A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP STUDY EVALUATING THE EFFICACY AND SAFETY OF CO-ADMINISTRATION OF TRIPLE COMBINATIONS OF OLMESARTAN MEDOXOMIL, AMLODIPINE BESYLATE, AND HYDROCHLOROTHIAZIDE COMPARED WITH THE CORRESPONDING OLMESARTAN-AMLODIPINE COMBINATION IN SUBJECTS WITH HYPERTENSION

Published: 17-04-2009
Last updated: 06-05-2024

Primary Objective1. The main objective of this study is to demonstrate that OM/AML/HCTZ triple combinations are more efficacious in lowering SeDBP than corresponding dual combinations of OM/AML after 10 weeks of double blind treatment.Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON35387

Source
ToetsingOnline

Brief title
Parallel study

Condition

- Vascular hypertensive disorders

Synonym
Essential hypertension, high blood pressure

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical
Source(s) of monetary or material Support: Daiichi Sankyo Europe GmbH

Intervention

Keyword: CS-8635, Essential hypertension, olmesartan-medoxomil/amlodipine/hydrochlorothiazide, Triple Combination Therapy

Outcome measures

Primary outcome

Primary efficacy endpoint: 1. Change from baseline to the end of Week 10 (end

of Period II) in mean trough SeDBP.

Secondary outcome

Secondary efficacy variables will include the following:

1. Change from baseline to Weeks 4, 6, and 8 (Period II) in mean trough SeDBP;

2. Change from baseline to Weeks 4, 6, 8, and 10 (Period II) in mean trough

SeSBP;

3. Number (%) of subjects achieving trough SeBP goals (listed below) at Weeks

4, 6, 8, and 10 (Period II):

• SeBP < 140/90 mmHg for non-diabetics

• SeBP < 130/80 mmHg for diabetics and those with chronic renal disease (defined as creatinine clearance >= 30mL/min and <= 60 mL/min) or chronic cardiovascular disease

4. Number (%) of subjects achieving trough SeBP thresholds (listed below) at Weeks 4, 6, 8, and 10 (Period II):

• SeBP <140/90 mmHg

• SeBP <130/85 mmHg

• SeBP <130/80 mmHg

• SeBP <120/80 mmHg

• SeDBP < 90 mmHg

• SeSBP < 140 mm Hg

5. Number (%) of subjects achieving trough seated BP goals and thresholds (listed above) while taking each of the available triple combinations (titration steps) in Periods III-VI;

6. Change in SeBP from immediately before the first dose to last dose of each triple combination titration step in Periods III-VI, especially for the purposes of comparing the following titration steps:

• OM/AML/HCTZ 20/5/12.5 mg vs. 40/5/12.5 mg in Period IV

• OM/AML/HCTZ 40/5/12.5 mg vs. 40/5/25 mg in Period V

• OM/AML/HCTZ 40/5/25 mg vs. 40/10/25 mg in Period VI

Study description

Background summary

It is expected that future BP goals will become even more rigorous and, consequently, more aggressive antihypertensive therapy will be needed. In the case of a fixed combination of OM, AML, and HCTZ, co-administration of the three components is expected to provide at least additive efficacy and assure more subjects reaching treatment goals with minimum titration, with the combination being more effective than any dual combination therapy. Benefits can be achieved through use of these three therapies in free combination; however, the use of a fixed combination will lead to a simplification of therapy and improved compliance, especially for those for whom this therapy would be most appropriate (subjects who require > 20/10 mmHg BP reduction). Poor compliance can contribute to the failure to achieve therapeutic goals and impact the incidence of future cardiovascular events. The use of FDC antihypertensive agents is now well established as a means of simplifying therapy, thus helping to prevent treatment failures that might result from missed doses.

Study objective

Primary Objective
1. The main objective of this study is to demonstrate that OM/AML/HCTZ triple combinations are more efficacious in lowering SeDBP than corresponding dual combinations of OM/AML after 10 weeks of double blind treatment.

Secondary Objectives-

Period I to II (Day 1 through Week 10)
1. To evaluate the antihypertensive efficacy for SeSBP lowering with co-administration of various doses of the triple combination OM/AML/HCTZ compared to the corresponding dual combinations of OM/AML after 4, 6, 8, and 10 weeks of double-blind treatment.
2. To evaluate the antihypertensive efficacy for SeDBP lowering with co-administration of various doses of the triple combination OM/AML/HCTZ compared to the corresponding dual combinations of OM/AML after 4, 6, and 8 weeks of double-blind treatment.
3. To evaluate the number (%) of subjects achieving BP goal (defined as blood pressure < 140/90 mmHg , < 130/80 mmHg for diabetics or those with chronic renal disease [defined as creatinine clearance, CrCl >= 30 mL/min and <= 60 mL/min] or chronic cardiovascular disease) after 4, 6, 8, and 10 weeks of double-blind treatment.
4. To evaluate the number (%) of subjects achieving respective SeBP thresholds of < 140/90 mmHg, < 130/85 mmHg, < 130/80 mmHg and < 120/80 mmHg, SeDBP < 90 mmHg and SeSBP < 140 mmHg after 4, 6, 8, and 10 weeks of double-blind treatment.
5. Exploratory evaluation of the results of the Patient Reported Outcomes (PRO) Questionnaires at baseline and Week 10.

Period III to VI (Week 11 through Week 54)
1. To gain long-term efficacy and safety experience with administration of a

sequential algorithm of triple combination treatments of OM/AML/HCTZ while treating subjects to BP goal as defined in the 3rd secondary objective for Periods I-II.
2. To evaluate the number (%) of subjects achieving BP goal and SeBP thresholds (defined in the 3rd and 4th secondary objective for Periods I-II) for each of the available triple combination therapies(see protocol page 38).
3. To evaluate under randomised, double-blind, controlled conditions, the benefit of triple therapy up-titration from OM/AML/HCTZ 20/5/12.5 mg to 40/5/12.5 mg (Period IV) and from 40/5/12.5 mg to 40/5/25 mg (Period V).
4. To evaluate under open-label conditions, the benefit of triple therapy up-titration from OM/AML/HCTZ 40/5/25 mg to 40/10/25 mg (Period VI see protocol page 39).
5. Exploratory evaluation of the results of the PRO Questionnaires at Week 26 and Week 54.

Study design

This is a Phase III multicentre study with a randomised double-blind placebo-controlled parallel-group part (Periods I-II) followed by a transition (Periods III-V) to an open-label titration part (Period VI). Approximately 230 sites in Europe will participate.

Periods I and II constitute the parallel-group controlled portion of the study. Period I is a double-blind, safety run-in period. At the start of Period I subjects will be randomised to receive a treatment sequence for Period I and Period II (placebo to dual, dual to dual or dual to triple combination therapy). Period II is a double-blind treatment period. During Period II, there will be 8 treatment regimens (three possible dual combinations, and five possible triple combinations).

During Periods III-VI, subjects will be on a triple combination.
Period III is a single-blind treatment period.
Periods IV and V are double-blind treatment periods.
Period VI is an open-label titration period.

Intervention

The following combinations of OM/AML/HCTZ in mg are possible during the study (intake once daily):
Period I: 20/5/0, 40/5/0, 40/10/0 or 0/0/0 (60 subjects)
Period II: 20/5/0, 20/5/12,5, 40/5/0, 40/5/12.5, 40/5/25, 40/10/0, 40/10/12.5 or 40/10/25
Period III: 20/5/12,5
Period IV: 20/5/12,5 or 40/5/12,5
Period V: 20/5/12,5, 40/5/12,5 or 40/5/25
Period VI: 20/5/12,5, 40/5/12,5, 40/5/25, 40/10/12,5 or 40/10/25

See also overview on page 43 of the study protocol.

Study burden and risks

Total study duration from Screening through follow-up will be approximately 59 weeks. The Screening/Washout period will be up to 3 weeks. Duration of subject treatment will be 54 weeks with the addition of a 2-week follow-up for safety assessment.

Inconvenience:
During this study 17 visits will take place.
For each visit the subject must come in the morning to the hospital or doctors practice.
Blood pressure measurements will be performed three times at each study visit.
Subjects must abstain from smoking or drinking coffee or alcohol for at least 2 hours prior to every clinic visit.
Subjects must abstain from physical exercise or exposure to cold for 30 minutes prior to blood pressure measurements.
During each visit vital signs will be measured.
Subjects will be asked to measure their blood pressure daily and record this in a patient diary.
Height will be measured during one study visit.
During 1 visit a complete medical history will take place.
During 2 visits a physical examination will take place.
During 4 study visits a 12-lead ECG will be recorded (additional ECGs may be performed if the study doctor thinks this is necessary).
During 4 study visits subjects will complete the Patient Reported Outcome (PRO) questionnaires.
During 5 study visits weight measurement will be taken.
During 5 study visits blood samples will be drawn and urine sample collected for laboratory safety analysis. Additional lab sample may be obtained if any clinically significant laboratory abnormalities are noted.
During 11 study visits a urine pregnancy test administered to female subjects of childbearing potential.
Subjects will be instructed to maintain their current dietary habits (including sodium intake), exercise and alcohol consumption and not to deviate from this regimen for the duration of the study.
The study doctor may ask the subject to come for an additional visit at any time during the study.
See page 158 from the study protocol.

Possible risks:

No new unexpected safety concerns were identified with open-label triple combination therapy over the 44-week treatment period in the studies CS8663-U-A301 and CS8663-A-E303. A higher frequency of edema was observed with 10 mg AML combination treatment regimens than with the 5 mg AML combination

treatment regimen. With the exception of edema, the safety profile in this study was consistent with the safety profile for an ARB, a dihydropyridine CCB, and a diuretic given as monotherapy. The incidence of hypotension was < 1.0% and did not appear to be dose related.
In the post marketing experience with subjects taking these three drugs concomitant dosing, the single most frequently reported adverse event was dizziness. The overall pattern of adverse event reactions received is consistent with the known safety profile for the three drugs.

The risks of this research are minimal as all medicines are registered in the Netherlands.

Contacts

Public
Daiichi Pharmaceutical

Zielstattstrasse 48
81379 Munich
DE
Scientific
Daiichi Pharmaceutical

Zielstattstrasse 48
81379 Munich
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female subjects aged 18 years or older.
2. Subjects with mean trough SeBP >= 160/100 mmHg (SeSBP >= 160 mmHg and SeDBP >= 100 mmHg) at Screening if not currently on antihypertensive medication (newly diagnosed subjects or subjects who are not taking any antihypertensive medication for at least 3 weeks).
OR:
Subjects with mean trough SeBP >= 160/100 mmHg (SeSBP >= 160 mmHg and SeDBP >= 100 mmHg) after washout of prior antihypertensive medication in subjects who discontinued their previous antihypertensive medication.The difference in mean SeSBP/SeDBP between the visit prior to randomisation and the randomisation visit must be <= 20/10 mmHg. Subjects not currently on HTN medication may meet this requirement at the screening visit (Visit 1) and the randomization visit (Visit 3). Subjects washing out of HTN medication must meet this requirement at least by Visit 2 (or Visit 2.1, if needed) and Visit 3. All subjects undergoing washout of their prior antihypertensive medication will have the opportunity to re-visit the study sites for additional visits during washout (Visits 2 and 2.1) to assess eligibility for randomisation.
3. Subjects freely sign ICF after the nature of the study and the disclosure of his/her data has been explained.
4. Female subjects of childbearing potential must be using adequate contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least three months prior to the start of this study [Visit 1]). Adequate contraceptives include hormonal intra-uterine devices, hormonal contraceptives (oral, depot, patch or injectable), and double barrier methods such as condoms or diaphragms with spermicidal gel or foam. If a female becomes pregnant during the study, she has to be withdrawn from the study immediately.

Exclusion criteria

1. Female subjects of childbearing potential who are pregnant or lactating.
2. Subjects with serious disorders which may limit the ability to evaluate the efficacy or safety of the investigational products, including cerebrovascular, cardiovascular, renal, respiratory, hepatic, gastrointestinal, endocrine or metabolic, haematologic or, neurologic, and psychiatric diseases. The same applies for immunocompromised and/or neutropenic subjects.
3. Subjects having a history of the following within the last six months: MI, unstable angina pectoris, percutaneous coronary intervention, heart failure, hypertensive encephalopathy, cerebrovascular accident (stroke), or transient ischaemic attack.
4. Subjects with clinically significant abnormal laboratory values at Screening, including subjects with one or more of the following:
• Aspartate aminotransferase (AST) > 3 times upper limit of normal (ULN)
• ALT > 3 times ULN
• Gamma-glutamyl transferase (GGT) > 3 times ULN

• Potassium above ULN (unless high value is due to haemolytic blood sample)
5. Subjects with secondary HTN of any aetiology such as renal disease, phaeochromocytoma, or Cushing*s syndrome.
6. Subjects with contraindication to OM, AML, HCTZ, or any of the excipients
7. Newly diagnosed subjects with a mean trough SeSBP > 200 mmHg or mean trough SeDBP > 115 mmHg or any subject with bradycardia (heart rate < 50 beats/min at rest documented by mean radial PR or ECG at Screening (Visit 1) or immediately before taking Period I study medication (Visit 3)).
8. Subjects already taking four or more antihypertensive medications.
9. Subjects with a mean trough SeSBP > 145 mmHg or mean trough SeDBP > 95 mmHg while taking three antihypertensive medications.
10. Subjects with a mean trough SeSBP > 160 mmHg or mean trough SeDBP > 100 mmHg while taking two antihypertensive medications.
11. Subjects with a mean trough SeSBP > 180 mmHg or mean trough SeDBP > 110 mmHg while taking one antihypertensive medication.
12. Subjects with ECG evidence of 2nd or 3rd degree atrio-ventricular (AV) block, atrial fibrillation, or other cardiac arrhythmia (requiring treatment).
13. Subjects with severe heart failure (New York Heart Association stage III IV), clinically significant aortic or mitral valve stenosis, uncorrected coarctation of the aorta, obstruction of cardiac outflow (obstructive, hypertrophic cardiomyopathy) or symptomatic coronary disease.
14. Subjects with clinical evidence of renal disease including reno-vascular occlusive disease, nephrectomy and/or renal transplant, bilateral renal artery stenosis, unilateral renal artery stenosis in a solitary kidney, or severe renal impairment as evidenced by CrCl < 30 mL/min calculated using the Cockcroft and Gault formula.
15. Subjects with clinically relevant hepatic impairment.
16. Subjects with biliary obstruction.
17. Subjects with uncontrolled Type 1 or Type 2 diabetes defined as glycosylated haemoglobin (HbA1c) > 9.0%. Diabetics must have documentation of HbA1c within 6 months of the Screening Visit, or must have their HbA1c assessed prior to randomisation. Note: Subjects with Type 1 or Type 2 diabetes controlled with insulin, diet or oral hypoglycaemic agents on a stable dose for at least 30 days may be included.
18. Subjects with a history of a wasting disease (e.g. cancer), autoimmune diseases, connective tissue diseases, major allergies or angioneurotic oedema.
19. Subjects who require or are taking any concomitant medication which may interfere with the objectives of the study.
20. Subjects with known malabsorption syndromes.
21. Subjects with psychiatric or emotional problems, which would invalidate the giving of informed consent or limit the ability of the subject to comply with study requirements.
22. Subjects on beta blockers or calcium channel blockers (CCBs) for both hypertension and either ischemia, post-MI prophylaxis or tachyarrhythmias.
23. Subjects with a history of alcohol and/or drug abuse.
24. Subjects who have received any investigational agent within 30 days prior to Screening.
25. Subjects who are unwilling or unable to provide informed consent or to participate satisfactorily for the entire study.
26. Subjects with malignancy during the past 2 years excluding squamous cell or basal cell carcinoma of the skin.
27. Subjects with signs or symptoms which could exacerbate the occurrence of hypotension

such as volume and salt depletion.
28. Subjects with any medical condition, which in the judgment of the Investigator would jeopardise the evaluation of efficacy or safety and/or constitute a significant safety risk to the subject.

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):	24-08-2009
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	hydrochlorothiazide (HCTZ)12.5-1 A Pharma
Generic name:	hydrochlorothiazide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	Olmesartan medoxomil (OM) / amlodipine besylate (AML) / hydrochlorothiazide (HCTZ) 40/10/25 mg, 40/1
Product type:	Medicine
Brand name:	Sevikar 20 mg /5 mg, 40 mg /5 mg and 40 mg /10 mg

Generic name:	Olmesartan medoxomil (OM) / amlodipine besylate (AML) 20 mg /5 mg, 40 mg /5 mg and 40 mg /10 mg
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-04-2009
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-06-2009
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-04-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	STEG: Stichting Therapeutische Evaluatie Geneesmiddelen (Almere)
Approved WMO Date:	09-12-2010
Application type:	Amendment
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	EUCTR2008-003534-25-NL
CCMO	NL27705.040.09