An Open-label, Single-Sequence Study to Evaluate the Effects of Diltiazem, a Moderate CYP3A4/5 Inhibitor, on the Pharmacokinetics and Pharmacodynamics of E5555 and its Metabolites in Healthy Subjects

Published: 20-09-2010
Last updated: 04-05-2024

Primary:to evaluate the effects of a moderate CYP3A4/5 inhibitor, diltiazem on the pharmacokinetics and pharmacodynamics (Thrombin and TRAP-induced platelet aggregation) of the study drug and its known metabolitessecundary:to evaluate the effects of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON34620

Source
ToetsingOnline

Brief title
E5555/diltiazem DDI study

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
cardiovascular events, thrombosis

Research involving

Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Atherosclerosis, Cardiovascular disease, CYP 3A4 inhibitor

Outcome measures

Primary outcome

Pharmacokinetics

Safety

Tolerability

Pharmacodynamics

Secondary outcome

n.a.

Study description

Background summary

The study drug to be given is a new, investigational compound that may eventually be used for the treatment of coronary artery disease and acute coronary syndrome (for example heart attack or a restriction in blood flow to the heart). In most cases, cardiovascular disease results from atherosclerosis (formation of abnormal fatty deposit in the vessel of the artery) or the formation of a clot (blockage) within the arteries of the heart. Atherosclerosis can result in completely or partially blocking of the blood flow to certain regions of the heart. Prevention or slowing down the formation of abnormal fatty deposit would prevent these vascular problems caused by exaggerated blood clotting. It is expected that the compound decreases the initiation of clot formation. Thus the study drug may be beneficial in the prevention or decrease of vascular problems caused by formation of potentially dangerous blood clots.

In this study you will also receive diltiazem (Cardizem® LA). Diltiazem LA is a registered drug, which belongs to a family of drugs known as *calcium channel blockers*. It causes reduction in blood pressure, hence it is used in treating patients with coronary artery disease, high blood pressure and abnormal heart rhythms. Since administration of the study drug with diltiazem to patients with cardiovascular disease is likely, our purpose in this study is to determine whether, and if so, in what extent diltiazem affects the metabolism (the breakdown and disposition) of the study drug in humans after administration.

Study objective

Primary:
to evaluate the effects of a moderate CYP3A4/5 inhibitor, diltiazem on the pharmacokinetics and pharmacodynamics (Thrombin and TRAP-induced platelet aggregation) of the study drug and its known metabolites

secundary:
to evaluate the effects of co-administration of diltiazem and the study drug on the pharmacokinetics of diltiazem and its metabolites.
to evaluate the effects of co-administration of diltiazem and the study drug on QTcF interval compared to the study drug alone.
to assess the safety and tolerability of a single dose of the study drug when given either alone or in combination with diltiazem

Study design

Design:
an open-label, randomized, two arm, single-sequence, crossover, drug-drug interaction study in twenty-four healthy male and/or healthy female subjects each receiving a single oral dose of the study drug in Period 1, and an oral dose of diltiazem once daily on Days 1-14 and a single oral dose of the study drug co-administered with diltiazem on Day 8 in Period 2; a washout of seven days between dosing

Procedures and assessments;
clinical laboratory (including PT and aPTT), vital signs, physical examination, weight, 12-lead ECG; at eligibility screening: medical history, urine drug screen, HBsAg, anti HCV, anti-HIV 1/2 and serum pregnancy test (females only); abbreviated physical examination, vital signs, 12-lead ECG, urine drug screen, serum pregnancy test (females only) and clinical laboratory (including PT and aPTT) to be repeated upon each admission; follow-up on Day 18 (Period 2)

Observation period:
Period 1: in clinic from -41 h up to 72 h after drug administration and ambulatory visits on Days 5 and 6
Period 2: in clinic from -41 h before diltiazem administration on Day 1 up to

168 h after drug administration on Day 8

Blood sampling:
for pharmacokinetics of E5555: pre-dose and 1, 2, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120 and 144 h post-dose (Period 1) and pre-dose and 1, 2, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 240 h post-dose on Day 8 (Period 2)

for pharmacokinetics of diltiazem: pre-diltiazem dose on Days 5 and 6, pre-diltiazem dose and 2, 4, 5, 6, 8, 10, 12, 14 and 16 h post-diltiazem dose on Day 7 and pre-diltiazem dose and 2, 4, 6, 8, 10, 12, 14, 16 and 24 h post-diltiazem dose on Day 8 (Period 2)

for TRAP- and thrombin-induced platelet aggregation: -24 h pre-dose, pre-dose, 1, 2, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120 and 144 h post-dose (Period 1), pre-dose and 1, 2, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 240 h post-dose on Day 8 (Period 2)

for arachidonic acid-induced platelet aggregation: -48 h pre-dose (Period 1)

Safety
adverse events: throughout the study; vital signs: pre-dose and 2, 4, 5, 6, 8, 12 and 23 h post-dose on Days -1 and 1 and once on Days -2, 2 and 4 (Period 1) and pre-dose and 4, 8, 12 h post-dose on Day 1 and pre-dose and 2, 4, 5, 6, 8, 12 and 23 h post-dose on Days 7 (relative to diltiazam dosing) and 8 and once on Days -2, 4, 9, 10, 12 and 15 (Period 2); weight: once on Day -1 (Period 1); 12-lead ECG: once on Days -2 and 4 (period 1) and once on Days -2, 1, 6, 10 and 15 (Period 2); clinical laboratory: once on Day 2 (Period 1) and once on Day 8 (Period 2)

Bioanalysis
analysis of E5555 and diltiazem samples using validated methods by Sponsor
analysis of TRAP- and thrombin-induced platelet aggregation by PRA
analysis of arachidonic acid-induced platelet aggregation by PRA

Intervention

Active substance: E5555

1 group with 2 dosing arms

arm 1
Period 1: single dose of 100 mg E5555
Period 2: single dose of 100 mg E5555 and a daily dose of 360 mg diltiazemduring during 14 days

Arm 2
Period 1: single dose of 300 mg E5555

Period 2: single dose of 300 mg E5555 and a daily dose of 360 mg diltiazemduring during 14 days

Study burden and risks

Procedures: pain, light bleeding, heamatoma, possibly an infection.

Contacts

Public
Eisai

Mosquito Way
Hatfield AL10 9SN
GB
Scientific
Eisai

Mosquito Way
Hatfield AL10 9SN
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy males or females
18-55 years
non smoker or have not used nicotine-containing products for at least 3 months prior to first

dosing
BMI between 18.0 and 32.0 kg/m2
no known personal or family medical history of bleeding disorders, or spontaneous gum bleeding by history

Exclusion criteria

1. A family history, past medical history or clinical signs and symptoms of a bleeding diathesis
2. History of any medical condition, which will result in an increased risk of bleeding including but not limited to active or recurrent gastric ulcers, recent head trauma or surgery, severe hypertension, bacterial endocarditis, etc
3. Subjects with a history of spontaneous gum bleeding or clinical signs and symptoms on physical exam
4. Clinically significant ocular disease or untreated visual or ocular symptoms
5. Clinically significant abnormal ECGs prior to dosing (Screening or Baselines) including a QT interval corrected for heart rate using Bazett*s formula (QTcB) > 450 ms for males and > 470 ms for females
6. Any history or past medical condition that will result in QTc prolongation or tachyarrhythmia such as Torsades de Pointes (includes hypokalemia, known family history of long QT syndrome, or any other known risk factors for Torsades de Pointes)
7. Subjects with renal insufficiency (i.e., a glomerular filtration rate (GFR) <60 mL/min/1.733)
8. A platelet count < 150,000 or > 390,000 per mL at Screening or Baseline Period 1
9. Abnormal (< 80%) arachidonic acid induced platelet aggregation at Baseline Period 1
10. History of unexplained syncope, hepato-biliary disease, sinus bradycardia, heart blocks, sick-sinus syndrome, cardiogenic shock, heart failure, seizures, or chronic obstructive lung disease
11. Systolic blood pressure < 100 millimeters of mercury (mmHg) at Screening or Baseline Period 1
12. A,PT, aPTT * 1.10 times ULN at Baseline (Period 1)
13. Received blood, donated blood, or experienced significant blood loss within 60 days prior to check-in
14. Previous history of anaphylactic or anaphylactoid reactions or known hypersensitivity to one or more drugs
15. Hypersensitivity to diltiazem or related compounds or ingredients in the formulation

Study design

Design

Study type:	Interventional

Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-10-2010
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cardizem® LA
Generic name:	Diltiazem
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-09-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-09-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	19-10-2010
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	EUCTR2010-022226-32-NL
CCMO	NL33760.056.10