A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2*P - TIMI 50)

Published: 24-10-2007
Last updated: 11-05-2024

Objectives:The following objectives are designed to address the effects of SCH 530348 when administered orally in addition to the standard of care for a minimum of 1 year in subjects with documented atherosclerotic disease.Primary Objective: The...

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

Summary

ID

NL-OMON37024

Source
ToetsingOnline

Brief title
TRA 2*P - TIMI 50

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Atherothrombotic Ischemic Events, Blood vessel disease

Research involving
Human

Sponsors and support

Primary sponsor: Schering-Plough
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Atherosclerotic ischemic events, Secondary prevention, Thrombin receptor antagonist

Outcome measures

Primary outcome

Criteria for Evaluation:

All suspected efficacy and bleeding endpoints will be adjudicated by an

independent Clinical Events Committee that is blinded to treatment.

Primary Efficacy Endpoint:

The primary efficacy endpoint of the study is the first occurrence of any

component of the composite of cardiovascular death, MI, stroke, and urgent

coronary revascularization.

Key Secondary Efficacy Endpoint: The key secondary efficacy endpoint is the

first occurrence of any component of the composite of cardiovascular death, MI,

and stroke.

Secondary outcome

Other Secondary Endpoints Related to Efficacy:

Other secondary efficacy endpoints include the first occurrence of any component of the following composites or individual components as indicated:

1. all-cause death, MI, stroke, and urgent coronary revascularization
2. cardiovascular death and MI
3. cardiovascular death, MI, stroke, urgent coronary revascularization, or urgent hospitalization for vascular cause of ischemic nature
4. all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
5. cardiovascular death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
6. the individual components of the composite primary efficacy endpoint
   a. cardiovascular death
   b. MI
   c. stroke
   d. urgent coronary revascularization
7. all-cause death

Exploratory Efficacy Endpoints:

These endpoints are not part of the objectives and are included to gather information for future consideration. The exploratory efficacy endpoints

include any component of the following composites:

1. all-cause death, MI, and stroke in subjects undergoing PCI at any time during participation in the study

2. all-cause death, MI, and stroke in subjects undergoing CABG at any time during participation in the study

Other Secondary Endpoints Related to Safety: Safety endpoints included as part of the objectives, in relative order of importance, comprise the incidences of the following:

1. composite of moderate and severe bleeding events according to the GUSTO classification

2. "clinically significant bleeding," defined as TIMI major or TIMI minor bleeding, or bleeding that requires unplanned medical treatment, surgical treatment, or laboratory evaluation even if it does not meet the criteria for TIMI major or TIMI minor bleeding

Exploratory Safety Endpoints: These endpoints are not part of the objectives and are included as additional ways to evaluate bleeding and to gather information for future consideration

1. severe bleeding events according to the GUSTO criteria

2. all major and minor bleeding events, according to the TIMI classification

3. nonCABG TIMI major and minor bleeding events

4. bleeding events that do not meet the TIMI criteria for major or minor

5. in subjects undergoing CABG at any time while still receiving study drug

a. incidence of blood product transfusions (eg, red blood cell, platelet)

b. bleeding assessed (1) by chest-tube drainage (a) through 8 hours after

surgery and (b) total drainage, and (2) by need for reoperation for bleeding

Study description

Background summary

The benefit of antiplatelet agents in secondary prevention of atherothrombotic events is well established. The present trial is designed to determine whether inhibition of the platelet PAR-1 receptor to stimulation by thrombin in addition to standard-of-care antiplatelet therapy (eg, aspirin, thienopyridines) can result in further incremental benefit, as determined by reduction in the incidence of atherothrombotic events relative to standard of care alone, in subjects with established coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral artery disease (PAD).

Study objective

Objectives:
The following objectives are designed to address the effects of SCH 530348 when administered orally in addition to the standard of care for a minimum of 1 year in subjects with documented atherosclerotic disease.

Primary Objective:
The primary objective is to evaluate the hypothesis that SCH 530348 added to standard of care will reduce the incidence of atherothrombotic ischemic events relative to standard of care alone, as measured by the composite of cardiovascular death, myocardial infarction (MI), stroke, and urgent coronary revascularization.

Key Secondary Objective:
The key secondary objective is to evaluate clinical benefit with respect to the composite of cardiovascular death, MI, and stroke.

Other Secondary Objectives Related to Efficacy: Other secondary efficacy objectives will include evaluation of the incidence of the following composites or individual components as indicated:
1. all-cause death, MI, stroke, and urgent coronary revascularization
2. cardiovascular death and MI
3. cardiovascular death, MI, stroke, urgent coronary revascularization, or

urgent hospitalization for vascular cause of ischemic nature
4. all-cause death, MI, stroke, any revascularization (including amputation for ischemic limb)
5. cardiovascular death, MI, stroke, any revascularization (including amputation for ischemic limb), or urgent hospitalization for vascular cause of ischemic nature
6. the individual components of the composite primary efficacy endpoint
a. cardiovascular death
b. MI
c. stroke
d. urgent coronary revascularization
7. all-cause death

Other Secondary Objectives Related to Safety:
Specific safety objectives, in relative order of importance, include evaluation of the incidences of the following:
1. composite of moderate and severe bleeding events according to the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries cooperative group) classification
2. "clinically significant bleeding," defined as TIMI (Thrombolysis in Myocardial Infarction Study Group) major or TIMI minor bleeding, or bleeding that requires unplanned medical treatment, surgical treatment, or laboratory evaluation even if it does not meet the criteria for TIMI major or TIMI minor bleeding

Study design

The study will be a multicenter, global, randomized, double-blind, placebo-controlled, balanced-parallel-groups investigation of orally administered SCH 530348 in the secondary prevention of ischemic events in men and women at least 18 years old who have evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems, to be conducted in conformance with Good Clinical Practice.
Following randomized treatment assignment and the beginning of dosing, subjects will return after 30 days, 4, 8, and 12 months, and every 6 months thereafter for scheduled efficacy/safety evaluations until the end of the study; that is, when a statistically defined number of efficacy endpoint events have been observed and every subject has participated in the study for at least 1 year. Subjects who discontinue treatment for any reason will continue to be followed by telephone contact for the occurrence of suspected efficacy endpoint and bleeding events, and will be included in endpoint analyses.
Among the committees formed to oversee conduct of the study will be an independent Data Safety Monitoring Board to protect further the rights, safety, and well being of subjects who will be participating in this study by monitoring the progress and results of the trial, and an independent Clinical Events Committee to review and adjudicate each suspected efficacy and bleeding

endpoint event while blinded to treatment.

Intervention

Test Product, Dose, Mode of Administration:
SCH 530348 administered as the bisulfate salt (all references to "SCH 530348" as a clinical test product imply "SCH 530348 bisulfate"). SCH 530348 oral 2.5 mg tablet taken once daily, with or without food.

Reference Therapy, Dose, Mode of Administration:
Placebo tablet to match SCH 530348 oral 2.5 mg tablet, taken as for SCH 530348.

Study burden and risks

The most frequently reported adverse events for SCH 530348 are zMild to moderate hematoma and associated pain at venipuncture sites, and incidental hematoma and bruising on extremities. Given the mechanism of action of the drug, investigators should be watchful for bruising, bleeding/hemorrhage/hematoma, thrombocytopenia, and neutropenia.

Contacts

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Scientific
Schering-Plough

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject may be of either sex and any race, and must be at least 18 years old.;2. Subject must have evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems as follows:
a.CAD as indicated by a history of presumed spontaneous MI (hospitalized with final diagnosis of MI, excluding periprocedural or definite secondary MI [eg, due to profound anemia or hypertensive emergency, troponin increase in sepsis]) 2 >= weeks but <= 12 months prior, or
b.ischemic (presumed thrombotic) CVD as indicated by a history of ischemic stroke (hospitalized with final diagnosis of nonhemorrhagic stroke) [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission] >= 2 weeks but <= 12 months prior, or
c. PAD as indicated by a history of intermittent claudication and
i. a resting ankle/brachial index (ABI) of <0.85, or
ii. amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia (note that enrollment of subjects entering with qualifying PAD will end when the total of the subset of subjects reaches ~15% of the planned total enrollment; investigators will be told when to stop enrollment of these subjects);3. Subject must be able and willing to give appropriate informed consent.;4. A woman of child-bearing potential who is currently sexually active must agree to use a medically accepted method of contraception prior to screening, while receiving protocol-specified medication, and for 2 months after stopping the medication.;5. A woman of child-bearing potential who is not currently sexually active must agree to use a medically accepted method of contraception should she become sexually active while participating in the study

Exclusion criteria

1. clinically unstable at the time of enrollment;2. any planned coronary revascularization or peripheral intervention;3. concurrent or anticipated treatment with warfarin (or derivatives, eg, phenprocoumon [but see notes in text for exceptions]), oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrollment;4. concurrent or anticipated treatment with a potent inducer (eg, rifampin) or potent inhibitor (eg, ketoconazole, erythromycin) of CYP3A4 isoenzymes (but see note in text for exceptions);5. history of a bleeding diathesis, or evidence of active abnormal bleeding within 30 days before enrollment;6. history at any time of intracranial hemorrhage (except "microhemorrhage" [eg, as detected on T2-weighted MRI]), intracranial or spinal cord surgery, or a central nervous system tumor or aneurysm;7.

documented sustained severe hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg) at enrollment or within the previous 10 days;8. severe valvular heart disease, as defined by the American College of Cardiology/American Heart Association;9. history within 2 weeks prior to enrollment of major surgery other than mentioned above or of ischemic (presumed thrombotic) stroke;10. known platelet count <100,000/mm3 within 30 days before enrollment;11. known active hepatobiliary disease, or known unexplained persistent increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activity to two times or more the upper limit of the reference range (upper limit of "normal" [>=2xULN]);12. any serious illness or any condition that the investigator feels would (a) pose a significant hazard to the subject if investigational therapy were initiated, or (b) would limit the prognosis of the subject, regardless of investigational therapy;13. any serious medical comorbidity (eg, active malignancy) such that the subject's life expectancy is <24 months;14. previous participation in the current study;15. current participation in any other study of investigational therapy, or participation in such a study within the last 30 days;16. known hypersensitivity to any component of the current investigational product;17. subject is a woman who is breast-feeding, pregnant, or who intends to become pregnant;18. subject is part of the staff personnel directly involved with this study, or is a family member of the investigational staff;19. Known current substance abuse at the time of enrollment

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:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-12-2007
Enrollment:	2000
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nog niet beschikbaar
Generic name:	Nog niet beschikbaar

Ethics review

Approved WMO Date:	24-10-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-12-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-02-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-03-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-03-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-03-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	11-04-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-05-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-08-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-09-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-09-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-01-2009
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-02-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-02-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-04-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	12-11-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-11-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-04-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-07-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	20-01-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2006-002942-12-NL
ClinicalTrials.gov	NCT00526474
CCMO	NL19068.003.07