A Phase 2 Open-Label, Multicenter Clinical Study of the Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Profiles of CGT9486 as a Single Agent in Patients With Advanced Systemic Mastocytosis

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This study has been transitioned to CTIS with ID 2024-511407-42-00 check the CTIS register for the current data. Part 1: dose optimizationTo identify a clinically active and tolerable systemic exposure range of bezuclastinib in subjects with...

Ethical review	Approved WMO
Status	Pending
Health condition type	White blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON53808

Source
ToetsingOnline

Brief title
A Study of CGT9486 in Patients With Advanced Systemic Mastocytosis

Condition

- White blood cell disorders

Synonym
Advanced Mastocytosis, mast cell accumulation, myeloid neoplasm

Research involving

Human

Sponsors and support

Primary sponsor: Cogent Biosciences, Inc.
Source(s) of monetary or material Support: Cogent Biosciences;Inc.

Intervention

Keyword: efficacy, mast cells, mastocytosis, safety

Outcome measures

Primary outcome

Part 1

Safety assessments and dose modifications

Pharmacokinetics (PK) and pharmacodynamic assessments

Overall Response Rate (ORR)

Part 2 Stage 1

• Safety assessments and dose modifications

• PK and pharmacodynamic assessments

• Overall Response Rate (ORR)

Part 2 Stage 2

ORR

Secondary outcome

Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from

baseline in laboratory results

Duration of response (DOR), defined as the date of the first documented response (CR, CRh, PR, or CI) to date of first documented and confirmed disease progression or death from any cause, whichever occurs first, based on modified IWG-MRT-ECNM response criteria

Time to response (TTR), defined as the date of first dose of study drug to the date of the first documented response (CR, CRh, PR, or CI) based on modified IWG-MRT-ECNM response criteria

Progression-free survival (PFS), defined as the date of first dose of study drug to the date of first documented confirmed disease progression or death from any cause, whichever occurs first

Overall survival (OS), defined as the date of first dose of study drug to the date of death from any cause

Pure Pathologic Response (PPR), including complete remission, complete remission with partial recovery of peripheral blood, and partial remission (Gotlib et al, 2020)

Changes in spleen and liver size assessed by magnetic resonance imaging (MRI)

Changes in the levels of serum tryptase

Changes in the levels of KIT D816V mutation allele burden in blood and bone marrow

Change in pathologic findings in the blood and bone marrow including mast cell infiltration, monocytosis, and eosinophilia

Plasma concentrations of bezuclastinib

Patient Global Impression of Change (PGIC) scale and change and percent change from baseline in the following patient-reported outcome measures: Patient Global Impression of Severity (PGIS) scale, Mastocytosis Quality of Life Questionnaire (MC-QoL), and Mastocytosis Activity Score (MAS) where appropriate translations are available (Siebenhaar et al, 2018; Siebenhaar et al, 2016)

Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results

PPR, including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission

Study description

Background summary

Systemic mastocytosis (SM) encompasses a variety of mast cell disorders characterized by accumulation and expansion of abnormal neoplastic mast cells

in various organs including the bone marrow, gastrointestinal tract, skin, liver, and spleen (Shomali and Gotlib, 2018). Mast cells play a role in immunoglobulin E-mediated immune responses, inflammation, and immune responses to infection. Accumulation of abnormal mast cells can lead to hematologic and non-hematologic organ damage. SM is characterized by mast cell infiltration of 1 or more extracutaneous organs with or without skin involvement (Shomali and Gotlib, 2018) and encompasses a spectrum of diagnoses that can range from a nonadvanced course to a more advanced course. AdvSM is an aggressive and life-threatening form of the disease. The molecular pathogenesis of SM is driven by activation of the KIT receptor. In 95% of cases, a KIT D816V mutation in exon 17 can be identified (Garcia-Montero et al, 2006; Jara-Acevedo et al, 2015; Vaes et al, 2017).

CGT9486 is an inhibitor of KIT exon mutations with potent activity against KIT exon 17 and 18 activation loop mutations. CGT9486 has been evaluated in a completed Phase 1/2 study in patients with GIST as a monotherapy and in combination with sunitinib. In addition, CGT9486 is being investigated in an ongoing phase 3 study in GIST, and ongoing Phase 2 studies in AdvSM (EHA 2022) and NonAdvSM. The results of this study are to be used to investigate CGT9486 for the treatment of AdvSM.

Study objective

This study has been transitioned to CTIS with ID 2024-511407-42-00 check the CTIS register for the current data.

Part 1: dose optimization
To identify a clinically active and tolerable systemic exposure range of bezuclastinib in subjects with AdvSM

Part 2 Stage 1: Dose Confirmation
To confirm the optimal dose of bezuclastinib in subjects with AdvSM

Part 2 Stage 2: Expansion
To determine the efficacy of bezuclastinib at the selected optimal dose in patients with AdvSM

Secondary (part 1 and part 2):
To characterize the safety and tolerability of bezuclastinib in patients with AdvSM
To evaluate additional efficacy parameters with bezuclastinib inpatients with AdvSM
To determine the effects of bezuclastinib on serum tryptase
To determine the effects of bezuclastinib on KIT D816V mutation allele burden
To evaluate histopathologic response in the blood and bone marrow
To assess the PK of bezuclastinib in patients with AdvSM
To assess patient-reported outcomes in patients with AdvSM

To explore the effect of bezuclastinib in subjects with AdvSM who are nonevaluable based on the modified IWG-MRT-ECNM response criteria.

Study design

This is a 2-part study of the KIT inhibitor CGT9486 in patients with AdvSM. Part 1 will consist of a dose optimization period to determine the optimal dose for patients with AdvSM. Approximately 28 subjects will be randomized to 1 of 4 dose cohorts of bezuclastinib. Part 2 will be conducted with a 2-stage design: Stage 1 will confirm the optimal dose of bezuclastinib, and Stage 2 will consist of an expansion period. Stage 1 will enroll approximately 20 subjects and Stage 2 will enroll approximately 75 subjects. Each 28-day period is 1 cycle.

Subjects will receive bezuclastinib at their assigned dose until confirmed disease progression, intolerable toxicity, Investigator decision, withdrawal of consent, or other protocol-specified reason for discontinuation of study drug.

Patient eligibility will be reviewed, and enrollment approved by an Eligibility Committee (EC) during the Screening Period. In addition, disease response will be adjudicated by the CRRC.

Intervention

In Part 1 of the study, approximately 28 subjects will be randomized to 1 of 4 dose cohorts of bezuclastinib Formulation A. Subjects will be randomized in a 1:1:1:1 manner.

Part 2 will be conducted with a 2-stage design: Stage 1 will confirm the optimal dose of bezuclastinib Formulation B, and Stage 2 will consist of an expansion period.

Study burden and risks

The potential benefits of the drug outweigh the expected risks. For the risk/benefit assessment, please refer to the Clinical Trial Protocol (Section 1.4) and Investigator's Brochure.

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. Diagnosed with 1 of the following advanced mastocytosis diagnoses by Eligibility Committee
a. Aggressive Systemic Mastocytosis (ASM)
b. Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)
c. Mast Cell Leukemia (MCL)

2. Measurable disease according to modified IWG-MRT-ECNM criteria. (A subset of patients inevaluble per mIWG-MRT-ECNM will be included in the study).

3. ECOG (0 to 3)

4. Have clinically acceptable local laboratory screening results (clinical chemistry, hematology) within certain limits.

Exclusion criteria

1. Persistent toxicity from previous therapy for Advanced Systemic Mastocytosis that has not resolved to <= Grade 1

2. Associated hematologic neoplasm requiring immediate antineoplastic therapy
3. Clinically significant cardiac disease
4. Known positivity for the FIP1L1 PDGFRA fusion (Patients with eosinophilia without detectable KIT D816V mutation must also lack the PDGFRA fusion mutation prior to enrollment)
5. Seropositive for human immunodeficiency virus (HIV) 1 or 2, or positive for hepatitis B surface antigen or hepatitis C virus (HCV) antibody
6. History of clinically significant bleeding event within 30 days before the first dose of study drug or need for therapeutic anticoagulation on study
7. Diagnosed with or treated for malignancy other than the disease under study within the prior 3 years before enrollment
8. Received any cytoreductive therapy or any investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon, and any antibody therapy less than 28 days, before screening bone marrow biopsy
9. Received hematopoietic growth factor support within 14 days before the first dose of study drug
10. Received strong CYP3A4 inhibitors or inducers before the first dose of study drug
11. Need for treatment with steroids

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2023
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	Bezuclastinib

Ethics review

Approved WMO Date:	30-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-03-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	22-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2024
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
EU-CTR	CTIS2024-511407-42-00
EudraCT	EUCTR2021-001010-10-NL
ClinicalTrials.gov	NCT04996875
CCMO	NL80629.056.22