A Pilot, Open-Label, Phase 2, Single-Center, Repeat Dose, Proof-of-Concept Safety, Pharmacodynamics and Efficacy Study of Orally Administered Dapansutrile Capsules in Subjects with Schnitzler*s Syndrome

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46617

Source
ToetsingOnline

Brief title
Pilot Study of Dapansutrile in Schnitzler's Syndrome

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
Schnitzler's syndrome

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Schnitzler's syndrome

Outcome measures

Primary outcome

Primary efficacy outcome will be the proportion of subjects with Grade 0 or 1

Schnitzler syndrome symptoms at the Day 14 visit.

Secondary outcome

Secondary efficacy outcome measures will be:

• Photographs of the posterior torso and/or other ares of the body that

display(ed) urticarial rash at Baseline

• Investigator Global Assessment of Disease Activity (5-point NRS)

• Subject-completed study diaries (to be completed daily)

o Subject Global Assessment of Disease Activity (11-point NRS)

o Subject Skin Assessment (5-point NRS)

o Ear (tympanic) body temperature measurements

• Time to relapse of SchS symptoms after cessation of dapansutrile capsules as

defined by the emergence of Grade 2 or higher SchS symptoms

• Subject Global Evaluation of Treatment

Study description

Background summary

Schnitzler*s syndrome is a rare autoinflammatory disorder characterized by chronic urticaria, bone pain, monoclonal immunoglobulin M gammopathy and intermittent fever. Treatment of Schnitzler*s syndrome remains a challenge although many therapeutic approaches, including corticosteroids, NSAIDs, colchicine, dapsone, thalidomide, interferon-α, rituximab, immunoglobulins and methotrexate, have all been described in the literature. Dependency on high doses of corticosteroids is common, entailing steroid toxicity. Immunosuppressive drugs are generally ineffective or fail to provide long-term remission despite short-term improvement.

Although the etiology of Schnitzler*s syndrome is unknown and the pathophysiology has yet to be fully elucidated, a case report by Pizzirani et al (2009) suggested that dysfunction of the inflammasome and IL-1β processing contributes to the underlying pathogenesis. In fact, peripheral blood mononuclear cells (PBMCs) or monocytes from patients with symptomatic Schnitzler*s syndrome produced more IL-1β and IL-6 upon stimulation with LPS relative to control PBMCs (Ryan 2008, Pizzirani 2009, de Koning 2015). Since IL-1β activity is modulated by the IL-1 receptor antagonist (IL-1Ra), which blocks binding of IL-1α and IL-1β to IL-1R1, the recombinant IL-1Ra anakinra was evaluated as a potential treatment and found to rapidly control all the symptoms of this syndrome. Clinical benefit of anakinra treatment is observed often within a few hours on urticaria and within a few days on C-reactive protein levels and leukocytosis. As there are no approved treatments for Schnitzler*s syndrome, anakinra has been used off-label.

The results of this proof-of-concept study will provide evidence on the potential utility of dapansutrile capsules in the treatment of Schnitzler's syndrome. Results from the study will guide the design for future clinical studies.

Study objective

The objectives of this clinical trial are as follows:
1. To assess the safety, tolerability, and pharmacokinetics of dapansutrile capsules after oral administration in subjects with chronic, well-controlled Schnitzler*s syndrome
2. To assess the clinical activity of dapansutrile capsules, including the change in symptoms of Schnitzler*s syndrome, upon withdrawal of anakinra therapy
3. To assess the pharmacodynamics and changes in inflammatory biomarkers after oral administration of dapansutrile capsules, upon withdrawal of anakinra therapy, and after all therapy has ende

Study design

This is a pilot, open-label Phase 2, single-center, repeat dose, single cohort, proof-of-concept, safety, pharmacodynamics and efficacy study of dapansutrile capsules to be conducted in subjects with Schnitzler*s syndrome (SchS) currently well controlled by anakinra therapy. At least 5 but no more than 10 subjects will be enrolled.

Subjects who are responsive to anakinra (Kineret®) for at least 6 weeks will be screened for eligibility at the Screening / Baseline (Day 1) visit. Following confirmation of eligibility, subjects will be enrolled, the first dose of dapansutrile will be administered at the clinical site and safety and efficacy assessments will be completed. Subjects will self-administer dapansutrile twice a day by mouth for 14 consecutive days. Subjects will continue their standard dose of anakinra for Days 1, 2 and 3 of the 14-day Treatment Period and will then cease taking anakinra. At the end of the 14-day Treatment Period subjects will remain off all medication for Schnitzler*s syndrome. Subjects will return to the study clinic on Days 5, 9, 14, 15, 16, 18, 21 for follow-up visits and will be contacted by telephone on Day 42 (± 3 days) for additional follow-up. Additionally, at the first signs of a relapse or worsening of SchS symptoms, subjects will visit the study clinic for assessments (the *Symptom Onset* visit or SOV) and to discuss with the Investigator when injections of anakinra should be resumed. The Day 15, 16 and 18 visits will only occur in the event that anakinra therapy has not been resumed.

Subjects will be given the option to remain in the Nijmegen area after the Day 14 visit and return to the study clinic for the Day 15, 16 and 18 visits. Alternatively, subjects will be given the option to have these visits conducted at their home by a trained study nurse.

Safety assessments will be conducted at each visit and subjects will capture the frequency and intensity of symptoms, including body temperature, using a paper diary. Safety and tolerability will be evaluated by monitoring the occurrence of AEs and changes in abbreviated physical examination findings, vital signs and clinical safety laboratory test results (chemistry, hematology and urinalysis) and inflammatory biomarkers. Clinical activity will be evaluated by: Subject Diary (completed daily), Subject Global Evaluation of Disease Activity, Investigator Global Assessment of Disease Activity, and analysis of biomarkers of inflammation, including changes in C-reactive protein (CRP). Daily diary assessments will be captured starting at the Screening / Baseline (Day 1) visit and will continue until Symptom Onset visit or Day 21 visit (whichever occurs latest).

Intervention

Dapansutrile capsules (100 mg each) will be self-administered for the duration

of the Treatment Period beginning at the Baseline visit on Day 1 and will continue for 14 days. The dose will consist of five 100 mg dapansutrile capsules taken by mouth twice each day (BID) approximately 12 hours apart for a total of 1 g of dapansutrile per day. If prior to the Day 14 visit, a subject experiences a worsening of symptoms, an increase in the dose or dose frequency of investigational drug up to a maximum of 2 g per day may be implemented at the discretion of the Investigator.

During the study blood draws will be performed for determination of pharmacokinetics, clinical chemistry and hematology and blood will be drawn and urine collected for PD biomarker analysis. Patients will need to keep a diary starting on the day of the Screening / Baseline (Day 1) visit until Symptom Onset visit or Day 21 visit (whichever occurs latest)

Study burden and risks

As there are no approved treatments for Schnitzler*s syndrome, anakinra has been used off-label and the clinical benefit of anakinra treatment is observed often within a few hours on urticaria and within a few days on C-reactive protein levels and leukocytosis. The short half-life of anakinra (4 to 6 hours) requires daily subcutaneous injections, which can be painful and occasionally lead to strong local injection site reactions. The study medication, dapansutrile capsules, is in clinical development for the treatment of Schnitzler*s syndrome and may reduce the inflammation caused by Schnitzler's syndrome.

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 the study diary
- withdrawal or postponement of standard care
- intake of 10 capsules per day (up to 20 if the dose is increased)
- undergoing study-related tests such as blood draws, physical examinations, 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 (blood draws)
- possible aggravation of your symptoms.

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 18 years old or older
2) Prior diagnosis of Schnitzler*s syndrome
3) Presence of Schnitzler*s syndrome that is well controlled by and responsive to anakinra for at least 6 weeks prior to the Screening/Baseline visit
4) Grade 0 SchS symptoms at the Screening/Baseline visit
5) 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
6) 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 as outlined in the protocol.

Exclusion criteria

1) Pregnant, nursing or intent to become pregnant during the study
2) Not responsive or well controlled by anakinra therapy for at least 3 months prior to the Screening/Baseline visit

3) Use or planned use of any prohibited concomitant medications/therapies such as immunotherapies or corticosteroids during the study (until relapse and resumption of anakinra injections)
4) Active infection within 3 days prior to the Screening/Baseline visit
5) History of or known positive for HIV, Hepatitis B surface antigen (HBsAg) or antibodies to Hepatitis C Virus (HCV)
6) Any other concomitant medical or psychiatric conditions, including alcohol or substance abuse, 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
7) Enrollment in any trial and/or use of any investigational product or device within the immediate 30-day period prior to the Screening/Baseline visit
8) Enrollment in any study previously sponsored by Olatec Therapeutics LLC, specifically Study OLT1177-01, Study OLT1177-02, Study OLT1177-03, Study OLT1177-04 or Study OLT1177-05

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):	14-05-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	16-01-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-003282-98-NL
CCMO	NL64155.091.17