A Multi-Center Phase 2/3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Safety and Efficacy Study of Dapansutrile Tablets in Subjects with an Acute Gout Flare

Published: 31-01-2023
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This study has been transitioned to CTIS with ID 2024-518844-20-00 check the CTIS register for the current data. Primary Objective:To evaluate the efficacy of dapansutrile as an acute gout flare treatment compared to placebo in reducing joint pain…

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

Summary

ID

NL-OMON53551

Source
ToetsingOnline

Brief title
OLT1177-08

Condition

- Joint disorders

Synonym
Gout

Research involving
Human

Sponsors and support

Primary sponsor: Olatec Therapeutics, Inc.
Source(s) of monetary or material Support: yes;by the industry/company as is described in question B6/B7 (sponsor of the research)

Intervention

Keyword: Acute Gout Flare, Dapansutrile, Multi-Center, Phase 2/3

Outcome measures

Primary outcome

The primary clinical activity outcome measurement will be:

• Change from baseline in the subject-assessed pain intensity score (100-mm VAS) in the target joint at 72 hours post initial loading dose for dapansutrile compared to placebo.

Secondary outcome

The secondary clinical activity outcome measurements will be:

• Change from baseline in the subject-assessed pain intensity score (100-mm VAS) in the target joint at 12, 24, 36, 48, and 60 hours post initial loading dose, and on Study Day 8 and Study Day 15

• Subject-assessed PGART on Study Day 8

• Change from baseline in the Investigator-assessed Target Joint Score (tenderness, swelling, erythema, warmth, and range of motion) at scheduled assessments through Study Day 15

• Investigator-assessed IGART at scheduled assessments through Study Day 8

• Proportion of subjects with a response (defined as a 20%, 50%, or 70% reduction from baseline without using Rescue Medication or Escape medication) in the subject-assessed pain intensity score (100-mm VAS) in the target joint

at 48 and 72 hours post initial loading dose, and on Study Day 8 and Study Day 15

• Time to intake of medication taken for non-response from first IMP administration, e.g., Rescue Medication and/or Escape Medication

• Proportion and number of subjects with Rescue Medication or Escape Medication use from the first IMP administration up to 12 hours, >12 to 24 hours, >24 to 48 hours, >48 to 72 hours, >72 hours to Day 8, and >Day 8 to Day 15

• Change from baseline in the subject-assessed QoL questionnaire (SF 12v2) at scheduled assessments through Study Day 15

• Change from baseline in the subject-assessed pain intensity score (100-mm VAS) in any actively flaring non-target joint(s) on Study Day 4, Study Day 8, and Study Day 15.

PK will be evaluated as follows:

• Changes in plasma dapansutrile concentrations and population PK parameters.

Safety criteria for evaluation are as follows:

• AEs during the clinical trial

• Physical examinations

• Vital signs (pulse, respiratory rate, resting blood pressure, temperature, and weight)

• Laboratory measures (chemistry, hematology, and urinalysis)

• ECGs.

Biomarkers will be evaluated as follows:

• Changes in plasma levels of circulating C-reactive protein (CRP),

neutrophils, and relevant inflammatory cytokines (e.g., interleukin [IL] 1β,

IL-6).

Study description

Background summary

Gout is the most common inflammatory arthritis, and it has had an increasing incidence over the past several decades due at least in part to the rise in medical comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type-2 diabetes mellitus, and chronic kidney disease (Punzi et al., 2020). Furthermore, demographic and behavioral trends suggest that a continued growth in the incidence of gout is likely (Kuo et al., 2015). Acute gout flares are a primary factor in the decreased health-related quality of life reported by patients with gout and can be debilitating and associated with decreased work productivity (Roddy and Doherty, 2010; Khanna et al., 2012).
Gout is a chronic autoinflammatory disease. Periodically, patients diagnosed with hyperuricemia and gout have a sudden onset of symptoms, or a *flare*, characterized by severe pain, joint swelling, redness, and/or warmth in one or more joints. Recurrent autoinflammatory acute gout flare episodes are driven by a hyperuricemia-associated activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome due to deposited monosodium urate (MSU) crystals in affected joints (Narang and Dalbeth, 2020).
Olatec*s investigational medicinal product (dapansutrile tablets) is in clinical development for the treatment of acute gout flares. Dapansutrile, a selective oral NLRP3 inhibitor, prevents the processing of the precursor forms of IL 1β and IL 18 and secretion of the bioactive forms of these highly inflammatory cytokines (Marchetti et al., 2018). In an acute gout flare, MSU crystals activate NLRP3, resulting in the production of active IL 1β in the affected joints (Martinon et al., 2006). Several studies in humans and mice have demonstrated that IL 1β is the pivotal cytokine in gouty inflammation and the causative agent mediating the symptoms of acute gout flares, including joint pain due to inflammation (Marchetti et al., 2018; Joosten et al., 2010; Schlesinger et al., 2012; Janssen et al., 2019; Dinarello, 2019). IL-1β release, in turn, leads to the downstream release of IL-6 and other cytokines and chemokines. Moreover, in gouty arthritis flares, increased synovial fluid neutrophils in the affected joints contribute to the intense inflammation. The neutrophil infiltration during the onset of gouty arthritis is predominantly

mediated by the NLRP3- and IL 1β-dependent IL-8 production.
For prompt and effective control of the clinical signs and symptoms in subjects with an acute gout flare, oral therapeutic agents that target the NLRP3-mediated response and inhibit the release of IL 1β, such as dapansutrile, are well-positioned to rapidly and significantly reduce or eliminate the acute autoinflammatory response.
The current standard of care for an acute gout flare in the US is to prescribe non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine (FitzGerald et al., 2020). Each of these therapies has limitations in their use in acute gout flares, such as the risks associated with NSAID use on common renal and cardiac comorbidities, the risks associated with chronic or recurrent high-dose steroid use in patients with hypertension and/or Type 1 or Type 2 diabetes, and the narrow therapeutic window with colchicine.
Given the limitations of currently available therapies, the development of new oral pharmaceutical therapies is warranted. Preferably, these new therapies should involve novel mechanisms of action or inhibition of new biological targets in order to achieve efficacy and also have safety and tolerability profiles that do not negatively impact medical comorbidities associated with gout. The Sponsor believes that dapansutrile has the potential to be one such therapy.
This clinical trial is designed to investigate the clinical activity and safety of dapansutrile tablets compared to placebo in subjects with an acute gout flare.

Study objective

This study has been transitioned to CTIS with ID 2024-518844-20-00 check the CTIS register for the current data.

Primary Objective:
To evaluate the efficacy of dapansutrile as an acute gout flare treatment compared to placebo in reducing joint pain at 72 hours post initial loading dose of Investigational Medicinal Product (IMP)

Secondary Objectives:
1. To further assess the clinical activity of dapansutrile compared to placebo in reducing joint pain at scheduled time points post initial loading dose of IMP
2. To assess the clinical activity of dapansutrile compared to placebo in treating signs and symptoms of an acute gout flare other than pain (tenderness, swelling, erythema, warmth, and range of motion)
3. To assess the use of and time to the first intake of any Rescue Medication and/or Escape Medication taken for non-response
4. To characterize the population pharmacokinetics (PK) of dapansutrile and exposure response relationship for efficacy and safety
5. To assess the safety and tolerability of dapansutrile compared to placebo

Exploratory Objective

1. To assess and compare changes in relevant circulating inflammatory biomarkers between dapansutrile and placebo

Study design

This is a multi-center Phase 2/3 randomized, double-blind, placebo-controlled, parallel-group safety and efficacy study with a 7-day period of IMP treatment conducted in subjects with an acute gout flare.
Up to 300 eligible subjects will be randomized (2:1) to one of the following treatment arms in order to have 255 evaluable subjects:
• Treatment Arm 1 (Dapansutrile): initial loading dose of 2000 mg dapansutrile on Study Day 1 followed by a maintenance regimen of 1000 mg dapansutrile starting 12 hours (-4 / +2 hours) later administered BID through the second dose on Study Day 7, inclusive (N = up to 200 subjects); or
• Treatment Arm 2 (Placebo): initial loading dose of matching placebo (to mimic dapansutrile dosing) on Study Day 1 followed by a maintenance regimen of matching placebo starting 12 hours (-4 / +2 hours) later administered BID through the second dose on Study Day 7, inclusive (N = up to 100 subjects).
Randomization will be stratified based on region (US vs EU).
At the Screening Visit, subjects with a known history of gout will provide informed consent and then be screened for initial eligibility during the quiescent phase of gout. When the subject experiences his/her next acute gout flare, the subject will return to the study site for the Baseline Visit/Study Day 1 and for confirmation of all eligibility criteria, at which time subject will be randomized into the study if eligibility criteria are met. Eligible subjects must have a documented acute gout flare in at least one joint but not more than three joints at the Baseline Visit/Study Day 1.If only one joint is affected at the Baseline Visit/Study Day 1, it will be designated as the *target joint*. If more than one joint is affected, then the currently most painful (according to the subject), actively flaring joint, among typical joints affected by gout at the time of the Baseline Visit/Study Day 1, will be designated as the *target joint* the other affected joint(s) will be designated as a *non-target joint(s)*. The location of the target joint and any actively flaring non-target joints at the time of the Baseline Visit/Study Day 1 will be recorded. Additional (pre-dose) baseline safety and efficacy assessments will be conducted, and the initial loading dose of IMP (i.e., dapansutrile or placebo) will be self-administered with water at the clinical site. Following their initial loading dose of IMP, subjects will remain in the clinic for a brief safety observation period, and once vital signs and any observed AEs are recorded 1 hour (± 15 minutes) post initial loading dose of IMP, the subjects will be released from the clinical site. Subjects will self-administer their second Study Day 1 dose of IMP at home approximately 12 hours later (with an allowance for the second Study Day 1 dose to be taken 8 to 14 hours post initial loading dose). For the remainder of IMP doses, subjects will self-administer IMP at home BID, with dosing occurring at approximately 12 hour intervals and at approximately the same time of day across Study Days.

Subjects will return to the clinical site for 3 additional visits (with the indicated visit windows allowed): Visit 2/Study Day 4 (+ 1 day), Visit 3/Study Day 8 (+ 2 days), and Visit 4/Study Day 15 (follow-up visit) (± 1 day). Additionally, all subjects may be contacted by telephone or SMS/text message for dosing compliance confirmation approximately every 24 - 48 hours during the Treatment Period. Subjects will be contacted by telephone on Study Day 36 (± 3 days) for additional safety follow up.

Assessments to evaluate safety, clinical activity (for pain and signs and symptoms other than pain in the target joint [tenderness, swelling, erythema, warmth, and range of motion]; for pain in the non-target joint[s]), and quality of life (QoL) will be conducted at study visits. Additionally, target joint pain assessments, IMP administration and any use of Rescue Medication, Escape Medication (defined as gout medications taken for non-response) and/or other prohibited medications taken will be captured through subject entries in an electronic Clinical Outcome Assessments (eCOA) study diary (eDiary). The eDiary target joint pain assessments should be completed by the subject prior to taking their dose of IMP for a given timepoint (e.g., a morning pain assessment should be completed before a dose of IMP is taken that morning).

Safety and tolerability will be evaluated by monitoring the occurrence of AEs and changes in physical examination findings, vital signs, clinical safety laboratory test results (chemistry, hematology, and urinalysis), and ECGs.

Intervention

Treatment arm 1 (Dapansutrile): iinitial loading dose of 2000 mg dapansutrile on Study Day 1 followed by a maintenance regimen of 1000 mg dapansutrile starting 12 hours (-4 / +2 hours) later administered BID through the second dose on Study Day 7

Treatment arm 2 (Placebo): mimics dapansutrile dosing

Study burden and risks

Please refer to the study schedule in the protocol (pg 56 - 58).

Participating in this study is approximately 36 days. Subjects will visit the hospital 4 times in the first 15 days.

During this study, the following tests and assessments can be done, but not necessarily during every visit:
- Physical Examination
- Blood test
- Urine sample for safety assessment
- If the subject is a woman of childbearing potential, she will be asked to

provide urine for pregnancy test.
- Fill in the ediary
- Electrocardiogram (ECG)
- Microscopic evaluation of synovial fluid or imaging evidence of urate deposition may be performed 1 time.

It is also possible for the subject to receive every 24 or 48 hours a text message to check whether the study drug and/or emergency drug has been taken appropriately.

Contacts

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New York 10065
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Scientific
Olatec Therapeutics, Inc.

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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 >= 18 years of age

2) Clinical diagnosis of gout according to the 2015 ACR/EULAR Gout Classification Criteria at the Screening visit or Baseline Visit/Study Day 1 (i.e. subject must have at least 8 points or meet sufficient criterion). In addition:
a. Newly presenting subjects: Diagnosis of gout must be confirmed in the target joint as indicated by either the presence of monosodium urate (MSU) crystals by microscopic evaluation of synovial fluid from the target joint or bursa OR by imaging evidence of urate deposition in the target joint or bursa at the Baseline Visit/Study Day 1
b. Previously diagnosed subjects: Confirmation of gout diagnosis as per criterion 2a; OR history of gout diagnosis per one of the following:
- documented history of the presence of MSU crystals in synovial fluid from the target joint or bursa; OR
- historical imaging report of urate deposition in the target joint or bursa in their medical record; OR
- documented history of 2 or more gout flares in the previous 18 months
3) Confirmation of a gout flare in the target joint that began within 96 hours prior to the Baseline Visit/Study Day 1, based on the presence (at the Baseline Visit/Study Day 1) of subject-reported target joint pain at rest of >= 50 mm on a 0 to 100-mm 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 safely participate in the study and complete all study procedures (with specific regard to cardiovascular, renal, and hepatic conditions), in the opinion of the Investigator
5) Able and willing to provide written informed consent prior to initiation of any study related procedures
6) Ability, in the opinion of the Investigator, to understand and comply with all the requirements of the study, which includes understanding restrictions regarding the use of Rescue Medication, Escape Medication and other prohibited medications, including other pain medications, as outlined in Section 4.10.3 of the protocol

Exclusion criteria

1) Woman of childbearing potential, or man whose sexual partner(s) is a woman of childbearing potential, who:
a. Is or intends to become pregnant (including use of fertility drugs) while participating in the study (through the Study Day 36 Follow-up call)
b. Is lactating/breastfeeding or plans to breastfeed while participating in the study (female subjects only)
c. Is not willing to use an acceptable, highly effective method of contraception until all follow-up procedures are complete (see protocol Section

4.10.2 for more details on acceptable forms of contraceptives)
2) Presence of any palpable and visible tophi by physical examination
3) Has >= 4 joints with an acute gout flare at the Baseline Visit/Study Day 1
4) Presence of rheumatoid arthritis or other acute inflammatory arthritis
5) Evidence/suspicion of infectious/septic arthritis
6) 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, in the opinion of the Investigator
7) Known history of any clinically significant or unstable medical condition or any other disorder, condition, or circumstance (including secondary pain, or recreational or medical use of substances that may alter pain perception such as cannabidiol [CBD]- and
tetrahydrocannabinol [THC]-containing substances, psilocybin, etc.) that, in the opinion of the Investigator, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments
8) 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
9) Use of any prohibited concomitant medications/therapies over the periods defined in Protocol Section 4.10.3 or planned use of any prohibited concomitant medications/therapies during the Treatment Period (including the use of paracetamol/acetaminophen within 4 hours prior to the Baseline Visit/Study Day 1 or other pain medications within 12 hours prior to the Baseline Visit/Study Day 1)
10) Use of any product containing paracetamol/acetaminophen within 4 hours prior to the Baseline Visit/Study Day 1 or planned use during the Treatment Period (with the exception of sponsor-provided Rescue Medication [paracetamol/acetaminophen], which is permitted after completion of the first target joint pain assessment on Study Day 4)
11) Meets 2 or more of the criteria for substance use disorder provided in Appendix 1 within 1 year of the Baseline Visit/Study Day 1
12) History of, or known positive for, human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibodies to hepatitis C virus (HCV) with a positive polymerase chain reaction (PCR) result for HCV
13) Known diagnosis of chronic kidney disease or known history of renal impairment (e.g., estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m2)
14) Enrollment in any trial and/or use of any investigational medicinal product or device within the immediate 1-year period prior to the Baseline Visit/Study Day 1
15) Enrollment in previous gout studies with dapansutrile
16) Positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, if tested, within 4 weeks of the Baseline Visit/Study Day 1
17) Active malignancy or recent malignancy with any systemic anti-cancer treatment (e.g., immunotherapy or chemotherapy) within the past 6 months
18) Has a serious illness that resulted in hospitalization in the 30 days

preceding the Baseline Visit/Study Day 1
19) Has a hypersensitivity or allergy to dapansutrile or other drugs in its class and/or the components of the IMP (dapansutrile tablets or placebo tablets)
20) Has a hypersensitivity or allergy to paracetamol/acetaminophen
21) Is an employee, family member, or student of the Investigator or clinical site

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:	Pending
Start date (anticipated):	30-08-2024
Enrollment:	45
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	OLT1177
Generic name:	Dapansutrile

Ethics review

Approved WMO

Date:	31-01-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Not approved

Date:	27-07-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	08-04-2024
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	17-06-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	09-09-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	CTIS2024-518844-20-00
EudraCT	EUCTR2019-002717-19-NL
ClinicalTrials.gov	NCT05658575
CCMO	NL82797.068.22