Interventional, randomized, double-blind, placebo-controlled, single-ascending dose study part investigating the safety, tolerability, and pharmacokinetic and -dynamic properties of Lu AF90103 and a double-blind, cross-over study part investigating the safety profile after infusion of Lu AF90103 at two rates to healthy men.

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* to evaluate the safety and tolerability of Lu AF90103 following single ascending intravenous (i.v.) doses* to investigate the pharmacokinetics (PK) of Lu AF90103 (prodrug) and Lu AF88361 (drug) in plasma and cerebrospinal fluid (CSF) following...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON50833

Source
ToetsingOnline

Brief title
CS0369

Condition

- Mood disorders and disturbances NEC

Synonym
Major Depressive Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Lundbeck
Source(s) of monetary or material Support: H. Lundbeck A/S

Intervention

Keyword: pharmacodynamic, pharmacokinetic, safety, tolerability

Outcome measures

Primary outcome

Main Endpoints

Safety

* adverse events

* absolute values and changes from baseline in clinical safety laboratory test values (incl. urine kidney biomarkers), vital signs, weight, and ECG parameter values

* potentially clinically significant clinical safety laboratory test values (incl. urine kidney biomarkers), vital signs, weight changes, and ECG parameter values

* changes from baseline in the Psychotomimetic States Inventory (PSI) and the Clinically Administered Dissociative States Scale (CADSS), used to assess psychotomimetic side effects.

Pharmacokinetics

* area under the concentration-time curve from zero to infinity in plasma and CSF (AUC0-inf) for Lu AF90103 and Lu AF88361, defined as AUC0-t + Clast × t* / ln2 (where Clast is the last quantifiable concentration and t* is the apparent elimination half-life)
* Concentration at time zero (C0) following infusion of Lu AF90103 in plasma,
* maximum observed concentration (Cmax) in plasma and CSF for Lu AF88361 and in CSF for Lu AF90103
* total clearance, defined as dose / AUC0-inf (plasma) (CL)
* apparent elimination half-life in plasma and CSF for Lu AF90103 and Lu AF88361 (t*)
* nominal time corresponding to the occurrence of Cmax for Lu AF90103 in CSF and Lu AF88361 in plasma and CSF (tmax)
* apparent volume of distribution, defined as CL × t* / ln2 (Vz)
* Plot of a cumulative excretion and amount remaining to be excreted for Lu AF90103 and Lu AF88361 will made based on urine data.
* Metabolic ratio (MR), defined as AUCmetabolite/AUC parent

Pharmacodynamics -EEG

* Changes to time matched baseline in AUC of medial prefrontal (FZ and CZ electrodes) high gamma (100-170 HZ) in the resting state

Secondary outcome

Not applicable

Study description

Background summary

The planned first-in-human study is an interventional, randomized, double-blind, placebo-controlled, single-ascending dose study investigating the safety, tolerability, and PK and PD properties of Lu AF90103 in healthy men. The aim is to develop an IV antidepressant that addresses depressive symptoms with fast and sustained efficacy that provides significant and clinically meaningful effect within 2 days of first administration, maintained effect after repeated treatment, and acceptable safety and tolerability compared to standard of care.

Study objective

* to evaluate the safety and tolerability of Lu AF90103 following single ascending intravenous (i.v.) doses
* to investigate the pharmacokinetics (PK) of Lu AF90103 (prodrug) and Lu AF88361 (drug) in plasma and cerebrospinal fluid (CSF) following administration of single ascending i.v. doses
* estimation of fraction of Lu AF90103 and Lu AF88361 eliminated in urine
* to investigate the pharmacodynamic (PD) effects of Lu AF90103 in healthy men by examining resting state quantitative electroencephalography (qEEG) parameters

Study design

This is an interventional study consisting of two parts. Part A is a randomized, double-blind, placebo-controlled, single-ascending dose study investigating the safety, tolerability, and pharmacokinetic and -dynamic properties of Lu AF90103 and Part B is a randomized, doubleblind, cross-over study to investigate the safety profile after administration of Lu AF90103 as an infusion over 15 min and 45 min to healthy men.

Intervention

The IMPs in this study are:
Lu AF90103 - 50 mg, powder for solution for infusion, intravenous
Placebo * powder for solution for infusion, intravenous

Study burden and risks

Since the study is being executed in healthy volunteers, there are no anticipated benefits of the IMP. Please see the IB for further information.

Contacts

Public
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Scientific
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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. The subject is able to read and understand the Informed Consent Form.
2. The subject has signed the study-specific Informed Consent Form.
3. The subject is a man
4. The subject is *18 and *45 years of age at the Screening Visit for Cohorts A1 to A6 (excluding cohort A2b) or *55 to *65 for subjects in the CSF sampling Cohorts A2b and A7.
5. The subject has a BMI *18.5 and *30 kg/m2, body weight *60kg, at the Screening Visit and at the Baseline Visit.

Exclusion criteria

1. The subject has taken disallowed medication <1 week prior to the first dose of IMP or <5 half-lives prior to the Screening Visit for any medication taken. Disallowed medication is any prescribed medication or over-the-counter medication as well as any herbal medicine known to interfere with the metabolic CYP pathways, such as St. John*s Wort, ginseng, milk thistle, and echinacea. Subjects who have taken any non-prescribed systemic or topical medication may participate in the study if, in the opinion of the investigator, the medication will not interfere with the study procedures, study results, or compromise safety.
2. The subject has orthostatic hypotension, defined as a decrease in systolic blood pressure *20 mmHg from supine to standing within 3 minutes, at the Screening Visit or at the Baseline Visit.
3. The subject has a QTc interval >430 ms (Fridericia*s correction) at the Screening Visit, as calculated by the ECG equipment and evaluated by the investigator. The ECG may be repeated if any of the values are out of range or abnormal.
4. The subject has or has had any clinically significant immunological, cardiovascular, respiratory, metabolic, renal, hepatic, gastrointestinal, endocrinological, haematological, dermatological, venereal, neurological, or psychiatric disease or other major disorder.
5. The subject has a family history of psychosis in a first degree relative

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2021

Enrollment:	92
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nap.
Generic name:	Nap.

Ethics review

Approved WMO Date:	14-04-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2022
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004271-39-NL
CCMO	NL77259.056.21