Study to clinically evaluate the QT/QTc interval prolongation potential of vericiguat in patients with stable coronary artery disease in a 2-arm, placebo-controlled, randomized, double-blind, double-dummy design including a vericiguat multiple-dose part with fixed up-titration periods and moxifloxacin as positive control (for assay sensitivity testing, nested into the placebo treatment)

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Ethical review	Approved WMO
Status	Completed
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON46553

Source
ToetsingOnline

Brief title
Bayer 18979

Condition

- Coronary artery disorders

Synonym
cardiovascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Artery Disease, coronary, moxifloxacin, vericiguat

Outcome measures

Primary outcome

The primary variable is the time-matched placebo-corrected change from baseline

of the QT interval corrected according to Fridericia (QTcF) after 10 mg

vericiguat at steady state

Regular recordings of triplicate ECGs at baseline, on the first and on the last

days of each treatment period and on Day 8 of the first and the last treatment

period.

Plasma concentrations of vericiguat at corresponding time points.

Secondary outcome

Not applicable

Study description

Background summary

Background
Vericiguat (BAY 1021189) has been developed in the research laboratories of Bayer AG,
Wuppertal, Germany and is co-developed with Merck, as a follow-up compound of the
already clinically investigated soluble guanylate cyclase (sGC) stimulator riociguat (approved
under the trade name Adempas and indicated for the treatment of pulmonary hypertension).
Vericiguat is a sGC stimulator and is intended to be used for the treatment of cardiovascular
diseases, especially heart failure (HF). Currently, vericiguat is being investigated in a Phase
III study in heart failure with reduced ejection fraction (HFrEF).
Soluble guanylate cyclase is an important regulator in the cardiovascular system and is present
in vascular cells. The endogenous activator of sGC is endothelial cell-derived nitric oxide
(NO). In smooth muscle cells, NO activates sGC, resulting in an increased intracellular cyclic
guanosine monophosphate (cGMP) level, which induces vasorelaxation as well as inhibition
of cell proliferation and migration.
Further details can be found in the latest available version of the investigator's brochure (IB),
which contains comprehensive information on the study drug.

Study objective

The objective of this study is to evaluate the effect of multiple doses of vericiguat on the QTc
interval in patients with stable CAD10 within the exposure range observed in Phase II/III
studies:
Primary objective:
* To investigate whether there is a clinically meaningful effect on QTc change from
baseline relative to placebo after administration of 10 mg at steady state
Secondary objectives:
* Vericiguat concentration * QT analysis at 10 mg steady state
* To evaluate the QT/QTc interval prolongation potential of vericiguat in

patients during
the up-titration
* To investigate the pharmacokinetics (PK) of vericiguat during the QTc observation
interval
* To investigate the safety and tolerability (represented by treatment-emergent adverse
events [TEAEs])
* To evaluate the effect of moxifloxacin on QT/QTc administered in the same study
setting for assay sensitivity testing

Study design

Multi-center, randomized, 2-arm, placebo-controlled, double-blind, doubledummy group design including a vericiguat multiple dose part with fixed uptitration periods and moxifloxacin as positive control to assess the potential impact of vericiguat on the QT interval.

Subjects will be randomized to one of the two treatment sequences:
- Treatment A Treatment B Treatment C Treatment D
- Treatment D Treatment A Treatment B Treatment C

Intervention

1. Name of active ingredient: Vericiguat:
Dose(s):
Treatment A: 2.5 mg vericiguat for 14 days (± 3 days)
Treatment A*: 2.5 mg vericiguat for 14 days (± 3 days)
Treatment B: 5 mg vericiguat for 14 days (± 3 days)
Treatment C: 10 mg vericiguat for 14 days (± 3 days)
Treatment C*: 10 mg vericiguat for 14 days (± 3 days)
Route of administration: Once daily oral administration
Duration of treatment: Vericiguat 42 days (range: 33-51)

2. Reference drug 1
Name of active ingredient: Moxifloxacin
Treatment D: Moxifloxacin on Day 8 (± 3 days) or Day 50 (± 3 days)
Dose(s); 400 mg moxifloxacin
Route of administration: Once daily oral administration
Duration of treatment: Single dose

3. Reference drug(s)
Name of active ingredient: Placebo (Treatment D)
Dose(s):
0 mg (matching placebo of 2.5/5 mg and 10 mg vericiguat)

0 mg (matching placebo of moxifloxacin)
Route of administration: oral
Duration of treatment:
Vericiguat placebo 10 mg: 14 days (range: 11-17 days) during Treatments A, A*, B and D
Vericiguat placebo 2.5 and 5 mg: 14 days (range: 11-17 days) during Treatments C, C* and D
Moxifloxacin placebo: 1 day: Day 8 (± 3 days) during Treatments A* or Day 50 (± 3 days) during Treatment C*

Study burden and risks

The disadvantages of participation in the study may be
- possible adverse effects/discomforts of the evaluations in the study.
- additional time;
- additional or longer hospital stays;
- additional tests;
- instructions you need to follow.

Contacts

Public
Bayer

Leverkusen D-51368
Leverkusen D-51368
DE
Scientific
Bayer

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DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

*Patients with stable CAD defined by
- clinically stable for at least 3 months
- coronary artery stenosis in any of the 3 main coronary vessels
- or history of myocardial infarction
* Sinus rhythm at screening
* Interpretable echocardiographic images
* Age: 30 to 80 years (inclusive)
* Body mass index (BMI): above/equal 18.0 and below/equal 36.0 kg/m²

Exclusion criteria

* Ejection fraction (EF) below 30% at screening
* Progressive angina with symptoms of worsening of angina within the <3 month
* History of recent myocardial infarction or unstable Angina
* Documented current relevant coronary stenosis *90% in any of the main 3 coronary vessels without bypass graft
* Symptomatic carotid stenosis, or transient ischemic attack or stroke within 3 months prior to the first screening or patients with stroke at more than 3 months prior to the first Screening
* Insulin dependent diabetes mellitus
* Clinically significant and persisting cardiac ischemia
* Atrial fibrillation, pacemaker, defibrillator, second and third degree atrial-ventricular (AV) block
* Known clinically relevant ventricular arrhythmias
* Clinically relevant heart failure with reduced left ventricular ejection fraction
* Significant valvular heart disease with moderate or severe aortic stenosis or any other significant stenosis; any other moderate or severe valvular failures
* Valve replacement
* Hypertrophic obstructive cardiomyopathy (HOCM)
* Previous or imminent cardiac transplantation
* Known long QT syndrome or prolongation of the QT interval with ongoing proarrhythmic conditions
* Co-medication with drugs known to have QT prolonging effect
* Intolerance of fluoroquinolones, including moxifloxacin
* History of serious adverse effects e.g. tendinitis and tendon rupture, arthralgia and effects on the peripheral and central nervous system while taking fluoroquinolones including

moxifloxacin
* History of tendon diseases or tendon injury caused by quinolones
* Treatment with fluoroquinolones, including moxifloxacin during the last 2 weeks
* Treatment with organic nitrates during the last 3 months prior to the first screening visit
* Treatment with riociguat during the last 3 months prior to the first screening visit
* Treatment with phosphodiesterase (PDE)-5 inhibitors during the last 14 days prior to the first screening visit
* Systolic blood pressure below 110 or above 160 mmHg at screening visit
* Diastolic blood pressure below 50 or above 100 mmHg at screening visit
* Heart rate below 50 or above 100 beats/min (taken from ECG measurement) at first screening visit
* Estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73m2 at first screening visit

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:	Completed
Start date (anticipated):	11-07-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Moxifloxacin
Generic name:	Avelox
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Vericiguat
Generic name:	Vericiguat

Ethics review

Approved WMO Date:	27-02-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2018
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
EudraCT	EUCTR2017-003094-33-NL
CCMO	NL64096.056.18

Study results

Date completed: 26-02-2019

Results posted: 28-02-2020

First publication
04-02-2020