A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Low Body Weight versus Higher Body Weight Aspirin-Treated Subjects with Stable Coronary Artery Disease

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Ethical review	Not approved
Status	Will not start
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON32918

Source
ToetsingOnline

Brief title
Plasugrel versus Clopidogrel in subjects with low body weight.

Condition

- Coronary artery disorders

Synonym
Coronary Artery Disease, illness of coronary arteries

Research involving

Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: de sponsor van het onderzoek Eli Lilly

Intervention

Keyword: clopidogrel, high-weight, low-weight, plasugrel

Outcome measures

Primary outcome

Criteria for Evaluation:

Efficacy: No efficacy measures will be collected in this study.

Safety: Laboratory measures, adverse events.

Pharmacokinetic: Blood samples will be collected for the determination of plasma concentrations of the prasugrel active metabolite (R-138727), prasugrel inactive metabolites (R-95913, R-106583, and R-119251), and the clopidogrel active metabolite (R-130964). Inactive metabolites of clopidogrel will not be analysed in this study.

Pharmacodynamic: LTA (ADP); VerifyNow® P2Y12; Vasodilator-associated stimulated phosphoprotein (VASP).

Secondary outcome

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Study description

Background summary

The TRITON-TIMI 38 Phase 3 clinical study (Study TAAL) revealed significantly

reduced rates of ischaemic events on prasugrel therapy compared to clopidogrel for the composite endpoint of CV death, MI, or stroke in subjects with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI); however, with prasugrel there was a greater risk of bleeding identified in subjects with low body weight (<60 kg). Reducing the prasugrel maintenance dose (MD) to 5 mg in subjects <60 kg in weight is expected to reduce exposure to prasugrel*s active metabolite to a range that will lower the risk of bleeding while providing efficacy comparable to that of 10-mg prasugrel MD in subjects >=60 kg (there are no direct efficacy outcomes for this study). The use of prasugrel for patients <60 kg is recommended at the lower MD of 5 mg in the European Summary of Product Characteristics (EU SPC) and in the United States Package Insert (USPI).
There is currently a lack of clinical data on the prasugrel 5-mg MD in subjects who are <60 kg. This study, which is a post-marketing commitment based on the Committee for Medicinal Products for Human Use (CHMP) review of the prasugrel marketing authorisation application, will test the hypothesis that a prasugrel 5-mg MD in subjects with low body weight will achieve a non-inferior pharmacodynamic (PD) effect to a 10-mg MD in subjects with higher body weight. This study will provide further support for the prasugrel 5-mg MD recommendation in subjects <60 kg in weight. In addition the approved clopidogrel 75-mg MD will be compared with the 5-mg and 10-mg MD of prasugrel.

Study objective

The primary objective of this study is to demonstrate non-inferiority by pharmacodynamic (PD) analysis of the prasugrel 5-mg maintenance dose (MD) in aspirin-treated subjects <60 kg with stable coronary artery disease (CAD) versus the prasugrel 10-mg MD in aspirin-treated subjects >=60 kg with stable CAD, as assessed by maximum platelet aggregation (MPA) to 20 µM ADP measured with light transmission aggregometry (LTA) at the pre-dose trough on day 12 ± 2 of the MD period (Study Period 1).

Study design

This Phase 1b study will be a multi-center, partially-blinded (single-blind for subjects Period 1; double-blind in Periods 2 and 3), double-dummy (5 mg prasugrel, 10 mg prasugrel, 75 mg clopidogrel with matching placebo), parallel group (two population arms), active comparator, multiple dose (30-42 days total), randomised sequence, 3 period (first period fixed, remaining two periods crossover within each population arm) study design (3 periods of 12 ± 2 days without intervening or terminal washout periods) in aspirin-treated subjects with stable coronary artery disease.

Intervention

Physical examination (1x during the study), ECG (1x), vital signs (5x).

The subjects of this study will not be subjected to a behavior change. No questionnaires will be taken, Diaries do not have to be kept.

Lichamelijk onderzoek (1 x gedurende dit onderzoek), ECG (1x), meten van lengte, gewicht (1x) en pols/ hartsag (5x)
De proefpersonen aan dit onderzoek worden niet onderworpen aan een gedragswijze. Er worden geen vragenlijsten afgenomen. Dagboeken worden ook niet bijgehouden.

Study burden and risks

Risks associated with study drug Prasugrel
Prasugrel has been taken by around 10,500 patients in clinical trials and is already approved in Europe as medication for patients with Acute Coronary Syndrome, however it has been tested as a treatment for stable Coronary Artery Disease only by a limited number of people. This medication is not yet approved on the market in the Netherlands.
The most common side effect is bleeding. The following examples may be signs of bleeding: Blood in the Urine; Blood in the Stool; Uncontrollable bleeding
Additional common side effects: Bleeding in the stomach or bowels, bleeding from a needle puncture site, Nose bleeds, Small red bruises on the skin (ecchymoses), Blood in urine
Hematoma (bleeding under the skin at the site of an injection, or into a muscle, causing swelling)
There are additional uncommon side effects of which your study doctor can tell you more if you would like to.

Risks associated with comparator drug
Clopidogrel

The most common side effect is bleeding. Bleeding may occur for example as bleeding in the stomach or bowels, bruising, haematoma, nose bleed, blood in the urine, bleeding in the eye or prolonged bleeding. Common side effects are: Diarrhoea, abdominal pain, indigestion or heartburn.
There are additional uncommon side effects of which study doctor can tell you more if would like to.

Risks and Discomforts associated with Aspirin
Aspirin may have undesirable side effects. People who are allergic to acetylsalicylic acid, or have asthma, persisting or recurring stomach problems (such as heartburn, upset stomach or stomach pain), ulcers, or bleeding problems should not take aspirin unless directed by a doctor.
Do not use aspirin if you are taking a prescription drug for thinning the blood, diabetes, gout, or arthritis, unless directed by a doctor. Combining aspirin or similar drugs with oral anti-diabetes drugs can decrease blood sugar levels more than expected.

Possible side effects of aspirin include stomach pain or discomfort, indigestion, heartburn, nausea, or vomiting. Less common side effects include unusual bleeding or bruising, black stools, severe diarrhea, ringing in the ears, severe headache, dizziness, drowsiness, confusion, changes in vision, changes in behavior, excessive sweating, and increased thirst.
The combination of study drug with other drugs prescribed for your condition may have other unknown risks or possible harmful interaction.

Risks associated with study procedures

Blood Sampling
As a result of blood sampling you might feel pain or be light-headed. You may experience some temporary discomfort, bleeding, bruising, or rarely, infection, at the site of a needle puncture you receive during the drawing of blood samples. The study blood draws might also increase the risk of anaemia caused by study medications.

ECG
The ECG is a painless procedure that requires you to lie still for a few minutes while electrodes are attached to your chest to record the activity of your heart. The ECG leads placed on your skin may cause slight discomfort during placement and removal. Some individuals are sensitive to the sticky patches used during an ECG, which may result in redness and sore skin in those areas.

In addition to the risks already described, prasugrel and clopidogrel, alone or in combination with Aspirin®, and the study procedures may have other unknown risks.

There may also be unknown risks to an embryo, fetus, or nursing infant.

Contacts

Public
Eli Lilly

Lilly Research Centre, Erl Wood Manor, Sunninghill Road
GU20 6PH Windelsham, Surrey
United Kingdom
Scientific
Eli Lilly

Lilly Research Centre, Erl Wood Manor, Sunninghill Road

GU20 6PH Windelsham, Surrey
United Kingdom

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants will include both male and female subjects with stable coronary artery disease (CAD) who are at least 18 years of age and less than 75 years of age (with subjects grouped by body weight, either <60 kg or >=60 kg), and who are not currently indicated for treatment with a thienopyridine. Stable coronary artery disease is defined as any of the following: Subjects diagnosed with chronic stable angina; prior history of unstable angina (including non-ST-segment elevation myocardial infarction) or acute myocardial infarction (AMI); previous coronary revascularisation including percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or CAD in at least one coronary vessel on previous angiography or noninvasive imaging procedure.

Exclusion criteria

Criteria for exclusion include (but not limited to):
• Unstable coronary artery disease.
• PCI or CABG within the previous 90 days.
• History of refractory ventricular arrhythmias within the last 6 months; an implanted defibrillator device; congestive heart failure within 6 months prior to screening; major surgery, or severe trauma, fracture or organ biopsy within 90 days prior to randomisation.
• Any planned surgical procedure or any coronary revascularisation (surgical or percutaneous) planned within 60 days following randomisation.
• Any known contraindication to treatment with an antiplatelet agent.
• Significant hypertension at the time of screening or randomisation.
• Clinically significant out-of-range values for platelet count or haemoglobin at screening, in the investigator*s opinion, or results of clinical laboratory tests at the time of screening that

are judged to be clinically significant for the study population, as determined by the investigator.
• Prior history or presence of significant bleeding disorders, abnormal bleeding tendency, or personal history of coagulation or bleeding disorders.
• Prior history or clinical suspicion of cerebral vascular malformations, intracranial neoplasm, transient ischaemic attack (TIA), or stroke.
• Prior history or presence of thrombocytopaenia or thrombocytosis.
• Use of antiplatelet agents (excluding aspirin) *10 days prior to screening; the use (or planned use) of heparin, oral anticoagulants, or fibrinolytic agents within 30 days of screening; or subjects receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDS) or cyclooxygenase-2 (COX-2) inhibitors that cannot be discontinued for the duration of the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Efient
Generic name:	prasugrel hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plavix

Generic name:	Clopidogrel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-12-2009
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Not approved Date:	11-05-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2009-012739-13-NL
CCMO	NL31008.100.09