A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Ranolazine on Major Adverse Cardiovascular Events in Subjects with a History of Chronic Angina Who Undergo Percutaneous Coronary Intervention with Incomplete Revascularization

Published: 09-01-2012
Last updated: 01-05-2024

The primary objective of this study is to:• Evaluate the efficacy of ranolazine as compared with placebowhen used as part of standard medical therapy in chronicangina subjects with incomplete revascularization post percutaneous coronary intervention...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON39458

Source
ToetsingOnline

Brief title
RIVER-PCI

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Chestpain, Chronic Angina Pectoris who undergo PCI with incomplete revascularization

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: The sponsor: Gilead Sciences;Inc.

Intervention

Keyword: Chronic Angina, Incomplete Revascularization, major adverse cardiovascular events (MACE), Ranolazine

Outcome measures

Primary outcome

The primary efficacy endpoint is the time from randomization to the first

occurrence of ischemia-driven revascularization or ischemia-driven

hospitalization without revascularization.

Secondary outcome

Secondary endpoints are:

• Time from randomization to sudden cardiac death

• Time from randomization to CV death

• Time from randomization to MI

Additional secondary endpoints will include:

• Evaluation of QoL and health related costs, as detailed in the Integrated QoL

Study and Health Economics Sub-Study

• Exploratory endpoints will include:

• Change in HbA1c in the subgroup of subjects with T2DM on ranolazine versus

placebo at Month 6 and 12 compared to baseline

• New onset T2DM in the ranolazine group versus the placebo group

• Worsening glucose control, defined as an increase of >= 1% in HbA1c, at Month

12 compared to baseline (in subjects with T2DM)

Safety endpoints will include:

• All-cause mortality

• Stroke

• TIA

• CV death, MI or stroke

• Heart failure hospitalization

• Overall adverse events and vital signs

Study description

Background summary

See Protocol V4.1 - Page 21 - Section 1.1 Background

Study objective

The primary objective of this study is to:
• Evaluate the efficacy of ranolazine as compared with placebowhen used as part of standard medical therapy in chronic
angina subjects with incomplete revascularization post percutaneous coronary intervention (PCI) on the incidence of
major adverse cardiovascular events (MACE), defined as the composite of cardiovascular (CV) death, myocardial infarction
(MI), or hospitalization for ischemia or angina

The secondary objectives of this study are to:
• Evaluate the efficacy of ranolazine as compared with placebo when used as part of standard medical therapy in chronic
angina subjects with incomplete revascularization post-PCI on the incidence of the individual components of the primary endpoint

• Evaluate the efficacy of ranolazine as compared with placebo when used as part of standard medical therapy in chronic
angina subjects with incomplete revascularization post-PCI on the incidence of repeat revascularization for ischemia or angina
• Evaluate the efficacy of ranolazine as compared with placebo when used as part of standard medical therapy in chronic
angina subjects with incomplete revascularization post-PCI on the incidence of sudden cardiac death
• Assess quality of life (QoL) in the ranolazine group as compared to the placebo group at Month 1, 6 and 12
• Assess the pharmacoeconomic benefit of ranolazine post-PCI
• Evaluate the tolerability and safety of ranolazine post-PCI

The exploratory objective of this study is to:
• Evaluate the anti-hyperglycemic effect of ranolazine in a subgroup of subjects with type 2 diabetes mellitus (T2DM)

Study design

Upon providing written consent, subjects will be seen in the catheterization laboratory, hospital, or outpatient clinic, and assessed for study participation during Screening. Subjects who undergo PCI for ACS or a non-ACS indication, and who meet all eligibility criteria, will be eligible for Randomization once stable post-PCI.

Prior to Randomization, a CK-MB and/or troponin I/T laboratory sample will be collected post-PCI to obtain a new baseline. For subjects randomized in-hospital prior to the day of planned discharge, the laboratory sample must be collected at least 3 hours post-PCI and the results must be reviewed prior to Randomization to verify stability and confirm subject eligibility. For subjects randomized in clinic or on the day of planned hospital discharge, the laboratory sample can be collected anytime post-PCI and Randomization may occur prior to the receipt of the results and irrespective of the result measured.

Once stable, subjects will be randomized after completing the PCI, but no later than 14 days post-PCI. In the case of a planned or possible staged procedure, subjects will be randomized once they are stable after the last PCI, but no later than 14 days after the last PCI. Subjects may be randomized starting on the day of PCI and anytime during the following 14 days. PCI is defined as an attempt to cross the lesion with a wire with the intention of performing revascularization.

Following PCI, subjects will be treated with standard medical therapies per the discretion of the Investigator unless contraindicated (eg, aspirin, any second anti-platelet agent, a lipid-lowering agent, beta-blocker, calcium channel blockers, nitrates, other antianginals, angiotensin converting enzyme [ACE] inhibitors, and/or angiotensin receptor blockers [ARBs]). Recommended standard

medical therapies are detailed in Appendix 7. Investigators are encouraged to follow practice guidelines for the treatment of CAD patients undergoing PCI.

Eligible subjects will be randomized 1:1 to receive either ranolazine or matching placebo. Randomization will be stratified by reason for undergoing PCI (ACS versus non-ACS indication) and history of DM (history of type 1 or type 2 DM versus no history of DM).

Subjects will take either ranolazine or matching placebo in addition to their standard medical therapies for a minimum of 1 year. Dosing of ranolazine or matching placebo will be 1 tablet twice daily for 7 days, followed by 2 tablets twice daily for the duration of the study (unless otherwise contraindicated).

Down-titration or interruption of study drug is permitted at any time during the study in the event of intolerance to the study drug. Subsequent up-titration to 2 tablets twice daily is also permitted at any time during the study per Investigator discretion.

In cases where the Investigator has concerns that renal function may deteriorate below 30mL/min/1.73m2, continuation and up titration of study drug are left to the discretion of the Investigator, and consultation with the Medical Monitor is recommended.

Subjects taking moderate CYPP3A4 inhibitors, such as diltiazem, verapamil, ciprofloxacin or erythromycin, will take a dose of 1 tablet (ranolazine or matching placebo) twice daily for the duration of the concomitant therapy.

During the Treatment and Follow-Up Period, study visits will occur at Randomization, Month 1, Month 6, and every 6 months thereafter until the End of Study. Safety assessments will include an abbreviated physical examination and vital signs. In addition, an ECG will be performed at Randomization and Month 1. Clinical laboratory samples will also be collected at Randomization, and at Months 1, 6 and 12, and will be analyzed by a central laboratory.

Subjects will be contacted at 1 week and 2 weeks after Randomization to assess for tolerability of study drug and encourage compliance with dosing. Subjects will also be contacted every 3 months in between study visits.

A QoL questionnaire, as detailed in the accompanying Integrated QoL Study and Health Economics Sub-Study (Appendix 6), will be administered at Randomization, Month 1, Month 6, and Month 12 (and at the End of Treatment visit for subjects who withdraw from the study any time prior to the Month 12 visit).

Upon permanent discontinuation of study drug for any reason, an End of Treatment visit will be performed for all subjects. Telephone follow-up will be conducted 14 (* 3) days after the last study drug dose to assess the subject*s condition.

Subjects who permanently discontinue study drug prior to the End of Study and have not withdrawn consent will enter the Extended Follow-Up Period and will continue to be followed until the End of Study, or withdrawal of consent. Such subjects will return to the site for study visits per the visit schedule established at the time of Randomization to be assessed for safety and for primary and secondary efficacy endpoint events, as well as heart failure hospitalizations and possible strokes/transient ischemic attacks (TIA). The subjects in Extended Follow-Up will also be contacted every 3 months in between visits. At the End of Study, the subjects will return to the site for an End of Extended Follow-Up visit.
All randomized subjects must be followed through to their final visit in accordance with their visit schedule established at the time of Randomization, regardless of treatment status.

Subjects who withdraw consent will continue to be followed for vital status from public records such as government vital statistics or obituaries.
During the study, an independent Data Safety Monitoring Board (DSMB) will monitor primary and secondary endpoint data and safety data at regular intervals.

All potential primary endpoint events and secondary clinical endpoint events (all repeat hospitalizations, all repeat coronary angiography with or without revascularization, all MIs, and all deaths), as well as heart failure hospitalizations and possible strokes/TIAs will be assessed and adjudicated by members of an independent Clinical Events Committee (CEC) blinded to treatment allocation. The study will continue until at least 1 year post-randomization follow-up has been achieved for all subjects, and at least 720 adjudicated first post-randomization primary endpoint events (ischemia-driven revascularization or ischemia-driven hospitalization without revascularization) have been observed.

Intervention

Ranolazine 500 mg administered orally twice daily for 7 days, followed by 1000 mg (two 500 mg tablets) administered orally twice daily (morning and evening, approximately 12 hours apart) for the duration of the study.

Subjects taking moderate CYP3A4 inhibitors, such as diltiazem, verapamil, ciprofloxacin, or erythromycin, will receive ranolazine 500 mg (one 500 mg tablet) administered orally twice daily (morning and evening, approximately 12 hours apart) for the duration of the concomitant therapy.

One matching placebo tablet, administered orally twice daily for 7 days, followed by two matching placebo tablets administered orally twice daily (morning and evening, approximately 12 hours apart) for the duration of the study.

Subjects taking moderate CYP3A4 inhibitors, such as diltiazem, verapamil, ciprofloxacin, or erythromycin, will receive one placebo tablet twice daily (morning and evening, approximately 12 hours apart) for the duration of the concomitant therapy.

Study burden and risks

An overview of the risks can be found in the informed consent form Appendix 2. Study procedures can be found in the appendix 2 of the protocol and in the informed consent form in Appendix 1.

Contacts

Public
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US
Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Written informed consent
2.Males and females aged 18 years and older
3.History of chronic angina defined as at least 2 episodes of anginal pain or discomfort in the chest, jaw, shoulder, back, neck, or arm that is precipitated by exertion or emotional stress, and relieved by rest or sublingual nitroglycerin, which occurred on at least 2 separate days and at least 14 days prior to PCI (in the case of staged PCI procedures, at least 14 days prior to the first PCI in the series). Subjects may or may not have additional angina episodes within the 14 days prior to their first PCI in the series, as well as any time prior to Randomization.
4.PCI for any indication (ACS or non-ACS). For the purposes of stratification at randomization, ACS will be defined as hospitalization for anginal pain or discomfort within the previous 24 hours to their hospitalization with any one (or more) of the following criteria:
i.Elevated troponin or creatinine kinase-MB (CK-MB) consistent with MI, as reported by local laboratory and measured prior to index PCI
ii.Electrocardiographic changes (including transient changes) comprising new or presumably new ST segment depression >= 0.1 mV (>= 1 mm), or ST segment elevation >=0.1 mV (>=1 mm) in at least 2 contiguous leads, or new or presumably new Left Bundle Branch Block
5. Randomization within 14 days post-PCI. In the case of staged PCI procedures, randomization has to occur within 14 days of the last PCI in the series. Subjects may be randomized starting
on the day of PCI and anytime during the following 14 days. PCI is defined as an attempt to cross the lesion with a wire with the intention of performing revascularization.
6.Post-PCI (post the last PCI for staged procedures) evidence of incomplete revascularization defined as the presence of one or more visually estimated >= 50% stenoses in one or more coronary arteries with reference vessel diameter of at least 2.0 mm, whether in the target vessel or in a non-target vessel regardless of the presence or absence of coronary collaterals. In the case of a subject post-CABG, incomplete revascularization is defined as the presence of one or more visually estimated >= 50% stenoses in an unbypassed epicardial vessel with a reference diameter >= 2.0 mm, or one or more visually estimated >= 50% stenoses in a bypass graft supplying an otherwise unrevascularized myocardial territory.
7.Clinically stable post-PCI. Subjects randomized in-hospital on day of planned discharge or in clinic are considered stable. Subjects randomized in-hospital prior to day of planned discharge are considered stable if they meet all of the following criteria:
i.CK-MB < 3 times the upper limit of normal (ULN) at least 3 hours post-PCI, or if >= 3 times the ULN with evidence of decreasing CK-MB (decreased by at least 20% from the prior measure), as reported by local laboratory. If CK-MB is not available, a subject must have evidence of normal or decreasing troponin levels (decreased by at least 20% from the prior measure) at least 3 hours post-PCI, as reported by local laboratory.
ii.Systolic blood pressure >= 90 mm Hg and not receiving pressors or inotropes
iii.No current requirement for an intra-aortic balloon pump (IABP) or any left ventricular assist device
iv.No current requirement for intravenous (IV) nitroglycerin
8.Ability and willingness to comply with all study procedures during the course of the study
9.Females of childbearing potential must have a negative pregnancy test at Screening

(unless surgically sterile or post-menopausal) and must agree to use highly effective contraception methods from Screening throughout the duration of study treatment and for 14 days following the last dose of study drug. See Section 8.7 for a description of acceptable methods of contraception and definition of post-menopausal status.

Exclusion criteria

1.Any future planned revascularization (including staged procedures) or possible planned revascularization (ie, planned stress test to assess the imminent need for additional revascularization). Future planned stress tests for purposes of monitoring are permitted but strongly discouraged. Subjects may be enrolled after the last PCI in the staged series or once a decision is made not to perform a follow up PCI, as long as Randomization occurs within 14 days from the last PCI. If a subject has had a stress test post-PCI and prior to Randomization and no further intervention is planned, the subject may be enrolled within 14 days from the last PCI.
2.Unrevascularized left main coronary artery stenosis >= 50%. Subjects with history of CABG to the left coronary system will be considered to have a revascularized left main if at least one graft is patent.
3.Major complication during or after the index PCI (in the case of staged PCI, the last in the series) including any of the following:
i.Major bleeding (TIMI Bleeding classification [Appendix 5] or any bleeding requiring >= 2 units of red blood cells)
ii.Coronary perforation requiring treatment
iii.Procedural complication requiring surgery (including CABG or peripheral vascular surgery)
4.Stroke within 90 days prior to Randomization, or any history of stroke with permanent major neurologic disability (eg, aphasia or significant motor dysfunction)
5.Cardiogenic shock within 90 days prior to Randomization (transient decreases in blood pressure without clinical sequelae are not considered to be cardiogenic shock)
6.New York Heart Association (NYHA) Class III or IV heart failure
7.Severe renal insufficiency as assessed by an estimated GFR < 30 mL/min/1.73m2 using the 4 variable modification of diet in renal disease (MDRD) equation (Appendix 8) per local laboratory (based on the last available measurement prior to Randomization, collected within 1 month prior to the index PCI [in the case of staged PCI, the last in the series])
8.Liver cirrhosis
9.Use of Class Ia, Ic, or Class III antiarrhythmics, except for amiodarone (as detailed in Appendix 4)
10.Current treatment with strong inhibitors of CYP3A (as detailed in Appendix 3)
11.Current treatment with CYP3A4 inducers or P-gp inducers (as detailed in Appendix 3)
12.Subjects taking > 20 mg simvastatin daily or > 40 mg lovastatin daily who cannot reduce the dose to 20 mg once daily for simvastatin or 40 mg once daily for lovastatin, or who cannot switch to another statin
13.Subjects taking greater than a total of 1000 mg daily of metformin who cannot reduce the dose to a maximum total of 1000 mg daily (additional anti-diabetic medications may be added as clinically indicated to allow subjects to decrease their metformin dose and maintain glycemic control)

14.Previous treatment with ranolazine for > 7 consecutive days within 30 days prior to Randomization, or known hypersensitivity or intolerance to ranolazine or to any of the excipients
15.Participation in another investigational drug or investigational device study within 30 days prior to Randomization (participation in registries is allowed)
16.Women who are pregnant or breast feeding
17.Non-CAD comorbid conditions (eg, advanced malignancy, severe aortic stenosis) which are likely to result in death within 2 years of Randomization
18.Any condition that in the opinion of the investigator would preclude compliance with the study protocol
Any condition that in the opinion of the investigator would preclude compliance with the study protocol

Study design

Design

Study phase:	3
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):	21-06-2012
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ranexa®
Generic name:	ranolazine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-01-2012
Application type:	First submission
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	09-05-2012
Application type:	First submission
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	25-06-2012
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	09-07-2012
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO	

Date:	27-03-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	07-08-2013
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	03-09-2014
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	TWOR: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (Rotterdam)

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	EUCTR2011-002507-15-NL
ClinicalTrials.gov	NCT01442038
CCMO	NL38766.101.11

Study results

Date completed:	10-12-2014
Actual enrolment:	26