A Phase-3 Randomized, Double-Blind, Efficacy and Safety Study Evaluating the Fixed Dose Combinations of TAK-491 Plus Chlorthalidone (40/12.5 mg and 40/25 mg) in Subjects With Grades 2 or 3 Essential Hypertension, Who Do Not Achieve Target Blood Pressure Following Treatment With TAK-491 40 mg Monotherapy.

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The objective of this phase-3 randomized study, with a double-blind treatment period of 8 weeksduration is to evaluate the efficacy and safety of the fixed dose combinations of TAK-491 pluschlorthalidone (40/12.5 mg and 40/25 mg) in subjects with...

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

Summary

ID

NL-OMON35852

Source
ToetsingOnline

Brief title
TAKEDA TAK-491CLD_307

Condition

- Vascular hypertensive disorders

Synonym
Grades 2 or 3 Hypertension/High blood pressure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Efficacy, Hypertension, Safety, Tak 491

Outcome measures

Primary outcome

Change from baseline to Week 8 in trough, sitting, clinic SBP.

Secondary outcome

* Change from baseline to Week 8 in trough, sitting, clinic DBP.

* Change from baseline to Week 8 in trough (22 to 24 hours after dosing) SBP as

measured by ABPM.

* Change from baseline to Week 8 in trough DBP as measured by ABPM.

* Change from baseline to week 8 in the following ABPM parameters:

- 24-hour mean SBP and DBP.

- Mean daytime (6 AM to 10 PM) SBP and DBP.

- Mean nighttime (12 AM to 6 AM) SBP and DBP.

- Mean SBP and DBP at 0 to 12 hours after dosing.

* Proportion of subjects who achieve target blood pressure at Week 8 as defined

by the following:

a) Trough, sitting clinic SBP <140 mm Hg (or <130 mm Hg for patients with

diabetes or CKD).

b) Trough, sitting, clinic DBP <90 mm Hg (or <80 mm Hg for patients with

diabetes or CKD).

c) Achieving both trough, sitting clinic SBP and DBP targets above.

Study description

Background summary

Nonclinical studies have indicated that TAK-491 reduces BP after single or multiple daily dosing
without tachycardia and without rebound hypertension after the withdrawal of treatment.
TAK-491 also demonstrated antiproteinuric effects in Wistar fatty rats with overt nephropathy and
increased insulin sensitivity in spontaneously hypertensive rats. TAK-491 is not expected to have
any untoward effects on the central nervous system or respiratory system. Its effect on the
cardiovascular system in conscious dogs was limited to a reduction in systolic BP (SBP), an
observation consistent with the pharmacodynamic profile of the compound.

TAK-491 has been evaluated in 17 phase 1 studies and 1 phase 2 study. The phase 3 program
consisted of 5 randomized, controlled, monotherapy studies of 6 weeks or 6 months duration;
2 randomized, controlled, 6-week studies in which TAK-491 was coadministered with the
thiazide-type diuretic chlorthalidone or the calcium channel blocker (CCB) amlodipine; and
2 open-label studies of up to 56 weeks duration. Results of the phase 3 program demonstrated that,
relative to placebo, the TAK-491 20, 40, and 80 mg doses produce clinically and statistically
significant reductions in SBP and diastolic blood pressure (DBP), as assessed by both ambulatory

blood pressure monitoring (ABPM) and clinic blood pressure measurements. The differences between doses were greater for subgroups of subjects characterized by more severe and/or resistant hypertension, including black subjects, subjects with renal impairment, and subjects with grade 3 hypertension. In each study, most of the blood pressure-lowering effect of TAK-491 was observed within 2 weeks of treatment; a plateau of effect was generally reached by week 4 and reductions were maintained through week 6 in short-term studies and over the long-term in two 6-month studies (and up to 1 year in open-label studies).
In two controlled studies, coadministration of TAK-491 with chlorthalidone (491-009) and amlodipine (491-010) provided additional blood pressure reduction compared with chlorthalidone or amlodipine monotherapy. In open-label studies, addition of diuretic therapy to treatment with TAK-491 led to additional blood pressure reductions in subjects who did not reach blood pressure targets after initiation of TAK-491.
In clinical studies, TAK-491 was well tolerated at doses up to 320 mg in healthy subjects and up to 80 mg in hypertensive subjects (maximal dose evaluated in this population).

Study objective

The objective of this phase-3 randomized study, with a double-blind treatment period of 8 weeks duration is to evaluate the efficacy and safety of the fixed dose combinations of TAK-491 plus chlorthalidone (40/12.5 mg and 40/25 mg) in subjects with grades 2 or 3 essential hypertension, who do not reach target blood pressure after 4 weeks of single-blind monotherapy treatment with TAK-491 40 mg. It will therefore determine whether the TAK-491CLD FDC can enable patients with essential hypertension not adequately controlled on 40 mg TAK-491 monotherapy alone to achieve target blood pressure. Patients with grades 2 or 3 hypertension [17] not controlled on TAK-491 40 mg monotherapy will be enrolled because these patients are likely to benefit from the addition of a second antihypertensive agent, in this case the diuretic chlorthalidone, to achieve target blood pressure. An FDC is also likely to improve patient compliance

compared with
co-administrating the two drugs separately.

Study design

This global phase-3 randomized study, with a double-blind treatment period of 8 weeks duration is designed to
evaluate the efficacy and safety of the fixed dose combinations (FDCs) of
TAK-491 plus chlorthalidone (40/12.5 mg
and 40/25 mg) in subjects with grades 2 or 3 essential hypertension who do not achieve target blood pressure
following 4 weeks of single-blind monotherapy treatment with TAK-491 40 mg. The subject must have grade 2-3
essential hypertension which is not adequately controlled, as defined by mean, trough, sitting, clinic SBP:
* >=160 to <=180 mm Hg in subjects who have not received any antihypertensive medication in the 14 days prior to
Visit 1
* >=150 to <=170 mm Hg in subjects taking 1 antihypertensive medication at Visit 1
* >=140 to <=160 mm Hg in subjects taking 2 antihypertensive medications at Visit 1
Approximately 390-405 patients (130-135/arm) will be randomized to one of the three active treatment arms at
approximately 130 sites in Europe.
Subjects will be screened approximately 4 weeks before enrolment into a 4-week single-blind TAK-491 40 mg
treatment period (Day -28 to Day -1). All subjects will participate in a
2-week, single-blind, placebo run-in period
(Days -42 to -29) immediately prior to the single-blind TAK-491 40 mg monotherapy treatment period. Subjects
taking antihypertensive medications at Visit 1 are required to participate in an additional 1-2-week washout period
(Days -56 or -49 to -42) of their previous antihypertensive agents. Subjects taking 2 antihypertensive medications
should stop the longer acting drug on Day -56 and then stop the second drug on Day -49. Subjects taking
1 antihypertensive medication should stop on Day -49 (unless this drug is chlorthalidone or amlodipine which must be
stopped on Day -56). All subjects on previous antihypertensive medications should have a minimum of 7 drug free
days prior to starting the placebo run-in. Subjects who have not received any antihypertensive medication in the
14 days prior to Visit 1 can start the placebo run-in as soon as all relevant inclusion and exclusion criteria, including
laboratory results, have been verified. Any subject taking other prohibited medications must stop taking these by
Day -42.

Subjects who qualify for the single-blind TAK-491 40 mg monotherapy treatment period [post-placebo run-in mean
24-hour systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM) of 140-175 mm Hg
inclusive and a sitting clinic SBP measurement of 160-190 mm Hg inclusive] will then receive 4 weeks treatment with
TAK-491 40 mg. Subjects who do not achieve target blood pressure following 4 weeks treatment with TAK-491
40 mg monotherapy (defined as trough, sitting, clinic SBP >= 140 mm Hg) will be randomized on Day 1 in a 1:1:1 ratio
to receive double-blind treatment with either TAK-491 40 mg alone, TAK-491CLD 40/12.5 mg or TAK-491CLD
40/25 mg for 8 weeks. Subjects achieving target blood pressure following 4 weeks of single-blind TAK-491 40 mg
monotherapy treatment period will not be eligible for randomization and will be withdrawn from the study.

Intervention

Taking investigational product.

Study burden and risks

Subjects not controlled on TAK-491 40 mg monotherapy will be enrolled because these subjects are likely to benefit from the addition of a second antihypertensive agent, in this case the potent diuretic chlorthalidone, to achieve target blood pressure. Initiation of combination treatment in these uncontrolled patients is consistent with hypertension guidelines.

The exclusion criteria for the study ensure that subjects with significant co-morbidity (e.g. severe cardiovascular disease or severe renal disease) who may be at risk by participation in the study are excluded. In addition, serum creatinine is being measured throughout the study and guidance for the management, withdrawal and follow-up of subjects with creatinine elevations is provided in Section 9.1.8.2 of the protocol. Patient safety is highlighted by having graded blood pressure entry criteria related to the number of antihypertensive medications being used by the subject, thereby reducing the chance of significant rebound hypertension following withdrawal of any medications during the washout period. If the patient is taking two antihypertensive medications, the withdrawal will be staggered with the longer acting medication being stopped first. Because of the long half-lives of chlorthalidone and amlodipine, these medications will be required to be washed-out during two
weeks prior to the start of the placebo run-in period. Subjects will also perform home blood pressure monitoring throughout the study. Finally, withdrawal criteria are clearly defined for subjects whose blood pressure

exceeds certain thresholds, outlined below.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• The subject has grade 2-3 essential hypertension which is not adequately controlled as defined by mean, trough,
sitting, clinic SBP: >=160 to <=180 mm Hg in subjects who have not received any antihypertensive medication in the 14 days prior to Visit 1.
- >=150 to <=170 mm Hg in subjects taking 1 antihypertensive medication at Visit 1.
- >=140 to <=160 mm Hg in subjects taking 2 antihypertensive medications at Visit 1.
• The subject has clinical laboratory test results (clinical chemistry, hematology, and complete urinalysis) within
the reference range for the testing laboratory or the investigator does not consider the

results to be clinically relevant for precluding entry in to the study in this hypertensive population.
• The subject is willing to discontinue current antihypertensive medications.
• The subject must have a post-placebo run-in, 24-hour mean SBP by ABPM of 140-175 mm Hg inclusive, and a sitting clinic SBP measurement of 160 to 190 mm Hg inclusive (determined by the mean of 3 sitting, trough, measurements on Day -29) to qualify for entry in to the 4 week single-blind TAK-491 40 mg monotherapy treatment testing period.
• The subject does not achieve target blood pressure (defined as clinic SBP >=140 mm Hg as determined by the mean of 3 sitting, trough, measurements) following 4 weeks single-blind treatment with TAK-491 40 mg monotherapy at Day -1, prior to randomization to double-blind treatment.

Exclusion criteria

• The subject has clinic DBP >110 mm Hg.
• The subject*s 3 SBP measurements at screening differ by more than 15 mm Hg (confirmed by a second set of three measurements).
• The subject is currently treated with more than 2 antihypertensive medications.
• The subject has secondary hypertension of any etiology (eg, renovascular disease, pheochromocytoma, Cushing*s syndrome).
•The subject has any history of myocardial infarction, heart failure, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, hypertensive encephalopathy, cerebrovascular accident, persistent or permanent atrial fibrillation or transient ischemic attack.
• The subject has clinically significant cardiac conduction defects (eg, third-degree atrioventricular block, sick sinus syndrome).
• The subject has severe renal dysfunction or disease [based on estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 at screening].
• The subject has poorly-controlled type 1 or 2 diabetes mellitus (hemoglobin A1c [HbA1c] >8.5%) at Screening

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:	Pending
Start date (anticipated):	26-09-2011
Enrollment:	28
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	TAK-491
Generic name:	Azilsartan Medoxomil plus Chorthalidone Fixed dose Combination

Ethics review

Approved WMO Date:	10-06-2011
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	28-09-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	20-10-2011
Application type:	First submission

Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	04-11-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-12-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	02-01-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	07-02-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO	

Date:	01-03-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	26-10-2012
Application type:	Amendment
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
Other	00
EudraCT	EUCTR2011-000220-16-NL
CCMO	NL36272.072.11