A Pharmacokinetic and Pharmacodynamic Comparison of Prasugrel and Clopidogrel in Very Elderly versus Non-Elderly 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-OMON32872

Source
ToetsingOnline

Brief title
Plasugrel versus Clopidogrel in elderly subjects.

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, elderly, non-elderly, plasugrel

Outcome measures

Primary outcome

Criteria for Evaluation:

Efficacy: No clinical 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) and the

clopidogrel active metabolite (R-130964). Inactive metabolites of prasugrel

and clopidogrel will not be analysed in this study.

Pharmacodynamic: LTA (ADP, AA, collagen and/or SDF-1β); VerifyNow® P2Y12;

VASP; flow cytometric markers at prespecified sites;

Secondary outcome

-

Study description

Background summary

The TRITON-TIMI 38 Phase 3 clinical trial (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 very elderly (>=75 years of age) subjects. Reducing the prasugrel maintenance dose (MD) to 5 mg in subjects >=75 years of age 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 <75 years of age (there are no direct efficacy outcomes for this study).
The use of prasugrel in patients >=75 years of age is generally not recommended in the European Union (EU). If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the patients age group >=75 years, then following a 60-mg loading dose a reduced maintenance dose (MD) of 5 mg should be prescribed, in accordance with the European Summary of Product Characteristics (EU SPC). The use of prasugrel is generally not recommended in these patients in the United States (US) as well, except in high-risk situations (patients with diabetes or history of myocardial infarction) where its effect appears to be greater and its use may be considered, in accordance with the US Package insert (USPI).
There is currently a lack of clinical data on the prasugrel 5-mg MD in subjects who are >=75 years of age. 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 the very elderly will achieve a non-inferior pharmacodynamic (PD) effect to a 10-mg MD in younger subjects. This study will provide further support for the prasugrel 5-mg MD recommendation in subjects >=75 years of age. 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 >=75 years of age with stable coronary artery disease (CAD) versus the prasugrel 10-mg MD in aspirin-treated subjects >=45 to <65 years of age 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).
The secondary objectives of the study are:
• To compare the PD between MD regimens (5 mg prasugrel, 10 mg prasugrel, and 75 mg clopidogrel) when co-administered with aspirin, as measured by LTA (MPA), VerifyNow® P2Y12 (PRU, device reported % inhibition) and VASP (PRI) within each age group (subjects >=75 years of age and subjects >=45 to <65 years of age).
• To compare the PD within MD regimens (5 mg prasugrel, 10 mg prasugrel, and 75 mg clopidogrel) when co-administered with aspirin, as measured by LTA (MPA), VerifyNow® P2Y12 (PRU, device reported % inhibition) and VASP (PRI) between subjects >=75 years of age and subjects >=45 to <65 years of age.
• To compare the PK of exposure to prasugrel's and clopidogrel's active metabolites and their relations to PD measurements between subjects >=75 years

and subjects >=45 to <65 years of age.
• To compare the PD between MD regimens (5 mg prasugrel, 10 mg prasugrel, and 75 mg clopidogrel) as assessed by exploratory analyses of other LTA agonists (for example, collagen and stromal cell-derived factor beta [SDF-1β]) within each age group.
• To compare the PD within MD regimens, as assessed by exploratory analyses of other LTA agonists (for example, collagen and SDF-1β) between subjects >=75 years of age and subjects >=45 to <65 years of age.
• To assess the safety and tolerability of each MD regimen (5 mg prasugrel, 10 mg prasugrel, and 75 mg clopidogrel) when co-administered with aspirin in subjects with stable CAD >=75 years of age and >=45 to <65 years of age.
• To compare MD regimens as assessed by exploratory analyses of flow cytometric markers (for example, CD11b Ligand, P-selectin, CD 40 Ligand, CD184, CD69, CD58, IFFITM1, PRKRA, C4 complement deposition, microparticles, platelet size, and PAC-1 Mab). Note: These exploratory flow cytometric markers will be collected only at prespecified sites.

Study design

This Phase 1b study will be a multi-center, partially-blinded study (single-blind for subjects in Period 1; double-blind in Periods 2 and 3), double-dummy (5 mg, 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 and the 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 this study), ECG (1x), vbody weight and length (1x) viital signs (5x).
Subjects of this study will not be submitted to a behavioural change. Questionnaires will not be taken. Diares will not be kept.

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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

This study will include male or female aspirin-treated subjects not indicated for a thienopyridine treatment with stable coronary artery disease (CAD) who are at least 45 years of age and who weigh at least 60 kg, with subjects grouped into one of the following: subjects â*¥75 years of age and subjects â*¥45 to <65 years of age. 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 from the study include (but are 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 thrombocytopenia 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:	20
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:	clopdidogrel
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	EUCTR2009-012409-20-NL
CCMO	NL30960.100.09