A randomized, vehicle-controlled, double-blind, Phase I/IIa, multiple-dose, multiple-cohort, Proof of Concept study in Healthy Volunteers and Patients with Cutaneous T-cell Lymphoma to characterize the safety, efficacy, and pharmacodynamics of topical bimiralisib

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HV cohort 1Primary Objectives* To characterize the local tolerability of topical bimiralisib after 21 days* To characterize the systemic PK of topical bimiralisib after 21 daysSecondary Objective* To characterize the safety of topical bimiralisib...

Ethical review	Approved WMO
Status	Completed
Health condition type	Lymphomas non-Hodgkin's T-cell
Study type	Interventional

Summary

ID

NL-OMON48135

Source
ToetsingOnline

Brief title
topical bimiralisib in HV and patients with CTCL

Condition

- Lymphomas non-Hodgkin's T-cell

Synonym
blood cancer affecting the skin

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bimiralisib, Cutaneous T-Cell Lymphoma, Pharmacodynamics, Topical

Outcome measures

Primary outcome

Application site assessment of erythema and edema

Change from baseline on composite Assessment of Index Lesions Disease Severity

Score (CAILS).

Secondary outcome

Healthy Volunteers: (S)AEs, Laboratory assessments, Systemic PK

MF patients:

* Application site assessment of erythema and edema, (S)AEs, Lab assessments,

Systemic PK

* Objective Response Rate (ORR) based on the CAILS: patients who achieved

partial (PR) or a complete response (CR) after six (6) weeks of treatment.

* Time To Response (TTR) based on ORR up to six (6) weeks

Study description

Background summary

Cutaneous T-cell Lymphoma (CTCL) is characterized by the abnormal accumulation of activated T-cells in the epidermis and dermis. The overall incidence of CTCL has increased from 2.8 per million population (1972) to 10.2 per million population as of 2009. This increase in incidence is thought to be a result of improved detection methods and more efficient medical coverage of the general population. CTCL in men and African-Americans have the highest incidence rates (Korgavkar 2013). The most common type of CTCL is Mycosis Fungoides (MF), which can progress through patch, plaque, and tumor phases. MF lesions often respond to skin directed therapies, like topical corticosteroids, topical mechlorethamin, and/or topical carmustine (Liner 2018). However, not all MF patients respond to these therapies and / or suffer from substantial side effects, highlighting the need for new safe and effective skin-directed therapy options.

Study objective

HV cohort 1
Primary Objectives
* To characterize the local tolerability of topical bimiralisib after 21 days
* To characterize the systemic PK of topical bimiralisib after 21 days
Secondary Objective
* To characterize the safety of topical bimiralisib after 21 days
Exploratory Objectives
* Bimiralisib skin concentrations (via skin biopsy)
* Changes in bimiralisib and/or vehicle treated skin as measured by various imaging modalities.

MF patients cohort 2
Primary Objective
* To evaluate the effect of bimiralisib versus placebo after 6 weeks of treatment on selected target lesions
Secondary Objectives
* To characterize local tolerability, safety, and systemic exposure of topical bimiralisib on target MF lesions.
* To characterize other parameters of efficacy of topical bimiralisib on target lesions.

Exploratory Objectives
* To explore the effect of topical bimiralisib on relevant tissue and plasma biomarkers with different methods
* To explore bimiralisib skin concentrations at the end of treatment.
* To explore the effect of bimiralisib after 12 weeks of treatment

Study design

The study is comprised of two (2) cohorts, separated by a data monitoring committee (DMC) review of the available data from Cohort 1. Cohort 1 will enroll six (6) healthy volunteers, for a treatment duration of 21 consecutive days. Cohort 2 will enroll 18 patients with MF stages 1A/1B, randomized 1:1 to two treatment arms (bimiralisib or placebo). Each patient will be treated for six (6) weeks (main treatment phase).

Healthy Volunteers: Cohort 1
Six (6) healthy volunteers will be concomitantly treated with bimiralisib and vehicle, applied to two (2) independent skin areas for 21 consecutive days:
* once daily (QD) vehicle on 100cm2,
* once daily (QD) bimiralisib 2.0% on 400cm2,
followed by a 2 week safety follow up. Initial healthy volunteer dosing will occur in-house for the first 4 days (3 nights) to establish a well-controlled start. For the remainder of the treatment period, subjects will visit the unit daily for application of study treatment (by study staff) and to monitor safety and local tolerability.

MF Patients: Cohort 2
Following a washout of any topical treatment of at least two weeks and any systemic treatment of at least 4 weeks, every patient will be treated with bimiralisib or vehicle for six weeks (i.e., the Main Treatment Period) on one or more (up to three) target lesion(s) with a total (combined) area of minimally 150cm2 and maximally 200cm2. This will be the basis for the primary analysis.
Extended Treatment Period * Cohort 2
For patients achieving at least a 15% reduction from baseline on CAILS at the end of the main six (6) week treatment period, an optional treatment extension is planned to evaluate whether an extension from six (6) to 12 weeks of treatment might further improve response to topical bimiralisib. Treatment extension will only be considered in the absence of safety / tolerability issues in the respective patient and only if the patient is willing to continue. The blind will be maintained throughout the treatment extension. Treatment extension will be followed by a four (4) week safety follow-up. It is important to note that response to treatment extension from 6 to 12 week constitutes an exploratory objective of the study, as opposed to the primary endpoint which solely considers the difference between placebo and active after the main six (6) week treatment period.
Any of the following will prevent treatment extension for a patient:
* no improvement of target lesions (individual percentage change from baseline of <15% on CAILS)
* progression of any lesion (non-target or target) requiring treatment (as measured by a clinically significant increase in modified Severity Weighted Assessment Tool (mSWAT) score
* complete response (CR = 100% change from baseline on CAILS) of the target lesions
* unacceptable toxicity

* the patient is unwilling to continue treatment in the study
Instead, the patient will directly enter the safety follow up of 4 weeks.

Potential Dose Levels for Cohort 2:
* Bimiralisib (or matching vehicle) 2.0% once daily (QD)
* Bimiralisib (or matching vehicle) 2.0% twice weekly (BIWK)
* Bimiralisib (or matching vehicle) 2.0% once weekly (QWK)

Intervention

Topical bimiralisib/vehicle non-aqueous gel to be administered to target lesion(s) of up to 400cm2 (in healthy volunteers) or up to 200cm2 (in MF patients) in the following dose levels:
* Vehicle
* bimiralisib 2.0% QWK
* bimiralisib 2.0% BIWK
* bimiralisib 2.0% QD
Patients are allowed to treat non-target lesions with a commercially available bland emollient at libitum, which is not considered IMP. The bland emollient will be provided by the site as required.

Study burden and risks

The dose justification for the first-on-human topical bimiralisib dose takes into account the safety profile of oral bimiralisib from more than 230 patients and therefore focusses (1) on the detection and prevention of strong skin reactions, and (2) keeping systemic exposure to bimiralisib as low as possible to reduce the risk for systemic adverse events to a minimum.

No benefit is foreseen for the healthy volunteers. For MF patients, treatment with bimiralisib may result in clinical benefit of the treated (target-) lesions. No clinical benefit is expected for the non-target lesions.

After oral administration of bimiralisib in patients with various oncologic diseases, the following adverse reactions have been observed, which are considered related to systemic exposure to bimiralisib: anemia, body weight decreased, depression, fatigue, gastro-intestinal signs and symptoms, increases in ALT and AST, pneumonitis, hyperglycemia, neutropenia, pruritus, and rash. As described in the dose justification, the selected doses for all participants in the current study are not expected to result in systemic exposures to bimiralisib concentrations that would be high enough to elicit the above described adverse events. At this time, it is unknown what the mechanism of action is for oral bimiralisib to cause the aforementioned skin reactions.
After topical administration in minipigs, erythema and edema have been observed after longer (>23 days) of treatment with higher dose concentrations (3.0% and higher) of topical bimiralisib gel. Therefore, it cannot be excluded that local

tolerability issues might occur in humans with treatment with similar dose concentrations that extend beyond four weeks, hence the primary endpoint of the Healthy Volunteer Cohort is the evaluation of the target area for events of erythema or other local skin reactions. If these kind of events occur, the protocol specifically requires the patient to interrupt dose administration until the event has resolved completely or at least has reduced in severity to Grade 1. Level of knowledge about mechanism of action
The drug bimiralisib inhibits the PI3K/mTOR pathway. This pathway plays a major role in various physiological processes including * but not limited to - glucose metabolism and immune response. This pathway is an ubiquitous pathway.

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

Healthy volunteers may be included in the study if they meet all the below inclusion criteria:
1. Males * 18 years of age
2. Fitzpatrick skin type I, II, III or IV
3. No clinical significant skin disease in the treatment area(s) and no hypertrophic scarring
4. Willing and able to washout and withhold any topical treatment in the treatment area (2 weeks)
5. Subjects must understand the investigational nature of this study and sign an independent ethics committee-approved written informed consent form prior to any study related procedure.
6. Willing to comply with all study requirements.
7. Subjects of reproductive potential must agree to use double contraception from screening until 90 days after discontinuing study treatment and withhold from any sperm donation.Patients may be included in the study if they meet all the below inclusion criteria:
1. Males or females * 18 years of age
2. Confirmed diagnosis of CTCL (MF): MF stage 1A or 1B (maximum T2N0M0B1) as per Modified ISCL/EORTC revisions (Olsen-2011):
a. Confirmed histopathological diagnosis from skin biopsy representative of current disease by pathologist with expertise in cutaneous lymphoma. The date of biopsy should be within the last 5 years. If diagnosis is not confirmed by light microscopic examination, ISCL diagnostic criteria must be used.
3. At least 1, 2 and up to 3 target lesions with a (combined) total size of at least 150 cm2
4. Willing and able to washout any previous topical treatment (at least 2 weeks) and any systemic treatment (at least 4 weeks) prior to first application of topical bimiralisib.
5. Otherwise healthy, i.e. absence of clinically significant or unstable disease, with acceptable organ function with lab values within normal range or as specified below:
a. eGFR (mCockcroft-Gault) > 30 mL/min.
b. AST and ALT <<= 2.5x ULN
c. Total bilirubin <<= 1.5x ULN (except patients with Gilbert*s syndrome, who may have total bilirubin <<= 3x ULN)
d. Platelet count ><= 100*000 /mm3
e. WBC count ><= 1500 /mm3
f. ANC count ><= 1500 /mm3
g. Fasting blood glucose <<= 125 mg/dL
6. Patient must understand the investigational nature of this study and sign an independent ethics committee/ approved written informed consent form prior to any study related procedure.
7. Willing to comply with all study requirements.
8. Patients of reproductive potential must agree to use double contraception

from screening until 90 days after discontinuing study treatment.
9. Females who had a menstrual cycle within 2 years of Screening must have a negative serum pregnancy test at Screening and a negative urine pregnancy test on their first dosing

Exclusion criteria

Healthy volunteers will be excluded from the study if they meet any of the below exclusion criteria:
1. Known hypersensitivity to any of the excipients of bimiralisib gel.
2. Evidence of any clinically significant active or unstable chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG) at screening or pre-dose). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
3. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis) at screening or pre-dose. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects;
4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening, or other known infection requiring antibiotic therapy within the last three months prior to the study.
5. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times in the past year;
6. Donation of blood or blood loss of >500 mL within 3 months prior to screening or donation of plasma within 14 days
7. Any condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subjectPatients will be excluded from the study if they meet any of the below exclusion criteria:
1. Known hypersensitivity to any of the excipients of bimiralisib gel.
2. Patients who are on (or will require) any systemic treatment to treat their disease (MF) during the study.
3. Concurrent severe and/or uncontrolled medical conditions that would, in the investigator*s judgment, contraindicate patient participation in the clinical study or require concomitant skin-directed or systemic therapy (e.g., active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.).
4. Has other active malignancies that require systemic treatment.

5. Has a known history of HIV infection or hepatitis (testing not mandatory).
6. Pregnant or nursing (lactating) women.
7. Has a known history of alcohol or drug abuse within the past 1 year.
8. Psychiatric illness, disability or social situation that would compromise the subject*s safety or ability to provide consent, or limit compliance with study requirements.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-07-2019
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PQR309
Generic name:	N.a.

Ethics review

Approved WMO

Date:	08-05-2019
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-01-2020
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	EUCTR2019-001383-30-NL
CCMO	NL69869.056.19

Study results

Date completed: 24-04-2020

Results posted: 07-10-2020

First publication
30-09-2020