A multicentre, double blind, randomised, placebo controlled, Phase II trial to evaluate Resminostat for maintenance treatment of patients with advanced stage (Stage IIB-IVB) mycosis fungoides (MF) or Sézary Syndrome (SS) that have achieved disease control with systemic therapy - the RESMAIN Study

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Primary ObjectiveThe primary objective is to determine if maintenance treatment with resminostat increases progression free survival (PFS) compared to placebo in patients with advanced stage (Stage IIB IVB) MF or SS that have achieved disease...

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

Summary

ID

NL-OMON55744

Source
ToetsingOnline

Brief title
RESMAIN Study (4SC-201-6-2015)

Condition

- Lymphomas non-Hodgkin's T-cell

Synonym
cutaneous lymphoma, Mycosis fungoides / Sézary Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: 4SC AG
Source(s) of monetary or material Support: the sponsor 4SC AG

Intervention

Keyword: Maintenance treatment, MF/SS, Phase II, Resminostat

Outcome measures

Primary outcome

Efficacy

All efficacy assessments will be done according to 2011 ISCL, the United States

Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of

the EORTC consensus statement of clinical endpoints and response criteria in MF

and SS.

Primary Endpoint

- PFS

PFS is defined as the time from date of randomisation to first date that

criteria for PD have been met according to the global response score or death

due to any cause in the absence of documented PD.

Secondary outcome

Key Secondary Endpoint

- TTSW (pruritus)

Secondary Endpoints

- TTP

- TTNT

- PFS2

- PFS3

- ORR (CR, PR)

- DOR

- OS

- HrQoL

o VAS (itching)

o FACT-G

o Skindex-29

- PK analysis (peripheral blood)

Safety Endpoints

- AEs

- vital signs (body weight, heart rate, systolic blood pressure [SBP],

diastolic blood pressure [DBP])

- 12-lead ECGs

- safety laboratory data (haematology, clinical chemistry)

Exploratory Endpoints

• Biomarkers

o descriptive analysis of changes in gene or protein expression related to

resminostat*s MoA

o exploratory analysis of potential biomarkers of response to resminostat

treatment

o exploratory analysis of potential prognostic biomarkers

• Other

o descriptive analysis of changes in requirement of anti itching treatment

o exploratory analysis of change of VAS itching score (e.g., as area under

the curve [AUC] per time period between treatment Arms)

o evaluation of efficacy of blinding using a survey including patients and

investigators

Study description

Background summary

(Below information is an extract from section 7 of the protocol. Please refer to the protocol for full information)

Primary CTCLs (cutaneous T-cell lymphomas) represent a heterogeneous group of extranodal Non Hodgkin*s lymphomas (NHL) that arise from malignant clonal transformation of skin homing and/or skin residing T-cells. CTCLs primarily affect the skin, but may ultimately involve lymph nodes, blood and visceral organs. The most common subtype of CTCL is mycosis fungoides (MF), accounting for ~60% of primary CTCL; Sézary Syndrome (SS), an erythrodermic and leukemic CTCL variant, occurs less frequently (~5% of primary CTCL)

CTCL is responsive to current treatment modalities even in advanced stage disease. However the duration of response (DOR) is generally relatively short and declines as the severity of the disease increases. None of the existing therapies applied in patients with CTCL are curative. Therefore, the key therapeutic challenge that remains is to make remissions more durable, thus halting disease progression, improving quality of life and prolonging progression free (PFS) and overall survival (OS). However, only few formal studies of maintenance therapy have been conducted in MF/SS and there is little evidence currently available to guide practice. There remains a high unmet

medical need to develop new agents to maintain long-term remissions and stabilisation of disease without overlapping toxicity with currently available treatment modalities, particularly in patients with advanced stage CTCL.

Histone deacetylases (HDACs) are enzymes that catalyse the removal of acetyl groups from histones, which results in changes of chromatin structures and gene transcription activity. In addition, HDACs can also regulate gene expression in an indirect fashion. HDACs are known to play a central role in the regulation of several cellular properties linked with the development and progression of cancer. Indeed, inhibition of HDACs is associated with anti proliferative and anti tumour activity.

Resminostat inhibits the enzymatic activity of various Class I, IIb and IV HDAC enzymes, including pronounced inhibition of HDAC6. Inhibition of HDACs enzymatic activity by resminostat leads to changes in acetylation status of histone and non-histone proteins, resulting in transcriptional activation as well as repression of genes mediating pleiotropic effects such as pathway modulation, cell growth arrest, differentiation and apoptosis.

Study objective

Primary Objective
The primary objective is to determine if maintenance treatment with resminostat increases progression free survival (PFS) compared to placebo in patients with advanced stage (Stage IIB IVB) MF or SS that have achieved disease control (complete response [CR], partial response [PR] or stable disease [SD]) with previous systemic therapy.

Secondary Objectives
Key Secondary Objective
• To determine if maintenance treatment with resminostat increases time to symptom (pruritus) worsening (TTSW) compared to placebo.

Secondary Objectives
• Compare time to progression (TTP) in patients when treated with resminostat vs placebo
• Compare time to next treatment (TTNT) in patients when treated with resminostat vs placebo
• Assess the effect of maintenance treatment with resminostat by means of PFS of subsequent treatments (PFS2, PFS3)
• Compare overall response rate (ORR, including CR, PR) in patients when treated with resminostat vs placebo
• Assess the ORR (including CR, PR) in patients who opted for rollover to resminostat
• Compare duration of response (DOR) in patients when treated with resminostat vs placebo
• Compare overall survival (OS) in patients when treated with resminostat vs

placebo
• Assess the safety and tolerability of resminostat
• Compare changes in health related quality of life (HrQoL) parameters in patients when treated with resminostat vs placebo
• Assess the pharmacokinetics (PK) of resminostat and metabolites.

Exploratory Objectives
• Analysis of protein- and ribonucleic acid- (RNA) biomarkers in peripheral blood and skin lesion biopsies
o Immuno-histochemistry (IHC)- based expression analysis of mode of action (MoA) related target proteins (e.g., histone deacetylase [HDAC] isoforms and RAD23B) as biomarkers of response to treatment
o changes in expression of circulating cytokines and chemokines related to immune oncology and cutaneous T-cell lymphoma (CTCL) disease (e.g., interleukin [IL] 22, IL 31, CCL17, vascular endothelial growth factor [VEGF]) in serum
o changes in expression of genes (e.g., related to HDAC-inhibition, immune oncology, and CTCL disease) in peripheral blood cells and skin lesion biopsies
• Evaluation of efficacy of blinding
• Changes in requirement of anti itching treatment.
• Change of VAS itching score (e.g., as area under the curve [AUC] per time period between treatment Arms)

Study design

This is a multicentre, double blind, randomised, placebo-controlled, prospective, efficacy trial. Patients will be randomised in a 1:1 ratio to oral treatment with resminostat or matching placebo. Patients will administer trial treatment on Days 1 - 5 of each cycle until disease progression or unacceptable toxicity. All Cycles are 14 days.

Patients who discontinued treatment for any reason other than progression will remain blinded and, after an End of Study (EOS) Visit, move to Survival FU. Patients who discontinue treatment due to progression will be unblinded and appropriate treatment or follow-up (FU) will be determined. Unblinded patients found to have been treated in Arm A (resminostat) will undergo the EOS Visit, then move to Survival FU. Unblinded patients found to have been treated in Arm B (placebo) will have the option of rolling over to resminostat treatment or may undergo EOS assessments and move to Survival FU.

Patients who rollover to resminostat will continue treatment per trial schedule (600 mg orally once a day on Days 1 - 5 of 14 day treatment cycles) and undergo safety and efficacy assessments according to the trial schedule, starting with Day 1, Cycle 1. Treatment of rollover patients may continue as long as they derive benefit from the treatment in the opinion of the investigator or until unacceptable toxicity. At that time, rollover patients will again undergo EOT assessments, EOS assessments and move to Survival FU.

It is planned that 150 patients will be enrolled, for a total of 75 patients in each treatment Arm.

Intervention

Resminostat (4SC 201) 600mg (3x200 mg film coated tablet) or matching placebo tablet.

Study burden and risks

Non-clinical and clinical data collected on the HDACi resminostat indicate a positive benefit-risk ratio for use of resminostat in patients with advanced cancers or haematological malignancies. Resminostat has the potential to address an unmet medical need in patients with advanced stage MF/SS to maintain long term remissions and improve quality of life at an acceptable safety profile and without compromising the immune function needed to limit life threatening infectious complications in CTCL.

Please refer to section 10.2.1 of the study protocol for a detailed assessment.

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.Patients with histologically confirmed MF (Stage IIB-IVB) or SS in an ongoing CR, PR or SD after at least one prior systemic therapy according to local standards (including but not limited to α-interferon, bexarotene, extracorporeal photopheresis, chemotherapy) or total skin electron beam irradiation
- the most recent systemic therapy must have been completed as planned or stopped due to unacceptable toxicity 2-12 weeks prior to randomisation, i.e. patients should not be
withdrawn from a treatment from which they derive benefit
2.Male or female >= 18 years
3.Written informed consent obtained prior to any trial specific procedure
4.Eastern Cooperative Oncology Group (ECOG) status score 0-2
5.Adequate haematological, hepatic and renal function, as demonstrated by:
a)haemoglobin >= 9.0 g/dl (International System [SI] of Units: 5.6 mmol/L)
b)absolute neutrophil count >= 1,000/mm3
c)platelets >= 75 × 109/L
d)alanine aminotransferase and aspartate amino-transferase <= 2 times upper limit of normal
e)total bilirubin <= 2 mg/dL (SI units: 34.2 µmol/L) (unless known Gilbert syndrome)
f)serum creatinine <= 1.5 mg/dL (SI units: 132 µmol/L)
g)prothrombin time International Normalised Ratio <= 2.3
6.Women of childbearing potential (not post-menopausal for 1 year and not surgically sterile) and males with partners of childbearing potential must be sexually abstinent (i.e. refraining
from heterosexual intercourse) or must use a highly effectivecontraception (at least one of the following: combined (oral, intravaginal or transdermal) or progestegen-only
(oral, injectable or implantable) hormonal contraceptives, intrauterine device,intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomy of the partner from the time of screening to 30 days (female patients) or 3 months (male patients) after the last dose of trial treatment
7.Adequate recovery from precedent non-haematological toxicities, excluding alopecia, to <= National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1
8.Able to comply with all the requirements of the protocol

Exclusion criteria

1.Patients with PD
2.Known central nervous system involvement
3.History and current cardiovascular complications, including unstable angina pectoris, uncontrolled hypertension, congestive heart failure (New York Heart Association [NYHA] Class III or IV) related to primary cardiac disease, a condition requiring anti arrhythmic therapy, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to randomisation
4.Baseline corrected QT (QTc) interval > 500 milliseconds [NOTE: QTcF is relevant]
5.History of additional risk factors for Torsade de Pointes (e.g., heart failure, hypokalaemia, family history of Long QT Syndrome)
6.Use of concomitant medications that are known to prolong the QT/QTc interval
7.Concurrent use of any other specific anti tumour therapy including psoralen photo chemotherapy (PUVA), chemotherapy, immunotherapy, hormonal therapy, radiation therapy, or experimental medications
8.Previous or concurrent cancer that is distinct in primary site or histology from CTCL, except curatively treated squamous-cell carcinoma of the skin stage 0-1 and curatively treated malignant melanoma stage 0-1A with a low risk of recurrence/metastasis as per assessment of the investigator, cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis and T1); any cancer curatively treated > 3 years prior to randomisation will be allowed
9.Current evidence of any uncontrolled clinically significant internal, psychiatric or neurologic disease
10.Altered mental status precluding understanding of the informed consent process and/or completion of the necessary trial procedures
11.Pregnant or breast feeding women
12.History of allergic reactions attributed to compounds of similar chemical or biological composition to the trial drugs
13.Active alcohol and/or drug abuse
14.Any other acute or chronic condition that, in the investigator*s opinion, would limit the patient*s ability to complete or participate in this trial

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2017
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Resminostat
Generic name:	-

Ethics review

Approved WMO Date:	20-07-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-11-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	05-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	31-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	26-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2016-000807-99-NL
CCMO	NL57945.058.16