 66.0	23.0, 62.0	26.0, 60.0	24.0, 59.0
Loes score	n	57	24	19	14
	Mean (SD)	0.32 (0.54)	0.35 (0.56)	4.53 (2.63)	5.93 (5.82)
	Median (Q1, Q3)	0.00 (0.00, 0.50)	0.00 (0.00, 1.00)	4.00 (3.00, 5.00)	3.00 (2.00, 9.50)
	Min, Max	0.0, 2.0	0.0, 2.0	1.0, 10.5	1.0, 22.0
NfL [pg/mL]	n	51	24	18	13
	Mean (SD)	12.33 (4.80)	13.39 (5.45)	17.06 (7.26)	20.65 (17.79)
	Median	11.00	11.50	15.50	15.00
	Min, Max	4.4, 28.0	5.0, 26.0	8.1, 41.0	9.7, 48.0

Baseline data missing for patients with no visible lesions for Loes score and NfL and for patients with cALD for NfL. Abbreviations: cALD – cerebral adrenoleukodystrophy; N – number of patients; NfL – neurofilament light chain; Q – quartile; SD – standard deviation.

The ALD study pre-specified secondary endpoints "Incidence of progression of cerebral lesions" and "Loes severity score on the MRI" and the ALD pre-specified, non-disease specific exploratory biomarkers NfL and non-disease specific secondary endpoints (CGI-S CGI-I PGI-I, EDSS) (as supporting data) were used for a post hoc cALD efficacy analysis. In addition a new analysis of "Incidence of progression of cerebral lesions" and "Loes severity score on the MRI" was done on existing data at data cut off, in the subgroup of participants with cALD at baseline and the subgroup with no visible MRI lesions at baseline. However, these post hoc sub-populations and sub-analyses were not predefined, a description of these sub-populations was not found in the initial demographics tables nor was a description of the sub-analyses included in the SAP (ICH E9 Statistical principles for clinical trials; CPMP/ICH/363/96).

Since the primary study endpoint of the ADVANCE study was not met, these secondary endpoints should be interpreted with caution. Nominally significant p-values of these two secondary endpoints are informative only and are not considered sufficient to support an indication in cALD, in the absence of the primary endpoint met, in the ALD population. No statistical analysis results of these secondary endpoints were provided for the post hoc defined subgroup of cALD patients, but these would not have been considered sufficient either, also considering the post hoc nature of these analyses.

Therefore, because of the primary endpoint failure, the data provided by ADVANCE study based on secondary endpoints only, do not support a positive B/R.

Data presented from the safety database (recording of SAE pointing to progression to or progression of cALD) cannot be taken into account as clinical efficacy endpoint.

Overall the data provided from the ADVANCE study do not allow to conclude positively on efficacy in support of the most recently proposed cALD indication (refer also to ground 1 assessment).

Data from NEXUS study:

The **NEXUS study**, an ongoing, open-label, Phase 3 multicentre study in male paediatric subjects, aged ≥ 2 and ≤ 12 years (Gd+ or Gd-), with a diagnosis of the cALD phenotype of X-linked ALD (n=23), has as primary endpoint to evaluate whether leriglitazone can halt progression of cALD at week 96 as determined by serial clinical and MRI investigations in paediatric subjects. Only 20 patients are considered evaluable since 3 patients did not reach the minimum of 24 weeks follow-up.

Based on published natural history data, in the age range of patients enrolled in NEXUS, the company defined that 10% or less of natural history patients show self-arrest of the disease (referencing Eichler et al., 2017; Liberato et al., 2019; Loes et al., 2003; Melhem et al., 2000; Raymond et al., 2019). However, these references also included patients older than 12 years at their first MRI and some also adults (Loes et al. 2003, Melhem et al., 2000) and show self-arrest over 10% (e.g. results from the cited Liberato et al., 2019, showed that 21% of the asymptomatic CCALD cases underwent spontaneous arrest, they tended to be older patients, with a median age of 14.4 years), and percentage of disease progression differed by Gd- and Gd+ groups. It was previously shown that patients with Gd+ brain lesions progress faster than ones with Gd- lesions at MRI, while lesion progression in adults is also on average slower compared with children (Zhu et al., 2020, Eichler et al. 2007). Therefore, the proportion of patients with self-arrested disease in a natural history data, may depend on the age and presence of Gd+ lesions at baseline of included patients, as well as the time to follow up MRI.

In the ground for re-examination, the company explained the NEXUS paediatric patients are being compared with natural history using patient-level data from the Mallack natural history (Mallack et al., 2021) dataset (Table 37), however, as applicant explained, the geographic regions are similar but not the same, the follow-up frequency will be different between the trial and the natural history dataset and the time period of data collection was between 2019 and 2024 for NEXUS, compared to 2001 and 2019 for the natural history dataset, so the preliminary results should be interpreted in line with these limitations.

Table 37. Baseline Characteristics of mITT Population from NEXUS and Eligible Ppatients from the Natural History Dataset

	NEXUS (N=23)	Natural history (N=24)
Age (yrs)		
Mean (SD)	7.70 (2.93)	5.83 (1.86)
Weighted mean (SD)*	6.4 (4.34)	6.6 (3.22)
LOES score		
Mean (SD)	1.83 (0.89)	1.60 (1.41)
Weighted mean (SD)*	1.7 (1.31)	1.6 (1.78)
Lesion volume (cc)		
Mean (SD)	2.68 (4.36)	3.47 (7.05)
Weighted mean (SD)*	3.5 (6.94)	3.0 (8.79)
Gd+ lesions N (%)		
Yes	14 (60.9)	11 (45.8)
Weighted percentage*	49.83	58.09

*Weighted by 1/propensity score for NEXUS patients and 1/(1-propensity score) for the natural history group, where propensity scores are obtained from a logistic regression with group (NEXUS vs. natural history) as the outcome, adjusting for baseline lesion volume, baseline Gd+ status, baseline LOES score and age.

The interim data from this study presented by the applicant showed that:

At Week 24, 8 out of 18 (44.4%, 95% confidence interval [CI]: 24.4-100%) patients met the arrested disease definition. In those patients who did not meet the arrested disease definition, all remained clinically stable and only one showed significant cerebral lesion growth.

At Week 96 or visit pre-HSCT (primary endpoint), 3 patients (38%) out of 12 evaluable patients met the primary endpoint definition of arrested disease at the end of the study.

Loes score (secondary endpoint) graphical data show a plateau profile for interim data however final data are not available yet.

While the interim results of the ongoing NEXUS study seem to indicate that leriglitazone may have some effect on progression of the cerebral lesions it is considered that these results do not provide sufficient proof of efficacy for Nezglyal, because at present, with only interim data available. While it is acknowledged that PDCO and SAG input was retrieved for the NEXUS study, the current interim clinical data are considered insufficient to provide proof of efficacy for Nezglyal.

Regardless of some uncertainties on the NEXUS trial (such as the most appropriate spontaneous natural history arrest rate), data from the NEXUS trial have been described by the SAG-N as relevant from a clinical perspective and data from the ADVANCE trial, to be hypothesis generating rather than being of confirmatory nature. Taking into account the data provided and also the input from the SAG-N experts, the CHMP considers the clinical data from the completed ADVANCE and ongoing NEXUS trials sufficient to support further research in cALD, but that these efficacy and safety data are not sufficient to currently establish a positive B/R in cALD patients, which could support a MA.

No clinical trial data are available in the 13 to 18 years of age group. Even leaving aside the fact that data submitted does not provide sufficient proof of efficacy in adult patients (ADVANCE study) and paediatric patients (boys 2-12 years of age; NEXUS study), extrapolation from these age groups to the adolescent population (13 to 18 years of age) is considered difficult and not straightforward. The SAG-N experts expressed some concerns whether efficacy and safety data could be fully extrapolated. In particular with regard to safety, the impact on bone fractures, growth and puberty was determined to be uncertain, and also the potential carcinogenicity of the product in a young population. While the experts noted the applicant's commitment to monitor carcinogenicity risk through a PASS and this was considered appropriate, it needs to be considered that the B/R is negative.

Data from compassionate use programs:

The applicant presented as part of the re-examination procedure data from 68 patients treated with leriglitazone under several compassionate use programs (Table 38).

Table 38. cALD Patients Treated with Leriglitazone to Date (CMA)

	ADVANCE ¹ n (%)	NEXUS ² n (%)	Compassionate Use ³ N=68 n (%)	Total n (%)
Gd- lesions	31 (94)	9 (39)	13 (19)	53 (43)
Gd+ lesions	2 (6)	14 (61)	55 (81)	71 (57)
Total	33 (100)	23 (100)	68 (100)	124 (100)

¹ADVANCE enrolled 116 AMN patients, 31 (27%) of whom had non-enhancing brain lesions at baseline. Two patients with enhancing brain lesions at baseline were enrolled in error. These two patients were considered protocol deviations and excluded from the secondary endpoint analysis "cerebral lesion progression", although included in the Loes analysis.

²NEXUS enrolled 23 patients; however, 3 patients did not reach the minimum of 24 weeks follow-up and thus were not considered evaluable. The interim and final analyses are therefore based on 20 patients.

³Under compassionate use, a broad range of cALD patients are being treated, including those with non-enhancing brain lesions and progressive disease and those with mild to debilitating symptoms. Complete data is not available for all treated patients, as 32 have been lost to follow up. Overall, post-baseline data is available for 36 patients.

Gd-: non-enhancing lesions; Gd+ enhancing lesions

Although the data presented from compassionate use may add some clinical relevance, they can only provide support for further investigating the efficacy of the product, but cannot provide sufficient support for a B/R in the context of a MA. Of note, the proportion of patients that is lost to follow up, 32 out of 68, is alarmingly high and will need to be discussed in detail in any future MAA.

Although safety data may be collected in compassionate use programs, such programs cannot replace clinical trials for efficacy investigational purposes. Compassionate use programs are not a substitute for properly conducted trials and therefore data provided from CUPs can only constitute supportive information in assessing the benefit/risk balance of a medicinal product.

General discussion and conclusion

The precedents of previous marketing authorisations discussed by the applicant are acknowledged however it should be noted that every marketing authorisation application is assessed on its own merit, based on the totality of the data presented in the application, in support of the claimed indication. The granting of a CMA in some of these cases does not justify by itself the approval of a Conditional Marketing Authorisation for Nezglyal, it is the totality of data which is taken into account in every individual dossier and for Nezglyal as well.

Taken together, the totality of the data presented from completed ADVANCE and ongoing NEXUS studies, as well as the data from compassionate use, do not provide sufficient proof of efficacy for Nezglyal in the claimed indication, therefore these data are not sufficient to support a positive B/R balance for Nezglyal in the claimed cALD indication. Considering also the assessment of ground #1 above, it is considered that the current ground for refusal is not resolved.

Point not resolved; the ground for refusal is maintained: "The limited data on patients with cerebral ALD (cALD) do neither allow for conclusions on efficacy, nor overrule the negative results from the pivotal trial."

5.1.4. Ground #4

Refusal Ground 4:

No appropriate mitigation measures could be determined for the very commonly reported adverse events oedema / weight gain in the pivotal trial.

Applicant's Grounds for re-examination:

Refusal Ground 4 has not been set within the context of a rare and fatal disease.

- No clinical consequences have been observed following oedema and weight gain in up to 5 years treatment.
- The severity of oedema remains mild/moderate and plateaus in incidence after six months of treatment.
- Weight gain secondary to both initial fluid retention and expected increased adipogenesis (an effect seen with other PPAR agonists) also plateaus after six months of treatment. Average weight gain was 5.8 kg in an adult population.

Within the context of a rare and fatal disease with a life-expectancy of 3-4 years, this is acceptable. Therefore, although the AEs (oedema and weight gain) cannot be prevented, the benefit/risk balance for this progressive and fatal condition remains positive. Oedema and weight gain occur as AEs with chronic use of other PPAR gamma agonists in much larger populations with less fatal conditions (e.g., Type 2 diabetes mellitus) and are tolerated. It is considered that no specific risk mitigation is required other than routine PV. No such mitigation measures are included in any label of other approved PPAR gamma agonists provoking the same AEs in different non-fatal conditions. In view of the above, the applicant submits that in the therapeutic context (a rare and fatal disease), and the assessment of acceptability of oedema and weight gain in other, less serious diseases are fully appreciated, it must be concluded that Refusal Ground 4 is not a valid ground for refusal and should not be maintained.

Assessment of the applicant grounds for re-examination

The average weight gain (5.8 kg in the adult population) was considered worrisome and together with the lack of convincing efficacy data rendered the benefit/risk negative.

In the response to the Ground #4 the applicant did not provide any new appropriate measures that could mitigate the very commonly reported adverse events oedema and weight gain in ADVANCE study which did not stabilise or resolve following dose reductions.

It should be noted that oedema and weight gain often led to dose reductions/suspensions (over 44%) and study discontinuations (nearly 20%) in a significant proportion of leriglitzzone-treated patients (Table 39). Therefore, it was initially not agreed that these adverse events do not affect leriglitzzone B/R.

Table 39. ADVANCE Trial Patient disposition (Safety Set)

Category	Placebo n (%)	Leriglitzzone n (%)	Overall n (%)
Patients randomized	39	77	116
Completed treatment	34 (87.2)	62 (80.5)	96 (82.8)
Discontinued from treatment	5 (12.8)	15 (19.5)	20 (17.2)
Adverse event	2 (5.1)	8 (10.4) ^a	10 (8.6)
Withdrawal of consent	3 (7.7)	6 (7.8)	9 (7.8)
Other	0	1 (1.3)	1 (0.9)
Completed the study	34 (87.2)	62 (80.5)	96 (82.8)

The applicant's statement in the re-examination document, that "As adult and paediatric patients have

a similar natural course of clinically progressive cALD and PK/PD, extrapolated safety from adults can be supportive for the paediatric population.” cannot be agreed without clear evidence.

In their answer, the applicant puts the importance of longer-term safety data into perspective considering that cALD is a rare and fatal disease with a life-expectancy of 3-4 years, however, refer to the research data of Raymond et al, 2019, in which median overall survival, from the time of cALD diagnosis, was 92 months in 3-15 year old patients (who never underwent HSCT).

Furthermore, the proposed dosing regimen has no clear substantiation from a PK and efficacy perspective, and appears not optimal also from a safety perspective (see also assessment details within grounds #2, section 5.1.2 above).

The applicant has proposed to evaluate several safety points further in several post-authorisation safety studies (PASS) as post-marketing commitments. In any case, the reported safety issues can be considered acceptable in view of the severity of the clinical condition and the unmet medical need and therefore are no longer considered a ground for refusal.

Therefore, the ground for refusal that 'No appropriate mitigation measures could be determined for the very commonly reported adverse events oedema / weight gain in the pivotal trial.' is no longer maintained.

5.1.5. Ground #5

Refusal Ground 5:

Taking into account the negative benefit-risk balance of Nezglyal, that it is unlikely that the applicant will be able to provide comprehensive data post authorisation and that the benefit to public health of the medicinal product's immediate availability on the market would not outweigh the risks inherent to the fact that additional data are still required, a conditional marketing authorisation cannot be granted.

Applicant's grounds for re-examination:

The CHMP has decided its position on the basis of several misunderstandings, in particular the perceived absence of cALD patients from the pivotal ADVANCE study, and an incomplete assessment of the applicant's D180 responses. This has adversely affected the conclusions on the scientific findings and the benefit-risk assessment. If the data sets (and their totality) are assessed, the applicant submits that there is no other conclusion than that the benefit-risk balance is positive, given the benefit to cALD patients that will ultimately die from their disease. The important benefit of immediate availability for the cALD population – as recognised by the extensive compassionate use programme and the unequivocal statements of treating clinicians – clearly outweigh the risks inherent to the fact that additional data are still required: As Prof. Fanny Mochel declared in writing, the patients in her programme would have died if they had not been treated with leriglitazone. The applicant urges the CHMP to take these important benefits into account. There are no safety reasons to deny a CMA: the onset of progressive cALD is fatal, and the main side effect (oedema) is a well-known class effect of thiazolidinediones. Oedema has no clinical effects on the patients and is an accepted side effect in many therapeutic areas including diabetes. The applicant fails to understand how the CHMP can assert that the provision of additional data is “unlikely”: clinical trials to provide additional data are already ongoing (and were ongoing at the time the CHMP assessment was made) and are expected to demonstrate a delay of death. The cALD study in children (NEXUS) has already met its primary endpoint with $\geq 5/20$ of patients meeting the end point of “arrested disease”. This translates in longer survival and maybe even in improved overall survival. Final data will be available in 2025. Another cALD study (CALYX) will enrol 40 patients with progressive cALD, with final results expected in 2027. An overview of the expected number of cALD patients who will be treated with leriglitazone in support

of the full MA is provided in Table 40. The applicant urges the CHMP, in order to carry out the assessments that have not yet been made, to submit the relevant scientific questions to the SAG-N. Refusal Ground 5 is premature because of the assessments that must still be made by the CHMP (taking account of the SAG-N responses to relevant questions). At present, therefore, Refusal Ground 5 is not supported by a full assessment of the evidence, and does not constitute a valid ground for refusal.

Table 40. cALD Patients Treated with Leriglitzzone by 2027 (Full MA)

	ADVANCE ¹	NEXUS ²	CALYX ³	Compassionate Use ⁴	Total n (%)
	n (%)	n (%)		n (%)	
Gd- lesions	31 (94)	9 (39)	--	14 (19)	54 (33)
Gd+ lesions	2 (6)	14 (61)	40 (100)	59 (81)	112 (67)
Total	33 (100)	23 (100)	40 (100)	73 (100)	166 (100)

¹ADVANCE enrolled 114 AMN patients, 31 (27%) of whom had non-enhancing brain lesions at baseline. Two patients with enhancing brain lesions at baseline were enrolled in error and were excluded from the secondary endpoint analysis “cerebral lesion progression”, although included in the Loes analysis

²NEXUS enrolled 23 patients; however, 3 patients did not reach the minimum of 24 weeks follow-up and thus were not considered evaluable. The interim and final analyses are therefore based on 20 patients.

³CALYX is an ongoing randomised controlled study in adult patients with progressive cALD, with a primary endpoint assessing time to death or bedridden with ventilatory support. Eligible patients are similar to the NEXUS Population 2 cohort, with respect to disease progression and severity.

⁴The compassionate use programme is ongoing. To date, 68 patients have been treated under compassionate use. For the full MA, it is expected that a minimum of 73 patients will be treated with leriglitzzone under compassionate use.

Gd-: non-enhancing lesions; Gd+: enhancing lesions; MA: marketing authorisation.

Assessment of the applicant grounds for re-examination

The number of cALD patients remains limited. In the completed ADVANCE trial only 31 (27%) patients have cALD (Gd- at MRI). The primary endpoint is the most important measure of any clinical trial on which all statistical analyses are based, and the primary endpoint which was chosen in ADVANCE was for the investigation of AMN and has no relevance for cALD (and did not show a significant result; P=0.914). None of the evaluated secondary endpoints related to a functional status or quality of life (EDSS, CGI-I, PGI-I, CGI-S, EQ-5D-5L) showed statistically significant differences between the treatment and the placebo groups in ALD patients. No statistical analysis was provided for these parameters in the subgroups of patients with cALD and patients with no visible lesions on MRI. Additional sub-analyses for cALD patients were provided for 2 secondary and some exploratory endpoints in ADVANCE; see assessment details within grounds #1 and #3 (sections of 5.1.1 and 5.1.3 above).

In the ongoing NEXUS trial (an open label study with no control group) there were 23 patients, of which 20 were evaluable.

NEXUS is a 96-week, open-label, multicentre study of once-daily oral leriglitzzone and included boys 2–12 years old with cALD with or without gadolinium-enhancing lesions. The primary endpoint is the proportion of patients with clinically and radiologically arrested disease at week 96 (success criteria: one-sided 95% confidence interval [CI] > 10%). The applicant provided data from the pre-defined 24-week interim assessment. Secondary endpoints include change from baseline in neurological function score (NFS) and Loes score (LS).

At Week 24, 8 out of 18 (44.4%, 95% confidence interval [CI]: 24.4-100%) patients met the arrested disease definition; in those patients who did not meet the arrested disease definition, all remained

clinically stable and only one showed significant brain lesion growth.

At the Week 96 or visit pre-HSCT, 3 patients (38%) out of 12 evaluable patients met the primary endpoint definition of arrested disease at the end of the study.

Graphical data of the Loes score (secondary endpoint) by Week 24 show a plateau profile for interim data, however final data are not available yet.

The fact that only preliminary, interim data are available in a small patient sample makes it difficult to draw conclusions based on this study let alone that these results would be sufficient to support a positive B/R.

Patients in a compassionate use program cannot provide reliable efficacy data as discussed above (see assessment of ground #3). The CALYX study could be important but results are only expected in 2027.

Taken together, the totality of the data presented from completed ADVANCE and ongoing NEXUS studies, as well as the data from compassionate use, do not provide sufficient proof of efficacy for Nezglyal in the claimed indication, therefore these data are not sufficient to support a positive B/R balance for Nezglyal in the claimed cALD indication.

The applicant is aiming for a conditional marketing authorisation (CMA) for Nezglyal in cALD. However, it has not been clearly outlined how the different criteria for fulfilment of a CMA would be fulfilled.

Concerning the criterion that the benefit-risk balance should be positive – this has not been demonstrated, as discussed above.

Concerning the unmet medical need criterion, Nezglyal cannot be considered to fulfil an unmet medical need as its efficacy in cALD has not been demonstrated.

Concerning the criterion that the applicant is likely to be able to provide comprehensive data post-authorisation, this is considered not to be demonstrated. The applicant proposed as specific obligations should the CMA be accepted, to submit the final results from the ongoing studies: NEXUS and CALYX. In what concerns the NEXUS paediatric study, although the study is ongoing and interim results have already been provided, due to its open-label design and limited sample size, is expected to provide efficacy and safety data very difficult to interpret and unlikely to be sufficient to provide comprehensive clinical data and support a positive B/R. In addition, the CALYX study concerns a different patient population (adult patients with progressive cALD), which only partially could support the proposed cALD indication (children and Gd- patients are not included). The SAG-N experts welcomed the conduction of the CALYX study as it is expected to answer several key questions on the efficacy and safety of leriglitazone in adults with cALD. However, the experts noted that it was unclear whether the results could be extrapolable to children with cALD. Therefore, some uncertainties remain whether this study can provide comprehensive data and support a positive B/R balance in the claimed indication.

Concerning the criterion that the benefit of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required, this still remains highly uncertain in the light of the concerns listed above, especially the negative B/R balance.

Point not resolved, the ground for refusal is maintained: "Taking into account the negative benefit-risk balance of Nezglyal, that it is unlikely that the applicant will be able to provide comprehensive data post authorisation and that the benefit to public health of the medicinal product's immediate availability on the market would not outweigh the risks inherent to the fact that additional data are still required, a conditional marketing authorisation cannot be granted."

5.1.6. Ground formerly under #5 (not individually submitted in re-examination submission)

Refusal Ground formerly under 5:

A positive benefit-risk balance of leriglitazone was neither established in the population of male adults with ALD, nor in post-hoc defined subpopulations of adults with early myeloneuropathy, or in paediatrics from 2 years of age or adults with cALD.

Applicant's grounds for re-examination:

The applicant has not submitted a specific ground for re-examination in relation to this ground for refusal.

Assessment of the applicant grounds for re-examination

In view of the indication requested by the applicant as part of the re-examination procedure, the grounds for re-examination submitted by the applicant in relation to refusal grounds 1# and 3#, and their assessment there (see corresponding sections of 5.1.1 and 5.1.3 above), the CHMP considered it is not necessary to maintain the above-mentioned ground for refusal.

5.2. Scientific Advisory Group-Neurology consultation

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG)-Neurology inviting the experts to provide their views on the CHMP grounds for refusal, and on the following questions taking into account the applicant's response.

The following CHMP questions to SAG-N were answered during the SAG-N May 15th 2024.

First of all, the SAG-N experts had some general comments on the CHMP Grounds for refusal:

The SAG-N experts expressed split views on whether the pivotal study should be considered as a failed study. Few experts considered that it was difficult to conclude that the pivotal study is a failed study because it was designed for evaluating efficacy and safety in the broad ALD spectrum and the new requested indication is narrower including only patients with cALD. On the other hand, other experts argued that the study should be considered as failed one based on pre-specified endpoints including relevant outcomes for the new pursued indication of cALD. While overall SAG-N experts agree that the mechanism of action of leriglitazone for the treatment of ALD is unclear, the SAG-N noted that mechanism of action is also not well-described for other authorised medicinal products for which a clear benefit was, however, demonstrated in the studies. Further, the current standard of care of patients with progressive cALD is bone marrow transplantation for which the exact mechanism of action to counteract progression of inflammation cALD is not fully elucidated. Thus, this ground, although agreed, it is not considered necessarily as a crucial aspect preventing a recommendation for a CMA.

The position of the SAG-N experts with regard to the CHMP adopted questions is given below.

1. Is there a benefit of leriglitazone in the cALD population considering the fact that the pivotal trial did not reach its primary and key secondary endpoints? Can a subpopulation in which leriglitazone is efficacious be identified?

The SAG-N experts expressed split views on this question. A minority of the SAG-N experts considered that the current available data do allow to conclude that leriglitazone is efficacious as a treatment for cALD. One of these experts noted that the difference on survival was remarkable between the placebo

and the treatment arms. While this expert acknowledged that survival was not included as an endpoint in the pivotal trial, he commented that the effect should not be ignored. According to the expert's view, survival was not included in the pivotal trial as primary or key / relevant secondary endpoint because the trial was designed for adults with myelopathy for which a slow progressing course leading to impairment of motor and sensory functions is the expected disease course and is not expected to see an impact on survival in the short - term.

On the other hand, the majority of the experts were not fully convinced that the current data are sufficient to conclude on a positive benefit in cALD due to the prespecified design of the trial aiming to evaluate treatment effects in patients with myelopathy, the formal failure of the pivotal study (i.e. pivotal trial did not meet the specified primary endpoint) and the fact that results supporting a potential effect on patients with cALD were post-hoc derived and hence, not considered confirmatory but rather exploratory or hypothesis generating. However, a couple of these experts noted that even if not conclusive, available data do suggest that there could be a signal for some benefit in the treatment of cALD.

2. What is the most appropriate accepted definition of progressive cALD and based on the proposed definition what is the most appropriate endpoint to measure progression of cerebral lesions in cALD?

Even if the appearance of clinical manifestations would imply a diagnosis of progressive cALD, the SAG-N experts expressed that the most widely accepted definition of progressive cALD is based on imaging in order to ensure an early diagnosis of the cALD phenotype and thus, the timely treatment with bone marrow transplantation. The appearance of a gadolinium enhancing lesion, or a new non-enhancing lesion or the extension of a previous lesion is considered sufficient to establish the diagnosis of progressive cALD.

An appropriate endpoint would be the stabilisation of the Loes score or the confirmed (1-2 months) disappearance of the gadolinium enhancement in priorly Gadolinium enhancing lesions as those are associated with rapid progressive forms.

3. Considering the totality of data regarding the influence of leriglitazone on the transformation of cALD to progressive cALD (with the caveat that data come from a subset of the ADVANCE study and interim data from an open-label study), what is the clinical relevance of the observed influence of leriglitazone on MRI progression?

Based on the well-known correlation between MRI findings and the clinical manifestations of cALD, the SAG-N experts considered that a stabilisation of the MRI brain lesion load could predict a positive impact on the clinical course. Even acknowledging that MRI positive findings come from the open label phase of the study, the observed MRI stabilisation is -in the view of the experts- clearly deviating from the expected natural course of the cALD phenotype. Thus, the results on MRI findings are perceived as relevant from a clinical perspective.

The lack of a standard MRI protocol specified in the ADVANCE study protocol was noted but the SAG-N experts confirmed that all sites used the same protocol for MRI acquisition and interpretation (scoring), thus ensuring standardisation of the MRI results. Reference: Engelen et al 2022 Neurology 99:940-951 (PMID: 36175155).

4. Is the course of cALD uniform across different age groups? Currently, there is a lack of data on the efficacy and safety of leriglitazone in the population of children aged 12-18. Could the SAG comment on this issue and whether data can be extrapolated from paediatrics aged 2-12 years, or adults to adolescents (12-18 years)?

Based on data from relevant literature, the SAG-N experts acknowledge that the course of cALD is considered as relatively uniform across all age groups, with respect both to clinical signs and delay of decline and death. However, the SAG-N experts are unsure whether the efficacy and safety data could be fully extrapolated towards the above-mentioned groups. In particular, with regards to the safety data, there might be some uncertainties around an impact on bone fractures, growth and puberty. The potential of carcinogenicity was discussed and not excluded based on the short duration of the study, notably in the younger population who will be by definition more exposed than adults to the medicinal product. However, the experts noted the applicant's commitment to monitor this risk through a PASS and this was considered an appropriate measure.

5. Please comment on the clinical relevance and manageability of the observed safety issues (oedema, weight gain) in the proposed target population of cALD patients.

From a patient perspective, these adverse drug reactions are not disregarded but considered proportional considering the severity of the condition. However, it is noted that there are no appropriate proposed measures to manage these ADR in the clinical setting.

6. Could the CALYX study contribute to answering critical questions concerning safety and efficacy?

Rationale: The CALYX study is a double-blind placebo-controlled study of 36 months in adult patients with cALD. This study will enrol 40 adult patients with progressive cALD. Enrolment has been initiated and the final study report is expected 3Q 2027.

The design of CALYX seems more appropriate than NEXUS for part of the sought indication of cALD. The double-blind placebo-controlled design (including the choice of endpoints) of the CALYX study seems appropriate to provide additional evidence for part of the proposed indication of cALD (in adults). Given the unmet medical need in ALD, the data from the CALYX study collected for a period of 36 months could offer additional justification regarding the potential impact of leriglitzone treatment on the overall survival of adult patients with cALD.

The SAG-N experts welcomed the conduction of the CALYX study as it is expected to answer several key questions on the efficacy and safety of leriglitzone in adults with cALD. However, the experts noted – in line with comment in question number 4 - that it was unclear whether the results could be extrapolable to children with cALD. Nevertheless, SAG experts also noted that conducting a placebo-controlled trial in children would not be considered by many investigators feasible and ethical.

5.3. Oral explanation at the CHMP

The applicant was invited to present its position during an oral explanation (OE). On 28 May 2024, a presentation to address the grounds for refusal was made in front of the CHMP plenary meeting.

However, after this OE, the Committee concluded that the grounds for refusal, with the uncertainties and concerns regarding the efficacy of Nezglyal as expressed above, still remained.

5.4. Overall conclusion on the grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group-Neurology.

The efficacy of Nezglyal in the claimed indication has not been demonstrated and the requirements for conditional marketing authorisation are not met.

5.5. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

5.6. Pharmacovigilance

5.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.6.2. Periodic Safety Update Reports submission requirements

N/A

5.7. Product information

N/A

5.8. New active substance claim

Following review of the available data in the context of the applicant's claim of new active substance status, the CHMP was of the view that leriglitzazone is not to be qualified as a new active substance.

Applicant's position as part of the grounds for re-examination:

This section addresses the CHMP conclusion with regard to the proposed status of leriglitzazone as a new active substance (NAS):

Leriglitzazone is an active metabolite of pioglitazone. No comparison was provided showing that the PK of leriglitzazone is different following pioglitazone or leriglitzazone administration (in non-clinical species and humans) or that administration of pioglitazone would not lead to efficacy and leriglitzazone leads to efficacy. Furthermore, no comparison was provided showing differences in safety profile in non-clinical species and humans.

The obvious conclusion from the data provided in Appendix E and in the grounds for re-examination, is that there is a unique pharmacodynamic difference between the leriglitzazone and other TZDs, including pioglitazone. Leriglitzazone has BBB penetrating properties and the capability to elicit a CNS effect - Pioglitazone does not. In contrast, leriglitzazone, which reaches effective doses in the CNS, has been shown to be a safe and effective treatment in cALD for reducing lesion progression in the brain.

APPENDIX E: LERIGLITAZONE AS A NEW ACTIVE SUBSTANCE (NAS)

Introduction

This document addresses the CHMP conclusion in the D195 JAR with regard to the proposed status of Leriglitzazone as a new active substance (NAS):

Leriglitzazone is an active metabolite of pioglitazone. No comparison was provided showing that the PK of leriglitzazone is different following pioglitazone or leriglitzazone administration (in non-clinical species and humans) or that administration of pioglitazone would not lead to efficacy and leriglitzazone leads to efficacy. Furthermore, no comparison was provided showing differences in safety profile in non-clinical species and humans.

Leriglitzazone, is a novel thiazolidinedione (TZD) peroxisome proliferator-activated receptor γ (PPAR γ) agonist. PPAR γ is a member of the nuclear receptor superfamily that plays an important role in physiological processes in the central nervous system (CNS), including cellular metabolism and repair. Cellular damage caused by long-term neurodegenerative disorders is associated with alterations of these metabolic processes leading to mitochondrial dysfunction, oxidative stress, and neuroinflammation.

For some time nonclinical studies have indicated the potential for PPAR γ agonists to be effective treatments for CNS diseases, but studies have failed to show efficacy because of the significant challenge of safely achieving blood-brain barrier (BBB) penetration.

Leriglitzazone is unique among TZDs in having the ability to safely penetrate the BBB at concentrations that are sufficient to treat patients with cerebral adrenoleukodystrophy (cALD). This significant difference in pharmacodynamic action differentiates leriglitzazone from all other TZD compounds, including pioglitazone, and justifies its position as a new active substance (NAS).

The evidence in support of this differentiation between leriglitzazone and pioglitazone is summarised below.

Non-clinical pharmacokinetic data

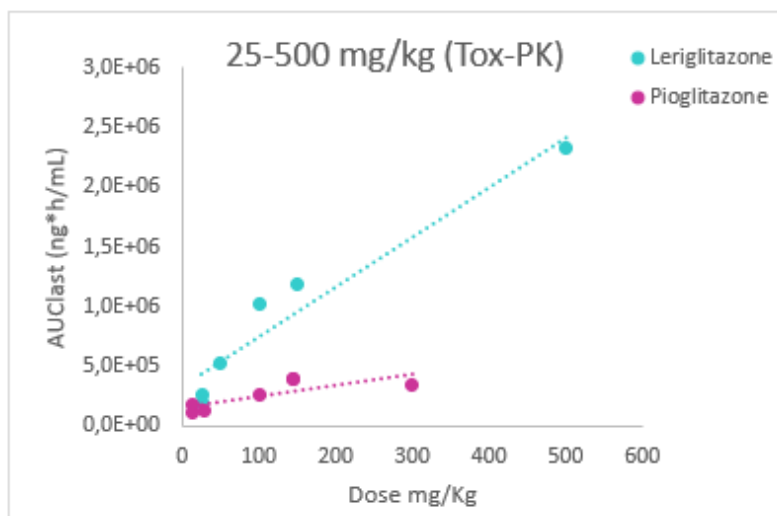
A comparative linear dose plasma exposure study has been reported in rats.

- for leriglitzazone, linear dose exposure has been shown up to 500 mg/kg.
- for pioglitazone linear dose exposure could not be established because dose exposure proportionality ceased when dosing 30 -100 mg/kg to reach a plateau at 100 mg/kg up to 300 mg/kg (highest tested dose, see Figure 17 below).

In the 13-week toxicology study in rats (CBN0016), toxicological effects were reached at a pioglitazone exposure of 234000 ng*h/ml (145 mg/kg) compared to 604000 ng*h/ml (50 mg/kg) for leriglitzazone. The adverse effects (AEs) seen were similar but were observed for pioglitazone at lower exposure levels than for leriglitzazone.

The no-observable AE level (NOAEL) was established as 14.5 mg/kg/day for pioglitazone (135000 ng*h/ml) compared with 25 mg/kg/day for leriglitzazone (320000 ng*h/ml).

Figure 17. AUC Exposure in ng.h/mL Achieved after Different Single Doses of Leriglitazone and Pioglitazone in a 13-Week Rat Study (CBN0016) and in a PK Rat Study (SAIDMPK/PK-14-12-641)



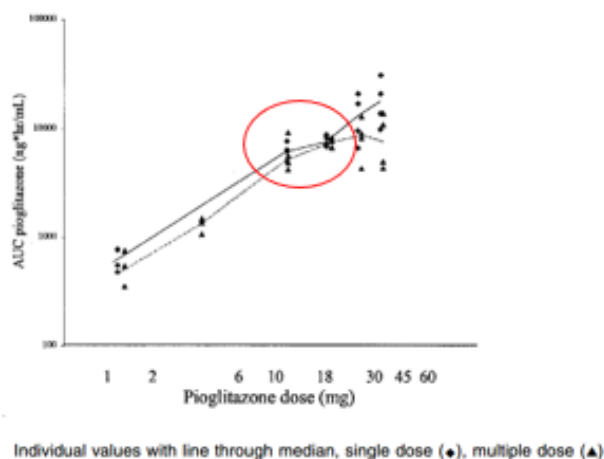
Human pharmacokinetic data

Human comparative pharmacokinetic (PK) data between leriglitazone and pioglitazone are considered here.

Comparative AUC exposure

Healthy volunteer PK data have shown that dose proportionality is lost for pioglitazone commencing at doses between doses of 30 to 60 mg (Figure 18).

Figure 18. AUC Exposure Achieved after Different Single and Multiple Doses of Pioglitazone in Healthy Volunteers (Eckland et al., 2000)



These data contrast with the dose proportionality data for leriglitazone, which has been confirmed up to 270 mg (Figure 19 and Table 41) and it allows going above at higher doses in order to achieve the target exposure for efficacy in CNS. Please note, that for pioglitazone the dose shown in the figure is the highest marketed dose and provides exposure well below the required target.

Leriglitazone clearly reaches the CNS in humans at concentrations that are sufficient to engage with the PPAR γ receptors. It has anti-inflammatory effects on the CNS because it crosses the BBB and reaches the required exposure in the CNS.

Figure 19. AUC Plasma Exposure in ng.h/ml, Achieved after Multiple Doses of Leriglitazone Administration with Either 135 mg or 270 mg (MT-1-01) and 180 mg (ADVANCE) and 45 mg of Pioglitazone (Budde et al., 2003)

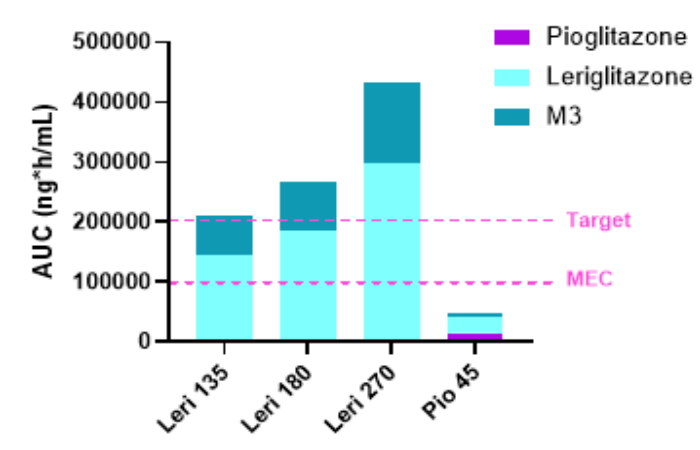


Table 41. Values for AUC Plasma Exposure Levels Shown In Figure 19

	AUClast (ng*h/mL)			
	Pioglitazone	Leriglitazone		
	45 mg	135 mg	180 mg	270 mg
	(Budde, 2003)	MT-1-01	ADVANCE	MT-1-01
Pioglitazone	14,565			
Leriglitazone	25,706	144,550	185,600	298,662
M3	7,289	65,251	81,664*	133,462
Total Active compounds	47,560	209,801	267,264	432,124

*Estimated from MT-1-01

The lack of effect of pioglitazone in CNS indications is thought to be due to insufficient CNS exposure at the highest approved (and tolerated) dose of 45 mg (Jojo et al., 2019).

Adiponectin studies

Adiponectin (an adipokine secreted by adipocytes) is used as a biomarker of engagement for PPAR γ agonists (Bouskila et al., 2005; Yang et al., 2004).

In nonclinical in-vivo studies, leriglitazone and pioglitazone both increased plasma adiponectin concentration between 150-200% at the minimal effective dose (Rodriguez-Pascau et al., 2021a).

In clinical studies, the long-term use of leriglitazone increased adiponectin by between +500-900% at the tested doses (ADVANCE and NEXUS studies), whereas the use of pioglitazone at the highest

approved dose of 45 mg/day led to an increase of only about 80% in plasma adiponectin after four months of treatment (Miyazaki et al., 2004).

CSF analyses

After administration of leriglitazone (135 and 270 mg) to healthy volunteers, cerebrospinal fluid (CSF) levels and metabolite M3 at the steady-state C_{max} (C_{maxss}) showed dose proportionality. The CNS exposure for leriglitazone is about 2% of the concentration in plasma, which is consistent with findings from rats at efficacious doses, which are also aligned with the concentrations required in cell-based studies (Table 42).

Table 42. C_{max} Plasma or Cerebrospinal Fluid (CSF) Levels at Steady-State (approx. 4 Hours after Administration) of Leriglitazone and Metabolite M3 after Repeated Doses of Leriglitazone (135 and 270 mg, MT-1-01 Clinical Study)

	C _{maxss} (ng/mL)			
	Leriglitazone 135 mg		Leriglitazone 270 mg	
	Plasma	CSF	Plasma	CSF
Leriglitazone	9,488	188	17,206	336
M3	4,296	13	8,400	21

It should be noted that for M3, only 0.3% of C_{max} in plasma is found in the CSF, consequently the M3 contribution to CNS efficacy is considered minimal.

Data on CSF levels of pioglitazone in humans are not publicly available. However, AUC plasma exposure obtained after pioglitazone administration are about five-fold lower than those of leriglitazone, even when considering all active forms derived from pioglitazone at the efficacy doses tested of 45 mg of pioglitazone (47560 h*ng/ml, Budde et al., 2003) and 180 mg of leriglitazone (267000 h*ng/ml).

According to the SmPC for Actos (Actos [pioglitazone] SmPC 2023) the unbound fraction of pioglitazone is listed as <1% compared to 3.6% for leriglitazone, indicating further that CSF levels of pioglitazone will be significantly lower than those of leriglitazone.

CNS clinical trials using pioglitazone versus leriglitazone

The current approved TZD compounds pioglitazone and rosiglitazone are not approved for any CNS indications because they are not able to sufficiently penetrate the BBB or unable to reach efficacious CNS concentrations.

The inability of pioglitazone to reach the brain at therapeutic concentrations has been confirmed in several clinical investigations of neurodegenerative disorders, where the BBB is not compromised, including:

- Amyotrophic lateral sclerosis (ALS),
- Parkinson’s disease (PD),
- Friedreich’s ataxia (FRDA) (Dupuis et al., 2012; NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015)
- Alzheimer’s Disease (AD) (Geldmacher et al., 2011), and
- ALD (ClinicalTrials.gov Identifier: NCT0386452 – Study completion reported in July 2019).

Where disruption to the BBB is known to occur – and the potential for exposure to the drug is increased – pioglitazone has shown moderate efficacy; for example in reducing brain lesions in relapsing-remitting multiple sclerosis (Negrotto et al., 2016).

The maximum dose of pioglitazone given during any CNS clinical trial has been 45 mg (QD) of pioglitazone suggesting that the investigators have been unable/unwilling to increase the dose level of pioglitazone due to safety concerns and further doses are not authorised.

Pioglitazone does not have a CNS effect at the highest approved dose tested (45 mg QD); the AUClast of all active compounds is 47.560 ng*h/ml. This is about 25% of the target exposure of leriglitazone (200.000 ng*h/ml). The AUC of pioglitazone in plasma is thought to be more than five-fold lower than that of leriglitazone at the therapeutically active dose. The highest tolerated concentration of pioglitazone in plasma ever established is at 70.400 ng*h/ml for one year in rats (US FDA regulatory NDA for the product Actos). This is well below the minimal effective dose.

It is reasonable to conclude from this that the pioglitazone dose would need to be increased many-fold to reach therapeutic effective levels in the CNS. Because pioglitazone does not exhibit dose proportionality, toxicity would prevent higher doses being tested since the therapeutic dose would have to be orders of magnitude higher than the 45 mg tested.

This is why higher doses of pioglitazone have not been tested and the drug has been shown to be ineffective in CNS related diseases.

Leriglitazone, in contrast, has been shown to reduce lesion progression and to delay/halt progressive cALD. The data from the clinical trials conducted are provided in the main body of this re-examination document.

Conclusion

The obvious conclusion from these data, and the information provided in the grounds for re-examination, is that there is a unique pharmacodynamic difference between the leriglitazone and other TZDs, including pioglitazone. Leriglitazone has the possibility to reach a dose level, that combined with its BBB penetrating properties allows eliciting a CNS effect. Pioglitazone does not.

To achieve the same effect as leriglitazone, the pioglitazone dose would need to be increased many-fold to reach therapeutically effective levels in the CNS. However, because pioglitazone does not exhibit dose proportionality it has been concluded that toxicity would prevent higher doses being tested. The required doses would need to be many orders of magnitude higher than the 45 mg tested. This is why higher doses of pioglitazone have not been tested and the drug has been shown to be ineffective in CNS related diseases.

In contrast, leriglitazone, which reaches effective doses in the CNS, has been shown to be a safe and effective treatment in cALD for reducing lesion progression in the brain.

Assessment of the applicant's position

Differences in PK properties are observed (e.g., distribution, dose-proportionality, different unbound fraction...) but **changes in PK alone are not sufficient to justify new active substance status** and clinically relevant changes should be demonstrated. From an efficacy perspective, CNS target exposure is claimed to be achieved which seems not to be the case with the other TZDs, especially pioglitazone.

For safety, comparative data are not available but the pioglitazone dose would need to be increased many-fold to reach therapeutically effective levels in the CNS and toxicity would prevent higher doses being tested.

It is worth noting that the default position is that a derivative of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy.

PD: The applicant states that Leriglitazone is unique among TZDs in having the ability to safely penetrate the BBB at concentrations that are sufficient to treat patients with cerebral adrenoleukodystrophy (cALD) and that this could justify its position as a new active substance (NAS). However, the PD properties should result in significant differences in safety and/or efficacy following optimal dose finding studies, and this was not demonstrated by the time of the opinion (see further below).

Efficacy:

The inability of pioglitazone to reach the brain at therapeutic concentrations has, according to the applicant, been confirmed in several clinical investigations of neurodegenerative disorders, where the BBB is not compromised, including:

- Amyotrophic lateral sclerosis (ALS),
- Parkinson's disease (PD),
- Friedreich's ataxia (FRDA) (Dupuis et al., 2012; NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators 2015)
- Alzheimer's Disease (AD) (Geldmacher et al., 2011), and
- ALD (ClinicalTrials.gov Identifier: NCT0386452 – Study completion reported in July 2019).

Where disruption to the BBB is known to occur – and the potential for exposure to the drug is increased – pioglitazone has shown moderate efficacy; for example in reducing brain lesions in relapsing-remitting multiple sclerosis (Negrotto et al., 2016).

Based on the preclinical data, the clinical doses of pioglitazone that would enable sufficient exposure in the CNS would need to be significantly higher (5-6 fold) than those used to treat Type II diabetes which would largely exceed the tolerated dose and would potentially present safety concerns for the patients.

Reference is made to the EMA guidelines "Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances." (EMA/CHMP/QWP/104223/2015) and the "Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance" (EMA/651649/2010).

"If the chemical active substance is structurally related as a salt, ester, ether, isomer, mixture of isomers, complex or derivative of an already approved active substance(s) in the European Union, it should be assessed whether it shares the same therapeutic moiety at the site of the biological activity as the already approved active substance and if so whether it differs significantly in properties with regard to safety and/or efficacy."

When a substance applied for exposes the patient to the same therapeutic moiety as the previously active substance(s) as part of a medicinal product(s) authorised in the European Union, the Applicant

should provide evidence that the related active substances differ significantly in properties with regard to safety and/or efficacy."

* Leriglitzazone is an active metabolite of pioglitazone. Administration of pioglitazone therefore results in leriglitzazone as a metabolite which can cross the BBB (in contrast to pioglitazone). It follows that leriglitzazone and pioglitazone share the same therapeutic moiety, i.e. leriglitzazone, at the site of the biological activity, i.e. the CSF (CNS). Therefore, according to above guidance, to be considered a NAS, it has to be demonstrated that leriglitzazone and pioglitazone differ significantly in properties with regard to safety and/or efficacy.

"Evidence likely to be sufficient to justify new active substance status includes:

** Changes to the overall efficacy at clinically relevant doses (e.g., clinically and statistically significant difference in the primary endpoint).*

Evidence unlikely to be sufficient:

** Changes to pharmacokinetics alone (that do not alter elements, as outlined in section 2.3.1)."*

Pioglitazone currently is authorised in adult patients at a maximum oral dosing of 45 mg QD. The proposed oral dosing for leriglitzazone is 136.6 mg QD (10 ml) to 163.9 mg QD (12 ml). According to the Nezgylal proposed PI, the leriglitzazone distribution is as follows: "Leriglitzazone is bound to human plasma protein binding in a percentage of 98% and the blood to plasma ratio is 0.598. The volume of distribution is 35.3 L. Leriglitzazone is bound to human plasma protein in a percentage of 98%. Leriglitzazone was detected in CSF from human volunteers 4 hours on Day 8, at 188 ng/mL and 332 ng/mL after the last dose of 135 and 270 mg leriglitzazone hydrochloride, respectively. It approximately corresponds to the 2% of total plasma concentration of leriglitzazone. M3 only passes the blood brain barrier to a very limited extent."

It follows that pioglitazone, administered orally at the clinically relevant dosing of 45 mg QD, cannot result in what is claimed to be the clinically relevant oral dosing of leriglitzazone in the CSF, since only a fraction of pioglitazone is biotransformed to leriglitzazone which subsequently can cross the BBB. Repeated daily oral dosing of pioglitazone does not result in accumulation of the compound or metabolites (Actos SmPC). Therefore, the assumed efficacy of the currently proposed clinically relevant daily oral doses of leriglitzazone (136.6 mg to 163.9 mg) cannot be obtained by pioglitazone and its currently approved daily dosing of 45 mg QD for diabetes indication, and therefore pioglitazone and leriglitzazone might differ in their overall efficacy in the proposed cALD indication at their respective currently considered clinically relevant dosing.

However, the above assumptions of significant clinical differences in properties with regard to safety and/or efficacy cannot be supported as efficacy of leriglitzazone in the proposed therapeutic cALD indication at the currently proposed daily leriglitzazone dosing has not been demonstrated, neither in the re-examination procedure.

Adding to the above, the NAS status should not be granted if a clinically relevant pioglitazone oral daily dose can be identified that results in similar clinical efficacy and safety in the concerned cALD indication as compared to direct administration of leriglitzazone. According to the applicant, based on the preclinical data, the clinical doses of pioglitazone that would enable sufficient exposure in the CNS would need to be significantly higher (5 to 6-fold) than those used to treat type II diabetes, which would largely exceed the tolerated daily dose and would potentially present safety concerns for the patients. The potential adverse events associated with the proposed higher pioglitazone dosing could indeed negatively affect the B/R in the searched cALD indication, on the other hand it is not clear at present whether leriglitzazone is clinically effective at its proposed daily dosing and neither whether such efficacy is achievable with lower leriglitzazone daily doses (as no proper dose finding studies were

performed and considering the high proportion of patients with dose reductions), which then in turn could be reached by higher pioglitazone doses. In the absence of (optimal) dose finding data for leriglitzazone, which are also required for a MA approval, this possibility cannot be formally excluded.

Conclusion:

In conclusion, too many uncertainties remain to confirm a NAS status of leriglitzazone.

Based on the review of data provided as part of the re-examination procedure, the CHMP maintains the view that leriglitzazone is a derivative to the known pioglitazone, previously authorised as a medicinal product in the European Union, and is not to be qualified as a new active substance, as insufficient evidence has been provided to demonstrate that it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance. Therefore, the NAS status is not supported.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

Disease or condition

Adrenoleukodystrophy (ALD) is a chromosome X-linked rare inherited neurodegenerative disorder that affects the brain, nerves and adrenal glands. ALD causes severe axonal damage in central and peripheral nervous system, resulting in a chronic progressive myelopathic and neuropathic adrenomyeloneuropathy (AMN) in adulthood. In addition to chronic neurodegeneration, acute inflammatory brain demyelination can appear, either in childhood or in adults, which is known as cerebral adrenoleukodystrophy (cALD), leading to rapid death or vegetative state.

Epidemiology and risk factors, screening tools/prevention

ALD has an estimated birth incidence of 1 in 20,000 worldwide (male and female) (Orphanet Report Series, 2020), and neither ethnicity nor country of birth is thought to have any impact on this (Raymond et al., 2018). The estimated prevalence is 0.35 per 10,000 people in the EU (EU/3/16/1770).

Childhood cALD occurs in 31-35% of ALD patients with onset typically between age 2 and 12 years of age. Recent literature reports that the majority of adult ALD men, i.e., up to 60%, will develop cALD over time, in addition to their myelopathy (50% in an observation period of 15.1 years in Suzuki et al., 2005; 63% with a mean of 10 years from myelopathy symptoms onset in de Beer et al., 2014).

Adults and boys undergo life-long MRI surveillance due to the risk of cALD conversion and live with the constant fear and anxiety of one day developing cALD (Patients listening session, 7 May 2021). There is currently no test or biomarker that can predict cALD onset in ALD patients.

Because ALD is a chromosome X-linked disease, women have been classically considered asymptomatic carriers. However, more recent studies have reported that most women became symptomatic with an onset of myelopathy during their fifth decade of life with a prominent sensory ataxia resulting in rates of decline in body sway that are comparable to males (Engelen et al., 2014; Horn et al., 2015; Keller et al., 2021). Women rarely develop cALD.

Aetiology and pathogenesis

ALD is caused by mutations of the ABCD1 gene that result in loss of function of the encoded ALD protein (ALDP), an ABCD transporter located in the peroxisomal membrane. Deficiency of the ALDP impairs peroxisomal β -oxidation of very long-chain fatty acids (VLCFAs) leading to its accumulation in plasma and tissues, particularly the brain, spinal cord, and adrenal glands (Contreras et al., 1994; Ofman et al., 2010; van Roermund et al., 2008). Additionally, mutations in the ABCD1 gene also cause changes in adhesion molecules and tight junctions in the brain endothelium, which in turn promote an increase in BBB permeability independently of VLCFA accumulation (Musolino et al., 2015).

Clinical presentation, diagnosis and prognosis

Adrenomyeloneuropathy (AMN)

Most ALD male patients reaching adulthood develop AMN, with onset usually in the late 20s, with slowly progressive spastic paraparesis and sensory ataxia (Engelen et al., 2012).

There are two neurophysiological systems typically affected in AMN patients: the corticospinal tract and the dorsal column. Degeneration of these systems impair proprioception, resulting in reduced ambulation and postural stability, respectively. Gait in ALD is affected by spasticity, weakness and impaired balance resulting in tripping and falling, limited walking distance or loss of ambulation (Zackowski et al., 2006; van Ballegoij et al., 2020; Godbole et al., 2021). The myelopathy also causes urinary and sometimes faecal incontinence (Engelen et al., 2012). The day-to-day functioning of these young patients is severely impacted by balance and ambulation dysfunction and general disability, resulting in assistive walking device and ultimately wheelchair use (Turk et al., 2020).

Cerebral adrenoleukodystrophy (cALD)

The greatest risk to ALD patients is the development of the fast progressing and finally fatal cALD, which is defined as appearance of progressive cerebral white matter lesions. These are initially indicative of oligodendrocyte degeneration and frequently progress with inflammation leading to disruption of the BBB. These lesions precede a rapid cognitive decline with loss of voluntary movements, inability to swallow, loss of communication, cortical blindness and total incontinence and death with a mean survival of only 3 years approximately (2.3 years in van Geel et al., 2001; 3.4 years in de Beer et al., 2014; 2.6 years in Koehler et al., (manuscript under preparation)), meaning that appearance of cALD is an end-of-life event. However, it was previously shown that patients with Gd+ brain lesions progress faster than ones with Gd- lesions at MRI, while lesion progression in adults is also on average slower compared with children (Zhu et al., 2020, Eichler et al. 2007).

In contrast to AMN, which occurs only in adults, cALD can appear during childhood and adulthood. No differences have been reported in the mechanisms related to the disease start or disease progression when comparing childhood and adult cerebral forms.

A diagnosis of ALD can be made by demonstration of increased levels of VLCFA in plasma. This is the most frequently used diagnostic technique. It is reliable for the diagnosis of affected males at any age, but false-negative results occur in approximately 15% of women heterozygous for X-ALD. Mutation analysis is the most reliable technique for heterozygote identification and is now available on a service basis (Moser et al., 2000). New-born screening for ALD is not implemented in most European countries (<https://www.technologynetworks.com/diagnostics/blog/a-landscape-assessment-of-newborn-screening-in-europe-359964>).

6.1.2. Available therapies and unmet medical need

There is currently no pharmacological treatment approved for patients with ALD. On 20 May 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Skysona (elivaldogene autotemcel), intended for the treatment of early cALD in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen-matched sibling haematopoietic stem cell donor is not available. However, shortly after approval, an application was submitted to withdraw Skysona from the European market by its Marketing Authorisation Holder, Bluebird bio. The withdrawal became effective on 18 Nov 2021.

Therapies designed to either reduce hyperlipidaemia (bezafibrate, lovastatin) (Engelen et al., 2012a; Engelen et al., 2010; Moraes et al., 2013) or lower dietary VLCFA intake (Moser et al., 1992) failed to slow myelopathy in ALD patients. Dietary supplementation with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) can normalise plasma VLCFA levels but clinical studies have shown that this does not prevent disease progression (van Geel et al., 1999). This apparent disconnect between reduced plasma VLCFA levels and functional outcome could result from the pathogenic cascade having already been triggered by the time of VLCFA increase.

If childhood cALD is detected in the early stages before major neurological disability appears, accumulated experience supports the use of Hematopoietic Stem Cell Transplantation (HSCT) to arrest the inflammatory demyelination. The procedure is, however, associated with serious and sometimes fatal complications, including those due to myeloablative conditioning, infection, graft-versus host disease (GVHD), and graft failure or rejection (Raymond et al., 2019). Since HSCT needs to be performed in early stages of the disease, and requires finding appropriate donors, this option is only available for a portion of paediatric cALD patients. Even if HSCT is successful, the transplanted patients can still develop myelopathy in adulthood indicating that HSCT only stabilises the inflammatory component of cALD.

In the current standard of care, adult patients with cALD are only offered the option for HSCT if myelopathy and their overall clinical condition are not too advanced, their lesions are not affecting certain brain regions and there aren't other relevant comorbidities. Importantly, there is no marker to predict when or where brain lesions may appear, hence all adult ALD patients are at risk of developing cerebral lesions that cannot be treated by HSCT. Even if HSCT is being performed, these patients bear a substantial risk of post-transplant complications and further neurocognitive decline and ultimately of death.

6.1.3. Main clinical studies

ADVANCE

The main evidence of efficacy in the initially proposed indication, submitted by the applicant, is completed Study MT-2-01 (Part 1), which was a phase 2/3, randomised, double-blind, placebo-controlled study in adult male AMN patients who received leriglitzazone or placebo. The study consisted of a 28 days screening period, after which the patients were randomised to placebo or leriglitzazone. A total of 116 patients were randomised to leriglitzazone (N=77) or placebo (N=39). Leriglitzazone dose was titrated in week 0-12 of the double-blind period based on a target plasma exposure of leriglitzazone of 200 µg·h/mL. Dose adjustments were allowed for safety/tolerability reasons.

The total duration of the double-blind period was 96 weeks. The 144-week open-label extension where 88 patients received leriglitzazone (OLE; Part 2) is currently completed. In general, the study design to investigate the indication proposed initially as part of the initial MA application, was in accordance to

the CHMP scientific advice, except for the comments on the total duration of the study. There were doubts that a study duration of 24 months would be sensitive enough to detect a treatment effect as the natural course of AMN is insufficiently known. The recommendation to implement safeguards into the design without compromising its methodological integrity was, however, not followed.

Male patients ≥ 18 to ≤ 65 years of age were eligible to enrol into the study if they had a genetic confirmation of ALD and clinical evidence of spinal cord involvement.

The primary endpoint related to the initially proposed indication was the change from baseline to Week 96 in total walking distance in the 6-minute walk test (6MWT).

The key secondary endpoints were Sway amplitude - total (mm) of body sway in the condition: eyes closed/feet apart, the Patient Global Impression Scale for Improvement (PGI-I), the total score on the Severity Score System for Progressive Myelopathy (SSPROM) and the Overall score of the Qualiveen Short Form Quality of Life Questionnaire for Urinary Disorders (Qualiveen-SF). Other important secondary endpoints were the EDSS step and the Loes severity score.

However, the primary and main secondary efficacy endpoints related to AMN are not relevant for the most recently proposed indication "Nezglyal is indicated for the treatment of male ALD patients aged 2 years and older with brain lesions to delay progression of cerebral adrenoleukodystrophy (cALD).".

For this most recently proposed cALD indication, the ALD study pre-specified secondary endpoints "Incidence of progression of cerebral lesions" and "Loes severity score on the MRI" and the ALD pre-specified, non-disease specific exploratory biomarkers NfL and non-disease specific secondary endpoints (CGI-S CGI-I PGI-I, EDSS) (as supporting data) are used for efficacy analysis.

In addition, a new analysis of "Incidence of progression of cerebral lesions" and "Loes severity score on the MRI" is done on existing data at data cut off (of the oral explanation), in the sub-group of participants with cALD at baseline and the subgroup with no visible MRI lesions at baseline.

Only 27% (n=31) of the adult patients in the ADVANCE trial had Gd- cALD at baseline. 2 patients that were Gd+ cALD were considered protocol deviations and therefore excluded from the secondary endpoint analysis "cerebral lesion progression", however they were still included in the "Loes" analysis as part of the FAS.

NEXUS

For the indication cALD, the ongoing NEXUS study is considered pivotal by the applicant.

NEXUS is a 96-week, open-label, multicentre study of once-daily oral leriglitzazone including 23 boys 2–12 years old with cALD with or without gadolinium-enhancing cerebral lesions at MRI. This study is analysed with reference to the natural history dataset. The primary endpoint is the proportion of cALD patients with clinically and radiologically arrested disease at week 96 (success criteria: one-sided 95% confidence interval [CI] > 10%). The applicant provided data from the pre-defined 24-week interim assessment and preliminary data from the week 96 endpoint, however the study is ongoing so the final data are awaited. Secondary endpoints include change from baseline in neurological function score (NFS) and Loes score (LS).

6.2. Favourable effects

Initial analyses:

In the completed ADVANCE study, there was no difference in change from baseline at week 96 in the primary endpoint (6MWT) between leriglitzazone and placebo. The least square mean change in 6MWT at week 96 was -31.8 m for placebo and -33.0 m for leriglitzazone. The least square mean difference

was -1.2 m (CI95% 22.6; 20.2, $p=0.91$). Results of the sensitivity analyses were in line with the results of the primary analysis.

Also for the key secondary endpoints (sway, PGI-I, SSPROM, Qualiveen-SF) no statistically significant differences between placebo and leriglitazone were observed after 96 weeks of treatment. For the body sway total score (eyes closed/feet apart) the difference in mean change was -1.05 mm (CI95%: -2.78; 0.68) between placebo and leriglitazone ($p=0.23$). In PGI-I there was no difference in patients' impression of improvement between placebo and leriglitazone ($p=0.22$). In SSPROM the difference in mean change was 2.32 (95%CI: -0.31;4.94) between placebo and leriglitazone ($p=0.083$). For the Qualiveen-SF score the difference in mean change was -0.12 (95%CI: -0.40; 0.16) between placebo and leriglitazone ($p=0.40$).

For the secondary endpoint EDSS step the difference in mean change was -0.34 (95%CI: -0.72, 0.05) between placebo and leriglitazone ($p=0.09$). For the Loes severity score the difference in median change was -0 (Hodges-Lehmann Estimate of treatment difference; 95%CI: 0.0, 0.0) between placebo and leriglitazone ($p=0.11$) which was also not statistically significant.

New analyses at re-examination

Completed ADVANCE study secondary endpoints related to brain lesion progression (Incidence of progression of cerebral lesions in cerebral MRI; Loes severity scores on MRI) favour leriglitazone over placebo (in overall ALD FAS ($N=83+33=116$) and in the ALD subgroups of patients with cALD ($N=33$) and patients with no visible MRI lesions ($N=83$). No statistical analyses were performed on these post hoc data within the cALD subpopulation at baseline (sought indication) and no visible lesions on MRI subpopulation at baseline.

None of the evaluated secondary endpoints related to a functional status or quality of life (EDSS, CGI-I, PGI-I, CGI-S, EQ-5D-5L) showed statistically significant differences between the treatment and the placebo groups in ALD patients. No such statistical analysis was provided for these parameters in the subgroups of patients with cALD at baseline (sought indication) and patients with no visible lesions on MRI at baseline. Moreover, CGI-S, CGI-I, PGI-I, EDSS, QoL are not disease-specific scales, nor is the exploratory biomarker NfL.

The ongoing NEXUS study in paediatric cALD boys 2-12 years treated with leriglitazone:

At Week 24, 8 out of 18 (44.4%, 95% confidence interval [CI]: 24.4-100%) patients met the arrested disease definition; in those patients who did not meet the arrested disease definition, all remained clinically stable and only one showed significant brain lesion growth.

At the Week 96 or visit pre-HSCT (primary endpoint), 3 patients (38%) out of 12 evaluable patients met the primary endpoint definition of arrested disease at the end of the study.

Loes score (secondary endpoint) by Week 24 graphical data show a plateau profile for interim data however final data are not available yet.

6.3. Uncertainties and limitations about favourable effects

Mode of action

Leriglitazone seems to have a general mode of action, not specific to (c)ALD. The applicant assumed that mitochondrial dysfunction and depolarisation, oxidative stress, inflammation and bioenergetic failure, hypothesised to contribute to the development and progression of ALD, is counteracted by PPAR γ . PPAR γ engagement of leriglitazone on molecular level is confirmed, however the relationship between PPAR γ receptor engagement and the pathophysiology/progression of ALD has not been

demonstrated. From the non-clinical data it appears that leriglitazone has a high affinity for monoamine oxidase (MAO)-B enzyme inhibition. Though the overall non-clinical data indicate that the mode of action of leriglitazone is most likely to be driven by PPAR γ agonism, a minor contribution of MAO-B to the leriglitazone-mediated effects cannot be ruled out based on the presented documentation. No relationship between leriglitazone's mechanism of action or the biomarker data and clinical progression of ALD was shown.

Dose finding

No formal dose finding study in patients with ALD was conducted to support the dosing regimen evaluated in the single pivotal study MT-2-01. A target exposure level was defined, based on the intention to provide maximal efficacy while remaining in the same range of the NOAEL dose level as determined in the non-clinical rodent studies. It cannot be excluded that a lower dose could have been efficacious. These findings cannot be confirmed in the currently conducted clinical trials. It therefore remains unclear whether the selected posology can be considered optimal.

The daily dose for ALD and cALD was based on target exposure level (100-130 $\mu\text{g}\cdot\text{h/mL}$). However, dose reductions/suspensions in order to better control for oedema and weight gain occurred frequently. At the end of the study 45.5% of patients received the recommended dose and 33.8% a reduced/suspended dose. Dose reductions/suspensions apparently did not result in a different effect size. 19.5% of the randomised patients to leriglitazone did not complete the double-blind phase.

Exposure

The current target population are male patients with cALD, children from 2 years of age and adults. The disease leads to changes in adhesion molecules and tight junctions in the brain endothelium, which in turn promote an increase in blood-brain-barrier permeability. The main metabolite of leriglitazone, M3, is pharmacologically active, but only passes the blood-brain barrier to a very limited extent (<1%). When the blood-barrier is intact, M3 does not contribute to the efficacy, but can contribute to the safety. Furthermore, when the disease progresses the blood-brain barrier may be affected and M3 may be able to pass the blood-brain barrier to a similar extent as leriglitazone. Therefore, characterisation of the variability in the pharmacokinetic behaviour of M3 and leriglitazone + M3 is of importance. The applicant investigated the PK of leriglitazone and M3 in adult patients with AMN, but not in patients with cALD. In paediatric patients, ontogeny of metabolic enzymes may affect the PK of leriglitazone and M3. Only very limited data is available in paediatric patients aged 3 years and older. No adequate PK data is available in younger children. Therefore, there is very limited data on the exposure in paediatric patients and no data on the exposure in patients with cALD supporting the last proposed indication. No adequate efficacy or PK data can be generated from patients in compassionate use programs.

Efficacy

The primary endpoint was not met. Almost no difference in effect was shown between the study arms. Thus, no efficacy of leriglitazone in the treatment of ALD was established.

No difference in change from baseline at week 96 between placebo and leriglitazone was observed in key secondary endpoints i.e., body sway total amplitude in eyes closed/feet apart condition, PGI-I, SSPROM total score and Qualiveen-SF overall score). Of the other secondary endpoints only for the Loes severity score a nominal $p=0.024$ was observed. For this score the analyses were conducted over the means though the medians are preferred because of the skewed distribution. Additional analysis based on median change, IQR and with corresponding Hoghes-Lehman estimates, showed that there is hardly a shift over time in Loes score in both groups. The difference over time just reflects that the baseline difference persist over week 48 and week 96.

In addition, the provided additional analyses with different cut-off scores of >0.5 or ≥ 1 for an 'abnormal' total Loes score at baseline indicate that patients on placebo were more advanced in terms of cerebral involvement. Furthermore, questions were raised about the results on cerebral progression in the context of the different severity of the groups, with placebo patients having longer disease duration and worse clinical score at baseline.

Sensitivity analyses conducted over the primary endpoint did not change the picture. Moreover, stratification by disease duration showed overall opposite results. Within the group of patients <10 years of myelopathy, less change from baseline was observed for leriglitazone compared to placebo. While for patients with >10 years of myelopathy, patients on leriglitazone showed more change from baseline than the patients on placebo. Moreover, a subgroup analysis of another definition but overlapping definition of early and late-stage disease (EDSS based) showed inconsistent results.

Study participants and Target population

The study population only partially reflects the target population proposed in the cALD indication, i.e., "Treatment of male ALD patients 2 years and older with brain lesions to delay progression of cerebral ALD (cALD)". The study population in the completed main study included ALD patients in the 18 - 65 years age range and, only 27% ($n=31$) (or 28% ($n=33$) taking into account the 2 Gd+ cALD patients) of subjects in the ADVANCE trial had cerebral ALD at baseline. Some patients were assessed as having cALD during DB or during the open-label extension.

The patients in the ongoing NEXUS trial do correspond to the proposed (paediatric subgroup) indication yet the currently available preliminary data from this trial are too limited to support a positive B/R.

New analyses at re-examination

ADVANCE

No relevant prespecified primary clinical endpoint pertinent to the cALD population was included in the SAP.

The data presented from the safety database (recording of SAE pointing to progression to or progression of cALD) cannot be taken into account as post hoc replacement of a properly defined primary clinical efficacy endpoint.

cALD subgroups are not represented in demographics tables of the original file and the additional analyses were not pre-specified in the SAP. This is an important point. Pre-specification of the analyses is essential to avoid bias (ICH E9 Statistical principles for clinical trials; CPMP/ICH/363/96). Post-hoc analyses should always be interpreted with caution and can only be supportive.

In addition, since the primary study endpoint was not met in the ADVANCE study, the secondary endpoints should be interpreted with caution. Nominally significant p-values of these secondary endpoints are informative only and are not considered sufficient to support an indication in cALD in the absence of the primary endpoint met, in the ALD population. No satisfactory statistical analysis results of these secondary endpoints were provided for the post hoc defined subgroup of cALD patients, but these would not have been considered sufficient either, also considering the post hoc nature of these analyses.

The cALD subgroup is only a small proportion ($N=33$) of the completed ADVANCE study population.

The study population of the ADVANCE only corresponds partially with the target population of the cALD indication (i.e. male ALD patients aged 2 years and older with brain lesions), as the study population in ADVANCE includes:

- patients with brain MRI with no visible lesions and patients with cALD (non-enhancing (Gd-) brain lesions).
- only adult patients ≥ 18 to ≤ 65 years, no paediatric cALD patients.

NEXUS:

A clinical efficacy functional score NFS is used to assess clinical efficacy, but this is part of the composite primary endpoint.

The study has an open-label design. Results are compared with a natural history data set (publications).

The study is still ongoing.

The fact that only preliminary, interim data in a small patient sample are available makes it difficult to draw conclusions based on this study let alone that these results would be sufficient to support a positive B/R.

It is not specified for which period of time Δ NFS should remain ≤ 1 point, to fulfil the criteria for clinical stability.

In the ongoing NEXUS study one patient showed significant lesion growth under leriglitazone.

The study population only partially corresponds with the target population of the indication: no paediatric cALD patients > 12 years of age and no adult cALD patients are included.

Uncertainty about ADVANCE trial:

According to Liberato et al, 2019 study (including both Gd+ and Gd- paediatric patients), 21% of the asymptomatic childhood CALD cases underwent spontaneous arrest. They tended to be older patients, with a median age of 14.4 years. Eighty-five to ninety percent of patients with Childhood CALD will progress to inflammatory demyelination. A total of 10%–15% of patients will have spontaneous arrest of disease (self-halted CCALD), without evidence of brain inflammation (according to Moser et al., 2000, Korenke et al. 1996, Melhem et al. 2000). Given the small number of patients with cALD (N=33) analysed in the post-hoc sub-group analysis in the ADVANCE study, it is not sure that the effects seen with respect to incidence of cerebral lesion progression (ADVANCE) are not partially obtained by chance (cases of spontaneous arrest instead of cases not progressing).

Consistency of the results across trials:

The analysis of the secondary endpoint in the ADVANCE study "incidence of cerebral lesion progression" in the cALD subgroup is not replicated by the ongoing open label NEXUS study in paediatric patients with cALD, since the primary endpoint in NEXUS is different, and the population investigated is also different:

	cALD ADVANCE	cALD NEXUS
Gd enhancement on MRI	Gd-	Gd+ and Gd-
Age	≥ 18 to ≤ 65 years	≥ 2 and ≤ 12 years

Data from compassionate use programs

Although safety data may be collected in compassionate use programs, such programs cannot replace clinical trials for efficacy investigational purposes. Compassionate use programs are not a substitute for properly conducted trials and therefore data provided from CUPs can only constitute supportive

information in assessing the benefit/risk balance of a medicinal product.

With respect to the data generated in several compassionate use programs with leriglitzazone, as stated above, although these data suggest some clinical relevance, they can only provide support for further investigating the product, but cannot provide sufficient support for a B/R in the context of a MA. Of note, the proportion of patients that is lost to follow up, 32 out of 68, is alarmingly high and will need to be discussed in detail in any future MAA.

6.4. Unfavourable effects

The safety of leriglitzazone has been evaluated in 110 adult male patients with ALD, who were exposed to leriglitzazone for at least two weeks to the target plasma exposure of 200 µg·h/mL, or a lower exposure down to 100 µg·h/mL (in case of dose reduction modifications). Most of the safety assessment relies on the 77 patients that were exposed to leriglitzazone in the placebo-controlled phase of the pivotal ADVANCE completed study. Supportive safety data comes from studies in boys with cALD (ongoing NEXUS study) and patient with Friedreich's Ataxia.

Almost all patients on leriglitzazone experienced an event related to the treatment (92.2%). Serious adverse events (SAEs) occurred in 18.2% of patients on leriglitzazone versus in 25.6% of patients on placebo. Mostly, these SAEs were single events observed in 1 or 2 patients, with the exception of adrenoleukodystrophy, reported in 6 (15.4%) patients in the placebo group only, referring to cALD progression. Per SOC, serious events were relatively balanced across the groups. One life-threatening event of anaphylactic shock occurred in the leriglitzazone group, but this was not considered treatment related. One death was reported during clinical studies with leriglitzazone.

The safety profile of leriglitzazone is dominated by oedema and weight gain; 'oedema peripheral' and 'weight increased' were reported most frequently and in the majority of patients treated with leriglitzazone (63.6% and 70.1%, respectively). Taking into account all reports ('Preferred Terms') of oedema, the incidence of oedema under leriglitzazone is 81.8%. A case of central oedema (ascites, during OLE) was also observed. Mean weight increase from baseline to Week 96 was 5.8 kg (Q1-Q3: 3.0-8.8) on leriglitzazone versus 1.3 kg (Q1-Q3: -1.5 – 4.0) on placebo. Oedema and weight gain were reported as non-serious and mild to moderate in nature. Nevertheless, a total of 41.6% of leriglitzazone-treated patients received dose reductions/suspensions and 20.8% of patients received diuretics due to the occurrence of oedema and/or weight gain. In addition, 6.5% of patients on leriglitzazone permanently withdrew from the study due to these adverse events. In OLE phase 39.4% patients from previous placebo who were switched to leriglitzazone dropped out due to adverse events, most often oedema-related events.

With regard to the other post-hoc defined AESIs, cardiovascular events (most often palpitations and tachycardia) occurred in 7.8% of patients on leriglitzazone versus 5.1% of patients on placebo. Among cardiovascular events were a case of increased jugular venous pressure and a case of atrial dilatation (MT-2-03, Friedreich's Ataxia). Hepatic events were reported in 5.2% of patients on leriglitzazone versus 2.6% on placebo and mostly concerned increased ALT/AST levels; one case of leriglitzazone-related hepatomegaly was reported. Abnormal urine cytology suspicious of urothelial carcinoma was observed, but no malignancies were confirmed. Haematological events most frequently comprised anaemia (15.6% on leriglitzazone vs. 2.6% on placebo), but also cytopenia were observed (1.3% - 3.9%) on leriglitzazone only. Bone fractures occurred in 9.1% of patients on leriglitzazone versus 5.1% of patients on placebo.

In general, adverse events more frequently led to dose adjustments in leriglitzazone-treated patients (44.2%) compared to placebo (5.1%). Similarly, adverse events that led to temporary and permanent

withdrawal from study medication were more frequent in the leriglitzazone group (10.4% and 11.7%, respectively) than in the placebo group (2.6% and 5.1%, resp.).

New analyses at re-examination

In the re-examination dossier, the applicant has presented the safety reporting of SAE of cerebral ALD in the ADVANCE study as 'diagnosis by treating physicians of progressive cALD'.

However this cannot be taken into account as an efficacy outcome. Moreover it was not pre-specified as an efficacy outcome in the initial trial design.

6.5. Uncertainties and limitations about unfavourable effects

Dosing

Almost half of all ALD patients treated with leriglitzazone (44%) received dose reductions/suspensions due to adverse events at some point during the pivotal study. Most dose reductions/suspensions occurred due to oedema and/or weight gain, but they did not impact the course of the events.

Oedema and weight gain

Following the May 2024 CHMP discussion, the manageability of oedema and weight gain is no longer a concern in the context of the cALD clinical condition. Oedema and weight gain occurred in the majority of leriglitzazone-treated patients (81.8% and 70.1%, respectively), which was much more compared to controls (17.9% and 23.1%, respectively). The events could neither be stabilised nor reversed by dose adjustments and/or diuretics. Mean weight continued to increase up to the end of the double-blind phase and half of all patients still had oedema at the end of the double-blind phase, irrespective of receiving treatment or not. The provided patchy data indicate that oedema and weight gain show a variable pattern, are generally of long duration, and cannot be mitigated. No risk factors could be identified for the development of these events. There are no adequate treatment options to manage oedema, apart from complete withdrawal of leriglitzazone, e.g., in case of intolerability or concerns of volume overload.

Carcinogenic potential

No bladder malignancies were reported in the study. However, PPAR γ compounds have been classified as 'probable human carcinogens', with carcinogenicity potentially existing beyond the site of the bladder. Carcinogenicity appears to be mediated by exaggerated pharmacologic effects observed as tissue hyperplasia. Hyperplastic changes were seen in the 6-month repeated dose toxicity study in rats under leriglitzazone (i.e., subcutaneous sarcoma, pituitary gland, mammary tissue, uterus). A carcinogenic potential of chronic high daily doses of leriglitzazone use cannot be excluded. Malignancies are anticipated to be observed only in long-term follow-up studies or post-marketing, as was the case with bladder cancer upon pioglitazone which exposes patients to several times lower doses of its metabolite leriglitzazone compared to Nezgylal as discussed by the applicant. The applicant proposed to evaluate this further in a post-authorisation safety study (PASS) as a post-marketing commitment. In the context of the negative opinion this is no longer of relevance.

Cardiac risk

Although the applicant confirmed that there were no signs of venous engorgement in the studied AMN population, i.e., in patients without cardiac risk factors, there is some evidence of leriglitzazone-related volume overload (including hepatomegaly). By the time of the CHMP opinion, it was not possible to determine whether volume overload would specifically precipitate cardiac events in patients with cardiac risk factors (e.g., refer to the Friedreich's ataxia patient with atrial dilatation).

Bone metabolism

Based on non-clinical and clinical data, a role of leriglitazone on bone density and associated adverse events (i.e., bone fractures) is considered likely. PPAR γ agonists were previously identified as having a role in bone metabolism, e.g., by inhibiting osteoblast formation and inducing osteocyte apoptosis, thereby reducing bone formation and contributing to the adverse effects on the bone. Effects of leriglitazone on bone metabolism are of particular concern for the paediatric population, as it may negatively affect bone growth.

Study discontinuation

Study discontinuation in the double-blind phase occurred more frequently in patients treated with leriglitazone than with placebo, often due to adverse events. However, reasons for study withdrawal were not always available. There are also no data on why 11.3% of patients on leriglitazone in the double-blind phase did not choose to enter the OLE phase to continue treatment. In addition, in the OLE phase, 39.4% patients from previous placebo who were switched to leriglitazone dropped out due to adverse events, most often oedema-related events. This percentage is much higher than drop-out due to AEs in the double-blind phase under leriglitazone. The increased drop-out rate due to AEs suggests that patients are not willing to adhere to leriglitazone treatment, also on the longer term.

Special populations

The safety of leriglitazone with respect to intrinsic factors (e.g., age) and extrinsic factors (e.g., hepatic impairment, renal impairment, patients at cardiac risk) has not been evaluated in the clinical studies. It remains uncertain how these in- and extrinsic factors impact the PK and safety of leriglitazone. The proposed product information dosing instructions, warnings, and/or recommendations could have been accepted as measures to mitigate risks.

Drug interaction studies

Clinical drug interaction data are lacking and the planned DDI studies do not sufficiently cover drug interactions expected to be of clinical relevance. This does not allow for adequate dosing instructions in case of co-administration with other medicinal products. This could pose a safety risk, especially in cases where co-administration leads to increased exposure to leriglitazone and thus to increased safety issues. The applicant had proposed to perform post-authorisation safety studies to evaluate this further.

Safety profile

Overall, in the context of the seriousness of the condition and the unmet medical need, the currently known safety profile of leriglitazone at the recommended doses could be considered acceptable and is not considered further as a ground for refusal by the CHMP.

New analyses at re-examination

In the compassionate use programmes, the proportion of patients that are lost to follow up, 32 out of 68, is alarmingly high and will need to be discussed in detail in any future MAA.

6.6. Effects Table

Table 43. Effects Table for Nezglyal (data cut-off: 12/12/2023)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Cerebral lesion progression	MRI based diagnosis (central readers) Cerebral lesion progression is defined as: -incidence of inflammatory lesions OR -growth of existing noninflammatory lesions since screening or baseline OR -Occurrence of new noninflammatory lesions after screening or baseline	% (Number of patients /total number of patients in study arm).	Leriglitzzone 3.9 (3/77)	Placebo 20.5 (8/39) p=0.007 p<0.01	Secondary endpoint Composite endpoint measuring more conditions than only progression to cALD with inflammatory lesions. The study population does not correspond with the target population of the indication - patients with normal brain MRI and patients with cALD (Gd- only). -only adult patients ≥18 to ≤65 years, no paediatric cALD patients included. 2 patients with Gd+ lesions were enrolled (1 in leriglitzzone, 1 in placebo); these patients were considered protocol deviations and were excluded from the secondary endpoint analysis "cerebral lesion progression", although included in the Loes analysis as part of the FAS. Here they are included since (n=116)	MT-2-01 ADVANCE Part 1
Cerebral lesion progression		% Number of patients /total number of patients in cALD or 'no visible lesions' subgroup of study arm.	16 (3/19)	36 (5/14)	Secondary endpoint New analysis on data existing at data cut off	
cALD subgroup					Analysis on subgroups - cALD patients at baseline. - patients with no visible lesions on MRI at baseline	
No visible MRI lesions subgroup			0 (0/58)	12 (3/25)	Subgroups are not represented in demographics tables of the original file.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
					The additional analysis is not pre-specified in the SAP.	
Cerebral lesion progression			After 2y: 7.3 (4/55)	N.A.		MT-2-01 Part 2
Change from baseline in Loes score			LS means change was 0.114 (95% CI: -0.1871, 0.4147)	LS means change was 0.696 (95% CI: 0.2948, 1.0977) LS means difference between the treatment groups was -0.582 (95% CI: -1.0877, -0.0772) P=0.024	Secondary endpoint The study population does not correspond with the target population of the indication - patients with normal brain MRI and patients with cALD. -only adult patients ≥ 18 to ≤ 65 years, no paediatric cALD patients included. 2 patients with Gd+ lesions were enrolled (1 in leriglitazone, 1 in placebo); these patients were considered protocol deviations and were excluded from the secondary endpoint analysis "cerebral lesion progression", although included in the Loes analysis as part of the FAS. Here they are included since (n=116)	MT-2-01 Part 1 Loes et al, 1994. Re-examination response
Change from baseline in Loes score cALD subgroup			(no raw data provided)	(no raw data provided)	----- Secondary endpoint New analysis on data existing at data cut off	
No visible MRI lesions subgroup			(no raw data provided)	(no raw data provided)	Analysis on subgroups - cALD patients at baseline. - patients with no visible lesions on MRI at baseline Subgroups are not represented in demographics tables of the original file. The additional analysis is not pre-specified in the SAP.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
NfL			(no raw data provided)	(no raw data provided)	Exploratory endpoint	MT-2-01 Part 1
MMP-9			(no raw data provided)	(no raw data provided)	Exploratory endpoint	MT-2-01 Part 1
DTI			(no raw data provided)	(no raw data provided)	Exploratory endpoint	MT-2-01 Part 1
CGI-S, CGI-I, PGI-I, EDSS, QoL					Secondary endpoints Non-specific for cALD	MT-2-01
Meeting of "arrested disease" criteria at 96 weeks after start of treatment	Arrested disease criteria defined as: - Δ NFS Baseline-w24: ≤ 1 point OR Baseline-w96: ≤ 5 points -Free of MFD -lack of lesion progression on MRI: - o No conversion to Gd+ lesions (Population 1) defined as GIS score of 0 - o Disappearance of persistent Gd+ lesions (Population 2) defined as change in GIS score from 1, 2 or 3 to 0. Persistent Gd+ lesions is defined as those present in ≥ 2 consecutive MRIs spanning a minimum of 6 months. - o No significant growth of T2/FLAIR lesions compared to the previous MRI (both populations) as assessed by central reading clinically stable defined as: (NFS) ≤ 1 and free of MFD	% Number of patients /total number of patients reaching 24 w /total number of patients reaching 96 w	Leriglitzazone 100% (18/18) 44.4% (8/18) 95%CI:24.4 -100%) 38(3/8)	N.A.	Primary endpoint Open-label study. The study population only partially corresponds with the target population of the indication. no paediatric cALD patients > 12 years of age and no adult patients are included. It is not specified for which period of time Δ NFS should remain ≤ 1 point, to fulfill the criteria for clinical stability.	MT-2-02 NEXUS
Sustained change from baseline in NFS	"Sustained change" is defined as the same total score for NFS items 1, 2, 4, 10, and 13 and no change >1 in NFS total score observed in two the consecutive Visits 6-8, and Visits 11-12, respectively. Lower NFS indicates better neurologic function.	Yes/no	Leriglitzazone (no results reported yet)	N.A.	Secondary endpoint Open-label study.	MT-2-02 NEXUS

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Change from baseline in Loes MRI severity score		Graphic al presentation of scores/time	Leriglitazone Plateau profile (preliminary data)	N.A.	Secondary endpoint Open-label study. Graphical comparison with Loes scores eli-cel and HSCT.	MT-2-02 Loes et al, 1994.
Change from baseline in T2/FL Lesion volume		Growth rate per month.	Leriglitazone growth rate/month natural history data is 2.5 times larger than in NEXUS. Plateau profile	N.A.	Exploratory endpoint Open-label study. Comparison with natural history dataset – linear mixed effect model.	D180 Responses, Mallack et al, 2021
NfL		Graphic al presentation	leriglitazone	N.A.	Exploratory endpoint Open-label study.	D180 Responses
MMP-9		Graphic al presentation	leriglitazone	N.A.	Exploratory endpoint Open-label study.	Idem
Unfavourable Effects						
Oedema	Incidence of any form of oedema	%	17.9	81.8%	How it can be resolved. Long-term consequences (e.g., volume overload). Consequences in patients at cardiac risk.	MT-2-01, Part 1
Weight increased	Incidence of weight increased	%	23.1	70.1	How it can be reversed or stopped	MT-2-01, Part 1
Weight increased	Mean (IQR)	kg	1.3 (-1.5 - 4.0)	5.8 (3.0 - 8.8)	How it can be reversed or stopped	MT-2-01, Part 1

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
SAE cerebral ALD/2y	Clinical appreciation.	% Number of patients /total number of patients in that group.	Leriglitzzone 0 (0/77)	Placebo 15.4 (6/39) P=0.001 P<0.005	Safety recording of SAE, not pre-specified as an efficacy outcome. According to the Cy this corresponds to clinical diagnosis of <u>progressive cALD</u>, but according to the listings 16.2.7.: <u>3/39 evolution to inflammatory form/ worsening of MRI white matter changes with contrast enhancement/ Inflammatory Gd-enhancing lesion on MRI</u> 2/39 progression to cALD/ conversion to cALD on MRI. 2/39 progression of lesions in the MRI/ cerebral lesion progression	MT2-01 Part 1
cALD subgroup /2y		----- % Number of patients /total number of patients in cALD or	----- 0 (0/19)	----- 21 (3/14)	Safety recording of SAE, not pre-specified as an efficacy outcome. New analysis on data existing at data cut off	
No visible MRI lesions Subgroup /2y		'no visible lesions' sub-group of study arm.	0 (0/58)	12 (3/25)	Analysis on subgroups - cALD patients at baseline. - patients with no visible lesions on MRI at baseline Subgroups are not represented in demographics tables of the original file. The additional analysis is not pre-specified in the SAP.	

Abbreviations: MFD: Major functional disabilities. NFS: Neurological Functional Score

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects and the associated uncertainties

In the study of Mallack et al, 2022, in cALD boys diagnosed with presymptomatic lesions, fifty percent of patients had lesional enhancement at diagnosis. In the remaining 50%, the median Kaplan-Meier (KM)-estimate of time from diagnosis-to-lesional enhancement was 6.0 months (95% CI 3.6–17.8).

When present, gadolinium enhancement (GdE+), a marker of active inflammation in the brain, is considered a critical predictive biomarker of rapidly progressive disease (Raymond, 2019, Melhem, 2000).

Affected boys eventually develop major functional disabilities (MFDs), including loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheelchair dependence, complete loss of voluntary movement, and ultimately death related to neurologic deterioration.

Clinical symptoms of cALD can be graded using the Neurologic Function Score (NFS), with a lower NFS indicating better neurologic function (Raymond, 2019).

In the study of Raymond et al, 2019 on survival and functional outcomes in boys with cerebral adrenoleukodystrophy with and without haematopoietic stem cell transplantation, in the untreated cohort, median OS was 92 months (95% CI, 41 to 219 months) from the time of cALD diagnosis. The applicant stated that a mean survival in cALD adult patients was shown to be only 3 years approximately (referencing 2.3 years in van Geel et al., 2001; 3.4 years in de Beer et al., 2014; 2.6 years in Koehler et al. (manuscript under preparation)).

According to the International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy (Engelen, 2022) BMT is recommended for cALD treatment, however there are strict eligibility criteria and outcome is poor in advanced disease.

The potential effects of leriglitazone on cerebral lesion progression in the cALD subpopulation of the completed ADVANCE study, could be clinically important, but there was no pre-specified relevant primary efficacy clinical outcome-measure for cALD in the ADVANCE ALD study. Since this is a failed study, secondary endpoints data cannot be considered sufficient to support a therapeutic cALD indication.

The study population of the completed ADVANCE study corresponds only partially with the target population of the proposed cALD indication (i.e. male ALD patients aged 2 years and older with brain lesions):

The study population in ADVANCE includes:

- patients with brain MRI with no visible lesions and patients with cALD (only non-enhancing (Gd-) brain lesions).
- only adult patients ≥ 18 to ≤ 65 years, no paediatric cALD patients.

Preliminary data obtained in the NEXUS study including boys 2-12 years of age could be clinically relevant. However this is an open label study and the study is still ongoing and final results are awaited. The NEXUS data at the primary endpoint at week 96 are preliminary and the data from the ongoing NEXUS trial have been described by the SAG-N as relevant from a clinical perspective (and data from the completed ADVANCE trial, to be hypothesis generating rather than being of confirmatory

nature). Taking into account the data provided and also the input from the SAG-N experts, the CHMP considers the presented clinical data from the NEXUS (and ADVANCE) trials sufficient to support further research in cALD, but currently not sufficient to establish a positive B/R in cALD patients, which could support a MA.

Furthermore, the fact that only interim results are available makes it difficult to draw conclusions based on this study let alone that these results would be sufficient to support a positive B/R.

Moreover, the ongoing NEXUS study population only partially corresponds with the target population of the claimed indication: no paediatric cALD patients >12 years of age and no adult cALD patients are included.

Importance of unfavourable effects and the associated uncertainties

Adverse events (mostly oedema and weight gain) led to dose reductions in almost half of the ALD patients treated with leriglitzazone. Withdrawal of treatment, often due to adverse events, is considered high and can be a reflection of the lack of tolerability of the product. This may not be surprising, considering the fact that the target dose was set at a tight safety margin of the NOAEL. Leriglitzazone treatment is associated with oedema and weight gain in the majority of ALD patients and cALD patients. There were no predefined criteria to treat these events in the pivotal study. The actions taken in response to oedema and weight gain (dose reductions/suspensions and/or diuretics) did not stabilise or reverse the events. Thus, oedema-related events appear not to be manageable. No risk factors were identified for the occurrence of these events. Following discussion at the CHMP plenary in May 2024, these events of oedema and weight gain were considered acceptable from a safety perspective, when considering the seriousness of the condition to be treated and the unmet medical need, and were not further considered a ground for refusal.

Although no malignancies were related to leriglitzazone treatment in ADVANCE study, concerns regarding the carcinogenic potential of leriglitzazone remain, especially since long-term daily use of high doses of the product would be anticipated. Hyperplastic changes, observed in non-clinical studies with leriglitzazone, and malignancies are anticipated to be observed only in long-term follow-up studies or post-marketing, as was the case with bladder cancer upon pioglitazone which expose patients to several times lower doses of its metabolite leriglitzazone compared to Nezglyal as discussed by the applicant (therefore the applicant proposed to evaluate carcinogenicity further as PASS).

There are uncertainties on the safe use and dosing of leriglitzazone in special patient populations (e.g., patients with hepatic impairment) and patients taking concomitant medications that inhibit CYP2C8 and CYP3A4), since safety and PK data are scarce or lacking. This may pose safety risks, especially in case of increased plasma exposure to leriglitzazone. The proposed SmPC dosing instructions, warnings, and/or recommendations could have been accepted as measures to mitigate risks pending results of additional studies to clarify these concerns (e.g. proposed two DDI studies and food effect study). In addition, specific long-term safety concerns may apply, e.g., effects on bone growth in children. Safety data in patients with cerebral ALD are limited and currently do not allow for comprehensive conclusions. However, altogether, the currently established safety profile of leriglitzazone at the recommended doses appears acceptable by the CHMP in the context of the seriousness of the condition and the unmet medical need, and is not considered further as a ground for refusal.

6.7.2. Balance of benefits and risks

The unmet medical need for a treatment of (c)ALD is acknowledged. Currently no approved medical treatments are available in the EU.

A single pivotal trial was completed in male adults with ALD. The results indicate that leriglitazone is not efficacious in the treatment of ALD. The limited data on subgroup of patients with cerebral ALD (cALD) from this completed trial do not allow for conclusions on efficacy in cALD. Also, the dosing regimen has no clear substantiation from a PK and efficacy perspective in cALD. No appropriate mitigation measures could be determined for the oedema/weight gain in cALD, however it was agreed, in the context of the seriousness of the condition and taking into account the opinion of the SAG-N experts, that safety is not considered further a ground for refusal. Finally, the requested cALD indication, which is "Treatment of male ALD patients aged 2 years and older with brain lesions to delay progression of cerebral adrenoleukodystrophy (cALD)", only partly corresponds to the ADVANCE studied population – adult male ALD patients – as the failed pivotal ADVANCE study is designed primarily to research the efficacy in the ALD, not cALD subgroup of patients. Additionally (adult) cALD patients with the presence of cerebral inflammatory (gadolinium [Gd]-enhancing) MRI lesions were excluded from this study while the proposed cALD indication include both Gd+ and Gd- subgroup of cALD patients, both children and adults. The interim data from presented NEXUS study in children with cerebral adrenoleukodystrophy (both Gd+ and Gd- MRI cerebral lesions) aged from 2 to 12 years have not allowed for the conclusion on efficacy as the study is still ongoing and final results are awaited.

The Nexus data at the primary endpoint at week 96 are preliminary and the data from the ongoing NEXUS trial have been described by the SAG-N as relevant from a clinical perspective (and data from the completed ADVANCE trial, to be hypothesis generating rather than being of confirmatory nature). Taking into account the data provided and also the input from the SAG-N experts, the CHMP considers the clinical data from the NEXUS (and ADVANCE) trials sufficient to support further research in cALD, but currently not sufficient to establish a positive B/R in cALD patients, which could support a MA.

No clinical trial data are available in the 13 to 18 years of age group. Even leaving aside the fact that data submitted does not provide sufficient proof of efficacy in adult patients (ADVANCE study) and paediatric patients (boys 2-12 years of age; NEXUS study), extrapolation from these age groups to the adolescent population (13 to 18 years of age) is considered difficult and not straightforward. While the PDCO seems to support the concept of extrapolation of efficacy data to 13-18 years of age based on PK/PD alone, the SAG-N experts expressed some concerns whether efficacy and safety data could be fully extrapolated. In particular with regard to safety, the impact on bone fractures, growth and puberty was determined to be uncertain, and also the potential carcinogenicity of the product in a young population.

With respect to the CUP data provided by the applicant, although safety data may be collected during CUPs, such programs cannot replace clinical trials for efficacy investigational purposes. CUPs are not a substitute for properly conducted trials and therefore data provided from CUPs can only constitute supportive information in assessing the benefit/risk balance of a medicinal product.

Overall, the totality of the data of paediatric patients and adults with cALD presented from ADVANCE and NEXUS studies, as well as the data from compassionate use, do not provide sufficient proof of efficacy for Nezglyal in the claimed indication and thus do not allow for conclusions to support a positive B/R in the applied cALD indication.

Concerns with respect to safety in cALD have been addressed by the applicant, and it was decided that the currently reported safety profile can be considered proportional considering the severity of the condition and the unmet medical need.

6.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the Nezglyal product were not available to support a full MA, a conditional marketing authorisation (CMA) for cALD was requested by the applicant at the later stages of the initial MAA procedure, and in this re-examination procedure for the indication "Treatment of male ALD patients aged 2 years and older with brain lesions to delay progression of cerebral adrenoleukodystrophy (cALD)".

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating life-threatening disease.

The CHMP considers that the product cannot be recommended for a conditional marketing authorisation since there is a lack of demonstration that the required CMA criteria are met:

1) The benefit-risk is considered negative (see benefit-risk discussion). A single pivotal trial was completed (ADVANCE) in male adults with ALD. The data indicate that leriglitazone is not efficacious in the treatment of ALD. The limited data on the subgroup of patients with cerebral ALD (cALD) and the post-hoc derived nature of the subgroup data from this completed trial do not allow for conclusions on efficacy in cALD. Also, the proposed dosing regimen has no clear substantiation from a PK and efficacy perspective, and appears also not optimal from a safety perspective. No appropriate mitigation measures could be determined for the oedema/weight gain. However it was agreed by the CHMP, taking into account the opinion of the SAG-N experts, the seriousness of the condition and the unmet medical need, that safety is not maintained as a ground for refusal. Moreover, the last requested indication, which is "Treatment of male ALD patients aged 2 years and older with brain lesions to delay progression of cerebral adrenoleukodystrophy (cALD)", only partly corresponds to the studied population of adult male ALD patients. The provided interim data of paediatric patients (from ongoing NEXUS with limited sample size, open label design without control arm) and subanalysis data in adults with cALD (from completed ADVANCE) do not allow for conclusions on efficacy in this proposed indication.

Thus, the efficacy of leriglitazone has not been shown in ALD, nor convincingly demonstrated in cALD and the benefit-risk balance of the product in the claimed cALD indication is negative.

2) The negative benefit-risk precludes fulfilling the condition of generating comprehensive data post-authorisation. Notwithstanding, it is considered that the applicant has not sufficiently demonstrated that he is able to provide comprehensive data post-authorisation. The ongoing NEXUS study had been initially proposed as a specific obligation (SOB) should the conditional marketing authorisation would have been accepted. This open-label study, for which interim results have been provided, includes boys aged 2-12 years with cALD, and only partly covers the sought indication in terms of age. In addition, due to its open-label design and limited sample size, it is expected that this study will provide efficacy and safety data very difficult to interpret and unlikely to be sufficient to provide clinical comprehensive data and confirm a positive benefit-risk balance in the context of a conditional marketing authorisation. In addition, the enrolling CALYX study was also proposed as an SOB. This is a double-blind placebo-controlled study of 36 months in adult patients with progressive cALD. Enrolment has been initiated and the final study report is only expected 3Q 2027. However, the CALYX study concerns a partially different patient population (adults with progressive cALD), which only partially could support the proposed indication. The design of CALYX seems more appropriate than NEXUS for part of the sought indication of cALD in terms of age and stage of the disease (only adult patients with progressive cALD are included). However, the same issues regarding extrapolation to paediatric patients would apply. Therefore, uncertainties remain whether this study can provide comprehensive data and confirm a positive B/R balance in the context of a conditional marketing authorisation.

3) The unmet medical need in ALD and cALD is acknowledged. Nezglyal cannot be considered to fulfil an unmet medical need as its efficacy in cALD has not been demonstrated.

4) Since efficacy is currently not established and thus a positive B/R balance has not been demonstrated (see B/R discussion), a benefit to public health of immediate availability does not outweigh the risks inherent in the fact that additional cALD data are still required.

Taking into account all the available evidence submitted by the applicant in writing and provided at the oral explanation before the CHMP, it was concluded in the re-examination procedure that the data do not establish the efficacy of Nezglyal in the claimed cALD indication. In light of the above, the CHMP was of the opinion that the benefit-risk balance for Nezglyal is not favourable.

Considering the above the CHMP concluded that the application does not meet the requirements for conditional marketing authorisation.

6.8. Conclusions

The overall benefit/risk balance of Nezglyal is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and, therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- Efficacy with regard to the primary and key secondary endpoints was not established in the single pivotal trial with ALD patients. The pivotal study is a failed study.
- No relationship between leriglitzazone's mechanism of action, or the biomarker data, and clinical progression of adrenoleukodystrophy (ALD) could be established. No exposure response relation has been established.
- The limited data on patients with cerebral ALD (cALD) do neither allow for conclusions on efficacy, nor overrule the negative results from the pivotal trial.
- Taking into account the negative benefit-risk balance of Nezglyal, that it is unlikely that the applicant will be able to provide comprehensive data post authorisation and that the benefit to public health of the medicinal product's immediate availability on the market would not outweigh the risks inherent to the fact that additional data are still required, a conditional marketing authorisation cannot be granted.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP is of the view that leriglitzazone is not to be qualified as a new active substance. The detailed position of the CHMP on the related grounds for re-examination submitted by the applicant at the time of this re-examination report is reflected in Section 5.8.