A Phase II Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of VS 6063 in Subjects with Malignant Pleural Mesothelioma

Published: 27-06-2013
Last updated: 24-04-2024

Primary Efficacy Objectives• To compare the overall survival (OS) in subjects with malignant pleural mesothelioma receiving VS-6063 or placebo.• To compare the progression free survival (PFS) in subjects with malignant pleural mesothelioma receiving...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mesotheliomas
Study type	Interventional

Summary

ID

NL-OMON40190

Source
ToetsingOnline

Brief title
VS-6063 Phase II Mesothelioma study

Condition

- Mesotheliomas
- Pleural disorders

Synonym
cancer of the lungpleura, pleural mesothelioma

Research involving
Human

Sponsors and support

Primary sponsor: Verastem
Source(s) of monetary or material Support: industry: Verastem

Intervention

Keyword: focal adhesion kinase, maintenance therapy, malignant pleural mesothelioma, VS-6063

Outcome measures

Primary outcome

Primary Efficacy Objectives

• To compare the overall survival (OS) in subjects with malignant pleural

mesothelioma receiving VS-6063 or placebo.

• To compare the progression free survival (PFS) in subjects with malignant

pleural mesothelioma receiving VS-6063 or placebo.

Secondary outcome

Secondary Efficacy Objective

• To assess Quality of Life (QoL) in subjects treated with VS-6063 or placebo

using the Lung Cancer Symptom Scale modified for mesothelioma (LCSS-Meso).

• To determine the objective response rate (ORR) in subjects receiving VS 6063

or placebo.

Exploratory Efficacy Objectives

• To determine the time to new lesion in subjects receiving VS-6063 or placebo.

• To evaluate the relationship of VS-6063 pharmacokinetics and outcome.

• To evaluate the population pharmacokinetics of VS-6063 in subjects with

malignant pleural mesothelioma.

Safety Objectives

• To evaluate the safety and tolerability of VS-6063 in subjects with malignant

pleural mesothelioma

Study description

Background summary

This is a phase II, randomized, double-blind, placebo-controlled, multicenter study of VS-6063 in subjects with malignant pleural mesothelioma who have not progressed (confirmed PR/SD) following at least 4 cycles of treatment with pemetrexed/cisplatin or pemetrexed/carboplatin. Approximately 40% of MPM patients have mutations in the NF-2 gene that lead to low Merlin protein (a tumor suppression protein) expression. In previous studies Merlinnegative subjects (subjects with mutations in the neurofibromatosis type 2 gene [NF2] leading to low Merlin expression) treated with FAK inhibitors had longer median PFS than did Merlin-positive (subjects with high Merlin protein expression).

In this study it is hypothesized that Merlin-low subjects may respond to VS-6063 (a FAK inhibitor) better than Merlin-high subjects. To account for possible differential response, this study will use an adaptive enrichment design, whereby enrollment may be restricted to subjects in the Merlin-low stratum after an interim analysis. Decisions regarding enrichment will be based on an interim analysis of PFS (a primary efficacy endpoint). In addition, a subsequent sample size re-estimation for the primary efficacy endpoint of OS will be performed.

Study objective

Primary Efficacy Objectives
• To compare the overall survival (OS) in subjects with malignant pleural mesothelioma receiving VS-6063 or placebo.
• To compare the progression free survival (PFS) in subjects with malignant pleural mesothelioma receiving VS-6063 or placebo.
Secondary Efficacy Objective
• To assess Quality of Life (QoL) in subjects treated with VS-6063 or placebo using the Lung Cancer Symptom Scale modified for mesothelioma (LCSS-Meso).
• To determine the objective response rate (ORR) in subjects receiving VS 6063 or placebo.
Exploratory Efficacy Objectives
• To determine the time to new lesion in subjects receiving VS-6063 or placebo.

• To evaluate the relationship of VS-6063 pharmacokinetics and outcome.
• To evaluate the population pharmacokinetics of VS-6063 in subjects with malignant pleural mesothelioma.
Safety Objectives
• To evaluate the safety and tolerability of VS-6063 in subjects with malignant pleural mesothelioma

Study design

This study is a Phase II, randomized, double-blind, placebocontrolled, multicenter study of VS-6063 in subjects with malignant pleural mesothelioma (MPM) who have not progressed (confirmed Response Evaluation Criteria in Solid Tumors [RECIST] status of PR [partial response] or SD [stable disease]) following >= 4 cycles of treatment with pemetrexed/cisplatin or pemetrexed/carboplatin.
Prior to entry and randomization to the study, tumor moesin-ezrinradixin-like protein (Merlin) status for each subject will be determined by immunohistochemistry performed at a central laboratory.
Subjects will be randomized in a 1:1 ratio to receive oral VS-6063 400 mg twice daily (BID) or matched placebo. Randomization will
be stratified by tumor Merlin status (high versus low).
Progression will be assessed both locally and by central review using RECIST Version 1.1. Subjects will continue to receive treatment until disease progression or other discontinuation criteria are met. Radiographic progression must be confirmed centrally before removal of subject from the study drug. Removal of subject for clinical progression will be at the discretion of the Investigator.
Response assessments will be performed every 6 weeks for the first 25 weeks. After 25 weeks of treatment, response assessments will be performed every 8 weeks. The same method of assessment should be used throughout the study.
Following documentation of non-fatal disease progression, all
subjects will be followed for survival by telephone contact every 2 months until death or the close of the study.

Intervention

Subjects will be randomized in a 1:1 ratio to receive oral VS-6063 400 mg twice daily (BID) or matched placebo. Randomization will be stratified by tumor Merlin status (high versus low).

Study burden and risks

It is expected that patients will be on the study for a minimum of 3.5 months :
28 day maximum screening period,
Approx.6 weeks of treatment followed by a 30 day follow up period. The answer on question E6 are based on this period.

From the start of the treatment onwards the patient will take one or two tablets BID. The patients keeps a dosing diary to write down the times the tablets were taken. the patient takes the study medication until disease progression is assessed with use of RECIST criteria.

The following assessments will be done.

For screening:
-informed consent, check in- and exclusion criteria, Merlin assessment, medical history, demographics, physical exam, Karnofsky score, ECG, vital signs, pregnancy test, clinical chemistry, hematology, coagulation parameters, urinalysis, quality of life assessment, disease assessment (CT scan), concomitant medications, adverse events.

At the start of the treatment:
-check in- and exclusion criteria, physical exam, Karnofsky score, ECG, vital signs, pregnancy test, clinical chemistry, hematology, coagulation parameters, urinalysis, quality of life assessment, review dosing diary, concomitant medications, adverse events.

Then every 3 weeks (week 4, 7, 10, 13, 16, 19, 22, 25):
physical exam, Karnofsky score, ECG, vital signs, clinical chemistry, hematology, coagulation parameters, urinalysis, quality of life assessment, review dosing diary, concomitant medications, adverse events.

Then every 4 weeks these same assessments will be repeated.

For the Pharmacokinetics the following blood samples are taken:
In week 4 before intake of the tablets and 1 and 4 hour after that
In week 7 before intake of the tablets and 2 and 6 hour after that
In week 10 before intake of the tablets
In week 13 before intake of the tablets

On day 1, 2 hours after intake of the tablets, an extra ECG will be made.

In week 1 and week 4 blood sampling will be done as well for biomarkers.

At screening and after that every 6 to 8 weeks a CT scan will be made during the hospital visit. This is used to assess the tumor size. If at end of treatment it has been longer than 28 days a CT scan was made, it will be repeated.

At the end of treatment:
physical exam, Karnofsky score, ECG, vital signs, pregnancy test, clinical chemistry, hemaotlogy, coagulation parameters, urinalysis, quality of life assessment, review dosing diary, concomitant medications, adverse events.

At 30 days follow-up:
physical exam, Karnofsky score, vital signs, quality of life assessment, concomitant medications, adverse events.

After this the patient will be called every 2 months until end of study or death of the patient.

Contacts

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Verastem

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Able to understand and give written informed consent and comply with study procedures.;2) Histologically proven diagnosis of MPM. All subjects must have biopsy material (archival tissue is acceptable) available for immunohistochemistry determination of Merlin status prior to enrollment.;3) Evaluable disease, or measurable disease as assessed by

RECIST version 1.1. ;4) Received only one prior chemotherapy regimen consisting of >= 4 cycles of pemetrexed/cisplatin or pemetrexed/carboplatin; subjects must have documentation of an ongoing response (confirmed PR or SD) following completion of this regimen. Subjects changing from cisplatin to carboplatin or vice versa within the same course of treatment because of platinum toxicity will be considered to have had first-line chemotherapy. Note: Subjects may have undergone previous surgical resection of their disease providing it was completed prior to initiation of chemotherapy. ;5) Received last dose of pemetrexed/cisplatin or pemetrexed/carboplatin therapy within <= 6 weeks of study entry. ;6) Have completed baseline quality of life evaluation as assessed by LCSS modified for mesothelioma ;7) Age >= 18 years.;8) Life expectancy >= 3 months.;9) All prior chemotherapy induced toxicities must have resolved to grade <= 1 prior to randomization. ;10) Performance status according to Karnofsky Performance Scale >= 70% (after palliative measures such as pleural drainage).;11) Corrected QT interval (QTc) < 470 ms (as calculated by the Fridericia correction formula).;12) Adequate bone marrow function (hemoglobin >= 9.0 g/dL; platelets >= 100 x 109/L; absolute neutrophil count >= 1.5 x 109/L) without the use of hematopoietic growth factors.;13) Adequate renal function (creatinine <=1.5 x ULN [upper limit of normal] and/or glomerular filtration rate of >= 50mL/min).;14) Adequate hepatic function (total bilirubin <=1.5 x ULN; aspartate transaminase and alanine transaminase <= 2.5x ULN).;15) Men and women of childbearing potential must agree to use adequate contraception (double barrier birth control) for the duration of study therapy and for 3 months after the last dose of VS 6063.

Exclusion criteria

Exclusion Criteria:
1) Currently enrolled in (or completed within 30 days before study drug administration) another investigational drug study.
2) Gastrointestinal (GI) condition that could interfere with the swallowing or absorption of study drug.
3) History of upper GI bleeding, ulceration, or perforation within 12 months prior to the first dose of study drug.
4) Known history of Gilbert*s Syndrome.
5) Known history of stroke or cerebrovascular accident within 6 months prior to the first dose of study drug.
6) Subjects with known infection with human immunodeficiency virus or Acquired Immune Deficiency Syndrome (AIDS) (testing not required).
7) Subjects with known infection with hepatitis A, B or C virus (testing not required).
8) Any evidence of serious active infections.
9) Major surgery within 28 days prior to the first dose of study drug.
10)Uncontrolled or severe concurrent medical condition (including uncontrolled brain metastases). Stable brain metastases either treated or being treated with a stable dose of steroids and/or anticonvulsants (no dose change within 28 days prior to the first dose of study drug), will be allowed.
11)Uncontrolled or severe cardiovascular disease, including myocardial infarct or unstable angina within 6 months prior to study treatment, New York Heart Association (NYHA) Class II

or greater congestive heart failure, serious arrhythmias requiring medication for treatment, clinically significant pericardial disease, or cardiac amyloidosis.
12)Known history of malignant hypertension.
13) Psychiatric illness or social situations that would limit compliance with study requirements.
14)History of another invasive malignancy in the last 5 years. Adequately treated non-invasive, non-melanoma skin cancers as well as in situ carcinoma of the cervix within the last 5 years
will be allowed.
15) Prior treatment with a focal adhesion kinase (FAK) inhibitor.
16)Women who are pregnant or breastfeeding.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2013
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	VS-6063
Generic name:	focal adhesion kinase

Ethics review

Approved WMO Date:	27-06-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-09-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-02-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	15-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2013-001033-40-NL
ClinicalTrials.gov	NCT01870609
CCMO	NL44213.031.13