Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Efficacy, Safety, and Tolerability of IMU-838 in Patients with Progressive Multiple Sclerosis

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This study has been transitioned to CTIS with ID 2024-514617-35-00 check the CTIS register for the current data. Primary Objective1. To evaluate the efficacy of IMU-838 versus placebo as measured by quantitative magnetic resonance imaging (MRI)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON54447

Source
ToetsingOnline

Brief title
CALLIPER Study

Condition

- Demyelinating disorders

Synonym
Multiple Sclerosis, Progressive Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Immunic AG
Source(s) of monetary or material Support: Immunic AG

Intervention

Keyword: Double Blind, IMU-838, Phase 2, Progressive Multiple Sclerosis

Outcome measures

Primary outcome

Primary Objective

1. Annualized rate of percent brain volume change (PBVC) during MT period

The primary endpoint will be analyzed on the mITT analysis set. The annualized rate of PBVC between BL and EoMT (or the last available MRI) will be assessed within a random intercept, random slope mixed model, accounting for treatment effect, and stratified for the same factors for which randomization was stratified. The null hypothesis of equal mean slopes of the 2 treatment arms will be tested (at a two-sided 5% level). Sensitivity analyses will be performed to assess the effect of different ICE handling strategies.

Secondary outcome

Annualized rate of change in BPF during MT period

Time to 24-week confirmed disability worsening based on expanded disability status scale (EDSS) during the MT period

Please refer to section 14.3.4.2 of the clinical study protocol for the

timepoints of evaluation for the above mentioned secondary end points

Study description

Background summary

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of neurological disability in young adults. It is characterized by multifocal recurrent events of neurological symptoms and signs, with variable recovery. Most patients eventually develop a progressive clinical course. Currently, the treatment options for patients with progressive MS remain extremely limited. For progressive MS, only a few treatments are approved by the FDA and by the EMA.

Currently, ocrelizumab is approved as a treatment for Primary Progressive Multiple Sclerosis (PPMS). Furthermore, ocrelizumab and ofatumumab have both been approved as treatments in patients with Secondary Progressive Multiple Sclerosis (SPMS). However, both treatments are accompanied by serious side effects, such as higher risk of infection, Progressive Multifocal Leukoencephalopathy (PML), and reactivation of Hepatitis B virus (HBV).

The investigational drug is vidofludimus calcium, a second generation DHODH inhibitor. Whereas the first generation DHODH inhibitors can have serious side effects, vidofludimus calcium selectively inhibits its target and has no structural similarities to its predecessors. After promising phase 1 trials, and (preliminary) results of phase 2 studies for other indications, this study ascertains the safety, efficacy, and tolerability for a novel treatment for progressive MS.

Study objective

This study has been transitioned to CTIS with ID 2024-514617-35-00 check the CTIS register for the current data.

Primary Objective
1. To evaluate the efficacy of IMU-838 versus placebo as measured by quantitative magnetic resonance imaging (MRI) analysis for whole brain atrophy in progressive multiple sclerosis (PMS) patients with the Structural Image Evaluation using Normalization of Atrophy (SIENA) method during the Main Treatment (MT) period

Secondary Objectives:
- To evaluate the efficacy of IMU-838 versus placebo as measured by

quantitative MRI analysis for whole-brain atrophy in PMS patients with the Structural Image Evaluation using the Brain Parenchymal Fraction (BPF) method during the MT period.
- To evaluate the efficacy of IMU-838 compared to placebo in terms of disability worsening during the MT period.
- To evaluate the efficacy of IMU-838 compared to placebo in terms of disability and other clinical assessments during the MT period.
- To evaluate the efficacy of IMU-838 compared to placebo in terms of MRI parameters during the MT period.
- To evaluate the efficacy of IMU-838 compared to placebo in terms of neurofilament light chain (NfL) level.
- To evaluate the safety and tolerability of IMU-838 compared to placebo during the MT period and evaluate the long-term safety and tolerability of IMU-838 during the open-label extension (OLE) period.

Study design

This study will be a multicenter, randomized, double-blind, placebo-controlled study with a blinded MT Period and an OLE Period to evaluate the efficacy, safety, and tolerability of IMU-838 in adult patients with PMS. The study will consist of the following periods:

• Screening Period: Approximately 28 days
• MT Period: Up to 120 weeks (approximately 2 years)
• OLE Period: Up to approximately 8 years

At each center, a 2-physician concept will be established, i.e., at each center there will be at least 1 treating physician and ideally 1 evaluating physician (and at least a deputy for each of the 2 physicians). The treating physician will be responsible for all aspects of the study except for neurological examinations, which will be done by the evaluating physician. This 2*physician concept ensures that the EDSS will be assessed blinded to other study-related assessments (for details on the 2*physician concept, please refer to Section 10.4.3 of the protocol). Table 1 and Table 2 of the protocol outline the timing of the procedures and assessments to be performed throughout the study.

Intervention

Main Treatment (MT) period

Participants will randomly be divided into two treatment groups: Placebo and study drug.
Participants will take the study drug or placebo once daily via oral administration.
Day 1-7: 22.5 mg of IMU-838 or placebo once daily
Day 8 onward: 45mg IMU-838 or placebo once daily

Open Label Extension (OLE) period
All participants will receive the study drug
Participants will take the study drug once daily via oral administration
Day 1-7: 22.5 mg of IMU-838 once daily
Day 8 onward: 45 mg of IMU-838 once daily

Study burden and risks

Please refer to the study schedules in the protocol, tables 1&2 (p21-29)

This study will take up to approximately 2 years for the Main Treatment (MT) period, but duration is dependent on when the participant enrolls. The minimum time in the MT period is 72 weeks. The MT can be followed by an Open Label Extension (OLE) period, which is optional and takes up to approximately 8 years.

Subjects will visit the hospital at week 4 and every 12 weeks during the MT period. If subjects enroll in the OLE period, they will visit the hospital at week 4 and every 24 weeks, up until week 120, after which it increases to every 72 weeks.

During the MT, the following tests and procedures can take place at a visit, but not necessarily at every visit:
- Concomitant medications/procedures takes/underwent
- Physical Examination, vital signs
- Visual acuity tests
- MRI scan (with contrast agent)
- Questionnaires (MFIS-5, Employment related, TSQM 1.4, PH-9, EDSS)
- Urine sample and analysis
- Pregnancy test for women of childbearing potential
- AE/SAE assessment
- ECG
- PK Sampling
- Determination of confirmed MS relapse and MS-related neurological symptoms
- IMP administration after PK sampling
- IMP dispensing and drug accountability
- Biomarkers (GFAP and NfL)
- Safety laboratory (hematology, blood biochemistry, coagulation)
- EBV-DNA shedding in saliva or EBV antibodies
- Leg function test
- Arm function test

During the OLE, the following tests and procedures can take place at a visit:
- Visual acuity testing
- Physical examination
- Vital Signs
- ECG
- New MS-related neurological symptoms, confirmation of MS relapse

- MRI (with or without Gd enhancement)
- Questionnaires (EDSS, MFIS-5, TSQM 1.4, PHQ-9)
- Safety Laboratory (hematology, blood biochemistry, urinalysis)
- Pregnancy test (for women of childbearing potential)
- IMP dispensing and drug accountability
- concomitant medications and procedures
- AE/SAE assessment

Contacts

Public
Immunic AG

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DE
Scientific
Immunic AG

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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. Adult patients, age 18 to 65 years (inclusive).
2. No evidence of relapse in the last 24 months before randomization,
AND

Patients diagnosed with either
a) SPMS, in patients showing evidence of Gd+ MRI lesions (active SPMS) in the brain or spinal cord, or without Gd+ MRI lesions (non-active SPMS) in the last 12 months, OR
b) PPMS according to 2017 revised McDonald Criteria and the 2013 revised classification of disease courses with a disease duration of the progressive disease of <=10 years
3. EDSS score at screening between 3.0 to 6.5 (both inclusive).
4. Evidence of disability worsening not temporarily related to a relapse in the last 24 months before randomization, adjudicated by a central independent reviewer, and documented as:
a) An increase of EDSS of at least 1.0 point with Screening EDSS of up to 5.5 (inclusive) and 0.5 point for Screening EDSS 6.0 or 6.5 (as documented in patient files in the last 24 months before randomization),
OR
b) A 20% worsening (or more) in 25-foot walk time or 9-hole peg test time in either hand (as documented in patient files in the last 24 months before randomization),
OR
c) A written summary of the clinical evidence of disability worsening in the previous 24 months before randomization through a retrospective assessment of disease worsening from patient files.

5. Female patients:
a) Must be of non-childbearing potential, i.e., surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before SV1) or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
b) If of childbearing potential, must have a negative pregnancy test at SV1 (blood test) and before the first IMP intake at Day 1 (urine test). They must agree not to attempt to become pregnant, must not donate ova, and must use a highly effective contraceptive method (see below) together with a barrier method between study consent and 30 days after the last intake of the IMP.
c) Highly effective forms of birth control are those with a failure rate of less than 1% per year and include:
i) Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation.
ii) Oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation.
iii) Intrauterine device or intrauterine hormone-releasing system.
iv) Bilateral tubal occlusion.
v) Vasectomized partner (i.e., the patient's male partner underwent effective surgical sterilization before the female patient entered the clinical study. And is the sole sexual partner of the female patient during the clinical study).
vi) Sexual abstinence (acceptable only if it is the patient's usual form of birth control/lifestyle choice; periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods

of contraception).
d) Barrier methods of contraception include:
i) Condom.
ii) Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository.
6. Male patients must agree not to father a child or to donate sperm starting at SV1, throughout the clinical study, and for 30 days after the last intake of the IMP. Male patients must also:
a) Abstain from sexual intercourse with a female partner (acceptable only if it is the patient's usual form of birth control/lifestyle choice), or
b) Use adequate barrier contraception during treatment with the IMP and until at least 30 days after the last intake of the IMP, and

Note: Simultaneous use of male and female condoms with or without any other contraception methods is not permitted.

c) If they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 4.
d) If they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP.
7. Willingness and ability to comply with the protocol.
8. Written informed consent given by the patient before the beginning of any study-related procedure.

For more information, please refer to the Clinical Study Protocol.

Inclusion Criteria for the Open Label Extension (OLE) Period
1. Completed 120 weeks of MT period or have confirmed 24-week disability worsening or the patient was in the MT period when the study reached the MT termination event, at which time, the patient could enter the OLE treatment period.

Exclusion criteria

MS-related exclusion criteria:
1. Any disease other than MS that may better explain the signs and symptoms, including a history of complete transverse myelitis.
2. Clinical signs or presence of laboratory findings suggestive for neuromyelitis optica spectrum disorders (NMOSD) or myelin oligodendrocyte glycoprotein (MOG)-associated encephalomyelitis (i.e., presence of aquaporin-4 antibodies or anti-MOG antibodies).
3. Any MRI finding, atypical for MS, including but not limited to a

longitudinally extensive spinal cord lesion.
4. Any active and uncontrolled coexisting autoimmune disease, other than MS (except for type 1 diabetes mellitus and inflammatory bowel disease).

Therapy-related exclusion criteria:
5. Any previous or current use of the following MS treatments:
a) alemtuzumab or belimumab, including their biosimilars,
b) cladribine,
c) total lymphoid irradiation, and
d) bone marrow or stem cell transplantation.
6. Any use of the following MS treatments before the date of randomization (see table in study protocol)
7. Any use of adrenocorticotrophic hormone (ACTH) or occasional use of systemic corticosteroids (oral or intravenous) 30 days before SV2.
8. Use of any investigational product within 8 weeks or 5× the respective PK half-life before the date of informed consent, whichever is longer, and throughout the study. For some investigational products, prolonged biological effects beyond 8 weeks should be considered.

For more information, please refer to Clinical Study Protocol.

Exclusion Criteria for the OLE Period:
Patients meeting any of the following criteria will be ineligible to participate in the OLE
Period of the study:
1. Any ongoing, clinically significant (as assessed by the Investigator) treatment-emergent AE or laboratory abnormality (including bloodbiochemistry and urinalysis) that can jeopardize the patient's safety, in agreement with the medical monitor.
2. Significant study or treatment non-compliance (<80% or >125%) during the MT period, and/or inability or unwillingness to follow instructions by study personnel.
3. The lack of interpretable BL or EoMT MRI or the omission of more than one other MRI during the MT.
4. Use of experimental/investigational drug (except for COVID-19 vaccines approved by emergency use authorization or similar expanded access schemes) and/or participation in another clinical study of an investigational drug throughout the duration of the OLE treatment period.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-07-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Vidofludimus Calcium
Generic name:	N/A

Ethics review

Approved WMO Date:	12-10-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2024

Application type:	Amendment
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
EU-CTR	CTIS2024-514617-35-00
EudraCT	EUCTR2021-000048-23-NL
ClinicalTrials.gov	NCT05054140
CCMO	NL78252.029.21