A RANDOMISED, DOUBLE-BLIND, ADD-ON STUDY OF HYDROCHLOROTHIAZIDE IN SUBJECTS WITH MODERATE TO SEVERE HYPERTENSION NOT ACHIEVING TARGET BLOOD PRESSURE ON OLMESARTAN MEDOXOMIL/AMLODIPINE FIXED DOSE COMBINATION 40/10 MG ALONE

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Primary: Period II (Week 8 to Week 16)1. To demonstrate the additional antihypertensive efficacy for seated diastolic blood pressure (SeDBP) gained by adding HCTZ 12.5 or 25 mg to the treatment regimen in subjects with moderate to severe HTN not…

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

Summary

ID

NL-OMON35561

Source
ToetsingOnline

Brief title
Add-on 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: Combination Therapy, CS-8635, Essential hypertension, olmesartan-medoxomil/amlodipine/hydrochlorothiazide

Outcome measures

Primary outcome

Primary efficacy endpoint: The mean change in trough SeDBP from the

randomisation visit (end of the OM/AML run-in period [Week 8]) to the end of

the double-blind Period II (Week 16).

Secondary outcome

Secondary efficacy endpoints will include the following:

1. Mean change from the double-blind randomisation visit (Week 8) to Week 12 in

trough SeDBP.

2. Mean change from the double-blind randomisation visit (Week 8) in trough

SeSBP to Week 12 and Week 16.

3. Mean changes from the double-blind randomisation visit (Week 8) to Week 16

in daytime, night-time, and 24 hour DBP and SBP, assessed by 24 hour ABPM.

4. Evaluation of the number (%) of subjects achieving BP goal and BP thresholds

at Weeks 16, 24, and 32.

5. Evaluation of the clinical benefit of up-titration from OM/AML/HCTZ

40/10/12.5 mg to 40/10/25 mg during Period IV in terms of conventional BP and

ABPM parameters.

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.
The rationale for the study design for each period attempts to elucidate issues concerning combination therapy that may occur in clinical practice.

Study objective

Primary: Period II (Week 8 to Week 16)
1. To demonstrate the additional antihypertensive efficacy for seated diastolic blood pressure (SeDBP) gained by adding HCTZ 12.5 or 25 mg to the treatment regimen in subjects with moderate to severe HTN not adequately controlled on OM/AML 40/10 mg alone at Week 16 (after 8 weeks of double-blind treatment) using conventional blood pressure (BP) measurement.
Secondary:
Period II (Week 8 to Week 16)
1. To evaluate the antihypertensive efficacy for SeDBP of the triple combinations OM/AML/HCTZ 40/10/12.5 and 40/10/25 mg vs. OM/AML 40/10 mg at Week 12 (after 4 weeks of double-blind treatment) (conventional BP measurement).
2. To evaluate the antihypertensive efficacy for seated systolic blood pressure (SeSBP) of the triple combinations OM/AML/HCTZ 40/10/12.5 and 40/10/25 mg vs. OM/AML 40/10 mg at Weeks 12 and 16 using conventional BP measurement.
3. To evaluate the antihypertensive efficacy from baseline (Week 8) to Week 16, in daytime, night-time, and 24-hour diastolic blood pressure (DBP) and systolic blood pressure (SBP), assessed by 24-hour ambulatory blood pressure measurement (ABPM).

4. To evaluate the number (%) of subjects achieving BP goal (defined as SeBP < 140/90 mmHg for non-diabetics and < 130/80 mmHg for diabetics and those with chronic renal disease [defined as creatinine clearance, CrCl >= 30 mL/min and <= 60 mL/min] or chronic cardiovascular disease), as well as 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 mm Hg at Weeks
12 and 16.
5. To evaluate the safety and tolerability of triple combination therapy during Weeks 8 to 16.
Periods III and IV (Week 16 to Week 32)
1. To evaluate the antihypertensive efficacy of up-titration to OM/AML/HCTZ 40/10/25 mg in subjects not reaching BP goal on OM/AML/HCTZ 40/10/12.5 mg based on changes from Week 24 to Week 32 in conventional BP measurement and in daytime, night-time, and 24-hour DBP and SBP assessed by 24-hour ABPM.
2. To evaluate the number (%) of subjects achieving BP goal and BP thresholds (defined in secondary objective number 4) at Week 32.
3. To evaluate the safety and tolerability of triple combination therapy during Weeks 16 to 32.

Study design

A phase III, multicentre, multinational, randomized, double-blind, Add-On Study of Hydrochlorothiazide in subjects with moderate to severe hypertension not achieving target blood pressure on Olmesartan Medoxomil/Amlodipine fixed dose combination 40/10 mg alone consisting of the following 4 periods.
1. Period I: Period I is an 8-week, single-blind, run-in period consisting of treatment with OM/AML 40/10 mg. A 5-week Screening/Taper-Off period will be conducted prior to Period I if appropriate.
2. Period II: At the end of Period I, subjects with a mean trough SeDBP >= 90 mmHg and a mean trough SeSBP >=140 mmHg will be randomized to double-blind treatment consisting of OM/AML/HCTZ 40/10/0, 40/10/12.5, or 40/10/25 mg combination therapy during Period II (1:1:1 randomization ratio).
3. Period III: At the end of Period II, all subjects completing Period II will enter Period III and receive single-blind treatment with OM/AML/HCTZ 40/10/12.5 mg for 8 weeks.
4. Period IV: Subjects not at BP goal at the end of Period III will be randomized to receive either OM/AML/HCTZ 40/10/12.5 (control group) or 40/10/25 mg in a double-blind manner (1:2 randomization ratio), for the remaining 8 weeks of the study (Period IV). Subjects at BP goal at the end of Period III will continue on OM/AML/HCTZ 40/10/12.5 mg during Period IV.

CS-8635 is consists of a triple combination of OM, AML, and HCTZ. In this study, the components are used in triple combinations matching the planned CS-8635 strengths. However, this study does not use a fixed CS-8635 formulation.

Intervention

This study will aim to demonstrate the additional antihypertensive efficacy for SeDBP gained by adding hydrochlorothiazide (HCTZ) in 12,5 mg or 25 mg to the treatment regimen in subjects with moderate to severe hypertension not adequately controlled on olmesartan medoxomil (OM) and amlodipine besylate (AML) 40/ 10 mg alone.

See Figure 3.1 on page 40 in the protocol.

Study burden and risks

Total study duration from Screening through follow-up will be approximately 39 weeks. The Screening/Taper-Off period will be up to 5 weeks. Duration of subject treatment will be 32 weeks with the addition of a 2-week follow-up for safety assessment.

Inconvenience:
During this study 11 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 at each study visit. Subjects must abstain from smoking or drinking coffee 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.
Subjects will be asked to measure their blood pressure daily and record this in a patient diary.
During 5 visits subjects will be asked to meet with their doctor also on the day before the visit so that a 24 hour ambulatory blood pressure monitoring device can be given to the subject.
3 ECGs will be performed during some study visits (additional ECGs may be performed if the study doctor thinks this is necessary).
During some visits a physical exam will take place.
Blood samples will be collected and Urine Analysis (by dipstick) will be performed at 6 visits (including a possible Unscheduled Visit or Safety Follow-up Visit) for routine laboratory tests. At these visits, a urine pregnancy test will also be performed if you are a woman 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. Subjects who smoke must abstain from smoking at least 2 hours prior to every clinic visit.
The study doctor may ask the subject to come for an additional visit at any time during the study.
See page 126 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. 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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Written informed consent obtained from male or female aged 18 years or older with a mean trough of >=SeBP 160/100 mmHg (SeSBP of >= 160 mmHg and SeDBP >= 100 mmHg) at Screening if not currently on antihypertensive medication (e.g. newly diagnosed subjects).
OR:
For subjects on monotherapy: mean trough SeBP of >= 150/95 mmHg (SeSBP of >= 150 mmHg and SeDBP >= 95 mmHg) at Screening.
OR:
For subjects on any combination of antihypertensive medications that includes either HCTZ, OM or AML for a duration of at least four weeks: mean trough SeBP of >= 140/90 mmHg (SeSBP of >= 140 mmHg and SeDBP >= 90 mmHg) at Screening.
OR:
For subjects on any other combination of antihypertensive medications that includes neither HCTZ, OM nor AML: mean trough SeSBP >= 160 mmHg, mean trough SeDBP >= 100mmHg, at the end of the taper-off period.

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, haematological or oncological, neurological, 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: myocardial infarction (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)
•Alanine aminotransferase (ALT) > 3 times ULN
•Gamma-glutamyltransferase (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.Subjects with a mean SeSBP > 200 mmHg or mean SeDBP > 115 mmHg or bradycardia (heart rate < 50 beats/min at rest documented by mean radial pulse rate [PR] or

electrocardiogram [ECG]) at Screening (Visit 1) or immediately before taking Period I study medication (Visit 2).
8.Subjects already taking four or more antihypertensive medications.
9.Subjects with ECG evidence of 2nd or 3rd degree atrio ventricular (AV) block, atrial fibrillation, or other cardiac arrhythmia (requiring treatment).
10.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.
11.Subjects with clinical evidence of renal disease including renovascular 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 of < 30 mL/min calculated using the Cockcroft and Gault formula.
12.Subjects with clinically relevant hepatic impairment.
13.Subjects with biliary obstruction.
14.Subjects with a history of a wasting disease (e.g. cancer), autoimmune diseases, connective tissue diseases, major allergies or angioneurotic oedema.
15.Subjects who require or are taking any concomitant medication which may interfere with the objectives of the study.
16.Subjects with known malabsorption syndromes.
17.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.
18.Subjects with a current history of alcohol and/or drug abuse.
19.Subjects who have received any investigational drug within 30 days prior to Screening.
20.Subjects who are unwilling or unable to provide Informed Consent or to participate satisfactorily for the entire study.
21.Signs or symptoms which could exacerbate the occurrence of hypotension such as volume and salt depletion.
22.Uncontrolled Type 1 or Type 2 diabetes defined as an HbA1c > 9.0%. Diabetics must have documentation of an HbA1c level within 6 months of the Screening Visit, or must have their HbA1c level documented 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.
23.Subjects with malignancy during the past 2 years excluding squamous cell or basal cell carcinoma of the skin.
24.A subject 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.
25.Subjects on beta blockers or calcium channel blockers (CCBs) for both hypertension and either ischemia, post-MI prophylaxis or tachyarrhythmia.

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):	02-12-2009
Enrollment:	22
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:	Sevikar 40 mg /10 mg
Generic name:	Olmesartan medoxomil (OM) / amlodipine besylate (AML) 40 mg /10 mg
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	23-03-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	24-09-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	06-10-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	15-10-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	16-10-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	26-10-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	14-12-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	23-12-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	19-03-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-04-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-07-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-07-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2008-003535-20-NL
CCMO	NL27429.068.09