

A Phase 1a Double-Blind, Randomized, Placebo-Controlled, Single and Multiple Ascending Dose Study of the Safety, Pharmacokinetics, and Pharmacodynamics of ABX-002 in Healthy Adult Subjects

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Part 1 Single Ascending Dose (SAD)- To evaluate the safety and tolerability of a single oral dose of prodrug, ABX-002, in healthy adult subjects
Part 2 Multiple Ascending Dose (MAD)-To evaluate the safety and tolerability of once daily oral doses of...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON50699

Source

ToetsingOnline

Brief title

SAD & MAD of ABX-002 in HV

Condition

- Neurological disorders congenital
- Demyelinating disorders

Synonym

adrenomyeloneuropathy, AMN disease

Research involving

Human

Sponsors and support

Primary sponsor: Autobahn Therapeutics, Inc.

Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: FIH, MAD, SAD, TR α -agonist

Outcome measures

Primary outcome

- Incidence of treatment-emergent AEs, serious adverse events, and suspected, unexpected serious adverse reaction

Secondary outcome

- PK (plasma, urine, CSF)
- PD
- electrocardiography effects based on **QTcF

Study description

Background summary

Adrenoleukodystrophy (ALD) is caused by an X-linked inactivating mutation in the ABCD1 gene, encoding for the ALD protein, which is responsible for degradation of very long chain fatty acids (VLCFAs). AMN is the most common phenotype and is characterized by tissue damage in the brain, spinal cord, and in the adrenal, testes, and peripheral nerves due to VLCFA accumulation. Currently, there are no FDA and EMA approved therapies to treat AMN.

ABX-002 is an orally administered prodrug that is hydrolyzed by the intracellular enzyme FAAH, thereby releasing the active metabolite LL-340001. LL-340001 is a TR α -selective thyromimetic structurally related to the thyroid hormone T3. Based on preclinical studies, LL-340001 might provide therapeutic benefit in AMN by enhancing the expression of ABCD2 (sharing redundancy with ABCD1) and in turn reduced VLCFA levels, thereby correcting the fundamental

biochemical abnormality in AMN. In addition, thyroid hormone enhances remyelination by stimulating the differentiation and maturation of oligodendrocyte precursor cells into myelin-producing oligodendrocytes (Fernandez 2004). The TR*-selective agonists have been shown to promote remyelination in nonclinical models, suggesting the potential for ABX-002 to ameliorate these damaging effects seen in progressive AMN disease (Hartley 2019).

Study objective

Part 1 Single Ascending Dose (SAD)

- To evaluate the safety and tolerability of a single oral dose of prodrug, ABX-002, in healthy adult subjects

Part 2 Multiple Ascending Dose (MAD)

-To evaluate the safety and tolerability of once daily oral doses of ABX-002 administered for 14 days and/or 28 days in healthy adult subjects

Study design

This is a Phase 1a, first-in-human, randomized, double-blind, placebo-controlled, SAD and MAD study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ABX-002 in healthy adult subjects. This study is comprised of 2 parts, Part 1 SAD and Part 2 MAD.

Intervention

SAD: single dose of ABX-002 (oral solution or oral capsule) or placebo (oral solution or capsule)

MAD: multiple doses of ABX-002 (oral solution or oral capsule) or placebo (oral solution or capsule) for either 14 consecutive days or 28 consecutive days

Study burden and risks

As this is a FIH study, the study design and population of healthy subjects are chosen to minimize confounding effects and maximize the opportunity to determine the safety, tolerability, and PK of ABX-002.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

2. Male or female * 18 to * 55 years of age at the time of the Screening Visit.
7. In good health based on medical history, physical examination (including neurological examination), vital sign measurements, and laboratory safety tests obtained at Screening.
8. No clinically significant abnormality on the single ECG performed at Screening and the triplicate ECG performed prior to the first administration of study drug. Single ECG performed at Screening may be repeated once.

Exclusion criteria

3. Estimated creatinine clearance of * 90 mL/min based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey 2009).
6. History or evidence of any of the following: myocardial infarction; cardiac valvulopathy; cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty); unstable angina; cerebrovascular accident, stroke, or transient ischemic attack; pacemaker; atrial fibrillation, flutter, or nonsustained or sustained VT; pulmonary arterial hypertension; sick sinus syndrome, second- or third-degree atrioventricular (AV) block; uncontrolled hypertension; congestive heart

- failure; personal or family history of sudden death or long QT syndrome; unexplained syncope or syncope within the last 3 years regardless of etiology; or history of hypokalemia.
8. Screening Holter monitor (24 hours) shows nonsustained VT, SVT lasting > 10 beats in a run or > 4 runs, atrial fibrillation, atrial flutter, or a pause > 4 seconds.
9. Mean pulse < 50 or > 100 bpm, mean systolic blood pressure >140 mm Hg, or mean diastolic blood pressure > 90 mm Hg at Screening measured in duplicate using a calibrated digital device. If the mean blood pressure exceeds the limits above, an additional set of blood pressure measurements will be obtained, and the subject may be included if pulse and BP parameters are within the permitted boundaries.
11. Troponin T out of the normal laboratory range at time of the Screening Visit.
18. Consumption of excessive amounts of caffeine, defined as > 4 servings of coffee, tea, cola, or other caffeinated beverages per day (1 serving is approximately 120 mg of caffeine). Refusal to abstain from caffeine-containing foods or caffeinated beverages (eg, coffee, tea, cola, energy drinks) 24 hours prior to Day -1 through discharge from the CRU after the final administration of study drug.
19. Refusal to abstain from grapefruit-containing foods or beverages or Seville orange-containing foods or beverages 14 days prior to Day -1 through the Follow-Up Visit
20. Refusal to abstain from consumption of cruciferous vegetables (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard greens) or charbroiled meats (meat grilled over any heat source with black marks) * 7 days prior to Day -1 through the Follow-Up Visit
25. Abnormal thyroid function tests (thyroid-stimulating hormone [TSH], triiodothyronine, free thyroxine [FT4]) out of the normal laboratory value ranges at the time of the Screening Visit.
26. Aspartate aminotransferase, alanine aminotransferase, or gamma-glutamyl transferase > 1.5 times the upper limit of normal at the time of the Screening Visit and at Day -1.
30. Personal history of epilepsy or familial history of epilepsy in a primary relative (eg, sibling, parent, child) as documented by medical records or by the history provided to the Investigator by the subject. Individuals with a personal history of febrile seizures or seizures related to medication, intoxication, or withdrawal.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Completed
Start date (anticipated):	27-10-2021
Enrollment:	96
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABX-002
Generic name:	NA

Ethics review

Approved WMO	
Date:	30-09-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	15-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	07-11-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20666

Source: Nationaal Trial Register

Title:

In other registers

Register	ID
EudraCT	EUCTR2021-004139-10-NL
CCMO	NL78983.056.21
OMON	NL-OMON20666

Study results

Date completed: 10-11-2021

Summary results

Trial ended prematurely