A Phase 2 Single-Center, Proof-of-Concept Safety and Efficacy Study of Orally Administered OLT1177 Capsules with Successive, Result-Dependent Dose Adaptation in Subjects with an Acute Gout Flare

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON47412

Source
ToetsingOnline

Brief title
OLT1177 Capsules for the Treatment of Acute Gout Flare

Condition

- Joint disorders

Synonym
Acute gout flare, Gout

Research involving

Human

Sponsors and support

Primary sponsor: Olatec Therapeutics LLC
Source(s) of monetary or material Support: Olatec Therapeutics LLC

Intervention

Keyword: Acute gout flare, Gout, OLT1177, urate

Outcome measures

Primary outcome

The primary clinical activity outcome will be the change in subject-reported pain intensity score from Baseline (Day 0) to Day 3 (evening; approximately 72 hours after the first dose) in the target joint (100-mm VAS).

Secondary outcome

The principle secondary clinical activity outcomes will be the subject-reported global evaluation of treatment at Day 7 (Likert scale). Additionally the following secondary clinical activity variables will be collected:

• Subject-reported pain intensity score in the target joint (100 mm-VAS)

• Subject-reported general disability score in the target joint (100 mm-VAS)

• Subject-reported walking disability score in the target joint (100 mm-VAS)

• Investigator-assessed Index Joint Score (tenderness, swelling, erythema, warmth)

• Investigator-assessed Global Rating of Disease (Likert scale)

• Blood levels of high sensitivity C-reactive protein (hsCRP), Serum Amyloid A protein (SAA) and inflammatory cytokines

If at any time during the study a subject is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare, the subject will be withdrawn from the study, considered a Treatment Failure and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID). In addition to the clinical activity variables described above, the number and proportion of Treatment Failures in each cohort will be captured and summarized in the study results

Safety variables collected in the study will be:

• Physical examination (abbreviated general and site specific examination)

• Vital Signs (pulse, resting blood pressure, temperature, respiration rate)

• Safety laboratory measures (chemistry, hematology and urinalysis)

• Safety electrocardiograms (ECGs)

• Adverse Events (AEs) during the clinical trial

Study description

Background summary

Gout is a chronic condition characterized by hyperuricemia and the presence of monosodium urate (MSU) crystals in affected joints. Gout is the most common inflammatory arthritis with an increasing incidence over the past several decades, due at least in part to the rise in comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type-2 diabetes mellitus, and chronic kidney disease (CKD).
Periodically, subjects suffering from gout have a sudden onset of symptoms, or a *flare,* which can include severe pain, joint swelling, redness and/or warmth due to inflammation secondary to intraarticular MSU crystals. Acute gout flares are a primary factor in the decreased health-related quality of life reported by subjects with gout and can be debilitating and associated with decreased work productivity.

The inciting factor may not be known, but the biological mechanism underlying the symptoms of an acute gout flare is a sudden and marked increase in synovial fluid neutrophils in affected joints, a process that is mediated by, among other markers, the pro-inflammatory cytokines, specifically interleukin (IL)-1β, which creates inflammation in the joint.

The current standard of care for an acute gout flare is non-steroidal anti-inflammatory drugs (NSAIDs), steroids or colchicine. Each of these therapies suffers from limitations in their application, due to risks associated with NSAID use and common comorbidities, risks associated with chronic or recurrent high dose steroid use or the narrow therapeutic window with colchicine.
The study medication OLT1177 is in clinical development for the treatment of acute gout flares. OLT1177 Capsules are an oral medication that blocks the processing of interleukin-1 and may reduce the inflammation and pain caused by the gout flare.

The results of this proof-of-concept study will provide evidence on the potential utility of the study medication (OLT1177 Capsules) in the treatment of acute gout flares. Results from the study will guide the design and dose selection for future clinical trials.

Study objective

The objectives of this clinical trial are as follows:
1. To assess the safety and tolerability of OLT1177 Capsule after oral administration in subjects with an acute gout flare
2. To assess the clinical activity of various doses of OLT1177 Capsule in treating signs and symptoms resulting from an acute gout flare
3. To assess OLT1177-induced changes in inflammatory biomarkers.

Study design

This is a Phase 2 single-center, sequential, adaptive dose progression proof-of-concept safety and efficacy study of orally administered OLT1177 capsules into be conducted in subjects with an acute gout flare. A total of approximately 24 eligible subjects will be enrolled sequentially in up to four cohorts of 8 subjects each.
The study will last approximately 35 days.

Subjects will be screened for eligibility at the Baseline visit and, if eligible, enrolled into the study. Following enrollment, Baseline assessments will be conducted and the first dose of investigational product will be administered. Subjects will take investigational product for up to eight (8) consecutive days (up to and including the planned Day 7 visit). Subjects will return to the study clinic on Days 3, 7 and 14 for follow-up visits and will be

contacted by telephone on Day 35 (± 3 days) for further follow-up.

Safety assessments will be conducted at each visit. Efficacy assessments as scored by the patient will be captured by a paper study diary. Safety and tolerability will be evaluated by monitoring the occurrence of AEs and changes in abbreviated physical examination findings, vital signs, clinical safety laboratory test results (chemistry, hematology and urinalysis) and ECGs. Efficacy will be evaluated by subject-reported pain and disability scales, Investigator*assessed Index Joint Score and Global Rating of Disease, and analysis of biomarkers of inflammation.

Rescue medication is not allowed in the first 12 hours after intake of the first dose of the study medication. The rescue medication (paracetamol 1g/dose) will be dispensed during the baseline visit. An explanation will be given to the patients to document the taken dose and time of dosing of rescue medication in the study diary. 12 hours after the first intake of study medication the patients, who can not bear the pain, are allowed to orally take 4 gram paracetamol (1g, 4x daily) during the treatment period (up to and including the day 7 visit). Other pain medication, steroids or treatment for the gout flare are not allowed during the treatment period.

If the patient considers the pain unbearable and would like to receive standard medical treatment for the gout flare, than the patient will be withdrawn for the study and considered a 'treatment failure'. The patient will then be treated with prednisolon (30mg/day) or colchicine (0.5 mg, 3x daily).

Intervention

OLT1177 Capsule (100 mg each) will be self-administered for the duration of the Treatment Period beginning at the Baseline visit and will continue through the Day 7 visit. Investigational product will be self-administered orally two times per day for Cohort 1, four times per day for Cohort 2, two times per day for Cohort 3 and one time per day for Cohort 4.

At the start of the study, synovial fluid will be collected once to check patient's eligibility. During the study blood draws will be performed for determination of pharmacokinetics, clinical chemistry and hematology. Patients will need to keep a diary for the first 14 days in study and complete questionnaires during the study visits.

Study burden and risks

The current standard of care for an acute gout flare is non-steroidal anti-inflammatory drugs (NSAIDs), steroids or colchicine. Each of these therapies suffers from limitations in their application, due to risks associated with NSAID use and common comorbidities, risks associated with

chronic or recurrent high dose steroid use or the narrow therapeutic window with colchicine.
The study medication OLT1177 is in clinical development for the treatment of acute gout flares. OLT1177 is an oral medication that blocks the processing of interleukin-1 and may reduce the inflammation and pain caused by the gout flare.

The burden and risks associated with participation in this study are summarized as follows:
- the time it will take to attend study visits and fill out study questionnaires/diary;
- postponement of standard care;
- intake of up to 20 capsules per day;
- undergoing study-related tests such as blood draws, physical examinations, electrocardiogram, and measurement of vital signs;
- possible side effects of the study drug (diarrhea, back pain, migraine, contact dermatitis, eczema, headache or allergic reaction);
- possible adverse effects/discomforts caused by the evaluations in the study (synovial fluid collection, blood draws, ECGs);
- possible worsening of gout symptoms.

The study medicine may reduce the inflammation and pain caused by acute gout flare, but this is not certain. Participation will contribute to the medical knowledge about the use of this study medicine and may help develop a better drug therapy for gout.

Contacts

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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 and female subjects between 18 and 80 years old, inclusive
2) Gout in a joint of a subject*s lower limbs (e.g. ankle, foot, knee, toe) as indicated by the presence of monosodium urate (MSU) crystals by microscopic evaluation of synovial fluid from the target joint and in accordance with ACR/EULAR 2015 Gout Classification Criteria
3) Confirmation of a gout flare in the target joint that began within 96 hours prior to the Baseline visit, based on presence of subject-reported joint pain at rest of >= 50 mm on a 0 - 100 mm visual analog scale (VAS) and at least two of the following criteria in the target joint:
a. Subject-reported flare
b. Subject-reported warm joint
c. Subject-reported swollen joint
4) Acceptable overall medical condition to be safely enrolled in and to complete the study (with specific regard to cardiovascular, renal and hepatic conditions) in the opinion of the Investigator
5) Ability to provide written, informed consent prior to initiation of any study-related procedures, and ability, in the opinion of the Investigator, to understand and comply with all the requirements of the study, which includes abstaining from use of pain or Rescue Medication (for 12 hours after first dose of investigational drug) and other prohibited medications as outlined in Section 5.6.3 of the protocol.

Exclusion criteria

1) Women of childbearing potential, or men whose sexual partner(s) is a woman of childbearing potential who:
a. Are or intend to become pregnant (including use of fertility drugs) during the study
b. Are nursing [female subjects only]
c. Are not using an acceptable, highly effective method of contraception until all follow-up procedures are complete. See Section 5.6.2 for more details on acceptable forms of

contraceptives.
2) Presence of an acute gout flare in more than one joint at the Baseline visit
3) Presence of another inflammatory arthritis in addition to gout
4) Presence or known history of other autoimmune conditions (e.g. systemic lupus erythematosus, hypophysitis, etc.)
5) Clinically significant general pain or non-gout related joint pain that would interfere with the subject*s ability to accurately assess pain in the target joint, at the discretion of the Investigator
6) Use of any prohibited concomitant medications/therapies over the periods defined in Section 5.6.3 or planned use of any concomitant medications/therapies during the Treatment Period (including the use of paracetamol within 4 hours prior to the Baseline visit or other pain medications within 12 hours prior to the Baseline visit)
7) Active infection within 3 days prior to the Baseline visit
8) History of or known positive for HIV, Hepatitis B surface antigen (HBsAg) or antibodies to Hepatitis C Virus (HCV)
9) Diagnosed with any form of internal cancer within the past 5 years
10) Any other concomitant medical or psychiatric conditions, diseases or prior surgeries that in the opinion of the Investigator would impair the subject from safely participating in the trial and/or completing protocol requirements
11) History of alcohol or substance abuse within the 12 months prior to the Baseline visit
12) Enrollment in any trial and/or use of any investigational product or device within the immediate 30-day period prior to the Baseline visit
13) Enrollment in any study previously sponsored by Olatec Therapeutics LLC, specifically Study OLT1177-01, Study OLT1177-02, Study OLT1177-03 or Study OLT1177-04
14) Known diagnosis of chronic kidney disease or known history of renal impairment (e.g. calculated glomerular filtration rate [GFR] less than 40 mL/min)

Study design

Design

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

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	18-05-2017
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n/a
Generic name:	dapansutrile

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	11-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2018
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	EUCTR2016-000943-14-NL
CCMO	NL58629.056.16

Study results

First publication
11-08-2020