A Randomized, Placebo-Controlled Crossover Study to Evaluate the Effect of Veliparib (ABT-888) on Cardiac Repolarization in Subjects with Relapsed or Refractory Solid Tumors

Published: 25-11-2013
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The objective of this study is to evaluate the effect of veliparib on QTcF.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON40461

Source
ToetsingOnline

Brief title
M12-020

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: Cardiac repolarization, Refractory solid tumors, Relapsed solid tumors, Veliparib

Outcome measures

Primary outcome

The primary objective of this study is to evaluate the effect of veliparib on

QTcF. Evaluation of this point will be done once 36 subjects have completed all

3 dosing periods.

Secondary outcome

Not applicable.

Study description

Background summary

Poly(ADP-ribose)-polymerase (PARP) 1 and 2 are nuclear enzymes that recognize DNA damage and facilitate DNA repair. Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP enzymes then poly(ADP-ribosyl)ate many nuclear target proteins, including those that facilitate DNA repair of both single-stranded or double-stranded DNA breaks. Thus PARP inhibition will result in less efficient DNA repair following a cytotoxic insult.

DNA damaging agents including cytotoxic chemotherapy and radiation therapy, remain a mainstay of treatment for many subjects with cancer. Veliparib is a potent oral PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutic agents, including alkylating agents, platinums, radiation, and topoisomerase inhibitors.

The effects of veliparib on cardiac repolarization were studied in in vitro and in vivo models. Collectively these nonclinical studies suggest potential risk of clinical QT/QTc prolongation with veliparib when used at the maximally

tolerated dose for veliparib monotherapy in humans.

Study objective

The objective of this study is to evaluate the effect of veliparib on QTcF.

Study design

This is a Phase 1, single-dose, placebo-controlled, single-blind, randomized, 3-period, 6 sequence crossover study enrolling approximately 48 subjects (36 completing subjects) with solid tumors.

The study will evaluate the effect of veliparib on QTcF. After meeting the selection criteria, 48 subjects will be assigned in equal numbers to six sequence groups.

Depending on the Sequence Group assigned, a single dose of veliparib (200 mg or 400 mg) or placebo will be administered orally on Period 1 Day 1. On Day 1 of the subsequent Periods, per the sequence group to which the subject is assigned, the other drug will be administered orally. Periods 1, 2 and 3 will each last for 3 to 7 days.

Intervention

Subjects who participate in the clinical trial will pay extra visits to the hospital. The study is divided in three periods. Each period lasts 3 to 7 days During these visits blood will be drawn for both standard and research purposes. Before and after study drug dosing series af triplicate ECGs will be performed.

Study burden and risks

The burden for the subject consists of extra visits to the site, extra blood draws besides the routine lab draws, and extra ECGs.

In Study M12-020, subjects will receive two single doses of veliparib and one dose of placebo over 9 to 21 days. Based upon preclinical and clinical data, veliparib is unlikely to have anti-cancer activity when administered in this manner. As durable responses have been observed with both veliparib as single agent therapy (BID, Days 1 - 28 of 28-day cycle) and in predefined doses in combination with cytotoxic therapy, subjects will have the option to participate in an extension study upon completion of Study M12-020.

Gastrointestinal toxicities such as nausea and vomiting are the most common toxicities with veliparib single-agent therapy and have occurred in some subjects following a single dose. In addition, 2 cases of seizure have

occurred in the Phase 1 single agent study (CTEP 8282) at the highest dose levels achieved to date (veliparib 400 and 500 mg BID). Confounding circumstances were identified in both of these cases; however, based upon the preclinical data, seizures are considered a potential risk of veliparib.
Anemia has been observed in clinical studies with continuously dosed single agent PARP inhibitors, including veliparib. As administered in this study, hematological effects are not anticipated.

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

- Confirmed solid malignancy that is metastatic or unresectable for which standard curative measures or other therapy that may provide clinical benefit do not exist or are no longer effective.

- Subjects with brain metastases must have clinically controlled neurologic sysptoms.
- Subject is able to swallow and retain oral medications and does not have uncontrolled emesis.
- Subject has adequate bone marrow, renal and hepatic function per local laboratory reference ranges.
- Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics
Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Exclusion criteria

- Subject has a screening or baseline (pre-dose on Day 1 of Period 1 at approximately 8 - 10 AM) corrected QT interval (QTc) interval by Fridericia's correction (QTcF) > 470 ms.
- Uncorrected serum potassium, serum magnesium, serum calcium or free thyroxine (FT4) and thyroid stimulating hormone (TSH) outside of normal reference ranges, or grade 2 hyponatremia or hypernatremia.
- Subject has severe ECG morphologic abnormalities that make QTc evaluation difficult.
- Subject has a history of cardiac conduction abnormalities including:
• PR interval > 220 ms or < 115 ms;
• evidence of second or third degree atrioventricular (AV) block;
• evidence of ventricular pre-excitation;
• intraventricular conduction delay with QRS duration > 136 ms;
• bradycardia as defined by sinus rate < 47 bpm.
- Subject has a significant history of cardiovascular disease including congenital long-QT syndrome, angina, myocardial ischemia or infarction, thrombotic or thromboembolic event in the last 6 months, myocarditis, angina on exertion, uncorrected hypocalcemia (<= 8.2 mg/dL), idiopathic cardiomyopathy, amyloid, tumor, sarcoid, scleroderma, syncope, epilepsy, hypertonic cardiomyopathy, or other clinically significant cardiac disease or baseline ECG abnormalities that could potentially confound subsequent analyses.
- Subject has received any anti-cancer therapies 21 days prior to the first dose of study drug, or has recovered to no better than a grade 2 or higher clinically significant adverse effect(s)/toxicity(s) of the previous therapy.
- Use of drugs with a known risk for QT prolongation and Torsades de Pointes within 7 days prior to the first study dose.
- Use of tobacco or nicotine-containing products within 12 hours prior to the first study dose.

Study design

Design

Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-05-2014
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Veliparib
Generic name:	Veliparib

Ethics review

Approved WMO Date:	25-11-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-04-2014
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-002028-18-NL
ClinicalTrials.gov	NCT02009631
CCMO	NL46329.042.13