A Phase 2/3 Study to Evaluate the Efficacy and Safety of Unesbulin in Unresectable or Metastatic, Relapsed or Refractory Leiomyosarcoma

Published: 11-08-2022
Last updated: 06-04-2024

Primary:• Progression-free survival (PFS) of unesbulin plus dacarbazine (DTIC) versus placebo plus DTICSecondary:Efficacy:• Overall survival (OS) of subjects treated with unesbulin plus DTIC versus placebo plus DTIC• Antitumor activity of unesbulin...

Ethical review	Approved WMO
Status	Pending
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53907

Source
ToetsingOnline

Brief title
PTC596-ONC-008-LMS

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Leiomyosarcoma, malignant smooth muscle tumor

Research involving
Human

Sponsors and support

Primary sponsor: PTC Therapeutics, Inc.

Source(s) of monetary or material Support: PTC therapeutics

Intervention

Keyword: Dacarbazine, Leiomyosarcoma, Sarcoma, Unesbulin

Outcome measures

Primary outcome

Endpoints:

Primary:

• PFS per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 assessed by an independent central imaging laboratory

Secondary outcome

Secondary:

Efficacy:

• The key secondary endpoint is OS

Other secondary efficacy endpoints:

• Objective response rate (ORR; proportion of subjects with best overall response [BOR] of either complete response [CR] or partial response [PR])

• Disease control rate (DCR) or clinical benefit rate (CBR), defined as the proportion of subjects with BOR of CR, PR, or at least 3 months of stable disease (SD)

• Duration of response (DoR)

Safety:

• Vital signs, physical examination, electrocardiograms (ECG), laboratory abnormalities, Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores, and adverse events (AEs)

Exploratory:

Efficacy:

• PFS, OS, ORR, DCR, and DoR in subjects with at least 4 prior lines of

treatment

PK:

• PK parameters of unesbulin in subjects who receive unesbulin plus DTIC: Cmax,

Tmax, and area under the concentration versus time curve from time zero to the

last sampled time or the last non-zero concentration (AUC0-t)

• PK parameters of DTIC and its inactive metabolite AIC in subjects who receive

unesbulin plus DTIC and placebo plus DTIC: Cmax, Tmax, and AUC0-t

PROs:

• 30-item score European Organisation for the Research and Treatment of Cancer

Quality of Life Questionnaire (EORTC QLQ-C30)

• EuroQol 5-level EQ-5D version (EQ-5D-5L)

Biomarkers:

• Genetic evaluation of the tumors by analyzing circulating cell-free tumor DNA

(ccfDNA)

Study description

Background summary

Leiomyosarcoma is a rare type of cancer arising from the soft tissue of the body. It spreads through the bloodstream and can affect many body parts including: the lungs, liver, blood vessels, or any other soft tissues in the body. Leiomyosarcoma is most often found in the abdomen or uterus. Sometimes, leiomyosarcoma can be removed by surgery. However, when leiomyosarcoma has spread to multiple parts of the body or is in a location where surgery is not

possible, patients are treated with chemotherapy medicines or other kinds of medications intended to shrink or stabilize the disease.

Study objective

Primary:
• Progression-free survival (PFS) of unesbulin plus dacarbazine (DTIC) versus placebo plus DTIC

Secondary:
Efficacy:
• Overall survival (OS) of subjects treated with unesbulin plus DTIC versus placebo plus DTIC
• Antitumor activity of unesbulin plus DTIC versus placebo plus DTIC
Safety:
• Safety and tolerability of unesbulin plus DTIC versus placebo plus DTIC

Exploratory:
Efficacy:
• Evaluate the antitumor activity of unesbulin plus DTIC versus placebo plus DTIC in subjects with at least 4 prior lines of treatment
Pharmacokinetics (PK):
• Evaluate the PK of unesbulin in the presence of DTIC in subjects with leiomyosarcoma (LMS)
• Evaluate the PK of DTIC/5 amino imidazole-4-carboxamide (AIC) alone and in the presence of unesbulin in subjects with LMS
Patient-reported outcomes (PROs):
• Compare the effect of unesbulin plus DTIC versus placebo plus DTIC on PROs, including health-related quality-of-life (HRQoL) assessments
Biomarkers:
• Measure genotype of subject tumors, assessed by blood sampling, at baseline and posttreatment

Study design

This is an international, multicenter, randomized, double-blind, placebo-controlled, Phase 2/3 study to compare the safety and efficacy of unesbulin plus DTIC versus placebo plus DTIC in subjects with unresectable or metastatic, relapsed or refractory LMS who have received at least 1 prior line of systemic therapy. Eligible subjects will be randomized 2:1 (unesbulin plus DTIC: placebo plus DTIC) to one of the following treatment groups:
• Unesbulin plus DTIC: Unesbulin 300 mg will be administered PO twice weekly (BIW) in each 3-week treatment cycle. DTIC 1000 mg/m2 will be administered IV once every 21 days (Q21D).
• Placebo plus DTIC: Matching placebo will be administered PO BIW in each

3-week treatment cycle. DTIC 1000 mg/m2 will be administered IV Q21D.
Randomization: Approximately 345 (300 subjects with 1 to 3 prior lines of systemic therapy for the primary analysis and 45 subjects with at least 4 prior lines of systemic therapy for the exploratory analysis)
Stratification: For approximately 300 subjects with 1 to 3 prior lines of treatment, randomization will be stratified as follows:
• Number of prior systemic therapies (1 or >1)
• ECOG PS score (0 or 1)
• Histological tumor type (uterine versus nonuterine LMS)
Forty-five subjects with at least 4 prior lines of treatment will be randomized and stratified as follows:
• ECOG PS score (0 or 1)
• Histological tumor type (uterine versus nonuterine LMS)
One treatment cycle will constitute 21 days. DTIC will be administered on Day 1 of each 3 week treatment cycle. Unesbulin/placebo tablets will be administered on Days 2 and 5 of Week 1 and Days 1 and 4 of Weeks 2 and 3 of each 3-week treatment cycle (Note: the preferable duration between 2 doses of unesbulin/placebo is approximately 72 hours). Approximately 12 randomized subjects will be assessed for PK of unesbulin, DTIC, and AIC (an inactive metabolite of DTIC). For Cycles 1 and 3, rich PK sampling will occur on Day 1 for DTIC and AIC, and on Day 2 for unesbulin. The target is for approximately 7 PK evaluable subjects in the unesbulin group to complete Cycle 3. For Cycles 2 and 4, sparse PK sampling will occur on Day 1 for DTIC and AIC.
All subjects will receive treatment until evidence of disease progression, unacceptable toxicity, or other withdrawal criteria are met. No crossover will be permitted.
An independent Data Monitoring Committee (DMC) has been established and will review safety data as per DMC charter. In addition, one interim efficacy analysis will be performed (by an external vendor) and reviewed by the DMC. Based on the results of the interim analysis, the DMC will make recommendations to either continue or stop the study. The DMC Charter (a separate document) and the DMC Statistical Analysis Plan (SAP) will provide detailed guidance for the conduct of these interim analyses.
Dose modifications/stopping criteria: If treatment-related toxicities are observed, a stepped reduction in the dose of DTIC is permitted beginning with the starting dose of 1000 mg/m2 to 850 mg/m2, followed by 700 mg/m2, 600 mg/m2, and 500 mg/m2. The following guidelines should be observed:
• If a subject requires a dose reduction of DTIC to less than 500 mg/m2, then DTIC should be discontinued.
• Subjects should receive all necessary supportive care including blood products, platelet transfusions, antiemetics, and antibiotics while being treated on this study.
• The use of granulocyte colony-stimulating factor (eg, pegfilgrastim) and erythropoietin or thrombopoietin-stimulating agents is permitted per institutional practice.
No dose reduction of unesbulin/placebo is permitted. Guidelines for unesbulin/placebo dosing when treatment-related toxicities continue beyond the

stepwise reduction of DTIC is detailed in the protocol.

Intervention

Investigational product, dosage, and mode of administration:
Unesbulin tablets for oral administration will be provided in strengths of 50 and 200 mg. Subjects will be treated with unesbulin 300 mg PO BIW in combination with DTIC administered IV Q21D. One treatment cycle will constitute 21 days. Unesbulin is to be administered on Days 2 and 5 of Week 1 and on Days 1 and 4 of Weeks 2 and 3.
Matching placebo tablets will be provided and should be administered on the same schedule as unesbulin.
Based on the results from a food effect assessment in the ongoing Phase 1b Study PTC596-ONC-007-LMS, it is recommended that unesbulin/placebo will be taken with food.

Duration of treatment:
Treatment will continue for each subject until evidence of disease progression, unacceptable toxicity, or any of the following reasons: withdrawal of consent by subject, pregnancy, significant noncompliance, withdrawal by investigator, or study discontinuation by the sponsor or regulatory authority

Reference therapy, dosage, and mode of administration:
DTIC for injection at 200 mg/vial will be provided (by the site or by the sponsor) and will be reconstituted with 19.7 mL of Sterile Water for Injection, USP. The resulting solution contains 10 mg/mL of DTIC having a pH of 3.0 to 4.0. The reconstitution step may be modified based on institutional policy and/or the availability of a specific strength of DTIC vial to obtain a resulting DTIC solution of 10 mg/ml. The calculated dose of the resulting solution is drawn into a syringe. The reconstituted solution is further diluted with 5% Dextrose Injection, USP or 0.9% Sodium Chloride injection and administered as an IV infusion over 1 hour ±30 minutes. Within 30 minutes before DTIC administration, the following premedication regimen is recommended: fosaprepitant 150 mg IV once, dexamethasone 20 mg PO once, and ondansetron 16 mg PO once. The premedication regimen as per institutional practice is allowed.
Placebo tablets will be supplied and administered in a blinded manner to subjects BIW in combination with DTIC per the same dosing schedule as for unesbulin

Study burden and risks

Taking part in the study can have pros and cons.
Taking part in the study may or may not provide direct medical benefit to the patient, that is not certain. An earlier study in leiomyosarcoma is ongoing and preliminary data suggest the drug may be beneficial to the patient and that the

drug is tolerable. It is hoped that this study might provide additional evidence that unesbulin helps patients with advanced leiosarcoma. In addition, it is hoped that the information learned from this study will benefit other patients with this disease in the future.
The patient's leiomyosarcoma may come back or get worse at any time during this study.

Taking part in the study can have these cons:
- the patient may experience the side effects or adverse effects of unesbulin or dacarbazin, as described in Section 6.
- Taking part in the study will cost the patient extra time.
- the patient has to comply with the study agreements.
- There may be some discomfort from the measurements during the study. For example: taking a blood sample can be a little painful. Or the patient could get a bruise as a result. Sometimes, people feel uncomfortable at the time of the blood draw. There is a small potential risk for a hematoma, a small collection of blood outside the blood vessel. This swelling generally spontaneously resolves over a few days. Occasionally people feel lightheaded or faint. There is also a small risk of infection whenever blood is drawn.

Contacts

Public
PTC Therapeutics, Inc.

Corporate Court 100
South Plainfield NJ07080
US
Scientific
PTC Therapeutics, Inc.

Corporate Court 100
South Plainfield NJ07080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is willing and able to provide informed consent 2. Willingness and ability to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions 3. Disease status including: a. Histological or cytological confirmation of LMS arising at any anatomic site except bone sarcoma b. Unresectable or metastatic, relapsed or refractory disease c. Measurable disease per RECIST 1.1 criteria d. Disease progression on previous treatment before screening or intolerability to other oncology treatments Demographics: 4. Age >=18 years 5. Male or female Performance status: 6. ECOG PS score of 0 or 1 Hematopoietic: 7. Absolute neutrophil count >=1500/mm3 without the use of growth factors in the past 7 days 8. Platelet count >=100000/mm3 without platelet transfusion in the past 14 days 9. Hemoglobin >=9 g/dL (packed red blood cell transfusion is not allowed within 7 days) Hepatic: 10. Bilirubin <= upper limit of normal (ULN) except for those patients with Gilbert's syndrome 11. Aspartate aminotransferase or alanine aminotransferase <3 times the ULN 12. Subjects with liver metastases may be enrolled Pulmonary: 13. Subjects with well-controlled asthma (eg, use of rescue medications <2 times per week over the last 12 months) or chronic obstructive pulmonary disease (eg, no exacerbations over the prior 3 months) may be enrolled. Renal: 14. Creatinine <1.5 times normal OR creatinine clearance >= 60 mL/min Prior therapeutics: 15. Toxicity from prior therapies recovered to Grade <=1 or subject*s baseline, except for alopecia. In addition, endocrinopathies associated with prior immunotherapy-based treatments that are well controlled on replacement medication are not exclusionary. Chemotherapy and targeted therapy: 16. At least 1 prior systemic cytotoxic or targeted therapy regimen for LMS, which may include but is not limited to single-agent doxorubicin or other anthracycline, doxorubicin plus ifosfamide, trabectin, pazopanib, or gemcitabine with or without docetaxel Surgery: 17. At least 4 weeks since prior surgery and recovered in the opinion of investigator Other: 18. Capable of swallowing oral medication 19. Women of childbearing potential (WOCBP; as defined by the Clinical Trials Facilitation and Coordination Group [CTFG]) must have a negative serum pregnancy test at screening and agree to abstinence or the use at least one of the following highly effective forms of contraception (with a failure rate of <1% per year when used consistently and correctly) (Clinical Trials Facilitation and Coordination Group 2020). Contraception or abstinence must be continued for the duration of the study and for at least 6 months after the last dose of study drug: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition

of ovulation: - Oral - Intravaginal - Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: - Oral - Injectable - Implantable • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomized partner with confirmed azoospermia All females will be considered of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been sterilized surgically (eg, bilateral salpingectomy, hysterectomy, bilateral oophorectomy). 20. Lactating females are not eligible unless they have agreed not to breastfeed their infants during treatment and for a period of 1 month following completion of treatment. 21. Males who are sexually active with WOCBP who have not had a vasectomy must agree to use a barrier method of birth control from the start of study drug administration through at least 6 months after the last dose of study drug. Males should not donate sperm from the start of study treatment through at least 6 months (1 sperm cycle, as defined by CTFG (Clinical Trials Facilitation and Coordination Group 2020) after the last dose of study drug).

Exclusion criteria

1. Received temozolomide or DTIC at any time 2. Any other systemic anticancer therapy including investigational agents <=3 weeks before initiation of study treatment. Additionally, subjects may not have received radiation <=3 weeks before initiation of study treatment. 3. Known intolerance to DTIC or one or more of the excipients in unesbulin. 4. Co-existing active infection or any co-existing medical condition likely to interfere with study procedures, including: a. Significant cardiovascular disease (New York Heart Association Class III or IV cardiac disease), myocardial infarction within the past 6 months, unstable angina, congestive heart failure requiring therapy, unstable arrhythmia or a need for antiarrhythmic therapy, or evidence of ischemia on ECG, marked baseline prolongation of QT/QTc (corrected QT) interval, eg, repeated demonstration of a QTc interval >500 msec (Long QT Syndrome [congenital]) 5. Human immunodeficiency virus, hepatitis B virus, or hepatitis C virus positivity 6. History of solid organ transplantation Therapeutics: 7. Known or suspected allergy or immediate or delayed hypersensitivity to unesbulin or DTIC, their excipients, or any agent given in this study Gastrointestinal: 8. Bowel obstruction, malabsorption, or other contraindication to oral medication 9. Gastrointestinal disease or other conditions that could affect absorption. Active peptic ulcer disease, active gastritis or previous history of gastric perforation within the last 2 years 10. Inflammatory bowel disease (including ulcerative colitis and Crohn*s disease), diverticulitis, cholecystitis, symptomatic cholangitis, or appendicitis Wounds/surgery: 11. Serious non-healing wound, ulcer, or bone fractures 12. Major surgery, open biopsy, or significant traumatic injury that has not recovered, in the opinion of the investigator, within 28 days of

baseline 13. Mucosal or internal bleeding Concomitant medications: 14. Concomitant strong CYP1A2 inhibitors (such as fluoroquinolones [broad spectrum quinolone antibiotics, including enoxacin and ciprofloxacin] and selective serotonin reuptake inhibitor [SSRI] agents fluvoxamine and fluoxetine) should be avoided on the same day that DTIC or unesbulin/placebo is administered. CYP1A2 inhibitors may inhibit the conversion of DTIC to its active metabolite and may increase the exposure of unesbulin. 15. Concomitant use of moderate CYP1A2 inducers (such as phenytoin, rifampin, ritonavir, teriflunomide, and barbiturates). Chronic use of marijuna should be avoided, but irregular use may be permitted at the discretion of the treating investigator. CYP1A2 inducers may increase the conversion of DTIC to its active metabolites. 16. Coadministration of acid-reducing agents should be avoided approximately 4 hours before and after unesbulin/placebo administration. 17. Immunization with a live vaccine within 30 days before starting study drug due to the risk of serious and life-threatening infections Other: 18. Prior malignancies, other than LMS, that required treatment or have shown evidence of recurrence (except for non-melanoma skin cancer, adequately treated cervical carcinoma in situ, prostate cancer in situ or any other low risk malignancy that is approved by the medical monitor) during the 5 years before initiation. Cancer treated with curative intent more than 5 years previously and without evidence of recurrence is not an exclusion. 19. Known coagulopathy or bleeding diathesis. Subjects on anticoagulation should be monitored closely and International Normalized Ratio and/or activated partial thromboplastin time (APTT)/prothrombin time (TP) should be within the required range where applicable. 20. Prior or ongoing clinically significant illness, medical or psychiatric condition, medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator*s opinion, could affect the safety of the subject, or alter the absorption, distribution, metabolism, or excretion of the study drugs, or could impair the assessment of study results. 21. History of brain metastases or leptomeningeal disease at any time in subject*s history, including treated central nervous system (CNS) disease

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2022
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dacarbazine (DTIC)
Generic name:	Tri dacarbazine citrat
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Unesbulin (PTC596)

Ethics review

Approved WMO

Date:	11-08-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	24-02-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	23-06-2023
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2022-000073-12-NL
ClinicalTrials.gov	NCT05269355
CCMO	NL81115.058.22