A Randomized, Open-Label, Phase 3 Study to Compare Long-Term Safety and Tolerability of the TAK-491 and Chlorthalidone Fixed-Dose Combination Versus Olmesartan Medoxomil and Hydrochlorothiazide Fixed-Dose Combination in Hypertensive Subjects With Moderate Renal Impairment

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The primary objective of this study is to evaluate the long-term safety and tolerability of the TAK-491CLD FDC in comparison to the OLM/HCTZ FDC in hypertensive subjects with moderate renal impairment.

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON36082

Source
ToetsingOnline

Brief title
TAK-491CLD_309

Condition

- Renal disorders (excl nephropathies)
- Vascular hypertensive disorders

Synonym
Hypertension with Moderate Renal Impairment / High bloodpressure with Moderate Kidney Failure

Research involving
Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Hypertension and Renal Impairment, Olmesartan Medoxomil and Hydrochlorothiazide FDC, Phase 3, TAK-491 and Chlorthalidone FDC

Outcome measures

Primary outcome

Primary endpoint of this study is the percentage of subjects with at least 1 AE

from Day 1 to Week 52.

Secondary outcome

Secondary Endpoints:

Percentage of subjects at final visit who reached their BP target:

• SBP/DBP (sitting, clinic), defined as <130/80 mmHg.

• SBP (sitting, clinic), defined as <130 mmHg.

• DBP (sitting, clinic), defined as <80 mmHg.

Additional Endpoints:

• Percentage of subjects with serum creatinine elevation greater than or equal

to 50% from baseline and greater than the upper limit of normal (ULN) OR eGFR <= 20 ml/min/1.73 m2 at the final visit (LOCF).

• Percentage of subjects with a creatinine elevation greater than or equal to 50% from baseline and greater than the ULN at each study visit and at final visit (LOCF).

• Percentage of subjects with a creatinine elevation greater than or equal to 30% from baseline and greater than the ULN at each study visit and at final visit (LOCF).

• Clinical safety laboratory tests, 12-lead ECG findings, and vital signs (including orthostatic vital signs).

• Change from Baseline in sitting, clinic SBP and DBP at each study visit.

• Population pharmacokinetics of TAK-536, TAK-536 M-II, and chlorthalidone in the TAK-491CLD treated group.

Study description

Background summary

A major component of blood pressure (BP) regulation is the renin-angiotensin-aldosterone system (RAAS), a system of hormone-mediated feedback interactions that results in the relaxation or constriction of blood vessels in response to various stimuli. Drugs that modulate the RAAS are used commonly worldwide for the treatment of hypertension. Of these, some block the synthesis of AII by inhibiting ACE (ACE inhibitors), while others inhibit the action of AII receptors (ARBs) by binding directly to the AT1 receptor, thereby allowing blood vessels to dilate, resulting in a reduction in BP. As a class, ARBs generally are considered more tolerable than other classes of antihypertensive agents, although there is still a need for compounds with improved tolerability and efficacy for the treatment of hypertension. TAK-491 is a prodrug that is rapidly hydrolyzed to the active moiety, TAK-536, which is a highly potent, long-acting ARB.

There are no known studies conducted to date that evaluate the safety of a RAAS blocker in combination with a chlorthalidone in renal impaired patients. This study is designed to evaluate renal safety, as well as general safety and tolerability of TAK-491CLD in comparison with OLM/HCTZ in hypertensive patients with moderate renal impairment.

Study objective

The primary objective of this study is to evaluate the long-term safety and tolerability of the TAK-491CLD FDC in comparison to the OLM/HCTZ FDC in hypertensive subjects with moderate renal impairment.

Study design

This is a global phase 3, 1-year (52-week), open-label, randomized comparison of the safety and tolerability of the TAK 491CLD FDC vs the OLM/HCTZ FDC in approximately 140 154 hypertensive subjects with moderate renal impairment.

Intervention

TAK-491CLD
• Day 1: All eligible subjects will receive a starting dose of TAK-491CLD 20/12.5 mg.
• Week 4 (and throughout the remainder of the study): Dose will be increased to TAK-491CLD 40/12.5 mg if needed to reach target BP.
• Week 8 (and throughout the remainder of the study): For subjects taking TAK-491CLD 40/12.5 mg, dose will be increased to TAK-491CLD 40/25 mg if needed to reach target BP.
•Week 12 (and throughout the remainder of the study): For subjects taking TAK-491CLD 40/25 mg or following down-titration due to tolerability issues, other antihypertensive treatments (except other ARBs or thiazide-type diuretics) can be added if needed to reach target BP. A calcium channel blocker, such as amlodipine, is recommended as the initial other class of antihypertensive agents.

OLM/HCTZ
• Day 1: All eligible subjects will receive a starting dose of OLM/HCTZ 20/12.5mg.
• Week 4 (and throughout the remainder of the study): Dose will be increased to OLM/HCTZ 20/25mg if needed to reach target BP.
• Week 8 (and throughout the remainder of the study): For subjects taking OLM/HCTZ 20/25mg or following down-titration due to tolerability issues, other antihypertensive treatments (except other ARBs or thiazide-type diuretics) will be added if needed to reach the target BP. A calcium channel blocker, such as amlodipine, is recommended as the initial other class of antihypertensive

agents.

Study burden and risks

Appropriate blood pressure management is particularly important in patients with chronic kidney disease due to the very high incidence of cardiovascular complications including stroke. Furthermore, blood pressure control can delay the progression of a number of different forms of chronic renal diseases. It is well known that RAAS blockade with either ACE inhibitors or ARBs delays renal disease progression.
Hypertensive patients with moderate renal impairment is a population with relatively more severe and resistant hypertension and, therefore, can benefit from effective FDC treatments such as an ARBs plus a thiazide-type diuretic for blood pressure control. There are no known studies conducted to date that evaluate the safety of a RAAS blocker in combination with a chlorthalidone in renal impaired patients. This study is designed to evaluate renal safety, as well as general safety and tolerability of TAK-491CLD in comparison with OLM/HCTZ in hypertensive patients with moderate renal impairment.

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

1. The subject is treated with 2 or 3 antihypertensive medications and on stable therapy, defined as >6 weeks on medication, and has a mean sitting clinic SBP >=135 and <=160 mmHg at the Screening Visit and on Day 1.
2. The subject has estimated glomerular filtration rate (eGFR) in the range of >=30 to <60 ml/min/1.73 m2 [Stage 3 chronic kidney disease (CKD)] at the Screening visit.
3. The subject is a man or woman and aged 18 years or older.
4. A female subject of childbearing potential who is sexually active with a male partner agrees to routinely use adequate contraception from signing of the informed consent through 30 days after the last study drug dose.
NOTE: Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, tubal ligation [performed more than one 1 year prior to Screening]) or who are postmenopausal (defined as at least 1 year since last regular menses).
5. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
6. The subject or, when applicable, the subject*s legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
7. The subject has clinical laboratory test results (clinical chemistry, hematology, and complete urinalysis) that the investigator does not consider to be clinically significant in this moderate renal impaired population.
8. The subject is willing to discontinue the current antihypertensive medications 2 days prior to randomization.

Exclusion criteria

1. The subject has received any investigational compound within 30 days prior to Screening or is currently participating in another investigational study.
2. The subject has been randomized/enrolled in a previous TAK-491 or TAK-491CLD study.
NOTE: This criterion does not apply to subjects who began participation in another TAK 491 or TAK-491CLD study but were not randomized/enrolled, nor does it apply to subjects who participated in observational studies that lacked an intervention or invasive procedure.
3. The subject receives a combination of OLM and HCTZ at the Screening visit.
4. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

5. The subject has a mean clinic DBP (sitting, trough) >110 mmHg on Day 1.
6. The subject has secondary hypertension of any etiology (eg, renovascular disease, pheochromocytoma, Cushing*s syndrome).
7. The subject has a recent history (within the last 6 months) of myocardial infarction, heart failure, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, hypertensive encephalopathy, cerebrovascular accident, or transient ischemic attack.
8. The subject has clinically significant cardiac conduction defects (ie, third-degree atrioventricular block, sick sinus syndrome).
9. The subject has hemodynamically significant left ventricular outflow obstruction due to aortic valvular disease.
10. The subject has severe renal dysfunction or disease [based on eGFR <30 mL/min/1.73m2 at screening] or nephrotic syndrome [defined as a urinary albumin/creatinine ratio >2000 mg/g at screening].
11. Subject has known or suspected unilateral or bilateral renal artery stenosis.
12. The subject has a history of cancer that has not been in remission for at least 5 years prior to the first dose of study drug. (This criterion does not apply to those subjects with basal cell or Stage 1 squamous cell carcinoma of the skin).
13. The subject has poorly-controlled type 1 or 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.5%) at Screening.
14. The subject has hypokalemia or hyperkalemia (defined as serum potassium outside of the normal reference range of the central laboratory).
15. The subject has an alanine aminotransferase or aspartate aminotransferase level of greater than 2.5 times the upper limit of normal, active liver disease, or jaundice.
16. The subject has any other known serious disease or condition that would compromise safety, might affect life expectancy, or make it difficult to successfully manage and follow the subject according to the protocol.
17. The subject has a history of hypersensitivity or allergies to ARBs or thiazide-type diuretics or other sulfonamide-derived compounds.
18. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within the past 2 years.
19. The subject is required to take excluded medications (see Section 7.3 Excluded Medications and Treatments).
20. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2011
Enrollment:	24
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	azilsartan medoxomil plus chlorthalidone fixed-dose combination
Product type:	Medicine
Brand name:	Olmetec Plus
Generic name:	olmesartan medoxomil-hydrochlorothiazide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-02-2011
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-07-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Approved WMO Date:	19-08-2011
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

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	EUCTR2010-023098-21-NL
CCMO	NL35552.072.11
Other	pending