A randomized open-label Phase 2a study to assess the pharmacokinetics and pharmacodynamic parameters of PXL770 after 12 weeks of treatment in male subjects with adrenomyeloneuropathy (AMN)

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The primary objective of the study is to assess the pharmacokinetics (PK) of PXL770 in AMN subjects at the dose of 500mg once daily (OD) and 250mg twice daily (BID) after 4 weeks of treatment.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON51808

Source
ToetsingOnline

Brief title
PXL770-011 / START770

Condition

- Neurological disorders congenital

Synonym
Adrenoleukodystrophy

Research involving

Human

Sponsors and support

Primary sponsor: Poxel S.A.
Source(s) of monetary or material Support: Poxel S.A.

Intervention

Keyword: adrenomyeloneuropathy, PXL770, X-linked Adrenoleukodystrophy

Outcome measures

Primary outcome

Primary plasma PK parameters of PXL770: Cmax and AUC0-24 at V3 for 500mg OD

treatment group and Cmax and AUC0-8 at V3 for 250mg BID treatment group.

Secondary outcome

- Pharmacokinetics

Secondary plasma PK parameters of PXL770:

o Ctrough at V3, V4 (Week 8) and V5-EoT,

o Cavg, CLss/F, AUC0-8 (for 500mg OD treatment group), tmax and AUClast at V3.

- Safety

Safety and tolerability will be assessed on the following parameters:

o Adverse events (AEs)

o Physical examination

o Weight, Body Mass Index (BMI)

o BP, heart rate (HR)

o 12-lead electrocardiogram (ECG)

o Biological parameters: biochemistry, hematology, coagulation

o Urinalysis

- Pharmacodynamics

Change from baseline in the following parameters:

o VLCFA in plasma in fasting conditions: C26:0, C26:0-Lyso-phosphatidylcholine

(Lyso-PC), C24:0 and C22:0

o NfL in plasma

o Lipids in serum: total cholesterol, high-density lipoprotein cholesterol

(HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides

o Glycemic parameters: fasting serum glucose and HbA1c

Study description

Background summary

X-linked adrenoleukodystrophy (ALD) is a rare and serious genetic neurometabolic disease that affects approximately 1 in 17,000 people. It is caused by mutations in the ABCD1 gene leading to a defect in the degradation of very long chain fatty acids (VLCFA). ALD is the most common disease among those classified as leukodystrophies. Symptoms of AMN may begin with progressive stiffness and loss of balance followed by spastic paraparesis, sensory dysfunction, loss of bladder and bowel function, and impotence. Importantly, disabilities associated with AMN frequently result in loss of the ability to ambulate such that walking aids or wheelchair use are frequently required by the sixth decade of life. Life expectancy of AMN patients is reduced when patients additionally develop cerebral demyelination and neuroinflammation, which occurs in about 20% of AMN patients within 10 years. Currently, there is no effective treatment for AMN; rather, medications and therapies are employed in a palliative manner. Therefore, there is an urgent need for new drug therapies.

Study objective

The primary objective of the study is to assess the pharmacokinetics (PK) of PXL770 in AMN subjects at the dose of 500mg once daily (OD) and 250mg twice

daily (BID) after 4 weeks of treatment.

Study design

This is a phase 2a, randomized, multi-center, open-label study with 2 parallel treatment groups in AMN subjects.

Intervention

Subjects will be randomized in a 1:1 ratio in one of the 2 treatment groups to receive either:
- PXL770 500mg OD
- PXL770 250mg BID
during 12 weeks

500mg OD treatment group
2 tablets per day in one administration. PXL770 tablets will be taken orally in the morning approximately 15 min before starting breakfast with a glass of water, except at V3 (Week 4) and V5-EoT (Week 12) where subjects will remain under fasting conditions from the previous evening up to 2h post-dose.

250mg BID treatment group
1 tablet to be taken orally in the morning and 1 tablet in the evening with a glass of water approximately 15 min before starting meal (breakfast and dinner), except at V3 and V5-EoT where subjects will remain under fasting conditions from the previous evening up to 2h post morning dose.

Study burden and risks

Side effects of the study drug PXL770
In all clinical studies, PXL770 was well tolerated with no serious concerns regarding safety.
The most frequently reported side effects have been observed with the majority being mild to moderate:
• Diarrhea
• Nausea
• Abdominal pain
• Headache
• Dizziness
• Increased levels of liver enzymes in the blood
One serious adverse event of increased levels of liver enzymes in the blood was reported for a subject with NAFLD. This event was considered as related to PXL770.

An allergic reaction is also possible.

Possible risks related to study procedures

Blood Sampling : faintness, inflammation of the vein, pain, bruising, or bleeding at the site puncture. There is also a slight possibility of infection.

Electrocardiogram : temporary discomfort during the removal of the sensors, skin irritation from the ECG patch adhesive.

Magnetic Resonance Imaging : this test requires to be confined in a small, partially enclosed space, on the back without moving. Some participants may feel emotional distress or fear of being in an enclosed space.

Sometimes contrast dye is given to a participant intravenously. This can lead to discomfort from the needle stick when the IV is inserted. The dye may cause a metallic taste in the mouth and cause to feel warm. It can also cause nausea and vomiting, but these are rare. The dye can also cause damage to the kidneys, which may lead to kidney failure. Participants can also have allergic reactions to the dye, but this is also rare.

Unknown risks
In addition to the risks listed above, there may be other rare, unforeseeable risks and side effects caused by the study drug, including allergic reactions, or interactions with other medications.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male subjects with either a confirmed diagnosis of AMN by genetic testing (mutation in the ATP binding cassette subfamily D (ABCD1 gene)) or a family history of X-linked adrenoleukodystrophy (ALD) together with an elevation in VLCFA obtained from overnight fasting plasma sample at Screening Visit (V1).
2. Age: >= 18 to <= 65 years at informed consent signature.
3. Normal brain magnetic resonance imaging (MRI) or brain MRI showing non-specific abnormalities that can be observed in AMN subjects without signs of cerebral form of ALD (C-ALD). MRI must be performed within 6 months prior to V2. If there is no available brain MRI within this period, a brain MRI must be performed before V2.
4. Appropriate steroid/adrenal hormone replacement if adrenal insufficiency is present.
5. Subjects with female partners of childbearing potential must agree to remain sexually abstinent or use condoms during the treatment phase until 2 weeks after the last IP intake. In addition, subjects must be willing to stop sperm donation during this time.
6. Capable of providing written informed consent. Subjects must have given written informed consent before any study-related activities are carried out.

Exclusion criteria

Target disease exclusions
1. Any progressive neurological disease other than AMN.
2. Arrested or progressing C-ALD as defined by cerebral lesions (except for non-specific abnormalities that can be observed in AMN subjects).
3. Prior receipt of an allogeneic hematopoietic stem cell transplant or gene therapy.
Medical history and concurrent disease exclusions
Cardiovascular diseases
4. Any uncontrolled cardiovascular disorder in addition to those listed in Exclusion Criteria #5, 6 and 7 that prevents subject*s participation in the

study per Investigator*s judgement.
5. Unstable arrhythmia or clinically significant arrhythmia diagnosed during the Screening Period, long QT syndrome, short QT syndrome, history of drug-induced Torsade de Pointes.
6. Uncontrolled high blood pressure (BP): diastolic BP >= 100 mmHg or systolic BP >= 160 mmHg with or without antihypertensive treatment at V1.
7. Any of the following disease within 6 months prior to V2:
- Myocardial infarction
- Unstable congestive heart failure
- Heart failure Class III or IV according to the New York Heart Association (NYHA)
- Coronary revascularization (coronary artery bypass graft (CABG) / percutaneous transluminal coronary angioplasty (PTCA))
- Unstable angina
- Transient ischemic attack, stroke or cerebrovascular disease.
Other diseases
8. Estimated glomerular filtration rate (eGFR)
<= 60 mL/min/1.73m² at V1 calculated by the chronic kidney disease - epidemiology collaboration (CKD-EPI) formula.
9. Active malignancy or malignancy with a complete remission date within 2 years prior to V2 (except for treated basal cell carcinoma or treated squamous cell carcinoma of the skin).
10. Uncontrolled hepatic disorder (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x the upper limit of normal (ULN) at V1).
11. Type 1 diabetes mellitus.
12. Type 2 diabetes mellitus (T2DM) if not on stable treatment (i.e., same doses and same drug(s)) for at least 6 months prior to V1 or uncontrolled T2DM (glycated hemoglobin (HbA1c) > 7.5% at V1).
13. Uncontrolled hypothyroidism (thyroid stimulating hormone (TSH) > 2 x ULN at V1).

Other exclusion conditions
14. Contra-indications for MRI procedure (e.g., the presence of paramagnetic materials in the body, such as aneurysm clips, pacemakers, intraocular metal or cochlear implants including allergies to anesthetics or contrast agents and claustrophobia).
15. Positive screen at V1 for hepatitis B surface antigen (HbsAg), antibody to the hepatitis C virus (Anti-HCV) with detected circulating ribonucleic acid (RNA), antibodies to human immunodeficiency (Anti-HIV) 1 and 2 virus.
16. Any excessive alcohol intake (>= 14 units of alcohol/week) within 1 year prior to V2, where a unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits.
17. Any recent drug abuse (< 6 months prior to V2) or medically uncontrolled current drug dependence per Investigator*s judgement (e.g.: opiate, tetrahydrocannabinol / cannabidiol, etc.).
18. Immunocompromised subjects such as subjects that underwent organ transplantation.

19. Any other known serious disease or other disease which in the Investigator*s opinion would exclude the subject from the study.
20. Mental handicap, limited capacity of recognition, inability to follow the study procedures as evaluated by the Investigator.
21. Known hypersensitivity to any of the constituents or excipients of the IP, or history of relevant drug and/or food allergies (e.g., anaphylactic, anaphylactoid reactions).
22. Use of Lorenzo*s oil, peroxisome proliferator-activated receptor γ (PPARγ) agonists (including thiazolidinediones), valproic acid, bezafibrate, or 4-phenyl-butyrate (4PBA) within 3 months prior to V1 and/or between V1 and V2.
23. Use of statins, vitamin A, E or lipoic acid or dietary regimens and any other medication (including vitamins, herbal and dietary supplements) taken for AMN unless the dosing regimen of any of these has been stable for at least 3 months prior to V1 and between V1 and V2.
24. Use of non-permitted medications related to the risk of drug-drug interaction (DDI) at V2: cytochrome P450 (CYP) 1A2 sensitive substrates (agomelatine, alosetron, duloxetine, melatonin, pirfenidone, ramelteon, selegiline, tacrine, tasimelteon, tizanidine, clozapine, olanzapine).
If the subject is eligible based on all other inclusion/exclusion criteria and if medically acceptable as per investigator's judgement, these medications should be stopped or switched prior to V2 otherwise subject should be withdrawn from the study.
25. Participation in another clinical study with intake of an active investigational product (e.g.: PPARγ and PPAR* agonists, Thyroid Hormone Receptor β (THRβ) agonists*) during the last 3 months prior to V1.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	14

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	PXL770
Generic name:	PXL770

Ethics review

Approved WMO Date:	17-02-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-006223-18-NL
CCMO	NL79930.018.22