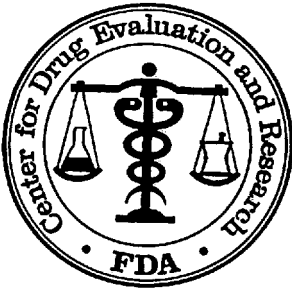


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200796Orig1s000

MEDICAL REVIEW(S)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 200796 Azilsartan medoxomil (Edarbi) for hypertension.

Sponsor: Takeda

Review date: 22 January 2011

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 200796
HFD-110/Childers/Targum

This memo conveys the Division's recommendation to issue an Approval letter for Edarbi for hypertension.

This application has been the subject of reviews of CMC (Shiromani and Jewell; 21 December 2010, 20 January 2011), biopharmaceutics (Chen; 20 December 2010, 18 January 2011), pharmacology/toxicology (Gatti and Link; 21 December 2011), clinical pharmacology (Menon-Andersen; 11 January 2011), and medical and statistics (Gordon and Lawrence; 16 December 2010, 3 January 2011). There is a comprehensive CDTL memo (Targum, 21 January 2011) with which I am largely in agreement.

What dose or doses should be approved remains somewhat in doubt, but at least 40- and 80-mg tablets are approvable with a 24-month expiry. Dissolution specifications have been set (I am unclear whether the sponsor has agreed) for tablets of 20, 40, and 80 mg.

Azilsartan medoxomil is an ester (same as olmesartan), cleaved at absorption. Azilsartan is an angiotensin receptor antagonist, apparently devoid of other relevant receptor mediated activities at relevant exposures.

In man, it is about 50% bioavailable, with no food effect. Exposure is dose-proportional. It is highly protein bound. Daily administration produces about 20% accumulation and a peak-trough ratio of about 5. It is thought to be primarily metabolized by 2C9, but exposure is not affected by the inhibitor fluconazole, nor does it affect exposure to tolbutamide (substrate). Moderate to severe renal impairment doubles exposure, clinically irrelevant. For no reason I see, the sponsor performed numerous other drug-drug interaction studies, showing no significant interactions.

The most comprehensive dose-response study incorporated doses of 5, 10, 20, 40, and 80 mg. By cuff and ABPM, 5 mg seems less effective, but there is little to distinguish doses of 10 to 80 mg. In a meeting 21 January, the sponsor presented cross-study and pooled analyses suggesting that 80 mg has a 1- to 2-mmHg larger effect (systolic) than 40 mg and maybe 3- to 4-mmHg larger effects than 20 mg. These analyses will probably be submitted by the sponsor in the next several weeks, and might influence the selection of dose or doses to be marketed.

The safety database includes over 4800 subjects studied at doses of 20 mg or greater, with over 200 at 80 mg for more than a year. The safety profile is the benign one typical of an ARB. Withdrawal rates from controlled studies are all quite low. There is apparently a small, non-progressive, reversible, dose-related effect on serum creatinine. The medical review describes it in terms of proportion of x-fold increases, so when you add another agent that bumps up serum creatinine—chlorthalidone—the number of

outliers increases, but the effects remain pretty small and reversible. There is no excess of real renal adverse events. I initially cited this phenomenon as a rationale to approve 40 mg and not 80 mg, but the effect seems fairly benign, the assay sensitivity is very high, and even a modest incremental effect on blood pressure probably has public health benefits.

So I can envision possibly approving 80 mg, based on review of dose response across the entire program, or 40 mg (if one has any concerns about the creatinine signal), but not both, as the blood pressure difference is too small to be detectable in clinical use and having both would delay someone who needs a greater blood pressure effect from getting effective additional therapy.

The review team has no consensus on whether 40 or 80 mg should be approved; it depends on how you interpret the creatinine data. There is, however, consensus that only one of these doses should be approved.

Standard labeling recommends starting a lower dose of other ARBs when adding to a diuretic. This might be the only rationale for naming or developing a suitable second dose. Safe use of initial therapy with chlorthalidone with azilsartan 80 mg should be examined with the sponsor's factorial study (needs review), so one can decide what to do with the general warning in this case.

Blacks, subject of a separate study, appear to respond, but less well, to azilsartan monotherapy. I have not seen data on use in blacks on background diuretics.

I and the rest of the review team find the application approvable. Selection of dose or doses is somewhat open, perhaps informed by the sponsor's expected submission. Likely, various options can be equally well defended.

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/s/

NORMAN L STOCKBRIDGE
02/08/2011

**Clinical Review
Safety Update**

Application Type NDA# 200796

Submission Type; Code: N_000, original
Letter Date August 25, 2010

Medical Reviewer Maryann Gordon, M.D.
Review Completion Date January 20, 2010

Established Name Azilsartan medoxomil

(Proposed) Trade Name Edarbi
Therapeutic Class Angiotensin II receptor blocker

Applicant Takeda Pharmaceuticals America, Inc
Priority Designation S

Formulation Tablets
Dosing Regimen Once daily
Indication Treatment of hypertension
Intended Population Hypertensive adults

Conclusions

There is a higher incidence rate of increased blood creatinine values in the subjects taking TAK-491 chlorthalidone combination compared to those taking TAK-491 HCTZ combination. There are no other safety conclusions that differ from the ones based on review of the ISS.

Background

The following safety information was added:

- Phase 3 Open-Label Pool: The ISS Phase 3 Open-Label Pool comprised integrated data from 1 completed (491-016) and 2 ongoing (491-006 and 491-301) phase 3 open-label studies.

- TAK-536 Program (under development in Japan): Updated SAE reports as of 01 June 2010 from these supportive phase 3 studies (536- CCT-005, OCT-002, OCT-003, and OCT-006).

- TAK-491CLD Program (b) (4) TAK-491 is also being evaluated as a fixed-dose combination (FDC) product with chlorthalidone.

Phase 3 open label pool

The following studies are included:

Table 2.a Study Design Summary: Phase 3 Open-Label Pool

Study Design and Study Number (Regions)		Study Entry Criteria Planned Sample Size	Treatment Duration and Dose/Regimen (a)	Endpoints
Open-label safety study with reversal phase (study completed and reported in the ISS)				
491-016 (US, Lat Am)	Open-label phase	Clinic DBP 95-119 mm Hg N=400	26 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)
	Reversal phase Double-blind Randomized Placebo-controlled	Subjects who completed the open-label phase	6 weeks Continue current dose of TAK-491; maintain stable dose(s) of background BP medication including CLD Substitute placebo for TAK-491; maintain stable dose(s) of background BP medication including CLD	Clinic BP (automated) Safety measures
Open-label safety study with 2 cohorts (additional interim data provided in this Safety Update)				
491-006 (b) (US, Lat Am)	Cohort 1	Clinic DBP 95-119 mm Hg N=350	56 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated and manual)
	Cohort 2 Uncontrolled Forced-titration Treat-to-target BP	Clinic DBP 95-119 mm Hg N=300	56 weeks Step 1: TAK-491 40→80 mg (same as Cohort 1) Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated and manual)
Open-label extension of a randomized, double-blind, controlled study (final data provided in this Safety Update)				
491-301 (OL) (US, Lat Am)	Uncontrolled Treat-to-target BP	Subjects who completed double-blind phase N=170	28 weeks Step 1: TAK-491 40 mg Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)

BP=blood pressure, CLD=chlorthalidone, DBP=diastolic blood pressure, Lat Am=Latin America, OL=open label, US=United States.

(a) All study drugs were administered QD.

(b) Cohort 1 is complete; Cohort 2 (initiated after enrollment of Cohort 1 was completed) is ongoing. Interim data cut occurred on 30 April 2010 (clinical database) and SAE data cut occurred on 01 June 2010 (pharmacovigilance database).

There were no new subjects added. However, the mean duration of exposure increased from a 215 days to 247 days. The subjects who were treated for at least 48 weeks increased from 270 in the ISS to 482 in the update.

Table 2.b Exposure Duration: Phase 3 Open-Label Pool

Exposure	ISS (a) N=1257	Update (a) N=1257
Days of exposure		
Mean (SD)	215.1 (113.64)	247.2 (127.91)
Median (min-max)	204.0 (1-427)	222.0 (1-427)
Cumulative exposure (n)		
≥1 day	1257	1257
≥2 weeks	1216	1216
≥4 weeks	1200	1200
≥8 weeks	1143	1143
≥12 weeks	1072	1087
≥24 weeks	943	1007
≥48 weeks	270	482

Source: Table 1.4.1.

Study pool included 491- 006 (interim), 016, and 301(OL).

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The subject disposition is shown below for the ISS as well as the update.

Table 2.c Subject Disposition: Phase 3 Open-Label Pool

Discontinuation Reason	Number (%) of Subjects (a)	
	ISS N=1257	Update N=1257
Overall (any discontinuation)	314 (25.0)	353 (28.1)
TEAE	84 (6.7)	88 (7.0)
Protocol deviation	24 (1.9)	25 (2.0)
Lost to follow-up	73 (5.8)	97 (7.7)
Voluntary withdrawal	90 (7.2)	98 (7.8)
Pregnancy	1 (<0.1)	1 (<0.1)
Lack of efficacy	10 (0.8)	11 (0.9)
Investigator discretion	6 (0.5)	6 (0.5)
Other	26 (2.1)	27 (2.1)

Source: Table 1.4.2.

TEAE=treatment-emergent adverse event.

Study pool included 491- 006 (interim), 016, and 301(OL).

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The percent of discontinuations for any reason increased from 25 % in the ISS to 28% in the update. The reason that had the largest change was “lost to follow up.”

Discontinuations for adverse events increased slightly.

Adverse events reported by at least 2% of subjects are shown below.

Table 2.d Common TEAEs (≥2% Incidence): Phase 3 Open-Label Pool

Preferred Term	Number (%) of Subjects (a)	
	ISS N=1257	Update N=1257
Overall (any TEAE)	795 (63.2)	838 (66.7)
Dizziness	136 (10.8)	143 (11.4)
Headache	108 (8.6)	113 (9.0)
Urinary tract infection	62 (4.9)	70 (5.6)
Fatigue	66 (5.3)	68 (5.4)
Upper respiratory tract infection	53 (4.2)	56 (4.5)
Back pain	30 (2.4)	37 (2.9)
Cough	31 (2.5)	37 (2.9)
Blood creatinine increased	29 (2.3)	36 (2.9)
Diarrhoea	35 (2.8)	36 (2.9)
Hypotension	36 (2.9)	36 (2.9)
Nasopharyngitis	25 (2.0)	35 (2.8)
Arthralgia	27 (2.1)	32 (2.5)
Nausea	30 (2.4)	30 (2.4)
Muscle spasms	27 (2.1)	28 (2.2)
Sinusitis	21 (1.7)	28 (2.2)
Oedema peripheral	23 (1.8)	27 (2.1)
Blood CK increased	26 (2.1)	26 (2.1)
Influenza	20 (1.6)	26 (2.1)

Source: [Tables 2.4.1](#) and [2.4.4.1](#).

Study pool included 491- 006 (interim), 016, and 301(OL).

CK=creatine phosphokinase.

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The overall reporting rate increased from 63% in the ISS to 67% in the update. The events that increased by at least 1% include dizziness and urinary tract infection.

Common adverse events by time interval are shown below.

Table 2.e Common TEAEs by Time Interval: Phase 3 Open-Label Pool

Preferred Term	Number (%) of Subjects (a)							
	1-3 Months		>3-6 Months		>6-9 Months		>9 Months	
	ISS N=1257	Update N=1257	ISS N=1040	Update N=1070	ISS N=918	Update N=979	ISS N=291	Update N=497
Overall (any TEAE)	632 (50.3)	639 (50.8)	334 (32.1)	346 (32.3)	149 (16.2)	198 (20.2)	77 (26.5)	131 (26.4)
Dizziness	96 (7.6)	98 (7.8)	29 (2.8)	30 (2.8)	9 (1.0)	12 (1.2)	6 (2.1)	8 (1.6)
Headache	80 (6.4)	80 (6.4)	20 (1.9)	21 (2.0)	8 (0.9)	11 (1.1)	4 (1.4)	7 (1.4)
UTI	37 (2.9)	37 (2.9)	13 (1.3)	14 (1.3)	10 (1.1)	13 (1.3)	2 (0.7)	6 (1.2)
Fatigue	53 (4.2)	53 (4.2)	5 (0.5)	6 (0.6)	2 (0.2)	3 (0.3)	2 (0.7)	1 (0.2)
URI	25 (2.0)	25 (2.0)	20 (1.9)	20 (1.9)	4 (0.4)	5 (0.5)	5 (1.7)	8 (1.6)
Back pain	17 (1.4)	17 (1.4)	8 (0.8)	9 (0.8)	4 (0.4)	6 (0.6)	1 (0.3)	5 (1.0)
Cough	14 (1.1)	14 (1.1)	12 (1.2)	12 (1.1)	2 (0.2)	5 (0.5)	2 (0.7)	5 (1.0)
Blood creatinine increased	13 (1.0)	15 (1.2)	8 (0.8)	8 (0.7)	4 (0.4)	6 (0.6)	0	3 (0.6)
Diarrhoea	22 (1.8)	22 (1.8)	8 (0.8)	9 (0.8)	3 (0.3)	3 (0.3)	0	0
Hypotension	21 (1.7)	21 (1.7)	16 (1.5)	16 (1.5)	4 (0.4)	4 (0.4)	1 (0.3)	1 (0.2)
Nasopharyngitis	10 (0.8)	11 (0.9)	9 (0.9)	10 (0.9)	5 (0.5)	8 (0.8)	3 (1.0)	7 (1.4)
Arthralgia	18 (1.4)	19 (1.5)	5 (0.5)	5 (0.5)	4 (0.4)	5 (0.5)	0	3 (0.6)
Nausea	26 (2.1)	26 (2.1)	2 (0.2)	2 (0.2)	3 (0.3)	3 (0.3)	0	0
Muscle spasms	17 (1.4)	17 (1.4)	7 (0.7)	7 (0.7)	2 (0.2)	3 (0.3)	1 (0.3)	2 (0.4)
Sinusitis	18 (1.4)	18 (1.4)	3 (0.3)	3 (0.3)	0	5 (0.5)	0	2 (0.4)
Oedema peripheral	12 (1.0)	12 (1.0)	5 (0.5)	6 (0.6)	2 (0.2)	4 (0.4)	1 (0.3)	2 (0.4)
Blood CK increased	19 (1.5)	19 (1.5)	1 (<0.1)	1 (<0.1)	2 (0.2)	2 (0.2)	3 (1.0)	3 (0.6)
Influenza	9 (0.7)	9 (0.7)	6 (0.6)	6 (0.6)	4 (0.4)	6 (0.6)	1 (0.3)	5 (1.0)

Source: Table 2.4.15.

Study pool included 491- 006 (interim), 016, and 301(OL).

CK=creatinine phosphokinase, URI=upper respiratory tract infection.

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

Half of the adverse events were reported in the first three months of the study. The reports for most adverse events tended to decreased with increasing length of study duration except for nasopharyngitis and influenza.

There were no additional deaths reported in the open label pool. There were 3 subjects (all taking 80 mg of TAK-491) with serious adverse events that were reported after the completion of the ISS: 47 year old female with anemia, 47 year old female with viral gastroenteritis, and 55 year old female with depression, psychotic disorder, post-traumatic stress disorder.

The discontinuation rate for adverse events was 9% for both the ISS and the safety update. There were 2 subjects who discontinued since the completion of the ISS: 59 year old female with chest pain that resolved and 41 year old male with hyperkalemia that also resolved.

Serum creatinine elevations, shown in the table below, were similar in both the ISS and the safety update.

Table 2.j Categorical Analyses of Creatinine Elevations: Phase 3 Open-Label Pool

Criterion Visit	n/N (%) (a)	
	ISS (N=1257)	Update (N=1257)
Subjects with $\geq 30\%$ change from Baseline and $>ULN$		
Any postbaseline visit	177/1218 (14.5)	185/1218 (15.2)
Final Visit	69/1218 (5.7)	70/1218 (5.7)
Subjects with $\geq 50\%$ change from Baseline and $>ULN$		
Any postbaseline visit	106/1218 (8.7)	112/1218 (9.2)
Final Visit	41/1218 (3.4)	45/1218 (3.7)

Source: Tables 3.4.7 and 3.4.9.

Study pool included 491- 006 (interim), 016, and 301(OL).

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

Overall, there is no change in the interpretation of the safety of TAK-491 with the addition of safety update data.

TAK-491CLD PHASE 3 STUDIES

TAK-491 is also being evaluated as a fixed dose product with chlorthalidone (TAK-491CLD) in the ongoing clinical development program being conducted under (b) (4)

(b) (4) To date, TAK-491CLD has been evaluated in 4 phase 1 studies (491CLD- 102, 103, 104, and 105), all of which were included in the TAK-491 NDA to provide supportive safety information. In addition, there are 4 phase 3 studies (491CLD- 301, 302, 303, and 308) that are ongoing and 1 phase 3 study (491CLD-306) that was recently completed.

Study 491-306 was a randomized, double-blind, parallel-group study comparing the efficacy and safety of TAK-491CLD fixed dose combination (FDC) with coadministration of TAK-491 and HCTZ in subjects with moderate to severe hypertension (SBP 160-190 mm Hg inclusive). All subjects initiated treatment with single-blind TAK-491 40 mg (2-week single-blind period), followed by the addition of chlorthalidone or HCTZ (8-week double-blind period) in the form of an FDC tablet (TAK-491 40 mg plus 12.5 mg of chlorthalidone) or coadministered TAK-491 40 mg plus 12.5 mg HCTZ. After 4 weeks of double-blind treatment (Week 6), subjects who did not reach their target blood pressure had their dose of chlorthalidone or HCTZ titrated to 25 mg, while subjects who did reach their target blood pressure continued chlorthalidone or HCTZ 12.5 mg for the duration of the study. Target blood pressure was defined as $<140/90$ mm Hg ($<130/80$ mm Hg for subjects with diabetes or chronic kidney disease), and dose titration at Week 6 was based on the mean of 3 sitting clinic blood pressure measurements.

There were 609 randomized subjects (303 on TAK-401 plus CLD and 306 on TAK-491 plus HCTZ). The incidence of withdrawals from study for adverse events was higher in the CLD combination (9%) compared to the HCTZ combination (6%).

	Number of Subjects (%)		
	TAK-491CLD (N = 303)	TAK-491+HCTZ (N = 306)	Total (N = 609)
Randomized But Not Treated	1 (0.3)	3 (1.0)	4 (0.7)
Completed Study Drug	252 (83.2)	260 (85.0)	512 (84.1)
Prematurely Discontinued Study Drug	51 (16.8)	46 (15.0)	97 (15.9)
Primary Reason for Discontinuation of Study Drug			
Adverse Event	28 (9.2)	19 (6.2)	47 (7.7)
Major Protocol Deviation	2 (0.7)	2 (0.7)	4 (0.7)
Lost to Follow-Up	3 (1.0)	2 (0.7)	5 (0.8)
Voluntary Withdrawal	16 (5.3)	14 (4.6)	30 (4.9)
Study Termination	0	0	0
Pregnancy	0	0	0
Lack of Efficacy	0	2 (0.7)	2 (0.3)
Other	2 (0.7)	7 (2.3)	9 (1.5)

Treated=treated with active single-blind/double-blind study drug.

Note 1: Subjects take TAK-491 40 mg in the study, with titration to 12.5 mg (Chlorthalidone [CLD] or Hydrochlorothiazide [HCTZ]) at Week 2, and then to 25 mg (CLD and HCTZ) at Week 6, if needed.

Note 2: Primary reasons for discontinuation of study drug are mutually exclusive and exhaustive categories.

Note 3: Subjects who are randomized but not treated will also be counted as prematurely discontinued study drug.
/proj/006/tak491_306/prod/programs/tdispo.sas Executed: 15APR2010 14:34 SAS V 9.1

The table below shows the adverse events reported by at least 2% of subjects in the CLD combination.

Table 15.3.1.4.1
Treatment-Emergent Adverse Events by Preferred Term
Safety Analysis Set

Preferred Term	Number of Subjects (%)		
	TAK-491CLD (N=302)	TAK-491+HCTZ (N=303)	Total (N=605)
Subjects With Any Treatment-Emergent AEs	158 (52.3)	144 (47.5)	302 (49.9)
Dizziness	37 (12.3)	32 (10.6)	69 (11.4)
Blood creatinine increased	39 (12.9)	27 (8.9)	66 (10.9)
Headache	16 (5.3)	16 (5.3)	32 (5.3)
Fatigue	11 (3.6)	10 (3.3)	21 (3.5)
Asthenia	9 (3.0)	6 (2.0)	15 (2.5)
Hypotension	7 (2.3)	3 (1.0)	10 (1.7)

There were a few more reports of dizziness, increased blood creatinine, asthenia and hypotension in the CLD combination compared to the HCTZ combination.

Two additional deaths were reported in the update:

-subject 1023/024 (TAK-491 40 mg), a 61-year-old, Black female had sudden death on Day 6 of the active treatment period. An autopsy was not performed and circumstances surrounding the death are unknown. The subject's relevant medical history included sleep apnea, obesity, and lower extremity pitting edema. The subject's baseline blood pressure was 191/104 mm Hg.

-Subject 1047/002 (TAK-491CLD 40 mg/12.5 mg), a 67-year-old, White male had sudden death on Day 15 of the active treatment period, when he did not wake from an afternoon nap. The subject had received single-blind TAK-491 40 mg for 2 weeks and a

single dose of double-blind TAK-491CLD 40 mg/12.5 mg. His blood pressure was 162/91 mm Hg at baseline and 131/82 mm Hg at the study visit on the day prior to his death. The subject's relevant medical history included obesity (body mass index >32). Acute cardiovascular insufficiency was provided as cause of death on the death certificate; an autopsy was not performed.

These types death are not unexpected in subjects with moderate to severe hypertension.

The table below shows the serious adverse events reported in this study.

Table 3.a Nonfatal SAEs by Treatment Group: 491CLD-306

Site/Subject Sex/Age	Most Recent Treatment	Preferred Term	Onset Day	Relationship to Drug (a)	Action/ Outcome
TAK-491CLD Treatment Group					
1010/019 Male/52	TAK-491 40 mg	Unstable angina	6	Not related	Drug withdrawn/ Resolved
		Coronary artery occlusion	6	Not related	Drug withdrawn/ Resolved
		Coronary artery stenosis	10	Not related	Not applicable (b)/ Resolved
1017/037 Female/72	TAK-491CLD 40 mg/12.5 mg	Blood creatinine increased	15	Definite	Drug withdrawn/ Not resolved
	TAK-491CLD 40 mg/12.5 mg	Renal failure chronic	21	Probable	Drug withdrawn/ Not resolved
1023/022 Female/57	TAK-491CLD 40 mg/12.5 mg	Chest discomfort	43	Not related	Drug withdrawn/ Resolved
1026/026 Female/68	TAK-491CLD 40 mg/12.5 mg	Gastrointestinal haemorrhage	48	Possible	Drug withdrawn/ Resolved
1032/002 Female/64	TAK-491CLD 40 mg/12.5 mg	Breast cancer	23	Not related	Not applicable (b)/ Not resolved
TAK-491+HCTZ Treatment Group					
1014/004 Male/71	TAK-491+HCTZ 40 mg+12.5 mg	Cerebrovascular accident	31	Possible	Drug withdrawn/ Resolved with sequelae
1021/003 Female/70	TAK-491+HCTZ 40 mg+12.5 mg	Pneumonia	61	Not related	Dose not changed/ Resolved
1022/039 Male/40	TAK-491+HCTZ 40 mg+12.5 mg	Chest pain (gastrointestinal etiology)	24	Not related	Drug withdrawn/ Resolved
1025/010 Female/70	TAK-491+HCTZ 40 mg+12.5 mg	Syncope	27	Possible	Drug withdrawn/ Resolved
		Renal failure acute	27	Possible	Drug withdrawn/ Resolved
		Pulmonary embolism	34	Not related	Not applicable (b)/ Resolved

Source: [Appendix E Table 15.3.2.2.](#)

(a) As judged by the investigator.

(b) Not applicable, as study drug had previously been withdrawn.

There were two reports of renal failure and one report of syncope.

The adverse events leading to discontinuation are shown below.

Table 3.b Permanent Study Withdrawal TEAEs (≥2 Subjects): 491CLD-306

Preferred Term	Number (%) of Subjects		
	TAK-491CLD N=302	TAK-491+HCTZ N=303	Total N=605
Blood creatinine increased	12 (4.0)	4 (1.3)	16 (2.6)
Dizziness	3 (1.0)	4 (1.3)	7 (1.2)
Hypotension	2 (0.7)	2 (0.7)	4 (0.7)
Blood urea increased	2 (0.7)	2 (0.7)	4 (0.7)
Blood sodium decreased	2 (0.7)	1 (0.3)	3 (0.5)
Syncope	1 (0.3)	1 (0.3)	2 (0.3)
Tachycardia	0	2 (0.7)	2 (0.3)
Hyperhidrosis	1 (0.3)	1 (0.3)	2 (0.3)
Headache	1 (0.3)	1 (0.3)	2 (0.3)

Source: [Appendix E Tables 15.3.1.10 and 15.3.2.1](#) and [Appendices 16.2.1.2 and 16.2.7.1](#).

There were more withdrawals for increased blood creatinine in the CLD combination (4%) compared to the HCTZ combination (1%). The other events were reported at similar rates.

Incidence rates of abnormal elevations of blood creatinine by study drug are shown below.

Table 3.c Categorical Analyses of Creatinine Elevations: 491CLD-306

	n/N (%)	
	TAK-491CLD N=302	TAK-491+HCTZ N=303
Subjects with Creatinine Elevations ≥30% above Baseline and >ULN		
Any postbaseline visit (a)	41/297 (13.8)	25/298 (8.4)
Final Visit (b)	15/297 (5.1)	4/298 (1.3)
Subjects with Creatinine Elevations ≥50% above Baseline and >ULN		
Any postbaseline visit (a)	26/297 (8.8)	14/298 (4.7)
Final Visit (b)	8/297 (2.7)	3/298 (1.0)

Source: [Appendix E Table 15.3.4.9](#).

(a) Experienced at least one creatinine increase with prespecified percentage above Baseline and > ULN.

(b) Last observation carried forward; the last observation collected up to 7 days (inclusive) after the last dose of active study medication.

There were more creatinine elevations (both ≥ 30% and ≥ 50%) in the CLD combination, any time post base as well as at final visit, compared to the HCTZ combination. Both drug groups had fewer elevations at final visit, implying that the abnormality resolves in most (but not all) subjects even with continued treatment.

TAK-536 studies

To date, TAK-536, the active moiety of TAK-491, has been evaluated in 18 phase 1 studies, 5 phase 2 studies, and 5 FDC studies (TAK-536 with pioglitazone), all of which were included in the TAK-491 NDA to provide supportive safety information.

Additionally, SAE reports as of 03 February 2010 were provided in the NDA for 4 ongoing phase 3 studies in Japan.

There were seven additional subjects with reports of serious adverse events. These are shown below.

Table 4.a SAEs as of 01 June 2010 by Treatment Group: TAK-536 Phase 3 Studies

Subject Sex/Age	Treatment	Preferred Term	Onset Day	Relationship to Drug (a)	Action/Outcome
536-OCT-002/0015-005 Female/61	Placebo	Cholelithiasis, pancreatitis acute	8	Not related	Drug withdrawn/ Resolved
536-OCT-002/0001-007 Male/67	TAK-536 10 mg	Cardiac failure	7	Not related	Drug withdrawn/ Resolved
536-OCT-002/0016-002 Male/61	TAK-536 10 mg	Subdural haematoma	8	Not related	Drug withdrawn/ Resolved with sequelae
536-OCT-006/0006-012 Female/78	TAK-536 40 mg	Aggravated cataract	82	Not related	Dose not changed/ Resolved
536-OCT-006/0021-011 Male/57	TAK-536 40 mg	Road traffic accident, ankle fracture	90	Not related	Drug withdrawn/ Resolved
536-OCT-006/0001-001 Male/71	TAK-536 40 mg	Hepatic neoplasm malignant	198	Not related	Drug withdrawn/ Not resolved
536-CCT-005/0032-016 Female/51	Blinded (b)	Breast cancer female	83	Not related	Drug withdrawn/ Not resolved

Source: [Appendix C](#).

(a) As judged by the investigator.

(b) TAK-536 40 mg or candesartan 12 mg.

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/s/

MARYANN GORDON

02/02/2011

Clinical study reviews:

Study 01-05-TL-491-008

Study 01-06-TL-491-019

Study 01-05-TL-491-005

Study 01-06-TL-491-011

Study -06-TL-491-016

Study 01-05-TL-491-009

Study 01-05-TL-491-010

Study TAK-491-301

Study 01-06-TL-491-020

TAK-536 (active metabolite) efficacy studies (reviewed by Shari Targum, M.D.)

Study 01-05-TL-491-008

A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 in Subjects With Essential Hypertension

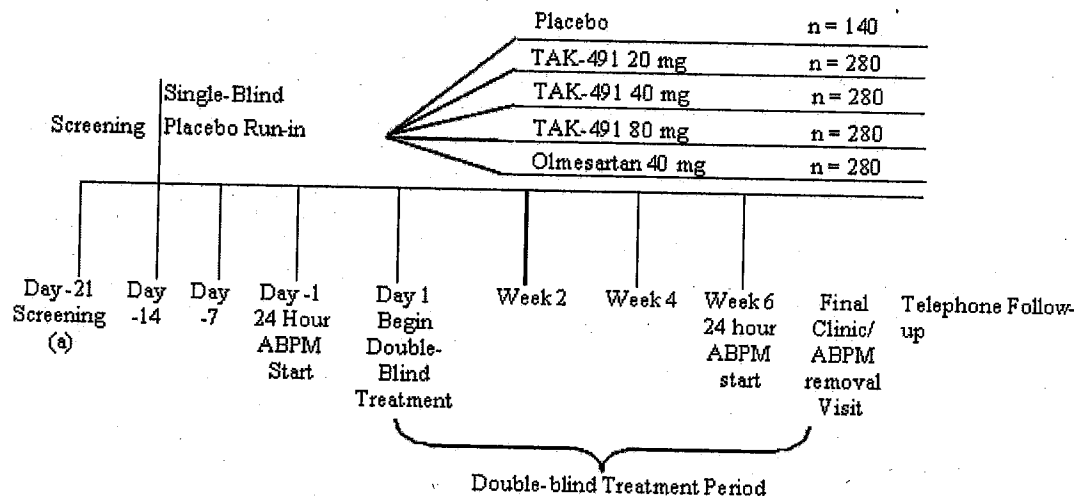
Investigators: 143 investigators enrolled subjects in the United States and Latin America
Study Period (years): 25 June 2007 to 08 October 2008

Primary objective: to evaluate the antihypertensive effect of TAK-491 compared with placebo and olmesartan after 6 weeks of treatment, as measured by the primary endpoint of change in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

Secondary objectives:

- The antihypertensive effect of TAK-491 compared with placebo and olmesartan after 6 weeks of treatment, as measured by the key secondary endpoint of trough clinic sitting SBP and by other ABPM and clinic measures of SBP and diastolic blood pressure (DBP).
- The safety and tolerability of TAK-491 compared with placebo and olmesartan.

Study design: multicenter, double-blind, randomized, placebo- and active-controlled, parallel-group study in subjects with essential hypertension. Qualified subjects were randomized (2:2:2:2:1) to receive TAK-491 20 mg QD, TAK-491 40 mg QD, TAK-491 80 mg QD, olmesartan 40 mg QD, or placebo QD for a 6-week, double-blind treatment period.



(a) Note: If the subject is on amlodipine the subject should discontinue this medication at Screening Day -28 extending the screening period for an additional 7 days (for a total of 14 days) for washout of medication prior to the Single-Blind Placebo Run-In Period.

The total duration of the study was approximately 11 weeks including a 6-week double-blind treatment period, and a safety follow up telephone call at 1 week after last dose of study drug.

Trough clinic sitting DBP and SBP were assessed at each visit. ABPM was performed on Day -1 for 24 hours before administration of the first dose of double-blind study medication, and at Week 6/Early Termination. A safety follow-up call was made 1 week after completion of the 6-week treatment period.

Study subjects

Inclusion criteria

- essential hypertension (trough clinic sitting SBP ≥ 150 and ≤ 180 mm Hg on day prior to randomization and 24-hour mean SBP ≥ 130 mm Hg and ≤ 170 mm Hg on Day 1.
- male or female, aged 18 years or older.
- female subjects of childbearing potential with exceptions
- normal or deemed normal clinical laboratory evaluations
- willing to discontinue current antihypertensive medications at screening.

Dosing

Subjects received the first dose of double-blind study medication on Day 1 in the clinic, after the ABPM equipment was removed and the 24-hour ABPM had passed quality control, 24-hour SBP met inclusion/exclusion criteria, and subjects met all other inclusion/exclusion criteria.

Subjects were instructed not to take double-blind study medication prior to reporting to the clinic on the morning of the Week 6/Early Termination Visit. This last dose of study medication was taken in the presence of the investigator or designee at 8:00 AM (± 2 hours), just before starting the 24-hour ABPM. On all other clinic visit days, subjects were also instructed to take their study medication at the clinic, after clinic SBP and DBP measurements.

Changes in the Conduct of the Study or Planned Analyses

Changes to the original protocol that occurred during the study are shown in the following table.

Table 9.f Protocol Amendments

Category	Reason for Change
Amendment 1, dated 12 February 2008	
Number of clinical centers	Increased number of centers from 150 to 170 to compensate for higher than expected rate of screening failures and run-in failures.
Inclusion criterion	Clarified lower limit for 24-hour mean SBP (ABPM) for consistency within the TAK-491 program, and added upper limit of ≤ 170 mm Hg to exclude subjects with excessively high blood pressure.
Exclusion criterion	Changed HbA1c cut-off to $>8.0\%$ (from $>9.5\%$) to exclude diabetic subjects without proper treatment control.
Excluded medications	Clarified text on antihypertensive treatment prior to Screening. Clarified tapering of antihypertensive medications during Screening. Added "atypical antipsychotic agents" as excluded medication, as these may decrease blood pressure and confound efficacy analysis. Defined "excluded medication time period".
Criteria for discontinuation or withdrawal	Under "Lack of Efficacy", clarified that subjects exceeding blood pressure thresholds of 180 mm Hg systolic and/or 114 mm Hg diastolic at any time during the study should be considered for withdrawal, if confirmed by a repeat-measurement after 48 hours.
Dose and regimen	Clarified timing of dosing during clinic visit days, and clarified ABPM randomization and repeat procedures.
Quality-of-Life (QOL) questionnaire	Deleted due to an unlikely noticeable difference in QOL assessment over such a short duration.
Vital sign procedure	Clarified timing and degree of cuff deflation for the 3 seated measurements of clinic blood pressure. Clarified instructions for single pulse measurement.
Concomitant medications	Clarified instructions on time period these were to be collected.
Contraception and pregnancy avoidance procedure	Clarified that Day -7 pregnancy test must be negative prior to receiving double-blind study medication.
ABPM procedures	Clarified ABPM randomization and repeat procedures.
ECG procedure	Deleted RR interval as it will be derived during data analysis.
Safety Follow-up telephone call	Clarified that this follow-up is required for all run-in failures, completed, and early terminated subjects.
Study Related Responsibilities	Updated contact and country information.
Throughout the protocol	Clarified language and presentation by formatting/adding/deleting/changing text.
Amendment 2, dated 13 January 2009	
Secondary objectives	Revised response criteria to define responders as those subjects who experienced a clinic DBP <90 mm Hg and/or a reduction in clinic DBP of ≥ 10 mm Hg; and/or a clinic SBP <140 mm Hg and/or a reduction in clinic SBP of ≥ 20 mm Hg.
Endpoints	Designated the first secondary endpoint as "the key secondary endpoint". Clarified endpoints by specifying "change from baseline to Week 6".
Sample size and sample size justification	Increased sample size from 1170 to 1260 subjects due to higher than expected missing or disqualified post-baseline ABPM data. Justification of sample size updated to also reflect secondary endpoint as well as non-inferiority analysis.
Efficacy analysis	Clarified definition of FAS and steps of the statistical testing procedure to control type 1 error (multiplicity of treatment group comparisons) in the efficacy analysis for the primary and the key secondary endpoint. Added non-inferiority analysis with defined margin, to be performed for the primary and the key secondary endpoint.
References	Added 2 literature references.
Throughout the protocol	Clarified language and presentation by formatting/adding/deleting/changing text.

In addition to the above protocol amendments, a change in the planned conduct of the study relating to cGFR occurred. Original cGFR results by (b) (4) were found to be incorrect (December 2009) due to a random systematic error that used the first subject's race in a batch of accessions being released from the Laboratory Information Management system. Therefore, all subjects in that batch were assumed to be of the same race. This error was specific to the cGFR determined by the Modification of Diet in Renal Disease (MDRD) Study method. Therefore, cGFR results were recalculated by (b) (4) using the following MDRD equation and the recalculated results were used for data summary and analysis: $cGFR = 186 \times (Cr [mg/dL])^{-1.154} \times Age^{-0.203} \times 1.212 [if \text{ Black}] \times 0.742 [if \text{ female}]$. In this equation Cr is a serum creatinine value. The multiplier for Black subjects in the equation was applied if the subject reported his or her race as "Black or African American" and the multiplier for female subjects was applied for those indicating their sex as "female".

RESULTS

A total of 1275 subjects were randomized; all but 3 subjects received double-blind medication. Two subjects in the TAK-491 40 mg treatment group and one subject in the TAK-491 80 mg treatment group were discontinued from the study prior to the start of dosing with double-blind study medication.

Protocol deviations

There were issues of noncompliance with the Statement of Investigator, Form FDA 1572 concerning Dr. Daniel Aimone (Argentina, 6099). The sponsor requested that the principal investigator prematurely discontinue all active subjects and the site was closed. The site had randomized 16 subjects

Seven subjects withdrew from the study because of major protocol deviations:

- 3 subjects in the placebo treatment group (6055/001, 6074/001, and 6140/011);
- 1 subject in the TAK-491 20 mg treatment group (6117/007);
- 1 subject in the TAK-491 40 mg treatment group (6004/001);
- 2 subjects in the TAK-491 80 mg treatment group (6060/004 and 6094/035).

Disposition of subjects

The outcomes of the 1275 randomized subjects are shown below.

No. and (percent) of subjects

	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=283	TAK-491 80 mg N=285	olmesartan 40 mg N=282
Completed study	130 (92)	259 (92)	261 (92)	261 (92)	268 (95)
Prematurely discontinued	12 (8)	24 (8)	22 (8)	24 (8)	14 (5)
Adverse event	5 (4)	11 (4)	3 (1)	6 (2)	4 (1)
Lack of effect	3	1	5	4 (1)	5 (2)
Other+	4	12	14	14	5

+includes protocol deviation, lost to follow up, voluntary withdrawal

Ninety-six randomized subjects (8%) prematurely discontinued from the study. The rates of drop outs for adverse events and lack of effect were similar for all treatment groups.

Demographics and medical history

The table below shows the demographic and baseline characteristics for the study subjects.

Table 10.a Summary of Demographic and Baseline Characteristics—Randomized Set

Characteristic	Treatment					Total N=1275
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=283	TAK-491 80 mg N=285	Olmesartan 40 mg N=282	
Gender, n (%)						
Male	76 (53.5)	133 (47.0)	142 (50.2)	149 (52.3)	140 (49.6)	640 (50.2)
Female	66 (46.5)	150 (53.0)	141 (49.8)	136 (47.7)	142 (50.4)	635 (49.8)
Age, yr						
Mean (SD)	59.4 (10.53)	57.1 (11.02)	57.4 (9.62)	58.1 (11.56)	58.9 (11.57)	58.0 (10.94)
Ethnicity, n (%)						
Hispanic or Latino	10 (7.0)	32 (11.3)	35 (12.4)	38 (13.3)	35 (12.4)	150 (11.8)
Non-Hispanic and Latino	74 (52.1)	141 (49.8)	137 (48.4)	131 (46.0)	134 (47.5)	617 (48.4)
Not collected (a)	58 (40.8)	110 (38.9)	111 (39.2)	116 (40.7)	113 (40.1)	508 (39.8)
Race, n (%) (b)						
American Indian or Alaska Native	29 (20.4)	51 (18.0)	49 (17.3)	52 (18.2)	50 (17.7)	231 (18.1)
Asian	3 (2.1)	7 (2.5)	7 (2.5)	4 (1.4)	4 (1.4)	25 (2.0)
Black or African American	16 (11.3)	32 (11.3)	31 (11.0)	31 (10.9)	31 (11.0)	141 (11.1)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	103 (72.5)	202 (71.4)	205 (72.4)	209 (73.3)	209 (74.1)	928 (72.8)
Multiracial	9 (6.3)	10 (3.5)	9 (3.2)	10 (3.5)	11 (3.9)	49 (3.8)
Weight, kg						
Mean (SD)	83.4 (18.95)	84.2 (21.53)	84.6 (20.37)	83.5 (19.61)	82.9 (19.63)	83.7 (20.13)
Height, cm						
Mean (SD)	166.1 (11.01)	165.7 (11.76)	166.1 (11.63)	166.3 (11.08)	166.1 (11.31)	166.0 (11.38)
BMI, kg/m ²						
Mean (SD)	30.0 (4.93)	30.4 (5.67)	30.6 (5.94)	30.0 (5.48)	29.8 (5.25)	30.2 (5.52)

Source: Table 15.1.7 and Appendix 16.2.4.1.

Age=(informed consent date – date of birth +1)/365.25, and was truncated at the decimal.

(a) Ethnicity was not collected at Latin American sites.

(b) For race, a subject may choose more than 1 category for race. Subjects who indicated more than 1 race category are included in each category indicated, and they are also included in the multiracial category. Thus, the sum of the number of subjects by racial category may be greater than the total number of subjects in the treatment group.

The demographics were similar for the treatment groups.. The percentage of black subjects was 11%. The percentage of subjects 65 years of age or older was 30% (Table 15.1.7).

The most common concurrent medical conditions were hypertension, hyperlipidemia, hypercholesterolemia), osteoarthritis, gastroesophageal reflux disease, gastritis).

Type 2 diabetes mellitus was reported between 9% and 13% of subjects in each group and diabetes mellitus was reported between 3% and 5% of subjects per group.

The most commonly reported ongoing cardiac conditions were sinus bradycardia (2% to 4%) and left ventricular hypertrophy (1% to 3%).

The list of the most frequently reported concomitant medications is shown below.

Table 10.f Summary of Concomitant Medications ($\geq 5\%$ in Any Treatment Group) by Preferred Term—Safety Analysis Set

Preferred Term	Treatment				
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
	N (%)				
Medications that started prior to Baseline and were ongoing					
Acetylsalicylic acid	26 (18.3)	56 (19.8)	53 (18.9)	57 (20.1)	72 (25.5)
Multivitamin	14 (9.9)	29 (10.2)	18 (6.4)	23 (8.1)	32 (11.3)
Metformin	7 (4.9)	18 (6.4)	23 (8.2)	17 (6.0)	23 (8.2)
Paracetamol	3 (2.1)	17 (6.0)	16 (5.7)	15 (5.3)	11 (3.9)
Ibuprofen	5 (3.5)	14 (4.9)	16 (5.7)	13 (4.6)	9 (3.2)
Omeprazole	3 (2.1)	15 (5.3)	10 (3.6)	7 (2.5)	9 (3.2)
Fish Oil	4 (2.8)	14 (4.9)	5 (1.8)	13 (4.6)	12 (4.3)
Atorvastatin calcium	5 (3.5)	6 (2.1)	7 (2.5)	6 (2.1)	14 (5.0)
Alprazolam	4 (2.8)	12 (4.2)	2 (0.7)	9 (3.2)	18 (6.4)
Medications that started after Baseline					
Paracetamol	9 (6.3)	12 (4.2)	10 (3.6)	10 (3.5)	12 (4.3)

Source: Tables 15.1.12.1, 15.1.12.2, and 15.1.12.3.

Note: WHO Drug Dictionary March 2008 version was used to code medication history.

Note: Preferred terms are sorted by decreasing frequency based on the total number of reports.

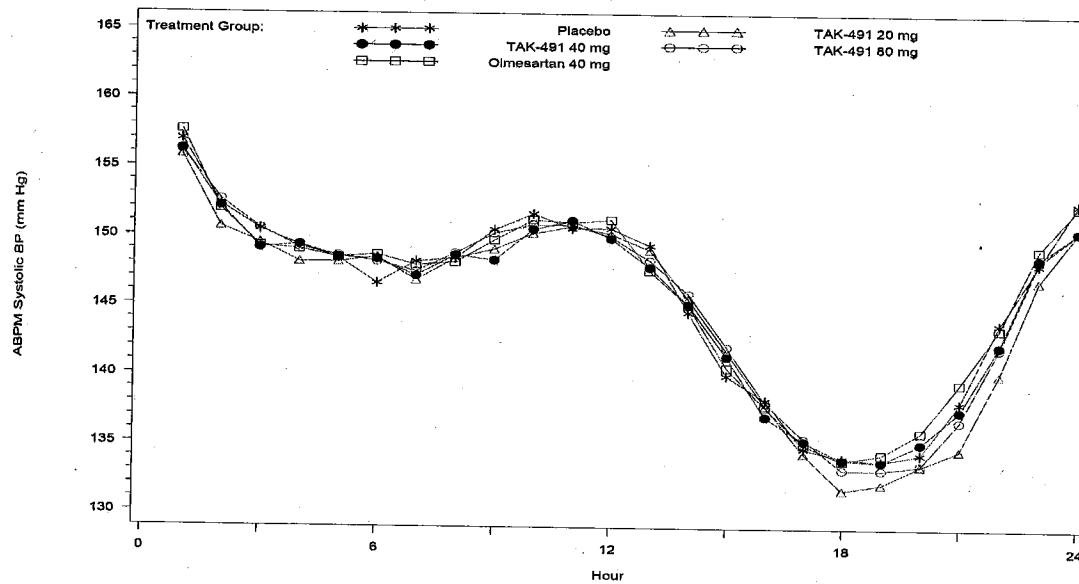
Baseline blood pressures

Blood pressures at baseline measured by the ambulatory blood pressure monitors (ABPM) are shown below.

SBP at baseline

Figure 15.2.1.5.1

ABPM Measurements: Systolic Blood Pressure (mm Hg) at Baseline by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



DBP at baseline

Figure 15.2.2.5.1

ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Baseline by Hour for the 0- to 24-Hour Interval
 Full Analysis Set

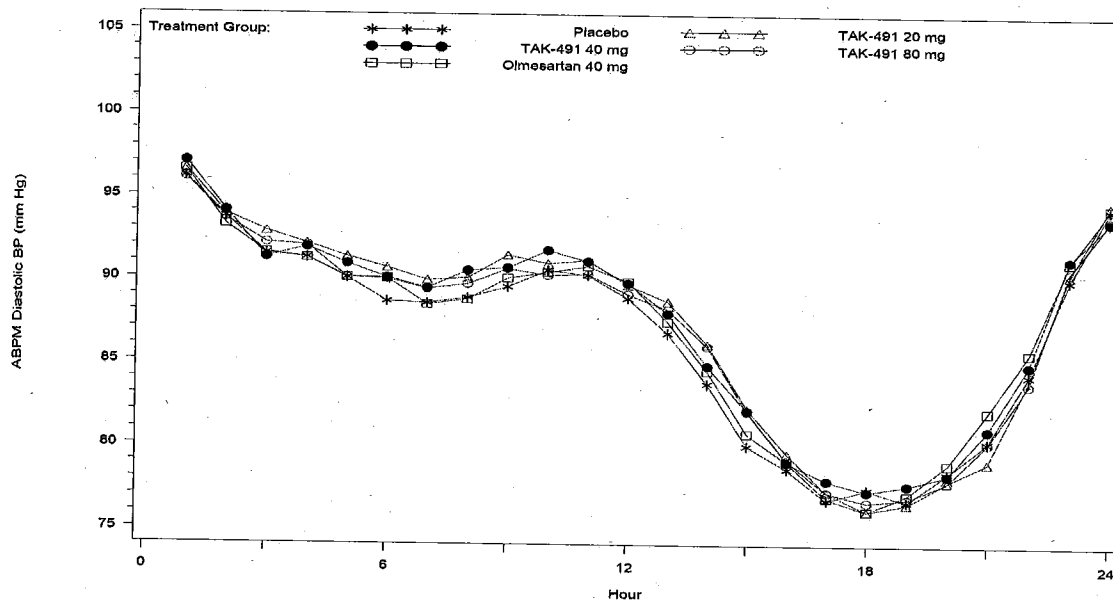


Table 10.b Summary of Baseline Efficacy Parameters—Randomized Set

	Treatment					P-value (a)
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=283	TAK-491 80 mg N=285	Olmesartan 40 mg N=282	
ABPM Parameters (mm Hg)						
N	142	282	281	282	282	
24-hour mean SBP						0.907
Mean (SD)	146.03 (12.470)	145.55 (9.743)	146.24 (10.206)	146.27 (9.939)	146.27 (9.835)	
Mean daytime (6 AM-10 PM) SBP						0.954
Mean (SD)	149.62 (12.437)	149.13 (9.708)	149.58 (10.246)	149.75 (10.204)	149.74 (9.990)	
Mean nighttime (12 AM-6 AM) SBP						0.623
Mean (SD)	135.43 (15.439)	134.27 (13.948)	136.03 (13.879)	135.24 (13.017)	135.66 (12.791)	
0- to 12-hour mean SBP						0.979
Mean (SD)	150.08 (12.710)	149.72 (10.039)	150.13 (10.974)	150.29 (10.511)	150.14 (10.271)	
Trough (22-24 hours) SBP						0.670
Mean (SD)	149.95 (14.635)	148.91 (13.083)	149.70 (12.694)	149.59 (13.057)	150.58 (12.808)	
24-hour mean DBP						0.936
Mean (SD)	87.15 (9.396)	87.63 (9.201)	87.97 (9.232)	87.67 (8.809)	87.52 (9.787)	
Mean daytime (6 AM-10 PM) DBP						0.942
Mean (SD)	90.30 (9.776)	90.96 (9.434)	91.12 (9.560)	90.82 (9.245)	90.73 (10.121)	
Mean nighttime (12 AM-6 AM) DBP						0.832
Mean (SD)	78.35 (10.746)	77.86 (10.876)	78.94 (10.788)	78.29 (10.163)	78.29 (10.965)	
0- to 12-hour mean DBP						0.919
Mean (SD)	90.83 (10.084)	91.47 (9.765)	91.60 (9.913)	91.28 (9.612)	90.98 (10.527)	
Trough (22-24 hours) DBP						0.882
Mean (SD)	92.16 (11.424)	92.61 (10.969)	92.74 (11.046)	92.10 (10.883)	92.99 (11.447)	

Blood pressure at baseline were similar across treatment groups.

Manual clinic blood pressures at baseline are shown below.

Table 10.b Summary of Baseline Efficacy Parameters—Randomized Set (continued)

	Treatment					P-value (a)
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=283	TAK-491 80 mg N=285	Olmesartan 40 mg N=282	
Clinic BP (mm Hg)						
N	142	283	281	284	282	
Clinic SBP						0.881
Mean (SD)	158.65 (11.403)	158.70 (11.589)	158.50 (12.246)	159.42 (12.024)	159.20 (12.093)	
Clinic DBP						0.732
Mean (SD)	91.27 (10.416)	92.43 (10.418)	92.18 (11.228)	92.13 (10.290)	91.44 (10.723)	

Source: Tables 15.1.8.1 and 15.1.8.2.

Note: Baseline value is the last observation before the first dose of double-blind study drug.

(a) The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

Overall, baseline blood pressures were similar regardless of treatment group and approximately 159/91 mmHg.

Primary efficacy variable

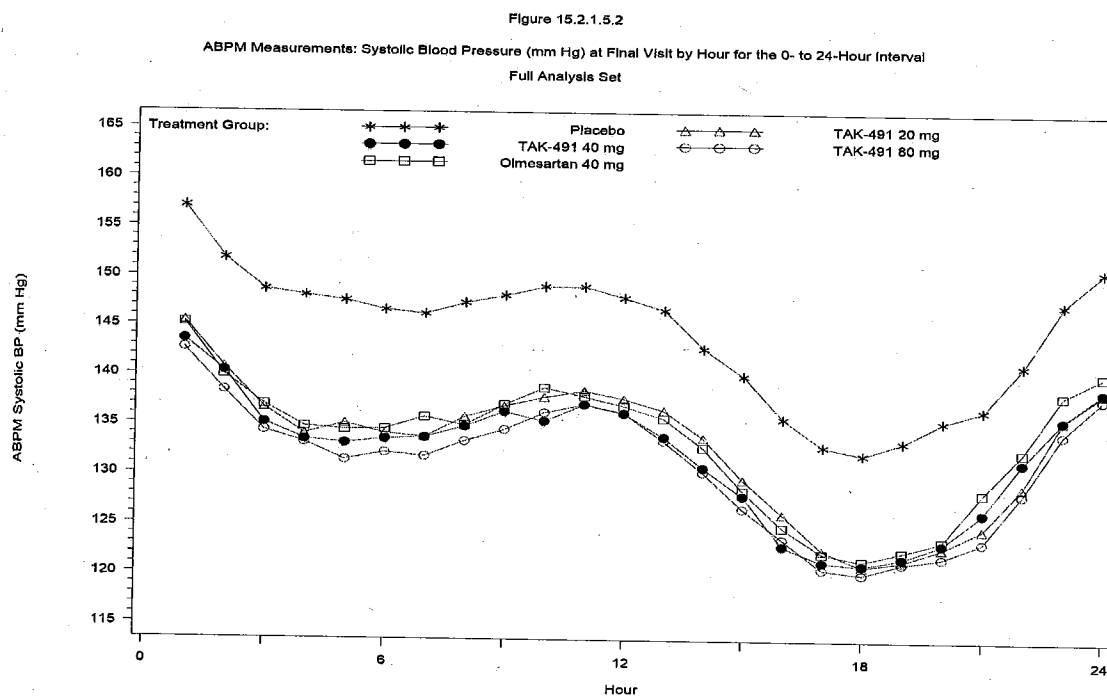
The primary efficacy variable was change from baseline at week 6 in 24-hour mean SBP by ABPM.

NB???Subjects who were excluded from the full efficacy analyses are listed in Appendix 16.2.3, along with

Statistical tables included and excluded subjects from site 6099.

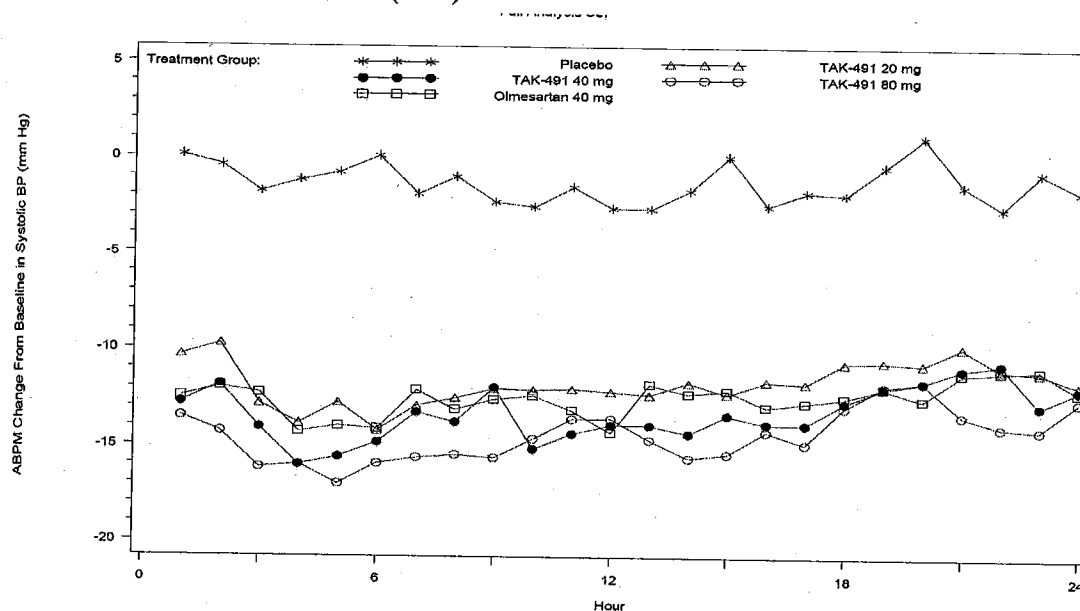
ABPM blood pressures at final visit

The figure showing 24-hour profiles at the final visit for SBP is shown below.



The change from baseline at week 6 in SBP as measured by 24 hour ABPM is shown in the figure below.

Figure 11.a Change From Baseline to Week 6 in SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)



The table below is a summary of the primary analysis for the SBP data obtained with ABPM.

**Table 11.a Summary of the Primary Analysis for the Primary Efficacy Variable:
Change From Baseline to Week 6 in the 24-hour Mean SBP by ABPM (FAS)**

Study Visit	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Baseline					
N	120	241	244	243	250
LS mean (SE)	146.29 (0.926)	145.41 (0.653)	145.99 (0.649)	146.15 (0.651)	146.47 (0.641)
Change from Baseline to Final ABPM baseline					
N	120	241	244	243	250
LS mean (SE)	-1.40 (1.004)	-12.15 (0.709)	-13.48 (0.704)	-14.62 (0.706)	-12.56 (0.696)
LS mean difference vs placebo (a)		-10.75	-12.08	-13.21	-11.15
(95% CI)		(-13.17, -8.34)	(-14.48, -9.67)	(-15.62, -10.81)	(-13.55, -8.76)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs placebo (multiple imputation analysis) (a)		-10.84	-12.05	-13.19	-11.12
(95% CI)		(-13.25, -8.42)	(-14.38, -9.72)	(-15.56, -10.82)	(-13.41, -8.82)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs olmesartan (b)		0.40	-0.92	-2.06	
(95% CI)		(-1.55, 2.35)	(-2.87, 1.02)	(-4.00, -0.12)	
P-value vs olmesartan		0.687	0.352	0.038*	
LS mean difference vs olmesartan (multiple imputation analysis) (b)		0.28	-0.94	-2.08	
(95% CI)		(-1.68, 2.24)	(-2.86, 0.99)	(-4.12, -0.03)	
P-value vs olmesartan		0.780	0.340	0.046*	

Source: Table 15.2.1.1.2.

LS mean data shown as mm Hg.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate).
Analyses include subjects with both a baseline and postbaseline value.

* Significant difference at 0.05 level and significant within the framework of the step-wise analysis of 24-hour mean SBP.

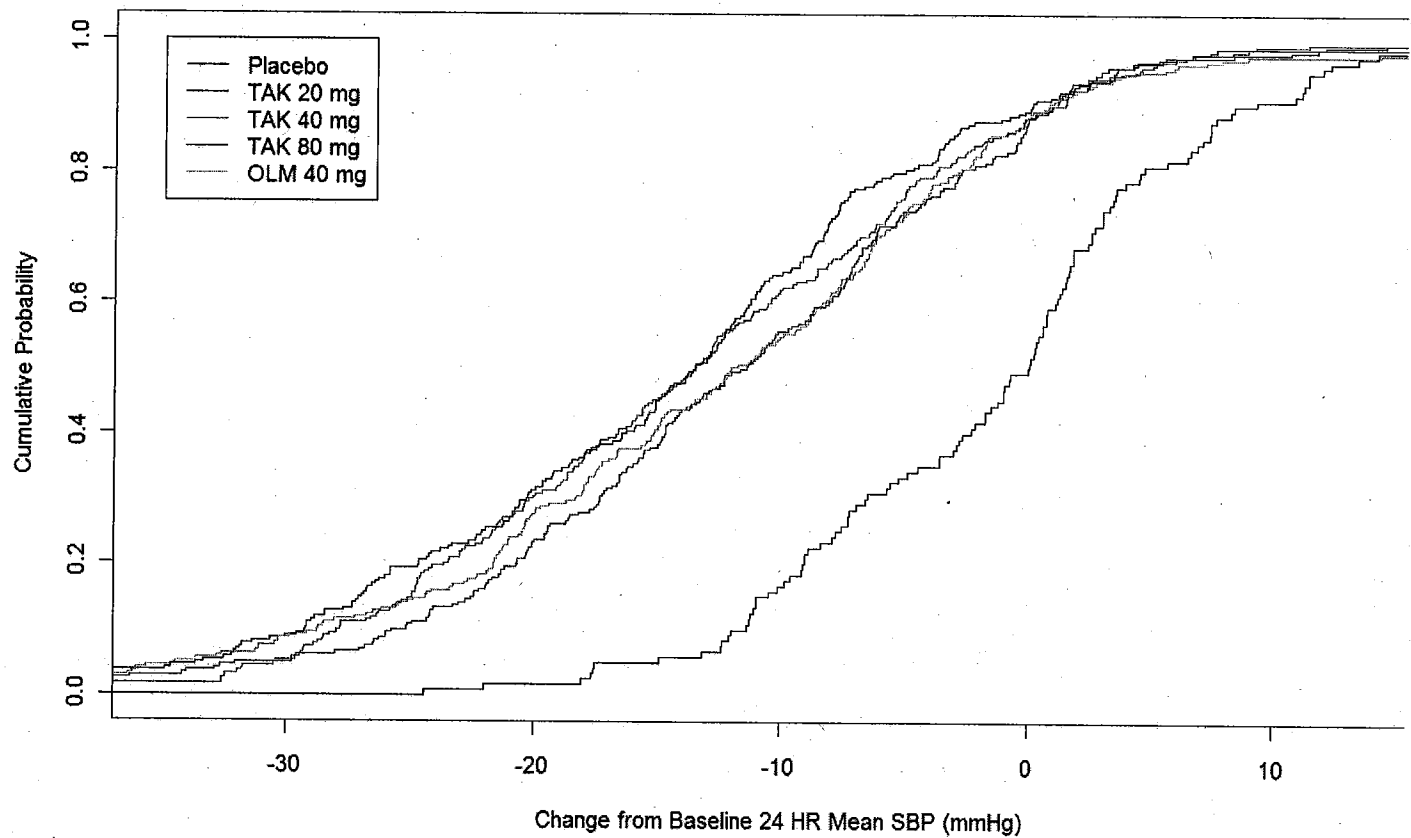
(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 dose group – LS mean change of olmesartan.

All active treatment groups had statistically significantly greater decreases in the change from baseline to Week 6 in 24-hour mean SBP compared to placebo ($P<0.001$). The changes in SBP between active treatment groups were similar. TAK 491 80 mg was not consistently superior to 40 mg and TAK 491 20 mg was an effective dose. TAK 491 was not superior to olmesartan.

The figure below shows the cumulative distribution plot using mean change in 24 hr ABPM SBP as the primary endpoint. The graph shows the proportion of subjects with x amount or better change in SBP.

Distribution of Primary Endpoint (24 HR SBP) Study 01-05-TL-491-008



The secondary efficacy variable was change from baseline at week 6 in trough clinic sitting SBP. The results are shown in the table and figure below.

Table 11.b Summary of Changes From Baseline in Trough Clinic Sitting SBP (LOCF, FAS)

Study Visit	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Baseline					
N	140	274	276	279	280
LS mean (SE)	158.74 (0.997)	158.48 (0.712)	158.50 (0.710)	159.35 (0.706)	159.16 (0.705)
Change from Baseline to Week 2					
N	135	254	261	261	270
LS mean change (SE)	-1.57 (1.244)	-11.61 (0.907)	-12.97 (0.895)	-14.34 (0.895)	-11.94 (0.880)
Change from Baseline to Week 4					
N	138	271	272	273	275
LS mean change (SE)	-3.15 (1.287)	-14.36 (0.918)	-13.97 (0.917)	-17.24 (0.915)	-14.44 (0.912)
Change from Baseline to Week 6					
N	140	274	276	279	280
LS mean change (SE)	-2.06 (1.337)	-14.28 (0.956)	-14.47 (0.952)	-17.58 (0.947)	-14.87 (0.945)
LS mean difference vs placebo (a)		-12.23	-12.42	-15.53	-12.81
(95% CI)		(-15.45, -9.00)	(-15.64, -9.20)	(-18.74, -12.31)	(-16.02, -9.60)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs placebo (multiple imputation analysis) (a)		-11.82	-12.13	-14.93	-12.64
(95% CI)		(-15.13, -8.51)	(-15.39, -8.88)	(-18.16, -11.70)	(-15.88, -9.39)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs olmesartan (b)		0.59	0.40	-2.71	
(95% CI)		(-2.05, 3.22)	(-2.24, 3.03)	(-5.34, -0.09)	
P-value vs olmesartan		0.662	0.768	0.043	
LS mean difference vs olmesartan (multiple imputation analysis) (b)		0.82	0.51	-2.29	
(95% CI)		(-1.82, 3.46)	(-2.11, 3.12)	(-4.89, 0.31)	
P-value vs olmesartan		0.542	0.705	0.085	

Source: Table 15.2.3.1.2.

LS mean data shown as mm Hg.

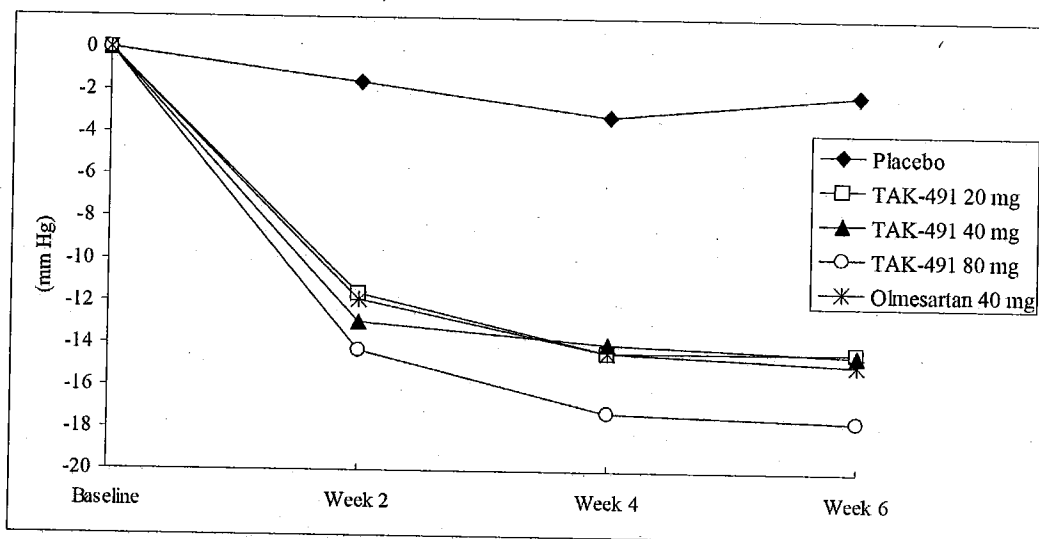
Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate). Analyses include subjects with both a baseline and postbaseline value.

*Significant difference at 0.05 level and significant within the framework of the step-wise analysis of clinic SBP.

(a) LS mean difference=LS mean change of each active group (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 dose group – LS mean change of olmesartan.

Figure 11.b Summary of Changes From Baseline in Trough Clinic Sitting SBP by Study Visit (LOCF, FAS)



Source: Table 15.2.3.1.2.

Note: LS mean values are presented.

Statistically significant differences in the change from Baseline to Week 6 in clinic SBP were observed for all the active treatment groups compared with placebo ($P < 0.001$).

The results seen with TAK-491 80 mg were numerically better (by about 3 mmHg) but not statistically different from olmesartan ($p = 0.043$).

TAK 491 80 mg was numerically better than the lower doses. TAK 491 20 and 40 mg were similar in blood pressure lowering effect.

Trough-to-peak ratio

Trough-to-peak ratio and the placebo-corrected trough-to-peak ratio are shown below for SBP.

Table 11.f Summary of Trough-to-Peak Ratios for SBP as Measured by ABPM (FAS)

		TAK-491			Olmesartan
		20 mg	40 mg	80 mg	40 mg
24-hour (a)	Placebo corrected trough-to-peak ratio	1.034	0.959	0.952	0.915
12-hour (b)	Placebo corrected trough-to-peak ratio	0.896	0.833	0.879	0.830

Source: Table 15.2.1.4.1.

Note: Analyses include subjects with both a baseline and postbaseline value. Peak response is defined as the change from Baseline in blood pressure observed during the peak effect interval (ie, the 2-hour ABPM interval in which the maximum blood pressure decrease was observed). Trough response is defined as the change from Baseline in the trough interval (hour 22 to 24). Trough-to-peak ratio was calculated as mean trough response divided by mean peak response. Placebo-corrected trough peak ratio was calculated as placebo-subtracted mean trough response divided by placebo-subtracted mean peak response.

(a) The peak effect interval was determined for each subject during the 24 hours after dosing.

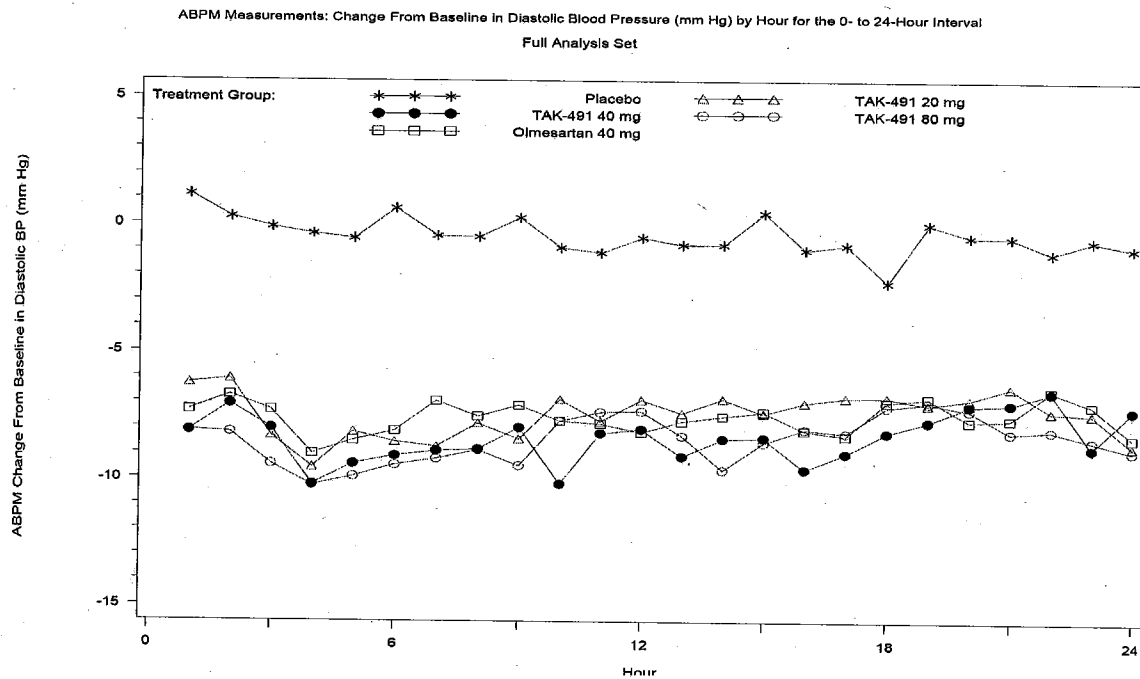
(b) The peak effect interval was determined for each subject during the 12 hours after dosing.

The ratios were near to 1 indicating that SBP effects were similar at peak and trough blood concentrations.

Change From Baseline to Week 6 in the 24-hour Mean DBP by ABPM

The ABPM 24 hour profiles for DBP change from baseline at endpoint are shown below.

Figure 15.2.2.5.3



All of the active drug groups lowered DBP more than placebo throughout the 24 hours. However, the active groups did not consistently differ from one another.

Table 11.c Summary of Changes From Baseline to Week 6 in the 24-hour Mean DBP by ABPM (FAS)

Study Visit	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Baseline					
N	120	241	244	243	250
LS mean (SE)	86.91 (0.841)	87.72 (0.593)	87.76 (0.590)	87.45 (0.591)	87.43 (0.583)
Change from Baseline to Final ABPM					
N	120	241	244	243	250
LS mean (SE)	-0.69 (0.649)	-7.47 (0.458)	-8.38 (0.455)	-8.61 (0.456)	-7.74 (0.449)
LS mean difference vs placebo (a)		-6.78	-7.68	-7.92	-7.04
(95% CI)		(-8.34, -5.22)	(-9.24, -6.13)	(-9.47, -6.36)	(-8.59, -5.50)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs placebo (multiple imputation analysis) (a)		-6.84	-7.76	-8.05	-7.19
(95% CI)		(-8.34, -5.35)	(-9.33, -6.19)	(-9.56, -6.54)	(-8.71, -5.66)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs olmesartan (a)		0.27	-0.64	-0.87	
(95% CI)		(-0.99, 1.52)	(-1.89, 0.62)	(-2.13, 0.38)	
P-value vs olmesartan		0.679	0.319	0.172	
LS mean difference vs olmesartan (multiple imputation analysis) (b)		0.34	-0.58	-0.86	
(95% CI)		(-0.92, 1.61)	(-1.83, 0.68)	(-2.08, 0.36)	
P-value vs olmesartan		0.593	0.366	0.166	

Source: Table 15.2.2.1.2.

LS mean data shown as mm Hg

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate).

Analyses include subjects with both baseline and postbaseline values.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 dose group – LS mean change of olmesartan.

Statistically significant differences in the change from Baseline to Week 6 in 24-hour mean DBP by ABPM were observed for all the TAK-491 treatment groups (20, 40, and 80 mg) compared with placebo ($P<0.001$). The different doses of TAK-491 were similar to one another.

The DBP differences between any dose of TAK-491 and olmesartan were small and insignificant.

The changes from baseline to week 6 in trough clinic sitting DBP are shown below.

Table 11.d Summary of Changes From Baseline in Trough Clinic Sitting DBP (LOCF, FAS)

Study Visit	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Baseline					
N	140	274	276	279	280
LS mean (SE)	91.09 (0.895)	92.54 (0.639)	92.08 (0.637)	92.11 (0.634)	91.41 (0.633)
Change from Baseline to Week 2					
N	135	254	261	261	270
LS mean (SE)	0.14 (0.724)	-5.35 (0.527)	-6.29 (0.520)	-6.16 (0.520)	-5.17 (0.512)
Change from Baseline to Week 4					
N	138	271	272	273	275
LS mean (SE)	-1.11 (0.737)	-7.07 (0.526)	-6.63 (0.525)	-7.83 (0.524)	-6.37 (0.522)
Change from Baseline to Week 6					
N	140	274	276	279	280
LS mean (SE)	0.21 (0.749)	-6.82 (0.535)	-6.86 (0.533)	-8.42 (0.530)	-6.91 (0.529)
LS mean difference vs placebo (a)		-7.02	-7.07	-8.62	-7.11
(95% CI)		(-8.83, -5.22)	(-8.87, -5.27)	(-10.42, -6.82)	(-8.91, -5.31)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs placebo (multiple imputation analysis) (a)		-6.69	-6.84	-8.41	-7.04
(95% CI)		(-8.59, -4.80)	(-8.68, -5.00)	(-10.26, -6.57)	(-8.85, -5.22)
P-value vs placebo		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs olmesartan (b)		0.09	0.04	-1.51	
(95% CI)		(-1.39, 1.56)	(-1.43, 1.52)	(-2.98, -0.04)	
P-value vs olmesartan		0.908	0.956	0.044*	
LS mean difference vs olmesartan (multiple imputation analysis) (b)		0.34	0.20	-1.37	
(95% CI)		(-1.20, 1.89)	(-1.27, 1.67)	(-2.84, 0.09)	
P-value vs olmesartan		0.664	0.793	0.066	

Source: Table 15.2.4.1.2.

LS mean data shown as mm Hg.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate).
Analyses include subjects with both baseline and postbaseline values.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active group (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 dose group – LS mean change of olmesartan.

All active treatment groups showed a significant decrease in clinic DBP at Week 6 compared to placebo. The difference in DBP decreases between olmesartan and TAK-491 80 mg was less than 2 mmHg.

The TAK 491 20 and 40 mg doses were similar to one another in lowering DBP. TAK 491 80 mg was numerically better than the lower doses.

Subgroup Analyses of the Primary and Secondary Efficacy Variables

Age

The majority of subjects were less than 65 years of age. The table below shows the 24 hour mean SBP according to age category and randomized drug group.

Table 11.j Analysis of 24-hour Mean SBP by Age and Race (FAS)

Subgroup Parameter Efficacy Endpoint	Placebo	TAK-491 20 mg	TAK-491 40 mg	TAK-491 80 mg	Olmesartan 40 mg
<65 years	N=95	N=205	N=214	N=197	N=185
Baseline					
N	81	173	182	167	160
LS mean (SE)	146.51 (1.148)	144.59 (0.786)	145.43 (0.766)	145.58 (0.800)	146.15 (0.817)
Change from Baseline					
LS mean (SE)	-2.07 (1.261)	-11.77 (0.863)	-13.80 (0.841)	-14.89 (0.878)	-13.30 (0.897)
LS mean difference vs placebo (a) (95% CI)		-9.70 (-12.70, -6.69)*	-11.73 (-14.70, -8.75)*	-12.82 (-15.84, -9.80)*	-11.23 (-14.26, -8.19)*
LS mean difference vs olmesartan (b) (95% CI)		1.53 (-0.91, 3.98)	-0.50 (-2.91, 1.91)	-1.59 (-4.06, 0.87)	
≥65 years	N=47	N=78	N=67	N=87	N=97
Baseline					
N	39	68	62	76	90
LS mean (SE)	145.84 (1.542)	147.52 (1.168)	147.64 (1.223)	147.40 (1.105)	147.05 (1.015)
Change from Baseline					
LS mean (SE)	-0.03 (1.629)	-13.11 (1.232)	-12.46 (1.291)	-14.02 (1.166)	-11.29 (1.071)
LS mean difference vs placebo (a) (95% CI)		-13.08 (-17.10, -9.06)*	-12.43 (-16.52, -8.34)*	-13.99 (-17.93, -10.05)*	-11.26 (-15.10, -7.43)*
LS mean difference vs olmesartan (b) (95% CI)		-1.82 (-5.03, 1.39)	-1.17 (-4.47, 2.13)	-2.73 (-5.84, 0.39)	
≥75 years	N=11	N=11	N=7	N=19	N=20
Baseline					
N	10	8	6	16	18
LS mean (SE)	147.64 (2.870)	147.88 (3.209)	148.12 (3.705)	146.81 (2.269)	143.92 (2.139)
Change from Baseline					
LS mean (SE)	-1.81 (3.250)	-9.58 (3.635)	-9.15 (4.197)	-10.98 (2.566)	-9.22 (2.447)
LS mean difference vs placebo (a) (95% CI)		-7.77 (-17.53, 2.00)	-7.33 (-17.97, 3.30)	-9.17 (-17.47, -0.87)*	-7.41 (-15.61, 0.79)
LS mean difference vs olmesartan (b) (95% CI)		-0.36 (-9.19, 8.47)	0.07 (-9.72, 9.86)	-1.76 (-8.89, 5.37)	

Footnotes for Table 11.j appear on the following page.

The effects of TAK 419 on lowering SBP for age groups <65 years and ≥ 65 years were similar. The effect was somewhat less for the subjects ≥ 75 years of age but the sample sizes for this group were small.

Race

Black subjects made up a small proportion of treated subjects (about 15%).

Table 11.j Analysis of 24-hour Mean SBP by Age and Race (FAS) (continued)

Subgroup Parameter Efficacy Endpoint	Placebo	TAK-491 20 mg	TAK-491 40 mg	TAK-491 80 mg	Olmesartan 40 mg
Caucasian	N=103	N=202	N=204	N=208	N=209
Baseline					
N	87	173	179	174	188
LS mean (SE)	146.49 (1.058)	145.40 (0.750)	146.14 (0.738)	146.39 (0.748)	146.03 (0.720)
Change from Baseline					
LS mean (SE)	-0.66 (1.173)	-12.82 (0.832)	-13.34 (0.818)	-15.58 (0.829)	-13.77 (0.798)
LS mean difference vs placebo (a) (95% CI)		-12.16 (-14.98, -9.33)*	-12.68 (-15.49, -9.87)*	-14.92 (-17.74, -12.10)*	-13.11 (-15.89, -10.33)*
LS mean difference vs olmesartan (b) (95% CI)		0.95 (-1.31, 3.21)	0.43 (-1.81, 2.67)	-1.81 (-4.07, 0.45)	
Black	N=16	N=32	N=30	N=31	N=31
Baseline					
N	14	26	23	26	27
LS mean (SE)	151.88 (2.992)	147.71 (2.195)	143.74 (2.334)*	147.88 (2.195)	147.87 (2.154)
Change from Baseline					
LS mean (SE)	-2.58 (2.774)	-6.57 (2.017)	-7.81 (2.169)	-7.73 (2.017)	-5.62 (1.979)
LS mean difference vs placebo (a) (95% CI)		-3.98 (-10.78, 2.81)	-5.23 (-12.28, 1.82)	-5.14 (-11.93, 1.65)	-3.04 (-9.78, 3.71)
LS mean difference vs olmesartan (b) (95% CI)		-0.95 (-6.55, 4.65)	-2.19 (-8.02, 3.63)	-2.11 (-7.71, 3.49)	
Other	N=32	N=58	N=56	N=56	N=54
Baseline					
N	27	48	50	51	47
LS mean (SE)	142.80 (1.984)	144.14 (1.488)	146.51 (1.458)	144.62 (1.444)*	148.88 (1.504)*
Change from Baseline					
LS mean (SE)	-2.97 (2.114)	-13.00 (1.582)	-16.17 (1.548)	-14.44 (1.533)	-12.92 (1.612)
LS mean difference vs placebo (a) (95% CI)		-10.03 (-15.21, -4.84)*	-13.20 (-18.38, -8.03)*	-11.48 (-16.61, -6.34)*	-9.95 (-15.22, -4.67)*
LS mean difference vs olmesartan (b) (95% CI)		-0.08 (-4.55, 4.40)	-3.25 (-7.64, 1.14)	-1.53 (-5.93, 2.87)	

Source: Tables 15.2.1.3.2 and 15.2.1.3.6.

LS mean data shown as mm Hg.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate). Analyses include subjects with both a baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group or olmesartan) - LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 dose group - LS mean change of olmesartan.

Overall, the blood pressure response to the active treatments in the black population was about half that seen in other populations.

Diastolic blood pressure changes for the black population are shown below.

ABPM Measurements: Summary of Diastolic Blood Pressure Parameters (mm Hg) by Study Visit and Race

Full Analysis Set

ABPM Measurement: 0- to 24-Hour Mean

Race: Black

Study Visit	Placebo (N=16)		TAK-491 20 mg (N=32)		TAK-491 40 mg (N=30)		TAK-491 80 mg (N=31)		Olmesartan 40 mg (N=31)	
	Value at Visit	Change From Baseline	Value at Visit	Change From Baseline	Value at Visit	Change From Baseline	Value at Visit	Change From Baseline	Value at Visit	Change From Baseline
Baseline ABPM										
N	14		26		23		26		27	
Mean	93.15		89.17		88.76		89.81		89.66	
SD	14.080		9.602		9.928		9.331		9.675	
Median	91.47		89.15		87.31		87.93		90.94	
Minimum	72.0		71.0		68.2		67.6		72.0	
Maximum	120.6		108.3		109.5		108.3		118.6	
Final ABPM										
N	14	14	26	26	23	23	26	26	27	27
Mean	92.15	-0.99	85.94	-3.23	83.51	-5.25	84.16	-5.65	84.98	-4.68
SD	14.222	4.857	12.015	7.062	9.735	7.133	9.975	7.545	11.651	8.387
Median	91.35	0.21	86.98	-4.90	82.81	-4.65	84.30	-5.40	82.07	-5.69
Minimum	64.7	-13.0	63.9	-18.6	65.4	-19.8	61.8	-24.4	65.8	-22.5
Maximum	120.1	5.8	111.5	13.6	102.5	7.9	108.8	10.8	113.4	19.2

Other subgroups

There were similar responses in blood pressure effects among subjects regardless of gender, BMI or degree of impaired renal function.

Dose response

Doses of TAK-491 20, 40, and 80 mg were significantly better in reducing the 24-hour mean SBP compared to placebo. However, the differences between the dose groups were small.

SAFETY

Duration of exposure

A total of 1275 subjects were randomized in the study. There were three subjects who were discontinued before starting double-blind treatment and, thus, were excluded from the safety population. All 1272 subjects included in the safety population received at least 1 dose of double-blind study medication.

Table 12.a Duration of Treatment With Study Medication in Days—Safety Analysis Set

Double-Blind Treatment (days)	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Mean (SD)	41.8 (6.28)	41.2 (7.45)	41.5 (6.44)	41.5 (7.03)	41.9 (5.38)
Median	43.0	43.0	43.0	43.0	43.0
Minimum, maximum	2, 50	1, 57	1, 56	1, 52	8, 55

Source: Table 15.1.14.

The mean days on treatment were similar for all treatment groups.

Serious safety

Deaths

There was one reported death during this study. Subject 6021/004 (TAK-491 20 mg) die on study day 33 of gastrointestinal hemorrhage and shock. The subject's medical history included

hospital admission because of liver cirrhosis, current ethanol abuse (alcoholism for 20 years – exclusionary and denied at screening), hepatitis C (exclusionary and not reported at screening), anemia, peptic ulcer disease, and a GI bleed (the previous year).

Serious adverse events.

The table below shows the reported serious adverse events by treatment groups.

Table 12.f All SAEs—Safety Analysis Set

SOC Preferred Term	Subjects (%)					Total N=1272
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282	
Subjects With Any Treatment-Emergent SAEs	3 (2.1)	8 (2.8)	0	1 (0.4)	2 (0.7)	14 (1.1)
Cardiac disorders	1 (0.7)	2 (0.7)	0	0	0	3 (0.2)
Atrial fibrillation	0	1 (0.4)	0	0	0	1 (0.1)
Coronary artery disease	1 (0.7)	0	0	0	0	1 (0.1)
Myocardial infarction	0	1 (0.4)	0	0	0	1 (0.1)
Gastrointestinal disorders	0	1 (0.4)	0	0	1 (0.4)	2 (0.2)
Gastrointestinal hemorrhage	0	1 (0.4)	0	0	0	1 (0.1)
Inguinal hernia	0	0	0	0	1 (0.4)	1 (0.1)
General disorders and administration site conditions	1 (0.7)	0	0	0	0	1 (0.1)
Chest pain	1 (0.7)	0	0	0	0	1 (0.1)
Hepatobiliary disorders	0	0	0	0	1 (0.4)	1 (0.1)
Cholecystitis chronic	0	0	0	0	1 (0.4)	1 (0.1)
Infections and infestations	0	3 (1.1)	0	0	0	3 (0.2)
Cellulitis	0	1 (0.4)	0	0	0	1 (0.1)
Lower respiratory tract infection	0	1 (0.4)	0	0	0	1 (0.1)
Pneumonia	0	1 (0.4)	0	0	0	1 (0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	1 (0.4)	0	0	0	1 (0.1)
Myelodysplastic syndrome	0	1 (0.4)	0	0	0	1 (0.1)
Nervous system disorders	0	2 (0.7)	0	1 (0.4)	0	3 (0.2)
Epilepsy	0	1 (0.4)	0	0	0	1 (0.1)
Ischemic stroke	0	1 (0.4)	0	0	0	1 (0.1)
Transient ischemic attack	0	0	0	1 (0.4)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (0.4)	0	0	0	1 (0.1)
Status asthmaticus	0	1 (0.4)	0	0	0	1 (0.1)
Vascular disorders	1 (0.7)	1 (0.4)	0	0	0	2 (0.2)
Ischemia	1 (0.7)	0	0	0	0	1 (0.1)
Shock	0	1 (0.4)	0	0	0	1 (0.1)

Source: Table 15.3.1.11.

Reports of serious adverse events were uncommon. Subject 6053/002 (TAK-491 80 mg) reported a transient ischemic attack after 5 days of double-blind study drug, with expressive aphasia for 15 to 20 minutes. Echocardiography revealed interauricular septum aneurism. Subject 6103/006 (TAK-491 20 mg) reported myelodysplastic syndrome after 33 days on study drug, which was attributed an earlier adverse event of bronchitis.

Discontinuations because of adverse event.

There were 29 subjects (2.3%) who discontinued the study because of treatment-emergent adverse events: 5 subjects (3.5%) in the placebo treatment group, 11 subjects (3.9%) in the TAK-491 20 mg treatment group, 3 subjects (1.1%) in the TAK-491 40 mg treatment group, 6 subjects (2.1%) in the TAK-491 80 mg treatment group, and 4 subjects (1.4%) in the olmesartan 40 mg treatment group. A listing of these subjects is shown below.

Table 12.h Listing of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation—Safety Analysis Set

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
Placebo					
6002/004	Hyperkalemia	1	Possible	Mild	Resolved
6051/014	Chest pain	47	Not related	Severe	Resolved
6054/010	Hypertension	23	Definite	Mild	Resolved
6068/007	Palpitations	12	Possible	Moderate	Resolved
	Dizziness	2	Possible	Mild	Resolved
6146/015	Coronary artery disease	16	Probable	Moderate	Resolved
TAK-491 20 mg					
6001/007	Pneumonia	29	Not related	Severe	Resolved
	Status asthmaticus	29	Not related	Severe	Resolved
6012/006	Flushing	18	Possible	Mild	Not resolved
6014/032	Palpitations	8	Probable	Severe	Resolved
6021/004	Gastrointestinal hemorrhage	32	Not related	Severe	Fatal
	Shock	32	Not related	Severe	Fatal
6042/005	Atrial fibrillation	22	Possible	Severe	Resolved
6049/011	Gastroesophageal reflux disease	8	Not related	Mild	Not resolved
6077/035	Diarrhea	7	Probable	Mild	Resolved
	Muscle spasms	7	Probable	Mild	Resolved
	Headache	7	Probable	Mild	Resolved
	Rash	7	Probable	Mild	Resolved
6087/002	Fatigue	6	Probable	Moderate	Resolved
	Headache	6	Probable	Mild	Not resolved
	Pollakiuria	6	Probable	Moderate	Not resolved
6103/006	Lower respiratory tract infection	33	Not related	Severe	Resolved
	Myelodysplastic syndrome	33	Not related	Mild	Resolved
6162/010	Cellulitis	11	Not related	Severe	Resolved
	Heat exhaustion	16	Not related	Moderate	Resolved
6168/020	Angina pectoris	42	Not related	Mild	Resolved
TAK-491 40 mg					
6024/020	Headache	36	Possible	Moderate	Unknown
6120/008	Hepatic enzyme increased	15	Not related	Mild	Resolved
6152/018	Basophilia	37	Possible	Mild	Not resolved

Table 12.h Listing of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation—Safety Analysis Set (continued)

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
TAK-491 80 mg					
6053/002	Transient ischemic attack	5	Not related	Mild	Resolved
6084/045	Asthenia	38	Definite	Mild	Resolved
	Dizziness	33	Definite	Moderate	Resolved
6084/051	Dizziness	19	Definite	Mild	Resolved
	Hypotension	19	Probable	Moderate	Resolved
6147/012	Transaminases increased	15	Possible	Moderate	Not resolved
6152/027	Dengue fever	37	Not related	Moderate	Resolving
6152/031	Headache	25	Possible	Mild	Resolved
	Hypertensive crisis	25	Possible	Moderate	Resolved
Olmesartan 40 mg					
6041/003	Dizziness	22	Probable	Moderate	Resolved
6078/003	Hypertension	28	Not related	Mild	Resolved
6105/049	Diarrhea	1	Possible	Mild	Resolved
6116/005	Hypotension	2	Definite	Moderate	Resolved

Source: Table 15.3.2.1.

(a) As judged by the investigator.

Table 12.h Listing of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation—Safety Analysis Set (continued)

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
TAK-491 80 mg					
6053/002	Transient ischemic attack	5	Not related	Mild	Resolved
6084/045	Asthenia	38	Definite	Mild	Resolved
	Dizziness	33	Definite	Moderate	Resolved
6084/051	Dizziness	19	Definite	Mild	Resolved
	Hypotension	19	Probable	Moderate	Resolved
6147/012	Transaminases increased	15	Possible	Moderate	Not resolved
6152/027	Dengue fever	37	Not related	Moderate	Resolving
6152/031	Headache	25	Possible	Mild	Resolved
	Hypertensive crisis	25	Possible	Moderate	Resolved
Olmesartan 40 mg					
6041/003	Dizziness	22	Probable	Moderate	Resolved
6078/003	Hypertension	28	Not related	Mild	Resolved
6105/049	Diarrhea	1	Possible	Mild	Resolved
6116/005	Hypotension	2	Definite	Moderate	Resolved

Source: Table 15.3.2.1.

(a) As judged by the investigator.

Two subjects receiving TAK-491 discontinued the study because of hepatic enzyme/transaminase increased (40 mg and 80 mg). Both subjects had baseline ALT values greater than 2 times the ULN that continued to be elevated throughout the study. The subject who was discontinued for an event of pollakiuria had blood urea nitrogen (BUN) and creatinine values that were within normal limits throughout the study. The subject with myelodysplastic syndrome had a concurrent lower respiratory tract infection, both of which resolved.

All adverse events

The evaluation of adverse events presented in this section focuses on treatment-emergent adverse events. Treatment-emergent adverse events were defined as adverse events that started after the first dose of double-blind study drug and no more than 14 days (or 30 days for an SAE) after the

last dose of double-blind study drug.

The table below shows the AE and SAE by treatment group.

Table 12.b Overview of Treatment-Emergent Adverse Events and SAEs—Safety Analysis Set

Number of Events and Subjects (%) with:	Treatment											
	Placebo N=142		TAK-491 20 mg N=283		TAK-491 40 mg N=281		TAK-491 80 mg N=284		Olmesartan 40 mg N=282		Total N=1272	
	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects
Any adverse event	82	51 (35.9)	230	109 (38.5)	187	101 (35.9)	245	117 (41.2)	209	107 (37.9)	953	485 (38.1)
Related	12		63		46		62		46		229	
Not related	70		167		141		183		163		724	
Mild	51		159		138		177		147		672	
Moderate	23		60		45		66		55		249	
Severe	8		11		4		2		7		32	
Leading to discontinuation (a)		6 (4.2)		11 (3.9)		3 (1.1)		6 (2.1)		4 (1.4)		30 (2.4)
SAEs	3	3 (2.1)	11	8 (2.8)	0	0	1	1 (0.4)	2	2 (0.7)	17	14 (1.1)
Deaths		0		1 (0.4)		0		0		0		1 (0.1)

Source: Table 15.3.1.1.

Note: Treatment-emergent adverse events leading to study drug discontinuation might include temporary drug interruption and permanent discontinuation.
(a) Includes all subjects who discontinued study drug at least once.

There was one death (TAK-491 20 mg). The reporting of adverse events was similar for all treatment groups. The incidence rates for drop outs because of adverse events were also similar.

The treatment-emergent adverse events reported by at least 2% of subjects in any treatment group) are shown below.

Table 12.d Treatment-Emergent Adverse Events Presented by Preferred Term With Incidence of $\geq 2\%$ of Subjects Among All Treatment Groups—Safety Analysis Set

Preferred Term	Subjects (%)					Total N=1272
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282	
Headache	10 (7.0)	13 (4.6)	9 (3.2)	16 (5.6)	9 (3.2)	57 (4.5)
Dyslipidemia	3 (2.1)	10 (3.5)	11 (3.9)	16 (5.6)	10 (3.5)	50 (3.9)
Dizziness	4 (2.8)	8 (2.8)	6 (2.1)	8 (2.8)	10 (3.5)	36 (2.8)
Urinary tract infection	1 (0.7)	8 (2.8)	5 (1.8)	8 (2.8)	4 (1.4)	26 (2.0)
Diarrhea	0	7 (2.5)	7 (2.5)	4 (1.4)	6 (2.1)	24 (1.9)
Nasopharyngitis	0	3 (1.1)	3 (1.1)	7 (2.5)	5 (1.8)	18 (1.4)
Back pain	0	4 (1.4)	1 (0.4)	3 (1.1)	8 (2.8)	16 (1.3)
Fatigue	1 (0.7)	6 (2.1)	2 (0.7)	2 (0.7)	5 (1.8)	16 (1.3)
Plasminogen activator inhibitor increased	0	5 (1.8)	1 (0.4)	4 (1.4)	6 (2.1)	16 (1.3)
Upper respiratory tract infection	4 (2.8)	3 (1.1)	1 (0.4)	3 (1.1)	2 (0.7)	13 (1.0)

Source: Table 15.3.1.4.

Note: If a subject experienced more than 1 episode of an adverse event, it is counted only once within a preferred term. Percentages are based on the total number of subjects in the safety analysis set for each treatment group.

Note: Adverse events are sorted by decreasing order of incidence based on the total number of adverse event reports.

Note: MedDRA (Version 11.1) was used for coding adverse events.

The most common reported adverse events included headache, dyslipidemia and dizziness. Overall, the incidence rates were fairly similar for all treatment groups. Headache was more common in the placebo group while dyslipidemia was reported somewhat more frequently for the active treatment groups.

Clinical laboratory values

12.4 Clinical Laboratory Evaluations

Serum Chemistry

Mean values at baseline and final visit and changes from baseline for chemistry values are shown below.

Table 12.i Summary of Serum Chemistry Changes from Baseline to Final Visit

Serum Chemistry	Placebo n=142		TAK-491 20 mg n=283		TAK-491 40 mg n=281		TAK-491 80 mg n=284		Olmesartan 40 mg n=282	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Creatinine (μmol/L)										
Baseline (a)	142	78.7 (18.05)	283	76.4 (17.21)	281	77.1 (17.61)	284	79.0 (20.42)	282	77.1 (17.00)
Final Visit (b)	140	79.4 (19.50)	277	77.8 (17.73)	276	79.3 (18.90)	280	80.8 (20.44)	280	78.7 (17.30)
Change	140	0.6 (9.28)	277	1.7 (9.39)	276	2.0 (9.96)	280	1.9 (9.74)	280	1.4 (10.34)
Potassium (mmol/L)										
Baseline (a)	142	4.27 (0.411)	283	4.24 (0.381)	281	4.26 (0.396)	284	4.26 (0.394)	282	4.26 (0.384)
Final Visit (b)	140	4.24 (0.426)	277	4.31 (0.400)	276	4.31 (0.377)	280	4.35 (0.396)	280	4.34 (0.421)
Change	140	-0.02 (0.444)	277	0.08 (0.404)	276	0.04 (0.380)	280	0.10 (0.379)	280	0.08 (0.399)
Sodium (mmol/L)										
Baseline (a)	142	140.1 (2.30)	283	139.8 (2.22)	281	140.0 (2.25)	284	139.7 (2.11)	282	139.7 (2.02)
Final Visit (b)	140	140.3 (2.09)	277	139.2 (2.62)	276	139.8 (2.30)	280	139.5 (2.44)	280	139.5 (2.69)
Change	140	0.2 (2.09)	277	-0.5 (2.59)	276	-0.2 (2.38)	280	-0.2 (2.53)	280	-0.2 (2.74)
Uric acid (μmol/L)										
Baseline (a)	142	321.1 (76.06)	283	321.7 (89.51)	281	325.9 (79.98)	284	329.4 (80.59)	282	316.0 (83.77)
Final Visit (b)	140	324.9 (73.68)	277	329.0 (88.45)	276	341.6 (88.37)	280	342.3 (88.54)	280	326.2 (89.09)
Change	140	3.6 (43.30)	277	8.8 (43.33)	276	15.0 (47.81)	280	13.4 (50.02)	280	9.3 (49.09)
Creatine kinase (U/L)										
Baseline (a)	142	120.1 (123.14)	283	123.6 (92.89)	281	114.5 (81.89)	284	139.6 (151.83)	282	116.8 (84.99)
Final Visit (b)	140	114.3 (100.72)	277	128.6 (97.80)	276	126.0 (95.49)	280	139.4 (122.21)	280	127.2 (101.62)
Change	140	-6.4 (80.72)	277	5.9 (80.30)	276	11.6 (73.34)	280	-0.9 (91.17)	280	9.8 (73.71)
ALT (U/L)										
Baseline (a)	142	28.3 (18.99)	283	29.4 (18.34)	281	28.6 (16.18)	284	28.9 (16.21)	282	26.3 (14.39)
Final Visit (b)	140	28.8 (18.49)	277	29.0 (17.62)	276	29.5 (25.63)	280	29.3 (19.09)	280	27.2 (15.77)
Change	140	0.5 (10.07)	277	-0.4 (17.03)	276	0.8 (23.28)	280	0.4 (12.47)	280	0.8 (10.59)
AST (U/L)										
Baseline (a)	142	25.1 (13.91)	283	25.4 (12.98)	281	24.9 (12.01)	284	25.2 (11.82)	282	23.5 (8.64)
Final Visit (b)	140	24.5 (10.77)	277	25.0 (11.96)	276	25.0 (18.15)	280	24.6 (13.05)	280	23.7 (10.11)
Change	140	-0.7 (8.37)	277	-0.5 (11.73)	276	0.1 (16.36)	280	-0.6 (6.78)	280	0.1 (7.47)
Alkaline phosphatase (U/L)										
Baseline (a)	142	85.4 (27.24)	283	84.7 (28.03)	281	86.0 (31.80)	284	84.0 (28.95)	282	82.2 (26.99)
Final Visit (b)	140	87.2 (28.49)	277	84.4 (27.28)	276	91.4 (117.40)	280	84.0 (32.10)	280	81.7 (26.70)
Change	140	1.5 (11.83)	277	-0.5 (9.92)	276	5.4 (111.91)	280	-0.1 (12.04)	280	-0.6 (10.94)
Total bilirubin (μmol/L)										
Baseline (a)	142	8.9 (4.76)	283	8.8 (4.50)	281	8.7 (4.07)	284	9.3 (4.95)	282	8.8 (4.07)
Final Visit (b)	140	8.6 (4.72)	277	8.1 (4.44)	276	8.4 (4.37)	280	8.2 (4.55)	280	8.4 (4.45)
Change	140	-0.3 (3.06)	277	-0.7 (3.27)	276	-0.3 (3.66)	280	-0.9 (3.47)	280	-0.5 (3.05)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

Mean changes from baseline in creatinine, potassium and uric acid were increased in the active treatment arms compared to placebo.

Mean values by study visit and changes from baseline for total cholesterol, HDL, calculated LDL cholesterol, and triglycerides are shown below.

Table 12.j Summary of Lipid Changes from Baseline to Final Visit

Serum Chemistry	Placebo n=142		TAK-491 20 mg n=283		TAK-491 40 mg n=281		TAK-491 80 mg n=284		Olmesartan 40 mg n=282	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total Cholesterol (mmol/L)										
Baseline (a)	122	5.15 (1.010)	251	5.24 (1.125)	248	5.30 (1.112)	244	5.24 (1.056)	252	5.22 (1.138)
Final Visit (b)	115	5.10 (0.958)	234	5.22 (1.068)	239	5.20 (1.077)	239	5.16 (0.967)	240	5.19 (0.954)
Change	115	-0.05 (0.589)	234	-0.06 (0.817)	239	-0.10 (0.731)	239	-0.09 (0.793)	240	-0.05 (0.844)
HDL Cholesterol (mmol/L)										
Baseline (a)	122	1.32 (0.453)	251	1.28 (0.366)	247	1.31 (0.381)	244	1.27 (0.335)	252	1.30 (0.388)
Final Visit (b)	115	1.32 (0.483)	233	1.27 (0.370)	238	1.29 (0.388)	239	1.24 (0.330)	238	1.29 (0.414)
Change	115	-0.01 (0.146)	233	-0.01 (0.164)	238	-0.01 (0.177)	239	-0.02 (0.164)	238	-0.03 (0.177)
Calculated LDL Cholesterol (mmol/L)										
Baseline (a)	121	3.05 (0.853)	246	3.14 (0.971)	237	3.17 (0.931)	238	3.19 (0.917)	248	3.11 (0.868)
Final Visit (b)	112	3.00 (0.810)	224	3.10 (0.880)	222	3.06 (0.894)	228	3.11 (0.856)	230	3.09 (0.823)
Change	112	-0.03 (0.557)	224	-0.09 (0.681)	222	-0.10 (0.606)	228	-0.09 (0.694)	230	-0.01 (0.585)
Triglycerides (mmol/L)										
Baseline (a)	122	1.74 (0.921)	251	1.80 (1.006)	248	1.90 (1.356)	244	1.76 (0.999)	252	1.88 (2.960)
Final Visit (b)	114	1.74 (0.875)	234	1.89 (1.229)	239	1.92 (1.259)	239	1.88 (1.269)	240	1.85 (1.207)
Change	114	0.01 (0.634)	234	0.08 (0.898)	239	0.02 (1.107)	239	0.11 (0.877)	240	-0.04 (2.825)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

Mean changes from baseline were small and generally not different among the treatment groups.

Marked changes in chemistry evaluations are shown below.

Table 12.k Marked Abnormalities in Serum Chemistries During Treatment—Safety Analysis Set

Laboratory Test	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
ALT >3 × ULN	0/140	1/277 (0.4)	2/276 (0.7)	2/280 (0.7)	1/280 (0.4)
AST >3 × ULN	0/140	1/277 (0.4)	2/276 (0.7)	1/280 (0.4)	1/280 (0.4)
Alkaline phosphatase >3 × ULN	0/140	0/277	1/276 (0.4)	1/280 (0.4)	0/280
Total bilirubin >2.0 × ULN	0/140	0/277	0/276	0/280	1/280 (0.4)
CK total >10 × ULN	0/140	1/277 (0.4)	0/276	0/280	0/280
Creatinine >1.5 × BL	0/140	1/277 (0.4)	4/276 (1.4)	2/280 (0.7)	3/280 (1.1)
GGT >3 × ULN	4/140 (2.9)	14/277 (5.1)	9/276 (3.3)	7/280 (2.5)	8/280 (2.9)
Potassium					
<3.0 mEq/L	0/140	1/277 (0.4)	0/276	0/280	0/280
>6.0 mEq/L	0/140	0/277 (0.4)	2/276 (0.4)	0/280	0/280
Sodium					
<130 mEq/L	1/140 (0.7)	3/277 (1.1)	1/276 (0.4)	0/280	2/280 (0.7)
>150 mEq/L	0/140	0/277	0/276	1/280 (0.4)	0/280
Uric acid >8.5 mg/dL (F), >10.5 (M)	0/140	6/277 (2.2)	3/276 (1.1)	1/280 (0.4)	1/280 (0.4)

Source: Tables 15.3.4.3 and 15.3.4.8.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline results are summarized in this table.

BL=baseline, CK=creatinine kinase, GGT=γ-glutamyl transferase.

There were few marked changes in the placebo group. The active treatment groups reported few more changes compared to placebo.

For example, creatinine >1.5 above baseline was reported by 10 subjects on active treatment but none on placebo. However, there was no dose response. Of note, the investigators stated that there was a trend for a drop in serum creatinine following discontinuation of study drug, suggesting a positive dechallenge.

The table below shows the number and percent of subjects with elevated creatinine at anytime during the active treatment phase of the study.

Table 12.l Summary of Subjects With a Creatinine Elevation —Safety Analysis Set

	Subjects (%)				
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Subjects with Creatinine Elevations at Any Postbaseline Visit					
≥30% from BL and >ULN	0/140	2/277 (0.7)	3/276 (1.1)	2/280 (0.7)	7/280 (2.5)
Subjects with Creatinine Elevations at Final Visit (a)					
≥30% from BL and >ULN	0/140	1/277 (0.4)	2/276 (0.7)	1/280 (0.4)	4/280 (1.4)
≥50% from BL and >ULN	0/140	1/277 (0.4)	0/276	1/280 (0.4)	2/280 (0.7)

Creatinine increases ≥30% from baseline and >ULN at any postbaseline visit were reported in

14 subjects, all randomized to active drug. There were four subjects with creatinine elevations of $\geq 50\%$ threshold. No adverse events were reported as a result any of these creatinine elevations.

Hematology

Mean values and changes from Baseline for hematology values by study visit were unremarkable.

Marked hematology abnormalities that occurred during the treatment period were sporadic. These are shown below.

Table 12.m Marked Abnormalities in Hematology—Safety Analysis Set

Laboratory Test	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Hematocrit/PCV					
<0.8 × Baseline	0/139	0/277	1/277 (0.4)	1/281 (0.4)	1/280 (0.4)
Hemoglobin					
>3 g/dL decrease	0/139	1/277 (0.4)	1/277 (0.4)	0/281	0/280
Platelet count					
<50×10 ⁹ /L or >700×10 ⁹ /L (a)	0/138	0/277	0/276	1/280 (0.4)	0/279
RBC					
<0.8 × Baseline	0/139	1/277 (0.4)	1/277 (0.4)	1/281 (0.4)	0/280
WBC					
<2×10 ⁹ /L or >20×10 ⁹ /L (a)	0/139	0/277	1/277 (0.4)	0/281	0/280

Source: Tables 15.3.4.1 and 15.3.4.8.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline values are included in this table.

(a) Only markedly abnormal elevations were observed.

Subject 6152/018 was withdrawn from study drug because of basophilia. According to the narrative, the “subject’s basophil count was WNL at the beginning of the study and throughout the study. Basophil count was 3% on Study Day 37 of the DB period and study drug was prematurely discontinued. Subject took Verapamil 160 mg PO beginning on Study Day 33 of the DB period and ongoing throughout the study. Subject experienced no other AEs and no additional concomitant medications were taken during the study.” The event was not described as serious.

Urinalysis

Mean values for urinalysis (including specific gravity and pH) and changes from baseline were unremarkable.

Vital Signs

There were no remarkable differences in weight across treatment groups at Baseline or in mean weight changes from Baseline at any subsequent visit (all within ± 0.3 kg).

There were no meaningful differences in sitting pulse at Baseline or at any visit with respect to change from Baseline across treatment groups.

Physical Findings

There were no major findings as a result of physical examinations in the safety population.

ECGs

There were 4 subjects with abnormal, clinically significant ECG results at Final Visit.

-Subject 6123/034 (olmesartan 40 mg) had an increase in the Fridericia QTc interval from 418 msec at Screening to 498 msec at Final Visit, with a change in QTc interval category from ≤ 430 msec to >450 -500 msec. A bundle branch block left was reported at Day 42.

-Subject 6147/002 (TAK-491 40 mg) had an adverse event of extrasystoles at Day 43 that was ongoing and mild.

-Subject 6162/017 (TAK-491 80 mg), who had a pretreatment event of electrocardiogram T-wave abnormal (nonspecific T-wave change on ECG at Day -22 that was ongoing) had electrocardiogram T-wave abnormal (worsening of nonspecific T-wave changes on ECG) at Day 42 that was ongoing and mild.

-subject 6149/024 (olmesartan 40 mg) had ECG signs of myocardial ischemia (ST elevation in lead II) at Day 43 that were ongoing and mild.

There is no evidence of an effect of study drug on ECG parameters.

Pregnancy

Subject 6058/006 (TAK-491 80 mg) was found to be pregnant on day 42. The subject refused follow-up, and the outcome of the pregnancy is unknown.

Reviewer's summary and conclusions

Efficacy: doses of TAK-491 20, 40, and 80 mg and olmesartan 40 mg were significantly better in reducing the 24-hour mean SBP and DBP compared to placebo. However, the differences between the dose groups were small.

The subject population was about 15% black. These subjects had a blood pressure response to TAK-491 20 mg, 40 mg, 80 mg and olmesartan 40 mg that was about half of what was seen in the white population.

Safety: all doses of TAK-491 and olmesartan 40 mg were reasonably well tolerated. The most commonly reported adverse events were headache, dyslipidemia, and dizziness. There was no dose response for these events. Increases in serum creatinine were observed in all active treatment groups, as were elevations in serum potassium and uric acid.

Conclusions: TAK-491 is an effective antihypertensive agent. There was no evidence of a dose response. As expected, black subjects had less blood pressure effect to both ARBs compared to white subjects. There is no obvious reason to prefer TAK-491 over olmesartan 40 mg.

Study 01-06-TL-491-019

Title: Double-Blind, Randomized, Placebo-Controlled, 5-Arm Titration Study to Evaluate the Efficacy and Safety of TAK-491 when Compared with Valsartan and Olmesartan in Subjects with Essential Hypertension

Investigators: 131 principal investigators enrolled subjects into the placebo-run period in the United States and Latin America.

Study Period: 02 April 2008 to 19 August 2009

Primary objective: to evaluate the antihypertensive effect of TAK-491 compared with placebo, olmesartan, and valsartan after 6 weeks of treatment, as measured by the primary endpoint of change in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

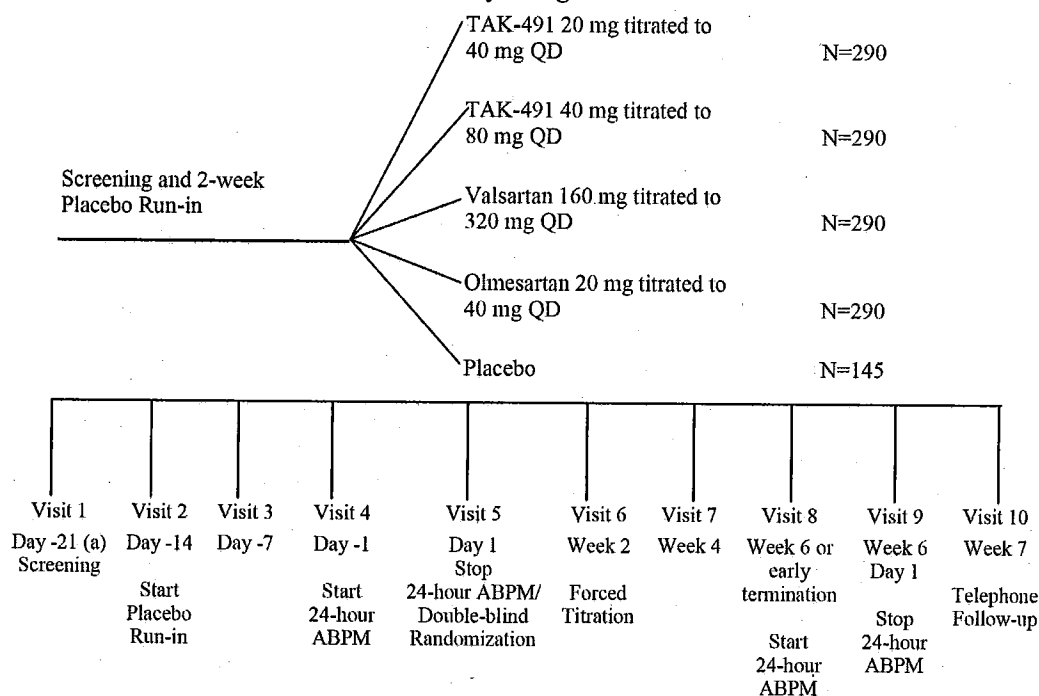
Secondary objectives:

- to evaluate the antihypertensive effect of TAK-491 compared with placebo, olmesartan, and valsartan after 6 weeks of treatment, as measured by the secondary endpoint of change in trough clinic sitting SBP and by other ABPM and clinic measures of SBP and diastolic blood pressure (DBP).
- to evaluate the safety and tolerability of TAK-491 compared with placebo, olmesartan, and valsartan.
- change from Baseline to Week 6 in the 24-hour mean DBP by ABPM.
- change from Baseline to Week 6 in trough clinic sitting DBP.
- change from Baseline to Week 6 in SBP and DBP using additional ABPM parameters (daytime mean [6 AM to 10 PM], nighttime mean [12 AM to 6 AM], blood pressure mean at 0 to 12 hours after dosing, and trough mean at 22 to 24 hours after dosing).
- proportion of subjects who achieved response criteria at Week 6:
 - a) clinic DBP <90 mm Hg and/or reduction of ≥ 10 mm Hg from Baseline.
 - b) clinic SBP <140 mm Hg and/or reduction of ≥ 20 mm Hg from Baseline.
 - c) clinic DBP <90 mm Hg and/or reduction of ≥ 10 mm Hg from Baseline AND clinic SBP <140 mm Hg and/or reduction of ≥ 20 mm Hg from Baseline.

Study design: multicenter, randomized, parallel-group, double-blind, placebo-controlled and active-controlled forced titration study designed to evaluate the efficacy and safety of TAK-491 compared with placebo, olmesartan, and valsartan in subjects with essential hypertension (trough clinic sitting SBP ≥ 150 mm Hg and ≤ 180 mm Hg and 24-hour mean SBP ≥ 130 mm Hg and ≤ 170 mm Hg).

Subjects were randomized, after a 2-week screening period, to receive TAK-491 20 mg, TAK-491 40 mg, valsartan 160 mg, olmesartan 20 mg, or placebo for 2 weeks. At the end of 2 weeks, subjects were force-titrated to the higher dose: TAK-491 40 mg or 80 mg, valsartan 320 mg, olmesartan 40 mg, or remained on placebo. Subjects remained at the higher dosage for the remainder of the study.

Figure 9.a Schematic of Overall Study Design



(a) If the subject was already on amlodipine, the subject was to discontinue this medication at Screening Day -28 extending the Screening Period for an additional 7 days (for a total of 14 days of Screening) for washout of medication prior to the single-blind placebo run-in period.

24-hour ABPM was conducted on Day -1 prior to the first dose of double-blind study medication and at Week 6 or early termination.. Clinic DBP and SBP were measured at screening, randomization, week 2 (prior to forced titration), Week 4, and Week 6.

Study subjects

Inclusion criteria

- essential hypertension (trough clinic sitting SBP ≥ 150 mm Hg and ≤ 180 mm Hg and 24-hour mean SBP ≥ 130 mm Hg and ≤ 170 mm Hg).
- male or female and aged 18 years or older.
- capable of understanding and complying with protocol requirements.
- signed a written, informed consent form prior to the initiation of any study procedures.
- females of childbearing potential (i.e., nonsterilized and premenopausal) who was sexually active agreed to use adequate contraception (as defined in the informed consent form) from Screening throughout the duration of the study.
- clinical laboratory evaluations (including clinical chemistry, hematology, and complete urinalysis) within the reference range for the testing laboratory or the results were deemed not clinically significant for inclusion into this study by the investigator.
- willing to discontinue current antihypertensive medications at Visit 1.

Stratification

Subjects were stratified by race: black and non-black.

Timing of dosing

Randomized subjects were instructed to withhold the last dose of double-blind study medication the morning of Week 6/Early Termination (Visit 8). The investigator or designee administered study medication in the clinic to the subject at 0800 (± 2 hours) immediately prior to the ABPM start.

Changes in the Conduct of the Study or Planned Analyses

There were 3 protocol amendments during the study: The major changes are shown below. Amendment 1 (December 12, 2008) had only minor changes.

Amendment 2 (April 16, 2009)

- The sample size was increased from 1170 to 1305 subjects because of higher than expected missing or disqualified postbaseline ABPM data. (The sample size per group was increased).
- Clinic SBP was prioritized as the key secondary endpoint to reflect the importance of this measurement in assessing efficacy of antihypertensive agents. Peak effect and trough-to-peak ratio were removed from the secondary endpoints and the time frame for each endpoint was added.
- The testing scheme was modified to control type 1 error. Part of this modification was the addition of noninferiority analyses to assess comparability of TAK-491 to olmesartan and valsartan. The stepwise testing for the primary endpoint (all comparisons of TAK-491 80 mg were made before comparisons of TAK-491 40 mg) was based on the dose response observed in study 01-05-TL-491-008.
- Subgroup analyses and exploratory analyses were prespecified.

Amendment 3 (June 1, 2009)

- The calculation of UACR was added to the list of laboratory parameters and collection times for creatinine and albumin were specified.
- The Safety Reporting section was updated to remove Argentina and Brazil.

Original cGFR results by [REDACTED] (b) (4) were found to be incorrect due to a random systematic error that used the first subject's race in a batch of accessions being released from the lab's Laboratory Information Management system. Therefore, all subjects in that batch were assumed to be of the same race. This error was specific to the cGFR determined by the Modification of Diet in Renal Disease (MDRD) Study method. Therefore, cGFR results were recalculated by [REDACTED] (b) (4) using the following MDRD equation and the recalculated results were used for data summary and analysis:
$$\text{cGFR} = 186 \times (\text{Cr [mg/dL]})^{-1.154} \times \text{Age}^{-0.203} \times 1.212 [\text{if Black}] \times 0.742 [\text{if female}],$$
where Cr is a serum creatinine value. The multiplier for Black subjects in the equation was applied if the subject reported his or her race as "Black or African American" and the multiplier for female subjects was applied for those indicating their sex as "female."

RESULTS

A total of 1291 subjects were randomized to receive double-blind treatment:

- 154 subjects randomized to placebo,
- 280 subjects randomized to TAK-491 20 mg,
- 285 subjects randomized to TAK-491 40 mg,
- 282 subjects randomized to valsartan 160 mg, and
- 290 subjects randomized to olmesartan 20 mg.

Excluded subjects:

Those subjects not included in any analyses were two randomized to receive TAK-491 80 mg (1191/001 and 1012/001) and four randomized to receive valsartan 320 mg (1017/004, 1064/015, 1128/002, and 1218/028). All six subjects were withdrawn before they received study drug.

In addition,

- subject 1191/003 was not randomized but inadvertently received treatment with TAK-491 80 mg. Data collected for this subject were included in the safety analyses only.
- subject 1191/002 was randomized to receive valsartan 320 mg but was treated with placebo. Data collected for this subject were included in the safety analysis (for the placebo group) and efficacy analysis.

Protocol deviations

There were no reports of the randomization code being broken prematurely for any subject.

Major protocol deviations are shown below by treatment groups.

Table 10.h Major Protocol Deviations (FAS)

	Treatment Group n (%)				
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=283	Valsartan 320 mg N=278	Olmesartan 40 mg N=290
Subjects with at least 1 major protocol deviation	11 (7.1)	25 (8.9)	24 (8.5)	25 (9.0)	22 (7.6)
Received wrong treatment	0	1 (0.4) (a)	0	1 (0.4) (b)	0
Study drug compliance <80%	0	1 (0.4)	3 (1.1)	5 (1.8)	1 (0.3)
Study drug compliance >120%	0	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.3)
Subject had Baseline 24-hour mean SBP <130 mm Hg	5 (3.2)	4 (1.4)	6 (2.1)	6 (2.2)	6 (2.1)
Subject took prohibited medications	6 (3.9)	17 (6.1)	13 (4.6)	12 (4.3)	14 (4.8)

Source: Table 15.1.5 and Appendix 16.2.2.5.

(a) Subject 1051/001 was randomized in error to receive TAK-491 40 mg.

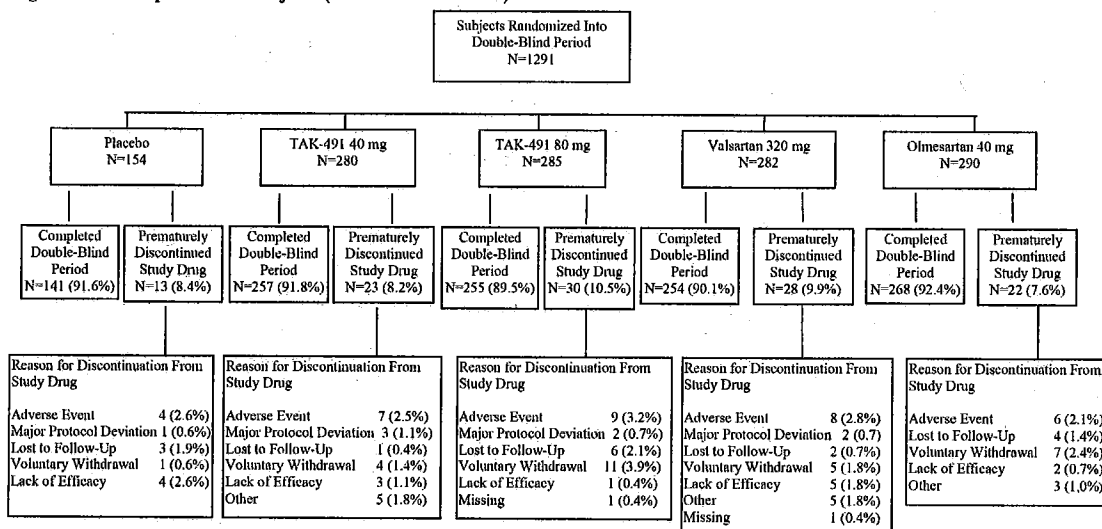
(b) Subject 1191/002 was randomized to receive valsartan 320 mg but was treated with placebo.

There were 107 subjects (8.3%) with at least 1 major protocol deviation. The impact of these deviations on the study results is probably negligible.

Disposition of subjects

The outcomes of the subjects in the different treatment groups are shown below.

Figure 10.b Disposition of Subjects (Double-Blind Period)



Most subjects completed the study (91.0%). The percentage of subjects per treatment group who were prematurely discontinued from the study ranged from 7.6% to 10.5%.

Demographics

The demographics of the subjects randomized to the various treatment groups are shown below.

Table 10.a Summary of Demographic Characteristics (Randomized Subjects)

Characteristic	Treatment Group				
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=285	Valsartan 320 mg N=282	Olmesartan 40 mg N=290
Sex, n (%)					
Male	90 (58.4)	147 (52.5)	151 (53.0)	152 (53.9)	159 (54.8)
Female	64 (41.6)	133 (47.5)	134 (47.0)	130 (46.1)	131 (45.2)
Age, years					
Mean (SD)	56.3 (10.98)	56.5 (11.64)	55.9 (11.12)	54.6 (10.87)	56.4 (10.91)
<45, n (%)	20 (13.0)	41 (14.6)	38 (13.3)	56 (19.9)	39 (13.4)
45 to 64, n (%)	98 (63.6)	170 (60.7)	184 (64.6)	178 (63.1)	185 (63.8)
≥65, n (%)	36 (23.4)	69 (24.6)	63 (22.1)	48 (17.0)	66 (22.8)
Ethnicity, n (%)					
Hispanic or Latino	19 (12.3)	35 (12.5)	48 (16.8)	49 (17.4)	38 (13.1)
Non-Hispanic and Latino	103 (66.9)	191 (68.2)	186 (65.3)	189 (67.0)	196 (67.6)
Not Collected (a)	32 (20.8)	54 (19.3)	51 (17.9)	44 (15.6)	56 (19.3)
Race (b), n (%)					
American Indian/ Alaska Native (c)	32 (20.8)	49 (17.5)	46 (16.1)	41 (14.5)	44 (15.2)
Asian	2 (1.3)	6 (2.1)	4 (1.4)	3 (1.1)	2 (0.7)
Black/ African American	27 (17.5)	51 (18.2)	49 (17.2)	51 (18.1)	54 (18.6)
Native Hawaiian/ Other Pacific Islander	1 (0.6)	1 (0.4)	0	0	3 (1.0)
White	96 (62.3)	177 (63.2)	190 (66.7)	189 (67.0)	191 (65.9)
Multiracial	4 (2.6)	4 (1.4)	4 (1.4)	2 (0.7)	4 (1.4)
Weight, kg	N=154	N=280	N=283	N=278	N=290
Mean (SD)	86.99 (20.500)	89.74 (20.504)	86.88 (20.807)	88.04 (20.070)	87.63 (19.836)
Height, cm					
Mean (SD)	168.2 (10.83)	167.9 (11.72)	167.8 (11.69)	167.9 (11.37)	167.4 (11.38)
BMI, kg/m²	N=154	N=280	N=283	N=278	N=290
Mean (SD)	30.50 (5.366)	31.71 (6.012)	30.70 (5.890)	31.09 (5.535)	31.13 (5.509)
Region, n (%)					
United States	122 (79.2)	226 (80.7)	234 (82.1)	238 (84.4)	234 (80.7)
Latin America	32 (20.8)	54 (19.3)	51 (17.9)	44 (15.6)	56 (19.3)

Source: Table 15.1.7 and Appendix 16.2.4.1.

(a) Ethnicity was not collected at Latin American sites.

(b) Subjects who indicated more than 1 race category were included in each category indicated and were also included in the multiracial category. Thus, the number and percentage of subjects in each category may not add up to the total number of subjects.

(c) Subjects who self-identified as being American Indian were predominantly from Latin America.

The demographic characteristics were generally similar among treatment groups. The distribution of men and women randomized in the study was similar, the mean age of subjects was around 56 years, and 21.8% of subjects ≥ 65 years of age. The percentage of black subjects was 17.2% to 18.6% across treatment groups.

Baseline blood pressure

24-hour ABPM at baseline for the different treatment groups are shown below.

Table 10.b Summary of ABPM SBP and DBP (mm Hg) at Baseline (Randomized Subjects)

Characteristic	Treatment Group					P-value (a)
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=285	Valsartan 320 mg N=282	Olmesartan 40 mg N=290	
Number of Subjects with Blood Pressure by ABPM at Baseline	153	277	280	278	289	
0- to 24-hour mean SBP						0.096
Mean (SD)	144.2 (10.57)	144.3 (9.87)	145.0 (9.54)	146.3 (10.45)	144.5 (9.52)	
Mean daytime (6 AM - 10 PM) SBP						0.150
Mean (SD)	147.5 (10.70)	147.7 (10.05)	148.6 (9.89)	149.6 (10.84)	148.1 (9.75)	
Mean nighttime (12 AM - 6 AM) SBP						0.209
Mean (SD)	134.1 (12.87)	134.3 (12.65)	134.3 (12.65)	136.2 (12.95)	133.8 (12.79)	
0- to 12-hour mean SBP						0.146
Mean (SD)	148.1 (11.28)	148.3 (10.45)	149.2 (10.54)	150.3 (11.24)	148.9 (10.08)	
Trough 22- to 24-hour mean SBP						0.566
Mean (SD)	148.1 (12.93)	147.7 (12.51)	149.1 (11.82)	149.2 (13.38)	148.1 (12.36)	
0- to 24-hour mean DBP						0.029*
Mean (SD)	88.7 (9.44)	87.9 (9.57)	88.6 (9.58)	90.2 (8.91)	87.9 (9.08)	
Mean daytime (6 AM - 10 PM) DBP						0.027*
Mean (SD)	91.9 (9.99)	91.2 (9.95)	91.8 (10.19)	93.6 (9.48)	91.2 (9.51)	
Mean nighttime (12 AM - 6 AM) DBP						0.355
Mean (SD)	79.5 (9.74)	79.0 (10.80)	79.5 (10.18)	80.5 (10.00)	78.9 (10.55)	
0- to 12-hour mean DBP						0.042*
Mean (SD)	92.4 (10.52)	91.8 (10.47)	92.4 (10.81)	94.2 (9.81)	91.8 (9.92)	
Trough 22- to 24-hour mean DBP						0.142
Mean (SD)	93.9 (10.92)	92.4 (10.80)	93.7 (10.91)	94.7 (11.26)	93.0 (10.65)	

Source: Table 15.1.8.1.

Note: Baseline was the last observation before the first dose of double-blind study drug.

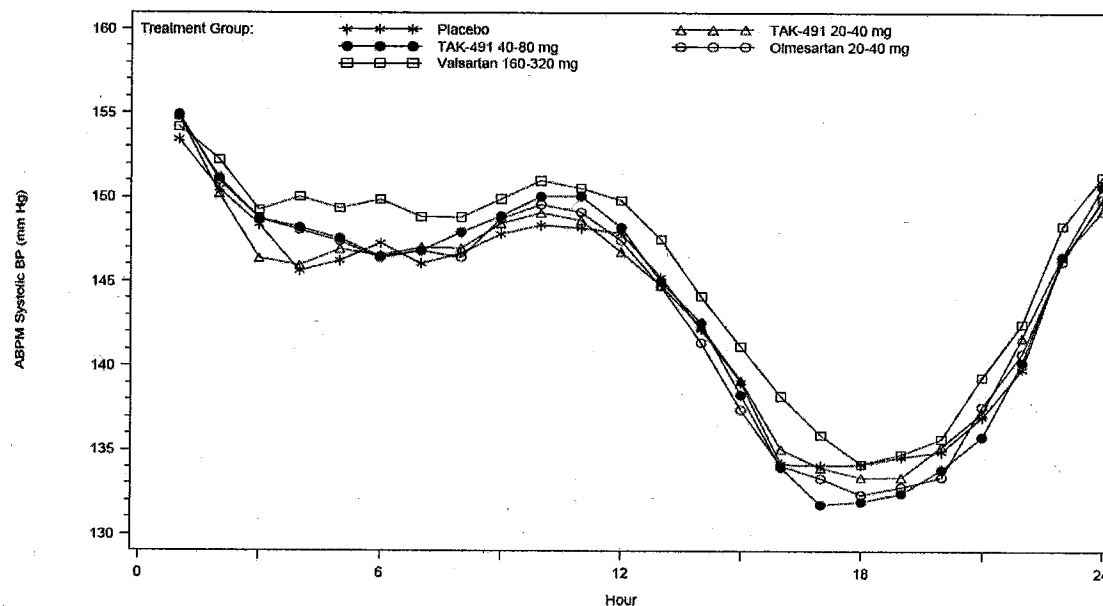
* Significant difference at 0.05 level.

(a) The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

At baseline, the 0 to 24-hour mean blood pressures ranged from 144 mm Hg to 146 mm Hg (systolic) and from 88 mmHg to 9 mmHg (diastolic). The subjects randomized to valsartan tended to have the highest mean baseline values.

The 24 hour SBP profiles at baseline are shown below.

Figure 11.a SBP by ABPM at Baseline by Treatment and Hour for the 0- to 24-Hour Interval (FAS)



The clinic BP recordings at baseline are shown below.

Table 10.c Summary of Trough Clinic Sitting SBP and DBP (mm Hg) at Baseline (Randomized Subjects)

Characteristic	Treatment Group					P-value (a)
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=285	Valsartan 320 mg N=282	Olmesartan 40 mg N=290	
Number of Subjects with Clinic Blood Pressure at Baseline	154	280	283	278	290	
Clinic SBP						0.691
Mean (SD)	156.3 (12.58)	157.3 (12.75)	157.9 (12.12)	157.1 (12.64)	157.9 (12.71)	
Clinic DBP						0.453
Mean (SD)	93.1 (10.92)	92.5 (10.83)	92.0 (10.70)	93.3 (9.99)	91.9 (9.49)	

Source: Table 15.1.8.2.

Note: Baseline value was the average of 3 sitting blood pressure values and was the last observation before the first dose of double-blind study drug.

(a) The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

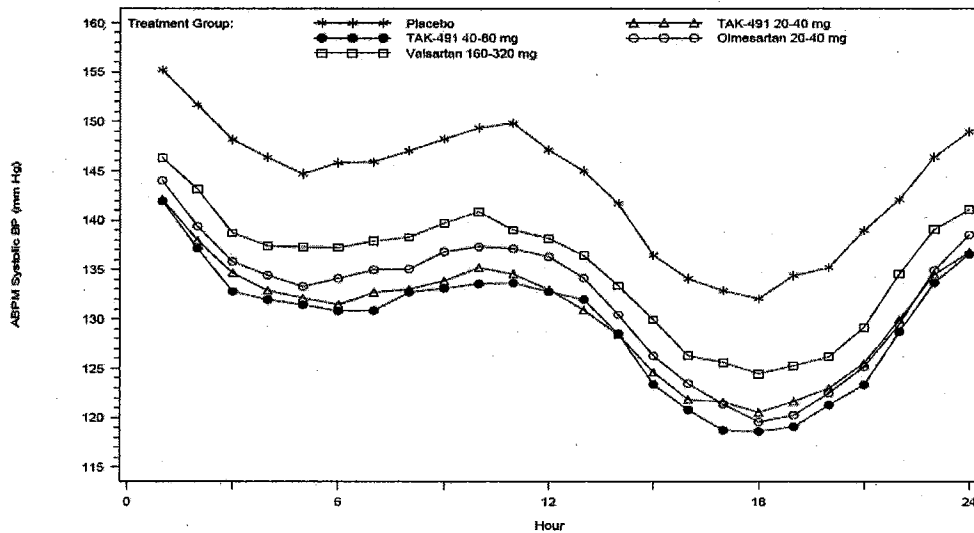
The clinic BP measurements at baseline were similar across the groups.

Primary efficacy variable

The primary efficacy variable was change from baseline at Week 6 in 24-hour SBP as measured by ABPM.

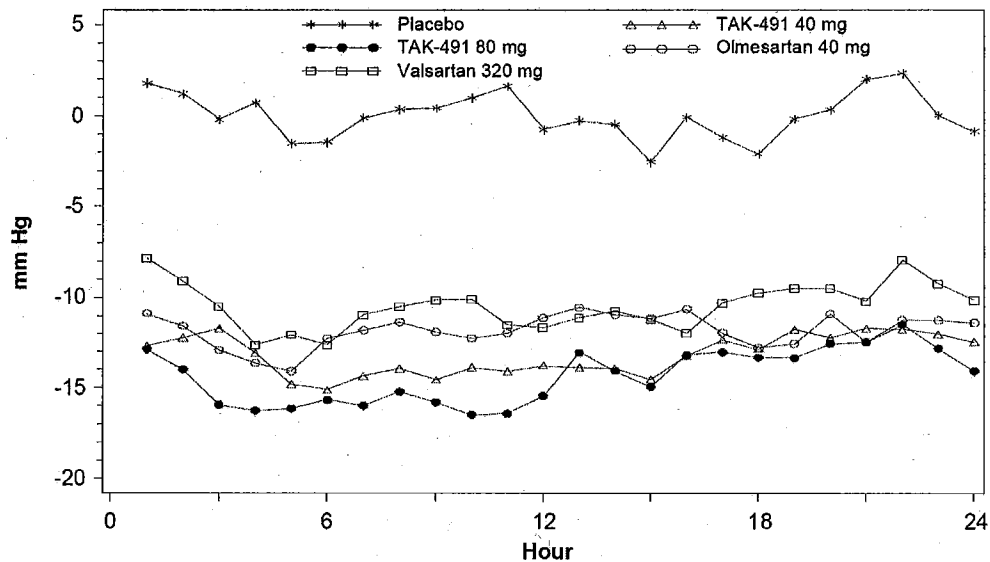
The 24-hour SBP profiles at the final visit for all treatment groups are shown in the figure below.

Figure 11.b SBP by ABPM at Final Visit by Treatment and Hour for the 0- to 24-Hour Interval (FAS)



The figure below shows the change from baseline in mean 24-hour SBP profiles.

Figure 11.c Change From Baseline in Mean SBP by ABPM by Treatment and Hour for the 0- to 24-hour Interval (FAS)



The numerical changes from baseline in 24-hour mean SBP and statistical comparisons are shown in the table below.

Table 11.a Change From Baseline to Week 6 in 24-hour Mean SBP (mm Hg) by ABPM (FAS)

Study Visit	Treatment Group				
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=283	Valsartan 320 mg N=278	Olmesartan 40 mg N=290
Baseline					
n	134	237	229	234	254
LS mean (SE)	144.30 (0.853)	144.42 (0.641) (a)	144.60 (0.652)	146.33 (0.645)	144.42 (0.619)
Change from Baseline to Final ABPM					
n	134	237	229	234	254
LS mean (SE)	-0.25 (0.917)	-13.42 (0.690)	-14.53 (0.702)	-10.22 (0.696)	-11.99 (0.666)
LS mean difference vs placebo (b)		-13.16	-14.27	-9.97	-11.73
(95% CI)		(-15.41, -10.91)	(-16.54, -12.01)	(-12.23, -7.71)	(-13.96, -9.51)
P-value vs placebo (c)		<0.001*	<0.001*	<0.001	<0.001
LS mean difference vs placebo (multiple imputation analysis) (b)		-13.16	-14.33	-9.69	-11.66
(95% CI)		(-15.41, -10.91)	(-16.52, -12.14)	(-11.89, -7.50)	(-13.90, -9.43)
P-value vs placebo (c)		<0.001	<0.001	<0.001	<0.001
LS mean difference vs olmesartan (d)		-1.43	-2.54		
(95% CI)		(-3.31, 0.45)	(-4.44, -0.64)		
P-value vs olmesartan (c)		0.136	0.009*		
LS mean difference vs valsartan (multiple imputation analysis) (d)		-1.50	-2.67		
(95% CI)		(-3.40, 0.41)	(-4.56, -0.77)		
P-value vs olmesartan (c)		0.123	0.006		
LS mean difference vs valsartan (e)		-3.20	-4.31		
(95% CI)		(-5.12, -1.27)	(-6.25, -2.37)		
P-value vs valsartan (c)		0.001	<0.001*		
LS mean difference vs valsartan (multiple imputation analysis) (e)		-3.47	-4.64		
(95% CI)		(-5.52, -1.41)	(-6.67, -2.60)		
P-value vs valsartan (c)		0.001	<0.001		

Source: Table 15.2.1.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

* Indicates significant difference at 0.05 level and significant within the framework of the stepwise analysis.

(a) Statistically significant difference at 0.05 level vs valsartan 320 mg.

(b) LS mean difference=LS mean change of each active group (TAK-491 40 mg, TAK-491 80 mg, olmesartan, or valsartan) - LS mean change of placebo group.

(c) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

(d) LS mean difference=LS mean change of each TAK-491 group - LS mean change of olmesartan.

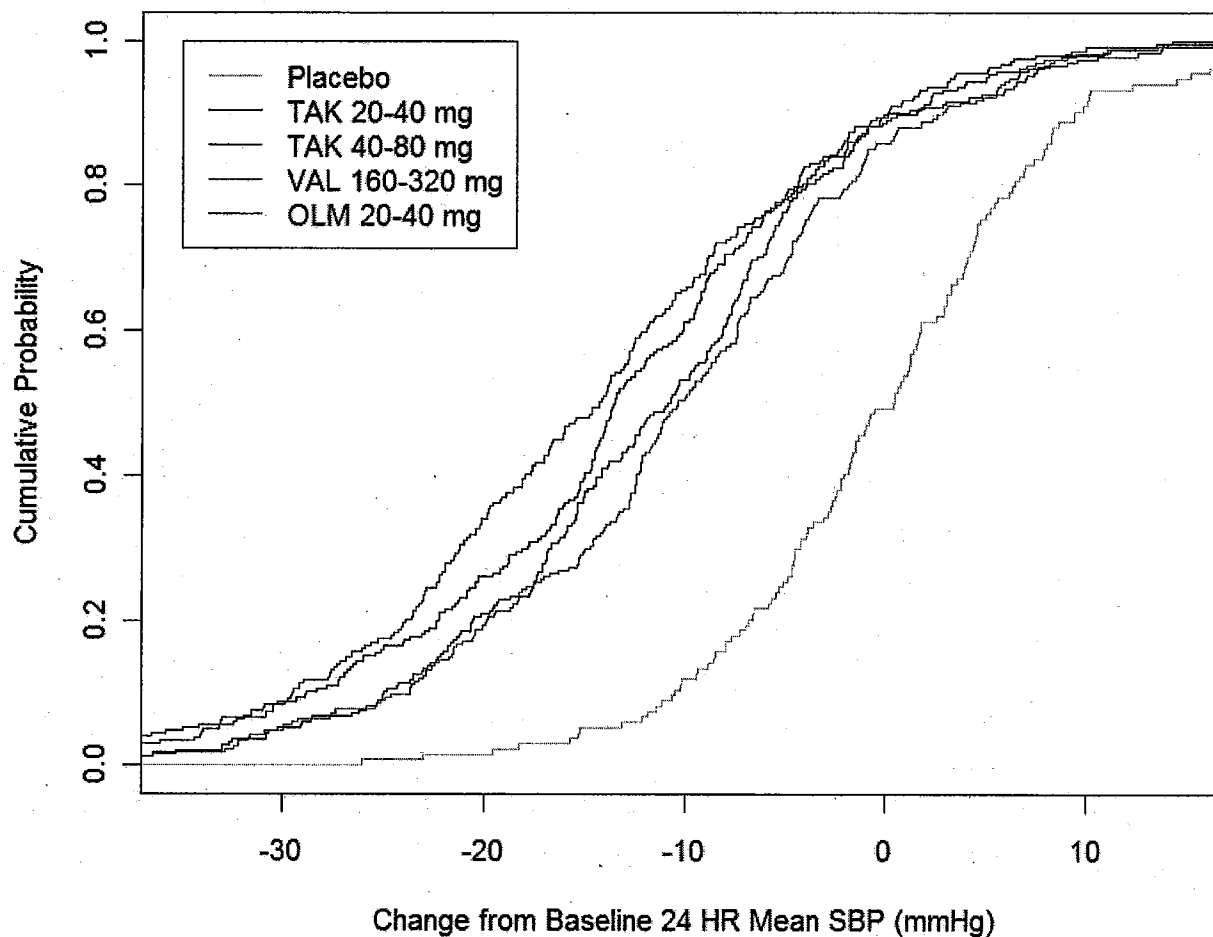
(e) LS mean difference=LS mean change of each TAK-491 group - LS mean change of valsartan.

Except for placebo, all treatment groups had a large decrease in SBP compared to baseline measurements. The treatment effect ranged between -14 and -10 mmHg and these declines were highly significant. Reductions in SBP for the two doses of TAK-491 were similar to one another.

Overall, the higher dose of TAK-491 (80 mg) had a greater ability to lower SBP compared to valsartan 320 mg (by about 3 mmHg) and olmesartan 40 mg (by about 4 mmHg). These differences were statistically significant. The effect of the lower dose of TAK-491 (40 mg) was not superior to the two active comparators.

The figure below is the cumulative distribution function for the ABPM SBP. There are 203 subjects not included in the figure.

Distribution of Primary Endpoint (24 HR SBP) Study 01-06-TL-491-019



Secondary efficacy variables

Clinic (sitting) SBP

The baseline means and mean changes from baseline in trough clinic SBP are shown below.

Table 11.b Change From Baseline in Mean Trough Clinic Sitting SBP (mm Hg) by Study Visit (LOCF, FAS)

Study Visit (mm Hg)	Treatment Group				
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=283	Valsartan 320 mg N=278	Olmesartan 40 mg N=290
Baseline (a)					
n	148	269	270	271	283
LS mean (SE)	156.32 (1.031)	157.11 (0.765)	157.95 (0.764)	157.28 (0.762)	157.89 (0.746)
Change from Baseline to Week 2					
n	131	248	250	248	251
LS mean change (SE)	-0.96 (1.228)	-12.73 (0.892)	-13.97 (0.888)	-8.84 (0.891)	-9.71 (0.886)
Change from Baseline to Week 4					
n	142	262	264	257	267
LS mean change (SE)	-0.72 (1.231)	-16.38 (0.906)	-16.72 (0.903)	-10.79 (0.915)	-12.72 (0.897)
Change from Baseline to Week 6					
n	148	269	270	271	283
LS mean change (SE)	-1.83 (1.293)	-16.38 (0.959)	-16.74 (0.957)	-11.31 (0.955)	-13.20 (0.935)
LS mean difference vs placebo (b)		-14.55	-14.92	-9.48	-11.37
(95% CI)		(-17.71, -11.40)	(-18.07, -11.76)	(-12.64, -6.33)	(-14.50, -8.24)
P-value vs placebo (c)		<0.001*	<0.001*	<0.001	<0.001
LS mean difference vs placebo (multiple imputation analysis) (b)		-14.28	-14.64	-9.17	-11.25
(95% CI)		(-17.49, -11.07)	(-17.88, -11.40)	(-12.37, -5.97)	(-14.40, -8.11)
P-value vs placebo (c)		<0.001	<0.001	<0.001	<0.001
LS mean difference vs olmesartan (d)		-3.18	-3.54		
(95% CI)		(-5.81, -0.55)	(-6.17, -0.92)		
P-value vs olmesartan (c)		0.018*	0.008*		
LS mean difference vs olmesartan (multiple imputation analysis) (d)		-3.03	-3.38		
(95% CI)		(-5.73, -0.33)	(-6.08, -0.68)		
P-value vs olmesartan (c)		0.028	0.014		
LS mean difference vs valsartan (e)		-5.07	-5.43		
(95% CI)		(-7.73, -2.42)	(-8.09, -2.78)		
P-value vs valsartan (c)		<0.001*	<0.001*		
LS mean difference vs valsartan (multiple imputation analysis) (e)		-5.11	-5.47		
(95% CI)		(-7.78, -2.44)	(-8.13, -2.81)		
P-value vs valsartan (c)		<0.001	<0.001		

Footnotes for Table 11.b are on the following page.

Source: Table 15.2.3.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level and significant within the framework of the stepwise analysis of clinic SBP.

(a) Baseline is the last observation before the first dose of double-blind study drug.

(b) LS mean difference=LS mean change of each active group (TAK-491 40 mg, TAK-491 80 mg, olmesartan, or valsartan) - LS mean change of placebo group.

(c) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

(d) LS mean difference=LS mean change of each TAK-491 group - LS mean change of olmesartan.

(e) LS mean difference=LS mean change of each TAK-491 group - LS mean change of valsartan.

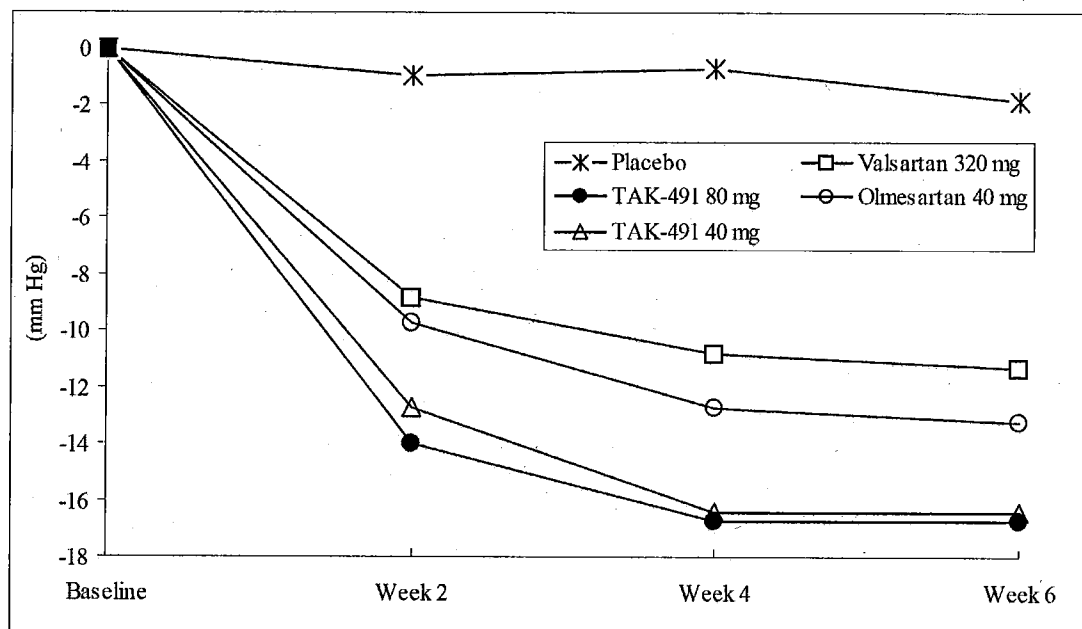
The range of SBP at baseline was 156-158 mmHg and there were no statistically significant differences between treatment groups.

At week 6, the decreases from baseline in trough clinic SBP were statistically significantly greater for all active treatment groups compared to placebo. The reductions, minus the placebo effect, ranged from 9 mmHg to 15 mmHg.

The differences between TAK-491 and both olmesartan and valsartan were around 3 mmHg.

The mean changes in clinic SBP from baseline at weeks 2, 4, and 6 are shown below for all treatment groups.

Figure 11.d Mean Change in Trough Clinic Sitting SBP by Study Visit (LOCF, FAS)



The dose of study drug was increased at week 2. The declines in SBP were similar at weeks 4 and 6.

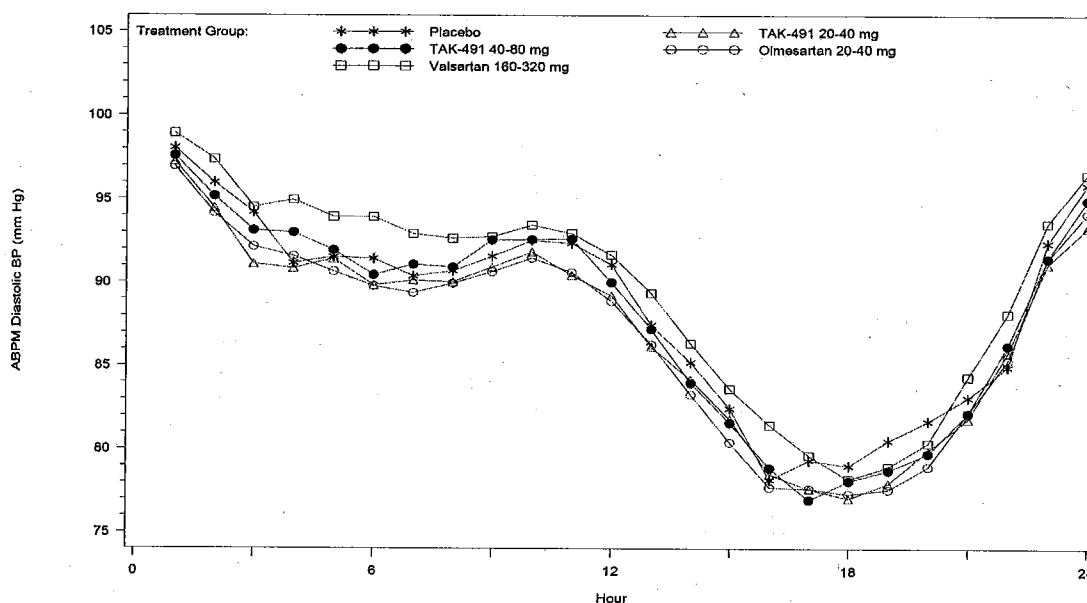
24-hour Mean DBP by ABPM

At Baseline, 24-hour mean DBP ranged from 87.58 mm Hg to 90.14 mm Hg across all treatment Groups. As with the 24-hour SBP, the valsartan group had the highest baseline 24-hour mean DBP by ABPM. The difference between the baseline for the valsartan and the TAK-491 (40 mg) groups was statistically significant.

The baselines for all treatment groups are shown below.

Figure 15.2.2.5.1

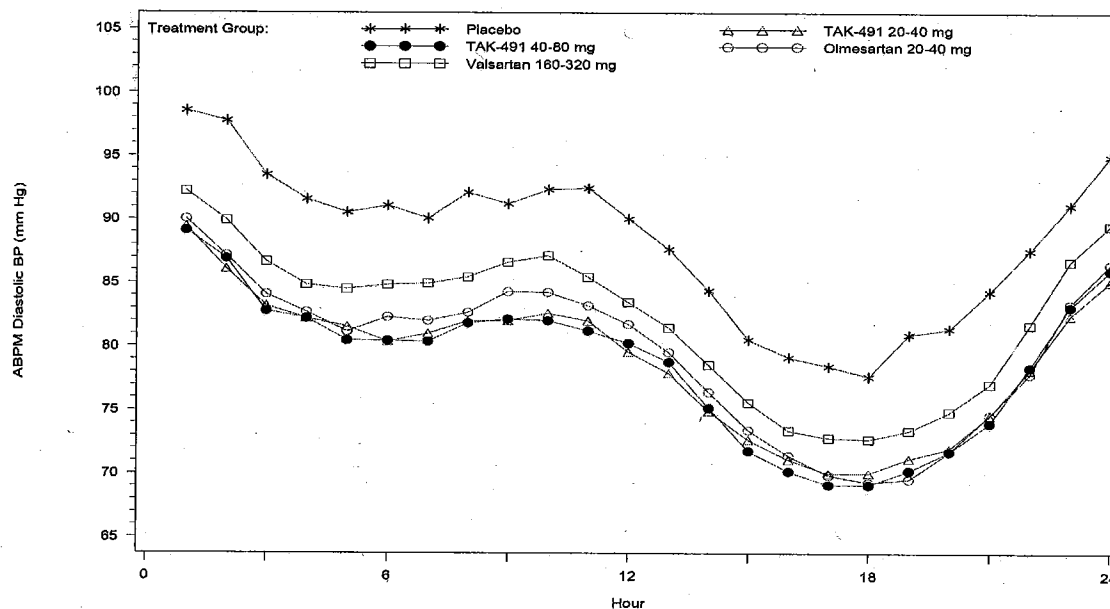
ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Baseline by Hour for the 0- to 24-Hour Interval
Full Analysis Set



The DBP as measured by the ABPM at the last visit are shown below.

Figure 15.2.2.5.2

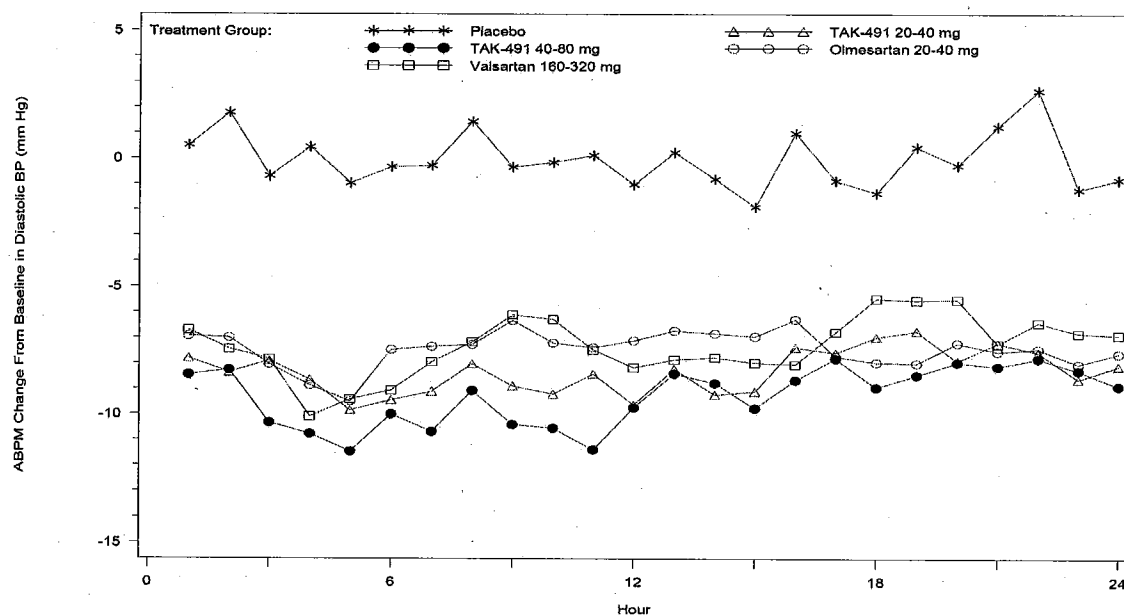
ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Final Visit by Hour for the 0- to 24-Hour Interval
Full Analysis Set



Changes from baseline at the last visit for all treatment groups are shown below.

Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



The table below shows the changes from baseline at week for the 24-hour mean DBP recorded by ABPM.

Table 11.c Change From Baseline to Week 6 in 24-hour Mean DBP (mm Hg) by ABPM (FAS)

Study Visit	Treatment Group				
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=283	Valsartan 320 mg N=278	Olmesartan 40 mg N=290
Baseline					
n	134	237	229	234	254
LS mean (SE)	88.88 (0.805)	87.68 (0.605) (a)	88.50 (0.616)	90.14 (0.609)	87.58 (0.585)
Change from Baseline to Final ABPM					
n	134	237	229	234	254
LS mean (SE)	-0.07 (0.627)	-8.65 (0.472)	-9.43 (0.480)	-7.09 (0.476)	-7.74 (0.456)
LS mean difference vs placebo (b)		-8.58	-9.36	-7.02	-7.67
(95% CI)		(-10.12, -7.04)	(-10.91, -7.81)	(-8.56, -5.47)	(-9.19, -6.15)
P-value vs placebo (c)		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs placebo (multiple imputation analysis) (b)		-8.65	-9.50	-7.08	-7.72
(95% CI)		(-10.14, -7.17)	(-11.01, -7.98)	(-8.65, -5.51)	(-9.23, -6.21)
P-value vs placebo (c)		<0.001*	<0.001*	<0.001*	<0.001*
LS mean difference vs olmesartan (d)		-0.91	-1.70		
(95% CI)		(-2.19, 0.38)	(-2.99, -0.40)		
P-value vs olmesartan (c)		0.166	0.011*		
LS mean difference vs olmesartan (multiple imputation analysis) (d)		-0.93	-1.78		
(95% CI)		(-2.26, 0.40)	(-3.03, -0.53)		
P-value vs olmesartan (c)		0.170	0.005*		
LS mean difference vs valsartan (e)		-1.56	-2.35		
(95% CI)		(-2.88, -0.24)	(-3.67, -1.02)		
P-value vs valsartan (c)		0.020*	<0.001*		
LS mean difference vs valsartan (multiple imputation analysis) (e)		-1.57	-2.42		
(95% CI)		(-2.91, -0.23)	(-3.77, -1.07)		
P-value vs valsartan (c)		0.022*	<0.001*		

Source: Table 15.2.2.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) Statistically significant difference at 0.05 level vs valsartan 320 mg.

(b) LS mean difference=LS mean change of each active group (TAK-491 40 mg, TAK-491 80 mg, olmesartan, or valsartan) - LS mean change of placebo group.

(c) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

(d) LS mean difference=LS mean change of each TAK-491 group - LS mean change of olmesartan.

(e) LS mean difference=LS mean change of each TAK-491 group - LS mean change of valsartan.

Except for placebo, all treatment groups had a large decrease in DBP compared to baseline measurements. The treatment effect ranged between -7 and -9 mmHg and these declines were highly significant. Reductions in DBP for the two doses of TAK-491 were similar to one another.

The differences between TAK-491 80 mg and the active comparators were around -2 mm Hg.

Trough to peak ratios

The placebo-corrected trough-to-peak ratio data are shown in the table below.

Table 11.h Trough-to-Peak Ratios for SBP and DBP as Measured by ABPM (FAS)

	Treatment Group			
	TAK-491 40 mg N=280	TAK-491 80 mg N=283	Valsartan 320 mg N=278	Olmesartan 40 mg N=290
SBP	N=237	N=229	N=234	N=254
24-hour (a) Placebo-corrected trough-to-peak ratio	0.798	0.866	0.771	0.892
12-hour (b) Placebo-corrected trough-to-peak ratio	0.802	0.833	0.827	0.872
DBP	N=237	N=229	N=234	N=254
24-hour (a) Placebo-corrected trough-to-peak ratio	0.828	0.801	0.683	0.988
12-hour (b) Placebo-corrected trough-to-peak ratio	0.847	0.790	0.746	1.029

Source: Tables 15.2.1.4.1 and 15.2.2.4.1.

Note: Analyses include subjects with both a Baseline and postbaseline value. Peak response is defined as the change from Baseline in blood pressure observed during the peak effect interval (ie, the 2-hour ABPM interval in which the maximum blood pressure decrease was observed). Trough response is defined as the change from Baseline in the trough interval (hours 22 to 24). Placebo-corrected trough-to-peak ratio was calculated as placebo-subtracted mean trough response divided by placebo-subtracted mean peak response.

(a) The peak effect interval was determined for each subject during the 24 hours after dosing.

(b) The peak effect interval was determined for each subject during the 12 hours after dosing.

The ratios ranged from 0.790 to 0.866 for all doses of TAK-491.

Subgroups

Subgroup analyses were conducted by age, race, gender, Baseline 24-hour mean SBP, BMI, and cGFR.

Table 11.i Subgroup Analyses of Change From Baseline to Week 6 in 24-hour Mean SBP (mm Hg) by ABPM (FAS)

Subgroup	Treatment Group				
	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	Olmесartan 40 mg
Age					
(<65 years)	n=102	n=176	n=180	n=193	n=193
Baseline LS mean (SE)	143.61 (0.970)	144.26 (0.739)	144.49 (0.730)	146.06 (0.705)	144.14 (0.705)
LS mean (SE) change to Week 6	-0.65 (1.047)	-13.35 (0.797)	-14.59 (0.788)	-9.80 (0.763)	-12.06 (0.761)
LS mean diff. vs placebo (a)		-12.70	-13.94	-9.15	-11.40
(95% CI)		(-15.28, -10.11)*	(-16.51, -11.36)*	(-11.69, -6.60)*	(-13.94, -8.86)*
LS mean diff. vs olmesartan (b)		-1.29	-2.53		
(95% CI)		(-3.45, 0.87)	(-4.68, -0.38)*		
LS mean diff. vs valsartan (c)		-3.55	-4.79		
(95% CI)		(-5.72, -1.38)*	(-6.94, -2.64)*		
(≥65 years)	n=32	n=61	n=49	n=41	n=61
Baseline LS mean (SE)	146.52 (1.792)	144.88 (1.298)	145.01 (1.448)	147.58 (1.583)	145.31 (1.298)
LS mean (SE) change to Week 6	0.87 (1.915)	-13.61 (1.387)	-14.24 (1.547)	-12.12 (1.696)	-11.79 (1.386)
LS mean diff. vs placebo (a)		-14.48	-15.11	-12.99	-12.66
(95% CI)		(-19.14, -9.82)*	(-19.96, -10.26)*	(-18.02, -7.96)*	(-17.31, -8.00)*
LS mean diff. vs olmesartan (b)		-1.82	-2.46		
(95% CI)		(-5.69, 2.04)	(-6.55, 1.64)		
LS mean diff. vs valsartan (c)		-1.49	-2.12		
(95% CI)		(-5.81, 2.83)	(-6.65, 2.41)		
(≥75 years)	n=4	n=14	n=14	n=7	n=9
Baseline LS mean (SE)	150.63 (5.825)	146.50 (3.114)	144.82 (3.114)	148.37 (4.403)	142.62 (3.883)
LS mean (SE) change to Week 6	-2.00 (6.378)	-12.33 (3.385)	-12.54 (3.388)	-7.48 (4.802)	-14.76 (4.255)
LS mean diff. vs placebo (a)		-10.33	-10.54	-5.48	-12.75
(95% CI)		(-24.88, 4.22)	(-25.15, 4.08)	(-21.51, 10.55)	(-28.34, 2.83)
LS mean diff. vs olmesartan (b)		2.42	2.21		
(95% CI)		(-8.57, 13.42)	(-8.73, 13.15)		
LS mean diff. vs valsartan (c)		-4.85	-5.06		
(95% CI)		(-16.69, 6.99)	(-16.95, 6.82)		

Footnotes for Table 11.i are found on the last page.

Table 11.i Subgroup Analyses of Change From Baseline to Week 6 in 24-hour Mean SBP (mm Hg) by ABPM (FAS) (Continued)

Subgroup	Treatment Group				
	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	Olmesartan 40 mg
Gender					
Male					
Baseline LS mean (SE)	n=75 143.72 (1.141)	n=121 144.53 (0.899)	n=125 144.34 (0.884)	n=123 145.71 (0.891)	n=140 144.08 (0.835)
LS mean (SE) change to Week 6	0.94 (1.165)	-12.38 (0.917)	-13.07 (0.902)	-9.39 (0.911)	-11.30 (0.853)
LS mean diff. vs placebo (a)		-13.32	-14.01	-10.33	-12.24
(95% CI)		(-16.23, -10.41)*	(-16.91, -11.12)*	(-13.24, -7.42)*	(-15.08, -9.41)*
LS mean diff. vs olmesartan (b)		-1.08	-1.77		
(95% CI)		(-3.54, 1.38)	(-4.21, 0.67)		
LS mean diff. vs valsartan (c)		-2.99	-3.68		
(95% CI)		(-5.53, -0.45)*	(-6.20, -1.16)*		
Female					
Baseline LS mean (SE)	n=59 145.04 (1.286)	n=116 144.30 (0.917)	n=104 144.92 (0.969)	n=111 147.01 (0.938)	n=114 144.83 (0.925)
LS mean (SE) change to Week 6	-1.76 (1.451)	-14.51 (1.036)	-16.27 (1.093)	-11.15 (1.062)	-12.82 (1.044)
LS mean diff. vs placebo (a)		-12.75	-14.51	-9.40	-11.06
(95% CI)		(-16.25, -9.25)*	(-18.08, -10.94)*	(-12.93, -5.86)*	(-14.58, -7.55)*
LS mean diff. vs olmesartan (b)		-1.69	-3.45		
(95% CI)		(-4.58, 1.20)	(-6.42, -0.48)*		
LS mean diff. vs valsartan (c)		-3.36	-5.12		
(95% CI)		(-6.28, -0.43)*	(-8.11, -2.12)*		
Race					
Caucasian					
Baseline LS mean (SE)	n=83 143.76 (1.081)	n=153 144.27 (0.796)	n=152 144.62 (0.799)	n=158 146.15 (0.784)	n=173 144.81 (0.749)
LS mean (SE) change to Week 6	0.60 (1.134)	-14.82 (0.835)	-16.21 (0.837)	-11.12 (0.823)	-12.69 (0.785)
LS mean diff. vs placebo (a)		-15.42	-16.81	-11.72	-13.29
(95% CI)		(-18.19, -12.66)*	(-19.58, -14.04)*	(-14.47, -8.97)*	(-16.00, -10.58)*
LS mean diff. vs olmesartan (b)		-2.14	-3.52		
(95% CI)		(-4.39, 0.11)	(-5.77, -1.27)*		
LS mean diff. vs valsartan (c)		-3.70	-5.09		
(95% CI)		(-6.01, -1.40)*	(-7.39, -2.78)		

Footnotes for Table 11.i are found on the last page.

Table 11.i Subgroup Analyses of Change From Baseline to Week 6 in 24-hour Mean SBP (mm Hg) by ABPM (FAS) (Continued)

Subgroup	Treatment Group				
	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	Olmesartan 40 mg
Race					
Black	n=24	n=40	n=37	n=38	n=42
Baseline LS mean (SE)	145.53 (1.995)	146.87 (1.545)	146.06 (1.607)	146.34 (1.585)	143.42 (1.508)
LS mean (SE) change to Week 6	0.17 (2.029)	-7.43 (1.574)	-8.73 (1.634)	-4.34 (1.613)	-5.79 (1.543)
LS mean diff. vs placebo (a)		-7.60	-8.90	-4.51	-5.96
(95% CI)		(-12.67, -2.53)*	(-14.04, -3.76)*	(-9.63, 0.60)	(-10.99, -0.94)*
LS mean diff. vs olmesartan (b)		-1.64	-2.94		
(95% CI)		(-6.00, 2.73)	(-7.38, 1.51)		
LS mean diff. vs valsartan (c)		-3.09	-4.39		
(95% CI)		(-7.53, 1.36)	(-8.92, 0.14)		
Other	n=31	n=48	n=43	n=40	n=43
Baseline LS mean (SE)	143.17 (1.815)	143.24 (1.458)	142.94 (1.541)	147.26 (1.597)	142.99 (1.541)
LS mean (SE) change to Week 6	-3.34 (1.884)	-14.10 (1.514)	-13.32 (1.600)	-12.01 (1.676)	-16.02 (1.600)
LS mean diff. vs placebo (a)		-10.76	-9.98	-8.67	-12.68
(95% CI)		(-15.52, -6.00)*	(-14.85, -5.11)*	(-13.65, -3.69)*	(-17.55, -7.81)*
LS mean diff. vs olmesartan (b)		1.92	2.70		
(95% CI)		(-2.42, 6.26)	(-1.76, 7.16)		
LS mean diff. vs valsartan (c)		-2.09	-1.31		
(95% CI)		(-6.55, 2.37)	(-5.89, 3.27)		
BMI					
<30 kg/m ²	n=68	n=107	n=119	n=105	n=122
Baseline LS mean (SE)	144.80 (1.189)	145.54 (0.948)	144.48 (0.899)	148.85 (0.957)	144.37 (0.888)
LS mean (SE) change to Week 6	-1.07 (1.344)	-13.41 (1.071)	-14.60 (1.017)	-10.55 (1.093)	-12.03 (1.005)
LS mean diff. vs placebo (a)		-12.34	-13.53	-9.48	-10.95
(95% CI)		(-15.71, -8.96)*	(-16.83, -10.22)*	(-12.89, -6.07)*	(-14.25, -7.66)*
LS mean diff. vs olmesartan (b)		-1.38	-2.57		
(95% CI)		(-4.27, 1.50)	(-5.37, 0.23)		
LS mean diff. vs valsartan (c)		-2.86	-4.05		
(95% CI)		(-5.87, 0.15)	(-6.99, -1.10)*		
≥30 kg/m ²	n=66	n=130	n=110	n=129	n=132
Baseline LS mean (SE)	143.80 (1.210)	143.49 (0.862)	144.74 (0.938)	144.28 (0.866)	144.46 (0.856)
LS mean (SE) change to Week 6	0.59 (1.257)	-13.43 (0.896)	-14.40 (0.974)	-10.05 (0.899)	-11.89 (0.889)
LS mean diff. vs placebo (a)		-14.03	-14.99	-10.64	-12.48
(95% CI)		(-17.06, -10.99)*	(-18.12, -11.87)*	(-13.68, -7.60)*	(-15.51, -9.46)*
LS mean diff. vs olmesartan (b)		-1.54	-2.51		
(95% CI)		(-4.02, 0.94)	(-5.10, 0.08)		
LS mean diff. vs valsartan (c)		-3.39	-4.35		
(95% CI)		(-5.88, -0.89)*	(-6.95, -1.75)*		

Footnotes for Table 11.i are found on the last page.

Table 11.i Subgroup Analyses of Change From Baseline to Week 6 in 24-hour Mean SBP (mm Hg) by ABPM (FAS) (Continued)

Subgroup	Treatment Group				
	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	Olmesartan 40 mg
Baseline 24-hour mean SBP					
< median (143.83 mm Hg)	n=71	n=134	n=109	n=104	n=134
Baseline LS mean (SE)	136.52 (0.540)	137.44 (0.393)	136.51 (0.436)	136.74 (0.446)	137.31 (0.393)
LS mean (SE) change to Week 6	1.60 (1.169)	-11.28 (0.852)	-12.89 (0.944)	-8.91 (0.966)	-10.14 (0.851)
LS mean diff. vs placebo (a)		-12.87	-14.48	-10.51	-11.74
(95% CI)		(-15.72, -10.03)*	(-17.43, -11.53)*	(-13.49, -7.53)*	(-14.58, -8.89)*
LS mean diff. vs olmesartan (b)		-1.14	-2.75		
(95% CI)		(-3.50, 1.22)	(-5.25, -0.25)*		
LS mean diff. vs valsartan (c)		-2.36	-3.97		
(95% CI)		(-4.90, 0.17)	(-6.62, -1.32)*		
≥ median (143.83 mm Hg)	n=63	n=103	n=120	n=130	n=120
Baseline LS mean (SE)	153.07 (0.862)	153.49 (0.674)	151.95 (0.625)	154.00 (0.600)	152.35 (0.625)
LS mean (SE) change to Week 6	-2.24 (1.434)	-15.72 (1.122)	-16.19 (1.041)	-11.75 (1.001)	-13.82 (1.040)
LS mean diff. vs placebo (a)		-13.49	-13.95	-9.51	-11.59
(95% CI)		(-17.06, -9.91)*	(-17.43, -10.47)*	(-12.95, -6.08)*	(-15.07, -8.11)*
LS mean diff. vs olmesartan (b)		-1.90	-2.37		
(95% CI)		(-4.91, 1.10)	(-5.25, 0.52)		
LS mean diff. vs valsartan (c)		-3.97	-4.44		
(95% CI)		(-6.92, -1.02)*	(-7.28, -1.59)*		
cGFR					
≥30 and <60 mL/min/1.73m ²	n=8 (d)	n=23	n=13 (e)	n=12	n=16
Baseline LS mean (SE)	150.15 (3.568)	147.98 (2.104)	147.54 (2.799)	147.92 (2.913)	147.39 (2.523)
LS mean (SE) change to Week 6	-3.32 (3.680)	-16.22 (2.164)	-19.05 (2.880)	-16.28 (2.997)	-14.39 (2.596)
LS mean diff. vs placebo (a)		-12.90	-15.73	-12.96	-11.08
(95% CI)		(-21.42, -4.37)*	(-25.07, -6.40)*	(-22.44, -3.49)*	(-20.08, -2.07)
LS mean diff. vs olmesartan (b)		-1.82	-4.66		
(95% CI)		(-8.57, 4.93)	(-12.40, 3.08)		
LS mean diff. vs valsartan (c)		0.06	-2.77		
(95% CI)		(-7.32, 7.44)	(-11.07, 5.53)		
≥60 and <90 mL/min/1.73m ²	n=68 (d)	n=118	n=113 (e)	n=129	n=136
Baseline LS mean (SE)	141.98 (1.213)	144.90 (0.921)	144.54 (0.941)	146.03 (0.881)	144.91 (0.858)
LS mean (SE) change to Week 6	0.55 (1.276)	-12.68 (0.964)	-13.55 (0.986)	-9.93 (0.924)	-12.57 (0.898)
LS mean diff. vs placebo (a)		-13.23	-14.10	-10.48	-13.12
(95% CI)		(-16.37, -10.08)*	(-17.27, -10.94)*	(-13.59, -7.38)*	(-16.18, -10.05)*
LS mean diff. vs olmesartan (b)		-0.11	-0.98		
(95% CI)		(-2.70, 2.48)	(-3.60, 1.63)		
LS mean diff. vs valsartan (c)		-2.74	-3.62		
(95% CI)		(-5.37, -0.12)*	(-6.27, -0.96)*		

Footnotes for Table 11.i are found on the last page.

Table 11.i Subgroup Analyses of Change From Baseline to Week 6 in 24-hour Mean SBP (mm Hg) by ABPM (FAS) (Continued)

Subgroup	Treatment Group				
	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	Olmesartan 40 mg
cGFR (continued)					
≥90 mL/min/1.73m ²	n=57 (d)	n=96	n=102 (e)	n=93	n=102
Baseline LS mean (SE)	146.43 (1.264)	142.97 (0.974)	144.43 (0.945)	146.53 (0.990)	143.29 (0.945)
LS mean (SE) change to Week 6	-0.85 (1.438)	-13.70 (1.108)	-15.11 (1.072)	-9.83 (1.128)	-10.81 (1.074)
LS mean diff. vs placebo (a)		-12.85	-14.26	-8.98	-9.96
(95% CI)		(-16.43, -9.27)*	(-17.79, -10.74)*	(-12.56, -5.40)*	(-13.49, -6.42)*
LS mean diff. vs olmesartan (b)		-2.89	-4.31		
(95% CI)		(-5.92, 0.13)	(-7.29, -1.32)*		
LS mean diff. vs valsartan (c)		-3.87	-5.29		
(95% CI)		(-6.99, -0.75)*	(-8.34, -2.23)*		

Source: Tables 15.2.1.3.2, 15.2.1.3.4, 15.2.1.3.6, 15.2.1.3.8, 15.2.1.3.10, and 15.2.1.3.12.

Note: Small n represents the number of subjects with a Baseline and postbaseline value.

Note: Subjects who were classified into more than 1 race category were classified as multiracial and summarized for each race selected; therefore, race categories were not mutually exclusive.

diff=difference, olm=olmesartan, pbo=placebo, val=valsartan

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active group (TAK-491 40 mg, TAK-491 80 mg, olmesartan, or valsartan) - LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 group - LS mean change of olmesartan.

(c) LS mean difference=LS mean change of each TAK-491 group - LS mean change of valsartan.

(d) One subject had either missing cGFR data or cGFR <30 mL/min/1.73 m².

Overall, the active treatment groups were superior to placebo in all subgroups. However, black subjects had smaller decreases in SBP compared to white subjects.

SAFETY

The safety analysis set included 1286 subjects: 155 in the placebo group, 280 in the TAK-491 40 mg group, 284 in the TAK-491 80 mg group, 277 in the valsartan 320 mg group, and 290 in the olmesartan 40 mg group. Subject 1191/003, who inadvertently received TAK-491 80 mg but was not randomized, was included in the safety analysis set for that treatment group.

Extent of Exposure

The mean duration of treatment is shown in the table below by treatment group.

Table 12.a Duration (Days) of Treatment With Study Medication (Safety Analysis Set)

	Treatment Group				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Mean (SD)	40.8 (8.09)	41.2 (7.32)	40.5 (8.96)	41.0 (7.80)	41.5 (7.22)
Median	42.0	42.0	42.0	43.0	42.5
Min - Max	1 - 59	1 - 57	1 - 54	1 - 51	1 - 55
	n (%)				
Completed 1 to 13 days	6 (3.9)	7 (2.5)	9 (3.2)	7 (2.5)	6 (2.1)
Completed 14 to 27 days	3 (1.9)	9 (3.2)	14 (4.9)	13 (4.7)	8 (2.8)
Completed 28 to 41 days	28 (18.1)	36 (12.9)	39 (13.7)	36 (13.0)	45 (15.5)
Completed ≥42 days	118 (76.1)	228 (81.4)	222 (78.2)	221 (79.8)	231 (79.7)

Source: Table 15.1.14.

The mean number of days was similar across the treatment groups.

Serious safety

Deaths

No deaths were reported for this study.

Serious adverse events

There were fourteen subjects who reported at least one serious adverse event. These are shown in the table below.

Table 12.f Summary of Treatment-Emergent SAEs (Safety Analysis Set)

Site/ Subject No.	Age/Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Action/ Outcome
Placebo						
1117/011	72/M	Intestinal obstruction due to adhesion (Abdominal adhesions)	29	41	Not related	Drug withdrawn/ Recovered/ Resolved
1203/019	64/M	Left ankle fracture due to fall (Fall)	11	Not available (a)	Not related	Drug withdrawn/ Recovering/ Resolving
TAK-491 40 mg						
1021/028	34/F	Worsening of anemia due to dysfunctional uterine bleeding (Dysfunctional uterine bleeding)	21	22	Not related	Dose not changed/ Recovered/Resolved
1047/028	37/M	Cholecystitis (Cholecystitis)	22	45	Not related	Not applicable/ Recovered/Resolved
		Cholelithiasis (Cholelithiasis)	22	45	Not related	Not applicable/ Recovered/Resolved
TAK-491 80 mg						
1012/032	60/M	Eye irritation (Eye irritation)	32	44	Not related	Dose not changed/ Recovered/Resolved
		Elevated BP (Blood pressure increased)	35	37	Not related	Dose not changed/ Recovered/Resolved
1074/124	57/F	Diverticulitis (Diverticulitis)	41	49	Not related	Drug withdrawn/ Resolved with sequela
1114/007	58/M	Upper digestive tract bleeding (Gastrointestinal haemorrhage)	16	24	Possible	Drug withdrawn/ Recovered/Resolved
Valsartan 320 mg						
1074/038	31/M	Drug overdose intentional, not suicidal with Seroquel (Intentional overdose)	18	19	Not related	Drug withdrawn/ Recovered/Resolved
1126/002	45/M	Deep vein thrombosis right leg (Deep vein thrombosis)	12	15	Not related	Drug withdrawn/ Recovered/Resolved
1176/009	57/F	Accidental fall (Fall)	33	36	Not related	Dose not changed/ Recovered/Resolved

Table 12.f Summary of Treatment-Emergent SAEs (Safety Analysis Set) (Continued)

Site/ Subject No.	Age/Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Action/ Outcome
Olmesartan 40 mg						
1023/049	52/M	Focal seizures (Partial seizures)	39	41	Not related	Drug withdrawn/ Recovered/Resolved
1061/026	69/F	Subdural hematoma (Subdural haematoma)	48	51	Not related	Not applicable/ Recovered/Resolved
1070/005	66/F	Right breast lobular carcinoma (Breast cancer)	27	Ongoing	Not related	Drug withdrawn/ Recovering/ Resolving
1086/036	60/M	Arm cellulitis (Cellulitis)	37	52	Not related	Dose not changed/ Recovered/Resolved
		Cat bite infection (Infected bites)	37	52	Not related	Dose not changed/ Recovered/Resolved

Source: Table 15.3.2.2.

Note: Events reported prior to Week 2 occurred while subjects were receiving their initial dose of study drug.

(a) The site could not contact the subject to get the end date for the fractured ankle because the subject moved with no forwarding address or phone number (source: Section 15.3.3.2).

These events were infrequent and not unusual for this population of subjects.

Discontinuations because of adverse events

There were 30 subjects who discontinued the study because of an adverse event.

These subjects are shown below.

Table 12.g Summary of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug (Safety Analysis Set)

Site/ Subject No.	Age/ Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Intensity
Placebo						
1115/003	73/F	High blood pressure (Hypertension)	9	9	Not related	Moderate
1117/011	72/M	Intestinal obstruction due to adhesion (Abdominal adhesions) (a)	29	41	Not related	Severe
1203/019	64/M	Left ankle fracture due to fall (Fall) (a)	11	Not available (b)	Not related	Severe
TAK-491 40 mg						
1021/007	57/F	Worsening of hypertension (Hypertension)	6	20	Possible	Moderate
1055/023	63/M	Headache (Headache)	25	26	Possible	Moderate
1060/022	50/F	Worsening heart palpitations (Palpitations)	27	36	Possible	Moderate
		Chest discomfort (Chest discomfort)	27	27	Possible	Moderate
1071/003	47/M	Foggy feeling (Feeling abnormal)	21	31	Probable	Mild
		Lightheadedness (Dizziness)	10	31	Probable	Moderate
		Anxiety (Anxiety)	10	31	Possible	Severe
1074/032	37/F	Hashimotos disease (Autoimmune thyroiditis)	≤31 (c)	Ongoing	Not related	Moderate
		Polycystic ovary disease (Polycystic ovaries)	≤31 (c)	Ongoing	Not related	Moderate
1076/004	49/M	Fatigue (Fatigue)	10	25	Not related	Mild
1210/006	65/M	Uncontrolled hypertension (Hypertension)	23	Ongoing	Definite	Mild
TAK-491 80 mg						
1012/090	54/F	Kidney stones (Nephrolithiasis)	34	34	Possible	Severe
1068/024	65/M	Diarrhea (Diarrhoea)	25	25	Possible	Moderate
		Worsening leg cramps (Muscle spasms)	22	26	Possible	Moderate
		Dizziness (Dizziness)	22	26	Possible	Severe
1074/098	67/M	Intermittent headaches (Headache)	1	9	Possible	Moderate
1074/124	57/F	Diverticulitis (Diverticulitis) (a)	41	49	Not related	Severe
1114/007	58/M	Upper digestive tract bleeding (Gastrointestinal haemorrhage) (a)	16	24	Possible	Severe
1203/036	68/F	Hypotension (Hypotension)	14	17	Definite	Moderate

Table 12.g Summary of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug (Safety Analysis Set) (Continued)

Site/ Subject No.	Age/ Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Intensity
TAK-491 80 mg						
1213/006	60/F	Eosinophilia (Eosinophilia)	34	Ongoing	Probable	Moderate
		Pruritus (Pruritus)	31	Ongoing	Probable	Moderate
		Rash (Rash)	33	Ongoing	Probable	Moderate
Valsartan 320 mg						
1045/001	64/F	Elevated blood pressure (Blood pressure increased)	21	Ongoing	Not related	Moderate
		Headaches (Headache)	21	33	Definite	Moderate
1074/038	31/M	Tachycardia (Tachycardia)	18	19	Not related	Severe
		Abdominal pain (Abdominal pain)	18	18	Possible	Severe
		Drug overdose intentional, not suicidal with Seroquel (Intentional overdose) (a)	18	19	Not related	Severe
		Dehydration (Dehydration)	18	19	Not related	Severe
		Lethargy (Lethargy)	18	19	Possible	Severe
		Tremors (Tremors)	18	18	Not related	Severe
		Exacerbation of anxiety (Anxiety)	17	19	Possible	Severe
1126/002	45/M	Deep vein thrombosis right leg (Deep vein thrombosis) (a)	12	15	Not related	Moderate
1203/034	63/F	Rapid heart beat (Heart rate increased)	2	16	Definite	Moderate
1212/001	75/F	Urticaria (Urticaria)	31	Ongoing	Probable	Moderate
1215/015	50/M	Edema in both feet and ankles (Oedema peripheral)	18	26	Not related	Mild
1218/013	50/M	Headache (Headache)	26	34	Not related	Moderate
Olmesartan 40 mg						
1016/017	53/F	Fatigue (Fatigue)	14	26	Possible	Moderate
1023/049	52/M	Focal seizures (Partial seizures) (a)	39	41	Not related	Severe
		Psychomotor seizures (Psychomotor seizures)	35	39	Not related	Moderate
1070/005	66/F	Right breast lobular carcinoma (Breast cancer) (a)	27	Ongoing	Not related	Severe
1073/001	64/M	Headache (Headache)	1	29	Probable	Severe
1076/044	62/F	Worsening headaches (Headache)	2	11	Probable	Moderate
1211/002	80/F	Worsening hypertension (Hypertension)	1	Ongoing	Not related	Severe

Source: Table 15.3.2.1 and Appendix 16.2.1.2.

Note: Events reported prior to Week 2 occurred while subjects were receiving their initial dose of study drug.

(a) Serious adverse event.

(b) The site could not contact the subject to get the end date for the fractured ankle because the subject moved with no forwarding address or phone number (source: Section 15.3.3.2).

(c) First day of double-blind dosing occurred on 30 September 2008 (Day 1). Event was recorded as 01 October 2008 (Day ≤31) (source: Section 15.3.3).

There were two reports of possible hypersensitivity reaction. There was one subject in the TAK-491 who reported eosinophilia, pruritis, and rash and one subject in the valsartan 320 mg group who reported urticaria.

There were an additional 4 subjects who were discontinued for events that started prior to study drug initiation:

1114/002 (placebo) reported leukocytosis,
1040/036 (TAK-491 80 mg) reported headache,
1047/006 (TAK-491 80 mg) reported leg edema,
1218/02 (valsartan) reported headache.

Adverse events

The number and percent of subjects reporting any adverse event, adverse events resulting in discontinuation, serious adverse events and reported deaths are shown below by treatment group.

Table 12.b Overview of Treatment-Emergent Adverse Events and SAEs (Safety Analysis Set)

Number (%) of Subjects with:	Treatment Group				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Adverse events	74 (47.7)	134 (47.9)	145 (51.1)	131 (47.3)	151 (52.1)
Related (a)	24 (15.5)	52 (18.6)	56 (19.7)	54 (19.5)	57 (19.7)
Mild	48 (31.0)	74 (26.4)	78 (27.5)	72 (26.0)	91 (31.4)
Moderate	23 (14.8)	50 (17.9)	54 (19.0)	52 (18.8)	50 (17.2)
Severe	3 (1.9)	10 (3.6)	13 (4.6)	7 (2.5)	10 (3.4)
Leading to discontinuation (b)	3 (1.9)	7 (2.5)	8 (2.8)	7 (2.5)	6 (2.1)
SAEs	2 (1.3)	2 (0.7)	3 (1.1)	3 (1.1)	4 (1.4)
Related (a)	0	0	1 (0.4)	0	0
Deaths	0	0	0	0	0

Source: Tables 15.3.1.1, 15.3.1.7, 15.3.1.8, and 15.3.2.2.

(a) Related-events attributed by investigator as definitely, probably, or possibly related to study drug.

(b) Adverse events leading to study drug discontinuation include those that led to temporary drug interruption or permanent discontinuation.

Overall, about 50% of subjects reported adverse event(s), slightly fewer placebo subjects discontinued because of an adverse event, there were few serious adverse events reported, and there were no reported deaths.

Common adverse events.

Adverse events reported by $\geq 2\%$ of subjects in any treatment group are shown below.

Table 12.d Treatment-Emergent Adverse Event Preferred Terms Reported for $\geq 2.0\%$ of Subjects in Any Treatment Group (Safety Analysis Set)

Preferred Term	Treatment Group n (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Headache	14 (9.0)	18 (6.4)	12 (4.2)	21 (7.6)	23 (7.9)
Dizziness	4 (2.6)	10 (3.6)	10 (3.5)	5 (1.8)	9 (3.1)
Nasopharyngitis	3 (1.9)	5 (1.8)	8 (2.8)	6 (2.2)	7 (2.4)
Urinary tract infection	5 (3.2)	9 (3.2)	6 (2.1)	3 (1.1)	6 (2.1)
Fatigue	1 (0.6)	3 (1.1)	7 (2.5)	4 (1.4)	13 (4.5)
Oedema peripheral	1 (0.6)	5 (1.8)	4 (1.4)	9 (3.2)	8 (2.8)
Plasminogen activator inhibitor increased	2 (1.3)	7 (2.5)	7 (2.5)	7 (2.5)	4 (1.4)
Diarrhoea	2 (1.3)	3 (1.1)	12 (4.2)	4 (1.4)	5 (1.7)
Blood creatine phosphokinase increased	2 (1.3)	7 (2.5)	6 (2.1)	5 (1.8)	4 (1.4)
Dyslipidaemia	1 (0.6)	6 (2.1)	7 (2.5)	3 (1.1)	4 (1.4)
Upper respiratory tract infection	2 (1.3)	1 (0.4)	8 (2.8)	6 (2.2)	4 (1.4)
Nausea	1 (0.6)	3 (1.1)	3 (1.1)	5 (1.8)	6 (2.1)
C-reactive protein increased	0	3 (1.1)	6 (2.1)	3 (1.1)	3 (1.0)
Hypertriglyceridaemia	4 (2.6)	4 (1.4)	3 (1.1)	1 (0.4)	2 (0.7)
Hypercholesterolaemia	5 (3.2)	1 (0.4)	2 (0.7)	2 (0.7)	1 (0.3)
Myalgia	0	1 (0.4)	7 (2.5)	1 (0.4)	0

Source: Table 15.3.1.4.

Headache was the most commonly reported adverse event and it was reported more often by the placebo group compared to the active treatment groups. On the other hand, fatigue and peripheral edema was more commonly reported by the active treatment groups compared to placebo. Dizziness and hypertriglyceridemia were less often reported by the valsartan group compared to the TAK-491 groups.

Selected adverse events.

The reporting rates for certain adverse events including hypotension and renal function are shown below.

Table 12.e Selected Treatment-Emergent Adverse Events Observed in Subjects Receiving Treatment for Hypertension (Safety Analysis Set)

Category Preferred Term	Treatment Group n (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
General					
Headache	14 (9.0)	18 (6.4)	12 (4.2)	21 (7.6)	23 (7.9)
Cough	2 (1.3)	2 (0.7)	2 (0.7)	3 (1.1)	3 (1.0)
Dizziness	4 (2.6)	10 (3.6)	10 (3.5)	5 (1.8)	9 (3.1)
Syncope	0	0	0	0	1 (0.3)
Blood Pressure					
Hypotension	0	1 (0.4)	1 (0.4)	0	1 (0.3)
Orthostatic hypotension	0	1 (0.4)	1 (0.4)	0	0
Blood pressure increased	0	0	1 (0.4)	1 (0.4)	0
Hypertension	1 (0.6)	2 (0.7)	0	0	1 (0.3)
Renal Function					
Urine albumin/creatinine ratio increased	1 (0.6)	1 (0.4)	1 (0.4)	0	2 (0.7)
Blood creatinine increased	1 (0.6)	3 (1.1)	1 (0.4)	0	1 (0.3)
Potassium Homeostasis					
Blood potassium increased	0	2 (0.7)	1 (0.4)	0	1 (0.3)
Hyperkalaemia	1 (0.6)	0	0	0	0
Blood potassium decreased	0	0	0	0	2 (0.7)
Hypokalaemia	0	0	0	0	1 (0.3)
Anemia					
Anaemia	0	1 (0.4)	0	0	1 (0.3)
Haemoglobin decreased	0	0	1 (0.4)	0	0
Haematocrit decreased	0	1 (0.4)	1 (0.4)	0	0
Edema					
Oedema peripheral	1 (0.6)	5 (1.8)	4 (1.4)	9 (3.2)	8 (2.8)

For the most part, these events were reported by a small number of subjects and the treatment groups showed similar reporting rates.

Clinical laboratory evaluations

Serum Chemistry

Mean values at baseline, final visit and change from baseline at final visit for ALT, aspartate aminotransferase (AST), alkaline phosphatase, creatine kinase (CK) total, creatinine, potassium, sodium, total bilirubin, and uric acid are shown below.

Table 12.h Serum Chemistry: Mean Changes From Baseline to the Final Visit (Safety Analysis Set)

Serum Chemistry	Treatment Group									
	Placebo N=155		TAK-491 40 mg N=280		TAK-491 80 mg N=284		Valsartan 320 mg N=277		Olmesartan 40 mg N=290	
Parameter (unit)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
ALT (U/L)										
Baseline (a)	155	25.8 (13.02)	280	27.6 (14.18)	284	27.7 (13.11)	277	30.9 (16.92)	290	29.7 (19.38)
Final visit (b)	152	26.6 (12.02)	276	27.5 (13.51)	274	30.0 (15.41)	271	31.5 (18.61)	285	29.2 (15.49)
Change	152	1.0 (7.07)	276	-0.2 (10.14)	274	2.4 (10.02)	271	0.8 (10.45)	285	-0.5 (14.75)
AST (U/L)										
Baseline (a)	155	22.9 (8.05)	280	24.6 (13.39)	284	24.3 (10.40)	277	25.5 (12.38)	290	26.0 (14.56)
Final visit (b)	152	24.0 (9.10)	276	24.9 (13.52)	274	25.1 (10.11)	271	26.3 (14.14)	285	25.3 (11.59)
Change	152	1.2 (6.17)	276	0.3 (16.56)	274	0.8 (8.48)	271	0.8 (9.94)	285	-0.7 (9.34)
Alkaline phosphatase (U/L)										
Baseline (a)	155	81.0 (20.10)	280	81.6 (25.35)	284	81.5 (23.84)	277	81.0 (23.92)	290	81.7 (23.91)
Final visit (b)	152	81.9 (21.41)	276	81.8 (25.79)	274	80.1 (25.19)	271	78.7 (21.09)	285	80.7 (22.98)
Change	152	1.0 (9.29)	276	-0.1 (10.10)	274	-1.4 (9.68)	271	-1.7 (10.36)	285	-0.7 (8.59)
Bilirubin, total (umol/L)										
Baseline (a)	155	8.0 (3.60)	280	8.6 (4.68)	284	8.4 (4.45)	277	7.9 (3.63)	290	8.0 (4.26)
Final visit (b)	152	8.2 (3.77)	276	8.1 (4.80)	274	8.1 (3.91)	271	7.8 (3.86)	285	7.4 (4.22)
Change	152	0.1 (2.68)	276	-0.5 (3.45)	274	-0.3 (3.11)	271	0.0 (3.42)	285	-0.6 (3.25)
CK-total (U/L)										
Baseline (a)	155	139.1 (99.43)	279	153.5 (275.84)	284	158.4 (525.24)	277	143.5 (127.49)	289	132.1 (112.75)
Final visit (b)	152	155.6 (142.76)	276	180.8 (664.20)	274	136.8 (100.37)	271	155.1 (143.01)	284	139.4 (107.95)
Change	152	15.7 (102.44)	276	27.4 (710.24)	274	-22.3 (536.57)	271	12.0 (118.82)	284	6.3 (102.46)
Creatinine (umol/L)										
Baseline (a)	155	79.9 (19.02)	280	79.8 (18.22)	284	77.7 (16.59)	277	79.6 (17.71)	290	77.9 (16.95)
Final visit (b)	152	81.0 (18.05)	276	82.3 (20.12)	274	81.3 (17.99)	271	81.0 (18.55)	285	79.2 (17.97)
Change	152	1.0 (8.62)	276	2.5 (10.65)	274	3.5 (9.62)	271	1.5 (8.70)	285	1.4 (8.45)
Potassium (mmol/L)										
Baseline (a)	155	4.26 (0.384)	280	4.25 (0.369)	284	4.22 (0.390)	277	4.21 (0.410)	290	4.23 (0.412)
Final visit (b)	152	4.18 (0.397)	276	4.33 (0.413)	274	4.33 (0.428)	271	4.28 (0.379)	285	4.26 (0.386)
Change	152	-0.07 (0.406)	276	0.09 (0.382)	274	0.10 (0.406)	271	0.06 (0.392)	285	0.03 (0.415)
Sodium (mmol/L)										
Baseline (a)	155	139.8 (2.22)	280	139.6 (2.11)	284	140.0 (2.14)	277	139.8 (2.19)	290	139.9 (2.02)
Final visit (b)	152	140.1 (2.20)	276	139.5 (2.39)	274	139.5 (2.03)	271	139.8 (2.24)	285	139.8 (2.24)
Change	152	0.3 (2.04)	276	-0.1 (2.24)	274	-0.5 (2.27)	271	0.1 (2.23)	285	0.0 (2.09)
Uric acid (umol/L)										
Baseline (a)	155	345.1 (84.50)	280	335.1 (84.10)	284	326.4 (78.12)	277	333.4 (79.58)	290	330.5 (77.02)
Final visit (b)	152	350.1 (88.53)	276	345.1 (87.45)	274	342.6 (83.93)	271	339.5 (82.92)	285	343.3 (78.60)
Change	152	5.6 (40.74)	276	9.7 (48.97)	274	16.3 (48.94)	271	5.9 (42.51)	285	13.0 (47.54)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

A summary of the mean change from Baseline to the Final Visit for each lipid parameter is presented in Table 12.i.

Regarding creatinine, there were larger mean increases from baseline at final visit for all active treatment groups compared to placebo (1 umol/L). The increase was the largest for TAK-491 80 mg (3.5 umol/L). The TAK-491 80 mg group also had the largest increase in potassium (0.10 mmol/L) and uric acid (16.3 umol/L) while the placebo group had a decline in potassium level (-0.07 mmol/L) and a smaller increase in uric acid (5.6 umol/L).

The lipid level changes are shown below for all treatment groups.

Table 12.i Lipids: Mean Changes From Baseline to the Final Visit (Safety Analysis Set)

Lipid Parameter (unit)	Treatment Group									
	Placebo N=155		TAK-491 40 mg N=280		TAK-491 80 mg N=284		Valsartan 320 mg N=277		Olmesartan 40 mg N=290	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
LDL-C (mmol/L)										
Baseline (a)	137	3.026 (0.8225)	240	3.161 (0.9498)	243	3.026 (0.8804)	238	3.139 (0.9674)	245	3.091 (0.8374)
Final visit (b)	129	2.943 (0.8002)	227	3.063 (0.9730)	227	2.887 (0.8691)	223	3.132 (0.8816)	231	3.078 (0.8743)
Change	129	-0.086 (0.5953)	227	-0.092 (0.5388)	227	-0.111 (0.5877)	223	-0.003 (0.6260)	231	-0.024 (0.5822)
Total cholesterol (mmol/L)										
Baseline (a)	140	5.095 (0.9639)	246	5.208 (1.1298)	251	5.112 (1.0522)	248	5.245 (1.1421)	253	5.117 (0.9439)
Final visit (b)	134	5.077 (0.9789)	236	5.129 (1.1216)	236	4.999 (1.0156)	236	5.202 (1.0163)	241	5.104 (1.0014)
Change	134	-0.024 (0.7831)	236	-0.064 (0.6087)	236	-0.085 (0.6780)	236	-0.056 (0.6868)	241	-0.027 (0.6785)
HDL-C (mmol/L)										
Baseline (a)	140	1.278 (0.3956)	246	1.286 (0.3762)	251	1.321 (0.3890)	248	1.279 (0.3609)	253	1.273 (0.3560)
Final visit (b)	134	1.314 (0.4096)	236	1.268 (0.3684)	236	1.302 (0.3890)	236	1.279 (0.3341)	241	1.255 (0.3494)
Change	134	0.025 (0.1636)	236	-0.024 (0.1682)	236	-0.013 (0.1728)	236	-0.003 (0.1761)	241	-0.011 (0.1621)
Triglycerides (mmol/L)										
Baseline (a)	140	1.794 (1.0217)	246	1.735 (1.1220)	250	1.768 (1.1286)	248	1.988 (2.4358)	253	1.715 (0.9862)
Final visit (b)	134	1.871 (1.5516)	236	1.859 (1.3307)	235	1.810 (1.0059)	236	1.836 (1.5324)	241	1.786 (1.3594)
Change	134	0.077 (1.1013)	236	0.147 (0.8589)	235	0.059 (0.8158)	236	-0.164 (1.3443)	241	0.041 (0.9862)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

The changes for all treatment groups appear to be inconsequential.

The number and percent of subjects with markedly abnormal reported laboratory values are shown below.

Table 12.j Percentage of Subjects With at Least 1 Markedly Abnormal Chemistry Value During Treatment (Safety Analysis Set)

Serum Chemistry Parameter (markedly abnormal criterion)	Treatment Group n/N (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
ALT (>3xULN)	1/152 (0.7)	1/276 (0.4)	1/274 (0.4)	0/271 (0.0)	0/285 (0.0)
AST (>3xULN)	1/152 (0.7)	2/276 (0.7)	2/274 (0.7)	2/271 (0.7)	3/285 (1.1)
Bilirubin, total (>2xULN)	2/152 (1.3)	1/276 (0.4)	0/274 (0.0)	0/271 (0.0)	1/285 (0.4)
CK total (>10xULN)	0/152 (0.0)	2/276 (0.7)	1/274 (0.4)	2/271 (0.7)	0/285 (0.0)
Creatinine (>1.5xBaseline)	0/152 (0.0)	2/276 (0.7)	3/274 (1.1)	1/271 (0.4)	2/285 (0.7)
GGT (>3xULN)	3/152 (2.0)	5/276 (1.8)	12/274 (4.4)	15/271 (5.5)	11/285 (3.9)
Potassium	0/152 (0.0)	0/276 (0.0)	1/274 (0.4)	1/271 (0.4)	0/285 (0.0)
(<3.0 mmol/L)	0/152 (0.0)	0/276 (0.0)	1/274 (0.4)	1/271 (0.4)	0/285 (0.0)
(>6.0 mmol/L)	0/152 (0.0)	0/276 (0.0)	0/274 (0.0)	0/271 (0.0)	0/285 (0.0)
Sodium	0/152 (0.0)	2/276 (0.7)	0/274 (0.0)	3/271 (1.1)	0/285 (0.0)
(<130 mmol/L)	0/152 (0.0)	2/276 (0.7)	0/274 (0.0)	3/271 (1.1)	0/285 (0.0)
(>150 mmol/L)	0/152 (0.0)	0/276 (0.0)	0/274 (0.0)	0/271 (0.0)	0/285 (0.0)
Uric acid (Males: >625 umol/L) (Females: >506 umol/L)	2/152 (1.3)	3/276 (1.1)	2/274 (0.7)	4/271 (1.5)	2/285 (0.7)

Source: Tables 15.3.4.7 and 15.3.4.8.
BUN=blood urea nitrogen

Abnormal values were uncommon in all treatment groups. The exception is GGT >3xULN. This increase was reported more often in the TAK-491 80 mg (4.4%), valsartan (5.5%), and olmesartan (3.9%) groups compared to placebo (2.0%).

There were 3 subjects who reported marked elevation of ALT values (one each for placebo, TAK-491 40 mg and TAK-491 80 mg). No subject was discontinued for this abnormality and none was discontinued because of it.

There were eight subjects who reported markedly abnormal creatinine¹ values anytime during the double blind phase: 2 (0.7%) TAK-491 40 mg, 3 (1.1%) TAK-491 80 mg, 1 (0.4%) valsartan 320 mg, and 2 (0.7%) olmesartan 40 mg. Two of the subjects (1039/019 and 1052/080, both taking TAK-491 40 mg) had their increased creatinine values reported as an adverse event.

Subject 1052/080 was a 44 year old black male who had a baseline creatinine value of 1.3 mg/dL that increased to 2.3 mg/dL at the last visit.

Subject 1039/019 was a 65 year old female had a creatinine value at baseline of 1.1 mg/dL that rose to 1.3 mg/dL at the last visit.

The table below shows the number and percent of subjects who met certain criteria² for abnormal creatinine increases at anytime during the double blind treatment phase.

¹ >1.5x baseline value

² Creatinine increase ≥30% from Baseline and >ULN at the Final Visit.

Table 12.k Summary of Subjects With Creatinine Elevation (Safety Analysis Set)

	Treatment Group n/N (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Subjects with Creatinine Elevations at Any Postbaseline Visit					
≥30% from Baseline and >ULN	0/152	4/276 (1.4)	3/274 (1.1)	2/271 (0.7)	2/285 (0.7)
≥50% from Baseline and >ULN	0/152	1/276 (0.4)	3/274 (1.1)	1/271 (0.4)	0/285
Subjects with Creatinine Elevations at Final Visit (a)					
≥30% from Baseline and >ULN	0/152	1/276 (0.4)	2/274 (0.7)	1/271 (0.4)	1/285 (0.4)
≥50% from Baseline and >ULN	0/152	1/276 (0.4)	0/274	1/271 (0.4)	0/285

Source: Table 15.3.4.9 and Appendix 16.2.8.3.3.

Note: A creatinine increase is defined as an increase from Baseline $\geq 30\% \times$ Baseline and >ULN.

(a) Last observation carried forward.

No placebo subject met the definition of creatinine elevation. The treatment group with the highest percent of subjects with $\geq 50\%$ from baseline and > ULN at anytime during the double blind treatment phase was TAK-491 80 mg. This percentage decreased to 0% when only the values obtained at the final visit were included.

Hematology

There were variable changes from baseline in the active treatment groups that were not greatly different from the changes in the placebo group. There were small decreases in mean hemoglobin in all of the active treatment groups

- TAK-491 (40 mg and 80 mg) (-0.27 g/dL and -0.31 g/dL, respectively),
- valsartan and olmesartan (-0.22 g/dL in each) treatment groups,
- placebo group (0.01 g/dL).

There were decreases as well for mean hematocrit/packed cell volume from baseline at the final visit for TAK-491 (40 mg and 80 mg) groups (-0.0086 and -0.0096, respectively), valsartan and olmesartan (-0.0074 and -0.0077, respectively) and placebo (-0.0005).

There were only sporadic markedly abnormal hematology values were observed. One clinically significant abnormality (eosinophilia) resulted in study discontinuation (TAK-491 80 mg, subject 1213/006). This subject also reported pruritus and rash.

The number and percent of subjects with markedly abnormal hematology values are shown in the table below.

Creatinine increase $\geq 50\%$ from Baseline and >ULN at the Final Visit.

Table 12.1 Percentage of Subjects With at Least 1 Markedly Abnormal Hematology Value During Treatment (Safety Analysis Set)

Hematology Parameter (markedly abnormal criterion)	Treatment Group n/N (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Hematocrit/PCV (<0.8×Baseline)	0/152 (0.0)	1/276 (0.4)	0/274 (0.0)	0/270 (0.0)	0/284 (0.0)
Hemoglobin (<Baseline - 3 g/dL)	0/152 (0.0)	1/276 (0.4)	0/274 (0.0)	0/270 (0.0)	0/284 (0.0)
White blood cell count	1/152 (0.7)	0/276 (0.0)	0/274 (0.0)	2/270 (0.7)	0/284 (0.0)
(<2×10 ⁹ /L)	0/152 (0.0)	0/276 (0.0)	0/274 (0.0)	0/270 (0.0)	0/284 (0.0)
(>20×10 ⁹ /L)	1/152 (0.7)	0/276 (0.0)	0/274 (0.0)	2/270 (0.7)	0/284 (0.0)

Source: Table 15.3.4.7 and 15.3.4.8.

There were few abnormal values in any of the treatment groups.

Urinalysis

There were no remarkable changes reported during the study.

Vital Signs and ECGs

Weight, sitting pulse and results were similar across treatment groups.

There were various changes in ECG parameters that were similar across treatment groups.

Reviewer's summary and conclusions

Efficacy: while baseline clinic BPs were similar for all treatment groups, the ABPM baseline BPs were significantly higher for valsartan group. All active treatment groups were superior to placebo in lowering SBP and DBP. The BP effects of TAK-491 40 mg and 80 mg were similar to one another. There is some evidence that TAK-491 was superior to valsartan 320 mg and olmesartan 40 mg but this was inconsistent.

Safety: in general, the active treatments were well tolerated. Commonly reported adverse events included headache and dizziness. The valsartan 320 mg group reported dizziness less often than the placebo and other active treatment groups. TAK-491 80 mg followed by TAK-491 40 mg had the largest increases in serum creatinine compared to the other treatment groups. TAK-491 80 mg followed by TAK-491 40 mg also had the largest increases in serum potassium.

Conclusions: the ARBs used in this trial were found to be effective in lowering blood pressure. There is evidence that TAK-491 40 mg and 80 mg increase serum creatinine more than valsartan 320 mg and olmesartan 40 mg so there is no reason to prefer TAK-491 over the other two available ARBs. Since there were only small differences in blood pressure effects between TAK-491 40 mg and 80 mg and TAK-491 80 had a worse effect on serum creatinine, doses of TAK-491 above 40 mg are not recommended.

Study 01-05-TL-491-005

Study No. (Study Abbreviation) No. of Sites-Country (a)		Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) - Randomized/Completed (e)
Study Start- End Dates					
01-05-TL-491-005 (491-005) 67-United States and Latin America 16 May 2006- 07 December 2006		Double blind, randomized, parallel- group, placebo controlled, dose ranging (Phase 2) Dose-response of antihypertensive effects of TAK-491 (Change from BL to Final Visit in sitting clinic DBP)	449 subjects with mild to moderate uncomplicated essential hypertension (DBP=95-114 mm Hg)	8 weeks	A: TAK-491 5 mg capsule B: TAK-491 10 mg capsule C: TAK-491 20 mg capsule D: TAK-491 40 mg capsule E: TAK-491 80 mg capsule F: OLM-M 20 mg capsule G: Placebo capsule 449 /404 A: 65/63 B: 65/59 C: 64/57 D: 63/59 E: 64/57 F: 64/57 G: 64/52

This was a multicenter, randomized, parallel group, double-blind, placebo-controlled, dose-ranging study in subjects with mild to moderate uncomplicated essential hypertension. After a 2-week, single-blind placebo run-in period, subjects who met entry criteria were randomized to receive TAK-491 5, 10, 20, 40, 80 mg, placebo, or olmesartan 20 mg QD for 8 weeks. Clinical DBP and SBP were measured at Screening (Day -21, Day -14 and Day -7), Randomization (Day 1), Week 1, Week 2, Week 4, Week 6, and Week 8. ABPM occurred at Day 1 and Week 8 or Early Termination.

Number of Subjects:

Planned: 420 subjects, 60 subjects per treatment group.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been male or nonpregnant, nonlactating women with mild to moderate uncomplicated essential hypertension (DBP ≥ 95 and ≤ 114 mm Hg at Placebo Run-in Day -14 and randomization Visit); aged 18 or older, inclusive; with clinical laboratory evaluations within the reference range for the testing laboratory; been able to comprehend and willing to sign an informed consent form, and willing to discontinue current antihypertensive medications at Screening Day -21.

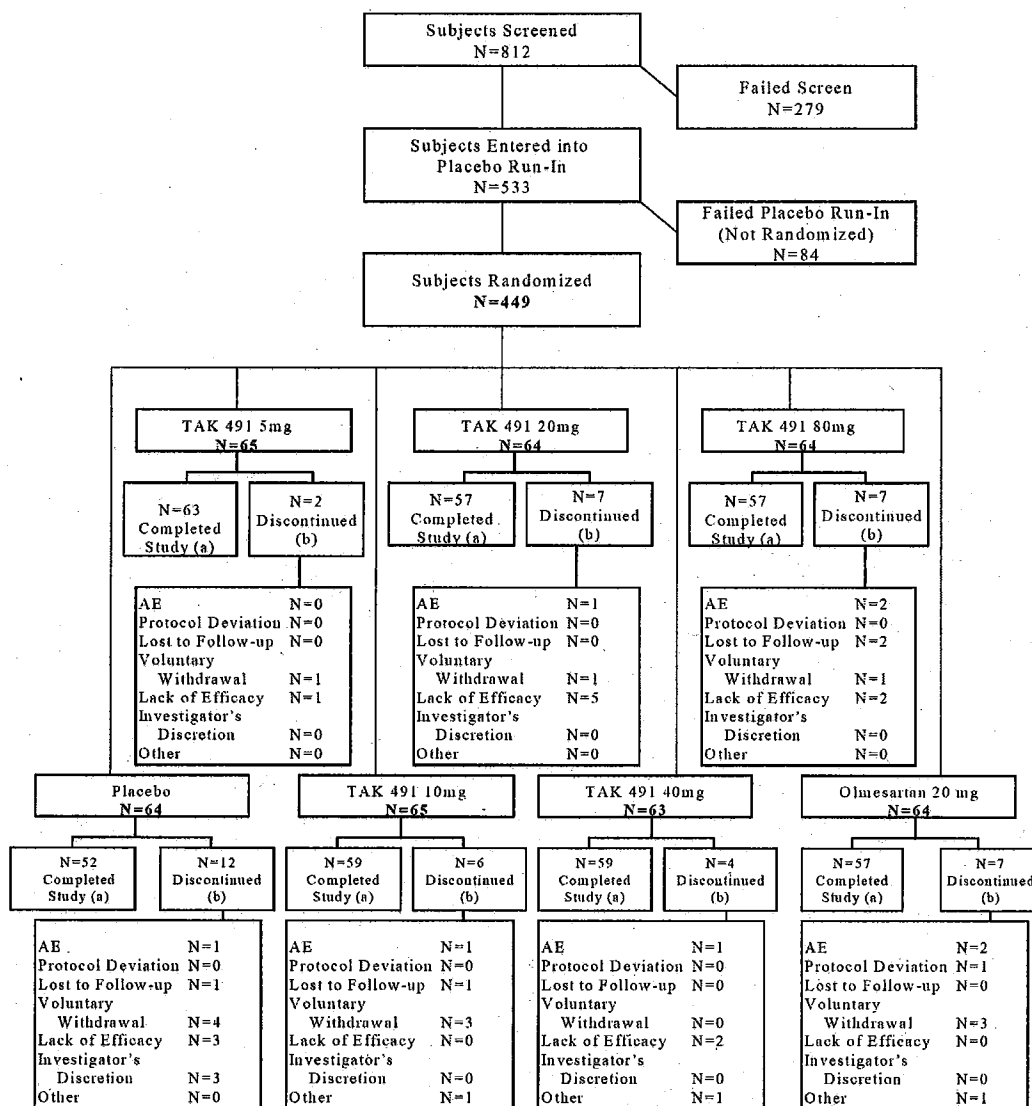
Efficacy endpoints:

Primary endpoint was the change from baseline at final visit in the sitting clinic DBP. The secondary efficacy variables were the change from baseline at final visit in sitting clinic SBP, standing SBP and DBP, as well as SBP and DBP measured by ABPM.

RESULTS

The disposition of subjects is shown below.

Figure 10.a Disposition of Subjects



Source: Table 15.1.2.

(a) For the purpose of this disposition figure, subjects who completed study were calculated as the total number randomized per treatment group minus those who discontinued.

(b) Subjects could have had more than 1 reason for discontinuation; only the primary reason is presented here.

Withdrawal categories are described in Section 9.3.3.

A total of 449 subjects were randomized and 404 subjects completed the study. There were 45 subjects who prematurely discontinued from the study: 12 placebo, 2 TAK-491 5 mg, 6 TAK-491 10 mg, 4 TAK-491 40 mg, and 7 in each of TAK-491 20 mg, 80 mg, and olmesartan 20 mg treatment groups. The most common reasons for premature withdrawal included voluntary withdrawal and lack of efficacy.

The demographic and baseline characteristics were fairly similar across all treatment groups: about half were male and about 10% were black.

RESULTS

Disposition of subjects

A total of 812 subjects were screened at 73 sites in United States, Mexico, Peru, and Argentina. Of these, 533 subjects entered the placebo run-in period, and 449 were randomized to treatment at 67 sites in the United States and Latin America; 63 to 65 subjects were randomized to each of the 7 treatment groups.

Table 15.1.2
Subject Disposition
All Randomized Subjects

Parameter	Placebo (N = 64)	TAK-491 5 mg (N = 65)	TAK-491 10 mg (N = 65)	TAK-491 20 mg (N = 64)	TAK-491 40 mg (N = 63)	TAK-491 80 mg (N = 64)	Olmesartan 20 mg (N = 64)
Number of subjects randomized	64	65	65	64	63	64	64
Failed to receive double-blind study medication	1 (1.6)	0	1 (1.5)	0	1 (1.6)	0	1 (1.6)
Completed 0 to less than 1 week	1 (1.6)	0	0	0	0	0	0
Completed 1 to less than 2 weeks	3 (4.7)	0	1 (1.5)	3 (4.7)	1 (1.6)	0	1 (1.6)
Completed 2 to less than 4 weeks	2 (3.1)	1 (1.5)	1 (1.5)	1 (1.6)	2 (3.2)	5 (7.8)	4 (6.3)
Completed 4 to less than 6 weeks	3 (4.7)	1 (1.5)	4 (6.2)	4 (6.3)	0	1 (1.6)	0
Completed 6 to less than 8 weeks	32 (50.0)	35 (53.8)	32 (49.2)	30 (46.9)	33 (52.4)	30 (46.9)	33 (51.6)
Completed >= 8 weeks	22 (34.4)	28 (43.1)	26 (40.0)	26 (40.6)	26 (41.3)	28 (43.8)	25 (39.1)
Number of subjects discontinued from study	12 (18.8)	2 (3.1)	6 (9.2)	7 (10.9)	4 (6.3)	7 (10.9)	7 (10.9)
Primary reason for discontinuation							
Adverse Event	1 (1.6)	0	1 (1.5)	1 (1.6)	1 (1.6)	2 (3.1)	2 (3.1)
Major Protocol Deviation	0	0	0	0	0	0	1 (1.6)
Lost to Follow-Up	1 (1.6)	0	1 (1.5)	0	0	2 (3.1)	0
Voluntary Withdrawal	4 (6.3)	1 (1.5)	3 (4.6)	1 (1.6)	0	1 (1.6)	3 (4.7)
Lack of Efficacy	3 (4.7)	1 (1.5)	0	5 (7.8)	2 (3.2)	2 (3.1)	0
Investigator's Discretion	3 (4.7)	0	0	0	0	0	0
Other	0	0	1 (1.5)	0	1 (1.6)	0	1 (1.6)

Most randomized subjects (406 of 449) completed at least 6 weeks of double blind treatment with double-blind study medication. The highest number of drop outs was in the placebo group (19%) followed by TAK-491 20 mg and 80 mg (11% each). Drop outs for adverse events were uncommon in all groups.

Primary efficacy

Blood pressure results are shown below.

Study Visit	Placebo N=61	TAK-491 5 mg N=65	TAK-491 10 mg N=63	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	OLM 20 mg N=63
Sitting Clinic DBP							
Baseline (a)							
N	61	65	63	64	62	64	63
LS mean (SE)	100.1 (0.56)	99.8 (0.55)	99.4 (0.55)	99.7 (0.55)	99.7 (0.56)	100.3 (0.55)	99.8 (0.55)
Week 8							
N	58	63	63	63	61	63	63
LS mean (SE)	-7.9 (1.12)	-10.8 (1.08)	-13.1 (1.08)	-11.5 (1.08)	-13.6 (1.10)	-11.6 (1.08)	-11.0 (1.08)
LS mean difference from Placebo (SE) (b)		-2.9	-5.3	-3.7	-5.7	-3.7	-3.2
95% CI of difference		(-5.96, 0.16)	(-8.33, -2.20)	(-6.73, -0.61)	(-8.80, -2.63)	(-6.77, -0.65)	(-6.24, -0.12)
P-value		0.063	<0.001*	0.019*	<0.001*	0.018*	0.042*
Sitting Clinic SBP							
Baseline (a)							
N	61	65	63	64	62	64	63
LS mean (SE)	150.8 (1.59)	150.2 (1.54)	152.4 (1.56)	149.1 (1.55)	150.6 (1.57)	151.2 (1.55)	150.3 (1.56)
Week 8							
N	58	63	63	63	61	63	63
LS mean (SE)	-4.9 (1.73)	-11.0 (1.66)	-15.7 (1.66)	-14.7 (1.66)	-17.1 (1.69)	-13.3 (1.66)	-13.5 (1.66)
LS mean difference from placebo (SE) (b)		-6.1	-10.8	-9.8	-12.3	-8.5	-8.7
95% CI of difference		(-10.84, -1.41)	(-15.51, -6.08)	(-14.53, -5.10)	(-17.02, -7.52)	(-13.19, -3.76)	(-13.39, -3.96)
P-value		0.011*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

All post-baseline P-values were determined by ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate).

CI=confidence interval.

* Significant difference at 0.05 level.

(a) Baseline value is the last observation before the first dose of double-blind study medication.

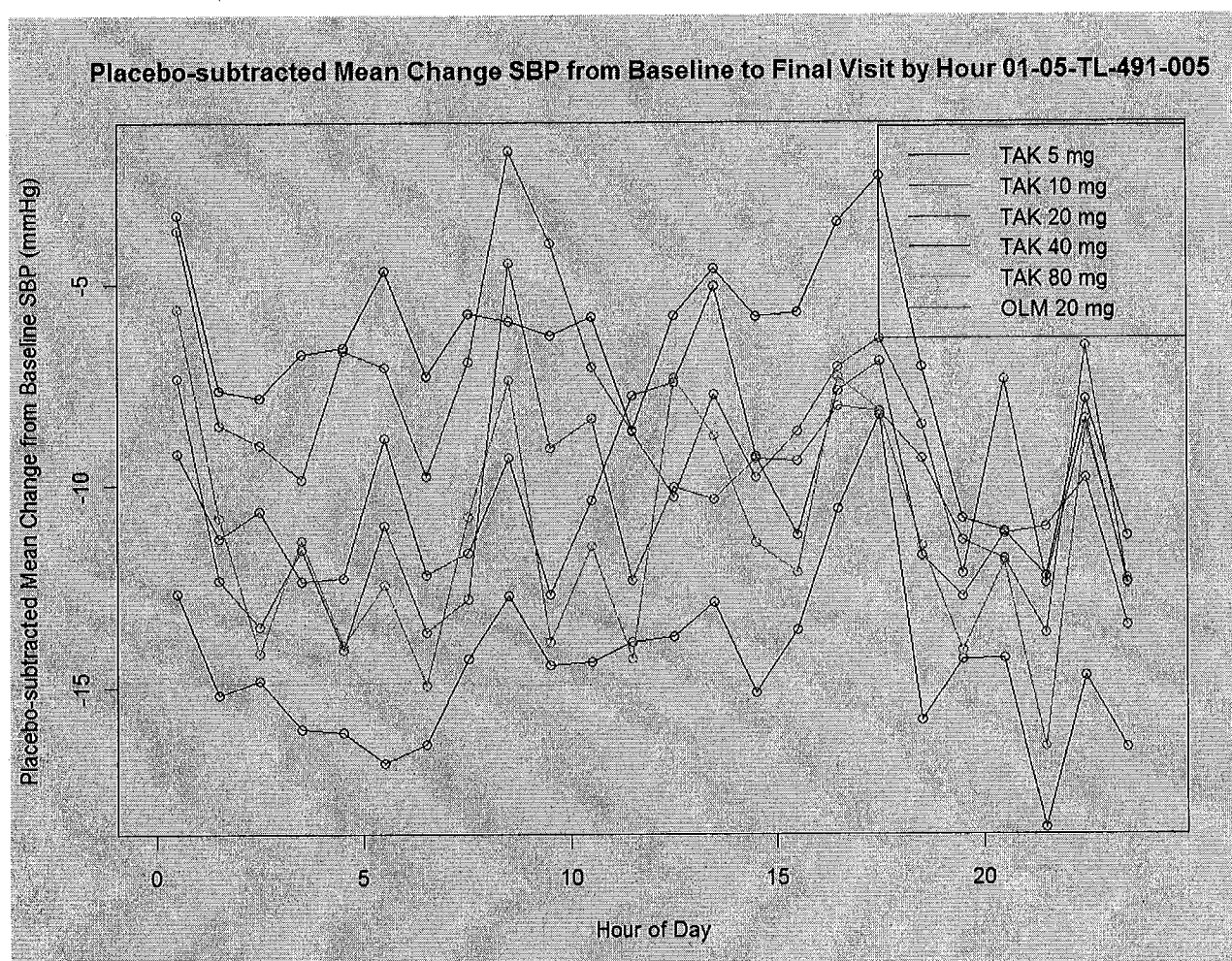
(b) LS mean difference=LS mean change of each active group (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

Mean baseline DBP measurements were similar for all treatment groups. At week 8, all the active treatments lowered DBP more than placebo did ($p < 0.05$ except for TAK-491 5 mg). The treatment effect for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan were -3 mmHg, -5 mmHg, -4 mmHg, -6 mmHg, -4 mmHg and -3 mmHg, respectively. These similar decreases in DBP indicates a lack of a dose response for TAK-491.

Mean baseline SBP measurements were similar for all treatment groups. At week 8, all the active treatments lowered SBP more than placebo did ($p < 0.001$ except for TAK-491 5 mg). The treatment effect for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan were -6 mmHg, -11 mmHg, -10 mmHg, -12 mmHg, -8 mmHg and -9 mmHg, respectively. As with DBP, there were only small differences between the active treatment groups in lowering SBP and there was not a dose response for TAK-491.

A reasonable starting dose of TAK-491 is 5 mg with a maximum dose 40 mg. TAK-491 doses above 5 mg are not superior to olmesartan 40 mg.

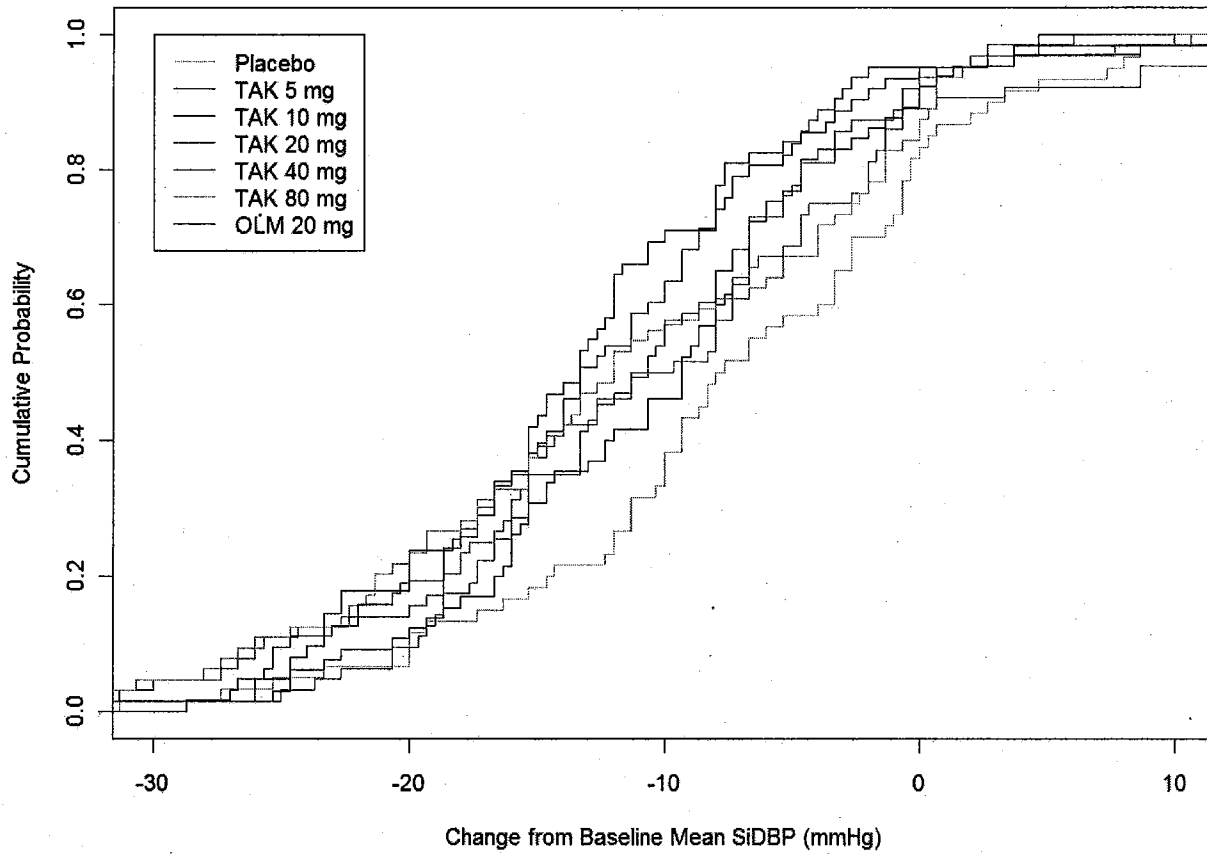
The following figure is mean placebo subtracted change from baseline ABPM SBP by hour.



There is not much evidence of a dose response.

The figure below is the cumulative distribution function for the sitting clinic DBP. There was one subjects who did not have post baseline clinic DBP.

Distribution of Primary Endpoint (SiDBP) Study 01-05-TL-491-005

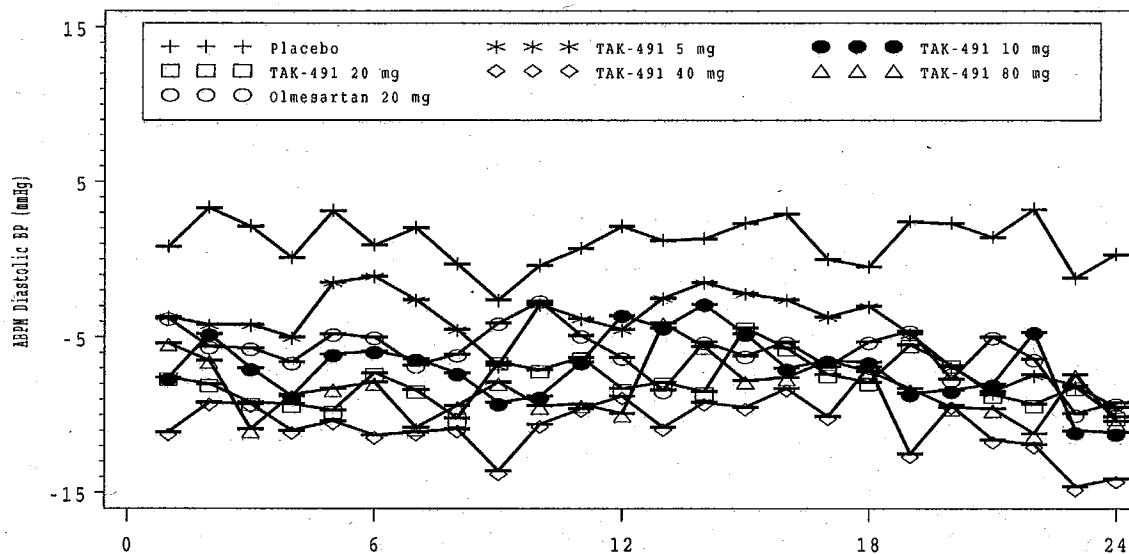


Secondary endpoints

ABPM

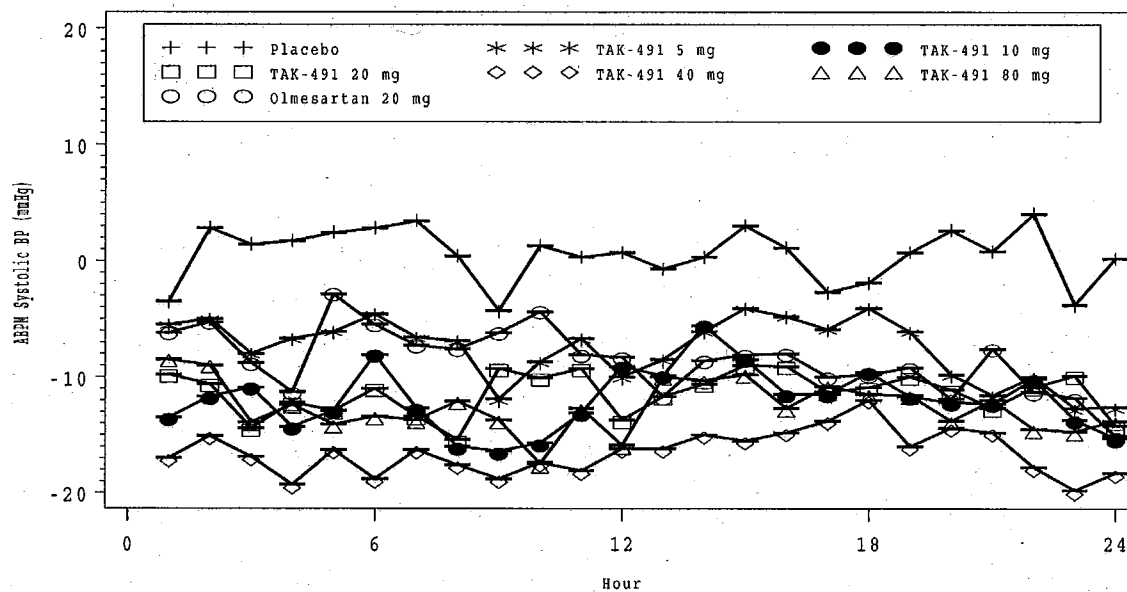
DBP and SBP 24 hour profiles, change from baseline at endpoint, are shown below.

Figure 15.2.5.3
ABPM Measurements: Change From Baseline in Mean Diastolic Blood Pressure (mmHg)
by Hour for the 0 - 24 Hour Interval
Full Analysis Set



SBP

Figure 15.2.6.3
ABPM Measurements: Change From Baseline in Mean Systolic Blood Pressure (mmHg)
by Hour for the 0 - 24 Hour Interval
Full Analysis Set



Safety

Deaths

There was 1 death during this study. Subject 5083/003 (olmesartan 20 mg), on study day 26 experienced a fatal cardiac arrest that were fatal.

Serious adverse events

There were 5 subjects who reported a serious adverse event.

Table 12.d Summary of Treatment-Emergent SAEs— Safety Set

Site/Subject No. Treatment	AE	Onset Day	Relationship to Drug (a)	Intensity	Action/Outcome
5084/006 Placebo	Gastrointestinal hemorrhage	Study Day 34	Not related	Moderate	Drug withdrawn/ Resolved
	Myocardial infarction	Study Day 34	Not related	Severe	Not applicable/ Resolved
5008/004 TAK-491 5 mg	Wound Infection	Study Day 42	Not related	Mild	Dose not changed/ Resolved
5061/012 TAK-491 10 mg	Hydrocephalus	Study Day 39	Not related	Moderate	Drug withdrawn/ Resolved
	Headache	Study Day 39	Not related	Moderate	Not applicable/ Resolved
5008/024 TAK-491 40 mg	Esophageal spasm	Study Day 57	Not related	Mild	Drug withdrawn/ Resolved
5083/003 Olmesartan 20 mg	Hypertensive heart disease	Study Day 26	Not related	Severe	Fatal
	Cardiac arrest	Study Day 26	Not related	Severe	Fatal

Source: Appendix 16.2.7.3.

(a) As judged by the investigator.

The above list reveals no obvious safety risk from any of the drugs studied.

Adverse events that resulted in study discontinuation

A total of 9 subjects prematurely discontinued the study because of adverse events.

Subject 5083/003 discontinued because of a fatal cardiac arrest and subjects 5008/024, 5061/012, 5084/006 discontinued because of a nonfatal serious adverse event.

The other subjects are listed below:

- subject 5009/001 (olmesartan 20 mg treatment group) reported dysuria and testicular pain;
- subject 5026/004 (TAK-491 20 mg treatment group) reported urticaria on study day 39;
- subject 5036/009 (TAK-491 80 mg treatment group) reported hypotension on study day 8;
- subject 5064/002 (TAK-491 80 mg treatment group) reported hypotension on study day 24;
- subject 5078/005 (placebo) reported blood pressure increased on study day 6.

The two reports of hypotension were reported by subjects randomized to TAK-491 80 mg.

All adverse events

The most commonly reported adverse events are shown below.

Table 12.c Treatment-Emergent AEs Presented by Preferred Term with Incidence of at Least 5 Subjects Total Among All Treatment Groups – Safety Set

Preferred Term	Placebo N=63	TAK-491 5 mg N=65	TAK-491 10 mg N=64	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	Olmesartan 20 mg N=63
Headache	3 (4.8)	2 (3.1)	2 (3.1)	7 (10.9)	3 (4.8)	3 (4.7)	5 (7.9)
Nasopharyngitis	4 (6.3)	0	3 (4.7)	3 (4.7)	1 (1.6)	3 (4.7)	1 (1.6)
Dizziness	2 (3.2)	1 (1.5)	3 (4.7)	4 (6.3)	2 (3.2)	1 (1.6)	1 (1.6)
Diarrhea	1 (1.6)	1 (1.5)	1 (1.6)	2 (3.1)	2 (3.2)	2 (3.1)	1 (1.6)
Dyslipidemia	1 (1.6)	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)	0	0
Fatigue	0	0	2 (3.1)	0	2 (3.2)	1 (1.6)	1 (1.6)
Upper respiratory tract infection	0	4 (6.2)	0	0	2 (3.2)	0	0
Cough	1 (1.6)	1 (1.5)	0	1 (1.6)	1 (1.6)	1 (1.6)	0
Vomiting	0	0	2 (3.1)	0	1 (1.6)	1 (1.6)	1 (1.6)

Source: Table 15.3.1.3.

Note: Data represent number (percentage) of subjects.

The most commonly reported events were regardless of treatment group included headache, nasopharyngitis, dizziness, diarrhea, dyslipidemia, fatigue, upper respiratory tract infection, cough and vomiting. There were only small differences between the treatment groups with respect to the incidence of these events and none appeared to be linked to the dose of TAK-491.

Clinical laboratory values

The following list subjects who reported adverse events related to serum chemistry values:

-subject 5029/005 (TAK-491 5 mg reported ALT and AST increased on study day 30 which resolved by Study Day 44. The elevated ALT (88 U/L) and AST (56 U/L) values were not considered markedly abnormal.

-subject 5040/018 (TAK-491 20 mg) reported hepatic enzyme increased on study day 49. ALT and AST values were elevated at Visit 9 (65 U/L and 42 U/L, respectively) and resolved by study day 63.

-subject 5034/010 (placebo) experienced AEs of blood glucose increased (10.2 mmol/L) and blood insulin increased (41.9 μ U/mL) on study day 3.

There were no withdrawals because of serum chemistry abnormalities.

Reports of marked abnormal chemistry values are shown below.

Table 12.e Marked Abnormalities in Serum Chemistries – Safety Set

Laboratory Test	Placebo N=63	TAK-491 5 mg N=65	TAK-491 10 mg N=64	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	OLM 20 mg N=63
ALT >3 × ULN	0	0	0	1 (1.6)	0	0	0
AST >3 × ULN	0	0	0	0	0	0	1 (1.6)
BUN >30 mg/dL	0	1 (1.5)	0	0	1 (1.6)	0	0
Creatinine >2 mg/dL	0	0	0	0	0	0	1 (1.6)
Potassium	0	0	0	0	0	0	0
Uric acid >8 mg/dL	0	3 (4.6)	2 (3.1)	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)

Source: Table 15.3.4.5.

OLM=olmesartan, ULN=upper limit of normal.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least one test result during a particular test was considered markedly abnormal. Only postbaseline values are included in this table.

Overall, there were very few reports and no pattern can be detected.

The following subjects reported hematology-related adverse events:

- subject 5092/004 (TAK-491 20 mg) reported elevated eosinophil count;
- subject 5079/009 (TAK-491 80 mg) reported increased hemoglobin (16.4 g/dL) and hematocrit (0.5 ratio) on Study Day 27.

There were no study withdrawals because of hematology abnormalities.

Urinalysis

There were no clinically meaningful changes in these data and no patterns of urinalysis abnormalities that would suggest a clinically meaningful treatment effect. Subject 5018/019 (placebo) reported WBCs urine positive on Study Day 55 as an adverse event.

There were no withdrawals due abnormalities in urinalysis test results

Vital Signs, ECGs, Physical Findings

There were no remarkable differences in weight across treatment groups at baseline, or in mean weight changes from baseline at endpoint.

There were no meaningful differences in sitting or standing pulse at baseline or at any visit with respect to change from baseline across treatment groups and no dose-related findings.

Mean sitting pulse increased slightly in the placebo group (0.30 bpm) and decreased slightly in the TAK-491 groups (range -0.43 to -2.22 bpm) and olmesartan group (-0.38 bpm). Mean heart rate increased in the placebo and olmesartan groups (1.3 and 2.0 bpm, respectively), and generally decreased or did not change in the TAK-491 groups (1.0, -0.1, -1.9, 0.1, -0.4 bpm in the 5, 10, 20, 40, and 80 mg groups, respectively).

Physical Findings

There were no major findings as a result of physical examinations in the safety population.

ECGs

There were no remarkable changes from Baseline to Final Visit with respect to the overall clinical interpretation of the 12-lead ECG and no meaningful differences between treatment groups.

Reviewer's summary and conclusions

Efficacy: DBP results at week 8 showed treatment effects for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan that were -3 mmHg, -5 mmHg, -4 mmHg, -6 mmHg, -4 mmHg and -3 mmHg, respectively. SBP results at week 8 showed treatment effects for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan that were -6 mmHg, -11 mmHg, -10 mmHg, -12 mmHg, -8 mmHg and -9 mmHg, respectively. As with DBP, there were only small differences between the active treatment groups in lowering SBP and there was not a dose response for TAK-491.

A reasonable starting dose of TAK-491 is 5 mg with a maximum dose 40 mg. TAK-491 doses above 5 mg are not superior to olmesartan 40 mg.

Safety: The most commonly reported events were regardless of treatment group included headache, nasopharyngitis, dizziness, diarrhea, dyslipidemia, fatigue, upper respiratory tract infection, cough and vomiting. There were only small differences between the treatment groups with respect to the incidence of these events and none appeared to be linked to the dose of TAK-491.

Conclusions: the results of this study support the opinion that doses of TAK-491 5 mg through 40 mg are safe and effective. TAK 491 80 mg did not produce better blood pressure effects compared to 40 mg. TAK -491 is not superior to olmesartan 20 mg.

Study 01-06-TL-491-011

Title

A Double-Blind, Randomized, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of TAK-491 in Black Subjects with Essential Hypertension.

There were 74 investigators enrolled subjects into the United States and Puerto Rico

Study Period October 30, 2007 to April 30, 2009

Primary objective

To evaluate the change in 24-hour mean ambulatory blood pressure monitoring (ABPM) systolic blood pressure (SBP) in response to TAK-491 compared to placebo for 6 weeks in Black subjects with essential hypertension.

Secondary:

- change in 24-hour mean ABPM diastolic blood pressure (DBP) in response to TAK-491 compared to placebo.
- change in trough, sitting clinic SBP, and DBP.
- To evaluate the treatment effect of TAK-491 on SBP and DBP using additional ABPM parameters.
- the proportion of subjects who achieve response criteria:
 - a) Clinic DBP <90 mm Hg and/ or reduction of ≥ 10 mm Hg from Baseline.
 - b) Clinic SBP <140 mm Hg and/ or reduction of ≥ 20 mm Hg from Baseline.
 - c) a and b.

Study design

Multicenter, randomized, parallel-group, double-blind placebo-controlled study in black subjects with essential hypertension. After a 2-week single-blind placebo run-in period, subjects who met the entry criteria were randomized to receive TAK-491 40 mg QD, TAK-491 80 mg QD, or placebo for 6 weeks. Clinic SBP and DBP were measured at screening, randomization, run-in period, and treatment period (Week 2, Week 4, and Week 6). ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 (or early termination) for 24 hours following the last administration of study medication.

Number of Subjects:

There were 411 subjects planned (137 per treatment group) and 413 randomized.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been black male or nonpregnant, nonlactating women with essential hypertension, defined as a postwashout trough clinic sitting SBP on Day -1 of 150-180 mm Hg, inclusive, and a 24-hour mean SBP on Day 1 of 130-170 mm Hg, inclusive; aged 18 years or older; with clinical laboratory evaluations within the reference range for the testing laboratory or results that were deemed not clinically significant; able to comprehend and willing to sign an informed consent form; and willing to discontinue current antihypertensive medication(s) at Screening (on Day -21/Day -28 if on amlodipine).

RESULTS

Demographics

Selected demographic features of the study population are shown below.

Characteristic	Treatment (Randomized Set)		
	Placebo N=138	TAK-491 40 mg N=138	TAK-491 80 mg N=137
Sex, n (%)			
Male	60 (43.5%)	60 (43.5%)	57 (41.6%)
Female	78 (56.5%)	78 (56.5%)	80 (58.4%)
Age, yr			
Mean (SD)	51.8 (11.25)	52.2 (10.63)	51.0 (10.06)
Race, n (%) (a)			
Black or African American	138 (100.0%)	138 (100.0%)	137 (100.0%)
Multiracial	1 (0.7%)	0	0
Weight, kg			
Mean (SD)	93.4 (21.02)	88.9 (19.43)	90.0 (19.81)
Height, cm			
Mean (SD)	168.7 (10.24)	168.3 (10.30)	169.2 (10.36)
BMI, kg/m ²			
Mean (SD)	32.9 (7.38)	31.4 (6.29)	31.6 (7.70)
Note: Age=(informed consent date – date of birth +1)/365.25, and was truncated at the decimal.			
(a) For race, a subject may choose more than 1 category for race. Subjects who indicated more than 1 race category are included in each category indicated, and they are also included in the multiracial category. Thus, the total number and percentage of subjects does not generally add up to the total number randomized.			

Overall, there were more females than males, the mean age was about 52 years, and all subjects were black or multiracial. The groups were well balanced.

Subject disposition

The number and percent of subjects who prematurely discontinued the study and the reasons for discontinuation are shown below.

	Treatment (All Randomized or Treated Subjects)		
	Placebo N=138	TAK-491 40 mg N=140	TAK-491 80 mg N=137
Number of subjects enrolled	138	140	137
Number subjects prematurely discontinued (%)	15 (10.9)	14 (10.0)	21 (15.3)
Primary reason for premature discontinuation			
AE	1 (0.7)	3 (2.1)	3 (2.2)
Protocol deviation	2 (1.4)	2 (1.4)	2 (1.5)
Lost to follow-up	0	2 (1.4)	4 (2.9)
Voluntary withdrawal	6 (4.3)	1 (0.7)	7 (5.1)
Lack of efficacy	3 (2.2)	1 (0.7)	0
Study termination	0	0	0
Pregnancy	0	0	0
Other	3 (2.2)	5 (3.6)	5 (3.6)

Overall, there were slightly more premature discontinuations in the TAK-491 80 mg group compared to the other groups.

Efficacy

Primary efficacy variable was change from baseline to week 6 in the 24-hour mean SBP by ABPM

A summary of the statistical comparisons between treatment groups is shown in the table below.

Table 11.a Change From Baseline to Week 6 in the 24-hour Mean SBP by ABPM (FAS)

Study Visit	Treatment			Overall P-Value
	Placebo N=138	TAK-491 40 mg N=135	TAK-491 80 mg N=137	
Baseline				
n	94	94	101	
LS mean (SE)	145.06 (1.044)	146.72 (1.044)	146.89 (1.007)	
Week 6				
n	94	94	101	
LS mean change (SE)	-2.70 (1.065)	-7.70 (1.063)	-10.48 (1.026)	<0.001*
LS mean difference (a)		-5.00	-7.78	
(95% CI)		(-7.97, -2.04)	(-10.69, -4.86)	
P-value vs placebo		0.001*	<0.001*	
Week 6: Sensitivity analysis using multiple imputation				
LS mean difference (a)		-5.04	-7.88	<0.001*
(95% CI)		(-8.35, -1.73)	(-10.78, -4.98)	
P-value vs placebo		0.004*	<0.001*	

Source: Table 15.2.1.1.2.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

Includes subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group) – LS mean change of placebo group.

At baseline, 24-hour mean SBP was similar between placebo and TAK-491 treatment groups (approximately 146 mm Hg).

At week 6, the placebo subtracted differences in 24-hour mean SBP for TAK-491 40 and 80 mg were -5 and -8 mmHg, respectively. The differences were significant compared to placebo but numerically less than those obtained from non black subjects in other studies.

The figures showing 24 hour SBP profile at baseline, final visit, and change from baseline at final visit are shown below.

Figure 11.a SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)

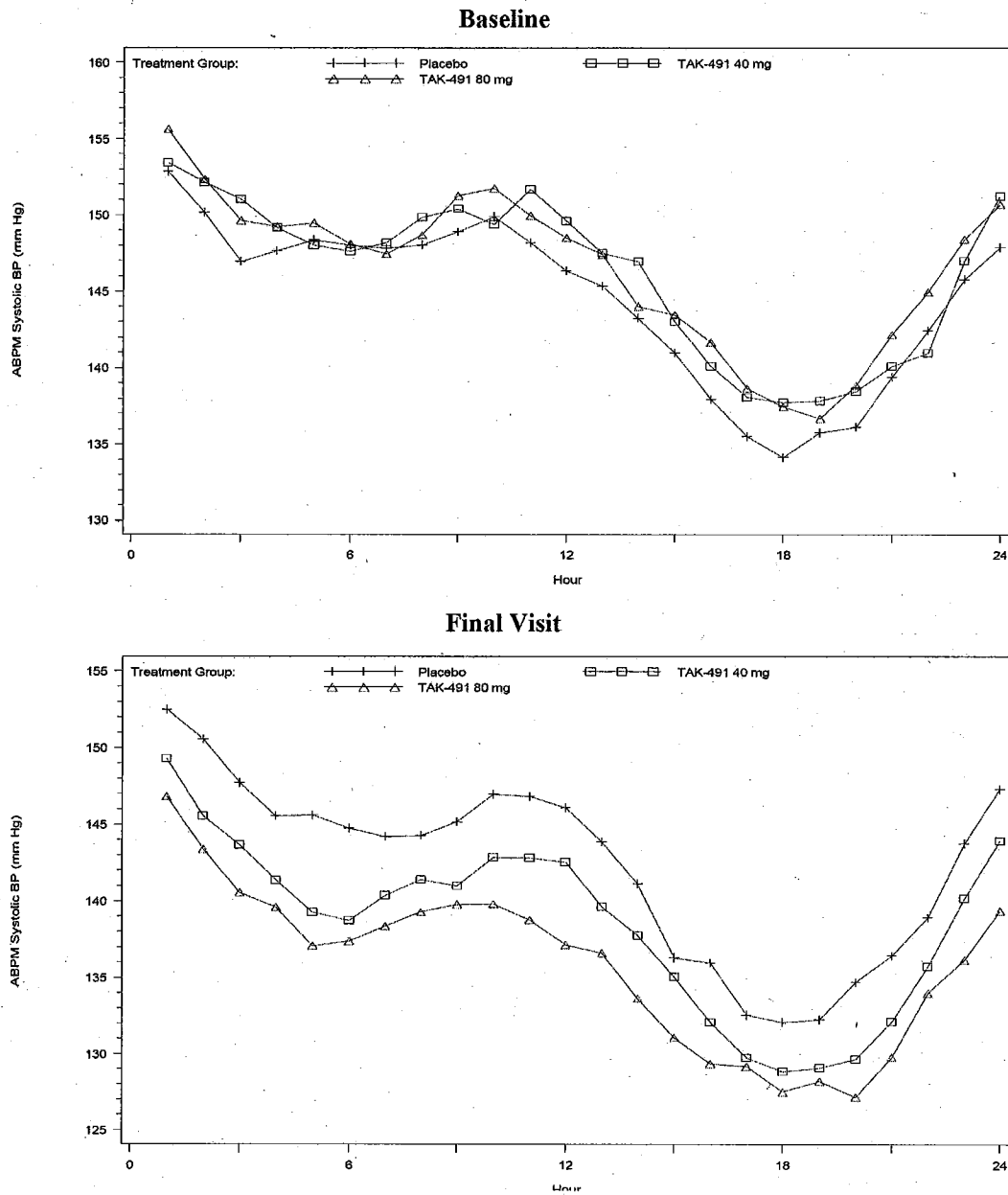
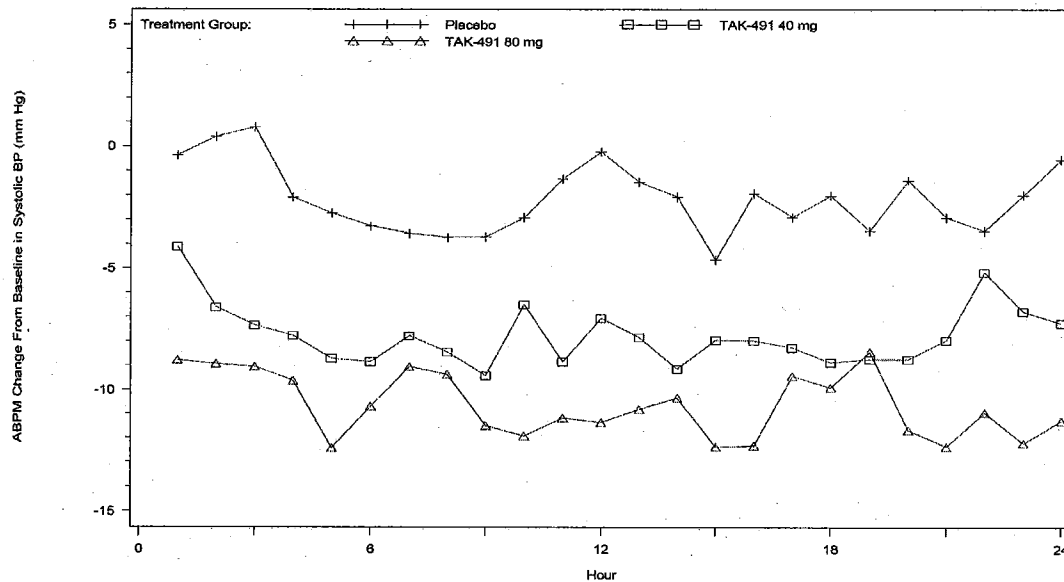


Figure 11.b Change From Baseline to Week 6 in SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)



DBP

The results for the 24 hour DBP using ABPM are shown below.

Table 11.c Summary of Change From Baseline to Week 6 in the 24-hour Mean DBP by ABPM (FAS)

Study Visit	Treatment			Overall P-Value
	Placebo N=138	TAK-491 40 mg N=135	TAK-491 80 mg N=137	
Baseline				
n	94	94	101	
LS mean (SE)	91.91 (0.945)	92.16 (0.945)	90.94 (0.912)	
Week 6				
n	94	94	101	
LS mean change (SE)	-1.49 (0.731)	-4.93 (0.732)	-7.27 (0.706)	<0.001*
LS mean difference (a)		-3.44	-5.77	
(95% CI)		(-5.47, -1.40)	(-7.78, -3.77)	
P-value vs placebo		0.001*	<0.001*	
Sensitivity analysis using multiple imputations (Week 6)				
LS mean difference (a)		-3.52	-5.68	<0.001*
(95% CI)		(-5.33, -1.72)	(-7.75, -3.62)	
P-value vs placebo		<0.001*	<0.001*	

Source: Table 15.2.2.1.2.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate). Includes subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

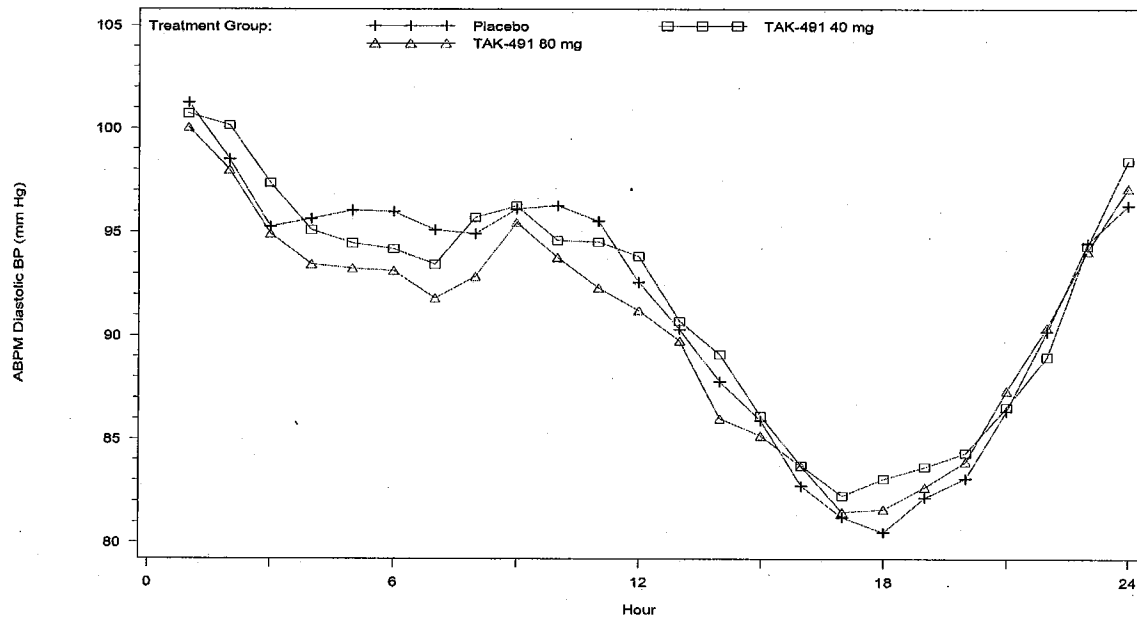
(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group) – LS mean change of placebo group.

At baseline, 24-hour mean DBP was similar between placebo and TAK-491 treatment groups (approximately 91 mm Hg).

At week 6, the placebo subtracted differences in 24-hour mean DBP for TAK-491 40 and 80 mg were -3 and -6 mmHg, respectively. The differences were significant compared to placebo but, as with SBP, numerically less than those obtained in non black populations in other studies.

The figures showing 24 hour DBP profile at baseline, final visit, and change from baseline at final visit are shown below.

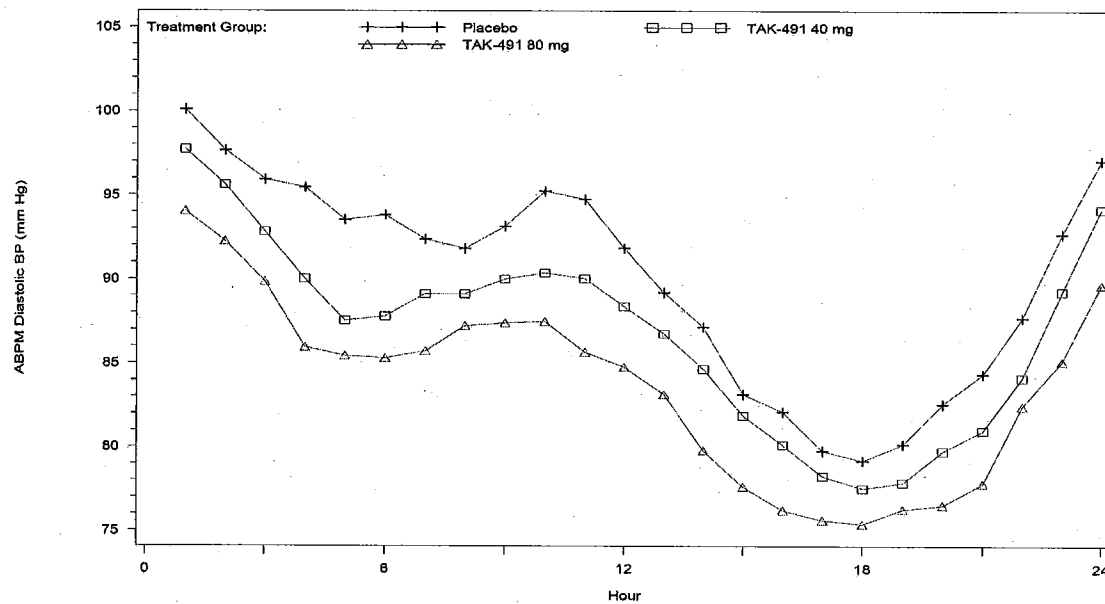
ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Baseline by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



24 hour DBP profile at final visit

Figure 15.2.2.5.2

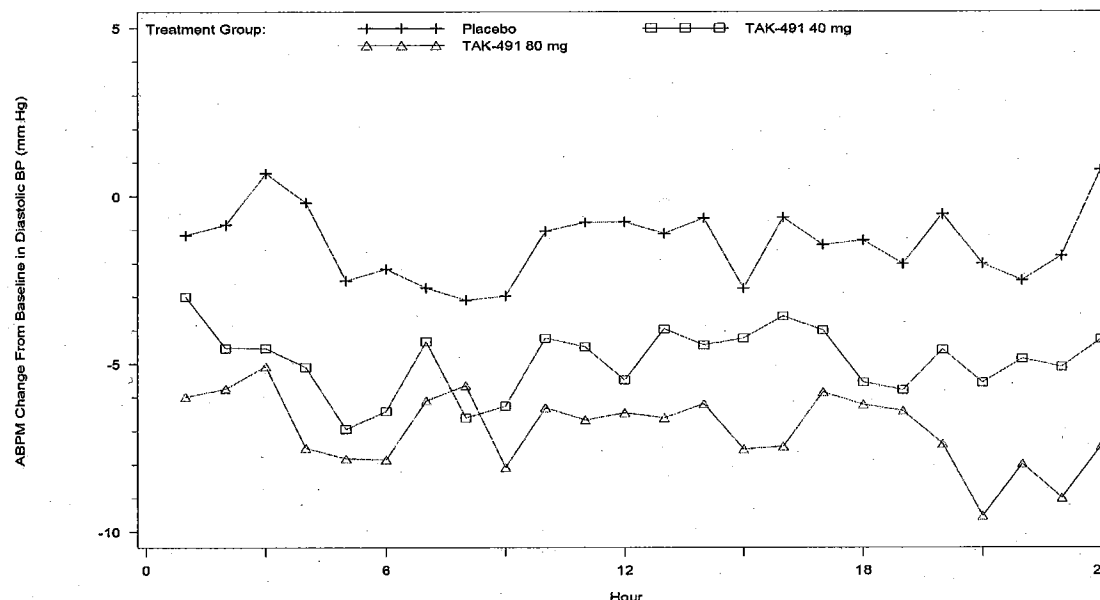
ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Final Visit by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



Change from baseline at final visit

Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
Full Analysis Set



Placebo corrected trough to peak ratios for SBP and DBP are shown below.

Table 11.g Summary of Trough-to-Peak Ratios for SBP and DBP as Measured by ABPM (FAS)

		TAK-491 40 mg N=135	TAK-491 80 mg N=137
SBP			
	n	94	101
24-hour (a)	Placebo corrected trough-to-peak ratio	0.896	0.942
12-hour (b)	Placebo corrected trough-to-peak ratio	0.988	1.064
DBP			
	n	94	101
24-hour (c)	Placebo corrected trough-to-peak ratio	1.202	1.263
12-hour (d)	Placebo corrected trough-to-peak ratio	1.408	1.641

Source: Tables 15.2.1.4.1 and 15.2.2.4.1.

Note: Includes subjects with both a Baseline and postbaseline value. Peak response is defined as the change from Baseline in blood pressure values by ABPM during the peak effect interval. Trough Peak ratio was calculated as mean trough response divided by mean peak response. Placebo corrected trough peak ratio was calculated as placebo response subtracted mean trough response divided by placebo response subtracted mean peak response.

(a) The peak effect interval was determined for each subject as the 2-hour interval during the 24 hours after dosing in which the maximum decrease from Baseline was observed for SBP.

(b) The peak effect interval was determined for each subject as the 2-hour interval during the 12 hours after dosing in which the maximum decrease from Baseline was observed for SBP.

(c) The peak effect interval was determined for each subject as the 2-hour interval during the 24 hours after dosing in which the maximum decrease from Baseline was observed for DBP.

(d) The peak effect interval was determined for each subject as the 2-hour interval during the 12 hours after dosing in which the maximum decrease from Baseline was observed for DBP.

The placebo-corrected peak and trough blood pressure lowering effects on SBP and DBP were similar (ratios that were ≥ 0.9).

Subgroup analyses

Subgroup analyses were conducted by age and sex (shown below), as well as for BMI, median baseline 24-hour mean SBP, and cGFR, to evaluate for differences in blood pressure effects of TAK-491.

Table 11.i Subgroup Analysis of 24-hour Mean SBP by ABPM (FAS)

Subgroup	Treatment		
	Placebo	TAK-491 40 mg	TAK-491 80 mg
Age			
<65 years			
n	83	82	91
LS mean at Baseline (SE)	144.73 (1.117)	145.77 (1.124)	146.70 (1.067)
LS mean Change to Week 6 (SE)	-2.30 (1.126)	-7.51 (1.131)	-11.12 (1.075)
LS mean Difference (95% CI) (a)		-5.21 (-8.35, -2.06)*	-8.82 (-11.89, -5.75)*
≥65 years			
n	11	12	10
LS mean at Baseline (SE)	147.51 (2.694)	153.22 (2.579)	148.65 (2.826)
LS mean Change to Week 6 (SE)	-5.72 (3.204)	-9.15 (3.108)	-4.34 (3.328)
LS mean Difference (95% CI) (a)		-3.43 (-12.73, 5.87)	1.38 (-8.00, 10.77)
Sex			
Male			
n	41	38	43
LS mean at Baseline (SE)	145.05 (1.582)	148.11 (1.643)	148.94 (1.545)
LS mean Change to Week 6 (SE)	-3.51 (1.635)	-6.65 (1.685)	-14.02 (1.589)
LS mean Difference (95% CI) (a)		-3.14 (-7.80, 1.52)	-10.51 (-15.05, -5.96)*
Female			
n	53	56	58
LS mean at Baseline (SE)	145.06 (1.383)	145.77 (1.346)	145.37 (1.322)
LS mean Change to Week 6 (SE)	-1.93 (1.385)	-8.42 (1.347)	-7.97 (1.323)
LS mean Difference (95% CI) (a)		-6.49 (-10.31, -2.68)*	-6.03 (-9.82, -2.25)*

There was a larger placebo effect in the older age group (-5.72 mmHg) compared to the younger age group (-2.3 mmHg).

TAK-491 80 mg was less effective in the older group than placebo. This could be the result of small sample size.

The results for the other subgroups are shown below.

Table 11.i Subgroup Analysis of 24-hour Mean SBP by ABPM (FAS) (continued)

Subgroup	Treatment		
	Placebo	TAK-491 40 mg	TAK-491 80 mg
BMI			
<30 (kg/m²)			
n	37	40	49
LS mean at Baseline (SE)	145.67 (1.685)	149.06 (1.621)	146.95 (1.465)
LS mean Change to Week 6 (SE)	-4.54 (1.811)	-7.73 (1.744)	-11.31 (1.568)
LS mean Difference (95% CI) (a)		-3.18 (-8.18, 1.81)	-6.77 (-11.51, -2.03)*
≥30 (kg/m²)			
n	55	54	52
LS mean at Baseline (SE)	144.61 (1.355)	144.98 (1.367)	146.83 (1.393)
LS mean Change to Week 6 (SE)	-1.67 (1.329)	-7.56 (1.341)	-9.83 (1.370)
LS mean Difference (95% CI) (a)		-5.89 (-9.61, -2.16)*	-8.16 (-11.93, -4.38)*
Baseline 24-hour mean SBP			
<Median (145.73 [mm Hg])			
n	47	50	48
LS mean at Baseline (SE)	137.34 (0.752)	138.56 (0.729)	138.46 (0.744)
LS mean Change to Week 6 (SE)	-0.56 (1.380)	-4.58 (1.335)	-8.76 (1.361)
LS mean Difference (95% CI) (a)		-4.03 (-7.83, -0.22)*	-8.20 (-12.04, -4.36)*
≥Median (145.73 [mm Hg])			
n	47	44	53
LS mean at Baseline (SE)	152.78 (0.976)	155.98 (1.009)	154.52 (0.919)
LS mean Change to Week 6 (SE)	-5.07 (1.647)	-10.71 (1.701)	-12.26 (1.536)
LS mean Difference (95% CI) (a)		-5.64 (-10.36, -0.92)*	-7.19 (-11.65, -2.74)*
eGFR			
30 ≤eGFR <60 (mL/min/1.73 m²)			
n	1	1	3
LS mean at Baseline (SE)	147.94 (12.568)	144.17 (12.568)	151.35 (7.256)
LS mean Change to Week 6 (SE)	-9.49 (2.724)	4.36 (2.825)	-8.92 (1.602)
LS mean Difference (95% CI) (a)		13.85 (-35.52, 63.22)	0.57 (-39.84, 40.97)
60 ≤eGFR <90 (mL/min/1.73 m²)			
n	39	47	43
LS mean at Baseline (SE)	145.24 (1.752)	148.91 (1.596)	147.36 (1.668)
LS mean Change to Week 6 (SE)	-3.30 (1.770)	-6.74 (1.610)	-9.89 (1.677)
LS mean Difference (95% CI) (a)		-3.44 (-8.20, 1.32)	-6.59 (-11.42, -1.77)*
90 ≤eGFR (mL/min/1.73 m²)			
Baseline ABPM: 0- to 24-hour mean SBP (mm Hg)			
n	54	46	54
LS mean at Baseline (SE)	144.87 (1.268)	144.53 (1.374)	146.00 (1.268)
LS mean Change to Week 6 (SE)	-2.13 (1.315)	-8.97 (1.425)	-10.94 (1.317)
LS mean Difference (95% CI) (a)		-6.84 (-10.67, -3.01)*	-8.81 (-12.49, -5.13)*

Source: Tables 15.2.1.3.2, 15.2.1.3.4, 15.2.1.3.6, 15.2.1.3.8, and 15.2.1.3.10.

Note: Includes subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group) - LS mean change of placebo group.

SAFETY RESULTS

Extent of Exposure

A total of 413 subjects were randomized in the study.

Three subjects (0049/010, 0053/021, 0075/036) in the TAK-491 40 mg treatment group were randomized but not treated and were excluded from the safety population (N=412). An additional two subjects (0053/015 and 0075/037) who received TAK-491 40 mg but were never randomized to this treatment group were only included in the safety analysis set.

The mean number of days of exposure to study drug for each treatment group is shown below.

Table 12.a Duration of Treatment With Study Medication in Days - Safety Analysis Set

Double-Blind Treatment (days)	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
Mean (SD)	41.6 (8.14)	41.4 (8.07)	39.4 (11.07)
Median	43.0	43.0	42.0
Minimum, Maximum	2, 63	1, 56	1, 56

Source: Table 15.1.14.

The mean number of days was similar across treatment groups.

Study completion

The numbers and percents of subjects who completed and those who did not complete the study are shown below.

Table 15.1.4
Disposition of Subjects
All Randomized or Treated Subjects

	Number of Subjects (%)			
	Placebo (N=138)	TAK-491 40 mg (N=140)	TAK-491 80 mg (N=137)	Total (N=415)
Randomized But Not Treated	0 (0.0)	3 (2.1)	0 (0.0)	3 (0.7)
Treated But Not Randomized	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.5)
Completed Study Drug	123 (89.1)	126 (90.0)	116 (84.7)	365 (88.0)
Prematurely Discontinued Study Drug	15 (10.9)	14 (10.0)	21 (15.3)	50 (12.0)
Reason for Discontinuation of Study Drug				
Adverse Event	1 (0.7)	3 (2.1)	3 (2.2)	7 (1.7)
Major Protocol Deviation	2 (1.4)	2 (1.4)	2 (1.5)	6 (1.4)
Lost to Follow-Up	0 (0.0)	2 (1.4)	4 (2.9)	6 (1.4)
Voluntary Withdrawal	6 (4.3)	1 (0.7)	7 (5.1)	14 (3.4)
Study Termination	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	3 (2.2)	1 (0.7)	0 (0.0)	4 (1.0)
Other	3 (2.2)	5 (3.6)	5 (3.6)	13 (3.1)

Most subjects completed the trial. However, the TAK-491 80 mg group had the highest percent of those who dropped out early.

Serious safety

Deaths

There were no deaths reported during the study.

Serious adverse events

The number and percent of subjects who reported a treatment-emergent serious safety adverse event after initiation of double-blind study drug and within 30 days after their last dose are shown below.

Table 12.f All SAEs - Safety Analysis Set

SOC Preferred Term	Placebo N=138	Subjects (%)		Total N=412
		TAK-491 40 mg N=137	TAK-491 80 mg N=137	
Subjects With Any Treatment-Emergent SAEs	0	3 (2.2)	1 (0.7)	4 (1.0)
Gastrointestinal disorders	0	0	1 (0.7)	1 (0.2)
Vomiting	0	0	1 (0.7)	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.7)	0	1 (0.2)
Diabetic ketoacidosis	0	1 (0.7)	0	1 (0.2)
Nervous system disorders	0	1 (0.7)	0	1 (0.2)
Cerebral hemorrhage	0	1 (0.7)	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	0	1 (0.7)	0	1 (0.2)
Asthma	0	1 (0.7)	0	1 (0.2)

While there were no serious adverse events reported by the placebo group, there were three subjects in TAK-491 40 mg and one subject in TAK-491 80 mg who reported a serious event. These four events are shown below.

Table 12.g Summary of Treatment-Emergent SAEs - Safety Analysis Set

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
TAK-491 40 mg					
0025/005	Diabetic ketoacidosis	11	Not related	Moderate	Resolved
0031/023	Cerebral hemorrhage	44	Not related	Severe	Resolved
0083/002	Asthma	20	Not related	Moderate	Resolved
TAK-491 80 mg					
0057/001	Vomiting (b)	20	Possible	Moderate	Resolved

Source: Table 15.3.2.2.

(a) As judged by the investigator.

(b) Study drug was discontinued.

The study drug was only discontinued prematurely for subject 0057/001. A cerebral hemorrhage was reported by subject 0031/023, a 57-year-old black woman randomized to TAK-491 40 mg. The event occurred on day 44, 2 days after discontinuation of study drug. The subject had a screening mean SBP of 172 mm Hg. Sitting blood pressures at week 2 and week 6 were 138/89 mmHg and 110/71 mmHg, respectively.

Discontinuations because of an adverse event

There were 6 subjects permanently discontinued the study because of an adverse event. These subjects are shown below.

Table 12.h Listing of Treatment-Emergent AEs Leading to Study Drug Discontinuation - Safety Analysis Set

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
Placebo					
0028/006	Blood pressure increased	9	Possible	Moderate	Resolved
TAK-491 40 mg					
0050/021	Arthritis	3	Not related	Mild	Not resolved
0075/039	Vertigo	11	Possible	Moderate	Not resolved
0088/005	Musculoskeletal stiffness	26	Not related	Mild	Resolving
TAK-491 80 mg					
0023/002	Hepatic enzyme increased	21	Definite	Severe	Resolved
0057/001	Vomiting (b)	20	Possible	Moderate	Resolved
0067/004	Worsening iron deficiency anemia (c)	-12	Not related	Moderate	Not resolved

Source: Table 15.3.2.1 and Appendix 16.2.7.1.

(a) As judged by the investigator.

(b) SAE.

(c) Subject 0067/004 experienced an AE of worsening iron deficiency anemia while taking placebo during Run-in. The subject was later randomized to TAK-491 80 mg and the AE continued. Study drug was discontinued.

Subject 0067/004 reported worsening iron deficiency anemia during the run in phase.

Subject 0023/002 (TAK-491 80 mg) reported hepatic enzyme increase from study day 21 to 63. The subject reported no relevant medical history, medication history, concurrent medical conditions, or concomitant medications. The subject reported a viral infection on study day 19 that resolved on day 26.

-Day 14: ALT and AST 465 U/L and 180 U/L, respectively.

-Day 21: the subject was discontinued from study drug.

-Day 26: ALT and AST 343 and 110 U/L, respectively.

-Day 35: ALT and AST 84 and 28 U/L, respectively.

Viral titer levels were unknown. Total bilirubin remained within normal limits throughout the duration of treatment.

All adverse events

Those adverse events reported by at least 2% of subjects in any treatment group are shown below.

Table 12.d Treatment-Emergent AEs Presented by Preferred Term With Incidence of ≥2% of Subjects In Any Treatment Groups - Safety Analysis Set

Preferred Term	Subjects (%)			
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137	Total N=412
Headache	3 (2.2)	6 (4.4)	9 (6.6)	18 (4.4)
Blood CK increased	6 (4.3)	4 (2.9)	3 (2.2)	13 (3.2)
Urinary tract infection	6 (4.3)	3 (2.2)	3 (2.2)	12 (2.9)
Plasminogen activator inhibitor increased	5 (3.6)	4 (2.9)	2 (1.5)	11 (2.7)
Dizziness	1 (0.7)	4 (2.9)	3 (2.2)	8 (1.9)
Oedema peripheral	1 (0.7)	4 (2.9)	3 (2.2)	8 (1.9)
Nasopharyngitis	3 (2.2)	2 (1.5)	2 (1.5)	7 (1.7)
Hyperlipidemia	1 (0.7)	3 (2.2)	1 (0.7)	5 (1.2)
Pain in extremity	1 (0.7)	1 (0.7)	3 (2.2)	5 (1.2)
Aspartate aminotransferase increased	0	1 (0.7)	3 (2.2)	4 (1.0)
C-reactive protein increased	3 (2.2)	0	1 (0.7)	4 (1.0)
Crystalline urine present	0	0	3 (2.2)	3 (0.7)

Source: Table 15.3.1.4.

Note: If a subject experienced more than 1 episode of an AE, it is counted only once within a SOC. Percentages are based on the total number of subjects in the safety analysis set for each treatment group.

Note: AEs are sorted by decreasing order of incidence based on the total number of AE reports.

CK=creatinine kinase.

Those events reported more often in both of the TAK-491 treatment groups compared to placebo include headache (TAK-491 40, 80 mg, and placebo: 4.4%, 6.6%, and 2.2%, respectively), dizziness (TAK-491 40, 80 mg, and placebo: 2.9%, 2.2%, and 0.7%, respectively) and edema (TAK-491 40, 80 mg, and placebo: 2.9%, 2.2%, and 0.7%, respectively).

Laboratory values

Serum Chemistry

Mean values at baseline, final visit and change from baseline at final visit for serum chemistries are shown below.

Table 12.i Summary of Serum Chemistry Changes From Baseline to Final Visit

Serum Chemistry	Placebo N=138		TAK-491 40 mg N=137		TAK-491 80 mg N=137	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Creatinine (μmol/L)						
Baseline (a)	138	83.7 (19.26)	137	85.1 (20.91)	136	84.1 (18.54)
Final Visit (b)	135	84.6 (19.33)	133	84.4 (19.43)	130	84.0 (17.73)
Change	135	0.9 (9.61)	133	-0.6 (9.25)	130	0.1 (11.31)
Potassium (mmol/L)						
Baseline (a)	138	4.15 (0.403)	137	4.09 (0.375)	136	4.14 (0.475)
Final Visit (b)	135	4.13 (0.436)	133	4.16 (0.419)	130	4.14 (0.422)
Change	135	-0.02 (0.378)	133	0.07 (0.388)	130	-0.01 (0.509)
Sodium (mmol/L)						
Baseline (a)	138	139.8 (2.29)	137	139.8 (2.12)	136	139.7 (1.89)
Final Visit (b)	135	140.3 (2.20)	133	139.9 (2.29)	130	139.6 (2.08)
Change	135	0.4 (2.28)	133	0.1 (2.17)	130	-0.2 (2.22)
Uric acid (μmol/L)						
Baseline (a)	138	329.5 (84.39)	137	331.3 (86.62)	136	325.8 (85.03)
Final Visit (b)	135	334.0 (79.71)	133	334.4 (93.57)	130	321.9 (86.79)
Change	135	3.8 (50.12)	133	3.9 (50.84)	130	-1.6 (50.06)
CK (U/L)						
Baseline (a)	138	211.9 (204.86)	137	208.3 (173.68)	136	212.1 (202.27)
Final Visit (b)	135	264.0 (527.59)	133	212.2 (193.20)	130	246.0 (395.58)
Change	135	53.2 (494.80)	133	2.6 (118.56)	130	29.8 (326.39)
ALT (U/L)						
Baseline (a)	138	26.6 (17.59)	137	24.6 (13.70)	136	24.5 (13.30)
Final Visit (b)	135	26.0 (15.11)	133	24.6 (14.06)	130	27.6 (31.51)
Change	135	-0.7 (11.52)	133	-0.2 (8.01)	130	3.1 (28.30)

**Table 12.i Summary of Serum Chemistry Changes From Baseline to Final Visit
(continued)**

Serum Lipid Chemistry	Placebo N=138		TAK-491 40 mg N=137		TAK-491 80 mg N=137	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Alkaline phosphatase (U/L)						
Baseline (a)	138	82.3 (23.25)	137	78.3 (21.85)	136	79.7 (21.22)
Final Visit (b)	135	82.2 (23.20)	133	79.0 (23.34)	130	80.5 (22.19)
Change	135	0.1 (8.16)	133	0 (8.30)	130	0.7 (9.58)
AST (U/L)						
Baseline (a)	138	25.8 (15.66)	137	22.9 (10.21)	136	24.5 (14.10)
Final Visit (b)	135	25.8 (14.72)	133	22.8 (8.06)	130	26.4 (17.83)
Change	135	0.1 (13.64)	133	-0.2 (7.00)	130	1.8 (10.77)
Total bilirubin (μmol/L)						
Baseline (a)	138	7.1 (3.50)	137	7.5 (4.28)	135	7.2 (3.63)
Final Visit (b)	135	7.0 (4.42)	133	7.0 (3.67)	129	6.5 (3.36)
Change	135	-0.1 (3.25)	133	-0.5 (2.88)	129	-0.6 (2.79)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

There were no consistent changes from baseline at final visit for any of the serum chemistry values in any of the treatment groups.

Mean values by study visit and changes from baseline for total cholesterol, HDL, calculated LDL cholesterol, and triglycerides are shown below.

Table 12.j Summary of Lipid Changes From Baseline to Final Visit

Serum Lipid Chemistry	Placebo N=138		TAK-491 40 mg N=137		TAK-491 80 mg N=137	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Total Cholesterol (mmol/L)						
Baseline (a)	114	5.066 (1.119)	111	4.989 (1.061)	113	5.138 (1.084)
Final Visit (b)	110	4.992 (1.176)	107	4.992 (1.089)	104	5.168 (1.058)
Change	110	-0.086 (0.511)	107	0.004 (0.599)	104	-0.023 (0.654)
HDL Cholesterol (mmol/L)						
Baseline (a)	114	1.381 (0.387)	111	1.468 (0.404)	113	1.446 (0.445)
Final Visit (b)	110	1.353 (0.356)	107	1.465 (0.470)	104	1.397 (0.458)
Change	110	-0.019 (0.165)	107	-0.005 (0.220)	104	-0.031 (0.162)
Calculated LDL Cholesterol (mmol/L)						
Baseline (a)	112	3.046 (0.855)	111	2.959 (0.941)	112	3.050 (1.012)
Final Visit (b)	108	3.018 (0.888)	105	2.949 (0.922)	102	3.111 (0.930)
Change	108	-0.040 (0.459)	105	-0.003 (0.555)	102	0.003 (0.550)
Triglycerides (mmol/L)						
Baseline (a)	114	1.420 (1.449)	111	1.231 (0.625)	113	1.388 (0.952)
Final Visit (b)	110	1.344 (1.494)	107	1.359 (1.239)	104	1.447 (1.253)
Change	110	-0.098 (0.496)	107	0.114 (1.126)	104	0.030 (0.730)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

Mean changes in all treatment groups were small and probably not clinically meaningful.

Marked serum chemistry abnormalities reported during the double-blind treatment period are shown below by treatment group.

Table 12.k Marked Abnormalities in Serum Chemistries During Treatment - Safety Analysis Set

Laboratory Test	Subjects n/N (%)		
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
ALT >3×ULN	0/135	1/133 (0.8)	2/131 (1.5)
AST >3×ULN	2/135 (1.5)	1/133 (0.8)	3/131 (2.3)
CK total >10×ULN	2/135 (1.5)	1/133 (0.8)	1/131 (0.8)
Creatinine >1.5×BL	1/135 (0.7)	0/133	2/131 (1.5)
GGT >3×ULN	9/135 (6.7)	6/133 (4.5)	7/131 (5.3)
Potassium <3.0 mmol/L,	1/135 (0.7)	0/133	2/131 (1.5)
Potassium >6.0 mmol/L	0/135	0/133	0/131
Uric acid >625 μmol/L (M), >506 μmol/L (F)	2/135 (1.5)	0/133	2/131 (1.5)

Source: Tables 15.3.4.3 and 15.3.4.8.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline results are summarized in this table.

M=male subject, F=female subject.

The reporting rates of marked abnormal chemistry values were infrequent and similar across treatment groups.

Abnormal creatinine values¹ were reported by one subject (0.7%) in the placebo group and 2 subjects (1.5%) in the TAK-491 80 mg group. By the final visit only the 2 subjects in the 80 mg TAK-491 treatment group still had creatinine values that were markedly abnormal.

Subject 0033/038 (TAK-491 80 mg) had a history of hypertension. Serum creatinine levels on day -28 and day 1 were 0.8 mg/dL and 0.6 mg/dL, respectively. On day 49 the creatinine value had increased to 1.2 mg/dL and urinalysis revealed WBC of > 50/hpf with +4 bacteriuria. There were no reported adverse events.

The table below shows the percentage of subjects with a creatinine elevation at any postbaseline visit during the study and at final visit, by treatment group.

¹Defined as >1.5× baseline value

Table 12.l Summary of Subjects With a Creatinine Elevation - Safety Analysis Set

	Subjects n/N (%)		
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
Subjects with Creatinine Elevations During Treatment			
≥30% from BL and >ULN	3/135 (2.2)	1/133 (0.8)	3/130 (2.3)
≥50% from BL and >ULN	1/135 (0.7)	0/133	1/130 (0.8)
Subjects with Creatinine Elevations at Final Visit (a)			
≥30% from BL and >ULN	1/135 (0.7)	1/133 (0.8)	1/130 (0.8)
≥50% from BL and >ULN	0/135	0/133	1/130 (0.8)

Source: Table 15.3.4.9 and Appendix 16.2.8.3.3.

(a) LOCF. Narratives are provided in Section 15.3.3.4.

BL=Baseline.

Hematology

Marked hematology abnormalities that occurred during the Double-Blind Treatment Period are shown in below.

Table 12.m Marked Abnormalities in Hematology During Treatment - Safety Analysis Set

Laboratory Test	Subjects n/N (%)		
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
Hematocrit/PCV (Ratio)	0/135	1/133 (0.8)	0/131
<0.8 × Baseline			
Platelet count	0/134	0/132	0/130
<50×10 ⁹ /L or >700×10 ⁹ /L			
WBC	0/135	0/133	0/131
<2×10 ⁹ /L or >20×10 ⁹ /L			

Source: Tables 15.3.4.1 and 15.3.4.8.

Note: A subject was classified as having marked abnormalities if at least 1 test result during treatment was considered markedly abnormal.

PCV=packed cell volume.

These abnormalities were rarely reported.

Urinalysis and vital signs

There were no patterns of urinalysis abnormalities, no remarkable differences in weight changes and no meaningful differences in sitting pulse.

ECG

There were no clinically meaningful changes in either the magnitude or direction of mean change for any ECG results, no subjects with abnormal, clinically significant ECG results at the final visit, and no remarkable changes from baseline to final visit with respect to the overall clinical interpretation of the 12-lead ECG. No subjects had a treatment-emergent adverse events because of ECG changes.

Reviewer's summary and conclusions

Efficacy: at week 6, the placebo subtracted differences in 24-hour mean SBP for TAK-491 40 and 80 mg were -5 and -8 mmHg, respectively. The placebo subtracted differences in 24-hour mean DBP for TAK-491 40 and 80 mg were -3 and -6 mmHg, respectively. The differences were significant compared to placebo but numerically less than those obtained from non black subjects in other studies.

Safety: Those events reported more often in both of the TAK-491 treatment groups compared to placebo include headache, dizziness, and edema.

Conclusions: TAK-491 is reasonably safe and effective in the black hypertensive population.

Study -06-TL-491-016

01-06-TL-491-016 (491-016)	Open-label phase followed by double-blind phase	Subjects with essential hypertension (DBP=95-119 mm Hg; for subjects with diabetes or chronic kidney disease, DBP=85-109 mm Hg)	32 weeks	<u>Open-label:</u> TAK-491 20 mg
49-United States and Latin America	<u>Open-label:</u> 26-week, titrate-to-target phase with possible addition of CLD (followed by AHT, if needed)	<u>Open-label:</u> 418 subjects	<u>Open-label:</u> 26 weeks	TAK-491 40 mg
22 June 2007-08 May 2009	<u>Double-blind:</u> Randomized, placebo-controlled, 6-week reversal phase using placebo or final OL titrated TAK-491 dose, in addition to their final OL other AHT, including CLD, as applicable	<u>Double-blind:</u> 299 subjects	<u>Double-blind:</u> 6 weeks	TAK-491 80 mg
	Safety and tolerability (OL+DB) (Change from BL [Week 26] to Final Visit in trough clinic sitting DBP [DB only])			TAK-491 80 mg with CLD 25 mg
				TAK-491 80 mg with CLD 25 mg with AHT
				<u>Open-label:</u> 418/299
				<u>Double-blind:</u> TAK-491 dose in OL
				TAK-491 dose in OL with CLD 25 mg
				TAK-491 dose in OL with CLD 25 mg and AHT
				Placebo
				Placebo with CLD 25 mg
				Placebo with CLD 25 mg and AHT
				<u>Double-blind:</u> 299/282
				TAK-491: 148/137
				Placebo: 151/145

Title: An 8-Month Phase 3, Open-Label Study With a Blinded Reversal Phase to Evaluate the Safety and Tolerability of TAK-491 in Subjects With Essential Hypertension

Investigators: 49 investigators in the United States and Latin America

Study Period: 22 June 2007 to 08 May 2009

Primary objective: to evaluate safety and tolerability of treatment with TAK-491 for 26 weeks in subjects with essential hypertension.

Secondary: to evaluate long-term efficacy of TAK-491 in a placebo-controlled, double-blind reversal phase after 26 weeks of open-label TAK-491 treatment in subjects with essential hypertension.

METHODOLOGY

This was a multicenter study consisting of 2 phases. The first phase was a 26-week open-label study in which subjects with essential hypertension were treated according to a titration-to-target blood pressure approach. After a 7-day screening period, eligible subjects were enrolled at a starting dose of TAK-491 40 mg once daily (QD). At Week 4, if the initial dose was tolerable, the dose was increased to TAK-491 80 mg QD. At Weeks 8 through 22, investigators could have added chlorthalidone and other antihypertensive agents in order to achieve the subject's target blood pressure. No dose titrations were to be made at or after Week 22. The results from this phase of the study is in the safety review.

Double-Blind Reversal Phase

The second phase was a 6-week, randomized, double-blind, placebo-controlled reversal study. At Week 26, subjects discontinued open label TAK-491 and were randomized to either TAK-491 at their final dose level at Week 26 or placebo, in addition to their current other antihypertensive medications, as applicable.

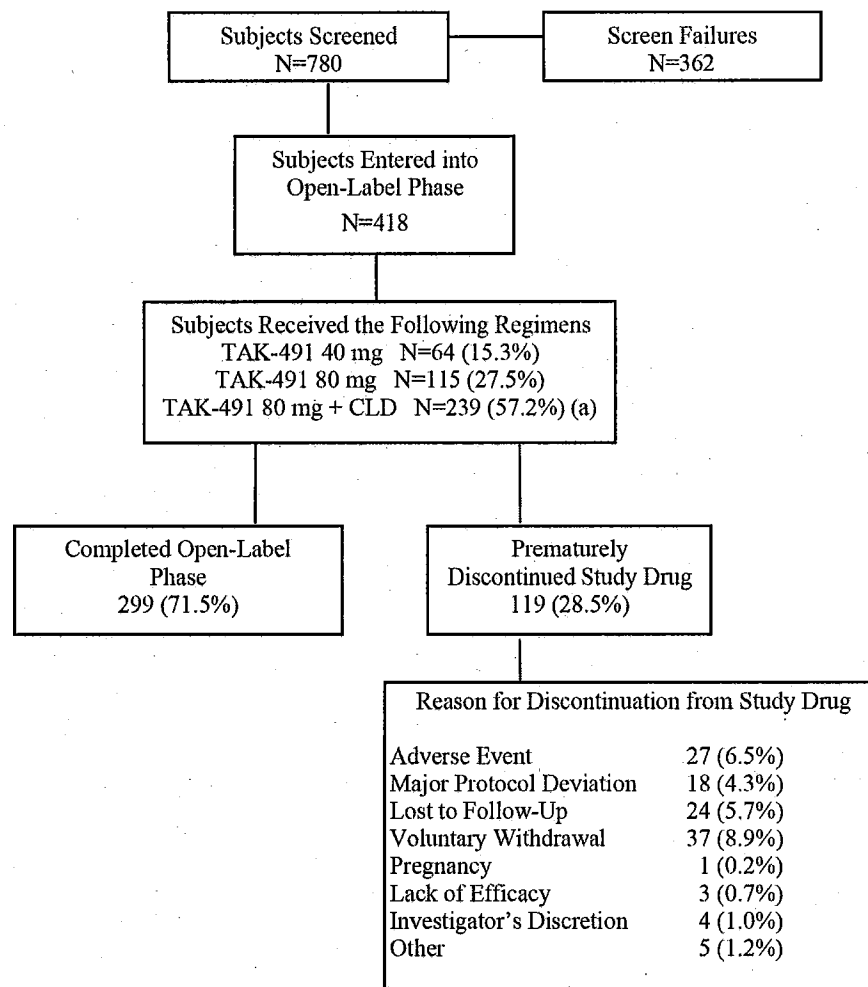
At the time of randomization, subjects receiving TAK-491 in combination with chlorthalidone were balanced between the placebo (92 [60.9%]) and TAK-491 (87 [58.8%]) groups.

Diagnosis and Main Criteria for Inclusion: to qualify for study participation, subjects must have been males or nonpregnant, nonlactating females at least 18 years of age, with essential hypertension (diastolic blood pressure [DBP] between 95 and 119 mm Hg, inclusive, or between 85 and 109 mm Hg, inclusive, for subjects with diabetes or chronic kidney disease); with clinical laboratory evaluations within the reference range for the testing laboratory; willing to discontinue antihypertensive medications at Screening Visit; and able to comprehend and willing to sign an informed consent form.

Efficacy: the primary efficacy endpoint was the change from Double-Blind Baseline (Week 26) to Final Visit during the double-blind reversal phase for trough clinic sitting DBP. The secondary efficacy endpoint was the change from Double-Blind Baseline (Week 26) to Final Visit during the double-blind reversal phase for trough clinic sitting SBP.

Doses used during the open label phase are shown in the figure below.

Figure 10.a Disposition of Subjects (Open-Label Phase)



Demographics: the table below shows the baseline characteristics of the subjects who went into the randomized, double blind treatment phase.

No important differences were observed between the treatment groups in demographic and Baseline characteristics in the FAS in the double-blind reversal phase.		
Characteristic	Placebo N=151	TAK-491 N=148
Sex, n (%)		
Male	77 (51.0)	72 (48.6)
Female	74 (49.0)	76 (51.4)
Age, years		
Mean (SD)	51.8 (9.72)	52.9 (9.59)
Min - Max	28 - 83	27 - 77
≥65, n (%)	11 (7.3)	18 (12.2)
Race, n (%)		
American Indian or Alaska Native	9 (6.0)	10 (6.8)
Asian	2 (1.3)	1 (0.7)
Black or African American	38 (25.2)	30 (20.3)
White	104 (68.9)	107 (72.3)
Multiracial	2 (1.3)	0
Body mass index, kg/m²		
Mean (SD)	32.94 (6.484)	33.61 (6.279)
Min - Max	20.3 - 57.9	22.2 - 53.4

Trough clinic sitting DBP

The primary efficacy endpoint was the change from double-blind baseline (Week 26) to final visit during the double-blind reversal phase for trough clinic sitting DBP. The baseline (at the end of the 26-week open label phase) and weeks 28, 30 and 32 (or last double blind visit) blood pressures are shown below.

**Table 11.c Summary of the Primary Analysis for the Primary Efficacy Variable:
Change From Double-Blind Baseline to Final Visit in Trough Clinic Sitting
DBP (mm Hg) - (LOCF, FAS)**

Study Visit	Treatment Group	
	Placebo N=151	TAK-491 N=148
Double-Blind Baseline/Week 26(a)	N=148	N=142
LS mean (SE)	82.25 (0.766)	83.50 (0.782)
P-value		0.255(b)
Week 28	N=137	N=129
LS mean change (SE)	5.95 (0.731)	-0.99 (0.753)
LS mean difference(c)		-6.94
95% CI		(-9.01, -4.88)
P-value		<0.001*(d)
Week 30	N=146	N=138
LS mean change (SE)	7.20 (0.714)	-1.31 (0.734)
LS mean difference(c)		-8.51
95% CI		(-10.53, -6.50)
P-value		<0.001*(d)
Final Visit/Week 32(e)	N=148	N=142
LS mean change (SE)	7.92 (0.712)	0.14 (0.726)
LS mean difference(c)		-7.78
95% CI		(-9.78, -5.78)
P-value		<0.001*(d)

Source: Table 15.2.1.1.2.

* Significant difference at 0.05 level.

(a) Double-Blind Baseline is the last observation before the first dose of double-blind study drug.

(b) P-value from a 1-way analysis of variance with term for treatment.

(c) LS mean difference=LS mean change of TAK-491 - LS mean change of placebo group.

(d) P-value from ANCOVA with terms for treatment (as a factor) and Double-Blind Baseline value (as a covariate).

(e) Final Visit was also Week 32 using LOCF.

Beginning at the first double-blind blood pressure measurement (Week 28) and continuing through the last measurement (Week 32), mean DBP and mean SBP were maintained in subjects who received TAK-491; in contrast, mean DBP and mean SBP increased among subjects who received placebo. The LS mean difference between TAK-491 and placebo at each scheduled double-blind dosing visit was statistically significantly different for both DBP and SBP ($P<0.001$).

Trough clinic sitting SBP

The baseline (at the end of the 26-week open label phase) and weeks 28, 30 and 32 (or last double blind visit) blood pressures are shown below.

**Table 11:d Summary of the Primary Analysis for the Secondary Efficacy Variable:
Change From Double-Blind Baseline to Final Visit in Trough Clinic Sitting
SBP (mm Hg) - (LOCF, FAS)**

Study Visit	Treatment Group	
	Placebo N=151	TAK-491 N=148
Double-Blind Baseline/Week 26(a)	N=148	N=142
LS mean (SE)	128.24 (1.321)	129.79 (1.349)
P-value		0.410(b)
Week 28	N=137	N=129
LS mean change (SE)	11.67 (1.087)	-0.83 (1.121)
LS mean difference(c)		-12.50
95% CI		(-15.58, -9.43)
P-value		<0.001*(d)
Week 30	N=146	N=138
LS mean change (SE)	12.48 (1.051)	-1.64 (1.082)
LS mean difference (c)		-14.11
95% CI		(-17.08, -11.14)
P-value		<0.001*(d)
Final Visit/Week 32(e)	N=148	N=142
LS mean change (SE)	12.97 (1.098)	0.59 (1.121)
LS mean difference(c)		-12.38
95% CI		(-15.47, -9.29)
P-value		<0.001*(d)

Source: Table 15.2.2.1.2.

* Significant difference at 0.05 level.

(a) Double-Blind Baseline is the last observation before the first dose of double-blind study drug.

(b) P-value from a 1-way analysis of variance with term for treatment.

(c) LS mean difference=LS mean change of TAK-491 - LS mean change of placebo group.

(d) P-value from ANCOVA with terms for treatment (as a factor) and Double-Blind Baseline value (as a covariate).

(e) Final Visit was also Week 32 using LOCF.

Beginning at the first double-blind SBP measurement (Week 28) and continuing through the last measurement (Week 32), mean SBP was maintained in subjects who continued to receive TAK-491. In contrast, mean SBP increased among subjects who received placebo, demonstrating a loss of efficacy after discontinuation of TAK-491.

Safety Results:

In the open-label phase, the most commonly reported adverse events were dizziness (8.9%) and headache (7.2%). Headache was the only adverse event reported by >5.0% of subjects (5.3% in the placebo group) in the double-blind phase.

Twenty-nine subjects (6.9% overall) in the open-label phase and 5 subjects (2 [1.3%] placebo and 3 [2.0%] TAK-491) in the double-blind reversal phase permanently or temporarily discontinued from study drug, at least in part because of safety issues.

Serious adverse events were reported for 8 subjects (1.9%) during the open-label phase. One placebo subject (0.7%) experienced a serious adverse event (hypertensive crisis) on Day 13 of the double-blind reversal phase. The event resolved on the following day. No deaths occurred during the open-label or double-blind reversal phase of the study.

Clinical laboratory parameters

Elevations of serum creatinine, BUN, and uric acid were more common in subjects who received TAK-491 plus chlorthalidone. Serum creatinine generally returned to baseline or near baseline levels either during treatment or after discontinuing study medication.

The table below shows the mean changes from open label baseline to week 26 for serum chemistries.

Table 12.o Serum Chemistry: Mean Changes From Open-Label Baseline to Week 26 Visit During the Open-Label Phase (Safety Analysis Set)

Serum Chemistry Parameter (unit)	TAK-491 N=179		TAK-491 plus CLD N=239		Total N=418	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
ALT (U/L)						
Open-Label Baseline (a)	179	31.5 (17.64)	239	30.0 (16.36)	418	30.6 (16.92)
Week 26	101	32.5 (21.84)	205	30.5 (19.73)	306	31.1 (20.43)
Change	101	1.9 (12.19)	205	0.4 (14.78)	306	0.9 (13.98)
AST (U/L)						
Open-Label Baseline (a)	179	26.3 (13.21)	239	25.0 (11.71)	418	25.5 (12.37)
Week 26	101	25.2 (14.32)	205	25.1 (14.29)	306	25.1 (14.28)
Change	101	0.8 (9.59)	205	-0.2 (12.82)	306	0.1 (11.85)
Alkaline phosphatase (U/L)						
Open-Label Baseline (a)	179	81.7 (26.28)	239	79.2 (23.70)	418	80.3 (24.84)
Week 26	101	75.0 (24.46)	205	73.6 (22.32)	306	74.1 (23.02)
Change	101	-5.8 (10.14)	205	-5.7 (12.39)	306	-5.7 (11.68)
Bilirubin, total (umol/L)						
Open-Label Baseline (a)	179	8.2 (3.89)	239	8.3 (3.99)	418	8.3 (3.95)
Week 26	101	7.5 (3.14)	205	7.5 (3.71)	306	7.5 (3.53)
Change	101	-0.8 (3.00)	205	-0.8 (3.33)	306	-0.8 (3.22)
Calcium (mmol/L)						
Open-Label Baseline (a)	179	2.392 (0.1025)	239	2.389 (0.1119)	418	2.390 (0.1079)
Week 26	101	2.396 (0.1062)	205	2.430 (0.0985)	306	2.419 (0.1022)
Change	101	0.005 (0.1054)	205	0.039 (0.1099)	306	0.028 (0.1095)
CK total (U/L)						
Open-Label Baseline (a)	179	141.0 (108.06)	239	188.8 (662.26)	418	168.3 (505.83)
Week 26	100	131.9 (85.86)	205	158.4 (153.14)	305	149.7 (135.25)
Change	100	-1.7 (54.62)	205	-40.1 (658.69)	305	-27.5 (540.79)
Creatinine (umol/L)						
Open-Label Baseline (a)	179	78.7 (18.75)	239	83.7 (20.44)	418	81.5 (19.87)
Week 26	101	81.4 (19.79)	205	94.3 (23.96)	306	90.0 (23.44)
Change	101	3.1 (12.98)	205	11.0 (16.53)	306	8.4 (15.86)

Footnotes for Table 12.o appear on the following page.

Glucose, fasting serum (mmol/L)						
Open-Label Baseline (a)	179	5.82 (1.202)	239	5.89 (1.381)	418	5.86 (1.306)
Week 26	100	6.03 (1.524)	205	6.26 (1.984)	305	6.19 (1.847)
Change	100	0.32 (1.212)	205	0.37 (1.341)	305	0.35 (1.298)
Potassium (mmol/L)						
Open-Label Baseline (a)	179	4.19 (0.375)	239	4.14 (0.401)	418	4.16 (0.390)
Week 26	101	4.36 (0.352)	205	4.13 (0.467)	306	4.21 (0.445)
Change	101	0.21 (0.357)	205	-0.01 (0.433)	306	0.06 (0.422)
Sodium (mmol/L)						
Open-Label Baseline (a)	179	139.3 (2.19)	239	139.7 (2.15)	418	139.5 (2.18)
Week 26	101	138.9 (2.63)	205	138.9 (2.94)	306	138.9 (2.84)
Change	101	-0.5 (2.41)	205	-0.8 (3.01)	306	-0.7 (2.83)
Uric acid (umol/L)						
Open-Label Baseline (a)	179	350.9 (93.01)	239	359.2 (90.65)	418	355.6 (91.65)
Week 26	101	355.9 (90.50)	205	424.3 (109.55)	306	401.7 (108.40)
Change	101	9.8 (46.24)	205	62.2 (86.09)	306	44.9 (79.17)

Source: Table 15.3.4.5.1.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of open-label study drug.

Mean creatinine was higher at open-label baseline in subjects who additionally received chlorthalidone (83.7 umol/L) than for subjects who received TAK-491 alone (78.7 umol/L). At Week 26, the mean increase from Open-Label Baseline in creatinine was 3.1 umol/L for subjects who received TAK-491 alone and 11.9 umol/L for subjects who additionally received chlorthalidone. There were no reported study discontinuations for elevated serum creatinine or renal impairment.

The mean change from double blind baseline to final visit for serum creatinine is shown below.

Table 12.q Serum Chemistry: Mean Changes From Double-Blind Baseline to Final Visit During the Double-Blind Reversal Phase (FAS) (Continued)

Serum Chemistry Parameter (unit)	Treatment Group			
	Placebo N=151		TAK-491 N=148	
	N	Mean (SD)	N	Mean (SD)
Creatinine (umol/L)				
Double-Blind Baseline	151	90.6 (22.76)	146	89.1 (24.05)
Final Visit	146	86.5 (19.19)	142	89.4 (24.93)
Change	146	-4.5 (12.42)	142	1.7 (19.13)

The group randomized to placebo had a drop in serum creatinine level of 4.5 umol/L compared to a small increase of 1.7 umol/L in the group remaining on TAK-491.

The following two subjects withdrew from the double blind treatment phase because of renal adverse events:

Subject 0021/015 (TAK-491), a 48 year old white male subject, discontinued from the study with an adverse event of renal impairment. The subject had relevant medical history of hypercholesterolemia, anxiety, and tobacco abuse, and entered the study with baseline values for serum creatinine, BUN, and potassium of 1.0 mg/dL, 12 mg/dL, and 3.8 mEq/L, respectively. Concomitant medications included fenofibrate and rosuvastatin calcium. Markedly abnormal creatinine values were reported at Week 8 (Day 58; 1.6 mg/dL) and Week 26 (Day 182; 1.9 mg/dL). Also at Weeks 8 (Day 58) and 26 (Day 182), BUN was 28 mg/dL and 33 mg/dL, respectively, and potassium was 5.0 mEq/L and 4.8 mEq/L, respectively. Renal impairment was recorded on Day 182 based on these abnormal laboratory findings and study drug was prematurely discontinued. The subject reported had no symptoms. The creatinine value returned to near Baseline level at the final measurement on Day 192.

Subject 0022/004 (TAK-491), a 58-year-old White female subject with history of edema peripheral, type 2 diabetes mellitus, and osteoarthritis, entered the study with a Baseline uric acid value within normal limits. Concomitant medications included (amlodipine/atorvastatin), (metformin/pioglitazone), and acetylsalicylic acid. Uric acid values increased through the duration of the study. Baseline uric acid and creatinine were 4.9 mg/dL and 1.0 mg/dL, respectively. The abnormal values for serum creatinine and uric acid were 1.1 mg/dL and 6.9 mg/dL at Week 26 (Day 180), which was reported as renal impairment on Day 200. The study drug was prematurely discontinued. The event was considered probably related to study drug and was ongoing at the end of the study. The subject was asymptomatic. The uric acid level was markedly abnormal (8.8 mg/dL) at the final measurement on Day 207 and serum creatinine was 1.2 mg/dL.

Reviewer's summary and conclusions

Efficacy: after 26 weeks of open label TAK-491, subjects were randomized either TAK-491 at their final dose level at Week 26 or placebo, in addition to their current other antihypertensive medications, as applicable. Beginning at the first double-blind blood pressure measurement (Week 28) and continuing through the last measurement (Week 32), mean DBP and mean SBP were maintained in subjects who received TAK-491; in contrast, mean DBP and mean SBP increased among subjects who received placebo. The LS mean difference between TAK-491 and placebo at each scheduled double-blind dosing visit was statistically significantly different for both DBP and SBP ($P < 0.001$).

Safety: headache and dizziness were the most frequently reported adverse events.

Conclusions: in this withdrawal trial, subjects who received open label TAK-491 for 26 weeks and then were randomized to placebo experienced an increase in their SBP and DBP. On the other hand, subjects who were randomized to continued TAK-491 experienced little change in their blood pressure. Safety was unremarkable.

Study 01-05-TL-491-009

Study No. (Study Abbreviation) No. of Sites-Country (a)					Treatment(s) (d) Randomized/Completed (e)	
Study Start- End Dates	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)			
01-05-TL-491-009 (491-009) 74-United States and Latin America 07 September 2007- 05 March 2009	Double-blind, randomized, placebo-controlled, parallel-group, 3- group Antihypertensive effect of TAK-491 when coadministered with CLD compared with CLD monotherapy (Change from BL to Week 6 in 24-hr mean SBP by ABPM)	551 subjects with moderate-to- severe essential hypertension (clinic SBP=160-190 mm Hg; 24-hour mean SBP= 140-180 mm Hg)	6 weeks		A: TAK-491 40 mg with CLD 25 mg B: TAK-491 80 mg with CLD 25 mg C: Placebo with CLD 25 mg 551/495 A: 185/169 B: 182/158 C: 184/168	

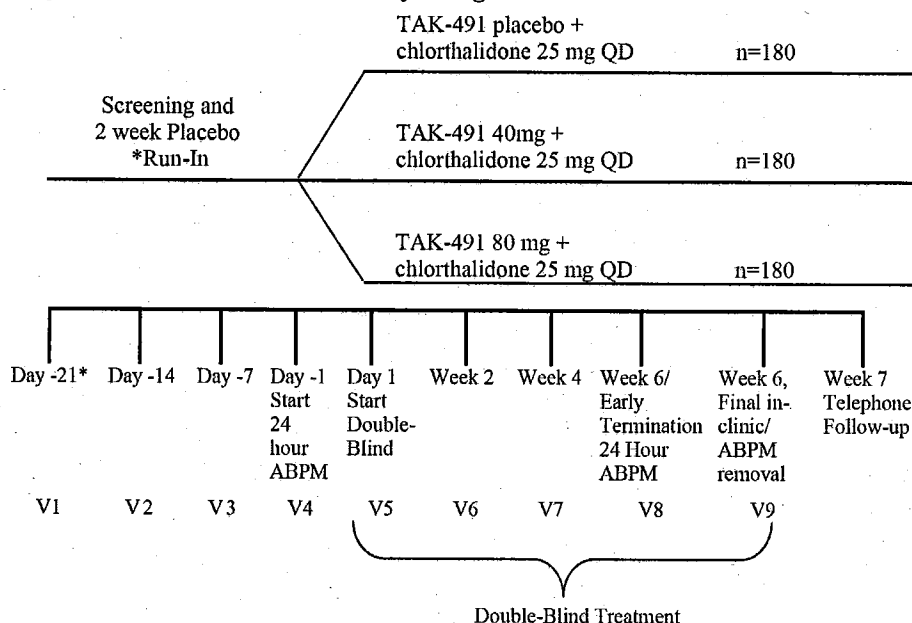
This was a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of TAK-491 when co-administered with chlorthalidone in subjects with essential hypertension.

There were 74 principle investigators in the United States and Latin America who randomized 551 subjects (4 randomized subjects did not receive study drug). The subjects were men or nonpregnant, nonlactating women at least 18 years of age with uncontrolled essential hypertension (clinic sitting SBP ≥ 160 mm Hg and ≤ 190 mm Hg inclusive, and 24-hour mean SBP ≥ 140 mm Hg and ≤ 180 mm Hg on day -1).

The primary endpoint was change from baseline at Week 6 in the 24 hour mean SBP as measured by ambulatory blood pressure monitor (ABPM).

After a 2-week run-in period of single-blind placebo, subjects who met the entry criteria were randomized to receive placebo plus chlorthalidone 25 mg QD (chlorthalidone monotherapy), TAK-491 40 mg QD plus chlorthalidone 25 mg QD, or TAK-491 80 mg QD plus chlorthalidone 25 mg QD for 6 weeks. ABPM was recorded day -1 for 24 hours prior to the first dose of double-blind study medication and at week 6 or early termination for 24 hours following the last administration of study medication. This is shown in the figure below.

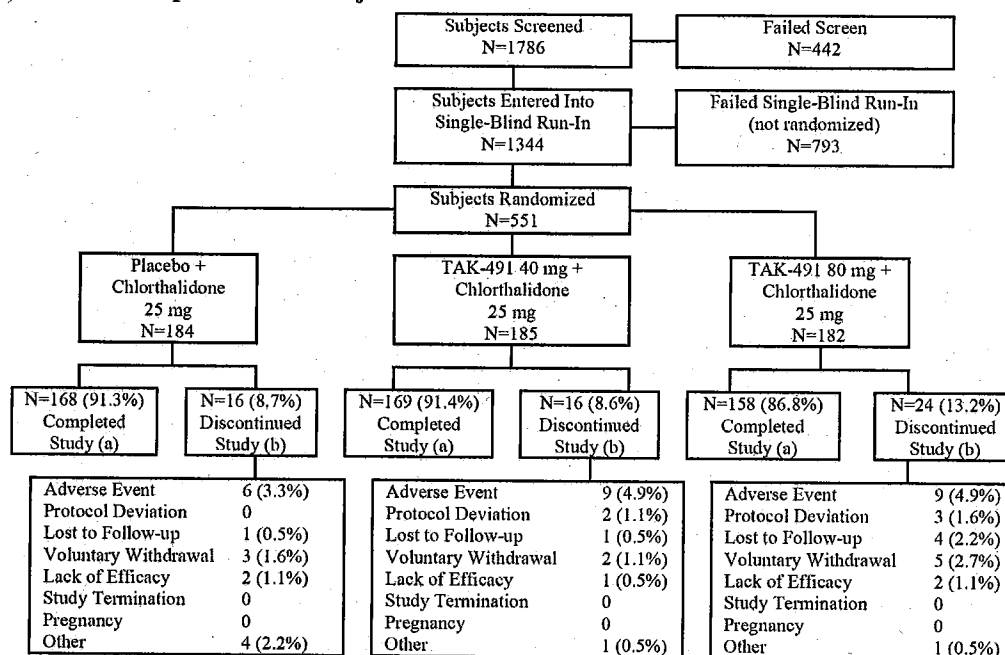
Figure 9.a Schematic of Study Design



*Note: If the subject was on amlodipine, the subject should have discontinued this medication at Screening Day-28 extending the screening period for an additional 7 days (for a total of 14 days of Screening) for washout of medication prior to the single-blind placebo Run-In Period.

There were 551 subjects randomized subjects. Three subjects were withdrawn before study drug was given and are not included in any of the analyses (2 in TAK-491 40 mg plus chlorthalidone and 1 in chlorthalidone monotherapy).

Figure 10.a Disposition of Subjects



Source: Tables 15.1.1, 15.1.2, and 15.1.4 and Appendix 16.2.1.2.

(a) For the purpose of this disposition figure, subjects who completed study were calculated as the total number randomized per treatment group minus those who discontinued.

(b) Subjects could have had more than 1 reason for discontinuation; only the primary reason is presented here. Withdrawal categories are described in Section 9.3.3.

The percentage of subjects who prematurely discontinued for any reason was 8.7% in the chlorthalidone monotherapy group, 8.6% in the TAK-491 40 mg plus chlorthalidone coadministration group, and 13.2% in the TAK-491 80 mg plus chlorthalidone coadministration group. The highest withdrawal rate, in the TAK-491 80 mg plus chlorthalidone coadministration group, had more voluntary withdrawals and lost to follow-up. A higher rate of withdrawals for adverse events cannot be ruled out for this treatment group.

Demographics

Demographic characteristics were similar across treatment groups. The average age was 59 years, there were slightly more men (52%) than women, 29% of subjects were at least 65 years of age, 59 % were white and 16% were black.

Baseline blood pressures are shown below.

Table 10.b Summary of Baseline Efficacy Parameters (Randomized Subjects)

	Treatment Group			P-value (a)
	Placebo + Chlorthalidone 25 mg N=184	TAK491 40 mg + Chlorthalidone 25 mg N=185	TAK491 80 mg + Chlorthalidone 25 mg N=182	
Blood Pressure by ABPM (mm Hg)				
n	179	181	177	
0- to 24-hour mean SBP				0.187
Mean (SD)	153.21 (9.343)	151.93 (9.401)	151.43 (9.729)	
Mean daytime (6 AM-10 AM) SBP				0.093
Mean (SD)	156.81 (9.486)	155.54 (9.310)	154.59 (10.019)	
Mean nighttime (12 AM-6 AM) SBP				0.783
Mean (SD)	142.21 (13.011)	141.24 (13.906)	141.96 (13.956)	
0- to 12-hour mean SBP				0.088
Mean (SD)	157.24 (9.881)	156.10 (9.658)	154.89 (10.459)	
Trough (22-24 hours) SBP				0.284
Mean (SD)	157.17 (12.398)	155.85 (13.059)	155.03 (13.098)	
0- to 24-hour mean DBP				0.751
Mean (SD)	89.72 (10.415)	90.44 (10.776)	90.47 (10.700)	
Mean daytime (6 AM-10 PM) DBP				0.809
Mean (SD)	93.09 (11.070)	93.82 (11.293)	93.65 (10.966)	
Mean nighttime (12 AM-6 AM) DBP				0.479
Mean (SD)	80.00 (10.872)	81.15 (11.936)	81.40 (12.137)	
0- to 12-hour mean DBP				0.864
Mean (SD)	93.55 (11.751)	94.21 (11.681)	93.94 (11.408)	
Trough (22-24 hours) DBP				0.617
Mean (SD)	94.98 (11.650)	96.03 (13.101)	96.13 (11.796)	
Clinic Blood Pressure (b) (mm Hg)				
n	181	184	182	
Clinic SBP				0.867
Mean (SD)	165.64 (14.461)	166.43 (13.587)	166.06 (14.207)	
Clinic DBP				0.488
Mean (SD)	93.36 (12.470)	94.76 (11.559)	94.44 (11.019)	

Source: Tables 15.1.8.1 and 15.1.8.2.

Note: Baseline value is the last observation before the first dose of double-blind study drug.

(a) The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

(b) SBP and DBP are based on the arithmetic mean of the 3 trough clinic sitting blood pressure measurements.

Baseline blood pressure were similar across treatment groups.

Medical history and current medical conditions were similar across treatment groups. The groups were also similar regarding past and current medications.

Efficacy

The change from baseline in 24-hour mean SBP as assessed by ABPM are shown below.

Table 11.a Change From Baseline to Week 6 in 24-hour Mean SBP by ABPM (FAS)

Study Visit	Treatment Group			Overall P-Value
	Placebo + Chlorthalidone 25 mg N=181	TAK491 40 mg + Chlorthalidone 25 mg N=184	TAK491 80 mg + Chlorthalidone 25 mg N=182	
Baseline	n=152	n=149	n=147	
LS mean (SE)	153.36 (0.766)	152.01 (0.774)	151.88 (0.779)	
Week 6				
LS mean change (SE)	-15.85 (0.957)	-31.72 (0.966)	-31.30 (0.973)	<0.001*
LS mean difference (a)		-15.86	-15.45	
(95% CI)		(-18.54, -13.19)	(-18.13, -12.76)	
P-value vs placebo + chlorthalidone		<0.001*	<0.001*	
Week 6: Sensitivity analysis using multiple imputation				
LS mean difference (a)		-15.86	-15.39	<0.001*
(95% CI)		(-18.61, -13.11)	(-18.01, -12.76)	
P-value vs placebo + chlorthalidone		<0.001*	<0.001*	

Source: Table 15.2.1.1.2.

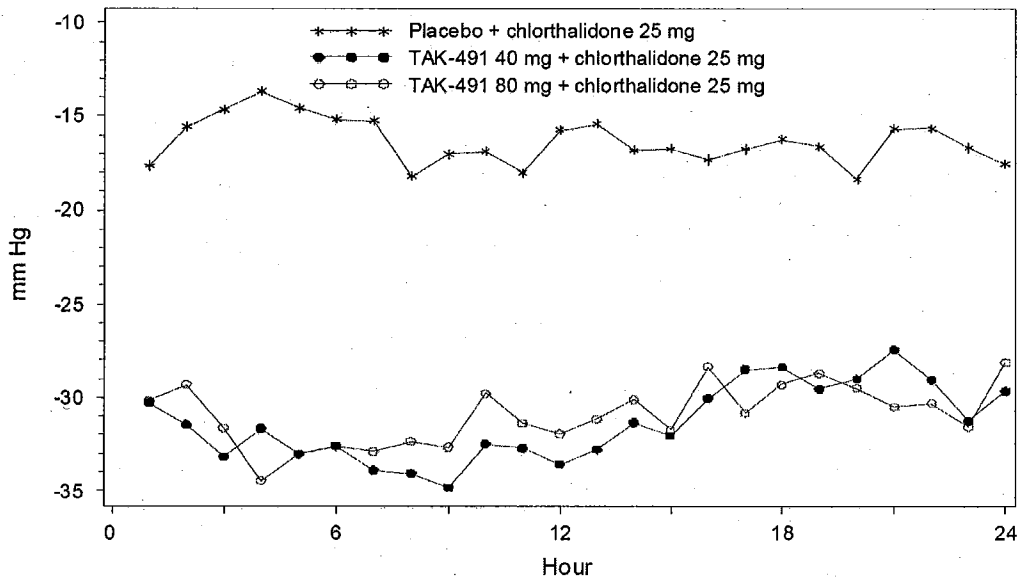
Analyses include subjects with both a baseline and postbaseline value.

* Significant difference at the 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 plus chlorthalidone coadministration group) – LS mean change of placebo group (chlorthalidone monotherapy group).

The baseline SBP values were around 152 mmHg for each treatment group. After 6 weeks the decrease from baseline was 16 mmHg for the chlorthalidone group. There was no difference between the TAK-491 plus chlorthalidone groups in the change in SBP from baseline (-31 mmHg from baseline). According to these results, both doses of TAK-491 decrease SBP an additional 15 mmHg when added to chlorthalidone.

Figure 11.a Change From Baseline to Week 6 in Mean SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)



DBP

Baseline and changes from baseline at week 6 are shown below by treatment group.

Table 11.c Change From Baseline to Week 6 in the 24-hour Mean DBP by ABPM (FAS)

Study Visit (mm Hg)	Treatment Group			Overall P-Value
	Placebo + Chlorthalidone 25 mg N=181	TAK491 40 mg + Chlorthalidone 25 mg N=184	TAK491 80 mg + Chlorthalidone 25 mg N=182	
Baseline	n=152	n=149	n=147	
LS mean (SE)	89.79 (0.854)	90.45 (0.863)	90.07 (0.869)	
Week 6				
LS mean change (SE)	-7.99 (0.619)	-18.28 (0.626)	-18.49 (0.630)	<0.001*(b)
LS mean difference (SE) (a)		-10.29	-10.49	
(95% CI)		(-12.02, -8.56)	(-12.23, -8.76)	
P-value vs placebo + chlorthalidone		<0.001*(b)	<0.001*(b)	
Week 6: Sensitivity analysis using multiple imputations				
LS mean difference (SE) (a)		-10.34	-10.59	<0.001*(b)
(95% CI)		(-12.05, -8.64)	(-12.38, -8.80)	
P-value vs placebo + chlorthalidone		<0.001*(b)	<0.001*(b)	

Source: Table 15.2.2.1.2.

Analyses include subjects with both a baseline and postbaseline value.

* Significant difference at the 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 plus chlorthalidone coadministration group) –

LS mean change of placebo group (chlorthalidone monotherapy group).

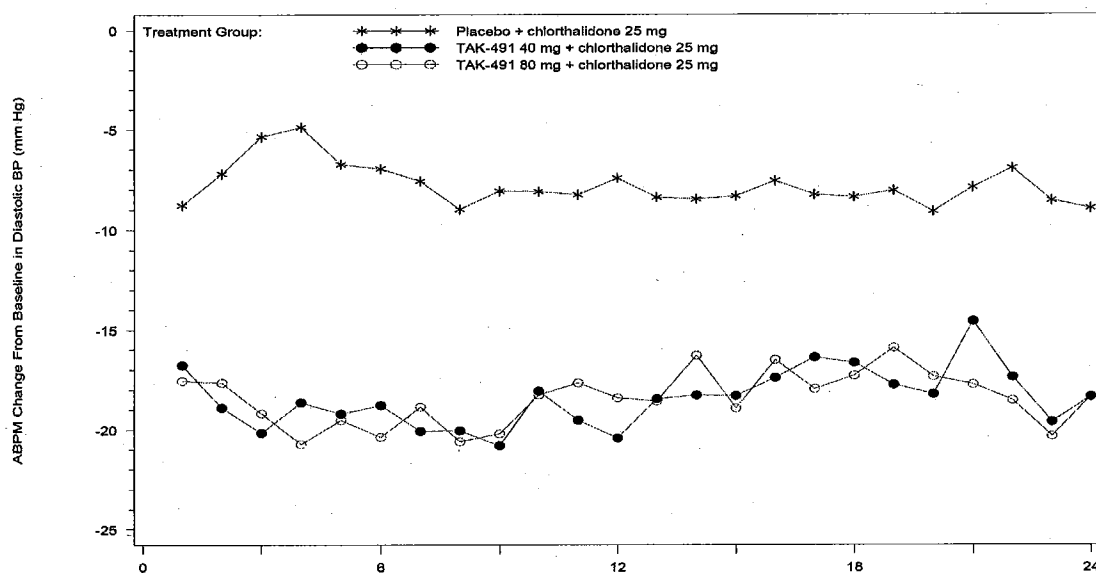
(b) P-value from analysis of covariance with terms for treatment (as a factor) and baseline value (as a covariate).

The baseline DBP values were around 90 mmHg for each treatment group. After 6 weeks the decrease from baseline was 8 mmHg for the chlorthalidone group. There was no difference between the TAK-491 plus chlorthalidone groups in the change in DBP from baseline (-18 mmHg). According to these results, both doses of TAK-491 decrease SBP an additional 10 mmHg when added to chlorthalidone.

The changes from baseline in DBP as measured by ABPM are shown in the figure below.

Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
Full Analysis Set



Results for the clinic BP measurements reflected what was observed with BP obtained using the ABPM.

Subgroups

The subgroups analyzed for BP effects include age, gender, race, BMI, baseline 24-hour mean SBP, and cGFR.

TAK-491 plus chlorthalidone produced greater blood pressure reductions compared to chlorthalidone alone in all subgroups examined.

SAFETY

Serious safety

Deaths

There was 1 death during this study in the chlorthalidone monotherapy group (subject 7090/008 experienced a fatal episode of cardiogenic shock).

Serious adverse events

There were seven subjects who reported serious adverse events. These are shown below.

Table 12.g Summary of Treatment-Emergent SAEs by Subject (Safety Analysis Set)

Treatment Site/Subject No.	Preferred Term	Onset Study Day	Relationship to Drug (a)	Action/Outcome
Chlorthalidone 25 mg + Placebo				
7090/008	Cardiac failure	7	Not related	Drug withdrawn/ resolved
	Cardiogenic shock	7	Not related	Not applicable/ fatal
	Pneumonia	7	Not related	Not applicable/ resolved
TAK-491 40 mg + Chlorthalidone 25 mg				
7010/001	Atrioventricular block complete	25	Not related	Not applicable/ resolved
	Heart rate decreased	25	Not related	Drug withdrawn/ resolved
	Syncope	25	Not related	Not applicable/ resolved
7024/004	Chest discomfort	13	Not related	Dose not changed/ resolved
7057/045	Hypertensive crisis	3	Not related	Drug withdrawn/ resolved
TAK-491 80 mg + Chlorthalidone 25 mg				
7036/015	Urinary tract infection	24	Not related	Dose not changed/ resolved
7051/002	Jaw fracture	41	Not related	Dose not changed/ resolved
	Skin laceration	41	Not related	Dose not changed/ resolved
	Syncope	41	Not related	Dose not changed/ resolved
7059/010	Lacunar infarction	18	Not related	Dose not changed/ resolved

Source: Table 15.3.2.2.

(a) As judged by the investigator.

One subject (7051/002) who reported syncope had been on study drug for 41 days and had a history of prior syncope. The other subject (7010/001) reported syncope as well as concurrent complete atrioventricular block and decreased heart rate after 25 days of treatment.

Discontinuations for adverse events

Those subjects who discontinued for safety reasons are shown below.

Table 12.h Summary of Adverse Events Resulting in Permanent Discontinuation (Safety Analysis Set)

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Outcome
Placebo plus Chlorthalidone				
7021/053	Heart rate increased	8	Possible	Resolving
7031/016	Headache	27	Possible	Resolved
7038/011	Hypertension	27	Probable	Resolved
7049/007	Alanine aminotransferase increased	1	Not related	Not resolved
	Gamma-glutamyltransferase increased	1	Not related	Not resolved
7054/009	Palpitations	7	Definite	Resolved
7090/008	Cardiac failure (b)	7	Not related	Resolved
TAK-491 40 mg plus Chlorthalidone				
7007/035	Orthostatic hypotension	4	Probable	Resolved
7010/001	Heart rate decreased (b)	25	Not related	Resolved
7013/012	Hypotension	5	Probable	Resolved
7014/025	Nausea	3	Probable	Resolved
	Dizziness	3	Probable	Resolved
	Hyperhidrosis	3	Probable	Resolved
	Hypotension	3	Probable	Resolved
7054/010	Dizziness	13	Not related	Resolved
7057/045	Hypertensive crisis (b)	3	Not related	Resolved
7067/017	Hepatic enzyme increased	2 (c)	Probable	Not resolved
7080/017	Dizziness	2	Possible	Resolved
7108/041	Hypotension	17	Probable	Resolved

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Outcome
TAK-491 80 mg plus Chlorthalidone				
7007/051 (d)	Tiredness	-21	Pretreatment	Resolved
	Dizziness	-21	Pretreatment	Resolved
7018/020	Asthenia	7	Probable	Resolved
7026/001	Pharyngitis streptococcal	14	Not related	Resolved
7057/042	Blood creatinine increased	14	Probable	Resolved
7057/061	Hypertensive crisis	16	Not related	Resolved
7057/063	Hypotension	2	Probable	Resolved
7068/045	Blood creatinine increased	29	Probable	Resolved
7071/003	Hypotension	42	Probable	Resolved
7108/007	Dry eye	1	Not related	Resolved

Source: Table 15.3.2.1 and Appendices 16.2.7.1 and 16.2.1.2.

(a) As judged by the investigator.

(b) Serious adverse event.

(c) Blood was drawn for analysis on Day 1.

(d) Subject 7007/051 was recorded as discontinued study due to adverse event on Day 4 (Appendix 16.2.1.2) at the request of the study monitor based on audit information, even though the events were not treatment emergent.

Adverse events of dizziness, hypotension, and asthenia were reported by subjects in the TAK-491 combination groups. The two subjects who discontinued study drug because of increased creatinine levels were in the TAK-491 80 mg combination group.

Clinical Laboratory Serum Chemistry

Table 12.i Serum Chemistry: Mean Changes From Baseline to the Final Visit (Safety Analysis Set)

Serum Chemistry	Placebo + Chlorthalidone 25 mg N=181		TAK-491 40 mg + Chlorthalidone 25 mg N=184		TAK-491 80 mg + Chlorthalidone 25 mg N=182	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Creatinine (μmol/L)						
Baseline (a)	181	79.6 (19.54)	184	76.9 (16.83)	181	79.9 (21.57)
Final Visit (b)	180	84.6 (21.89)	181	90.0 (24.94)	176	93.7 (26.73)
Change	180	5.0 (11.36)	181	13.3 (17.58)	176	13.6 (16.66)

The increases from baseline in creatinine levels in the TAK-491 combination groups at final visit were more than double the increases reported in the chlorthalidone monotherapy group.

Markedly abnormal serum chemistry values

The table below displays the number and percent of subjects who reported one or more abnormal chemistry values.

Table 12.k Subjects with at least 1 Markedly Abnormal Serum Chemistry Value During Treatment (Safety Analysis Set)

Laboratory Test	Treatment Group n/N (%)		
	Placebo + Chlorthalidone 25 mg N=181	TAK-491 40 mg + Chlorthalidone 25 mg N=184	TAK-491 80 mg + Chlorthalidone 25 mg N=182
ALT (>3 × ULN)	1/180 (0.6)	1/181 (0.6)	2/177 (1.1)
AST (>3 × ULN)	1/180 (0.6)	1/181 (0.6)	0/177
Alkaline phosphatase (>3 × ULN)	0/180	1/181 (0.6)	0/177
CK total (>3 × ULN)	0/180	0/181	0/177
Creatinine (>1.5 × BL)	4/180 (2.2)	14/181 (7.7)	14/177 (7.9)
GGT (>3 × ULN)	10/180 (5.6)	10/181 (5.5)	4/177 (2.3)
Potassium (<3.0 mmol/L)	10/180 (5.6)	0/181	1/177 (0.6)
(≥6.0 mmol/L)	0/180	0/181	0/177
Sodium (<130 mmol/L)	3/180 (1.7)	2/181 (1.1)	2/177 (1.1)
(≥150 mmol/L)	0/180	0/181	0/177
Total bilirubin (>2.0 × ULN)	0/180	1/181 (0.6)	0/177
Uric acid (Men: >625 μmol/L; Women: >506 μmol/L)	12/180 (6.7)	22/181 (12.2)	24/177 (13.6)

Source: Tables 15.3.4.3 and 15.3.4.8.

ALT=alanine aminotransferase, CK=creatinine kinase.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline results are summarized in this table.

Markedly abnormal uric acid values were observed at a higher incidence in the TAK-491 40 mg

and 80 mg plus chlorthalidone groups (12.2% and 13.6%, respectively) compared with the chlorthalidone monotherapy group (6.7%).

There was a greater percentage of subjects reporting markedly elevated¹ creatinine values in the TAK-491 40 mg plus chlorthalidone (7.7%) and TAK-491 80 mg plus chlorthalidone (7.9%) compared with the chlorthalidone monotherapy group (2.2%).

Table 12.1 Summary of Subjects With a Creatinine Elevation (Safety Analysis Set)

	Treatment Group n/N (%)		
	Placebo + Chlorthalidone 25 mg N=181	TAK-491 40 mg + Chlorthalidone 25 mg N=184	TAK-491 80 mg + Chlorthalidone 25 mg N=182
Subjects with Creatinine Elevations at Any Postbaseline Visit (a)			
≥30% from BL and >ULN	3/180 (1.7)	18/181 (9.9)	26/176 (14.8)
≥50% from BL and >ULN	1/180 (0.6)	10/181 (5.5)	15/176 (8.5)
Subjects with Creatinine Elevations at Final Visit (a)			
≥30% from BL and >ULN	2/180 (1.1)	15/181 (8.3)	19/176 (10.8)
≥50% from BL and >ULN	1/180 (0.6)	8/181 (4.4)	9/176 (5.1)

Source: Tables 15.3.4.10.1 and 15.3.4.10.2.

BL=baseline; ULN=upper limit of normal.

(a) Data are based on CV units.

There was a higher percentage of subjects with elevated serum creatinine in the TAK-491 combination groups compared to chlorthalidone alone, and it appears to be related to the dose of TAK-491.

There was one subject (7057/042, TAK-491 80 mg plus chlorthalidone) who discontinued because of increased creatinine after 23 days of treatment. This 81 year old female had a baseline creatinine of 1.1 mg/dl which continued to increase at every visit (1.8 mg/dL maximum). Concomitant medication included allopurinol and her uric acid levels were elevated. Creatinine levels declined to 1.2 mg/dL about 2 weeks after drug was stopped.

Follow-up data were obtained for 14 of 18 subjects with an elevated creatinine value at the Final Visit and these data are shown below. One subject (chlorthalidone monotherapy) died from cardiogenic shock.

¹ An increase ≥50% from baseline

Table 12.m Follow-up Creatinine Values (mg/dL) for All Subjects with Creatinine Elevations $\geq 30\%$ and $>ULN$ at the Final Visit

Subject	Screening Cr Value (mg/dL)	Cr ULN (mg/dL)	Baseline Cr Value (mg/dL)	Final Visit		Follow-up Visit	
				Cr Value (mg/dL)	Mean SBP/DBP Change From Baseline (mmHg)	Creatinine Value (mg/dL)	Days Since Final Visit (a)
Subjects With $\geq 30\%$ but $<50\%$ Creatinine Elevations From Baseline and $>ULN$							
7007053/ TAK-491 40 mg + CLD	1.2	1.0	1.1	1.6	-54/-13	1.1	260
7007071/ TAK-491 80 mg + CLD	1.0	1.0	1.0	1.3	-40/-18	1.6	192
7010034/ TAK-491 80 mg + CLD	0.9	1.0	0.8	1.1	-35/-12	0.8 (c)	107
7012007/ TAK-491 80 mg + CLD	1.3	1.0	1.2	1.6	-40/-18	1.2	36
7012010/ TAK-491 40 mg + CLD (b)	1.3	1.4	1.3	1.9	-57/-29	1.4	12
7015009/ TAK-491 80 mg + CLD	1.0	1.0	0.8	1.2	-66/-22	0.9 (c)	105
7020031/ TAK-491 40 mg + CLD	1.2	1.4	1.3	1.8	-46/-18	1.1	156
7020034/ TAK-491 40 mg + CLD	0.8	1.0	1.0	1.3	--	0.9 (c)	122
7023014/ TAK-491 40 mg + CLD	0.9	1.0	0.8	1.1	-68/-42	1.0 (c)	364
7036009/ TAK-491 80 mg + CLD	0.9	1.0	0.9	1.3	-51/-25	0.9 (c)	117
7042001/ TAK-491 80 mg + CLD	0.9	1.0	0.9	1.3	-38/-25	0.9	181
7044038/ TAK-491 80 mg + CLD	1.1	1.4	1.1	1.5	-53/-24	1.0 (c)	113
7056010/ CLD monotherapy	1.0	1.0	0.9	1.2	-12/-15	1.0	148
7056026/ TAK-491 40 mg + CLD (b)	1.1	1.4	1.1	1.5	-31/-4	1.2	50
7056029/ TAK-491 80 mg + CLD	1.3	1.0	1.2	1.6	-46/-13	1.4 (c)	107
7057042/ TAK-491 80 mg + CLD (b)	1.0	1.0	1.1	1.6	-19/-5	1.2	12
7057057/ TAK-491 80 mg + CLD	0.8	1.0	0.8	1.2	-35/-7	0.7 (c)	151
7058015/ TAK-491 80 mg + CLD (b)	1.5	1.4	1.6	2.1	-44/-12	1.7	29
7059003/ TAK-491 80 mg + CLD (b)	0.8	1.0	0.8	1.1	-56/-28	0.9 (c)	144
7108009/ TAK-491 40 mg + CLD	1.5	1.4	1.2	1.7	-31/-17	1.3 (c)	119

Subject	Final Visit					Follow-up Visit	
	Screening Cr Value (mg/dL)	Cr ULN (mg/dL)	Baseline Cr Value (mg/dL)	Cr Value (mg/dL)	Mean SBP/DBP Change From Baseline	Creatinine Value (mg/dL)	Days Since Final Visit (a)
					(mmHg)		
Subjects With $\geq 50\%$ Creatinine Elevations From Baseline and $>ULN$							
7001011/ TAK-491 80 mg + CLD	1.0	1.4	1.0	1.5	-67/-37	NCS (c)	--
7004017/ TAK-491 40 mg + CLD	1.1	1.0	0.9	1.4	-61/-15	--	--
7006007/ TAK-491 40 mg + CLD	1.2	1.4	1.2	2.1	-57/-18	1.3	14
7010007/ TAK-491 40 mg + CLD	1.2	1.4	1.0	1.8	-39/-22	1.1	159
7012008/ TAK-491 80 mg + CLD	1.2	1.4	1.2	2.1	-35/-17	1.3 (c)	288
7018015/ TAK-491 40 mg + CLD (b)	0.9	1.0	0.9	3.1	-80/-33	0.8 (c)	44
7018020/ TAK-491 80 mg + CLD (b)	0.9	1.0	0.8	1.5	--	1.0	15
7023005/ TAK-491 40 mg + CLD	0.8	1.0	0.8	1.3	-50/-32	0.8 (c)	438
7029003/ TAK-491 80 mg + CLD	0.7	1.0	0.6	1.4	-45/-20	0.7 (c)	263
7029019/ TAK-491 40 mg + CLD	1.0	1.4	0.9	1.6	-40/-21	0.8	196
7056023/ TAK-491 80 mg + CLD (b)	1.0	1.4	0.8	1.7	-21/0	1.1	56
7068032/ TAK-491 80 mg + CLD (b)	1.0	1.4	1.2	1.8	-23/0	1.3	8
7090008/ CLD monotherapy	1.2	1.0	1.1	1.9	--	--	--
7105010/ TAK-491 40 mg + CLD	0.8 (d)	1.0	0.8	1.4	-48/-25	0.8 (c)	49
7105029/ TAK-491 40 mg + CLD	0.9	1.0	0.8	1.3	-64/-34	--	--
7108004/ TAK-491 40 mg + CLD	0.8	1.0	0.7	1.6	-19/-24	0.9	8

Source: Tables 15.3.4.11.1 and 15.3.4.11.2 and Appendices 16.1.4.3, 16.1.7, and 16.2.7.1.

Note: Follow-up data include all information received up to 04 January 2010. *Italicized* subject number indicates follow-up serum creatinine values were not obtained. **Bold** subject number with **bold** screening, baseline and follow-up serum creatinine values indicates subject's follow-up value remained above the ULN and Baseline at the last follow-up evaluation.

CLD=chlorthalidone; Cr=creatinine; NCS=not clinically significant (as reported by investigator, value not provided).

(a) Because follow-up was unscheduled, there is variation in the number of days since Final Visit; as such, the number of days since Final Visit for follow-up data does not necessarily reflect the number of days before creatinine levels normalized.

(b) Increased blood creatinine was reported as an adverse event during the double-blind Treatment period.

(c) Follow-up serum creatinine value was evaluated for follow-up at a local lab and may not be recorded in the clinical database, but is provided in Appendix 16.1.4.3.

(d) The screening value obtained on Day -21 is presented, since the baseline value was not obtained for this subject

In most cases, the serum creatinine decreased to around baseline levels when the study drug was stopped.

Hematology

The number and percent of subjects with markedly abnormal hematology values are Shown below by treatment group.

Table 12.n Subjects with at least 1 Markedly Abnormal Hematology Value During Treatment (Safety Analysis Set)

Laboratory Test	Treatment Group n/N (%)		
	Placebo + Chlorthalidone 25 mg N=181	TAK-491 40 mg + Chlorthalidone 25 mg N=184	TAK-491 80 mg + Chlorthalidone 25 mg N=182
Hematocrit/PCV			
<0.8 × baseline value	0/180	4/181 (2.2)	3/177 (1.7)
Hemoglobin			
>3 g/dL decrease	0/180	2/181 (1.1)	1/177 (0.6)
Platelet count			
<50×10 ⁹ /L or >700×10 ⁹ /L	0/180	0/181	0/175
RBC			
<0.8 × baseline value	0/180	1/181 (0.6)	3/177 (1.7)

Source: Tables 15.3.4.1 and 15.3.4.8.

PCV=packed cell volume.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline values are included in this table.

There were few markedly abnormal hematology values reported but those reported were by subjects in the TAK-491 combination groups. None were reported as a serious adverse event or resulted in study discontinuation.

Urinalysis

There were no clinically meaningful treatment-related changes in the mean urinalysis data and no urinalysis abnormality was reported as a serious adverse event and none resulted in study discontinuation.

Vital Signs, ECGs, and Physical Findings

There were no clinically meaningful differences in changes for weight, sitting pulse, ECG parameters, or physical findings across treatment groups.

Individual Subject Changes

ECG changes reported as adverse events:

-Subject 7031/016 (chlorthalidone monotherapy) reported T wave inversion on Day 31 which later resolved.

-Subject 7108/033 (TAK-491 40 mg plus chlorthalidone) reported first degree a-v block on Day 30. The subject voluntarily withdrew from the study on Day 30 stating he was unable to make study visits.

-Subject 7021/038 (chlorthalidone monotherapy) reported atrial fibrillation on Day 43 which resolved.

-Subject 7015/009 (TAK-491 80 mg plus chlorthalidone) reported intermittent flattening of ST segments on Day 45.

-Subject 7029/003 (TAK-491 80 mg plus chlorthalidone) reported "mild" prolonged QT interval on day 43 (QTcB was 532 msec and QTcF was 531 msec).

-Subject 7024/004 (TAK-491 40 mg plus chlorthalidone) reported T wave inversion.

Reviewer's summary and conclusions

Efficacy: after 6 weeks the decrease from baseline for SBP was 16 mmHg for the chlorthalidone group. There was no difference between the TAK-491 40 mg and 80 mg plus chlorthalidone groups in the change in SBP from baseline (-31 mmHg from baseline). According to these results, doses of TAK-491 40 mg and 80 mg decrease SBP an additional 15 mmHg when added to chlorthalidone.

After 6 weeks the decrease from baseline for DBP was 8 mmHg for the chlorthalidone group. There was no difference between the TAK-491 40 mg and 80 mg plus chlorthalidone groups in the change in DBP from baseline (-18 mmHg). According to these results, both doses of TAK-491 decrease SBP an additional 10 mmHg when added to chlorthalidone.

Safety: there were two reports of syncope in the TAK-491 (40 mg and 80 mg) plus chlorthalidone.

There were two subjects in the TAK-491 80 mg plus chlorthalidone group who discontinued study drug because of increased creatinine levels. Creatinine levels declined to 1.2 mg/dL about 2 weeks after drug was stopped.

The increases from baseline in creatinine levels in the TAK-491 40 mg and 80 mg combination groups at final visit were more than double the increases reported in the chlorthalidone monotherapy group. There was a greater percentage of subjects reporting markedly elevated² creatinine values in the TAK-491 40 mg plus chlorthalidone (7.7%) and TAK-491 80 mg plus chlorthalidone (7.9%) compared with the chlorthalidone monotherapy group (2.2%). In most cases stopping study drug resulted in serum creatinine returning to near baseline levels.

Markedly abnormal uric acid values were observed at a higher incidence in the TAK-491 40 mg and 80 mg plus chlorthalidone groups (12.2% and 13.6%, respectively) compared with the chlorthalidone monotherapy group (6.7%).

Conclusions: the use of TAK-491 40 mg and 80 mg to chlorthalidone resulted in large decreases in SBP and DBP. However, there were two reports of syncope in the combination groups and worsening serum creatinine levels.

² An increase $\geq 50\%$ from baseline

Table 12.g Summary of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug (Safety Analysis Set) (Continued)

Site/ Subject No.	Age/ Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Intensity
TAK-491 80 mg						
1213/006	60/F	Eosinophilia (Eosinophilia)	34	Ongoing	Probable	Moderate
		Pruritus (Pruritus)	31	Ongoing	Probable	Moderate
		Rash (Rash)	33	Ongoing	Probable	Moderate
Valsartan 320 mg						
1045/001	64/F	Elevated blood pressure (Blood pressure increased)	21	Ongoing	Not related	Moderate
		Headaches (Headache)	21	33	Definite	Moderate
1074/038	31/M	Tachycardia (Tachycardia)	18	19	Not related	Severe
		Abdominal pain (Abdominal pain)	18	18	Possible	Severe
		Drug overdose intentional, not suicidal with Seroquel (Intentional overdose) (a)	18	19	Not related	Severe
		Dehydration (Dehydration)	18	19	Not related	Severe
		Lethargy (Lethargy)	18	19	Possible	Severe
		Tremors (Tremors)	18	18	Not related	Severe
		Exacerbation of anxiety (Anxiety)	17	19	Possible	Severe
1126/002	45/M	Deep vein thrombosis right leg (Deep vein thrombosis) (a)	12	15	Not related	Moderate
1203/034	63/F	Rapid heart beat (Heart rate increased)	2	16	Definite	Moderate
1212/001	75/F	Urticaria (Urticaria)	31	Ongoing	Probable	Moderate
1215/015	50/M	Edema in both feet and ankles (Oedema peripheral)	18	26	Not related	Mild
1218/013	50/M	Headache (Headache)	26	34	Not related	Moderate
Olmesartan 40 mg						
1016/017	53/F	Fatigue (Fatigue)	14	26	Possible	Moderate
1023/049	52/M	Focal seizures (Partial seizures) (a)	39	41	Not related	Severe
		Psychomotor seizures (Psychomotor seizures)	35	39	Not related	Moderate
1070/005	66/F	Right breast lobular carcinoma (Breast cancer) (a)	27	Ongoing	Not related	Severe
1073/001	64/M	Headache (Headache)	1	29	Probable	Severe
1076/044	62/F	Worsening headaches (Headache)	2	11	Probable	Moderate
1211/002	80/F	Worsening hypertension (Hypertension)	1	Ongoing	Not related	Severe

Source: Table 15.3.2.1 and Appendix 16.2.1.2.

Note: Events reported prior to Week 2 occurred while subjects were receiving their initial dose of study drug.

(a) Serious adverse event.

(b) The site could not contact the subject to get the end date for the fractured ankle because the subject moved with no forwarding address or phone number (source: Section 15.3.3.2).

(c) First day of double-blind dosing occurred on 30 September 2008 (Day 1). Event was recorded as 01 October 2008 (Day ≤31) (source: Section 15.3.3).

There were two reports of possible hypersensitivity reaction. There was one subject in the TAK-491 who reported eosinophilia, pruritis, and rash and one subject in the valsartan 320 mg group who reported urticaria.

There were an additional 4 subjects who were discontinued for events that started prior to study drug initiation:

1114/002 (placebo) reported leukocytosis,
1040/036 (TAK-491 80 mg) reported headache,
1047/006 (TAK-491 80 mg) reported leg edema,
1218/02 (valsartan) reported headache.

Adverse events

The number and percent of subjects reporting any adverse event, adverse events resulting in discontinuation, serious adverse events and reported deaths are shown below by treatment group.

Table 12.b Overview of Treatment-Emergent Adverse Events and SAEs (Safety Analysis Set)

Number (%) of Subjects with:	Treatment Group				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Adverse events	74 (47.7)	134 (47.9)	145 (51.1)	131 (47.3)	151 (52.1)
Related (a)	24 (15.5)	52 (18.6)	56 (19.7)	54 (19.5)	57 (19.7)
Mild	48 (31.0)	74 (26.4)	78 (27.5)	72 (26.0)	91 (31.4)
Moderate	23 (14.8)	50 (17.9)	54 (19.0)	52 (18.8)	50 (17.2)
Severe	3 (1.9)	10 (3.6)	13 (4.6)	7 (2.5)	10 (3.4)
Leading to discontinuation (b)	3 (1.9)	7 (2.5)	8 (2.8)	7 (2.5)	6 (2.1)
SAEs	2 (1.3)	2 (0.7)	3 (1.1)	3 (1.1)	4 (1.4)
Related (a)	0	0	1 (0.4)	0	0
Deaths	0	0	0	0	0

Source: Tables 15.3.1.1, 15.3.1.7, 15.3.1.8, and 15.3.2.2.

(a) Related-events attributed by investigator as definitely, probably, or possibly related to study drug.

(b) Adverse events leading to study drug discontinuation include those that led to temporary drug interruption or permanent discontinuation.

Overall, about 50% of subjects reported adverse event(s), slightly fewer placebo subjects discontinued because of an adverse event, there were few serious adverse events reported, and there were no reported deaths.

Common adverse events.

Adverse events reported by $\geq 2\%$ of subjects in any treatment group are shown below.

Table 12.d Treatment-Emergent Adverse Event Preferred Terms Reported for $\geq 2.0\%$ of Subjects in Any Treatment Group (Safety Analysis Set)

Preferred Term	Treatment Group n (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Headache	14 (9.0)	18 (6.4)	12 (4.2)	21 (7.6)	23 (7.9)
Dizziness	4 (2.6)	10 (3.6)	10 (3.5)	5 (1.8)	9 (3.1)
Nasopharyngitis	3 (1.9)	5 (1.8)	8 (2.8)	6 (2.2)	7 (2.4)
Urinary tract infection	5 (3.2)	9 (3.2)	6 (2.1)	3 (1.1)	6 (2.1)
Fatigue	1 (0.6)	3 (1.1)	7 (2.5)	4 (1.4)	13 (4.5)
Oedema peripheral	1 (0.6)	5 (1.8)	4 (1.4)	9 (3.2)	8 (2.8)
Plasminogen activator inhibitor increased	2 (1.3)	7 (2.5)	7 (2.5)	7 (2.5)	4 (1.4)
Diarrhoea	2 (1.3)	3 (1.1)	12 (4.2)	4 (1.4)	5 (1.7)
Blood creatine phosphokinase increased	2 (1.3)	7 (2.5)	6 (2.1)	5 (1.8)	4 (1.4)
Dyslipidaemia	1 (0.6)	6 (2.1)	7 (2.5)	3 (1.1)	4 (1.4)
Upper respiratory tract infection	2 (1.3)	1 (0.4)	8 (2.8)	6 (2.2)	4 (1.4)
Nausea	1 (0.6)	3 (1.1)	3 (1.1)	5 (1.8)	6 (2.1)
C-reactive protein increased	0	3 (1.1)	6 (2.1)	3 (1.1)	3 (1.0)
Hypertriglyceridaemia	4 (2.6)	4 (1.4)	3 (1.1)	1 (0.4)	2 (0.7)
Hypercholesterolaemia	5 (3.2)	1 (0.4)	2 (0.7)	2 (0.7)	1 (0.3)
Myalgia	0	1 (0.4)	7 (2.5)	1 (0.4)	0

Source: Table 15.3.1.4.

Headache was the most commonly reported adverse event and it was reported more often by the placebo group compared to the active treatment groups. On the other hand, fatigue and peripheral edema was more commonly reported by the active treatment groups compared to placebo. Dizziness and hypertriglyceridemia were less often reported by the valsartan group compared to the TAK-491 groups.

Selected adverse events.

The reporting rates for certain adverse events including hypotension and renal function are shown below.

Table 12.e Selected Treatment-Emergent Adverse Events Observed in Subjects Receiving Treatment for Hypertension (Safety Analysis Set)

Category Preferred Term	Treatment Group n (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
General					
Headache	14 (9.0)	18 (6.4)	12 (4.2)	21 (7.6)	23 (7.9)
Cough	2 (1.3)	2 (0.7)	2 (0.7)	3 (1.1)	3 (1.0)
Dizziness	4 (2.6)	10 (3.6)	10 (3.5)	5 (1.8)	9 (3.1)
Syncope	0	0	0	0	1 (0.3)
Blood Pressure					
Hypotension	0	1 (0.4)	1 (0.4)	0	1 (0.3)
Orthostatic hypotension	0	1 (0.4)	1 (0.4)	0	0
Blood pressure increased	0	0	1 (0.4)	1 (0.4)	0
Hypertension	1 (0.6)	2 (0.7)	0	0	1 (0.3)
Renal Function					
Urine albumin/creatinine ratio increased	1 (0.6)	1 (0.4)	1 (0.4)	0	2 (0.7)
Blood creatinine increased	1 (0.6)	3 (1.1)	1 (0.4)	0	1 (0.3)
Potassium Homeostasis					
Blood potassium increased	0	2 (0.7)	1 (0.4)	0	1 (0.3)
Hyperkalaemia	1 (0.6)	0	0	0	0
Blood potassium decreased	0	0	0	0	2 (0.7)
Hypokalaemia	0	0	0	0	1 (0.3)
Anemia					
Anaemia	0	1 (0.4)	0	0	1 (0.3)
Haemoglobin decreased	0	0	1 (0.4)	0	0
Haematocrit decreased	0	1 (0.4)	1 (0.4)	0	0
Edema					
Oedema peripheral	1 (0.6)	5 (1.8)	4 (1.4)	9 (3.2)	8 (2.8)

For the most part, these events were reported by a small number of subjects and the treatment groups showed similar reporting rates.

Clinical laboratory evaluations

Serum Chemistry

Mean values at baseline, final visit and change from baseline at final visit for ALT, aspartate aminotransferase (AST), alkaline phosphatase, creatine kinase (CK) total, creatinine, potassium, sodium, total bilirubin, and uric acid are shown below.

Table 12.h Serum Chemistry: Mean Changes From Baseline to the Final Visit (Safety Analysis Set)

		Treatment Group									
		Placebo		TAK-491		TAK-491		Valsartan		Olmesartan	
		N=155		40 mg		80 mg		320 mg		40 mg	
		N=155		N=280		N=284		N=277		N=290	
Serum Chemistry	Parameter (unit)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
ALT (U/L)											
	Baseline (a)	155	25.8 (13.02)	280	27.6 (14.18)	284	27.7 (13.11)	277	30.9 (16.92)	290	29.7 (19.38)
	Final visit (b)	152	26.6 (12.02)	276	27.5 (13.51)	274	30.0 (15.41)	271	31.5 (18.61)	285	29.2 (15.49)
	Change	152	1.0 (7.07)	276	-0.2 (10.14)	274	2.4 (10.02)	271	0.8 (10.45)	285	-0.5 (14.75)
AST (U/L)											
	Baseline (a)	155	22.9 (8.05)	280	24.6 (13.39)	284	24.3 (10.40)	277	25.5 (12.38)	290	26.0 (14.56)
	Final visit (b)	152	24.0 (9.10)	276	24.9 (13.52)	274	25.1 (10.11)	271	26.3 (14.14)	285	25.3 (11.59)
	Change	152	1.2 (6.17)	276	0.3 (16.56)	274	0.8 (8.48)	271	0.8 (9.94)	285	-0.7 (9.34)
Alkaline phosphatase (U/L)											
	Baseline (a)	155	81.0 (20.10)	280	81.6 (25.35)	284	81.5 (23.84)	277	81.0 (23.92)	290	81.7 (23.91)
	Final visit (b)	152	81.9 (21.41)	276	81.8 (25.79)	274	80.1 (25.19)	271	78.7 (21.09)	285	80.7 (22.98)
	Change	152	1.0 (9.29)	276	-0.1 (10.10)	274	-1.4 (9.68)	271	-1.7 (10.36)	285	-0.7 (8.59)
Bilirubin, total (umol/L)											
	Baseline (a)	155	8.0 (3.60)	280	8.6 (4.68)	284	8.4 (4.45)	277	7.9 (3.63)	290	8.0 (4.26)
	Final visit (b)	152	8.2 (3.77)	276	8.1 (4.80)	274	8.1 (3.91)	271	7.8 (3.86)	285	7.4 (4.22)
	Change	152	0.1 (2.68)	276	-0.5 (3.45)	274	-0.3 (3.11)	271	0.0 (3.42)	285	-0.6 (3.25)
CK total (U/L)											
	Baseline (a)	155	139.1 (99.43)	279	153.5 (275.84)	284	158.4 (525.24)	277	143.5 (127.49)	289	132.1 (112.75)
	Final visit (b)	152	155.6 (142.76)	276	180.8 (664.20)	274	136.8 (100.37)	271	155.1 (143.01)	284	139.4 (107.95)
	Change	152	15.7 (102.44)	276	27.4 (710.24)	274	-22.3 (536.57)	271	12.0 (118.82)	284	6.3 (102.46)
Creatinine (umol/L)											
	Baseline (a)	155	79.9 (19.02)	280	79.8 (18.22)	284	77.7 (16.59)	277	79.6 (17.71)	290	77.9 (16.95)
	Final visit (b)	152	81.0 (18.05)	276	82.3 (20.12)	274	81.3 (17.99)	271	81.0 (18.55)	285	79.2 (17.97)
	Change	152	1.0 (8.62)	276	2.5 (10.65)	274	3.5 (9.62)	271	1.5 (8.70)	285	1.4 (8.45)
Potassium (mmol/L)											
	Baseline (a)	155	4.26 (0.384)	280	4.25 (0.369)	284	4.22 (0.390)	277	4.21 (0.410)	290	4.23 (0.412)
	Final visit (b)	152	4.18 (0.397)	276	4.33 (0.413)	274	4.33 (0.428)	271	4.28 (0.379)	285	4.26 (0.386)
	Change	152	-0.07 (0.406)	276	0.09 (0.382)	274	0.10 (0.406)	271	0.06 (0.392)	285	0.03 (0.415)
Sodium (mmol/L)											
	Baseline (a)	155	139.8 (2.22)	280	139.6 (2.11)	284	140.0 (2.14)	277	139.8 (2.19)	290	139.9 (2.02)
	Final visit (b)	152	140.1 (2.20)	276	139.5 (2.39)	274	139.5 (2.03)	271	139.8 (2.24)	285	139.8 (2.24)
	Change	152	0.3 (2.04)	276	-0.1 (2.24)	274	-0.5 (2.27)	271	0.1 (2.23)	285	0.0 (2.09)
Uric acid (umol/L)											
	Baseline (a)	155	345.1 (84.50)	280	335.1 (84.10)	284	326.4 (78.12)	277	333.4 (79.58)	290	330.5 (77.02)
	Final visit (b)	152	350.1 (88.53)	276	345.1 (87.45)	274	342.6 (83.93)	271	339.5 (82.92)	285	343.3 (78.60)
	Change	152	5.6 (40.74)	276	9.7 (48.97)	274	16.3 (48.94)	271	5.9 (42.51)	285	13.0 (47.54)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

A summary of the mean change from Baseline to the Final Visit for each lipid parameter is presented in Table 12.i.

Regarding creatinine, there were larger mean increases from baseline at final visit for all active treatment groups compared to placebo (1 umol/L). The increase was the largest for TAK-491 80 mg (3.5 umol/L). The TAK-491 80 mg group also had the largest increase in potassium (0.10 mmol/L) and uric acid (16.3 umol/L) while the placebo group had a decline in potassium level (-0.07 mmol/L) and a smaller increase in uric acid (5.6 umol/L).

The lipid level changes are shown below for all treatment groups.

Table 12.i Lipids: Mean Changes From Baseline to the Final Visit (Safety Analysis Set)

Lipid Parameter (unit)	Treatment Group									
	Placebo N=155		TAK-491 40 mg N=280		TAK-491 80 mg N=284		Valsartan 320 mg N=277		Olmesartan 40 mg N=290	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
LDL-C (mmol/L)										
Baseline (a)	137	3.026 (0.8225)	240	3.161 (0.9498)	243	3.026 (0.8804)	238	3.139 (0.9674)	245	3.091 (0.8374)
Final visit (b)	129	2.943 (0.8002)	227	3.063 (0.9730)	227	2.887 (0.8691)	223	3.132 (0.8816)	231	3.078 (0.8743)
Change	129	-0.086 (0.5953)	227	-0.092 (0.5388)	227	-0.111 (0.5877)	223	-0.003 (0.6260)	231	-0.024 (0.5822)
Total cholesterol (mmol/L)										
Baseline (a)	140	5.095 (0.9639)	246	5.208 (1.1298)	251	5.112 (1.0522)	248	5.245 (1.1421)	253	5.117 (0.9439)
Final visit (b)	134	5.077 (0.9789)	236	5.129 (1.1216)	236	4.999 (1.0156)	236	5.202 (1.0163)	241	5.104 (1.0014)
Change	134	-0.024 (0.7831)	236	-0.064 (0.6087)	236	-0.085 (0.6780)	236	-0.056 (0.6868)	241	-0.027 (0.6785)
HDL-C (mmol/L)										
Baseline (a)	140	1.278 (0.3956)	246	1.286 (0.3762)	251	1.321 (0.3890)	248	1.279 (0.3609)	253	1.273 (0.3560)
Final visit (b)	134	1.314 (0.4096)	236	1.268 (0.3684)	236	1.302 (0.3890)	236	1.279 (0.3341)	241	1.255 (0.3494)
Change	134	0.025 (0.1636)	236	-0.024 (0.1682)	236	-0.013 (0.1728)	236	-0.003 (0.1761)	241	-0.011 (0.1621)
Triglycerides (mmol/L)										
Baseline (a)	140	1.794 (1.0217)	246	1.735 (1.1220)	250	1.768 (1.1286)	248	1.988 (2.4358)	253	1.715 (0.9862)
Final visit (b)	134	1.871 (1.5516)	236	1.859 (1.3307)	235	1.810 (1.0059)	236	1.836 (1.5324)	241	1.786 (1.3594)
Change	134	0.077 (1.1013)	236	0.147 (0.8589)	235	0.059 (0.8158)	236	-0.164 (1.3443)	241	0.041 (0.9862)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

The changes for all treatment groups appear to be inconsequential.

The number and percent of subjects with markedly abnormal reported laboratory values are shown below.

Table 12.j Percentage of Subjects With at Least 1 Markedly Abnormal Chemistry Value During Treatment (Safety Analysis Set)

Serum Chemistry Parameter (markedly abnormal criterion)	Treatment Group n/N (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
ALT (>3xULN)	1/152 (0.7)	1/276 (0.4)	1/274 (0.4)	0/271 (0.0)	0/285 (0.0)
AST (>3xULN)	1/152 (0.7)	2/276 (0.7)	2/274 (0.7)	2/271 (0.7)	3/285 (1.1)
Bilirubin, total (>2xULN)	2/152 (1.3)	1/276 (0.4)	0/274 (0.0)	0/271 (0.0)	1/285 (0.4)
CK total (>10xULN)	0/152 (0.0)	2/276 (0.7)	1/274 (0.4)	2/271 (0.7)	0/285 (0.0)
Creatinine (>1.5xBaseline)	0/152 (0.0)	2/276 (0.7)	3/274 (1.1)	1/271 (0.4)	2/285 (0.7)
GGT (>3xULN)	3/152 (2.0)	5/276 (1.8)	12/274 (4.4)	15/271 (5.5)	11/285 (3.9)
Potassium	0/152 (0.0)	0/276 (0.0)	1/274 (0.4)	1/271 (0.4)	0/285 (0.0)
(<3.0 mmol/L)	0/152 (0.0)	0/276 (0.0)	1/274 (0.4)	1/271 (0.4)	0/285 (0.0)
(>6.0 mmol/L)	0/152 (0.0)	0/276 (0.0)	0/274 (0.0)	0/271 (0.0)	0/285 (0.0)
Sodium	0/152 (0.0)	2/276 (0.7)	0/274 (0.0)	3/271 (1.1)	0/285 (0.0)
(<130 mmol/L)	0/152 (0.0)	2/276 (0.7)	0/274 (0.0)	3/271 (1.1)	0/285 (0.0)
(>150 mmol/L)	0/152 (0.0)	0/276 (0.0)	0/274 (0.0)	0/271 (0.0)	0/285 (0.0)
Uric acid (Males: >625 umol/L) (Females: >506 umol/L)	2/152 (1.3)	3/276 (1.1)	2/274 (0.7)	4/271 (1.5)	2/285 (0.7)

Source: Tables 15.3.4.7 and 15.3.4.8.
BUN=blood urea nitrogen

Abnormal values were uncommon in all treatment groups. The exception is GGT >3xULN. This increase was reported more often in the TAK-491 80 mg (4.4%), valsartan (5.5%), and olmesartan (3.9%) groups compared to placebo (2.0%).

There were 3 subjects who reported marked elevation of ALT values (one each for placebo, TAK-491 40 mg and TAK-491 80 mg). No subject was discontinued for this abnormality and none was discontinued because of it.

There were eight subjects who reported markedly abnormal creatinine¹ values anytime during the double blind phase: 2 (0.7%) TAK-491 40 mg, 3 (1.1%) TAK-491 80 mg, 1 (0.4%) valsartan 320 mg, and 2 (0.7%) olmesartan 40 mg. Two of the subjects (1039/019 and 1052/080, both taking TAK-491 40 mg) had their increased creatinine values reported as an adverse event.

Subject 1052/080 was a 44 year old black male who had a baseline creatinine value of 1.3 mg/dL that increased to 2.3 mg/dL at the last visit.

Subject 1039/019 was a 65 year old female had a creatinine value at baseline of 1.1 mg/dL that rose to 1.3 mg/dL at the last visit.

The table below shows the number and percent of subjects who met certain criteria² for abnormal creatinine increases at anytime during the double blind treatment phase.

¹ >1.5x baseline value

² Creatinine increase ≥30% from Baseline and >ULN at the Final Visit.

Table 12.k Summary of Subjects With Creatinine Elevation (Safety Analysis Set)

	Treatment Group n/N (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Subjects with Creatinine Elevations at Any Postbaseline Visit					
≥30% from Baseline and >ULN	0/152	4/276 (1.4)	3/274 (1.1)	2/271 (0.7)	2/285 (0.7)
≥50% from Baseline and >ULN	0/152	1/276 (0.4)	3/274 (1.1)	1/271 (0.4)	0/285
Subjects with Creatinine Elevations at Final Visit (a)					
≥30% from Baseline and >ULN	0/152	1/276 (0.4)	2/274 (0.7)	1/271 (0.4)	1/285 (0.4)
≥50% from Baseline and >ULN	0/152	1/276 (0.4)	0/274	1/271 (0.4)	0/285

Source: Table 15.3.4.9 and Appendix 16.2.8.3.3.

Note: A creatinine increase is defined as an increase from Baseline ≥30%×Baseline and >ULN.

(a) Last observation carried forward.

No placebo subject met the definition of creatinine elevation. The treatment group with the highest percent of subjects with ≥ 50% from baseline and > ULN at anytime during the double blind treatment phase was TAK-491 80 mg. This percentage decreased to 0% when only the values obtained at the final visit were included.

Hematology

There were variable changes from baseline in the active treatment groups that were not greatly different from the changes in the placebo group. There were small decreases in mean hemoglobin in all of the active treatment groups

- TAK-491 (40 mg and 80 mg) (-0.27 g/dL and -0.31 g/dL, respectively),
- valsartan and olmesartan (-0.22 g/dL in each) treatment groups,
- placebo group (0.01 g/dL).

There were decreases as well for mean hematocrit/packed cell volume from baseline at the final visit for TAK-491 (40 mg and 80 mg) groups (-0.0086 and -0.0096, respectively), valsartan and olmesartan (-0.0074 and -0.0077, respectively) and placebo (-0.0005).

There were only sporadic markedly abnormal hematology values were observed. One clinically significant abnormality (eosinophilia) resulted in study discontinuation (TAK-491 80 mg, subject 1213/006). This subject also reported pruritus and rash.

The number and percent of subjects with markedly abnormal hematology values are shown in the table below.

Creatinine increase ≥50% from Baseline and >ULN at the Final Visit.

Table 12.1 Percentage of Subjects With at Least 1 Markedly Abnormal Hematology Value During Treatment (Safety Analysis Set)

Hematology Parameter (markedly abnormal criterion)	Treatment Group n/N (%)				
	Placebo N=155	TAK-491 40 mg N=280	TAK-491 80 mg N=284	Valsartan 320 mg N=277	Olmesartan 40 mg N=290
Hematocrit/PCV (<0.8×Baseline)	0/152 (0.0)	1/276 (0.4)	0/274 (0.0)	0/270 (0.0)	0/284 (0.0)
Hemoglobin (<Baseline - 3 g/dL)	0/152 (0.0)	1/276 (0.4)	0/274 (0.0)	0/270 (0.0)	0/284 (0.0)
White blood cell count	1/152 (0.7)	0/276 (0.0)	0/274 (0.0)	2/270 (0.7)	0/284 (0.0)
(<2×10 ⁹ /L)	0/152 (0.0)	0/276 (0.0)	0/274 (0.0)	0/270 (0.0)	0/284 (0.0)
(>20×10 ⁹ /L)	1/152 (0.7)	0/276 (0.0)	0/274 (0.0)	2/270 (0.7)	0/284 (0.0)

Source: Table 15.3.4.7 and 15.3.4.8.

There were few abnormal values in any of the treatment groups.

Urinalysis

There were no remarkable changes reported during the study.

Vital Signs and ECGs

Weight, sitting pulse and results were similar across treatment groups.

There were various changes in ECG parameters that were similar across treatment groups.

Reviewer's summary and conclusions

Efficacy: while baseline clinic BPs were similar for all treatment groups, the ABPM baseline BPs were significantly higher for valsartan group. All active treatment groups were superior to placebo in lowering SBP and DBP. The BP effects of TAK-491 40 mg and 80 mg were similar to one another. There is some evidence that TAK-491 was superior to valsartan 320 mg and olmesartan 40 mg but this was inconsistent.

Safety: in general, the active treatments were well tolerated. Commonly reported adverse events included headache and dizziness. The valsartan 320 mg group reported dizziness less often than the placebo and other active treatment groups. TAK-491 80 mg followed by TAK-491 40 mg had the largest increases in serum creatinine compared to the other treatment groups. TAK-491 80 mg followed by TAK-491 40 mg also had the largest increases in serum potassium.

Conclusions: the ARBs used in this trial were found to be effective in lowering blood pressure. There is evidence that TAK-491 40 mg and 80 mg increase serum creatinine more than valsartan 320 mg and olmesartan 40 mg so there is no reason to prefer TAK-491 over the other two available ARBs. Since there were only small differences in blood pressure effects between TAK-491 40 mg and 80 mg and TAK-491 80 mg had a worse effect on serum creatinine, doses of TAK-491 above 40 mg are not recommended.

Study 01-05-TL-491-005

Study No. (Study Abbreviation)	No. of Sites-Country (a)	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
01-05-TL-491-005 (491-005)	67-United States and Latin America	Double blind, randomized, parallel-group, placebo controlled, dose ranging (Phase 2)	449 subjects with mild to moderate uncomplicated essential hypertension (DBP=95-114 mm Hg)	8 weeks	A: TAK-491 5 mg capsule B: TAK-491 10 mg capsule C: TAK-491 20 mg capsule D: TAK-491 40 mg capsule E: TAK-491 80 mg capsule F: OLM-M 20 mg capsule G: Placebo capsule
16 May 2006-07 December 2006		Dose-response of antihypertensive effects of TAK-491 (Change from BL to Final Visit in sitting clinic DBP)			449 /404 A: 65/63 B: 65/59 C: 64/57 D: 63/59 E: 64/57 F: 64/57 G: 64/52

This was a multicenter, randomized, parallel group, double-blind, placebo-controlled, dose-ranging study in subjects with mild to moderate uncomplicated essential hypertension. After a 2-week, single-blind placebo run-in period, subjects who met entry criteria were randomized to receive TAK-491 5, 10, 20, 40, 80 mg, placebo, or olmesartan 20 mg QD for 8 weeks. Clinical DBP and SBP were measured at Screening (Day -21, Day -14 and Day -7), Randomization (Day 1), Week 1, Week 2, Week 4, Week 6, and Week 8. ABPM occurred at Day 1 and Week 8 or Early Termination.

Number of Subjects:

Planned: 420 subjects, 60 subjects per treatment group.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been male or nonpregnant, nonlactating women with mild to moderate uncomplicated essential hypertension (DBP \geq 95 and \leq 114 mm Hg at Placebo Run-in Day -14 and randomization Visit); aged 18 or older, inclusive; with clinical laboratory evaluations within the reference range for the testing laboratory; been able to comprehend and willing to sign an informed consent form, and willing to discontinue current antihypertensive medications at Screening Day -21.

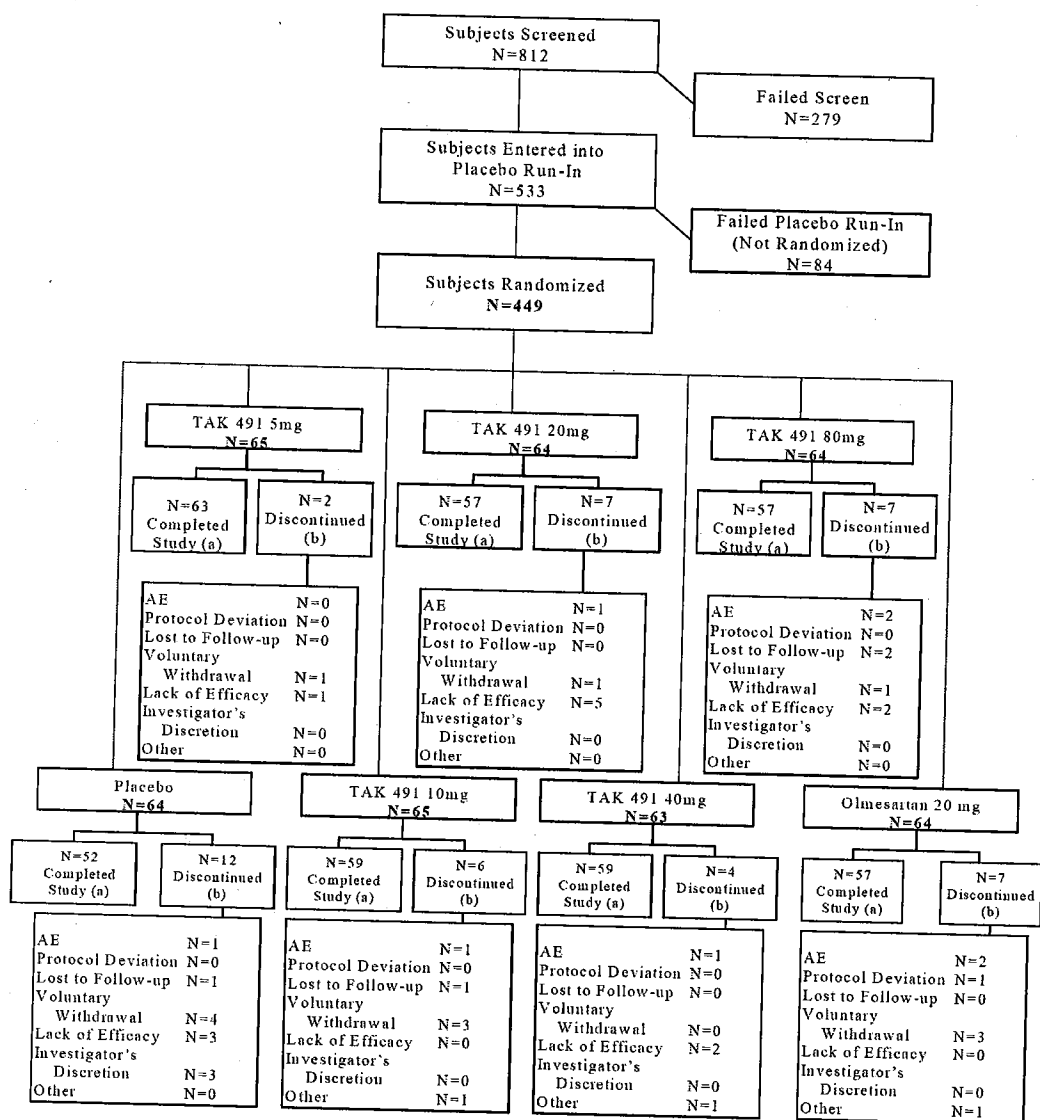
Efficacy endpoints:

Primary endpoint was the change from baseline at final visit in the sitting clinic DBP. The secondary efficacy variables were the change from baseline at final visit in sitting clinic SBP, standing SBP and DBP, as well as SBP and DBP measured by ABPM.

RESULTS

The disposition of subjects is shown below.

Figure 10.a Disposition of Subjects



Source: Table 15.1.2.

(a) For the purpose of this disposition figure, subjects who completed study were calculated as the total number randomized per treatment group minus those who discontinued.

(b) Subjects could have had more than 1 reason for discontinuation; only the primary reason is presented here. Withdrawal categories are described in Section 9.3.3.

A total of 449 subjects were randomized and 404 subjects completed the study. There were 45 subjects who prematurely discontinued from the study: 12 placebo, 2 TAK-491 5 mg, 6 TAK-491 10 mg, 4 TAK-491 40 mg, and 7 in each of TAK-491 20 mg, 80 mg, and olmesartan 20 mg treatment groups. The most common reasons for premature withdrawal included voluntary withdrawal and lack of efficacy.

The demographic and baseline characteristics were fairly similar across all treatment groups: about half were male and about 10% were black.

RESULTS

Disposition of subjects

A total of 812 subjects were screened at 73 sites in United States, Mexico, Peru, and Argentina. Of these, 533 subjects entered the placebo run-in period, and 449 were randomized to treatment at 67 sites in the United States and Latin America; 63 to 65 subjects were randomized to each of the 7 treatment groups.

Table 15.1.2
Subject Disposition
All Randomized Subjects

Parameter	Placebo (N = 64)	TAK-491 5 mg (N = 65)	TAK-491 10 mg (N = 65)	TAK-491 20 mg (N = 64)	TAK-491 40 mg (N = 63)	TAK-491 80 mg (N = 64)	Olmesartan 20 mg (N = 64)
Number of subjects randomized	64	65	65	64	63	64	64
Failed to receive double-blind study medication	1 (1.6)	0	1 (1.5)	0	1 (1.6)	0	1 (1.6)
Completed 0 to less than 1 week	1 (1.6)	0	0	0	0	0	0
Completed 1 to less than 2 weeks	3 (4.7)	0	1 (1.5)	3 (4.7)	1 (1.6)	0	1 (1.6)
Completed 2 to less than 4 weeks	2 (3.1)	1 (1.5)	1 (1.5)	1 (1.6)	2 (3.2)	5 (7.8)	4 (6.3)
Completed 4 to less than 6 weeks	3 (4.7)	1 (1.5)	4 (6.2)	4 (6.3)	0	1 (1.6)	0
Completed 6 to less than 8 weeks	32 (50.0)	35 (53.8)	32 (49.2)	30 (46.9)	33 (52.4)	30 (46.9)	33 (51.6)
Completed >= 8 weeks	22 (34.4)	28 (43.1)	26 (40.0)	26 (40.6)	26 (41.3)	28 (43.8)	25 (39.1)
Number of subjects discontinued from study	12 (18.8)	2 (3.1)	6 (9.2)	7 (10.9)	4 (6.3)	7 (10.9)	7 (10.9)
Primary reason for discontinuation							
Adverse Event	1 (1.6)	0	1 (1.5)	1 (1.6)	1 (1.6)	2 (3.1)	2 (3.1)
Major Protocol Deviation	0	0	0	0	0	0	1 (1.6)
Lost to Follow-Up	1 (1.6)	0	1 (1.5)	0	0	2 (3.1)	0
Voluntary Withdrawal	4 (6.3)	1 (1.5)	3 (4.6)	1 (1.6)	0	1 (1.6)	3 (4.7)
Lack of Efficacy	3 (4.7)	1 (1.5)	0	5 (7.8)	2 (3.2)	2 (3.1)	0
Investigator's Discretion	3 (4.7)	0	0	0	0	0	0
Other	0	0	1 (1.5)	0	1 (1.6)	0	1 (1.6)

Most randomized subjects (406 of 449) completed at least 6 weeks of double blind treatment with double-blind study medication. The highest number of drop outs was in the placebo group (19%) followed by TAK-491 20 mg and 80 mg (11% each). Drop outs for adverse events were uncommon in all groups.

Primary efficacy

Blood pressure results are shown below.

Study Visit	Placebo N=61	TAK-491 5 mg N=65	TAK-491 10 mg N=63	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	OLM 20 mg N=63
Sitting Clinic DBP							
Baseline (a)							
N	61	65	63	64	62	64	63
LS mean (SE)	100.1 (0.56)	99.8 (0.55)	99.4 (0.55)	99.7 (0.55)	99.7 (0.56)	100.3 (0.55)	99.8 (0.55)
Week 8							
N	58	63	63	63	61	63	63
LS mean (SE)	-7.9 (1.12)	-10.8 (1.08)	-13.1 (1.08)	-11.5 (1.08)	-13.6 (1.10)	-11.6 (1.08)	-11.0 (1.08)
LS mean difference from Placebo (SE) (b)		-2.9	-5.3	-3.7	-5.7	-3.7	-3.2
95% CI of difference		(-5.96, 0.16)	(-8.33, -2.20)	(-6.73, -0.61)	(-8.80, -2.63)	(-6.77, -0.65)	(-6.24, -0.12)
P-value		0.063	<0.001*	0.019*	<0.001*	0.018*	0.042*
Sitting Clinic SBP							
Baseline (a)							
N	61	65	63	64	62	64	63
LS mean (SE)	150.8 (1.59)	150.2 (1.54)	152.4 (1.56)	149.1 (1.55)	150.6 (1.57)	151.2 (1.55)	150.3 (1.56)
Week 8							
N	58	63	63	63	61	63	63
LS mean (SE)	-4.9 (1.73)	-11.0 (1.66)	-15.7 (1.66)	-14.7 (1.66)	-17.1 (1.69)	-13.3 (1.66)	-13.5 (1.66)
LS mean difference from placebo (SE) (b)		-6.1	-10.8	-9.8	-12.3	-8.5	-8.7
95% CI of difference		(-10.84, -1.41)	(-15.51, -6.08)	(-14.53, -5.10)	(-17.02, -7.52)	(-13.19, -3.76)	(-13.39, -3.96)
P-value		0.011*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

All post-baseline P-values were determined by ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate).

CI=confidence interval.

* Significant difference at 0.05 level.

(a) Baseline value is the last observation before the first dose of double-blind study medication.

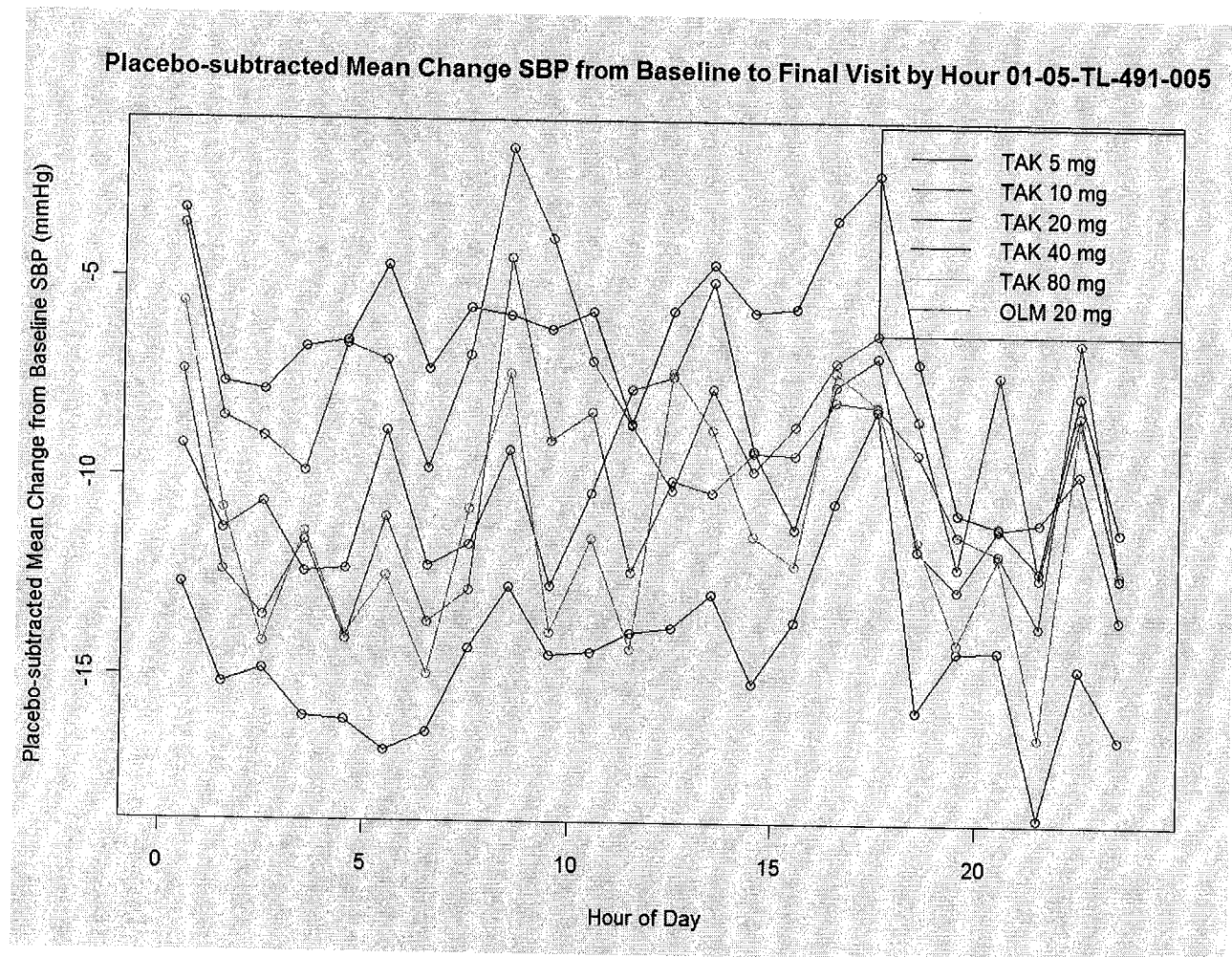
(b) LS mean difference=LS mean change of each active group (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

Mean baseline DBP measurements were similar for all treatment groups. At week 8, all the active treatments lowered DBP more than placebo did ($p < 0.05$ except for TAK-491 5 mg). The treatment effect for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan were -3 mmHg, -5 mmHg, -4 mmHg, -6 mmHg, -4 mmHg and -3 mmHg, respectively. These similar decreases in DBP indicates a lack of a dose response for TAK-491.

Mean baseline SBP measurements were similar for all treatment groups. At week 8, all the active treatments lowered SBP more than placebo did ($p < 0.001$ except for TAK-491 5 mg). The treatment effect for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan were -6 mmHg, -11 mmHg, -10 mmHg, -12 mmHg, -8 mmHg and -9 mmHg, respectively. As with DBP, there were only small differences between the active treatment groups in lowering SBP and there was not a dose response for TAK-491.

A reasonable starting dose of TAK-491 is 5 mg with a maximum dose 40 mg. TAK-491 doses above 5 mg are not superior to olmesartan 40 mg.

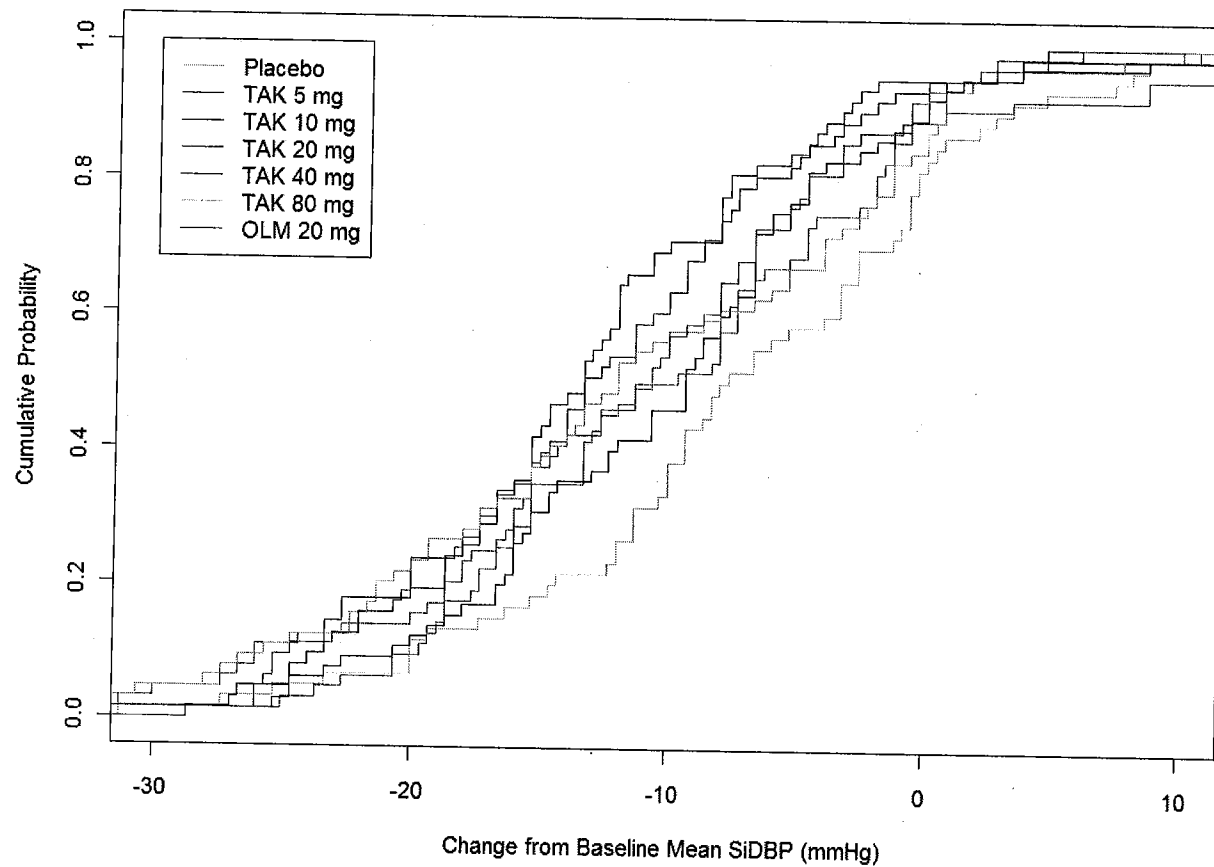
The following figure is mean placebo subtracted change from baseline ABPM SBP by hour.



There is not much evidence of a dose response.

The figure below is the cumulative distribution function for the sitting clinic DBP. There was one subjects who did not have post baseline clinic DBP.

Distribution of Primary Endpoint (SiDBP) Study 01-05-TL-491-005

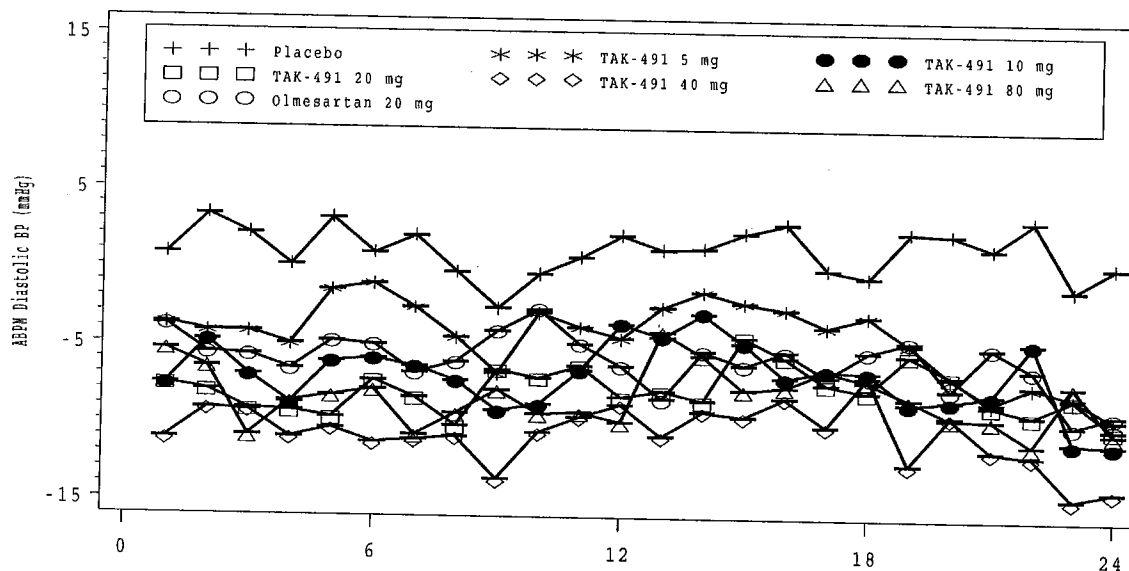


Secondary endpoints

ABPM

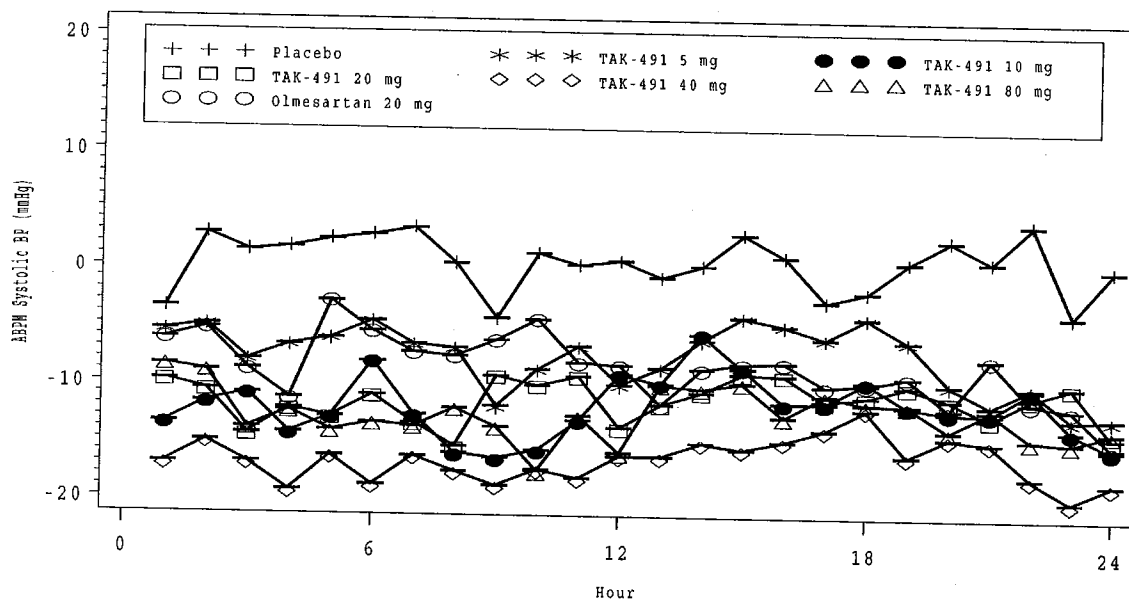
DBP and SBP 24 hour profiles, change from baseline at endpoint, are shown below.

Figure 15.2.5.3
 ABPM Measurements: Change From Baseline in Mean Diastolic Blood Pressure (mmHg)
 by Hour for the 0 - 24 Hour Interval
 Full Analysis Set



SBP

Figure 15.2.6.3
 ABPM Measurements: Change From Baseline in Mean Systolic Blood Pressure (mmHg)
 by Hour for the 0 - 24 Hour Interval
 Full Analysis Set



Safety

Deaths

There was 1 death during this study. Subject 5083/003 (olmesartan 20 mg), on study day 26 experienced a fatal cardiac arrest that were fatal.

Serious adverse events

There were 5 subjects who reported a serious adverse event.

Table 12.d Summary of Treatment-Emergent SAEs-- Safety Set

Site/Subject No. Treatment	AE	Onset Day	Relationship to Drug (a)	Intensity	Action/Outcome
5084/006 Placebo	Gastrointestinal hemorrhage	Study Day 34	Not related	Moderate	Drug withdrawn/ Resolved
	Myocardial infarction	Study Day 34	Not related	Severe	Not applicable/ Resolved
5008/004 TAK-491 5 mg	Wound Infection	Study Day 42	Not related	Mild	Dose not changed/ Resolved
5061/012 TAK-491 10 mg	Hydrocephalus	Study Day 39	Not related	Moderate	Drug withdrawn/ Resolved
	Headache	Study Day 39	Not related	Moderate	Not applicable/ Resolved
5008/024 TAK-491 40 mg	Esophageal spasm	Study Day 57	Not related	Mild	Drug withdrawn/ Resolved
5083/003 Olmesartan 20 mg	Hypertensive heart disease	Study Day 26	Not related	Severe	Fatal
	Cardiac arrest	Study Day 26	Not related	Severe	Fatal

Source: Appendix 16.2.7.3.

(a) As judged by the investigator.

The above list reveals no obvious safety risk from any of the drugs studied.

Adverse events that resulted in study discontinuation

A total of 9 subjects prematurely discontinued the study because of adverse events.

Subject 5083/003 discontinued because of a fatal cardiac arrest and subjects 5008/024, 5061/012, 5084/006 discontinued because of a nonfatal serious adverse event.

The other subjects are listed below:

- subject 5009/001 (olmesartan 20 mg treatment group) reported dysuria and testicular pain;
- subject 5026/004 (TAK-491 20 mg treatment group) reported urticaria on study day 39;
- subject 5036/009 (TAK-491 80 mg treatment group) reported hypotension on study day 8;
- subject 5064/002 (TAK-491 80 mg treatment group) reported hypotension on study day 24;
- subject 5078/005 (placebo) reported blood pressure increased on study day 6.

The two reports of hypotension were reported by subjects randomized to TAK-491 80 mg.

All adverse events

The most commonly reported adverse events are shown below.

Table 12.c Treatment-Emergent AEs Presented by Preferred Term with Incidence of at Least 5 Subjects Total Among All Treatment Groups – Safety Set

Preferred Term	Placebo N=63	TAK-491 5 mg N=65	TAK-491 10 mg N=64	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	Olmesartan 20 mg N=63
Headache	3 (4.8)	2 (3.1)	2 (3.1)	7 (10.9)	3 (4.8)	3 (4.7)	5 (7.9)
Nasopharyngitis	4 (6.3)	0	3 (4.7)	3 (4.7)	1 (1.6)	3 (4.7)	1 (1.6)
Dizziness	2 (3.2)	1 (1.5)	3 (4.7)	4 (6.3)	2 (3.2)	1 (1.6)	1 (1.6)
Diarrhea	1 (1.6)	1 (1.5)	1 (1.6)	2 (3.1)	2 (3.2)	2 (3.1)	1 (1.6)
Dyslipidemia	1 (1.6)	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)	0	0
Fatigue	0	0	2 (3.1)	0	2 (3.2)	1 (1.6)	1 (1.6)
Upper respiratory tract infection	0	4 (6.2)	0	0	2 (3.2)	0	0
Cough	1 (1.6)	1 (1.5)	0	1 (1.6)	1 (1.6)	1 (1.6)	0
Vomiting	0	0	2 (3.1)	0	1 (1.6)	1 (1.6)	1 (1.6)

Source: Table 15.3.1.3.

Note: Data represent number (percentage) of subjects.

The most commonly reported events were regardless of treatment group included headache, nasopharyngitis, dizziness, diarrhea, dyslipidemia, fatigue, upper respiratory tract infection, cough and vomiting. There were only small differences between the treatment groups with respect to the incidence of these events and none appeared to be linked to the dose of TAK-491.

Clinical laboratory values

The following list subjects who reported adverse events related to serum chemistry values:

- subject 5029/005 (TAK-491 5 mg reported ALT and AST increased on study day 30 which resolved by Study Day 44. The elevated ALT (88 U/L) and AST (56 U/L) values were not considered markedly abnormal.
- subject 5040/018 (TAK-491 20 mg) reported hepatic enzyme increased on study day 49. ALT and AST values were elevated at Visit 9 (65 U/L and 42 U/L, respectively) and resolved by study day 63.
- subject 5034/010 (placebo) experienced AEs of blood glucose increased (10.2 mmol/L) and blood insulin increased (41.9 µIU/mL) on study day 3.

There were no withdrawals because of serum chemistry abnormalities.

Reports of marked abnormal chemistry values are shown below.

Table 12.e Marked Abnormalities in Serum Chemistries – Safety Set

Laboratory Test	Placebo N=63	TAK-491 5 mg N=65	TAK-491 10 mg N=64	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	OLM 20 mg N=63
ALT >3 × ULN	0	0	0	1 (1.6)	0	0	0
AST >3 × ULN	0	0	0	0	0	0	1 (1.6)
BUN >30 mg/dL	0	1 (1.5)	0	0	1 (1.6)	0	0
Creatinine >2 mg/dL	0	0	0	0	0	0	1 (1.6)
Potassium	0	0	0	0	0	0	0
Uric acid >8 mg/dL	0	3 (4.6)	2 (3.1)	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)

Source: Table 15.3.4.5.

OLM=olmesartan, ULN=upper limit of normal.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least one test result during a particular test was considered markedly abnormal. Only postbaseline values are included in this table.

Overall, there were very few reports and no pattern can be detected.

The following subjects reported hematology-related adverse events:

- subject 5092/004 (TAK-491 20 mg) reported elevated eosinophil count;
- subject 5079/009 (TAK-491 80 mg) reported increased hemoglobin (16.4 g/dL) and hematocrit (0.5 ratio) on Study Day 27.

There were no study withdrawals because of hematology abnormalities.

Urinalysis

There were no clinically meaningful changes in these data and no patterns of urinalysis abnormalities that would suggest a clinically meaningful treatment effect. Subject 5018/019 (placebo) reported WBCs urine positive on Study Day 55 as an adverse event.

There were no withdrawals due abnormalities in urinalysis test results

Vital Signs, ECGs, Physical Findings

There were no remarkable differences in weight across treatment groups at baseline, or in mean weight changes from baseline at endpoint.

There were no meaningful differences in sitting or standing pulse at baseline or at any visit with respect to change from baseline across treatment groups and no dose-related findings.

Mean sitting pulse increased slightly in the placebo group (0.30 bpm) and decreased slightly in the TAK-491 groups (range -0.43 to -2.22 bpm) and olmesartan group (-0.38 bpm). Mean heart rate increased in the placebo and olmesartan groups (1.3 and 2.0 bpm, respectively), and generally decreased or did not change in the TAK-491 groups (1.0, -0.1, -1.9, 0.1, -0.4 bpm in the 5, 10, 20, 40, and 80 mg groups, respectively).

Physical Findings

There were no major findings as a result of physical examinations in the safety population.

ECGs

There were no remarkable changes from Baseline to Final Visit with respect to the overall clinical interpretation of the 12-lead ECG and no meaningful differences between treatment groups.

Reviewer's summary and conclusions

Efficacy: DBP results at week 8 showed treatment effects for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan that were -3 mmHg, -5 mmHg, -4 mmHg, -6 mmHg, -4 mmHg and -3 mmHg, respectively. SBP results at week 8 showed treatment effects for TAK-491 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and olmesartan that were -6 mmHg, -11 mmHg, -10 mmHg, -12 mmHg, -8 mmHg and -9 mmHg, respectively. As with DBP, there were only small differences between the active treatment groups in lowering SBP and there was not a dose response for TAK-491.

A reasonable starting dose of TAK-491 is 5 mg with a maximum dose 40 mg. TAK-491 doses above 5 mg are not superior to olmesartan 40 mg.

Safety: The most commonly reported events were regardless of treatment group included headache, nasopharyngitis, dizziness, diarrhea, dyslipidemia, fatigue, upper respiratory tract infection, cough and vomiting. There were only small differences between the treatment groups with respect to the incidence of these events and none appeared to be linked to the dose of TAK-491.

Conclusions: the results of this study support the opinion that doses of TAK-491 5 mg through 40 mg are safe and effective. TAK 491 80 mg did not produce better blood pressure effects compared to 40 mg. TAK -491 is not superior to olmesartan 20 mg.

Study 01-06-TL-491-011

Title

A Double-Blind, Randomized, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of TAK-491 in Black Subjects with Essential Hypertension.

There were 74 investigators enrolled subjects into the United States and Puerto Rico

Study Period October 30, 2007 to April 30, 2009

Primary objective

To evaluate the change in 24-hour mean ambulatory blood pressure monitoring (ABPM) systolic blood pressure (SBP) in response to TAK-491 compared to placebo for 6 weeks in Black subjects with essential hypertension.

Secondary:

- change in 24-hour mean ABPM diastolic blood pressure (DBP) in response to TAK-491 compared to placebo.
- change in trough, sitting clinic SBP, and DBP.
- To evaluate the treatment effect of TAK-491 on SBP and DBP using additional ABPM parameters.
- the proportion of subjects who achieve response criteria:
 - a) Clinic DBP <90 mm Hg and/ or reduction of ≥ 10 mm Hg from Baseline.
 - b) Clinic SBP <140 mm Hg and/ or reduction of ≥ 20 mm Hg from Baseline.
 - c) a and b.

Study design

Multicenter, randomized, parallel-group, double-blind placebo-controlled study in black subjects with essential hypertension. After a 2-week single-blind placebo run-in period, subjects who met the entry criteria were randomized to receive TAK-491 40 mg QD, TAK-491 80 mg QD, or placebo for 6 weeks. Clinic SBP and DBP were measured at screening, randomization, run-in period, and treatment period (Week 2, Week 4, and Week 6). ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 (or early termination) for 24 hours following the last administration of study medication.

Number of Subjects:

There were 411 subjects planned (137 per treatment group) and 413 randomized.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been black male or nonpregnant, nonlactating women with essential hypertension, defined as a postwashout trough clinic sitting SBP on Day -1 of 150-180 mm Hg, inclusive, and a 24-hour mean SBP on Day 1 of 130-170 mm Hg, inclusive; aged 18 years or older; with clinical laboratory evaluations within the reference range for the testing laboratory or results that were deemed not clinically significant; able to comprehend and willing to sign an informed consent form; and willing to discontinue current antihypertensive medication(s) at Screening (on Day -21/Day -28 if on amlodipine).

RESULTS

Demographics

Selected demographic features of the study population are shown below.

Characteristic	Treatment (Randomized Set)		
	Placebo N=138	TAK-491 40 mg N=138	TAK-491 80 mg N=137
Sex, n (%)			
Male	60 (43.5%)	60 (43.5%)	57 (41.6%)
Female	78 (56.5%)	78 (56.5%)	80 (58.4%)
Age, yr			
Mean (SD)	51.8 (11.25)	52.2 (10.63)	51.0 (10.06)
Race, n (%) (a)			
Black or African American	138 (100.0%)	138 (100.0%)	137 (100.0%)
Multiracial	1 (0.7%)	0	0
Weight, kg			
Mean (SD)	93.4 (21.02)	88.9 (19.43)	90.0 (19.81)
Height, cm			
Mean (SD)	168.7 (10.24)	168.3 (10.30)	169.2 (10.36)
BMI, kg/m ²			
Mean (SD)	32.9 (7.38)	31.4 (6.29)	31.6 (7.70)

Note: Age=(informed consent date – date of birth +1)/365.25, and was truncated at the decimal.
(a) For race, a subject may choose more than 1 category for race. Subjects who indicated more than 1 race category are included in each category indicated, and they are also included in the multiracial category. Thus, the total number and percentage of subjects does not generally add up to the total number randomized.

Overall, there were more females than males, the mean age was about 52 years, and all subjects were black or multiracial. The groups were well balanced.

Subject disposition

The number and percent of subjects who prematurely discontinued the study and the reasons for discontinuation are shown below.

	Treatment (All Randomized or Treated Subjects)		
	Placebo N=138	TAK-491 40 mg N=140	TAK-491 80 mg N=137
Number of subjects enrolled	138	140	137
Number subjects prematurely discontinued (%)	15 (10.9)	14 (10.0)	21 (15.3)
Primary reason for premature discontinuation			
AE	1 (0.7)	3 (2.1)	3 (2.2)
Protocol deviation	2 (1.4)	2 (1.4)	2 (1.5)
Lost to follow-up	0	2 (1.4)	4 (2.9)
Voluntary withdrawal	6 (4.3)	1 (0.7)	7 (5.1)
Lack of efficacy	3 (2.2)	1 (0.7)	0
Study termination	0	0	0
Pregnancy	0	0	0
Other	3 (2.2)	5 (3.6)	5 (3.6)

Overall, there were slightly more premature discontinuations in the TAK-491 80 mg group compared to the other groups.

Efficacy

Primary efficacy variable was change from baseline to week 6 in the 24-hour mean SBP by ABPM

A summary of the statistical comparisons between treatment groups is shown in the table below.

Table 11.a Change From Baseline to Week 6 in the 24-hour Mean SBP by ABPM (FAS)

Study Visit	Treatment			Overall P-Value
	Placebo N=138	TAK-491 40 mg N=135	TAK-491 80 mg N=137	
Baseline				
n	94	94	101	
LS mean (SE)	145.06 (1.044)	146.72 (1.044)	146.89 (1.007)	
Week 6				
n	94	94	101	
LS mean change (SE)	-2.70 (1.065)	-7.70 (1.063)	-10.48 (1.026)	<0.001*
LS mean difference (a)		-5.00	-7.78	
(95% CI)		(-7.97, -2.04)	(-10.69, -4.86)	
P-value vs placebo		0.001*	<0.001*	
Week 6: Sensitivity analysis using multiple imputation				
LS mean difference (a)		-5.04	-7.88	<0.001*
(95% CI)		(-8.35, -1.73)	(-10.78, -4.98)	
P-value vs placebo		0.004*	<0.001*	

Source: Table 15.2.1.1.2.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate). Includes subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group) – LS mean change of placebo group.

At baseline, 24-hour mean SBP was similar between placebo and TAK-491 treatment groups (approximately 146 mm Hg).

At week 6, the placebo subtracted differences in 24-hour mean SBP for TAK-491 40 and 80 mg were -5 and -8 mmHg, respectively. The differences were significant compared to placebo but numerically less than those obtained from non black subjects in other studies.

The figures showing 24 hour SBP profile at baseline, final visit, and change from baseline at final visit are shown below.

Figure 11.a SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)

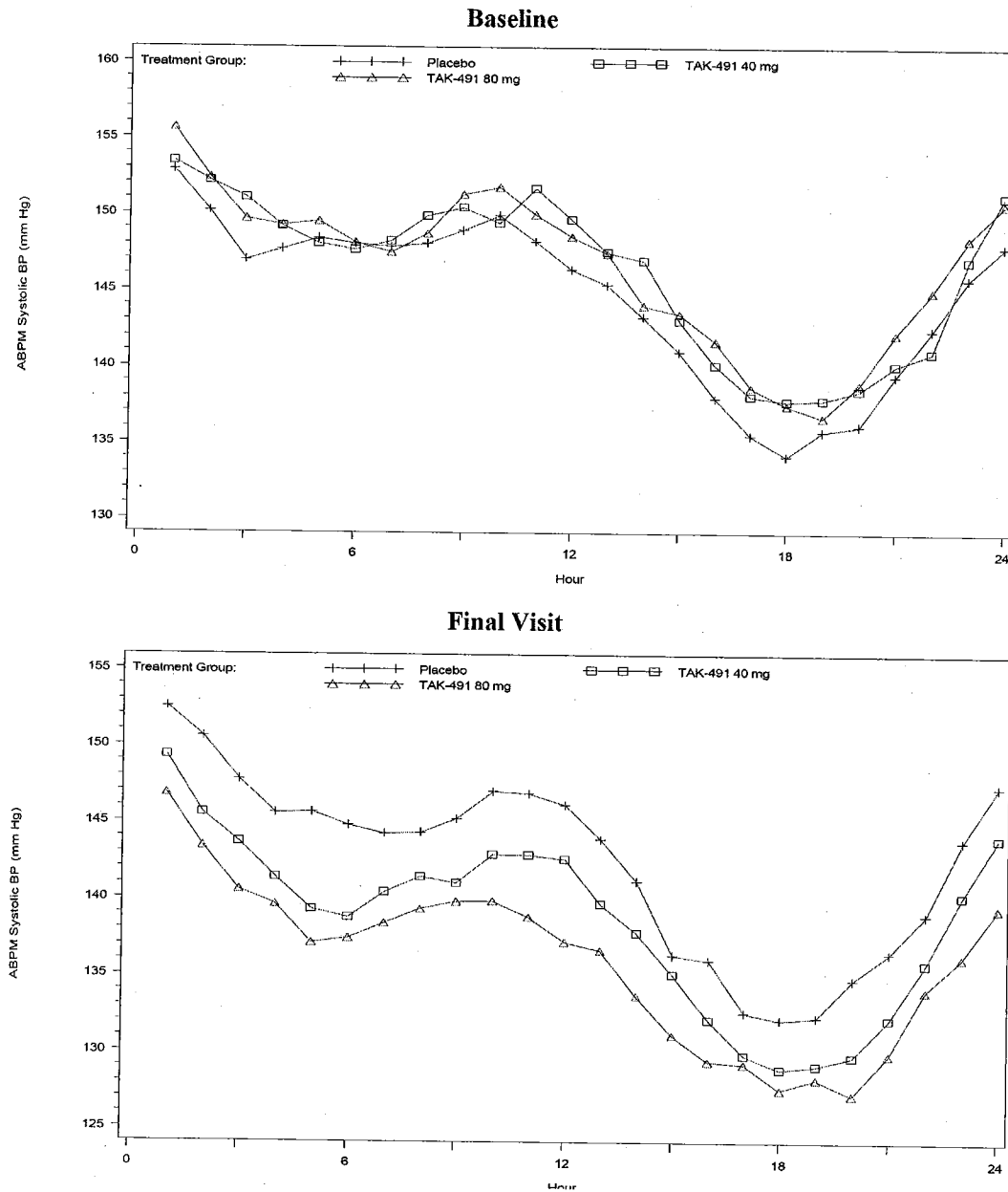
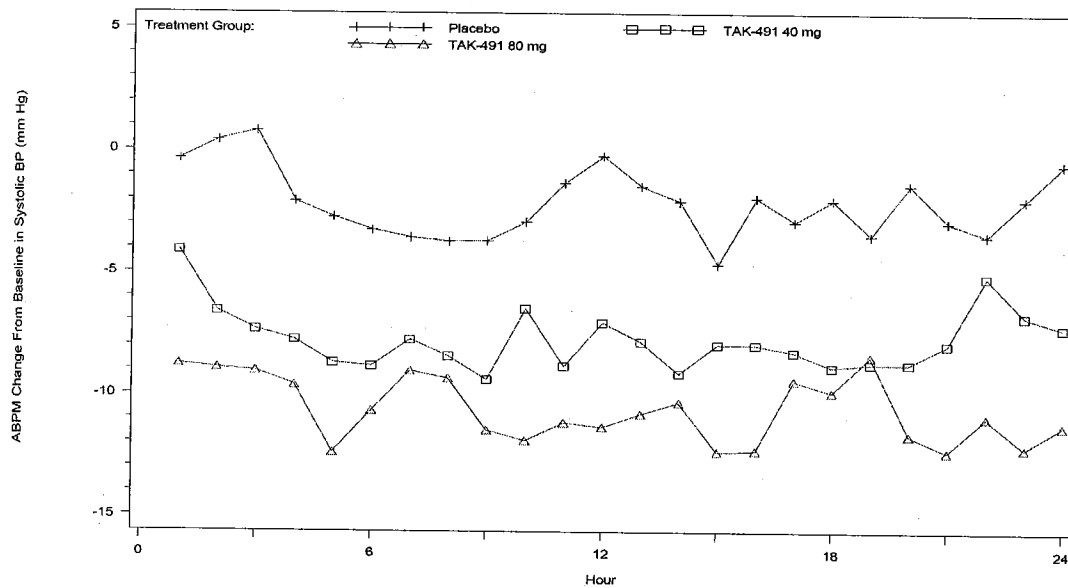


Figure 11.b Change From Baseline to Week 6 in SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)



DBP

The results for the 24 hour DBP using ABPM are shown below.

Table 11.c Summary of Change From Baseline to Week 6 in the 24-hour Mean DBP by ABPM (FAS)

Study Visit	Treatment			Overall P-Value
	Placebo N=138	TAK-491 40 mg N=135	TAK-491 80 mg N=137	
Baseline				
n	94	94	101	
LS mean (SE)	91.91 (0.945)	92.16 (0.945)	90.94 (0.912)	
Week 6				
n	94	94	101	
LS mean change (SE)	-1.49 (0.731)	-4.93 (0.732)	-7.27 (0.706)	<0.001*
LS mean difference (a)		-3.44	-5.77	
(95% CI)		(-5.47, -1.40)	(-7.78, -3.77)	
P-value vs placebo		0.001*	<0.001*	
Sensitivity analysis using multiple imputations (Week 6)				
LS mean difference (a)		-3.52	-5.68	<0.001*
(95% CI)		(-5.33, -1.72)	(-7.75, -3.62)	
P-value vs placebo		<0.001*	<0.001*	

Source: Table 15.2.2.1.2.

Note: Postbaseline P-value was from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate). Includes subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

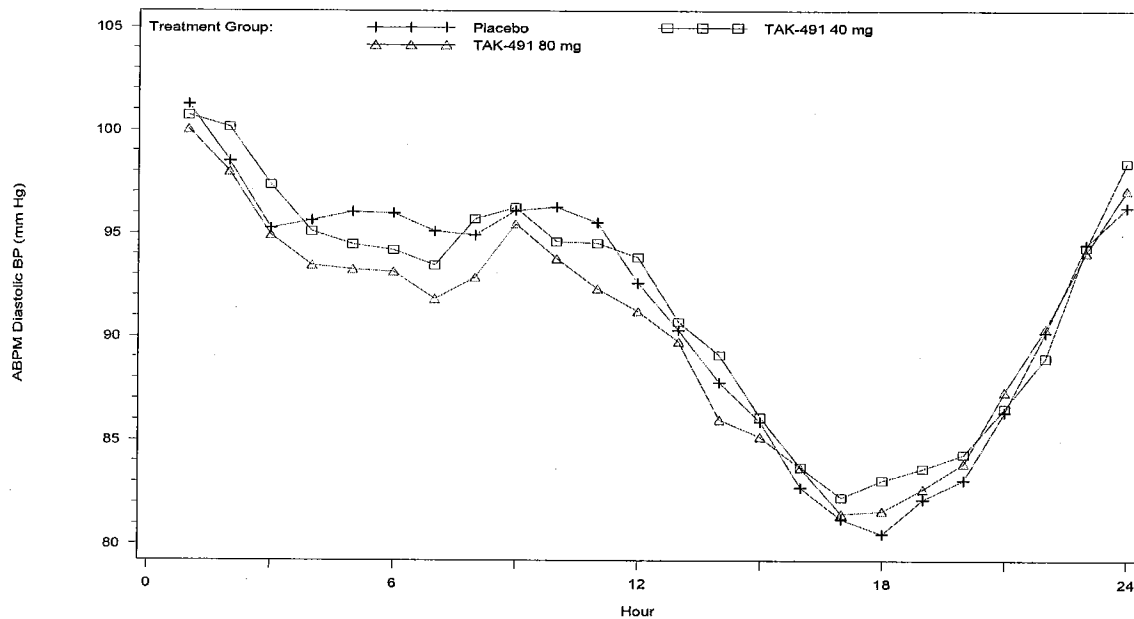
(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group) – LS mean change of placebo group.

At baseline, 24-hour mean DBP was similar between placebo and TAK-491 treatment groups (approximately 91 mm Hg).

At week 6, the placebo subtracted differences in 24-hour mean DBP for TAK-491 40 and 80 mg were -3 and -6 mmHg, respectively. The differences were significant compared to placebo but, as with SBP, numerically less than those obtained in non black populations in other studies.

The figures showing 24 hour DBP profile at baseline, final visit, and change from baseline at final visit are shown below.

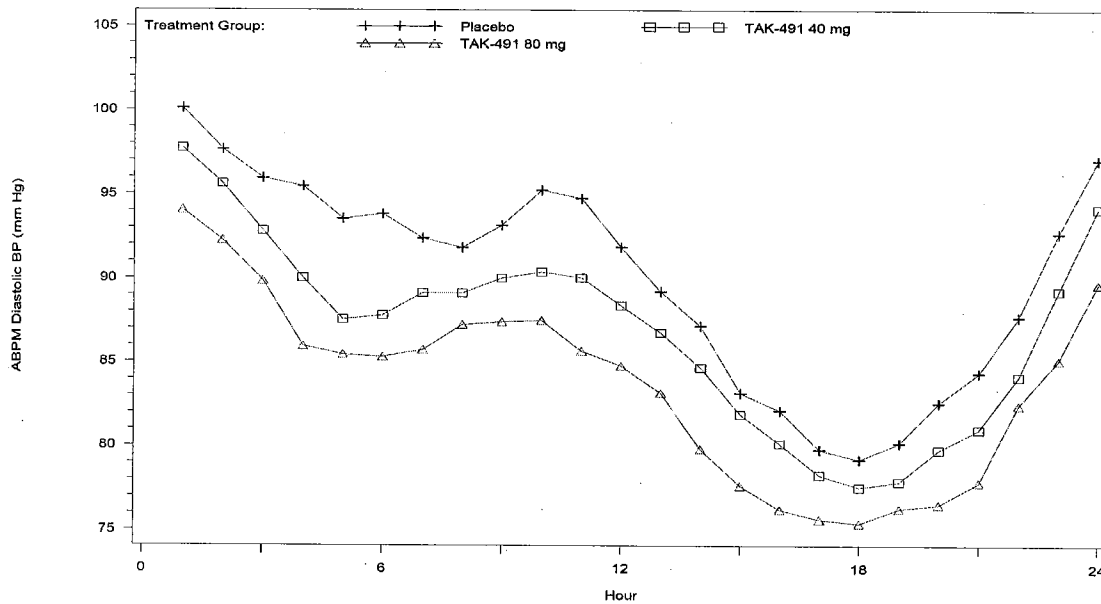
ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Baseline by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



24 hour DBP profile at final visit

Figure 15.2.2.5.2

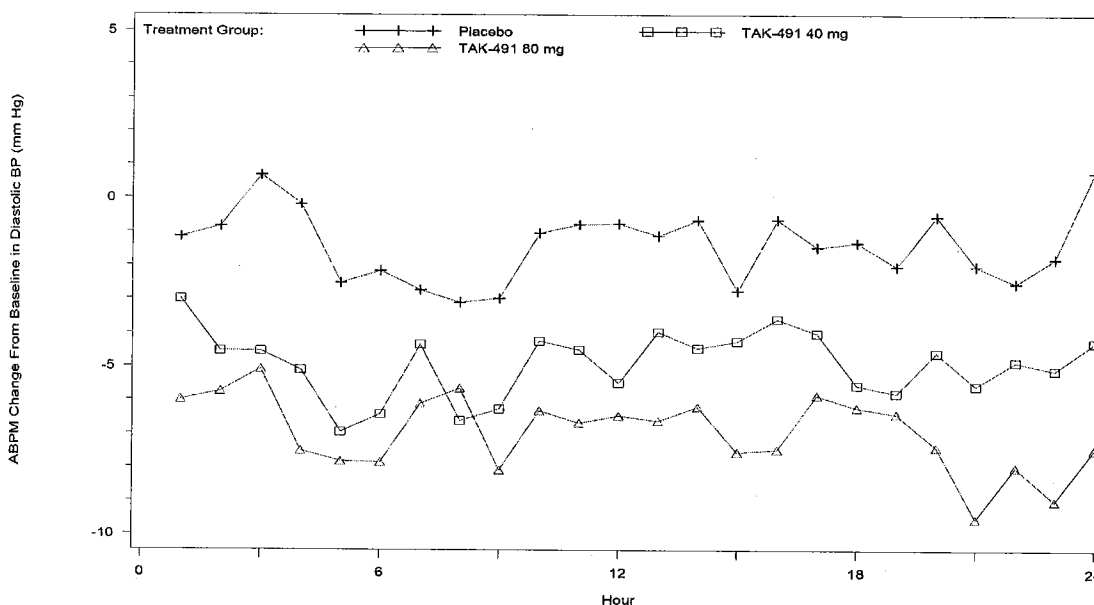
ABPM Measurements: Diastolic Blood Pressure (mm Hg) at Final Visit by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



Change from baseline at final visit

Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
Full Analysis Set



Placebo corrected trough to peak ratios for SBP and DBP are shown below.

Table 11.g Summary of Trough-to-Peak Ratios for SBP and DBP as Measured by ABPM (FAS)

		TAK-491 40 mg N=135	TAK-491 80 mg N=137
SBP			
	n	94	101
24-hour (a)	Placebo corrected trough-to-peak ratio	0.896	0.942
12-hour (b)	Placebo corrected trough-to-peak ratio	0.988	1.064
DBP			
	n	94	101
24-hour (c)	Placebo corrected trough-to-peak ratio	1.202	1.263
12-hour (d)	Placebo corrected trough-to-peak ratio	1.408	1.641

Source: Tables 15.2.1.4.1 and 15.2.2.4.1.

Note: Includes subjects with both a Baseline and postbaseline value. Peak response is defined as the change from Baseline in blood pressure values by ABPM during the peak effect interval. Trough Peak ratio was calculated as mean trough response divided by mean peak response. Placebo corrected trough peak ratio was calculated as placebo response subtracted mean trough response divided by placebo response subtracted mean peak response.

(a) The peak effect interval was determined for each subject as the 2-hour interval during the 24 hours after dosing in which the maximum decrease from Baseline was observed for SBP.

(b) The peak effect interval was determined for each subject as the 2-hour interval during the 12 hours after dosing in which the maximum decrease from Baseline was observed for SBP.

(c) The peak effect interval was determined for each subject as the 2-hour interval during the 24 hours after dosing in which the maximum decrease from Baseline was observed for DBP.

(d) The peak effect interval was determined for each subject as the 2-hour interval during the 12 hours after dosing in which the maximum decrease from Baseline was observed for DBP.

The placebo-corrected peak and trough blood pressure lowering effects on SBP and DBP were similar (ratios that were ≥ 0.9).

Subgroup analyses

Subgroup analyses were conducted by age and sex (shown below), as well as for BMI, median baseline 24-hour mean SBP, and cGFR, to evaluate for differences in blood pressure effects of TAK-491.

Table 11.i Subgroup Analysis of 24-hour Mean SBP by ABPM (FAS)

Subgroup	Treatment		
	Placebo	TAK-491 40 mg	TAK-491 80 mg
Age			
<65 years			
n	83	82	91
LS mean at Baseline (SE)	144.73 (1.117)	145.77 (1.124)	146.70 (1.067)
LS mean Change to Week 6 (SE)	-2.30 (1.126)	-7.51 (1.131)	-11.12 (1.075)
LS mean Difference (95% CI) (a)		-5.21 (-8.35, -2.06)*	-8.82 (-11.89, -5.75)*
≥65 years			
n	11	12	10
LS mean at Baseline (SE)	147.51 (2.694)	153.22 (2.579)	148.65 (2.826)
LS mean Change to Week 6 (SE)	-5.72 (3.204)	-9.15 (3.108)	-4.34 (3.328)
LS mean Difference (95% CI) (a)		-3.43 (-12.73, 5.87)	1.38 (-8.00, 10.77)
Sex			
Male			
n	41	38	43
LS mean at Baseline (SE)	145.05 (1.582)	148.11 (1.643)	148.94 (1.545)
LS mean Change to Week 6 (SE)	-3.51 (1.635)	-6.65 (1.685)	-14.02 (1.589)
LS mean Difference (95% CI) (a)		-3.14 (-7.80, 1.52)	-10.51 (-15.05, -5.96)*
Female			
n	53	56	58
LS mean at Baseline (SE)	145.06 (1.383)	145.77 (1.346)	145.37 (1.322)
LS mean Change to Week 6 (SE)	-1.93 (1.385)	-8.42 (1.347)	-7.97 (1.323)
LS mean Difference (95% CI) (a)		-6.49 (-10.31, -2.68)*	-6.03 (-9.82, -2.25)*

There was a larger placebo effect in the older age group (-5.72 mmHg) compared to the younger age group (-2.3 mmHg).

TAK-491 80 mg was less effective in the older group than placebo. This could be the result of small sample size.

The results for the other subgroups are shown below.

Table 11.i Subgroup Analysis of 24-hour Mean SBP by ABPM (FAS) (continued)

Subgroup	Treatment		
	Placebo	TAK-491 40 mg	TAK-491 80 mg
BMI			
<30 (kg/m²)			
n	37	40	49
LS mean at Baseline (SE)	145.67 (1.685)	149.06 (1.621)	146.95 (1.465)
LS mean Change to Week 6 (SE)	-4.54 (1.811)	-7.73 (1.744)	-11.31 (1.568)
LS mean Difference (95% CI) (a)		-3.18 (-8.18, 1.81)	-6.77 (-11.51, -2.03)*
≥30 (kg/m²)			
n	55	54	52
LS mean at Baseline (SE)	144.61 (1.355)	144.98 (1.367)	146.83 (1.393)
LS mean Change to Week 6 (SE)	-1.67 (1.329)	-7.56 (1.341)	-9.83 (1.370)
LS mean Difference (95% CI) (a)		-5.89 (-9.61, -2.16)*	-8.16 (-11.93, -4.38)*
Baseline 24-hour mean SBP			
<Median (145.73 [mm Hg])			
n	47	50	48
LS mean at Baseline (SE)	137.34 (0.752)	138.56 (0.729)	138.46 (0.744)
LS mean Change to Week 6 (SE)	-0.56 (1.380)	-4.58 (1.335)	-8.76 (1.361)
LS mean Difference (95% CI) (a)		-4.03 (-7.83, -0.22)*	-8.20 (-12.04, -4.36)*
≥Median (145.73 [mm Hg])			
n	47	44	53
LS mean at Baseline (SE)	152.78 (0.976)	155.98 (1.009)	154.52 (0.919)
LS mean Change to Week 6 (SE)	-5.07 (1.647)	-10.71 (1.701)	-12.26 (1.536)
LS mean Difference (95% CI) (a)		-5.64 (-10.36, -0.92)*	-7.19 (-11.65, -2.74)*
cGFR			
30 ≤cGFR <60 (mL/min/1.73 m²)			
n	1	1	3
LS mean at Baseline (SE)	147.94 (12.568)	144.17 (12.568)	151.35 (7.256)
LS mean Change to Week 6 (SE)	-9.49 (2.724)	4.36 (2.825)	-8.92 (1.602)
LS mean Difference (95% CI) (a)		13.85 (-35.52, 63.22)	0.57 (-39.84, 40.97)
60 ≤cGFR <90 (mL/min/1.73 m²)			
n	39	47	43
LS mean at Baseline (SE)	145.24 (1.752)	148.91 (1.596)	147.36 (1.668)
LS mean Change to Week 6 (SE)	-3.30 (1.770)	-6.74 (1.610)	-9.89 (1.677)
LS mean Difference (95% CI) (a)		-3.44 (-8.20, 1.32)	-6.59 (-11.42, -1.77)*
90 ≤cGFR (mL/min/1.73 m²)			
Baseline ABPM: 0- to 24-hour mean SBP (mm Hg)			
n	54	46	54
LS mean at Baseline (SE)	144.87 (1.268)	144.53 (1.374)	146.00 (1.268)
LS mean Change to Week 6 (SE)	-2.13 (1.315)	-8.97 (1.425)	-10.94 (1.317)
LS mean Difference (95% CI) (a)		-6.84 (-10.67, -3.01)*	-8.81 (-12.49, -5.13)*

Source: Tables 15.2.1.3.2, 15.2.1.3.4, 15.2.1.3.6, 15.2.1.3.8, and 15.2.1.3.10.

Note: Includes subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 dose group) - LS mean change of placebo group.

SAFETY RESULTS

Extent of Exposure

A total of 413 subjects were randomized in the study.

Three subjects (0049/010, 0053/021, 0075/036) in the TAK-491 40 mg treatment group were randomized but not treated and were excluded from the safety population (N=412). An additional two subjects (0053/015 and 0075/037) who received TAK-491 40 mg but were never randomized to this treatment group were only included in the safety analysis set.

The mean number of days of exposure to study drug for each treatment group is shown below.

Table 12.a Duration of Treatment With Study Medication in Days - Safety Analysis Set

Double-Blind Treatment (days)	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
Mean (SD)	41.6 (8.14)	41.4 (8.07)	39.4 (11.07)
Median	43.0	43.0	42.0
Minimum, Maximum	2, 63	1, 56	1, 56

Source: Table 15.1.14.

The mean number of days was similar across treatment groups.

Study completion

The numbers and percents of subjects who completed and those who did not complete the study are shown below.

Table 15.1.4
Disposition of Subjects
All Randomized or Treated Subjects

	Number of Subjects (%)			
	Placebo (N=138)	TAK-491 40 mg (N=140)	TAK-491 80 mg (N=137)	Total (N=415)
Randomized But Not Treated	0 (0.0)	3 (2.1)	0 (0.0)	3 (0.7)
Treated But Not Randomized	0 (0.0)	2 (1.4)	0 (0.0)	2 (0.5)
Completed Study Drug	123 (89.1)	126 (90.0)	116 (84.7)	365 (88.0)
Prematurely Discontinued Study Drug	15 (10.9)	14 (10.0)	21 (15.3)	50 (12.0)
Reason for Discontinuation of Study Drug				
Adverse Event	1 (0.7)	3 (2.1)	3 (2.2)	7 (1.7)
Major Protocol Deviation	2 (1.4)	2 (1.4)	2 (1.5)	6 (1.4)
Lost to Follow-Up	0 (0.0)	2 (1.4)	4 (2.9)	6 (1.4)
Voluntary Withdrawal	6 (4.3)	1 (0.7)	7 (5.1)	14 (3.4)
Study Termination	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of Efficacy	3 (2.2)	1 (0.7)	0 (0.0)	4 (1.0)
Other	3 (2.2)	5 (3.6)	5 (3.6)	13 (3.1)

Most subjects completed the trial. However, the TAK-491 80 mg group had the highest percent of those who dropped out early.

Serious safety

Deaths

There were no deaths reported during the study.

Serious adverse events

The number and percent of subjects who reported a treatment-emergent serious safety adverse event after initiation of double-blind study drug and within 30 days after their last dose are shown below.

Table 12.f All SAEs - Safety Analysis Set

SOC Preferred Term	Subjects (%)			
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137	Total N=412
Subjects With Any Treatment-Emergent SAEs	0	3 (2.2)	1 (0.7)	4 (1.0)
Gastrointestinal disorders	0	0	1 (0.7)	1 (0.2)
Vomiting	0	0	1 (0.7)	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.7)	0	1 (0.2)
Diabetic ketoacidosis	0	1 (0.7)	0	1 (0.2)
Nervous system disorders	0	1 (0.7)	0	1 (0.2)
Cerebral hemorrhage	0	1 (0.7)	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	0	1 (0.7)	0	1 (0.2)
Asthma	0	1 (0.7)	0	1 (0.2)

While there were no serious adverse events reported by the placebo group, there were three subjects in TAK-491 40 mg and one subject in TAK-491 80 mg who reported a serious event. These four events are shown below.

Table 12.g Summary of Treatment-Emergent SAEs - Safety Analysis Set

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
TAK-491 40 mg					
0025/005	Diabetic ketoacidosis	11	Not related	Moderate	Resolved
0031/023	Cerebral hemorrhage	44	Not related	Severe	Resolved
0083/002	Asthma	20	Not related	Moderate	Resolved
TAK-491 80 mg					
0057/001	Vomiting (b)	20	Possible	Moderate	Resolved

Source: Table 15.3.2.2.

(a) As judged by the investigator.

(b) Study drug was discontinued.

The study drug was only discontinued prematurely for subject 0057/001. A cerebral hemorrhage was reported by subject 0031/023, a 57-year-old black woman randomized to TAK-491 40 mg. The event occurred on day 44, 2 days after discontinuation of study drug. The subject had a screening mean SBP of 172 mm Hg. Sitting blood pressures at week 2 and week 6 were 138/89 mmHg and 110/71 mmHg, respectively.

Discontinuations because of an adverse event

There were 6 subjects permanently discontinued the study because of an adverse event. These subjects are shown below.

Table 12.h Listing of Treatment-Emergent AEs Leading to Study Drug Discontinuation - Safety Analysis Set

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Intensity	Outcome
Placebo					
0028/006	Blood pressure increased	9	Possible	Moderate	Resolved
TAK-491 40 mg					
0050/021	Arthritis	3	Not related	Mild	Not resolved
0075/039	Vertigo	11	Possible	Moderate	Not resolved
0088/005	Musculoskeletal stiffness	26	Not related	Mild	Resolving
TAK-491 80 mg					
0023/002	Hepatic enzyme increased	21	Definite	Severe	Resolved
0057/001	Vomiting (b)	20	Possible	Moderate	Resolved
0067/004	Worsening iron deficiency anemia (c)	-12	Not related	Moderate	Not resolved

Source: Table 15.3.2.1 and Appendix 16.2.7.1.

(a) As judged by the investigator.

(b) SAE.

(c) Subject 0067/004 experienced an AE of worsening iron deficiency anemia while taking placebo during Run-in. The subject was later randomized to TAK-491 80 mg and the AE continued. Study drug was discontinued.

Subject 0067/004 reported worsening iron deficiency anemia during the run in phase.

Subject 0023/002 (TAK-491 80 mg) reported hepatic enzyme increase from study day 21 to 63. The subject reported no relevant medical history, medication history, concurrent medical conditions, or concomitant medications. The subject reported a viral infection on study day 19 that resolved on day 26.

-Day 14: ALT and AST 465 U/L and 180 U/L, respectively.

-Day 21: the subject was discontinued from study drug.

-Day 26: ALT and AST 343 and 110 U/L, respectively.

-Day 35: ALT and AST 84 and 28 U/L, respectively.

Viral titer levels were unknown. Total bilirubin remained within normal limits throughout the duration of treatment.

All adverse events

Those adverse events reported by at least 2% of subjects in any treatment group are shown below.

Table 12.d Treatment-Emergent AEs Presented by Preferred Term With Incidence of $\geq 2\%$ of Subjects In Any Treatment Groups - Safety Analysis Set

Preferred Term	Subjects (%)			
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137	Total N=412
Headache	3 (2.2)	6 (4.4)	9 (6.6)	18 (4.4)
Blood CK increased	6 (4.3)	4 (2.9)	3 (2.2)	13 (3.2)
Urinary tract infection	6 (4.3)	3 (2.2)	3 (2.2)	12 (2.9)
Plasminogen activator inhibitor increased	5 (3.6)	4 (2.9)	2 (1.5)	11 (2.7)
Dizziness	1 (0.7)	4 (2.9)	3 (2.2)	8 (1.9)
Oedema peripheral	1 (0.7)	4 (2.9)	3 (2.2)	8 (1.9)
Nasopharyngitis	3 (2.2)	2 (1.5)	2 (1.5)	7 (1.7)
Hyperlipidemia	1 (0.7)	3 (2.2)	1 (0.7)	5 (1.2)
Pain in extremity	1 (0.7)	1 (0.7)	3 (2.2)	5 (1.2)
Aspartate aminotransferase increased	0	1 (0.7)	3 (2.2)	4 (1.0)
C-reactive protein increased	3 (2.2)	0	1 (0.7)	4 (1.0)
Crystal urine present	0	0	3 (2.2)	3 (0.7)

Source: Table 15.3.1.4.

Note: If a subject experienced more than 1 episode of an AE, it is counted only once within a SOC. Percentages are based on the total number of subjects in the safety analysis set for each treatment group.

Note: AEs are sorted by decreasing order of incidence based on the total number of AE reports.

CK=creatinine kinase.

Those events reported more often in both of the TAK-491 treatment groups compared to placebo include headache (TAK-491 40, 80 mg, and placebo: 4.4%, 6.6%, and 2.2%, respectively), dizziness (TAK-491 40, 80 mg, and placebo: 2.9%, 2.2%, and 0.7%, respectively) and edema (TAK-491 40, 80 mg, and placebo: 2.9%, 2.2%, and 0.7%, respectively).

Laboratory values

Serum Chemistry

Mean values at baseline, final visit and change from baseline at final visit for serum chemistries are shown below.

Table 12.i Summary of Serum Chemistry Changes From Baseline to Final Visit

Serum Chemistry	Placebo N=138		TAK-491 40 mg N=137		TAK-491 80 mg N=137	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Creatinine (μmol/L)						
Baseline (a)	138	83.7 (19.26)	137	85.1 (20.91)	136	84.1 (18.54)
Final Visit (b)	135	84.6 (19.33)	133	84.4 (19.43)	130	84.0 (17.73)
Change	135	0.9 (9.61)	133	-0.6 (9.25)	130	0.1 (11.31)
Potassium (mmol/L)						
Baseline (a)	138	4.15 (0.403)	137	4.09 (0.375)	136	4.14 (0.475)
Final Visit (b)	135	4.13 (0.436)	133	4.16 (0.419)	130	4.14 (0.422)
Change	135	-0.02 (0.378)	133	0.07 (0.388)	130	-0.01 (0.509)
Sodium (mmol/L)						
Baseline (a)	138	139.8 (2.29)	137	139.8 (2.12)	136	139.7 (1.89)
Final Visit (b)	135	140.3 (2.20)	133	139.9 (2.29)	130	139.6 (2.08)
Change	135	0.4 (2.28)	133	0.1 (2.17)	130	-0.2 (2.22)
Uric acid (μmol/L)						
Baseline (a)	138	329.5 (84.39)	137	331.3 (86.62)	136	325.8 (85.03)
Final Visit (b)	135	334.0 (79.71)	133	334.4 (93.57)	130	321.9 (86.79)
Change	135	3.8 (50.12)	133	3.9 (50.84)	130	-1.6 (50.06)
CK (U/L)						
Baseline (a)	138	211.9 (204.86)	137	208.3 (173.68)	136	212.1 (202.27)
Final Visit (b)	135	264.0 (527.59)	133	212.2 (193.20)	130	246.0 (395.58)
Change	135	53.2 (494.80)	133	2.6 (118.56)	130	29.8 (326.39)
ALT (U/L)						
Baseline (a)	138	26.6 (17.59)	137	24.6 (13.70)	136	24.5 (13.30)
Final Visit (b)	135	26.0 (15.11)	133	24.6 (14.06)	130	27.6 (31.51)
Change	135	-0.7 (11.52)	133	-0.2 (8.01)	130	3.1 (28.30)

**Table 12.i Summary of Serum Chemistry Changes From Baseline to Final Visit
(continued)**

Serum Lipid Chemistry	Placebo N=138		TAK-491 40 mg N=137		TAK-491 80 mg N=137	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Alkaline phosphatase (U/L)						
Baseline (a)	138	82.3 (23.25)	137	78.3 (21.85)	136	79.7 (21.22)
Final Visit (b)	135	82.2 (23.20)	133	79.0 (23.34)	130	80.5 (22.19)
Change	135	0.1 (8.16)	133	0 (8.30)	130	0.7 (9.58)
AST (U/L)						
Baseline (a)	138	25.8 (15.66)	137	22.9 (10.21)	136	24.5 (14.10)
Final Visit (b)	135	25.8 (14.72)	133	22.8 (8.06)	130	26.4 (17.83)
Change	135	0.1 (13.64)	133	-0.2 (7.00)	130	1.8 (10.77)
Total bilirubin (μmol/L)						
Baseline (a)	138	7.1 (3.50)	137	7.5 (4.28)	135	7.2 (3.63)
Final Visit (b)	135	7.0 (4.42)	133	7.0 (3.67)	129	6.5 (3.36)
Change	135	-0.1 (3.25)	133	-0.5 (2.88)	129	-0.6 (2.79)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

There were no consistent changes from baseline at final visit for any of the serum chemistry values in any of the treatment groups.

Mean values by study visit and changes from baseline for total cholesterol, HDL, calculated LDL cholesterol, and triglycerides are shown below.

Table 12.j Summary of Lipid Changes From Baseline to Final Visit

Serum Lipid Chemistry	Placebo N=138		TAK-491 40 mg N=137		TAK-491 80 mg N=137	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Total Cholesterol (mmol/L)						
Baseline (a)	114	5.066 (1.119)	111	4.989 (1.061)	113	5.138 (1.084)
Final Visit (b)	110	4.992 (1.176)	107	4.992 (1.089)	104	5.168 (1.058)
Change	110	-0.086 (0.511)	107	0.004 (0.599)	104	-0.023 (0.654)
HDL Cholesterol (mmol/L)						
Baseline (a)	114	1.381 (0.387)	111	1.468 (0.404)	113	1.446 (0.445)
Final Visit (b)	110	1.353 (0.356)	107	1.465 (0.470)	104	1.397 (0.458)
Change	110	-0.019 (0.165)	107	-0.005 (0.220)	104	-0.031 (0.162)
Calculated LDL Cholesterol (mmol/L)						
Baseline (a)	112	3.046 (0.855)	111	2.959 (0.941)	112	3.050 (1.012)
Final Visit (b)	108	3.018 (0.888)	105	2.949 (0.922)	102	3.111 (0.930)
Change	108	-0.040 (0.459)	105	-0.003 (0.555)	102	0.003 (0.550)
Triglycerides (mmol/L)						
Baseline (a)	114	1.420 (1.449)	111	1.231 (0.625)	113	1.388 (0.952)
Final Visit (b)	110	1.344 (1.494)	107	1.359 (1.239)	104	1.447 (1.253)
Change	110	-0.098 (0.496)	107	0.114 (1.126)	104	0.030 (0.730)

Source: Table 15.3.4.5.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

Mean changes in all treatment groups were small and probably not clinically meaningful.

Marked serum chemistry abnormalities reported during the double-blind treatment period are shown below by treatment group.

Table 12.k Marked Abnormalities in Serum Chemistries During Treatment - Safety Analysis Set

Laboratory Test	Subjects n/N (%)		
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
ALT >3×ULN	0/135	1/133 (0.8)	2/131 (1.5)
AST >3×ULN	2/135 (1.5)	1/133 (0.8)	3/131 (2.3)
CK total >10×ULN	2/135 (1.5)	1/133 (0.8)	1/131 (0.8)
Creatinine >1.5×BL	1/135 (0.7)	0/133	2/131 (1.5)
GGT >3×ULN	9/135 (6.7)	6/133 (4.5)	7/131 (5.3)
Potassium <3.0 mmol/L,	1/135 (0.7)	0/133	2/131 (1.5)
Potassium >6.0 mmol/L	0/135	0/133	0/131
Uric acid >625 μmol/L (M), >506 μmol/L (F)	2/135 (1.5)	0/133	2/131 (1.5)

Source: Tables 15.3.4.3 and 15.3.4.8.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline results are summarized in this table.

M=male subject, F=female subject.

The reporting rates of marked abnormal chemistry values were infrequent and similar across treatment groups.

Abnormal creatinine values³ were reported by one subject (0.7%) in the placebo group and 2 subjects (1.5%) in the TAK-491 80 mg group. By the final visit only the 2 subjects in the 80 mg TAK-491 treatment group still had creatinine values that were markedly abnormal.

Subject 0033/038 (TAK-491 80 mg) had a history of hypertension. Serum creatinine levels on day -28 and day 1 were 0.8 mg/dL and 0.6 mg/dL, respectively. On day 49 the creatinine value had increased to 1.2 mg/dL and urinalysis revealed WBC of > 50/hpf with +4 bacteriuria. There were no reported adverse events.

The table below shows the percentage of subjects with a creatinine elevation at any postbaseline visit during the study and at final visit, by treatment group.

³Defined as >1.5× baseline value

Table 12.l Summary of Subjects With a Creatinine Elevation - Safety Analysis Set

	Subjects n/N (%)		
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
Subjects with Creatinine Elevations During Treatment			
≥30% from BL and >ULN	3/135 (2.2)	1/133 (0.8)	3/130 (2.3)
≥50% from BL and >ULN	1/135 (0.7)	0/133	1/130 (0.8)
Subjects with Creatinine Elevations at Final Visit (a)			
≥30% from BL and >ULN	1/135 (0.7)	1/133 (0.8)	1/130 (0.8)
≥50% from BL and >ULN	0/135	0/133	1/130 (0.8)

Source: Table 15.3.4.9 and Appendix 16.2.8.3.3.

(a) LOCF. Narratives are provided in Section 15.3.3.4.

BL=Baseline.

Hematology

Marked hematology abnormalities that occurred during the Double-Blind Treatment Period are shown in below.

Table 12.m Marked Abnormalities in Hematology During Treatment - Safety Analysis Set

Laboratory Test	Subjects n/N (%)		
	Placebo N=138	TAK-491 40 mg N=137	TAK-491 80 mg N=137
Hematocrit/PCV (Ratio)	0/135	1/133 (0.8)	0/131
<0.8 × Baseline			
Platelet count	0/134	0/132	0/130
<50×10 ⁹ /L or >700×10 ⁹ /L			
WBC	0/135	0/133	0/131
<2×10 ⁹ /L or >20×10 ⁹ /L			

Source: Tables 15.3.4.1 and 15.3.4.8.

Note: A subject was classified as having marked abnormalities if at least 1 test result during treatment was considered markedly abnormal.

PCV=packed cell volume.

These abnormalities were rarely reported.

Urinalysis and vital signs

There were no patterns of urinalysis abnormalities, no remarkable differences in weight changes and no meaningful differences in sitting pulse.

ECG

There were no clinically meaningful changes in either the magnitude or direction of mean change for any ECG results, no subjects with abnormal, clinically significant ECG results at the final visit, and no remarkable changes from baseline to final visit with respect to the overall clinical interpretation of the 12-lead ECG. No subjects had a treatment-emergent adverse events because of ECG changes.

Reviewer's summary and conclusions

Efficacy: at week 6, the placebo subtracted differences in 24-hour mean SBP for TAK-491 40 and 80 mg were -5 and -8 mmHg, respectively. The placebo subtracted differences in 24-hour mean DBP for TAK-491 40 and 80 mg were -3 and -6 mmHg, respectively. The differences were significant compared to placebo but numerically less than those obtained from non black subjects in other studies.

Safety: Those events reported more often in both of the TAK-491 treatment groups compared to placebo include headache, dizziness, and edema.

Conclusions: TAK-491 is reasonably safe and effective in the black hypertensive population.

Study -06-TL-491-016

01-06-TL-491-016 (491-016)	Open-label phase followed by double-blind phase	Subjects with essential hypertension (DBP=95-119 mm Hg; for subjects with diabetes or chronic kidney disease, DBP=85-109 mm Hg)	32 weeks	<u>Open-label:</u>
49-United States and Latin America	<u>Open-label:</u>		26 weeks	TAK-491 20 mg
22 June 2007-08 May 2009	26-week, titrate-to-target phase with possible addition of CLD (followed by AHT, if needed)	<u>Open-label:</u> 418 subjects	<u>Double-blind:</u> 6 weeks	TAK-491 40 mg
	<u>Double-blind:</u>	<u>Double-blind:</u> 299 subjects		TAK-491 80 mg
	Randomized, placebo-controlled, 6-week reversal phase using placebo or final OL titrated TAK-491 dose, in addition to their final OL other AHT, including CLD, as applicable			TAK-491 80 mg with CLD
				25 mg
				TAK-491 80 mg with CLD
				25 mg with AHT
				<u>Open-label:</u> 418/299
				<u>Double-blind:</u>
				TAK-491 dose in OL
				TAK-491 dose in OL with CLD
				25 mg
				TAK-491 dose in OL with CLD
				25 mg and AHT
				Placebo
				Placebo with CLD 25 mg
				Placebo with CLD 25 mg and AHT
				<u>Double-blind:</u> 299/282
				TAK-491: 148/137
				Placebo: 151/145

Title: An 8-Month Phase 3, Open-Label Study With a Blinded Reversal Phase to Evaluate the Safety and Tolerability of TAK-491 in Subjects With Essential Hypertension

Investigators: 49 investigators in the United States and Latin America

Study Period: 22 June 2007 to 08 May 2009

Primary objective: to evaluate safety and tolerability of treatment with TAK-491 for 26 weeks in subjects with essential hypertension.

Secondary: to evaluate long-term efficacy of TAK-491 in a placebo-controlled, double-blind reversal phase after 26 weeks of open-label TAK-491 treatment in subjects with essential hypertension.

METHODOLOGY

This was a multicenter study consisting of 2 phases. The first phase was a 26-week open-label study in which subjects with essential hypertension were treated according to a titration-to-target blood pressure approach. After a 7-day screening period, eligible subjects were enrolled at a starting dose of TAK-491 40 mg once daily (QD). At Week 4, if the initial dose was tolerable, the dose was increased to TAK-491 80 mg QD. At Weeks 8 through 22, investigators could have added chlorthalidone and other antihypertensive agents in order to achieve the subject's target blood pressure. No dose titrations were to be made at or after Week 22. The results from this phase of the study is in the safety review.

Double-Blind Reversal Phase

The second phase was a 6-week, randomized, double-blind, placebo-controlled reversal study. At Week 26, subjects discontinued open label TAK-491 and were randomized to either TAK-491 at their final dose level at Week 26 or placebo, in addition to their current other antihypertensive medications, as applicable.

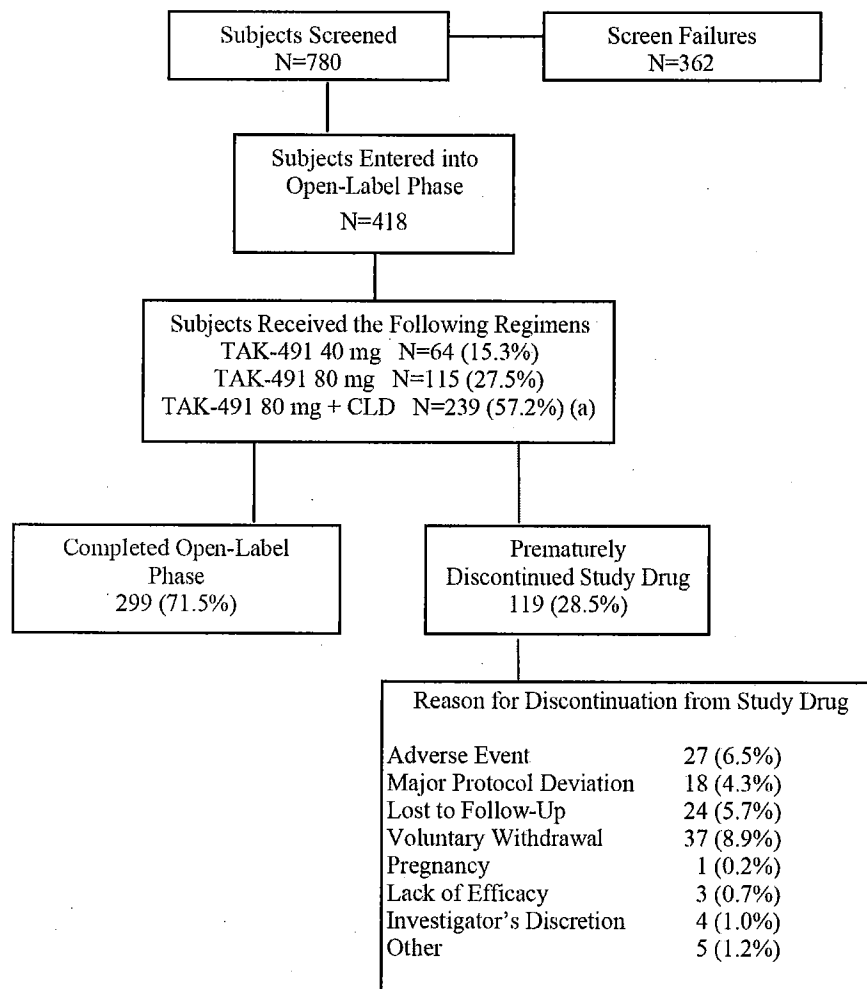
At the time of randomization, subjects receiving TAK-491 in combination with chlorthalidone were balanced between the placebo (92 [60.9%]) and TAK-491 (87 [58.8%]) groups.

Diagnosis and Main Criteria for Inclusion: to qualify for study participation, subjects must have been males or nonpregnant, nonlactating females at least 18 years of age, with essential hypertension (diastolic blood pressure [DBP] between 95 and 119 mm Hg, inclusive, or between 85 and 109 mm Hg, inclusive, for subjects with diabetes or chronic kidney disease); with clinical laboratory evaluations within the reference range for the testing laboratory; willing to discontinue antihypertensive medications at Screening Visit; and able to comprehend and willing to sign an informed consent form.

Efficacy: the primary efficacy endpoint was the change from Double-Blind Baseline (Week 26) to Final Visit during the double-blind reversal phase for trough clinic sitting DBP. The secondary efficacy endpoint was the change from Double-Blind Baseline (Week 26) to Final Visit during the double-blind reversal phase for trough clinic sitting SBP.

Doses used during the open label phase are shown in the figure below.

Figure 10.a Disposition of Subjects (Open-Label Phase)



Demographics: the table below shows the baseline characteristics of the subjects who went into the randomized, double blind treatment phase.

No important differences were observed between the treatment groups in demographic and Baseline characteristics in the FAS in the double-blind reversal phase.		
Characteristic	Placebo N=151	TAK-491 N=148
Sex, n (%)		
Male	77 (51.0)	72 (48.6)
Female	74 (49.0)	76 (51.4)
Age, years		
Mean (SD)	51.8 (9.72)	52.9 (9.59)
Min - Max	28 - 83	27 - 77
≥65, n (%)	11 (7.3)	18 (12.2)
Race, n (%)		
American Indian or Alaska Native	9 (6.0)	10 (6.8)
Asian	2 (1.3)	1 (0.7)
Black or African American	38 (25.2)	30 (20.3)
White	104 (68.9)	107 (72.3)
Multiracial	2 (1.3)	0
Body mass index, kg/m²		
Mean (SD)	32.94 (6.484)	33.61 (6.279)
Min - Max	20.3 - 57.9	22.2 - 53.4

Trough clinic sitting DBP

The primary efficacy endpoint was the change from double-blind baseline (Week 26) to final visit during the double-blind reversal phase for trough clinic sitting DBP. The baseline (at the end of the 26-week open label phase) and weeks 28, 30 and 32 (or last double blind visit) blood pressures are shown below.

**Table 11.c Summary of the Primary Analysis for the Primary Efficacy Variable:
Change From Double-Blind Baseline to Final Visit in Trough Clinic Sitting
DBP (mm Hg) - (LOCF, FAS)**

Study Visit	Treatment Group	
	Placebo N=151	TAK-491 N=148
Double-Blind Baseline/Week 26(a)	N=148	N=142
LS mean (SE)	82.25 (0.766)	83.50 (0.782)
P-value		0.255(b)
Week 28	N=137	N=129
LS mean change (SE)	5.95 (0.731)	-0.99 (0.753)
LS mean difference(c)		-6.94
95% CI		(-9.01, -4.88)
P-value		<0.001*(d)
Week 30	N=146	N=138
LS mean change (SE)	7.20 (0.714)	-1.31 (0.734)
LS mean difference(c)		-8.51
95% CI		(-10.53, -6.50)
P-value		<0.001*(d)
Final Visit/Week 32(e)	N=148	N=142
LS mean change (SE)	7.92 (0.712)	0.14 (0.726)
LS mean difference(c)		-7.78
95% CI		(-9.78, -5.78)
P-value		<0.001*(d)

Source: Table 15.2.1.1.2.

* Significant difference at 0.05 level.

(a) Double-Blind Baseline is the last observation before the first dose of double-blind study drug.

(b) P-value from a 1-way analysis of variance with term for treatment.

(c) LS mean difference=LS mean change of TAK-491 - LS mean change of placebo group.

(d) P-value from ANCOVA with terms for treatment (as a factor) and Double-Blind Baseline value (as a covariate).

(e) Final Visit was also Week 32 using LOCF.

Beginning at the first double-blind blood pressure measurement (Week 28) and continuing through the last measurement (Week 32), mean DBP and mean SBP were maintained in subjects who received TAK-491; in contrast, mean DBP and mean SBP increased among subjects who received placebo. The LS mean difference between TAK-491 and placebo at each scheduled double-blind dosing visit was statistically significantly different for both DBP and SBP ($P<0.001$).

Trough clinic sitting SBP

The baseline (at the end of the 26-week open label phase) and weeks 28, 30 and 32 (or last double blind visit) blood pressures are shown below.

**Table 11.d Summary of the Primary Analysis for the Secondary Efficacy Variable:
Change From Double-Blind Baseline to Final Visit in Trough Clinic Sitting
SBP (mm Hg) - (LOCF, FAS)**

Study Visit	Treatment Group	
	Placebo N=151	TAK-491 N=148
Double-Blind Baseline/Week 26(a)	N=148	N=142
LS mean (SE)	128.24 (1.321)	129.79 (1.349)
P-value		0.410(b)
Week 28	N=137	N=129
LS mean change (SE)	11.67 (1.087)	-0.83 (1.121)
LS mean difference(c)		-12.50
95% CI		(-15.58, -9.43)
P-value		<0.001*(d)
Week 30	N=146	N=138
LS mean change (SE)	12.48 (1.051)	-1.64 (1.082)
LS mean difference (c)		-14.11
95% CI		(-17.08, -11.14)
P-value		<0.001*(d)
Final Visit/Week 32(e)	N=148	N=142
LS mean change (SE)	12.97 (1.098)	0.59 (1.121)
LS mean difference(c)		-12.38
95% CI		(-15.47, -9.29)
P-value		<0.001*(d)

Source: Table 15.2.2.1.2.

* Significant difference at 0.05 level.

(a) Double-Blind Baseline is the last observation before the first dose of double-blind study drug.

(b) P-value from a 1-way analysis of variance with term for treatment.

(c) LS mean difference=LS mean change of TAK-491 - LS mean change of placebo group.

(d) P-value from ANCOVA with terms for treatment (as a factor) and Double-Blind Baseline value (as a covariate).

(e) Final Visit was also Week 32 using LOCF.

Beginning at the first double-blind SBP measurement (Week 28) and continuing through the last measurement (Week 32), mean SBP was maintained in subjects who continued to receive TAK-491. In contrast, mean SBP increased among subjects who received placebo, demonstrating a loss of efficacy after discontinuation of TAK-491.

Safety Results:

In the open-label phase, the most commonly reported adverse events were dizziness (8.9%) and headache (7.2%). Headache was the only adverse event reported by >5.0% of subjects (5.3% in the placebo group) in the double-blind phase.

Twenty-nine subjects (6.9% overall) in the open-label phase and 5 subjects (2 [1.3%] placebo and 3 [2.0%] TAK-491) in the double-blind reversal phase permanently or temporarily discontinued from study drug, at least in part because of safety issues.

Serious adverse events were reported for 8 subjects (1.9%) during the open-label phase. One placebo subject (0.7%) experienced a serious adverse event (hypertensive crisis) on Day 13 of the double-blind reversal phase. The event resolved on the following day. No deaths occurred during the open-label or double-blind reversal phase of the study.

Clinical laboratory parameters

Elevations of serum creatinine, BUN, and uric acid were more common in subjects who received TAK-491 plus chlorthalidone. Serum creatinine generally returned to baseline or near baseline levels either during treatment or after discontinuing study medication.

The table below shows the mean changes from open label baseline to week 26 for serum chemistries.

Table 12.o Serum Chemistry: Mean Changes From Open-Label Baseline to Week 26 Visit During the Open-Label Phase (Safety Analysis Set)

Serum Chemistry Parameter (unit)	TAK-491 N=179		TAK-491 plus CLD N=239		Total N=418	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
ALT (U/L)						
Open-Label Baseline (a)	179	31.5 (17.64)	239	30.0 (16.36)	418	30.6 (16.92)
Week 26	101	32.5 (21.84)	205	30.5 (19.73)	306	31.1 (20.43)
Change	101	1.9 (12.19)	205	0.4 (14.78)	306	0.9 (13.98)
AST (U/L)						
Open-Label Baseline (a)	179	26.3 (13.21)	239	25.0 (11.71)	418	25.5 (12.37)
Week 26	101	25.2 (14.32)	205	25.1 (14.29)	306	25.1 (14.28)
Change	101	0.8 (9.59)	205	-0.2 (12.82)	306	0.1 (11.85)
Alkaline phosphatase (U/L)						
Open-Label Baseline (a)	179	81.7 (26.28)	239	79.2 (23.70)	418	80.3 (24.84)
Week 26	101	75.0 (24.46)	205	73.6 (22.32)	306	74.1 (23.02)
Change	101	-5.8 (10.14)	205	-5.7 (12.39)	306	-5.7 (11.68)
Bilirubin, total (umol/L)						
Open-Label Baseline (a)	179	8.2 (3.89)	239	8.3 (3.99)	418	8.3 (3.95)
Week 26	101	7.5 (3.14)	205	7.5 (3.71)	306	7.5 (3.53)
Change	101	-0.8 (3.00)	205	-0.8 (3.33)	306	-0.8 (3.22)
Calcium (mmol/L)						
Open-Label Baseline (a)	179	2.392 (0.1025)	239	2.389 (0.1119)	418	2.390 (0.1079)
Week 26	101	2.396 (0.1062)	205	2.430 (0.0985)	306	2.419 (0.1022)
Change	101	0.005 (0.1054)	205	0.039 (0.1099)	306	0.028 (0.1095)
CK total (U/L)						
Open-Label Baseline (a)	179	141.0 (108.06)	239	188.8 (662.26)	418	168.3 (505.83)
Week 26	100	131.9 (85.86)	205	158.4 (153.14)	305	149.7 (135.25)
Change	100	-1.7 (54.62)	205	-40.1 (658.69)	305	-27.5 (540.79)
Creatinine (umol/L)						
Open-Label Baseline (a)	179	78.7 (18.75)	239	83.7 (20.44)	418	81.5 (19.87)
Week 26	101	81.4 (19.79)	205	94.3 (23.96)	306	90.0 (23.44)
Change	101	3.1 (12.98)	205	11.0 (16.53)	306	8.4 (15.86)

Footnotes for Table 12.o appear on the following page.

Glucose, fasting serum (mmol/L)						
Open-Label Baseline (a)	179	5.82 (1.202)	239	5.89 (1.381)	418	5.86 (1.306)
Week 26	100	6.03 (1.524)	205	6.26 (1.984)	305	6.19 (1.847)
Change	100	0.32 (1.212)	205	0.37 (1.341)	305	0.35 (1.298)
Potassium (mmol/L)						
Open-Label Baseline (a)	179	4.19 (0.375)	239	4.14 (0.401)	418	4.16 (0.390)
Week 26	101	4.36 (0.352)	205	4.13 (0.467)	306	4.21 (0.445)
Change	101	0.21 (0.357)	205	-0.01 (0.433)	306	0.06 (0.422)
Sodium (mmol/L)						
Open-Label Baseline (a)	179	139.3 (2.19)	239	139.7 (2.15)	418	139.5 (2.18)
Week 26	101	138.9 (2.63)	205	138.9 (2.94)	306	138.9 (2.84)
Change	101	-0.5 (2.41)	205	-0.8 (3.01)	306	-0.7 (2.83)
Uric acid (umol/L)						
Open-Label Baseline (a)	179	350.9 (93.01)	239	359.2 (90.65)	418	355.6 (91.65)
Week 26	101	355.9 (90.50)	205	424.3 (109.55)	306	401.7 (108.40)
Change	101	9.8 (46.24)	205	62.2 (86.09)	306	44.9 (79.17)

Source: Table 15.3.4.5.1.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of open-label study drug.

Mean creatinine was higher at open-label baseline in subjects who additionally received chlorthalidone (83.7 umol/L) than for subjects who received TAK-491 alone (78.7 umol/L). At Week 26, the mean increase from Open-Label Baseline in creatinine was 3.1 umol/L for subjects who received TAK-491 alone and 11.9 umol/L for subjects who additionally received chlorthalidone. There were no reported study discontinuations for elevated serum creatinine or renal impairment.

The mean change from double blind baseline to final visit for serum creatinine is shown below.

Table 12.q Serum Chemistry: Mean Changes From Double-Blind Baseline to Final Visit During the Double-Blind Reversal Phase (FAS) (Continued)

Serum Chemistry Parameter (unit)	Treatment Group			
	Placebo N=151		TAK-491 N=148	
	N	Mean (SD)	N	Mean (SD)
Creatinine (umol/L)				
Double-Blind Baseline	151	90.6 (22.76)	146	89.1 (24.05)
Final Visit	146	86.5 (19.19)	142	89.4 (24.93)
Change	146	-4.5 (12.42)	142	1.7 (19.13)

The group randomized to placebo had a drop in serum creatinine level of 4.5 umol/L compared to a small increase of 1.7 umol/L in the group remaining on TAK-491.

The following two subjects withdrew from the double blind treatment phase because of renal adverse events:

Subject 0021/015 (TAK-491), a 48 year old white male subject, discontinued from the study with an adverse event of renal impairment. The subject had relevant medical history of hypercholesterolemia, anxiety, and tobacco abuse, and entered the study with baseline values for serum creatinine, BUN, and potassium of 1.0 mg/dL, 12 mg/dL, and 3.8 mEq/L, respectively. Concomitant medications included fenofibrate and rosuvastatin calcium. Markedly abnormal creatinine values were reported at Week 8 (Day 58; 1.6 mg/dL) and Week 26 (Day 182; 1.9 mg/dL). Also at Weeks 8 (Day 58) and 26 (Day 182), BUN was 28 mg/dL and 33 mg/dL, respectively, and potassium was 5.0 mEq/L and 4.8 mEq/L, respectively. Renal impairment was recorded on Day 182 based on these abnormal laboratory findings and study drug was prematurely discontinued. The subject reported had no symptoms. The creatinine value returned to near Baseline level at the final measurement on Day 192.

Subject 0022/004 (TAK-491), a 58-year-old White female subject with history of edema peripheral, type 2 diabetes mellitus, and osteoarthritis, entered the study with a Baseline uric acid value within normal limits. Concomitant medications included (amlodipine/atorvastatin), (metformin/pioglitazone), and acetylsalicylic acid. Uric acid values increased through the duration of the study. Baseline uric acid and creatinine were 4.9 mg/dL and 1.0 mg/dL, respectively. The abnormal values for serum creatinine and uric acid were 1.1 mg/dL and 6.9 mg/dl at Week 26 (Day 180), which was reported as renal impairment on Day 200. The study drug was prematurely discontinued. The event was considered probably related to study drug and was ongoing at the end of the study. The subject was asymptomatic. The uric acid level was markedly abnormal (8.8 mg/dL) at the final measurement on Day 207 and serum creatinine was 1.2 mg/dL.

Reviewer's summary and conclusions

Efficacy: after 26 weeks of open label TAK-491, subjects were randomized either TAK-491 at their final dose level at Week 26 or placebo, in addition to their current other antihypertensive medications, as applicable. Beginning at the first double-blind blood pressure measurement (Week 28) and continuing through the last measurement (Week 32), mean DBP and mean SBP were maintained in subjects who received TAK-491; in contrast, mean DBP and mean SBP increased among subjects who received placebo. The LS mean difference between TAK-491 and placebo at each scheduled double-blind dosing visit was statistically significantly different for both DBP and SBP ($P < 0.001$).

Safety: headache and dizziness were the most frequently reported adverse events.

Conclusions: in this withdrawal trial, subjects who received open label TAK-491 for 26 weeks and then were randomized to placebo experienced an increase in their SBP and DBP. On the other hand, subjects who were randomized to continued TAK-491 experienced little change in their blood pressure. Safety was unremarkable.

Study 01-05-TL-491-009

Study No. (Study Abbreviation)	No. of Sites-Country (a)	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
01-05-TL-491-009 (491-009)	74-United States and Latin America	Double-blind, randomized, placebo-controlled, parallel-group, 3-group Antihypertensive effect of TAK-491 when coadministered with CLD compared with CLD monotherapy (Change from BL to Week 6 in 24-hr mean SBP by ABPM)	551 subjects with moderate-to-severe essential hypertension (clinic SBP=160-190 mm Hg; 24-hour mean SBP=140-180 mm Hg)	6 weeks	A: TAK-491 40 mg with CLD 25 mg B: TAK-491 80 mg with CLD 25 mg C: Placebo with CLD 25 mg 551/495 A: 185/169 B: 182/158 C: 184/168

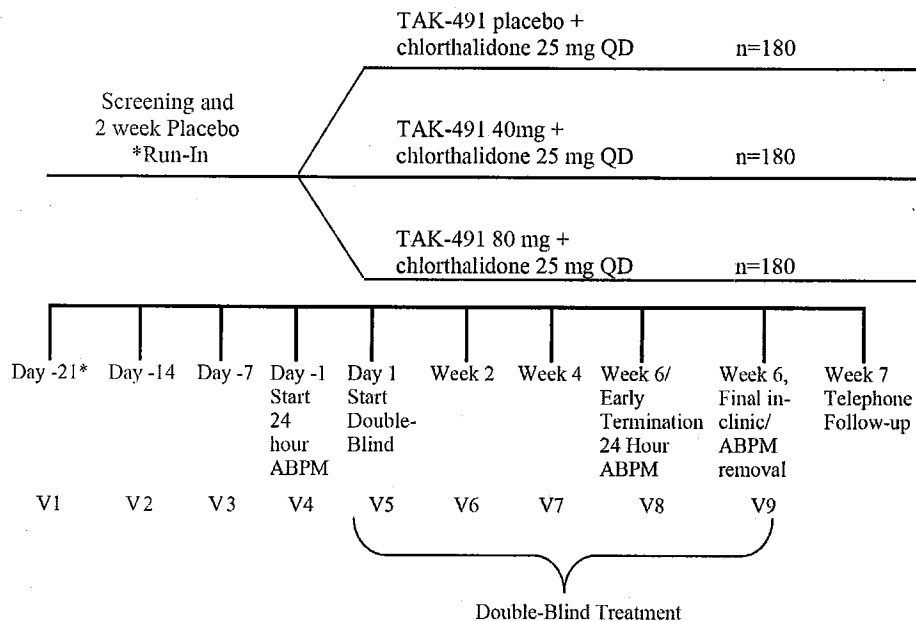
This was a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of TAK-491 when co-administered with chlorthalidone in subjects with essential hypertension.

There were 74 principle investigators in the United States and Latin America who randomized 551 subjects (4 randomized subjects did not receive study drug). The subjects were men or nonpregnant, nonlactating women at least 18 years of age with uncontrolled essential hypertension (clinic sitting SBP ≥ 160 mm Hg and ≤ 190 mm Hg inclusive, and 24-hour mean SBP ≥ 140 mm Hg and ≤ 180 mm Hg on day -1).

The primary endpoint was change from baseline at Week 6 in the 24 hour mean SBP as measured by ambulatory blood pressure monitor (ABPM).

After a 2-week run-in period of single-blind placebo, subjects who met the entry criteria were randomized to receive placebo plus chlorthalidone 25 mg QD (chlorthalidone monotherapy), TAK-491 40 mg QD plus chlorthalidone 25 mg QD, or TAK-491 80 mg QD plus chlorthalidone 25 mg QD for 6 weeks. ABPM was recorded day -1 for 24 hours prior to the first dose of double-blind study medication and at week 6 or early termination for 24 hours following the last administration of study medication. This is shown in the figure below.

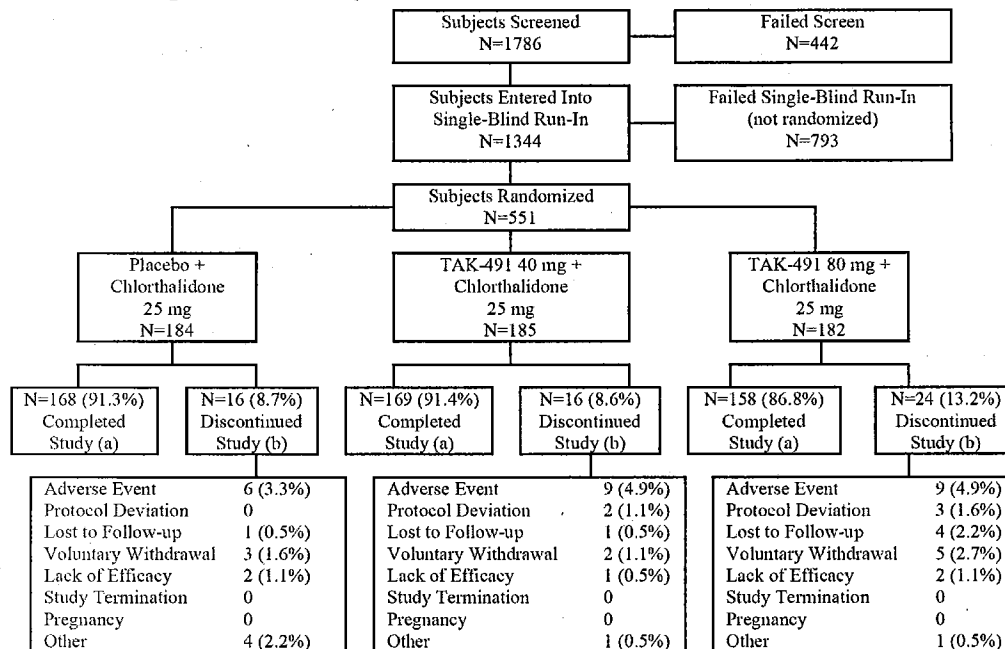
Figure 9.a Schematic of Study Design



*Note: If the subject was on amlodipine, the subject should have discontinued this medication at Screening Day-28 extending the screening period for an additional 7 days (for a total of 14 days of Screening) for washout of medication prior to the single-blind placebo Run-In Period.

There were 551 subjects randomized subjects. Three subjects were withdrawn before study drug was given and are not included in any of the analyses (2 in TAK-491 40 mg plus chlorthalidone and 1 in chlorthalidone monotherapy).

Figure 10.a Disposition of Subjects



Source: Tables 15.1.1, 15.1.2, and 15.1.4 and Appendix 16.2.1.2.

(a) For the purpose of this disposition figure, subjects who completed study were calculated as the total number randomized per treatment group minus those who discontinued.

(b) Subjects could have had more than 1 reason for discontinuation; only the primary reason is presented here. Withdrawal categories are described in Section 9.3.3.

The percentage of subjects who prematurely discontinued for any reason was 8.7% in the chlorthalidone monotherapy group, 8.6% in the TAK-491 40 mg plus chlorthalidone coadministration group, and 13.2% in the TAK-491 80 mg plus chlorthalidone coadministration group. The highest withdrawal rate, in the TAK-491 80 mg plus chlorthalidone coadministration group, had more voluntary withdrawals and lost to follow-up. A higher rate of withdrawals for adverse events cannot be ruled out for this treatment group.

Demographics

Demographic characteristics were similar across treatment groups. The average age was 59 years, there were slightly more men (52%) than women, 29% of subjects were at least 65 years of age, 59 % were white and 16% were black.

Baseline blood pressures are shown below.

Table 10.b Summary of Baseline Efficacy Parameters (Randomized Subjects)

	Treatment Group			P-value (a)
	Placebo + Chlorthalidone 25 mg N=184	TAK491 40 mg + Chlorthalidone 25 mg N=185	TAK491 80 mg + Chlorthalidone 25 mg N=182	
Blood Pressure by ABPM (mm Hg)				
n	179	181	177	
0- to 24-hour mean SBP				0.187
Mean (SD)	153.21 (9.343)	151.93 (9.401)	151.43 (9.729)	
Mean daytime (6 AM-10 AM) SBP				0.093
Mean (SD)	156.81 (9.486)	155.54 (9.310)	154.59 (10.019)	
Mean nighttime (12 AM-6 AM) SBP				0.783
Mean (SD)	142.21 (13.011)	141.24 (13.906)	141.96 (13.956)	
0- to 12-hour mean SBP				0.088
Mean (SD)	157.24 (9.881)	156.10 (9.658)	154.89 (10.459)	
Trough (22-24 hours) SBP				0.284
Mean (SD)	157.17 (12.398)	155.85 (13.059)	155.03 (13.098)	
0- to 24-hour mean DBP				0.751
Mean (SD)	89.72 (10.415)	90.44 (10.776)	90.47 (10.700)	
Mean daytime (6 AM-10 PM) DBP				0.809
Mean (SD)	93.09 (11.070)	93.82 (11.293)	93.65 (10.966)	
Mean nighttime (12 AM-6 AM) DBP				0.479
Mean (SD)	80.00 (10.872)	81.15 (11.936)	81.40 (12.137)	
0- to 12-hour mean DBP				0.864
Mean (SD)	93.55 (11.751)	94.21 (11.681)	93.94 (11.408)	
Trough (22-24 hours) DBP				0.617
Mean (SD)	94.98 (11.650)	96.03 (13.101)	96.13 (11.796)	
Clinic Blood Pressure (b) (mm Hg)				
n	181	184	182	
Clinic SBP				0.867
Mean (SD)	165.64 (14.461)	166.43 (13.587)	166.06 (14.207)	
Clinic DBP				0.488
Mean (SD)	93.36 (12.470)	94.76 (11.559)	94.44 (11.019)	

Source: Tables 15.1.8.1 and 15.1.8.2.

Note: Baseline value is the last observation before the first dose of double-blind study drug.

(a) The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

(b) SBP and DBP are based on the arithmetic mean of the 3 trough clinic sitting blood pressure measurements.

Baseline blood pressure were similar across treatment groups.

Medical history and current medical conditions were similar across treatment groups. The groups were also similar regarding past and current medications.

Efficacy

The change from baseline in 24-hour mean SBP as assessed by ABPM are shown below.

Table 11.a Change From Baseline to Week 6 in 24-hour Mean SBP by ABPM (FAS)

Study Visit	Treatment Group			Overall P-Value
	Placebo + Chlorthalidone 25 mg N=181	TAK491 40 mg + Chlorthalidone 25 mg N=184	TAK491 80 mg + Chlorthalidone 25 mg N=182	
Baseline	n=152	n=149	n=147	
LS mean (SE)	153.36 (0.766)	152.01 (0.774)	151.88 (0.779)	
Week 6				
LS mean change (SE)	-15.85 (0.957)	-31.72 (0.966)	-31.30 (0.973)	<0.001*
LS mean difference (a)		-15.86	-15.45	
(95% CI)		(-18.54, -13.19)	(-18.13, -12.76)	
P-value vs placebo + chlorthalidone		<0.001*	<0.001*	
Week 6: Sensitivity analysis using multiple imputation				
LS mean difference (a)		-15.86	-15.39	<0.001*
(95% CI)		(-18.61, -13.11)	(-18.01, -12.76)	
P-value vs placebo + chlorthalidone		<0.001*	<0.001*	

Source: Table 15.2.1.1.2.

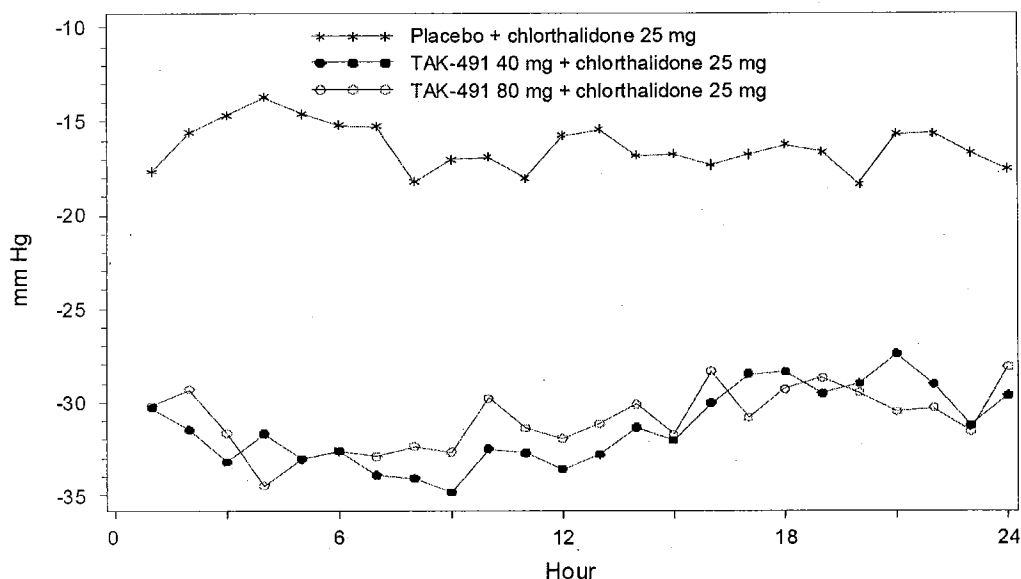
Analyses include subjects with both a baseline and postbaseline value.

* Significant difference at the 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 plus chlorthalidone coadministration group) – LS mean change of placebo group (chlorthalidone monotherapy group).

The baseline SBP values were around 152 mmHg for each treatment group. After 6 weeks the decrease from baseline was 16 mmHg for the chlorthalidone group. There was no difference between the TAK-491 plus chlorthalidone groups in the change in SBP from baseline (-31 mmHg from baseline). According to these results, both doses of TAK-491 decrease SBP an additional 15 mmHg when added to chlorthalidone.

Figure 11.a Change From Baseline to Week 6 in Mean SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)



DBP

Baseline and changes from baseline at week 6 are shown below by treatment group.

Table 11.c Change From Baseline to Week 6 in the 24-hour Mean DBP by ABPM (FAS)

Study Visit (mm Hg)	Treatment Group			Overall P-Value
	Placebo + Chlorthalidone 25 mg N=181	TAK491 40 mg + Chlorthalidone 25 mg N=184	TAK491 80 mg + Chlorthalidone 25 mg N=182	
Baseline	n=152	n=149	n=147	
LS mean (SE)	89.79 (0.854)	90.45 (0.863)	90.07 (0.869)	
Week 6				
LS mean change (SE)	-7.99 (0.619)	-18.28 (0.626)	-18.49 (0.630)	<0.001*(b)
LS mean difference (SE) (a)		-10.29	-10.49	
(95% CI)		(-12.02, -8.56)	(-12.23, -8.76)	
P-value vs placebo + chlorthalidone		<0.001*(b)	<0.001*(b)	
Week 6: Sensitivity analysis using multiple imputations				
LS mean difference (SE) (a)		-10.34	-10.59	<0.001*(b)
(95% CI)		(-12.05, -8.64)	(-12.38, -8.80)	
P-value vs placebo + chlorthalidone		<0.001*(b)	<0.001*(b)	

Source: Table 15.2.2.1.2.

Analyses include subjects with both a baseline and postbaseline value.

* Significant difference at the 0.05 level.

(a) LS mean difference=LS mean change of each active treatment (TAK-491 plus chlorthalidone coadministration group) –

LS mean change of placebo group (chlorthalidone monotherapy group).

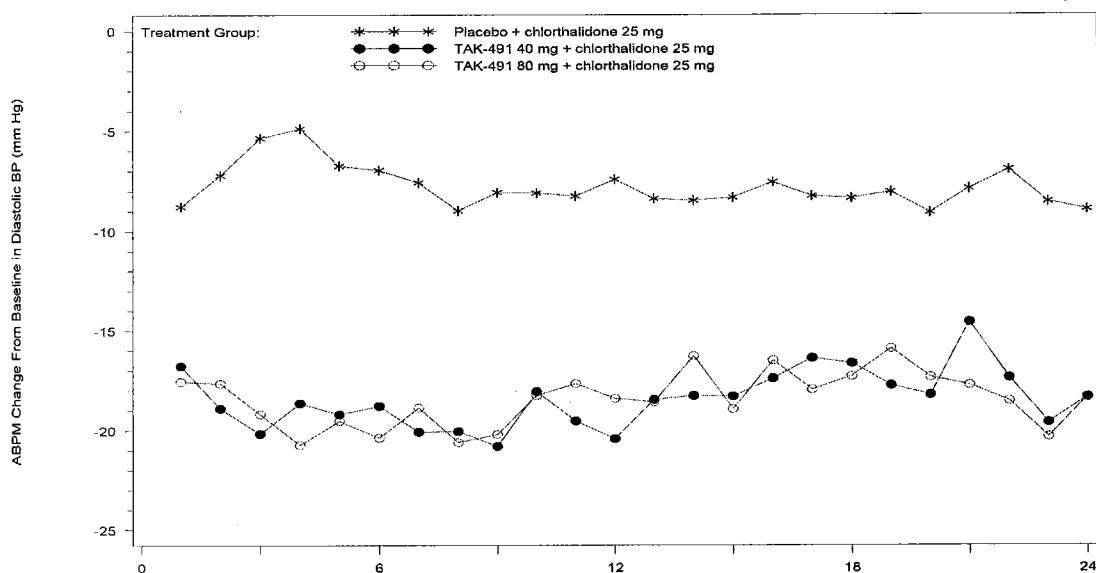
(b) P-value from analysis of covariance with terms for treatment (as a factor) and baseline value (as a covariate).

The baseline DBP values were around 90 mmHg for each treatment group. After 6 weeks the decrease from baseline was 8 mmHg for the chlorthalidone group. There was no difference between the TAK-491 plus chlorthalidone groups in the change in DBP from baseline (-18 mmHg). According to these results, both doses of TAK-491 decrease SBP an additional 10 mmHg when added to chlorthalidone.

The changes from baseline in DBP as measured by ABPM are shown in the figure below.

Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
 Full Analysis Set



Results for the clinic BP measurements reflected what was observed with BP obtained using the ABPM.

Subgroups

The subgroups analyzed for BP effects include age, gender, race, BMI, baseline 24-hour mean SBP, and cGFR.

TAK-491 plus chlorthalidone produced greater blood pressure reductions compared to chlorthalidone alone in all subgroups examined.

SAFETY

Serious safety

Deaths

There was 1 death during this study in the chlorthalidone monotherapy group (subject 7090/008 experienced a fatal episode of cardiogenic shock).

Serious adverse events

There were seven subjects who reported serious adverse events. These are shown below.

Table 12.g Summary of Treatment-Emergent SAEs by Subject (Safety Analysis Set)

Treatment Site/Subject No.	Preferred Term	Onset Study Day	Relationship to Drug (a)	Action/Outcome
Chlorthalidone 25 mg + Placebo				
7090/008	Cardiac failure	7	Not related	Drug withdrawn/ resolved
	Cardiogenic shock	7	Not related	Not applicable/ fatal
	Pneumonia	7	Not related	Not applicable/ resolved
TAK-491 40 mg + Chlorthalidone 25 mg				
7010/001	Atrioventricular block complete	25	Not related	Not applicable/ resolved
	Heart rate decreased	25	Not related	Drug withdrawn/ resolved
	Syncope	25	Not related	Not applicable/ resolved
7024/004	Chest discomfort	13	Not related	Dose not changed/ resolved
7057/045	Hypertensive crisis	3	Not related	Drug withdrawn/ resolved
TAK-491 80 mg + Chlorthalidone 25 mg				
7036/015	Urinary tract infection	24	Not related	Dose not changed/ resolved
7051/002	Jaw fracture	41	Not related	Dose not changed/ resolved
	Skin laceration	41	Not related	Dose not changed/ resolved
	Syncope	41	Not related	Dose not changed/ resolved
7059/010	Lacunar infarction	18	Not related	Dose not changed/ resolved

Source: Table 15.3.2.2.

(a) As judged by the investigator.

One subject (7051/002) who reported syncope had been on study drug for 41 days and had a history of prior syncope. The other subject (7010/001) reported syncope as well as concurrent complete atrioventricular block and decreased heart rate after 25 days of treatment.

Discontinuations for adverse events

Those subjects who discontinued for safety reasons are shown below.

Table 12.h Summary of Adverse Events Resulting in Permanent Discontinuation (Safety Analysis Set)

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Outcome
Placebo plus Chlorthalidone				
7021/053	Heart rate increased	8	Possible	Resolving
7031/016	Headache	27	Possible	Resolved
7038/011	Hypertension	27	Probable	Resolved
7049/007	Alanine aminotransferase increased	1	Not related	Not resolved
	Gamma-glutamyltransferase increased	1	Not related	Not resolved
7054/009	Palpitations	7	Definite	Resolved
7090/008	Cardiac failure (b)	7	Not related	Resolved
TAK-491 40 mg plus Chlorthalidone				
7007/035	Orthostatic hypotension	4	Probable	Resolved
7010/001	Heart rate decreased (b)	25	Not related	Resolved
7013/012	Hypotension	5	Probable	Resolved
7014/025	Nausea	3	Probable	Resolved
	Dizziness	3	Probable	Resolved
	Hyperhidrosis	3	Probable	Resolved
	Hypotension	3	Probable	Resolved
7054/010	Dizziness	13	Not related	Resolved
7057/045	Hypertensive crisis (b)	3	Not related	Resolved
7067/017	Hepatic enzyme increased	2 (c)	Probable	Not resolved
7080/017	Dizziness	2	Possible	Resolved
7108/041	Hypotension	17	Probable	Resolved

Site/Subject No. Treatment	Preferred Term	Onset Study Day	Relationship to Drug (a)	Outcome
TAK-491 80 mg plus Chlorthalidone				
7007/051 (d)	Tiredness	-21	Pretreatment	Resolved
	Dizziness	-21	Pretreatment	Resolved
7018/020	Asthenia	7	Probable	Resolved
7026/001	Pharyngitis streptococcal	14	Not related	Resolved
7057/042	Blood creatinine increased	14	Probable	Resolved
7057/061	Hypertensive crisis	16	Not related	Resolved
7057/063	Hypotension	2	Probable	Resolved
7068/045	Blood creatinine increased	29	Probable	Resolved
7071/003	Hypotension	42	Probable	Resolved
7108/007	Dry eye	1	Not related	Resolved

Source: Table 15.3.2.1 and Appendices 16.2.7.1 and 16.2.1.2.

(a) As judged by the investigator.

(b) Serious adverse event.

(c) Blood was drawn for analysis on Day 1.

(d) Subject 7007/051 was recorded as discontinued study due to adverse event on Day 4 (Appendix 16.2.1.2) at the request of the study monitor based on audit information, even though the events were not treatment emergent.

Adverse events of dizziness, hypotension, and asthenia were reported by subjects in the TAK-491 combination groups. The two subjects who discontinued study drug because of increased creatinine levels were in the TAK-491 80 mg combination group.

Clinical Laboratory Serum Chemistry

Table 12.i Serum Chemistry: Mean Changes From Baseline to the Final Visit (Safety Analysis Set)

Serum Chemistry	Placebo + Chlorthalidone 25 mg N=181		TAK-491 40 mg + Chlorthalidone 25 mg N=184		TAK-491 80 mg + Chlorthalidone 25 mg N=182	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Creatinine (μmol/L)						
Baseline (a)	181	79.6 (19.54)	184	76.9 (16.83)	181	79.9 (21.57)
Final Visit (b)	180	84.6 (21.89)	181	90.0 (24.94)	176	93.7 (26.73)
Change	180	5.0 (11.36)	181	13.3 (17.58)	176	13.6 (16.66)

The increases from baseline in creatinine levels in the TAK-491 combination groups at final visit were more than double the increases reported in the chlorthalidone monotherapy group.

Markedly abnormal serum chemistry values

The table below displays the number and percent of subjects who reported one or more abnormal chemistry values.

Table 12.k Subjects with at least 1 Markedly Abnormal Serum Chemistry Value During Treatment (Safety Analysis Set)

Laboratory Test	Treatment Group n/N (%)		
	Placebo + Chlorthalidone 25 mg N=181	TAK-491 40 mg + Chlorthalidone 25 mg N=184	TAK-491 80 mg + Chlorthalidone 25 mg N=182
ALT (>3 × ULN)	1/180 (0.6)	1/181 (0.6)	2/177 (1.1)
AST (>3 × ULN)	1/180 (0.6)	1/181 (0.6)	0/177
Alkaline phosphatase (>3 × ULN)	0/180	1/181 (0.6)	0/177
CK total (>3 × ULN)	0/180	0/181	0/177
Creatinine (>1.5 × BL)	4/180 (2.2)	14/181 (7.7)	14/177 (7.9)
GGT (>3 × ULN)	10/180 (5.6)	10/181 (5.5)	4/177 (2.3)
Potassium (<3.0 mmol/L)	10/180 (5.6)	0/181	1/177 (0.6)
(>6.0 mmol/L)	0/180	0/181	0/177
Sodium (<130 mmol/L)	3/180 (1.7)	2/181 (1.1)	2/177 (1.1)
(>150 mmol/L)	0/180	0/181	0/177
Total bilirubin (>2.0 × ULN)	0/180	1/181 (0.6)	0/177
Uric acid (Men: >625 μmol/L; Women: >506 μmol/L)	12/180 (6.7)	22/181 (12.2)	24/177 (13.6)

Source: Tables 15.3.4.3 and 15.3.4.8.

ALT=alanine aminotransferase, CK=creatinine kinase.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline results are summarized in this table.

Markedly abnormal uric acid values were observed at a higher incidence in the TAK-491 40 mg

and 80 mg plus chlorthalidone groups (12.2% and 13.6%, respectively) compared with the chlorthalidone monotherapy group (6.7%).

There was a greater percentage of subjects reporting markedly elevated⁴ creatinine values in the TAK-491 40 mg plus chlorthalidone (7.7%) and TAK-491 80 mg plus chlorthalidone (7.9%) compared with the chlorthalidone monotherapy group (2.2%).

Table 12.1 Summary of Subjects With a Creatinine Elevation (Safety Analysis Set)

	Treatment Group n/N (%)		
	Placebo + Chlorthalidone 25 mg N=181	TAK-491 40 mg + Chlorthalidone 25 mg N=184	TAK-491 80 mg + Chlorthalidone 25 mg N=182
Subjects with Creatinine Elevations at Any Postbaseline Visit (a)			
≥30% from BL and >ULN	3/180 (1.7)	18/181 (9.9)	26/176 (14.8)
≥50% from BL and >ULN	1/180 (0.6)	10/181 (5.5)	15/176 (8.5)
Subjects with Creatinine Elevations at Final Visit (a)			
≥30% from BL and >ULN	2/180 (1.1)	15/181 (8.3)	19/176 (10.8)
≥50% from BL and >ULN	1/180 (0.6)	8/181 (4.4)	9/176 (5.1)

Source: Tables 15.3.4.10.1 and 15.3.4.10.2.

BL=baseline; ULN=upper limit of normal.

(a) Data are based on CV units.

There was a higher percentage of subjects with elevated serum creatinine in the TAK-491 combination groups compared to chlorthalidone alone, and it appears to be related to the dose of TAK-491.

There was one subject (7057/042, TAK-491 80 mg plus chlorthalidone) who discontinued because of increased creatinine after 23 days of treatment. This 81 year old female had a baseline creatinine of 1.1 mg/dl which continued to increase at every visit (1.8 mg/dL maximum). Concomitant medication included allopurinol and her uric acid levels were elevated. Creatinine levels declined to 1.2 mg/dL about 2 weeks after drug was stopped.

Follow-up data were obtained for 14 of 18 subjects with an elevated creatinine value at the Final Visit and these data are shown below. One subject (chlorthalidone monotherapy) died from cardiogenic shock.

⁴ An increase ≥50% from baseline

Table 12.m Follow-up Creatinine Values (mg/dL) for All Subjects with Creatinine Elevations $\geq 30\%$ and $>ULN$ at the Final Visit

Subject					Final Visit	Follow-up Visit		
	Screening Cr Value (mg/dL)	Cr ULN (mg/dL)	Baseline Cr Value (mg/dL)	Cr Value (mg/dL)	Mean SBP/DBP Change From Baseline (mmHg)	Creatinine Value (mg/dL)	Days Since Final Visit (a)	
Subjects With $\geq 30\%$ but $<50\%$ Creatinine Elevations From Baseline and $>ULN$								
7007053/ TAK-491 40 mg + CLD	1.2	1.0	1.1	1.6	-54/-13	1.1	260	
7007071/ TAK-491 80 mg + CLD	1.0	1.0	1.0	1.3	-40/-18	1.6	192	
7010034/ TAK-491 80 mg + CLD	0.9	1.0	0.8	1.1	-35/-12	0.8 (c)	107	
7012007/ TAK-491 80 mg + CLD	1.3	1.0	1.2	1.6	-40/-18	1.2	36	
7012010/ TAK-491 40 mg + CLD (b)	1.3	1.4	1.3	1.9	-57/-29	1.4	12	
7015009/ TAK-491 80 mg + CLD	1.0	1.0	0.8	1.2	-66/-22	0.9 (c)	105	
7020031/ TAK-491 40 mg + CLD	1.2	1.4	1.3	1.8	-46/-18	1.1	156	
7020034/ TAK-491 40 mg + CLD	0.8	1.0	1.0	1.3	--	0.9 (c)	122	
7023014/ TAK-491 40 mg + CLD	0.9	1.0	0.8	1.1	-68/-42	1.0 (c)	364	
7036009/ TAK-491 80 mg + CLD	0.9	1.0	0.9	1.3	-51/-25	0.9 (c)	117	
7042001/ TAK-491 80 mg + CLD	0.9	1.0	0.9	1.3	-38/-25	0.9	181	
7044038/ TAK-491 80 mg + CLD	1.1	1.4	1.1	1.5	-53/-24	1.0 (c)	113	
7056010/ CLD monotherapy	1.0	1.0	0.9	1.2	-12/-15	1.0	148	
7056026/ TAK-491 40 mg + CLD (b)	1.1	1.4	1.1	1.5	-31/-4	1.2	50	
7056029/ TAK-491 80 mg + CLD	1.3	1.0	1.2	1.6	-46/-13	1.4 (c)	107	
7057042/ TAK-491 80 mg + CLD (b)	1.0	1.0	1.1	1.6	-19/-5	1.2	12	
7057057/ TAK-491 80 mg + CLD	0.8	1.0	0.8	1.2	-35/-7	0.7 (c)	151	
7058015/ TAK-491 80 mg + CLD (b)	1.5	1.4	1.6	2.1	-44/-12	1.7	29	
7059003/ TAK-491 80 mg + CLD (b)	0.8	1.0	0.8	1.1	-56/-28	0.9 (c)	144	
7108009/ TAK-491 40 mg + CLD	1.5	1.4	1.2	1.7	-31/-17	1.3 (c)	119	

Subject	Final Visit					Follow-up Visit	
	Screening Cr Value (mg/dL)	Cr ULN (mg/dL)	Baseline Cr Value (mg/dL)	Mean SBP/DBP Change From	Creatinine Value (mg/dL)	Days Since Final Visit (a)	
				Baseline (mmHg)			
Subjects With ≥ 50% Creatinine Elevations From Baseline and >ULN							
7001011/ TAK-491 80 mg + CLD	1.0	1.4	1.0	1.5	-67/-37	NCS (c)	--
7004017/ TAK-491 40 mg + CLD	1.1	1.0	0.9	1.4	-61/-15	--	--
7006007/ TAK-491 40 mg + CLD	1.2	1.4	1.2	2.1	-57/-18	1.3	14
7010007/ TAK-491 40 mg + CLD	1.2	1.4	1.0	1.8	-39/-22	1.1	159
7012008/ TAK-491 80 mg + CLD	1.2	1.4	1.2	2.1	-35/-17	1.3 (c)	288
7018015/ TAK-491 40 mg + CLD (b)	0.9	1.0	0.9	3.1	-80/-33	0.8 (c)	44
7018020/ TAK-491 80 mg + CLD (b)	0.9	1.0	0.8	1.5	--	1.0	15
7023005/ TAK-491 40 mg + CLD	0.8	1.0	0.8	1.3	-50/-32	0.8 (c)	438
7029003/ TAK-491 80 mg + CLD	0.7	1.0	0.6	1.4	-45/-20	0.7 (c)	263
7029019/ TAK-491 40 mg + CLD	1.0	1.4	0.9	1.6	-40/-21	0.8	196
7056023/ TAK-491 80 mg + CLD (b)	1.0	1.4	0.8	1.7	-21/0	1.1	56
7068032/ TAK-491 80 mg + CLD (b)	1.0	1.4	1.2	1.8	-23/0	1.3	8
7090008/ CLD monotherapy	1.2	1.0	1.1	1.9	--	--	--
7105010/ TAK-491 40 mg + CLD	0.8 (d)	1.0	0.8	1.4	-48/-25	0.8 (c)	49
7105029/ TAK-491 40 mg + CLD	0.9	1.0	0.8	1.3	-64/-34	--	--
7108004/ TAK-491 40 mg + CLD	0.8	1.0	0.7	1.6	-19/-24	0.9	8

Source: Tables 15.3.4.11.1 and 15.3.4.11.2 and Appendices 16.1.4.3, 16.1.7, and 16.2.7.1.

Note: Follow-up data include all information received up to 04 January 2010. *Italicized* subject number indicates follow-up serum creatinine values were not obtained. **Bold** subject number with **bold** screening, baseline and follow-up serum creatinine values indicates subject's follow-up value remained above the ULN and Baseline at the last follow-up evaluation.

CLD=chlorthalidone; Cr=creatinine; NCS=not clinically significant (as reported by investigator, value not provided).

(a) Because follow-up was unscheduled, there is variation in the number of days since Final Visit; as such, the number of days since Final Visit for follow-up data does not necessarily reflect the number of days before creatinine levels normalized.

(b) Increased blood creatinine was reported as an adverse event during the double-blind Treatment period.

(c) Follow-up serum creatinine value was evaluated for follow-up at a local lab and may not be recorded in the clinical database, but is provided in Appendix 16.1.4.3.

(d) The screening value obtained on Day -21 is presented, since the baseline value was not obtained for this subject

In most cases, the serum creatinine decreased to around baseline levels when the study drug was stopped.

Hematology

The number and percent of subjects with markedly abnormal hematology values are Shown below by treatment group.

Table 12.n Subjects with at least 1 Markedly Abnormal Hematology Value During Treatment (Safety Analysis Set)

Laboratory Test	Treatment Group n/N (%)		
	Placebo + Chlorthalidone 25 mg N=181	TAK-491 40 mg + Chlorthalidone 25 mg N=184	TAK-491 80 mg + Chlorthalidone 25 mg N=182
Hematocrit/PCV			
<0.8 × baseline value	0/180	4/181 (2.2)	3/177 (1.7)
Hemoglobin			
>3 g/dL decrease	0/180	2/181 (1.1)	1/177 (0.6)
Platelet count			
<50×10 ⁹ /L or >700×10 ⁹ /L	0/180	0/181	0/175
RBC			
<0.8 × baseline value	0/180	1/181 (0.6)	3/177 (1.7)

Source: Tables 15.3.4.1 and 15.3.4.8.

PCV=packed cell volume.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline values are included in this table.

There were few markedly abnormal hematology values reported but those reported were by subjects in the TAK-491 combination groups. None were reported as a serious adverse event or resulted in study discontinuation.

Urinalysis

There were no clinically meaningful treatment-related changes in the mean urinalysis data and no urinalysis abnormality was reported as a serious adverse event and none resulted in study discontinuation.

Vital Signs, ECGs, and Physical Findings

There were no clinically meaningful differences in changes for weight, sitting pulse, ECG parameters, or physical findings across treatment groups.

Individual Subject Changes

ECG changes reported as adverse events:

- Subject 7031/016 (chlorthalidone monotherapy) reported T wave inversion on Day 31 which later resolved.
- Subject 7108/033 (TAK-491 40 mg plus chlorthalidone) reported first degree a-v block on Day 30. The subject voluntarily withdrew from the study on Day 30 stating he was unable to make study visits.
- Subject 7021/038 (chlorthalidone monotherapy) reported atrial fibrillation on Day 43 which resolved.
- Subject 7015/009 (TAK-491 80 mg plus chlorthalidone) reported intermittent flattening of ST segments on Day 45.
- Subject 7029/003 (TAK-491 80 mg plus chlorthalidone) reported "mild" prolonged QT interval on day 43 (QTcB was 532 msec and QTcF was 531 msec).
- Subject 7024/004 (TAK-491 40 mg plus chlorthalidone) reported T wave inversion.

Reviewer's summary and conclusions

Efficacy: after 6 weeks the decrease from baseline for SBP was 16 mmHg for the chlorthalidone group. There was no difference between the TAK-491 40 mg and 80 mg plus chlorthalidone groups in the change in SBP from baseline (-31 mmHg from baseline). According to these results, doses of TAK-491 40 mg and 80 mg decrease SBP an additional 15 mmHg when added to chlorthalidone.

After 6 weeks the decrease from baseline for DBP was 8 mmHg for the chlorthalidone group. There was no difference between the TAK-491 40 mg and 80 mg plus chlorthalidone groups in the change in DBP from baseline (-18 mmHg). According to these results, both doses of TAK-491 decrease SBP an additional 10 mmHg when added to chlorthalidone.

Safety: there were two reports of syncope in the TAK-491 (40 mg and 80 mg) plus chlorthalidone.

There were two subjects in the TAK-491 80 mg plus chlorthalidone group who discontinued study drug because of increased creatinine levels. Creatinine levels declined to 1.2 mg/dL about 2 weeks after drug was stopped.

The increases from baseline in creatinine levels in the TAK-491 40 mg and 80 mg combination groups at final visit were more than double the increases reported in the chlorthalidone monotherapy group. There was a greater percentage of subjects reporting markedly elevated⁵ creatinine values in the TAK-491 40 mg plus chlorthalidone (7.7%) and TAK-491 80 mg plus chlorthalidone (7.9%) compared with the chlorthalidone monotherapy group (2.2%). In most cases stopping study drug resulted in serum creatinine returning to near baseline levels.

Markedly abnormal uric acid values were observed at a higher incidence in the TAK-491 40 mg and 80 mg plus chlorthalidone groups (12.2% and 13.6%, respectively) compared with the chlorthalidone monotherapy group (6.7%).

Conclusions: the use of TAK-491 40 mg and 80 mg to chlorthalidone resulted in large decreases in SBP and DBP. However, there were two reports of syncope in the combination groups and worsening serum creatinine levels.

⁵ An increase $\geq 50\%$ from baseline

Study 01-05-TL-491-010

Study No. (Study
Abbreviation)
No. of Sites-Country
(a)

Study Start- End Dates	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
01-05-TL-491-010 (491-010) 65-United States and Latin America 03 October 2007- 03 April 2009	Double-blind, randomized, placebo-controlled, parallel-group, 3- group (Phase 2) Dose-response of the antihypertensive effect of TAK-491 when coadministered with AML compared with AML monotherapy (Change from BL in the 24-hr mean SBP by ABPM)	567 subjects* with moderate to severe essential hypertension (trough clinic sitting SBP=160- 190 mm Hg; 24-hr mean SBP=140-180 mm Hg) *1 subject in Group A was not randomized but received double-blind treatment	6 weeks	A: TAK-491 40 mg with AML 5 mg B: TAK-491 80 mg with AML 5 mg C: Placebo with AML 5 mg 566/532 A: 190/180 B: 188/177 C: 189/175

Title of Study:

A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 When Coadministered With Amlodipine 5 mg in Subjects With Essential Hypertension

Primary objective:

To evaluate the antihypertensive effect of TAK-491 when coadministered with amlodipine compared with amlodipine monotherapy, as measured by the primary endpoint of 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

Secondary objectives:

- To evaluate the antihypertensive effect of TAK-491 plus amlodipine coadministration compared with amlodipine monotherapy, as measured by the key secondary endpoint of trough clinic sitting SBP and by other ABPM and clinic measures of SBP and diastolic blood pressure (DBP).
 - To evaluate the safety and tolerability of TAK-491 plus amlodipine coadministration.
- Each secondary endpoint is listed under Criteria for Evaluation.

Study methods:

This was a phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of TAK-491 when combined with amlodipine 5 mg once daily (QD) in subjects with essential hypertension (trough clinic sitting SBP \geq 160 mm Hg and \leq 190 mm Hg and 24-hour mean SBP \geq 140 mm Hg and \leq 180 mm Hg). After a 2-week run-in period of single-blind placebo, subjects who met the entry criteria were randomized to receive placebo plus amlodipine 5 mg QD, TAK-491 40 mg QD plus amlodipine 5 mg QD, or TAK-491 80 mg QD plus amlodipine 5 mg QD for 6 weeks. ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 or early termination for 24 hours following the last administration of study medication. Clinic DBP and SBP were measured at Screening, randomization (Day 1), Week 2, Week 4, and Week 6.

Number of subjects:

Full analysis set contains 562 subjects

Demographics

The subjects' demographics are shown below.

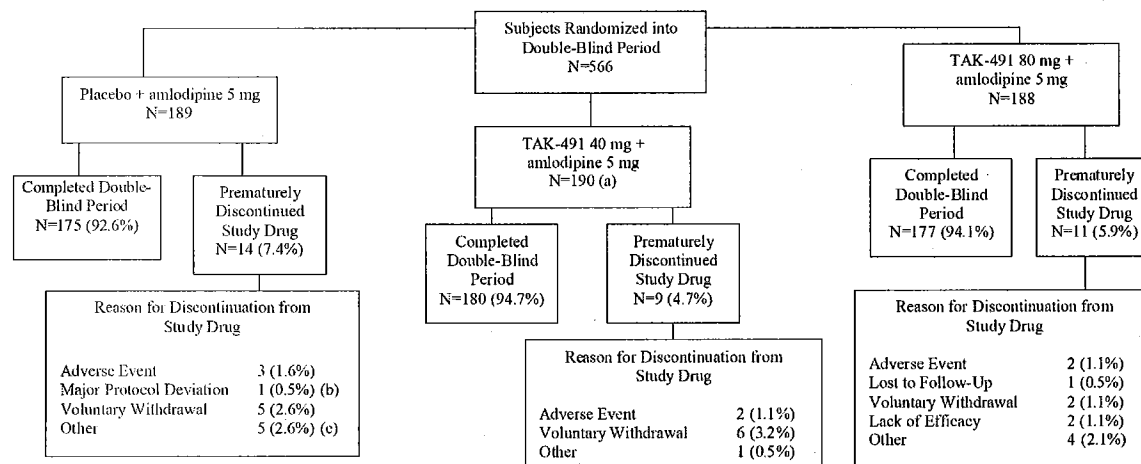
Characteristic	Treatment Groups		
	Placebo + amlodipine 5 mg N=189	TAK-491 40 mg + amlodipine 5 mg N=189	TAK-491 80 mg + amlodipine 5 mg N=188
Sex, n (%)			
Male	94 (49.7)	90 (47.6)	103 (54.8)
Female	95 (50.3)	99 (52.4)	85 (45.2)
Age, year			
Mean (SD)	58.9 (11.04)	57.8 (11.44)	58.2 (11.84)
Ethnicity, n (%)			
Hispanic or Latino	16 (8.5)	21 (11.1)	20 (10.6)
Non-Hispanic or Latino	111 (58.7)	110 (58.2)	110 (58.5)
Not collected (a)	62 (32.8)	58 (30.7)	58 (30.9)
Race, n (%) (b)			
American Indian/Alaska Native (c)	42 (22.2)	35 (18.5)	38 (20.2)
Asian	6 (3.2)	12 (6.3)	10 (5.3)
Black/African American	30 (15.9)	29 (15.3)	30 (16.0)
Native Hawaiian/Other Pacific Islander	0	1 (0.5)	1 (0.5)
White	111 (58.7)	114 (60.3)	109 (58.0)
Multiracial	0	2 (1.1)	0
Weight, kg	N=185	N=189	N=188
Mean (SD)	82.36 (18.626)	84.06 (19.345)	84.64 (20.240)
Height, cm	N=189	N=188	N=188
Mean (SD)	165.4 (11.82)	165.0 (10.29)	166.7 (11.60)
Body mass index, kg/m ²	N=185	N=188	N=188
Mean (SD)	30.02 (5.382)	30.77 (6.172)	30.26 (5.517)
(a) Ethnicity was not collected at Latin American sites.			
(b) Subjects who indicated more than 1 race category were included in each category indicated and were also included in the multiracial category. Thus, the number and percentage of subjects in each category may not add up to the total number of subjects.			
(c) Subjects who self-identified as being American Indian were predominantly from Latin America.			

The groups were fairly well balanced.

Disposition of subjects

The outcomes of the study subjects are shown below.

Figure 10.b Disposition of Subjects (Double-Blind Period)



Source: Table 15.1.4 and Appendices 16.2.1.2 and 16.2.1.3.

(a) Includes Subject 8017/012 who was treated with TAK-491 40 mg + amlodipine 5 mg but not randomized.

(b) Subject 8046/006 was prematurely discontinued due to a major protocol deviation but was not treated.

(c) Three of the five subjects were randomized but not treated: Subject 8022/003 was accidentally randomized, but did not qualify due to 24-hour mean ABPM reading; Subject 8004/047 did not meet inclusion criteria and was entered in IVRS in error, and Subject 8004/048 was randomized into IVRS in error and was removed.

Most subjects completed the trial.

Primary efficacy endpoint

Mean SBP at baseline and mean change from baseline at endpoint as measured by ABPM are shown below.

Table 11.a Change From Baseline to Week 6 in 24-Hour Mean SBP (mm Hg) by ABPM (FAS)

Study Visit	Treatment Group			Overall P-value
	Placebo + amlodipine 5 mg N=185	TAK-491 40 mg + amlodipine 5 mg N=189	TAK-491 80 mg + amlodipine 5 mg N=188	
Baseline	N=166	N=165	N=166	
LS mean (SE)	153.90 (0.761)	152.55 (0.764)	154.41 (0.761)	0.204 (a)
Week 6				
LS mean change (SE)	-13.60 (0.754)	-24.79 (0.757)	-24.51 (0.754)	<0.001 (b)
LS mean difference (c)		-11.19	-10.91	
(95% CI)		(-13.29, -9.09)	(-13.00, -8.81)	
P-value vs placebo + amlodipine 5 mg		<0.001* (b)	<0.001* (b)	
Week 6: Sensitivity analysis using multiple imputations				
LS mean difference (c)		-11.24	-10.84	<0.001 (b)
(95% CI)		(-13.31, -9.17)	(-12.89, -8.80)	
P-value vs placebo + amlodipine 5 mg		<0.001* (b)	<0.001* (b)	

Source: Table 15.2.1.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) P-value from a 1-way ANOVA with term for treatment.

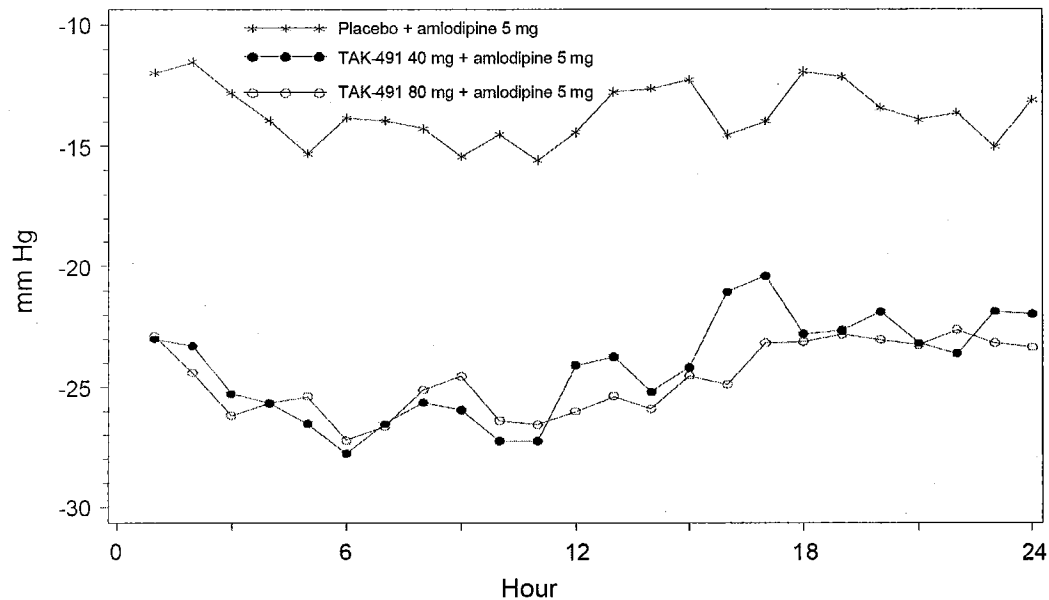
(b) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

(c) LS mean difference=LS mean change of each active group (TAK-491 plus amlodipine coadministration group) - LS mean change of placebo group (amlodipine monotherapy group).

The SBP at baseline was similar for the three treatment groups. At week 6, there were greater decreases from baseline for the TAK-491 40 mg and 80 mg combinations (both by about 25 mmHg) compared to amlodipine 5 mg alone (-14 mmHg).

The figure below shows the change from baseline at week 6 systolic blood pressure 24 hour profile by ABPM.

Figure 11.a Change From Baseline to Week 6 in Mean SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)



As expected, the combination of TAK-491 plus another antihypertensive such as amlodipine results in greater SBP control compared to one antihypertensive taken alone.

Mean DBP at baseline and mean change from baseline at endpoint as measured by ABPM are shown below.

Table 12.f Summary of Treatment-Emergent SAEs (Safety Analysis Set)

Site/ Subject No.	Age/Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Action/Outcome
Placebo + amlodipine 5 mg						
8044/018	58/M	Chest pain attributed to stress (Chest pain) (a)	26	26	Possible	Dose not changed/ Recovered/Resolved
TAK-491 40 mg + amlodipine 5 mg						
8006/011	61/M	Syncopal episode (Syncope)	31	32	Definite	Drug withdrawn/ Recovered/Resolved
TAK-491 80 mg + amlodipine 5 mg						
8064/025	60/M	Urinary tract infection (Urinary tract infection)	26	38	Not related	Dose not changed/ Recovered/Resolved
8082/008	58/F	Twisted ovarian cyst (Ovarian cyst torsion)	14	21	Not related	Drug withdrawn/ Recovered/Resolved

Source: Table 15.3.2.2.

(a) Treatment-emergent adverse event was not cardiovascular related.

Discontinuations because of adverse events

Table 12.g Summary of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug (Safety Analysis Set)

Site/Subject No.	Age/Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Intensity
Placebo + amlodipine 5 mg						
8038/005	73/M	Flushing facial (Flushing)	1	4	Probable	Moderate
8069/010	55/F	Lower limbs edema (Oedema peripheral)	4	14	Definite	Mild
8077/007	78/F	Edema (Oedema)	6	Ongoing	Definite	Moderate
TAK-491 40 mg + amlodipine 5 mg						
8006/011	61/M	Syncopal episode (Syncope) (a)	31	32	Definite	Severe
8048/003	73/F	Edema right knee (Oedema peripheral)	22	27	Probable	Moderate
		Cellulitis (Cellulitis)	1	6	Probable	Moderate
TAK-491 80 mg + amlodipine 5 mg						
8001/031	47/F	Hypokalemia (Hypokalaemia)	1	Ongoing	Not related	Severe
8082/008	58/F	Twisted ovarian cyst (Ovarian cyst torsion) (a)	14	21	Not related	Severe

Source: Table 15.3.2.1.

(a) Serious adverse event.

There is nothing of particular concern in the serious safety data.

All adverse events

Table 11.c Change From Baseline to Week 6 in 24-Hour Mean DBP (mm Hg) by ABPM (FAS)

Study Visit	Treatment Group			Overall P-value
	Placebo + amlodipine 5 mg N=185	TAK-491 40 mg + amlodipine 5 mg N=189	TAK-491 80 mg + amlodipine 5 mg N=188	
Baseline				
n	166	165	166	
LS mean (SE)	92.94 (0.839)	92.49 (0.842)	93.12 (0.839)	0.863 (a)
Week 6				
n	166	165	166	
LS mean change (SE)	-7.79 (0.490)	-15.26 (0.492)	-15.43 (0.490)	<0.001* (b)
LS mean difference (c)		-7.48	-7.65	
(95% CI)		(-8.84, -6.11)	(-9.01, -6.28)	
P-value vs placebo + amlodipine 5 mg		<0.001* (b)	<0.001* (b)	
Week 6: Sensitivity analysis using multiple imputations				
LS mean difference (c)		-7.55	-7.70	
(95% CI)		(-8.89, -6.21)	(-9.09, -6.30)	
P-value vs placebo + amlodipine 5 mg		<0.001* (b)	<0.001* (b)	

Source: Table 15.2.2.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

(a) P-value from a 1-way ANOVA with term for treatment.

(b) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

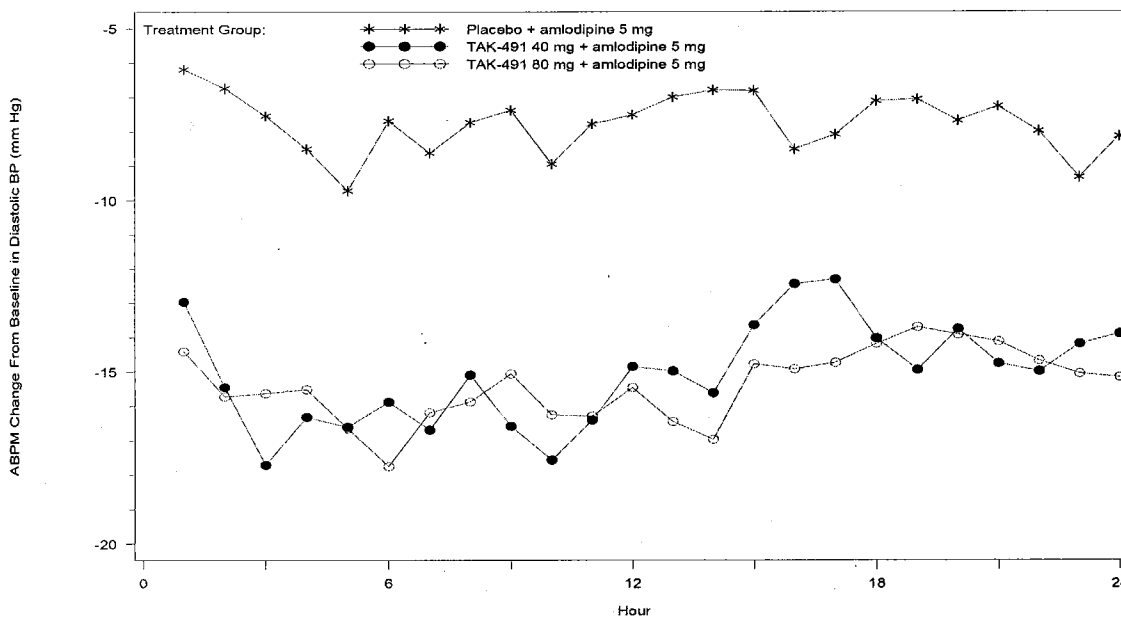
(c) LS mean difference=LS mean change of each active group (TAK-491 plus amlodipine coadministration group) - LS mean change of placebo group (amlodipine monotherapy group).

The DBP at baseline was similar for the three treatment groups. At week 6, there were greater decreases from baseline for the TAK-491 40 mg and 80 mg combinations (both by about 15 mmHg) compared to amlodipine 5 mg alone (-7 mmHg).

The figure below shows the change from baseline at week 6 diastolic blood pressure 24 hour profile by ABPM.

Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
Full Analysis Set



As expected, the combination of TAK-491 plus another antihypertensive such as amlodipine results in greater DBP control compared to one antihypertensive taken alone.

SAFETY

Serious safety

Deaths

No deaths were reported during the study.

Serious adverse events

Four subjects (1 amlodipine monotherapy, 1 TAK-491 40 mg plus amlodipine coadministration, and 2 TAK-491 80 mg plus amlodipine coadministration) reported a serious adverse event. These subjects are described below.

Table 12.d Treatment-Emergent Adverse Event Preferred Terms Reported for $\geq 2.0\%$ of Subjects in Any Treatment Group (Safety Analysis Set)

Preferred Term	Treatment Group n (%)		
	Placebo + amlodipine 5 mg N=185	TAK-491 40 mg + amlodipine 5 mg N=190	TAK-491 80 mg + amlodipine 5 mg N=188
Headache	10 (5.4)	11 (5.8)	10 (5.3)
Dyslipidaemia	7 (3.8)	9 (4.7)	7 (3.7)
Oedema peripheral	9 (4.9)	4 (2.1)	4 (2.1)
Plasminogen activator inhibitor increased	5 (2.7)	3 (1.6)	5 (2.7)
Nasopharyngitis	3 (1.6)	4 (2.1)	5 (2.7)
Urinary tract infection	2 (1.1)	4 (2.1)	5 (2.7)
Dizziness	4 (2.2)	3 (1.6)	3 (1.6)
Diarrhoea	2 (1.1)	6 (3.2)	0
Fatigue	0	5 (2.6)	3 (1.6)
Upper respiratory tract infection	4 (2.2)	1 (0.5)	3 (1.6)
C-reactive protein increased	3 (1.6)	0	4 (2.1)
Oedema	4 (2.2)	1 (0.5)	1 (0.5)

Source: Table 15.3.1.4.

The adverse events were similar for the three treatment groups with the exception of more peripheral edema reported in the amlodipine monotherapy group.

Clinical laboratory values

Abnormal serum chemistries

The number and percent of subjects reporting abnormal chemistry values are shown below.

Table 12.j Percentage of Subjects With at Least 1 Markedly Abnormal Chemistry Value During Treatment (Safety Analysis Set)

Serum Chemistry Parameter (markedly abnormal criterion)	Treatment Group n/N (%)		
	Placebo + amlodipine 5 mg N=185	TAK-491 40 mg + amlodipine 5 mg N=190	TAK-491 80 mg + amlodipine 5 mg N=188
ALT (>3×ULN)	0/179 (0.0)	1/188 (0.5)	0/183 (0.0)
CK total (>10×ULN)	0/179 (0.0)	0/188 (0.0)	2/183 (1.1)
Calcium	0/179 (0.0)	1/188 (0.5)	0/183 (0.0)
(<0.8×ULN)	0/179 (0.0)	0/188 (0.0)	0/183 (0.0)
(>1.2×ULN)	0/179 (0.0)	1/188 (0.5)	0/183 (0.0)
Creatinine (>1.5× Baseline)	1/179 (0.6)	1/188 (0.5)	2/183 (1.1)
γ-Glutamyl transferase (>3×ULN)	6/179 (3.4)	9/188 (4.8)	8/183 (4.4)
Potassium	0/179 (0.0)	2/188 (1.1)	2/183 (1.1)
(<3.0 mmol/L)	0/179 (0.0)	1/188 (0.5)	1/183 (0.5)
(>6.0 mmol/L)	0/179 (0.0)	1/188 (0.5)	1/183 (0.5)
Uric acid (Males: >625 umol/L) (Females: >506 umol/L)	1/179 (0.6)	2/188 (1.1)	0/183 (0.0)

Source: Tables 15.3.4.7 and 15.3.4.8.

With the exception of GGT, there were few abnormalities reported for any of these treatment groups. The incidence rates for abnormal GGT were similar for the groups.

Subject 8001/031 (TAK-491 80 mg plus amlodipine coadministration) discontinued the study prematurely because of hypokalemia. Serum potassium levels were low on study day 1.

Abnormal serum creatinine

Table 12.k Summary of Subjects With Creatinine Elevation (Safety Analysis Set)

	Treatment Group n/N (%)		
	Placebo + amlodipine 5 mg N=185	TAK-491 40 mg + amlodipine 5 mg N=190	TAK-491 80 mg + amlodipine 5 mg N=188
Subjects with Creatinine Elevations at Any Postbaseline Visit			
≥30% from Baseline and >ULN	0/179 (0.0)	2/188 (1.1)	3/183 (1.6)
≥50% from Baseline and >ULN	0/179 (0.0)	1/188 (0.5)	1/183 (0.5)
Subjects with Creatinine Elevations at Final Visit (a)			
≥30% from Baseline and >ULN	0/179 (0.0)	1/188 (0.5)	1/183 (0.5)
≥50% from Baseline and >ULN	0/179 (0.0)	0/188	0/183

Source: Table 15.3.4.9 and Appendix 16.2.8.3.3.

Note: A creatinine increase is defined as an increase from Baseline ≥30%×Baseline and >ULN.

(a) LOCF.

Few abnormal creatinine values were reported for these treatment groups.

Abnormal hematology values

The number and percent of subjects reporting abnormal hematology values are shown below.

Table 12.1 Percentage of Subjects With at Least 1 Markedly Abnormal Hematology Value During Treatment (Safety Analysis Set)

Hematology Parameter (markedly abnormal criterion)	Treatment Group n/N (%)		
	Placebo + amlodipine 5 mg N=185	TAK-491 40 mg + amlodipine 5 mg N=190	TAK-491 80 mg + amlodipine 5 mg N=188
Hematocrit/PCV ($<0.8 \times$ Baseline)	0/179 (0.0)	1/188 (0.5)	1/183 (0.5)
Platelet count	1/178 (0.6)	0/187 (0.0)	0/183 (0.0)
($<50 \times 10^9/L$)	0/178 (0.0)	0/187 (0.0)	0/183 (0.0)
($>700 \times 10^9/L$)	1/178 (0.6)	0/187 (0.0)	0/183 (0.0)

Source: Tables 15.3.4.7 and 15.3.4.8.

Only isolated markedly abnormal hematology values were observed. No markedly abnormal hematology values were reported as SAEs or led to premature discontinuation.

Reviewer's summary and conclusions

Efficacy: the SBP at baseline was similar for the three treatment groups. At week 6, there were greater decreases from baseline for the TAK-491 40 mg and 80 mg combinations in both SBP and DBP compared to amlodipine 5 mg alone. There was no group randomized to TAK-491 alone.

Safety: there was one report of syncope (TAK-491 40 mg combination) which resulted in study drug discontinuation. The effects on heart rate for all treatment groups were negligible.

Conclusions: TAK 491 plus amlodipine 5 mg is better in lowering blood pressure compared to amlodipine 5 mg alone.

Study TAK-491-301

Title of Study:

A Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 With Valsartan in Subjects With Essential Hypertension

Study Sites:

103 sites enrolled subjects into the placebo run-in period in the United States and Latin America

Study Period (years):

09 November 2007 to 03 September 2009 (double-blind phase completed)

04 March 2009 to 30 October 2009 (interim data cut for the ongoing open-label extension phase)

Objective

Primary:

The primary objective was to evaluate the antihypertensive effect of TAK-491 compared with valsartan 320 mg after 6 months of treatment, as measured by the primary endpoint of change in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

Secondary:

Secondary objectives were to evaluate:

- The antihypertensive effect of TAK-491 compared with valsartan 320 mg after 6 months of treatment, as measured by the key secondary endpoint of trough clinic sitting SBP and by other ABPM and clinic measures of SBP and diastolic blood pressure (DBP).
- The safety and tolerability of TAK-491 compared to valsartan 320 mg.

Each secondary endpoint is listed under Criteria for Evaluation.

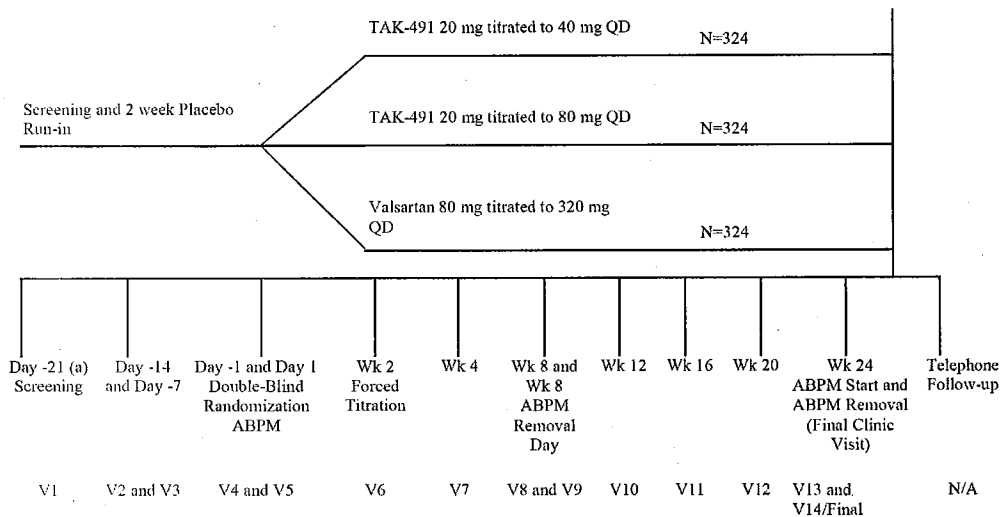
Methodology

This was a phase 3, multicenter, double-blind, randomized, parallel-group, active-controlled study to evaluate the efficacy and safety of TAK-491 compared to valsartan over a 6-month treatment period in subjects with essential hypertension (trough clinic sitting SBP ≥ 150 mm Hg and ≤ 180 mm Hg on Day -1 and 24-hour mean SBP ≥ 130 mm Hg and ≤ 170 mm Hg on Day 1). Subsequent to the 6-month double-blind treatment period, subjects could have continued in an optional 28-week open-label extension phase with TAK-491 to contribute to the long-term safety evaluation.

After a 2-week run-in period of single-blind placebo, subjects who met the entry criteria were randomized to receive TAK-491 20 mg once daily (QD) force titrated to 40 mg QD after 2 weeks, TAK-491 20 mg QD force titrated to 80 mg QD after 2 weeks, or valsartan 80 mg QD force titrated to 320 mg QD after 2 weeks, with treatment for 6 months. ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication, at Week 8, and at Week 24 or Early Termination for 24 hours following the last administration of double-blind study medication. Clinic DBP and SBP were measured at Screening (Day -21/-28, Day -14, Day -7, Day -1), randomization (Day 1), Weeks 2, 4, 8, 12, 16, 20, and 24 of the double-blind treatment phase. Following completion of the double-blind treatment phase, all available subjects were offered the option of continuing in a 28-week extension phase with open-label TAK-491 40 mg.

After 4 weeks in the open-label extension phase, hydrochlorothiazide and any other antihypertensive agents (except angiotensin II receptor blockers) could have been added to achieve target blood pressure. Clinic DBP and SBP were measured at Weeks 28, 32, 36, 44, and 52 of the open-label extension phase.

Figure 9.a Schematic of Study Design



The open label portion of the study is currently ongoing and only interim results of data collected up through 30 October 2009 are presented in this report.

Number of Subjects:

Double-Blind Treatment Phase: 982 subjects;

Open-Label Extension Phase: enrolled: 170 subjects (The open-label extension phase of the study was added to the protocol nearly 14 months after the start of the study. Thus, 170 only subjects had entered into the open-label extension phase due to the delayed implementation of this phase.)

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been male or nonpregnant, nonlactating female subjects at least 18 years of age, with essential hypertension (trough clinic sitting SBP ≥ 150 mm Hg and ≤ 180 mm Hg on Day -1 and 24-hour mean SBP > 130 and ≤ 170 mm Hg on Day 1); with clinical laboratory evaluations within the reference range for the testing laboratory or results that were deemed not clinically significant; willing to discontinue current antihypertensive medication(s) at Screening; and able to comprehend and willing to sign an informed consent form.

Duration of Treatment:

24 weeks (double- treatment phase) with optional 28-week extension (open-label extension phase).

Results

Subject Disposition:

A total of 984 subjects were randomized in the double-blind treatment phase; 327 subjects were randomized to TAK-491 20 mg titrated to 40 mg QD, 329 subjects were randomized to TAK-491 20 mg titrated to 80 mg QD, and 328 subjects were randomized to valsartan 80 mg titrated to 320 mg QD.

Among the 984 randomized subjects, 2 were randomized in error to the valsartan 320 mg group and were withdrawn before study drug was administered (these subjects were not included in the safety or efficacy analyses).

Double-Blind Treatment Phase	Treatment Group		
	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg
Number of subjects randomized	327	329	328
Number (%) of subjects who discontinued	78 (23.9)	80 (24.3)	82 (25.0)
Primary reason for discontinuation			
Adverse event	20 (6.1)	26 (7.9)	19 (5.8)
Major protocol deviation	3 (0.9)	2 (0.6)	3 (0.9)
Lost to follow-up	12 (3.7)	12 (3.6)	11 (3.4)
Voluntary withdrawal	22 (6.7)	22 (6.7)	22 (6.7)
Pregnancy	1 (0.3)	0	0
Lack of Efficacy	16 (4.9)	9 (2.7)	25 (7.6)
Other	4 (1.2)	9 (2.7)	2 (0.6)

The percentage of subjects who prematurely discontinued for any reason was 23.9%, 24.3%, and 25.0% in the TAK-491 40 mg, TAK-491 80 mg, and valsartan 320 mg groups, respectively. There were more withdrawals for adverse events in the TAK-491 80 mg compared to valsartan and TAK-491 40 mg dose.

Demographics

The demographic characteristics are shown below.

Double-Blind Treatment Phase		Treatment Group		
Characteristic	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=328	
Sex, n (%)				
Male	164 (50.2)	169 (51.4)	176 (53.7)	
Female	163 (49.8)	160 (48.6)	152 (46.3)	
Age, year				
Mean (SD)	57.8 (12.08)	56.8 (10.72)	58.1 (10.88)	
Ethnicity, n (%)				
Hispanic or Latino	15 (4.6)	17 (5.2)	18 (5.5)	
Non-Hispanic or Latino	214 (65.4)	219 (66.6)	212 (64.6)	
Not Collected	98 (30.0)	93 (28.3)	98 (29.9)	
Race, n (%)				
American Indian/Alaska Native	27 (8.3)	16 (4.9)	22 (6.7)	
Asian	7 (2.1)	7 (2.1)	7 (2.1)	
Black/African American	49 (15.0)	50 (15.2)	49 (14.9)	
Native Hawaiian/Other Pacific Islander	0	1 (0.3)	1 (0.3)	
White	247 (75.5)	256 (77.8)	251 (76.5)	
Multiracial	3 (0.9)	1 (0.3)	1 (0.3)	
Weight, kg	N=327	N=329	N=326	
Mean (SD)	86.14 (21.698)	85.87 (19.009)	87.70 (21.045)	
Height, cm				
Mean (SD)	166.6 (11.76)	166.8 (11.80)	167.2 (11.33)	
Body mass index, kg/m ²	N=327	N=329	N=326	
Mean (SD)	30.78 (5.688)	30.73 (5.269)	31.15 (5.828)	
Note: Ethnicity was not collected at Latin American sites.				
Note: Subjects who indicated more than 1 race category were included in each category indicated and were also included in the multiracial category. Thus, the number and percentage of subjects in each category may not add up to the total number of subjects.				

Mean age ranged from 56.8 to 58.1 years across treatment groups. Men and women were nearly equally represented in each group. The percentage of black subjects was 14.9% to 15.2% across treatment groups, and 4.9% to 8.3% of subjects reported being American Indian, most of whom enrolled at Latin American sites. Female reproductive status and smoking history were also relatively similar among treatment.

Efficacy

Mean 24-hour mean SBP at baseline were similar in the treatment groups.

Efficacy Results:

The results of the primary efficacy analysis, change from Double-Blind Baseline to Week 24 in 24-hour SBP by ABPM, are shown below.

Table 11.a Change From Baseline to Week 24 in 24-Hour Mean SBP (mm Hg) by ABPM (LOCF, FAS)

Study Visit	Treatment Group		
	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
Baseline			
N	284	271	277
LS mean (SE)	145.64 (0.564)	145.11 (0.578)	145.12 (0.572)
Week 24 (LOCF)			
LS mean change (SE)	-14.93 (0.698)	-15.32 (0.715)	-11.29 (0.707)
LS mean difference (a)	-3.64	-4.03	
(95% CI)	(-5.59, -1.69)	(-6.01, -2.06)	
P-value vs valsartan 320 mg	<0.001* (b)	<0.001* (b)	
Week 24: Sensitivity analysis using multiple imputations			
LS mean difference (a)	-4.07	-4.42	
(95% CI)	(-5.99, -2.14)	(-6.36, -2.48)	
P-value vs valsartan 320 mg	<0.001* (b)	<0.001* (b)	

Source: Table 15.2.1.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

* Significant difference at 0.05 level.

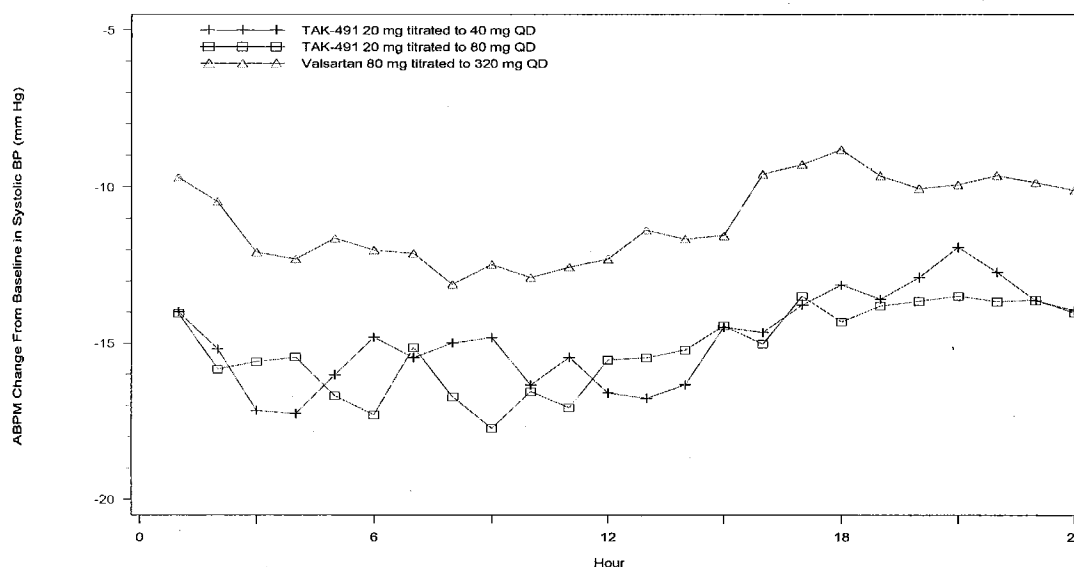
(a) LS mean difference=LS mean change of TAK-491 dose group - LS mean change of valsartan group.

(b) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

Numerically and statistically significantly greater decreases in 24-hour mean SBP were observed for each of the TAK-491 treatment groups (40 mg and 80 mg) compared with valsartan 320 mg (by about 4 mm Hg; (P<0.001).

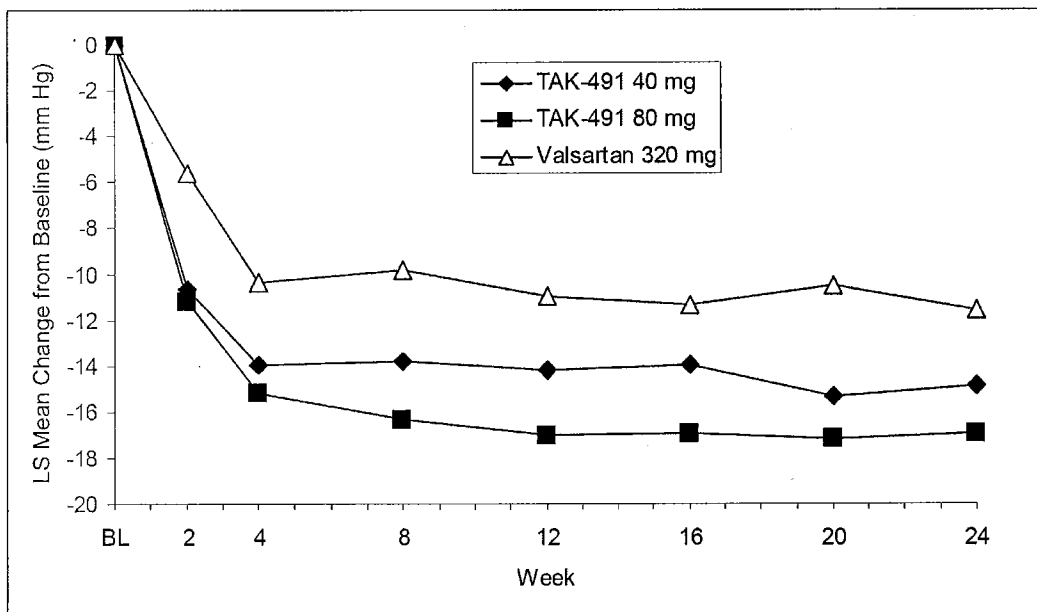
The SBP 24 hour ABPM profiles for the treatment groups, change from baseline, are shown below.

Figure 11.a Change From Baseline to Week 24 in Mean SBP by ABPM by Hour for the 0- to 24-Hour Interval (LOCF, FAS)



The results of the key secondary efficacy variable, change from Double-Blind Baseline to Week 24 in trough clinic sitting SBP (referred to as clinic SBP) are shown below.

Figure 11.b Mean Trough Clinic SBP by Study Visit (LOCF, FAS)



DBP

Mean 24-hour mean DBP at baseline were similar in the treatment groups.

The results of the change from baseline at week 24 in 24-hour DBP by ABPM, are shown below.

Table 11.c Change From Baseline to Week 24 in 24-Hour Mean DBP (mm Hg) by ABPM (LOCF, FAS)

Study Visit	Treatment Group		
	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
Baseline			
N	284	271	277
LS mean (SE)	87.38 (0.541)	87.80 (0.554)	87.17 (0.548)
Week 24 (LOCF)			
N	284	271	277
LS mean change (SE)	-9.23 (0.459)	-9.77 (0.470)	-7.07 (0.465)
LS mean difference (a)	-2.16	-2.69	
(95% CI)	(-3.44, -0.88)	(-3.99, -1.40)	
P-value vs valsartan 320 mg	<0.001* (b)	<0.001* (b)	
Week 24: Sensitivity analysis using multiple imputations			
LS mean difference (a)	-2.42	-2.92	
(95% CI)	(-3.75, -1.09)	(-4.39, -1.46)	
P-value vs valsartan 320 mg	<0.001* (b)	<0.001* (b)	

Source: Table 15.2.2.1.2.

Primary analyses include subjects with both a Baseline and postbaseline value.

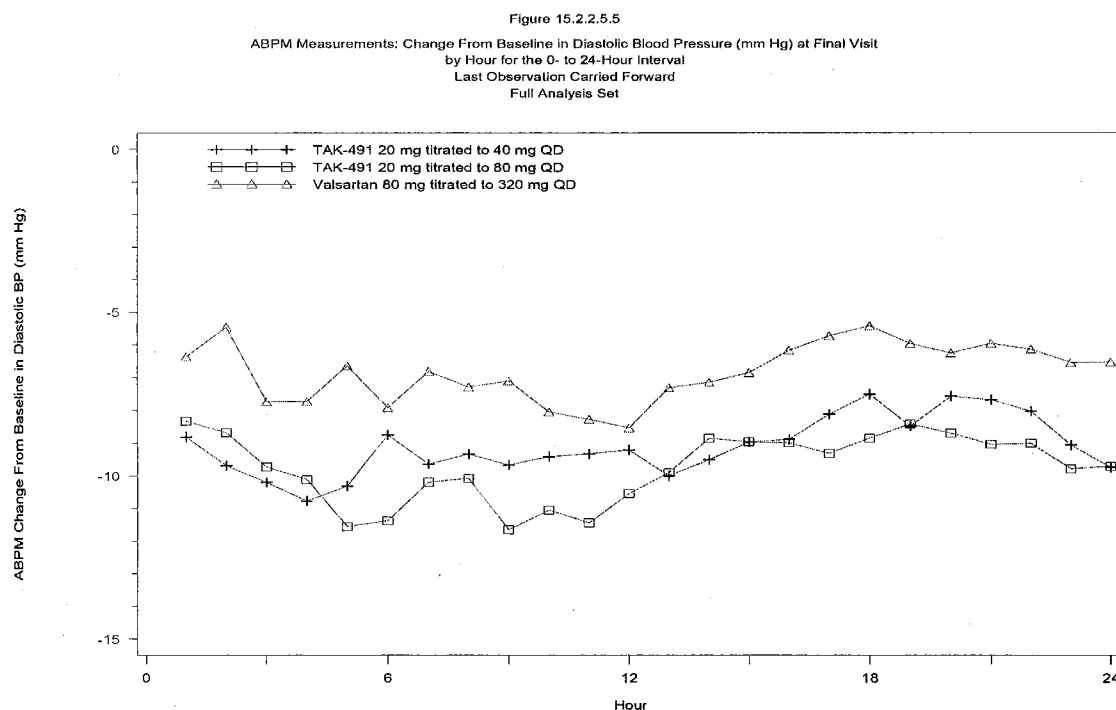
* Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of TAK-491 group - LS mean change of valsartan group.

(b) P-value from ANCOVA with terms for treatment (as a factor) and Baseline value (as a covariate).

Numerically and statistically significantly greater decreases in 24-hour mean DBP were observed for each of the TAK-491 treatment groups (40 mg and 80 mg) compared with valsartan 320 mg (by about 2-3 mm Hg; (P<0.001).

The 24 hour DBP profiles change from baseline at final visit are shown below.



SAFETY

The duration of treatment for the three treatment groups is shown below.

Table 12.a Duration (Days) of Double-Blind Treatment With Study Medication (Safety Analysis Set)

	Treatment Group		
	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
Mean (SD)	145.3 (49.07)	142.1 (53.99)	142.2 (51.88)
Median	168.0	168.0	168.0
Min - Max	1 - 187	1 - 183	1 - 189
	n (%)		
Completed 1 to 13 days	3 (0.9)	14 (4.3)	10 (3.1)
Completed 14 to 27 days	15 (4.6)	14 (4.3)	10 (3.1)
Completed 28 to 55 days	17 (5.2)	16 (4.9)	21 (6.4)
Completed 56 to 83 days	15 (4.6)	12 (3.6)	18 (5.5)
Completed 84 to 111 days	11 (3.4)	8 (2.4)	9 (2.8)
Completed 112 to 139 days	10 (3.1)	10 (3.0)	7 (2.1)
Completed 140 to 167 days	68 (20.8)	55 (16.7)	67 (20.6)
Completed ≥168 days	188 (57.5)	200 (60.8)	184 (56.4)

Source: Table 15.1.15.1.

The median duration of treatment was similar (168 days).

The following table shows the reports of adverse events, the discontinuations for adverse events, and the reported deaths by treatment group.

Table 12.d Overview of Treatment-Emergent Adverse Events and SAEs During the Double-Blind Treatment Phase (Safety Analysis Set)

Number (%) of Subjects with:	Treatment Group		
	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
Adverse events	214 (65.4)	215 (65.3)	192 (58.9)
Related (a)	80 (24.5)	92 (28.0)	76 (23.3)
Mild	88 (26.9)	97 (29.5)	85 (26.1)
Moderate	104 (31.8)	94 (28.6)	89 (27.3)
Severe	22 (6.7)	24 (7.3)	18 (5.5)
Leading to discontinuation (b)	23 (7.0)	27 (8.2)	20 (6.1)
SAEs	8 (2.4)	5 (1.5)	8 (2.5)
Related (a)	2 (0.6)	3 (0.9)	1 (0.3)
Deaths	1 (0.3)	0	1 (0.3)

Source: Tables 15.3.1.1.1, 15.3.1.1.7, 15.3.1.1.8, and 15.3.2.1.2.

(a) Related events were attributed by investigator as definitely, probably, or possibly related to study drug.

(b) Treatment-emergent adverse events leading to study drug discontinuation include those that led to temporary drug interruption or permanent discontinuation.

There were 2 reported deaths (TAK-491 40 mg and valsartan). Slightly fewer subjects discontinued valsartan because of adverse events compared to the TAK-491 groups (6.1% for valsartan compared to 7% and 8.2% for TAK-491 40 mg and 80 mg, respectively).

Serious safety

Deaths

There were 2 deaths reported during the double-blind treatment phase of this study; 1 subject in the TAK-491 40 mg group and 1 subject in the valsartan 320 mg group.

- Subject 1061/043, a 37-year-old male, suffered unwitnessed sudden death around day 104, 16 days after the subject had taken the last documented study drug dose (TAK-491 40 mg). Last clinic visit (day 89), BP was 171/84 mm Hg. The autopsy report confirmed cardiac arrest as the cause of death resulting from hypertensive and arteriosclerotic cardiovascular disease. The subject had a medical history of type 2 diabetes mellitus and alcohol abuse.
- Subject 1030/001, a 61-year-old male, had an unwitnessed death on Day 58 while receiving valsartan 320 mg. The subject had no complaints at the study visit performed earlier the same day. Laboratory results from the visit were normal. Clinic blood pressures obtained at the study visit ranged from 136/77 mm Hg to 148/79 mm Hg. No autopsy was performed. The subject had a medical history of syncope, and hyperlipidaemia.

Serious adverse events

The individual reported serious adverse events are shown below.

Table 12.1 Summary of Treatment-Emergent SAEs During the Double-Blind Treatment Phase (Safety Analysis Set)

Site/ Subject No.	Age/ Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Action/Outcome
TAK-491 40 mg						
1038/011	51/M	Diabetes mellitus type 2 exacerbation (Type 2 diabetes mellitus)	96	99	Possible	Dose not changed/ Recovered/Resolved
1049/010	55/M	C6 vertebral body fracture due to fall (Cervical vertebral fracture)	109	110	Not related	Drug withdrawn/ Recovered with sequela
1061/038	61/F	Asthma (Asthma)	117	133	Not related	Dose not changed/ Recovered/Resolved
1061/043	37/M	Pancreatitis (Pancreatitis)	45	47	Not related	Dose not changed/ Recovered/Resolved
		Arteriosclerotic cardiovascular disease (Arteriosclerosis)	104	104	Not related	Drug withdrawn/Fatal
		Hypertensive cardiovascular disease (Hypertension)	104	104	Not related	Not applicable/ Not recovered/Not resolved
1085/015	47/M	Renal impairment (Renal impairment)	169	181	Probable	Dose not changed/ Recovered/Resolved
1140/004	78/F	Acute heart failure (Cardiac failure acute)	12	29	Not related	Drug withdrawn/ Recovered/Resolved
1155/009	23/F	Acute non-lithiasis cholecystitis (Cholecystitis acute)	145	150	Not related	Drug withdrawn/ Recovered/Resolved
		Hepatitis A (Hepatitis A)	145	152	Not related	Dose not changed/ Recovered/Resolved
1155/016	41/M	Severe prolonged hypoglycemia (Hypoglycaemia)	42	44	Not related	Dose not changed/ Resolved with sequela
TAK-491 80 mg						
1008/017	63/M	Myocardial infarction (Myocardial infarction)	130	156	Possible	Drug withdrawn/ Recovered/Resolved
1030/008	54/M	Non acute myocardial infarction by ECG (Silent myocardial infarction)	113	Ongoing	Possible	Drug withdrawn/Not recovered/Not resolved
1041/013	45/M	Atypical chest pain (Chest pain)	122	122	Not related	Drug withdrawn/ Recovered/Resolved
1044/002	57/M	Bipolar/manic episode (Bipolar I disorder)	17	22	Possible	Drug withdrawn/ Recovered/Resolved
1055/001	65/M	Invasive adenocarcinoma of distal oesophagus (Oesophageal adenocarcinoma)	35	Ongoing	Not related	Drug withdrawn/ Not recovered/Not resolved
Valsartan 320 mg						
1026/025	58/M	Fractured right ankle due to fall (Fall)	49	Ongoing	Not related	Drug withdrawn/ Recovering/Resolving
1030/001	61/M	Arteriosclerotic cardiovascular disease (Arteriosclerosis)	58	58	Possible	Drug withdrawn/Fatal

Table 15.3.2.1.2 (continued)

Site/ Subject No.	Age/ Sex	Event Description (Preferred Term)	Start Day	Stop Day	Relationship to Study Drug	Action/Outcome
Valsartan 320 mg						
1049/011	70/F	Abdominal pain (Abdominal pain)	91	97	Not related	Not applicable/ Recovered/Resolved
1062/020	65/M	Worsening of coronary artery disease (Coronary artery disease)	93	Ongoing	Not Related	Drug withdrawn/ Recovering/Resolving
1067/004	62/M	Gout was actual discharge diagnosis. Cellulitis was not treated at hospital after labs were done, it was confirmed to gout – discharged summary of gout faxed on 9/26/08 (Gout)	55	63	Not related	Dose not changed/ Recovered/Resolved
1117/006	77/M	Silent myocardial infarction (Silent myocardial infarction)	54	57	Not related	Not applicable/ Resolved with sequela
1134/013	76/M	Scrotal abscess (Scrotal abscess)	10	14	Not related	Drug withdrawn/ Recovered/Resolved
1161/058	68/M	Erysipela (Erysipelas)	38	62	Not related	Not applicable/ Recovered/Resolved

Source: Table 15.3.2.1.2.

Note: Events reported prior to Week 2 occurred while subjects were receiving their initial dose of study drug (TAK-491 20 mg or valsartan 80 mg).

There were 21 subjects (8, 5, and 8, for TAK-491 40 mg, TAK-491 80 mg, and valsartan) who reported a serious adverse event during the double-blind treatment phase of the study. Cardiovascular complaints tended to predominate.

Discontinuations for adverse events

During the double-blind treatment phase, a total of 70 subjects (23, 27, and 20 subjects for TAK-491 40 mg, TAK-491 80 mg and valsartan, respectively) permanently discontinued from study drug because of adverse events.

Adverse events leading to discontinuation during the double-blind treatment phase that were reported in more than 1 subject included

- hypotension (2 [0.6%] TAK-491 40 mg subjects, 5 [1.5%] TAK-491 80 mg subjects, and 2 [0.6%] valsartan 320 mg subjects),
- dizziness (4 [1.2%] TAK-491 40 mg subjects, 3 [0.9%] TAK-491 80 mg subjects, and 1 [0.3%] valsartan 320 mg subject),
- headache (2 [0.6%] TAK-491 40 mg subjects, 3 [0.9%] TAK-491 80 mg subjects, and 2 [0.6%] valsartan 320 mg subjects),
- hypertension (2 [0.6%] TAK-491 40 mg subjects and 3 [0.9%] TAK-491 80 mg subjects),
- blood pressure increased (2 [0.6%] TAK-491 40 mg subjects and 1 [0.3%] valsartan 320 mg subject),
- diarrhea (1 [0.3%] TAK-491 80 mg subject and 1 [0.3%] valsartan 320 mg subject),
- fatigue (1 [0.3%] TAK-491 40 mg subject and 1 [0.3%] valsartan 320 mg subject),
- edema peripheral (2 [0.6%] valsartan 320 mg subjects),
- dizziness postural (2 [0.6%] TAK-491 80 mg subjects), and
- arteriosclerosis (1 [0.3%] TAK-491 40 mg subject and 1 [0.3%] valsartan 320 mg subject).

Reports of dizziness, hypotension and/or syncope were associated with permanent discontinuation of treatment for 16 subjects (4 TAK-491 40 mg, 8 TAK-491 80 mg, and 4 valsartan 320 mg).

Hypertension, blood pressure increased, or hypertensive crisis led to permanent discontinuation of treatment for 9 subjects (4 TAK-491 40 mg, 4 TAK-491 80 mg, and 1 valsartan 320 mg).

All adverse events

The adverse events reported by at least 17 subjects are shown below.

Table 15.3.1.1.4
Treatment-Emergent Adverse Events by Preferred Term - Double Blind
Safety Analysis Set

Preferred Term	Number of Subjects (%)			
	TAK-491 20 mg titrated to 40 mg QD (N=327)	TAK-491 20 mg titrated to 80 mg QD (N=329)	Valsartan 80 mg titrated to 320 mg QD (N=326)	Total (N=982)
Subjects With Any Treatment-Emergent AEs	214 (65.4)	215 (65.3)	192 (58.9)	621 (63.2)
Headache	33 (10.1)	29 (8.8)	28 (8.6)	90 (9.2)
Dizziness	27 (8.3)	29 (8.8)	15 (4.6)	71 (7.2)
Urinary tract infection	26 (8.0)	25 (7.6)	16 (4.9)	67 (6.8)
Fatigue	14 (4.3)	9 (2.7)	9 (2.8)	32 (3.3)
Nasopharyngitis	12 (3.7)	6 (1.8)	14 (4.3)	32 (3.3)
Arthralgia	8 (2.4)	10 (3.0)	12 (3.7)	30 (3.1)
Blood creatine phosphokinase increased	8 (2.4)	13 (4.0)	8 (2.5)	29 (3.0)
Dyslipidaemia	5 (1.5)	8 (2.4)	13 (4.0)	26 (2.6)
Upper respiratory tract infection	7 (2.1)	9 (2.7)	10 (3.1)	26 (2.6)
Back pain	10 (3.1)	8 (2.4)	6 (1.8)	24 (2.4)
Hypercholesterolaemia	8 (2.4)	8 (2.4)	6 (1.8)	22 (2.2)
Pain in extremity	7 (2.1)	10 (3.0)	4 (1.2)	21 (2.1)
Diarrhoea	7 (2.1)	8 (2.4)	4 (1.2)	19 (1.9)
Nausea	9 (2.8)	3 (0.9)	7 (2.1)	19 (1.9)
Oedema peripheral	5 (1.5)	5 (1.5)	9 (2.8)	19 (1.9)
Bronchitis	5 (1.5)	10 (3.0)	2 (0.6)	17 (1.7)

Note: Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 14 days (or 30 days for a serious adverse event) after the last dose of double-blind study drug or before the first dose of open-label study drug.

Note: If a subject experienced more than 1 episode of an adverse event, it is counted only once within a preferred term. Percentages are based on the total number of subjects in the safety analysis set for each treatment group.

Note: AEs are sorted by decreasing order of incidence based on the total number of AE reports.

Note: MedDRA Dictionary (Version 11.1) was used for coding adverse events.

There were somewhat fewer subjects who reported adverse events by the valsartan group (59%) compared to TAK-491 40 mg and TAK-491 80 mg (65% for both dose groups).

There was a lower incidence rate for the reporting of dizziness by the valsartan group (5%) compared to TAK-491 40 mg and TAK-491 80 mg (8% and 9%, respectively). This imbalance was also seen for urinary tract infection.

Clinical laboratory parameters

Chemistry

The following table shows the baseline, endpoint and change from baseline at endpoint values for various chemistry parameters.

Table 12.p Serum Chemistry: Mean Changes From Double-Blind Baseline to Final Visit During the Double-Blind Treatment Phase (Safety Analysis Set)

Serum Chemistry Parameter (unit)	Treatment Group					
	TAK-491 40 mg N=327		TAK-491 80 mg N=329		Valsartan 320 mg N=326	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
ALT (U/L)						
Double-Blind Baseline (a)	327	27.7 (13.77)	329	29.3 (18.39)	326	27.5 (13.55)
Final Visit (b)	325	28.2 (15.64)	316	30.1 (18.24)	323	28.7 (16.66)
Change	325	0.5 (10.80)	316	0.9 (14.83)	323	1.1 (12.82)
AST (U/L)						
Double-Blind Baseline (a)	327	24.5 (9.52)	329	25.1 (11.78)	326	24.2 (9.65)
Final Visit (b)	325	24.6 (10.36)	316	26.0 (14.53)	323	24.9 (11.46)
Change	325	0.1 (7.56)	316	1.1 (11.65)	323	0.7 (8.16)
Alkaline phosphatase (U/L)						
Double-Blind Baseline (a)	327	81.9 (24.79)	329	80.8 (25.06)	326	82.5 (23.37)
Final Visit (b)	325	78.8 (23.19)	316	79.8 (24.78)	323	81.4 (23.17)
Change	325	-2.9 (13.84)	316	-1.1 (14.97)	323	-0.8 (13.30)
Bilirubin, total (umol/L)						
Double-Blind Baseline (a)	327	8.4 (3.81)	329	8.9 (8.16)	326	8.3 (4.10)
Final Visit (b)	325	7.5 (3.56)	316	7.6 (5.02)	323	8.1 (4.55)
Change	325	-0.9 (3.17)	316	-1.2 (5.02)	323	-0.2 (3.46)
CK total (U/L)						
Double-Blind Baseline (a)	327	133.6 (110.56)	329	122.2 (95.59)	326	130.8 (100.93)
Final Visit (b)	324	139.2 (116.58)	316	128.6 (94.19)	323	140.0 (119.02)
Change	324	5.3 (77.56)	316	7.4 (95.47)	323	9.6 (101.04)
Creatinine (umol/L)						
Double-Blind Baseline (a)	327	79.7 (19.42)	329	77.6 (16.76)	326	79.0 (16.77)
Final Visit (b)	325	83.2 (22.16)	316	82.9 (20.02)	323	80.3 (18.38)
Change	325	3.4 (13.03)	316	5.6 (12.62)	323	1.3 (9.30)
Potassium (mmol/L)						
Double-Blind Baseline (a)	327	4.27 (0.411)	329	4.24 (0.381)	326	4.25 (0.401)
Final Visit (b)	325	4.40 (0.477)	316	4.35 (0.402)	323	4.27 (0.429)
Change	325	0.13 (0.435)	316	0.11 (0.400)	323	0.02 (0.398)
Sodium (mmol/L)						
Double-Blind Baseline (a)	327	139.9 (2.19)	329	139.7 (2.50)	326	139.7 (2.10)
Final Visit (b)	325	139.7 (2.41)	316	139.5 (2.27)	323	139.8 (2.12)
Change	325	-0.1 (2.34)	316	-0.2 (2.70)	323	0.1 (2.14)
Uric acid (umol/L)						
Double-Blind Baseline (a)	327	337.6 (82.87)	329	321.9 (84.41)	326	337.2 (80.68)
Final Visit (b)	325	360.1 (91.21)	316	346.8 (90.93)	323	347.1 (83.51)
Change	325	22.2 (53.20)	316	26.1 (58.02)	323	10.4 (54.31)

Source: Table 15.3.4.1.4.

Note: N at each visit includes subjects who had both a Baseline value and a value at that visit. SI units are reported.

(a) Baseline value is the last observation obtained before the first dose of double-blind study drug.

(b) Last observation carried forward.

The increase in creatinine levels from baseline was larger for the TAK-491 80 mg (5.6 umol/L) compared to valsartan (1.3 umol/L) and TAK-491 40 mg (3.4 umol/L).

Individual Subject Changes

Shifts to high creatinine values were greater in the TAK-491 groups: TAK-491 80 mg 6.7% and TAK-491 40 mg 3.5% compared to valsartan 320 mg groups 2.3%. There was a greater shift from normal to high in serum creatinine with TAK-491 as compared to valsartan.

Table 12.t Number of Subjects With Shifts in Serum Chemistry Values From Normal at Double-Blind Baseline to High or Low at the Final Visit During the Double-Blind Treatment Phase – Safety Analysis Set

Chemistry Parameters	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
Shift From Normal to High n/N (%)			
ALT	12/294 (4.1)	23/291 (7.9)	17/291 (5.8)
AST	9/298 (3.0)	18/295 (6.1)	19/303 (6.3)
Albumin	7/316 (2.2)	5/307 (1.6)	2/318 (0.6)
Alkaline phosphatase	1/310 (0.3)	4/298 (1.3)	4/313 (1.3)
BUN	19/302 (6.3)	16/301 (5.3)	14/310 (4.5)
Bicarbonates	0/317	1/308 (0.3)	2/321 (0.6)
Bilirubin total	2/320 (0.6)	4/308 (1.3)	2/318 (0.6)
CK total	21/267 (7.9)	26/273 (9.5)	30/271 (11.1)
Calcium	11/300 (3.7)	11/292 (3.8)	11/310 (3.5)
Chloride	1/324 (0.3)	0/315	0/323
Creatinine	11/312 (3.5)	21/312 (6.7)	7/311 (2.3)
Fasting serum glucose	10/312 (3.2)	8/304 (2.6)	6/305 (2.0)
GGT	19/254 (7.5)	23/246 (9.3)	16/257 (6.2)
Potassium	12/312 (3.8)	5/303 (1.7)	3/312 (1.0)
Protein total	3/305 (1.0)	9/299 (3.0)	4/316 (1.3)
Sodium	4/321 (1.2)	0/315	1/321 (0.3)
Uric acid	32/303 (10.6)	21/295 (7.1)	22/300 (7.3)
Shift From Normal to Low n/N (%)			
Potassium	4/312 (1.3)	5/303 (1.7)	9/312 (2.9)
Sodium	4/321 (1.2)	5/315 (1.6)	0/321

Source: Table 15.3.4.1.5 and Appendices 16.2.8.3.1 through 16.2.8.3.5.

The percentage of subjects with ≥ 1 markedly abnormal chemistry value during the double-blind treatment phase is shown below by treatment group.

Table 12.v Percentage of Subjects With at Least 1 Markedly Abnormal Chemistry Value During the Double-Blind Treatment Phase (Safety Analysis Set)

Serum Chemistry Parameter (markedly abnormal criterion)	Treatment Group n/N (%)		
	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
ALT (>3×ULN)	4/326 (1.2)	4/319 (1.3)	4/323 (1.2)
AST (>3×ULN)	2/326 (0.6)	2/319 (0.6)	5/323 (1.5)
Bilirubin, total (>2×ULN)	1/326 (0.3)	1/319 (0.3)	1/323 (0.3)
CK total (>10×ULN)	3/326 (0.9)	0/319	2/323 (0.6)
Calcium	1/326 (0.3)	0/319	0/323
(<0.8×LLN)	0/326	0/319	0/323
(>1.2×ULN) v ar	1/326 (0.3)	0/319	0/323
Creatinine (>1.5× Double-Blind Baseline)	10/326 (3.1)	12/319 (3.8)	2/323 (0.6)
GGT (>3×ULN)	25/326 (7.7)	25/319 (7.8)	22/323 (6.8)
Potassium	7/326 (2.1)	1/319 (0.3)	2/323 (0.6)
(<3.0 mmol/L)	1/326 (0.3)	0/319	0/323
(>6.0 mmol/L)	6/326 (1.8)	1/319 (0.3)	2/323 (0.6)
Sodium	6/326 (1.8)	2/319 (0.6)	2/323 (0.6)
(<130 mmol/L)	5/326 (1.5)	2/319 (0.6)	2/323 (0.6)
(>150 mmol/L)	1/326 (0.3)	0/319	0/323
Uric acid (Males: >625 umol/L) (Females: >506 umol/L)	9/326 (2.8)	11/319 (3.4)	6/323 (1.9)

Source: Tables 15.3.4.1.6 and 15.3.4.1.7.

LLN=lower limit of normal, ULN=upper limit of normal

A greater percentage of subjects had at least 1 markedly abnormal creatinine value in the TAK-491 40 mg and TAK-491 80 mg groups (3.1% and 3.8%, respectively) compared to subjects in the valsartan 320 mg group (0.6%). One subject in the TAK-491 40 mg group (Subject 085/015) reported a serious adverse event renal impairment. This subject was not discontinued from the study.

A greater percentage of subjects had at least 1 markedly abnormal uric acid value in the TAK-491 40 mg and TAK-491 80 mg groups (2.8% and 3.4%, respectively) compared to subjects in the valsartan 320 mg group (1.9%).

Chemistry values reported as a serious adverse event

TAK-491 40 mg treatment group: renal impairment [Subject 1085/015] and hypoglycemia [Subject 1155/016]). Subject 1085/015 had transient increase in serum creatinine but remained on study drug. No subjects in either the TAK-491 80 mg or valsartan 320 mg treatment groups reported a similar event.

Six chemistry-related adverse events (2 TAK-491 40 mg, 3 TAK-491 80 mg, and 1 valsartan 320 mg) resulted in premature discontinuation from the double-blind treatment phase. Renal failure chronic (worsening) was reported by subject 1134/022) in the TAK-491 40 mg group.

Hematology

The table below shows the number and percent of subjects with shifts in hematology values from normal at double-blind baseline to high or low at the final visit of the double blind treatment phase.

Table 12.cc Number of Subjects with Shifts in Hematology Values from Normal at Double-Blind Baseline to High or Low at the Final Visit During the Double-Blind Treatment Phase – Safety Analysis Set

Hematology Parameters	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
	Shift from Normal to High n/N (%)		
Platelet count	9/303 (3.0)	7/285 (2.5)	9/294 (3.1)
WBC count	6/313 (1.9)	9/307 (2.9)	2/309 (0.6)
Hematocrit	Shift from Normal to Low n/N (%)		
Hematocrit	17/296 (5.7)	26/285 (9.1)	16/293 (5.5)
Hemoglobin	20/294 (6.8)	14/276 (5.1)	14/294 (4.8)
Platelet count	0/303	4/285 (1.4)	0/294
RBC count	14/305 (4.6)	17/292 (5.8)	6/308 (1.9)
WBC count	6/313 (1.9)	2/307 (0.7)	1/309 (0.3)

Source: Table 15.3.4.1.5 and Appendices 16.2.8.3.1 through 16.2.8.3.5.

There was a higher percentage of subjects who shifted from normal to low hematocrit in the TAK-491 80 mg group (9.1%) compared to the TAK-491 40 mg (5.7%) and valsartan 320 mg (5.5%) groups. In addition, the valsartan group had lower percentage of subjects with shifts from normal at baseline to low at endpoint for hemoglobin and RBC count compared to the TAK-491 groups.

The table below shows the markedly abnormal laboratory values by treatment group.

Table 12.dd Percentage of Subjects With at Least 1 Markedly Abnormal Hematology Value During Double-Blind Treatment (Safety Analysis Set)

Hematology Parameter (markedly abnormal criterion)	Treatment Group n/N (%)		
	TAK-491 40 mg N=327	TAK-491 80 mg N=329	Valsartan 320 mg N=326
Hematocrit/PCV ($<0.8 \times$ Baseline)	1/326 (0.3)	5/319 (1.6)	1/323 (0.3)
Hemoglobin ($<$ Baseline-3.0 g/dL)	1/326 (0.3)	3/319 (0.9)	0/323
Platelet count	1/326 (0.3)	0/319	0/322
($<50 \times 10^9/L$)	0/326	0/319	0/322
($>700 \times 10^9/L$)	1/326 (0.3)	0/319	0/322
RBC count ($<0.8 \times$ Baseline)	2/326 (0.6)	4/319 (1.3)	1/323 (0.3)
WBC count	1/326 (0.3)	2/319 (0.6)	1/323 (0.3)
($<2 \times 10^9/L$)	0/326	2/319 (0.6)	1/323 (0.3)
($>20 \times 10^9/L$)	1/326 (0.3)	0/319	0/323

Source: Tables 15.3.4.1.6 and 15.3.4.1.7.

PCV=packed cell volume, RBC=red blood cell, WBC=white blood cell.

There were more subjects in the TAK-491 80 mg group who reported markedly abnormally low hematocrit, hemoglobin, and RBC count compared to the other treatment groups. However, none was reported as a serious adverse event or led to premature discontinuation.

Reviewer's summary and conclusions

Efficacy: there were numerically and statistically significantly greater decreases in 24-hour mean SBP were observed for each of the TAK-491 treatment groups (40 mg and 80 mg) compared with valsartan 320 mg (by about 4 mm Hg; ($P<0.001$)). There were numerically and statistically significantly greater decreases in 24-hour mean DBP were observed for each of the TAK-491 treatment groups (40 mg and 80 mg) compared with valsartan 320 mg (by about 2-3 mm Hg; ($P<0.001$)).

Safety: there were somewhat fewer subjects discontinued valsartan because of adverse events compared to the TAK-491 groups (6.1% for valsartan compared to 7% and 8.2% for TAK-491 40 mg and 80 mg, respectively). There were somewhat fewer subjects who reported adverse events by the valsartan group (59%) compared to TAK-491 40 mg and TAK-491 80 mg (65% for both dose groups). There was a lower incidence rate for the reporting of dizziness by the valsartan group (5%) compared to TAK-491 40 mg and TAK-491 80 mg (8% and 9%, respectively). This imbalance was also seen for urinary tract infection.

The shifts to high creatinine values were greater in the TAK-491 groups: TAK-491 80 mg 6.7% and TAK-491 40 mg 3.5% compared to valsartan 320 mg groups 2.3%. There was a greater shift from normal to high in serum creatinine with TAK-491 as compared to valsartan.

A greater percentage of subjects had at least 1 markedly abnormal creatinine value in the TAK-491 40 mg and TAK-491 80 mg groups (3.1% and 3.8%, respectively) compared to subjects in the valsartan 320 mg group (0.6%). One subject in the TAK-491 40 mg group (Subject 085/015) reported a serious adverse event renal impairment. This subject was not discontinued from the study.

A greater percentage of subjects had at least 1 markedly abnormal uric acid value in the TAK-491 40 mg and TAK-491 80 mg groups (2.8% and 3.4%, respectively) compared to subjects in the valsartan 320 mg group (1.9%).

Six chemistry-related adverse events (2 TAK-491 40 mg, 3 TAK-491 80 mg, and 1 valsartan 320 mg) resulted in premature discontinuation from the double-blind treatment phase. Renal failure chronic (worsening) was reported by subject 1134/022) in the TAK-491 40 mg group.

There was a higher percentage of subjects who shifted from normal to low hematocrit in the TAK-491 80 mg group (9.1%) compared to the TAK-491 40 mg (5.7%) and valsartan 320 mg (5.5%) groups. In addition, the valsartan group had lower percentage of subjects with shifts from normal at baseline to low at endpoint for hemoglobin and RBC count compared to the TAK-491 groups.

There were more subjects in the TAK-491 80 mg group who reported markedly abnormally low hematocrit, hemoglobin, and RBC count compared to the other treatment groups. However, none was reported as a serious adverse event or led to premature discontinuation.

Conclusions: while there was better blood pressure control with TAK-491 80 mg compared to valsartan, the safety (particularly reports of dizziness and abnormally elevated creatinine values) with TAK-491 80 mg was more disconcerting.

Study 01-06-TL-491-020

No. of Sites-Country (a)	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
01-06-TL-491-020 (491-020)	Double-blind, randomized, parallel-group, 3-arm	885 subjects* with essential hypertension (clinic SBP=150- 180 mm Hg)	24 weeks (2 weeks, then titrated to the higher dose for 22 weeks)	A: TAK-491 20 mg → 40 mg B: TAK-491 20 mg → 80 mg C: Ramipril 2.5 mg → 10 mg
101-Europe and Russia 18 February 2007- 21 April 2009	Antihypertensive effect of TAK-491 compared with ramipril for 6 months (Change from BL to Week 24 in clinic SBP)	*1 subject in Group C was not randomized but received double-blind treatment		884/784 A: 295/265 B: 294/264 C: 296/255

Title: A Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 With Ramipril in Subjects With Essential Hypertension.

Investigator(s): 101 investigators enrolled subjects in placebo run-in period in Europe and Russia.

Study Period: 24 January 2008 to 21 April 2009

Primary objective: to evaluate the change in clinic systolic blood pressure (SBP) in response to TAK-491 compared with ramipril for 6 months in subjects with essential hypertension.

METHODOLOGY

This was a multicenter, double-blind, randomized, parallel-group study in subjects with essential hypertension (sitting SBP between 150 and 180 mm Hg, inclusive). The total duration of the study was up to 32 weeks, including up to 28 days of Screening (with washout for any antihypertensive medication, followed by a 14-day single-blind placebo Run-in Period, a 24-week double-blind Treatment Period, and a safety follow-up telephone call at 1 week after last dose of study drug.

Subjects who qualified for study entry at Screening discontinued their previous antihypertensive medications on Day -21 (Day -28 if on amlodipine), prior to starting the 14-day single-blind placebo Run-in Period on Day -14. On Day -1, subjects who continued to meet the entry criteria were randomized to receive TAK-491 20 mg once daily (QD) or ramipril 2.5 mg, for 2 weeks, and were then up-titrated to either TAK-491 40 or 80 mg or ramipril 10 mg. Double-blind treatment was continued for a total of 6 months. Subjects were evaluated at Screening (Day -28 or Day -21), Day -14, Day -7, Day -1, Day 1 (randomization), Week 2, and Week 4 and then every 4 weeks up to the end of the 24-week Treatment Period. Trough clinic sitting SBP and DBP were assessed at each visit. ABPM was performed on Day -1 for 24 hours before administration of the first dose of double-blind study medication, and at Week 24/Early Termination (ie, completion or withdrawal) for 24 hours following administration of the last dose of study medication. If possible, subjects who withdrew were evaluated at an Early Termination Visit, which was scheduled as soon as possible after withdrawal, were contacted for Safety Follow-up 1 week after withdrawal.

Diagnosis and Main Criteria for Inclusion: to qualify for study participation, subjects must have been male or nonpregnant, nonlactating women with essential hypertension, defined as a postwashout trough clinic sitting SBP on Day -1 of 150 to 180 mm Hg, inclusive; aged 18 years or older; with clinical laboratory evaluations within the reference range for the testing laboratory or results that were deemed not clinically significant; able to comprehend and willing to sign an informed consent form; and willing to discontinue current antihypertensive medication(s) at Screening (on Day -21/-28).

Primary endpoint: the primary endpoint was change from baseline to Week 24 in trough clinic, sitting mean SBP.

RESULTS

Subject Disposition:

A total 884 subjects were randomized to treatment at 101 sites; 295 and 294 subjects were randomized to each of the TAK-491 (40 and 80 mg) treatment groups, respectively, and 295 to the ramipril treatment group. Of the 884 randomized subjects, all but 5 subjects received double-blind medication. In addition, subject 001, at site 0028, was given double-blind medication at Visit 2 in error. The subject was not randomized but, has been included in the Safety Set.

A total of 96 subjects (10.9%) prematurely discontinued from the study:
29 subjects (9.8%) in the TAK-491 40 mg treatment group,
29 subjects (9.9%) in the TAK-491 80 mg treatment group, and
38 subjects (12.8%) in the ramipril 10 mg treatment group.

Subject Demographics

Demographic and baseline characteristics were similar among treatment groups in all randomized subjects.

Characteristic	Treatment			Overall N=884
	TAK-491 40 mg N=295	TAK-491 80 mg N=294	Ramipril 10 mg N=295	
Sex, n (%)				
Male	159 (53.9)	158 (53.7)	146 (49.5)	463 (52.4)
Female	136 (46.1)	136 (46.3)	149 (50.5)	421 (47.6)
Age, yr				
Mean (SD)	56.9 (11.49)	56.8 (11.30)	56.8 (10.49)	56.9 (11.09)
Weight, kg				
Mean (SD)	85.9 (16.02)	85.2 (14.68)	85.9 (15.69)	85.7 (15.46)
Height, cm				
Mean (SD)	170.4 (9.51)	170.0 (9.23)	170.5 (9.30)	170.3 (9.34)
BMI, kg/m ²				
Mean (SD)	29.6 (4.78)	29.5 (4.66)	29.5 (4.58)	29.5 (4.67)
Clinic measurement parameters				
n	294	293	292	
Clinic SBP (mm Hg)				0.472 (a)
Mean (SD)	160.7 (7.34)	161.4 (7.65)	161.2 (8.50)	
Clinic DBP (mm Hg)				0.297 (a)
Mean (SD)	94.7 (9.45)	95.6 (8.67)	94.5 (8.89)	

(a) P-value. The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

Baseline blood pressures were similar and were approximately 161/95 mmHg.

The change from baseline at week 24 for sitting trough clinic SBP for all treatment groups is shown below.

Summary of the Primary Analysis: Change From Baseline to Week 24 in the Sitting Trough Clinic SBP (FAS, LOCF)

Study Visit	Treatment		
	TAK-491 40 mg N=294	TAK-491 80 mg N=293	Ramipril 10 mg N=292
Baseline			
N	291	289	290
LS mean (SE)	160.85 (0.451)	161.48 (0.452)	161.42 (0.451)
Change from baseline at Week 24			
N	291	289	290
LS mean (SE)	-20.63 (0.946)	-21.24 (0.949)	-12.22 (0.948)
LS mean difference vs ramipril (a)	-8.41	-9.03	
95% CI	(-11.04, -5.78)	(-11.66, -6.39)	
P-value vs ramipril	<0.001*	<0.001*	
Week 24: Sensitivity analysis using multiple imputation			
N	294	293	292
LS mean difference vs ramipril (a)	-8.82	-9.59	
95% CI	(-11.60, -6.03)	(-12.27, -6.90)	
P-value vs ramipril	<0.001*	<0.001*	

Note: Blood pressure values are the arithmetic mean of nonmissing values of the 3 trough sitting blood pressure measurements. Includes subjects with both a baseline and postbaseline value. Baseline is the last nonmissing visit prior to first dose of double-blind study medication.

*=Significant difference at 0.05 level.

(a) LS mean difference=LS mean change of each treatment (TAK-491 dose group) – LS mean change of ramipril 10 mg group.

TAK-491, at doses of 40 and 80 mg, resulted in significantly ($P<0.001$) greater reductions in mean clinic SBP (-20.63 and -21.24 mm Hg, respectively) than ramipril 10 mg QD (-12.22 mm Hg) and was superior to ramipril 10 mg, based on the primary endpoint of clinic mean SBP, with a treatment difference (95% CI) of -8.41 mm Hg (-11.04, -5.78) and -9.03 mm Hg (-11.66, -6.39), respectively.

In addition, TAK-491, at doses of 40 and 80 mg QD, resulted in significantly ($P<0.001$) greater reductions of mean clinic DBP than ramipril 10 mg, with a treatment difference (95% CI) of -5.31 mm Hg (-6.85, -3.78) and -5.66 mm Hg (-7.21, -4.12), respectively. TAK-491, at doses of 40 and 80 mg QD, was significantly ($P<0.001$) better than ramipril 10 mg in reducing the blood pressure from baseline to Week 24 in 24-hour mean SBP and DBP by ABPM; and SBP and DBP by ABPM for mean daytime, mean nighttime, and 22- to 24-hour mean trough.

Safety results

Deaths

There were no reported deaths.

Serious adverse events

The highest incidence of serious adverse events was reported in the TAK-491 80 mg group (4.1%) compared to TAK-491 40 mg (2.7%) and ramipril (2.0%). These events are shown below.

Table 12.f Summary of Treatment-Emergent SAEs (Safety Analysis Set)

Site/Subject No.	Age/Sex	Preferred Term	Start Day	Stop Day	Relationship to Study Drug	Action/Outcome
TAK-491 40 mg						
0006/008	49/F	Cataract	1	28	Not related	Dose not changed/ Recovered resolved
0007/015	76/F	Atrial fibrillation	101	110	Not related	Dose not changed/ Recovered resolved
0017/003	50/M	Hepatitis C	117	164	Not related	Drug withdrawn/ Resolved with sequelae
0056/003	83/F	Urosepsis	73	Ongoing	Not related	Drug withdrawn/Not recovered not resolved
0076/002	59/M	Appendicitis	178	185	Not related	Not applicable/ Recovered resolved
0085/006	64/M	Grand mal convulsion	56	56	Not related	Dose not changed/ Recovered resolved
0094/004	64/M	Lung neoplasm malignant	50	Ongoing	Not related	Dose not changed/Not recovered not resolved
0121/013	42/F	Ankle fracture	125	Ongoing	Not related	Dose not changed/ Recovering resolving
TAK-491 80 mg						
0006/001	48/F	Ischaemic stroke	38	53	Not related	Drug withdrawn/ Resolved with sequelae
0006/005	70/M	Road traffic accident	85	113	Not related	Dose not changed/ Recovered resolved
0007/006	61/M	Cerebral ischaemia	96	106	Not related	Dose not changed/ Recovered resolved
0041/005	58/F	Atrial fibrillation	143	144	Possible	Not applicable/ Recovered resolved
0045/005	75/M	Hyperkalaemia	109	112	Possible	Dose not changed/ Recovered resolved
0047/002	71/M	Syncope	27	27	Definite	Drug withdrawn/ Recovered resolved
0066/010	48/M	Salivary gland calculus	46	70	Not related	Dose not changed/ Recovered resolved
0069/007	77/M	Angina pectoris	48	53	Not related	Drug withdrawn/ Recovered resolved
0071/026	68/F	Retinal detachment	42	46	Not related	Dose not changed/ Resolved with sequelae
0072/006	68/M	Renal cancer	161	Ongoing	Not related	Dose not changed/Not recovered not resolved
0089/005	54/F	Upper respiratory tract infection and Laryngeal oedema	86	98	Not related	Dose not changed/ Recovered resolved
0089/023	48/M	Hydrocele	130	158	Not related	Dose not changed/ Recovered resolved

Site/Subject No.	Age/Sex	Preferred Term	Start Day	Stop Day	Relationship to Study Drug	Action/Outcome
Ramipril 10 mg						
0057/008	68/M	Appendicitis	67	83	Not related	Drug withdrawn/ Recovered resolved
0074/013	66/M	Acute coronary syndrome	67	77	Possible	Drug withdrawn/ Recovered resolved
0074/018	64/M	Epilepsy	56	56	Not related	Drug withdrawn/ Recovered resolved
0089/006	51/M	Fall	8	206	Not related	Dose not changed/ Recovered resolved
0089/021	56/M	Hepatitis C	29	109	Not related	Drug withdrawn/ Recovered with sequelae
0122/004	51/M	Urosepsis	149	156	Not related	Drug withdrawn/ Recovered resolved

Source: Table 15.3.2.2.

F=female, M=male.

Treatment-emergent adverse events leading to permanent study discontinuation occurred in 30 subjects (7, 2.4% TAK 491 40 mg, 9, 3.1% TAK 491 80 mg, 14, 4.8% ramipril 10 mg). The events reported by the TAK-491 groups are shown below.

Table 12.g Summary of Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation (Safety Analysis Set)

Site/Subject No.	Age/Sex	Preferred Term	Start Day	Stop Day	Relationship to Study Drug	Action/Outcome
TAK-491 40 mg						
0017/003	50/M	Hepatitis C	117	164	Not related	Drug withdrawn/Resolved with sequelae
0027/014	76/M	Azotaemia	83	Ongoing	Probable	Drug withdrawn/Unknown
0056/003	83/F	Urosepsis	73	Ongoing	Not related	Drug withdrawn/Not recovered not resolved
0119/004	70/M	Toxic skin eruption	99	Ongoing	Possible	Drug withdrawn/Not recovered not resolved
0122/001	60/M	Nausea	132	156	Probable	Drug withdrawn/Recovered resolved
0130/006	61/M	Exercise tolerance decreased	20	41	Possible	Drug withdrawn/Recovered resolved
0133/007	73/M	Dizziness	33	Ongoing	Possible	Drug withdrawn/Not recovered not resolved
TAK-491 80 mg						
0006/001	48/F	Ischaemic stroke	38	53	Not related	Drug withdrawn/Resolved with sequelae
0040/012	54/F	Drug hypersensitivity	26	Ongoing	Possible	Drug withdrawn/Not recovered not resolved
		and				Drug withdrawn/Recovered resolved
0041/005	58/F	Dermatitis allergic	12	17	Probable	Drug withdrawn/Recovered resolved
		Hypotension	134	135	Probable	Drug withdrawn/Recovered resolved
0047/002	71/M	Syncope	27	27	Definite	Drug withdrawn/Recovered resolved
0059/013	64/F	Nasopharyngitis	8	21	Not related	Drug withdrawn/Recovered resolved
0069/003	53/M	Nausea	19	24	Not related	Drug withdrawn/Recovered resolved
0069/007	77/M	Angina pectoris	48	53	Not related	Drug withdrawn/Recovered resolved
0113/010	59/M	Headache	27	33	Possible	Drug withdrawn/Recovered resolved
0143/016	69/F	Hypotension	114	140	Possible	Drug withdrawn/Recovered resolved

All adverse events

The table below shows the most frequently reported adverse events.

Table 12.d Treatment-Emergent Adverse Events Presented by Preferred Term With Incidence of $\geq 2\%$ of Subjects in Any Treatment Group—Safety Analysis Set

Preferred Term	Subjects (%)			
	TAK-491 40 mg N=294	TAK-491 80 mg N=293	Ramipril 10 mg N=293	Total N=880
Nasopharyngitis	19 (6.5)	13 (4.4)	17 (5.8)	49 (5.6)
Headache	12 (4.1)	10 (3.4)	14 (4.8)	36 (4.1)
Cough	3 (1.0)	4 (1.4)	24 (8.2)	31 (3.5)
Blood creatine kinase increased	6 (2.0)	9 (3.1)	4 (1.4)	19 (2.2)
Dizziness	8 (2.7)	7 (2.4)	4 (1.4)	19 (2.2)
Back pain	5 (1.7)	11 (3.8)	2 (0.7)	18 (2.0)
Confusion	7 (2.4)	4 (1.4)	1 (0.3)	12 (1.4)
Hypotension	4 (1.4)	6 (2.0)	2 (0.7)	12 (1.4)
γ -Glutamyl transferase increased	7 (2.4)	1 (0.3)	3 (1.0)	11 (1.3)

Source: Table 15.3.1.4.

Note: If a subject experienced more than 1 episode of an adverse event, it is counted only once within a preferred term. Percentages are based on the total number of subjects in the safety analysis set for each treatment group.

Note: Adverse events are sorted by decreasing order of incidence based on the total number of adverse event reports.

Note: MedDRA (Version 11.1) was used for coding adverse events.

Dizziness and hypotension were more common in the TAK-491 treatment groups compared to ramipril. As expected, cough was reported by the ramipril group at a much higher rate compared to TAK-491.

The reporting rate for selected adverse events are shown below.

Table 12.e Selected Treatment-Emergent Adverse Events Commonly Observed in Subjects With Hypertension (Safety Analysis Set)

Category	Preferred Term	Subjects (%)		
		TAK-491 40 mg N=294	TAK-491 80 mg N=293	Ramipril 10 mg N=293
General				
	Headache	12 (4.1)	10 (3.4)	14 (4.8)
	Cough	3 (1.0)	4 (1.4)	24 (8.2)
	Dizziness	8 (2.7)	7 (2.4)	4 (1.4)
	Syncope	0	2 (0.7)	1 (0.3)
	Dizziness postural	1 (0.3)	0	0
Blood Pressure				
	Hypotension	4 (1.4)	6 (2.0)	2 (0.7)
	Blood pressure increased	1 (0.3)	1 (0.3)	2 (0.7)
	Hypertension	0	1 (0.3)	1 (0.3)
	Hypertensive crisis	0	1 (0.3)	0
Renal Function				
	Blood creatinine increased	2 (0.7)	3 (1.0)	0
	GFR decreased	1 (0.3)	3 (1.0)	0
	Renal impairment	1 (0.3)	0	1 (0.3)
	Renal failure	0	1 (0.3)	0
Potassium Homeostasis				
	Blood potassium increased	2 (0.7)	1 (0.3)	0
	Hyperkalemia	0	2 (0.7)	0
Anemia				
	Anemia	0	1 (0.3)	0
Edema				
	Edema peripheral	2 (0.7)	2 (0.7)	1 (0.3)
Investigations				
	Hemoglobin decreased	1 (0.3)	2 (0.7)	0
	Hematocrit decreased	0	1 (0.3)	0

Of the 12 subjects with hypotension, 10 were in the TAK-491 groups (6 subjects in TAK-491 80 mg group and 4 in the TAK-491 40 mg).

Two subjects had an event of syncope following treatment with TAK-491 80 mg and 1 subject following ramipril. Subject 0047/002, treated with TAK491 80 mg, was withdrawn from study drug.

There were two subjects who reported hyperkalemia, both in the TAK-491 80 mg groups. One subject (0045/005) reported hyperkalemia as a serious adverse event as well as chronic renal failure. hyperkalemia. The other subject (0034/007) reported hyperkalemia as a non serious adverse event.

Two subjects experienced an event of renal impairment: 1 subject (0015/004) following TAK-491 40 mg and 1 subject following ramipril (0059/001).

Clinical laboratory

Mean creatinine at baseline was similar among all treatment groups. There were larger changes from baseline at the final visit in TAK-491 80 mg (0.4 umol/L) and TAK-491 40 mg (1.0 umol/L) treatment groups compared to ramipril (0.4 umol/L).

There were larger increases from baseline for serum potassium and uric acid in the TAK-491 groups compared to ramipril.

Shift changes

Shifts from normal to high were greater in the TAK-491 40 and 80 mg groups compared with the ramipril group for BUN, chloride, potassium, and uric acid. Shifts from normal to high were slightly greater in the TAK-491 80 mg group compared with the TAK-491 40 mg and ramipril groups for creatinine and bilirubin.

The shift from normal to low calcium was greater in the TAK-491 40 and 80 mg groups compared with the ramipril group.

Markedly abnormal chemistry values

Table 12.j Marked Abnormalities in Serum Chemistries During Treatment—Safety Analysis Set

Laboratory Test	Subjects (%)		
	TAK-491 40 mg N=294	TAK-491 80 mg N=293	Ramipril 10 mg N=293
ALT >3×ULN	5/290 (1.7)	2/289 (0.7)	4/290 (1.4)
AST >3×ULN	5/290 (1.7)	1/289 (0.3)	3/290 (1.0)
BUN >3×ULN	0/290	1/289 (0.3)	0/290
Bilirubin >2×ULN	1/290 (0.3)	1/289 (0.3)	0/290
Calcium			
(<0.8×LLN)	4/290 (1.4)	1/289 (0.3)	2/290 (0.7)
(>1.2×ULN)	0/290	0/289	0/290
Creatinine >1.5×BL (SI units)	8/290 (2.8)	6/289 (2.1)	1/290 (0.3)
GGT >3×ULN	13/290 (4.5)	10/289 (3.5)	15/290 (5.2)
Potassium			
(<3.0 mEq/L CV units)	0/290	0/289	1/290 (0.3)
(>6.0 mEq/L CV units)	8/290 (2.8)	11/289 (3.8)	5/290 (1.7)
Sodium			
(<130 mEq/L CV units)	2/290 (0.6)	0/289	4/290 (1.4)
(>150 mEq/L CV units)	8/290 (2.8)	6/289 (2.1)	3/290 (1.0)
Uric acid >8.5 mg/dL (F), >10.5 (M) (CV units)	12/290 (4.1)	10/289 (3.5)	2/290 (0.7)

Source: Tables 15.3.4.7 and 15.3.4.8.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline results are summarized in this table.

BL=baseline, BUN=blood urea nitrogen, CV=conventional, F=female, GGT=γ-glutamyl transferase, LLN=lower limit of normal, M=male, SI=International system of units, ULN=upper limit of normal.

The number and percents of subjects who reported abnormal creatinine values are shown below.

Table 12.k Summary of Subjects With Creatinine Increase—Safety Analysis Set

	Subjects (%)		
	TAK-491 40 mg N=294	TAK-491 80 mg N=293	Ramipril 10 mg N=293
Subjects with Creatinine Elevations at Any Postbaseline Visit			
Total $\geq 1.3 \times \text{BL}$ and $> \text{ULN}$ (CV units)	7/290 (2.4) (a)	9/289 (3.1)	1/290 (0.3)
$\geq 1.5 \times \text{BL}$ and $> \text{ULN}$ (CV units)	4/290 (1.4)	4/289 (1.4)	0/290
Subjects with Creatinine Elevations at Final Visit (b)			
Total $\geq 1.3 \times \text{BL}$ and $> \text{ULN}$ (CV units) (a)	2/290 (0.7)	1/289 (0.3)	0/287
$\geq 1.5 \times \text{BL}$ and $> \text{ULN}$ (CV units)	1/290 (0.3)	0/289	0/287

Source: Table 15.3.4.10 and 15.3.4.11.

Note: A predefined creatinine increase was defined as change $\geq 1.3 \times$ baseline and $> \text{ULN}$.

BL=baseline, CV=conventional (mg/dL) units, ULN=upper limit of normal.

(a) The 7 subjects include 1 subject (0042/010) with a medically impossible elevation due to data entry error in the database. A file note was added to the trial master file.

(b) LOCF.

There were more subjects with elevated serum creatinine levels in the TAK-491 groups compared to ramipril. It appears that most of these abnormalities resolved at or before the final visit.

Hematology

Marked hematology abnormalities reported during the double-blind treatment period are shown below by treatment group.

Table 12.l Marked Abnormalities in Hematology During Treatment—Safety Analysis Set

Laboratory Test	Subjects (%)		
	TAK-491 40 mg N=294	TAK-491 80 mg N=293	Ramipril 10 mg N=293
Hematocrit/PCV			
$< 0.8 \times$ baseline	3/290 (1.0)	3/288 (1.0)	4/290 (1.4)
Hemoglobin			
$< \text{baseline} - 30 \text{ g/L}$	3/290 (1.0)	2/289 (0.7)	4/290 (1.4)
RBC $< 0.8 \times$ baseline	2/290 (0.7)	2/289 (0.7)	4/290 (1.4)
WBC			
$< 2 \times 10^9/\text{L}$ or $> 20 \times 10^9/\text{L}$	0/290	1/289 (0.3)	0/290

Source: Tables 15.3.4.1 and 15.3.4.8.

Note: Data represent number (percentage) of subjects. A subject was classified as having marked abnormalities if at least 1 test result during a particular test was considered markedly abnormal. Only postbaseline values are included in this table.

PCV=packed cell volume, RBC=red blood cell, WBC=white blood cell.

The reporting rates for abnormal hematology values were similar across treatment groups.

Reviewer's summary and conclusions

Efficacy: TAK-491 40 and 80 mg treatments were superior to ramipril in lowering blood pressure.

Safety: The overall incidence of adverse events was similar with TAK-491 40 mg and ramipril therapy (38.1% and 38.6%, respectively), but higher in the TAK-491 80 mg group (43.7%). While cough was more commonly reported in the ramipril group, hypotension, dizziness, increased blood creatine kinase, and back-pain were higher in the TAK-491 treatment groups.

The incidence rates of reported serious adverse events were 2.7%, 4.1%, and 2.0% in the TAK-491 40 and 80 mg and ramipril treatment groups, respectively. The frequency of elevated creatinine, uric acid, and potassium was higher with TAK-491 compared with ramipril.

Conclusions: while TAK-491 treatment groups were superior to ramipril in lowering blood pressure, ramipril had a superior safety profile.

TAK-536 (active metabolite) efficacy studies

Study No. (Study Abbreviation) No. of Sites-Country (a)	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
01-03-TL-536-002 (536-002) 47-United States and Latin America 25 August 2004-27 June 2005	Double-blind, randomized, placebo-controlled, parallel-group, dose-ranging, 7-group (Phase 2) Dose-response of the antihypertensive effect of TAK 536 (Change from BL at Final Visit in average sitting clinic DBP)	574 subjects with mild to moderate uncomplicated essential hypertension (DBP=95-114 mm Hg)	8 weeks	A: TAK-536 2.5 mg B: TAK-536 5 mg C: TAK-536 10 mg D: TAK-536 20 mg E: TAK-536 40 mg F: OLM-M 20 mg G: Placebo 574 /491 A: 82/69 B: 82/72 C: 82/72 D: 83/71 E: 82/73 F: 82/71 G: 81/63

Serious safety findings:

There were no deaths reported during the study. A total of 9 serious adverse events were reported in 8 subjects during the study. These subjects, all randomized to TAK-536, are shown below.

Table 12.d Summary of Treatment –Emergent SAEs

Subject / Treatment	Adverse Event	Onset Day	Relationship to Drug (a)	Intensity	Action/ Outcome
10387 TAK-536 10 mg	Acute myocardial infarction	87 (b)	Not related	Moderate	None / recovered
10462 TAK-536 40 mg	Transient ischemic attack	17	Not related	Mild	Study drug discontinued / recovered
10566 TAK-536 5 mg	Atrial fibrillation	13	Not related	Severe	None / recovered
10230 TAK-536 20 mg	Angina pectoris (c)	82 (b)	Not related	Severe	None / recovered
	Coronary artery disease	83 (b)	Not related	Moderate	None/ unchanged
10330 TAK-536 10 mg	Angina pectoris	20	Not related	Moderate	None / recovered
10541 TAK-536 5 mg	Pancreatitis	40	Not related	Moderate	Study drug discontinued / recovered
10197 TAK-536 40 mg	Noncardiac chest pain	6	Not related	Severe	Study drug interrupted / recovered
10104 TAK-536 20 mg	Acute myocardial infarction	6	Not related	Severe	Study drug discontinued / recovered

Source: Appendix 16.2.12.3.

(a) As judged by the investigator.

(b) Occurred after discontinuation of study drug.

(c) Subject 10230, originally reported as having SAEs of angina pectoris and coronary artery disease, was subsequently updated by the investigator as having an SAE of coronary artery disease with angina of moderate severity that was unrelated to study medication and from which she recovered.

The serious events are mostly related to the cardiovascular system and not unexpected in this hypertensive patient population.

Study No. (Study Abbreviation) No. of Sites-Country (a)				
Study Start-End Dates	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
TAK-536/CCT-001 (536-CCT-001) 38-Japan 04 July 2007- 21 July 2008	Double-blind, randomized, placebo-controlled, parallel-group, dose-ranging (Phase 2) Dose-response of the antihypertensive effect of TAK-536 (Change from BL at Week 12 in sitting trough DBP)	588 Japanese subjects* with hypertension (sitting DBP=95-109 mm Hg, sitting SBP=150-179 mm Hg) *1 subject in Group G (placebo) was excluded from all of the analysis sets due to major protocol deviation	12 weeks	A: TAK-536 5 mg B: TAK-536 10 mg C: TAK-536 20 mg D: TAK-536 40 mg E: TAK-536 80 mg F: Candesartan cilexetil 8 mg for 4 weeks→12 mg for 8 weeks G: Placebo 587/528 A: 89/84 B: 83/71 C: 85/78 D: 82/79 E: 84/76 F: 82/73 G: 83/67

This study was conducted in Japan.

Serious safety

No deaths were reported during the study. A total of 6 serious adverse events were reported during the study (one subject in each of the the TAK-536 treatment groups and 1 subject in the candesartan group). These are shown below.

Table 12.c Summary of All SAEs, Presented by PT

AEs	Subject/ Treatment	Relatedness	Intensity	Action/ Outcome
Fall	06-021 TAK-536 5 mg	Not related	severe	Drug Withdrawn Recovering/ resolving
Road traffic accident	11-003 TAK-536 10 mg	Not related	severe	Drug Withdrawn Recovering/ resolving
Rectal cancer	22-010 TAK-536 20 mg	Not related	moderate	Dose Not Changed Recovering/ resolving
Gastric ulcer haemorrhage	32-011 TAK-536 40 mg	Possible	moderate	Drug Withdrawn Recovered/ resolved
Chest pain	25-004 TAK-536 80 mg	Possible	mild	Drug Withdrawn Recovered/ resolved
Bronchitis	04-002 C.C.	Not related	moderate	Drug Withdrawn Recovered/ resolved

Source: Table 16.2.7.6

These events are not unexpected in a hypertensive population. The fall reported by subject #06-021 was the result of a skiing accident.

Study No. (Study Abbreviation)	No. of Sites-Country (a)	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
GHBA-590 (536-GHBA-590)	25-United States 30 June 1994- 27 March 1995	Double-blind, randomized, placebo-controlled, parallel-group (Phase 2) Antihypertensive effect of TAK-536 versus placebo (Change in BL sitting DBP)	230 subjects with moderate uncomplicated essential hypertension (sitting DBP=100-114 mm Hg and SBP ≤190 mm Hg)	8 weeks	I: TAK-536 0.5 mg II: TAK-536 1 mg III: TAK-536 2.5 mg IV: TAK-536 5 mg V: Placebo 230*/208 I: 43/41 II: 40/37 III: 40/37 IV: 43/41 V: 40/34 *Total subjects randomized and completed is presented for the double-blind treatment period. The individual group presentation is based upon the intent-to-treat set (206 subjects). Please refer to the CSR for details.

5.4.2. Incidence of First Dose Hypotension on Day 1

The number and percentage of patients in each treatment group who experienced a decrease from baseline ≥ 30 mmHg in standing systolic blood pressure on Day 1 of the double-blind period is presented in Table 19.1, Section 10 and summarized in Table T. Although there is a higher incidence of clinically significant decreases in blood pressure on Day 1 in the TAK-536 0.5 mg, 2.5 mg, and 5.0 mg groups, no apparent dose response is present among the four active treatment groups. Overall, the highest incidence of decreases in standing systolic blood pressure greater than or equal to 30 mmHg among patients receiving active treatment occurred at Hour 8 (9.0%, 15/166).

Table T
Incidence of First Dose Hypotension^a on Day 1

Double-Blind Study Day		Placebo N=40	TAK-536 0.5 mg N=43	TAK-536 1.0 mg N=40	TAK-536 2.5 mg N=40	TAK-536 5.0 mg N=43
Day 1, Hr. 4	N (%)	0	1 (2)	0	0	2 (4)
Day 1, Hr. 6	N (%)	1 (2)	2 (4)	2 (5)	1 (2)	3 (6)
Day 1, Hr. 8	N (%)	0	7 (16)	1 (2)	4 (10)	3 (6)
Day 1, Hr. 24	N (%)	0	1 (2)	0	1 (2)	4 (9)

Data Source: Table 19.1, Section 10.

^a First dose hypotension on Day 1 defined by a decrease from baseline in standing systolic blood pressure of ≥ 30 mmHg.

Serious safety

There were no deaths listed in the study report. There were 2 reported serious adverse events: stroke (placebo subject #4019) and atrial fibrillation (TAK-536 0.5 mg subjects #4209).

Study No. (Study Abbreviation) No. of Sites-Country (a)				
Study Start- End Dates	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
GHBA-774 (536-GHBA-77-1) 3-United States 06 October 1994- 19 February 1995	Double-blind, randomized, crossover (Phase 2) Antihypertensive effect of TAK-536 versus placebo (Change from BL at Days 28 and 56 in sitting BP)	43 subjects with moderate uncomplicated essential hypertension (mean sitting DBP=100-114 mm Hg)	8 weeks (4 weeks then crossover to alternative treatment for 4 weeks)	A: TAK-536 10 mg→Placebo B: Placebo→ TAK-536 10 mg 43/40 A: 20/19 B: 23/21

Serious safety

No patient died in this study or had a serious adverse event. One patient was discontinued from the study because of an adverse event after the patient had received the last dose of double-blind treatment as shown in Table 18, Appendix 8.1. Following is a brief narrative summary of this patient who was discontinued from the study because of an adverse event.

The placebo subject reported supraventricular tachycardia on study day 60.

01-06-TL-OP1536-003 (536OPI-003) 34-United States 25 June 2006-12 May 2007* *Study was terminated early on 12 May 2007. All subjects discontinued at that time.	Double-blind, randomized, placebo-controlled, parallel-group A1C reduction when TAK-536 is coadministered with PIO compared with PIO alone (Change from BL at the Final Visit in A1C)	96 subjects with T2DM (A1C level=9.0%-11.0%), stable on metformin treatment at least 8 weeks, and with hypertension (SBP>170 mm Hg and DBP>100 mm Hg)	<i>Study terminated early; 780 subjects were planned for 24 weeks.</i>	A: AD-4833-536 FDC 45 mg+ placebo B: AD-4833-536 FDC 45 mg+ 20 mg C: AD-4833-536 FDC 45 mg+ 40 mg 96/26* A: 31/11 B: 33/8 C: 32/7 *All subjects discontinued at the time of study termination; these numbers represent those subjects still enrolled at the time of study termination.
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Serious safety

No deaths were reported during the study. There were two reported serious adverse events: Subject 7001/005 (AD-4833-536 45 mg + 20 mg) reported a scrotal abscess and subject 7031/003 (AD-4833-536 45 mg + 20 mg) reported infective cholecystitis.

Study No. (Study Abbreviation)	No. of Sites-Country (a)	Study Design Primary Objective (Endpoint)	Population (b) No. and Type (criteria)	Treatment Duration (c)	Treatment(s) (d) Randomized/Completed (e)
01-04-TL-OP1-525 (536OP1-525) 100-United States and Latin America 28 July 2004- 06 October 2005		Double-blind, randomized, placebo-controlled, parallel-group, 2-group, proof-of-concept PIO plus TAK-536 on glycemic control in subjects with T2DM	705 subjects* with T2DM (A1C level of 8%-10%, SBP=111-160 mm Hg, DBP=61-100 mm Hg) *1 subject in Group B was not randomized but received double-blind treatment	<u>Lead-in:</u> 6 days <u>Double-blind:</u> 24 weeks	<u>Lead-in:</u> PIO 15 mg <u>Double-blind:</u> A: PIO 15 mg with TAK-536 5 mg B: PIO 15 mg with TAK-536 40 mg C: PIO 15 mg with placebo D: PIO 45 mg with TAK-536 5 mg E: PIO 45 mg with TAK-536 40 mg F: PIO 45 mg with placebo 704/571 A: 119/95 B: 115/91 C: 119/93 D: 118/93 E: 115/95 F: 118/104

Serious safety

There were two reported deaths: one subject in the pioglitazone 45 mg plus TAK-536 5 mg treatment group had sudden cardiac death and one subject in the pioglitazone 15 mg plus placebo treatment group had a hemorrhagic stroke.

Serious adverse events are shown in the table below.

Table 12.d SAEs (Pooled Pioglitazone Groups)

Preferred Term	Treatment		
	PIO+Placebo N=236	PIO+TAK-536 5 mg N=235	PIO+TAK-536 40 mg N=227
With any SAE	8 (3.4)	8 (3.4)	8 (3.4)
Cardiac disorders			
Myocardial infarction	0	0	2 (0.9)
Coronary artery disease	0	0	1 (0.4)
Gastrointestinal disorders			
Pancreatitis	1 (0.4)	0	0
General disorders and administration site conditions			
Noncardiac chest pain	0	1 (0.4)	0
Sudden cardiac death	0	1 (0.4)	0
Hepatobiliary disorders			
Cholecystitis	0	0	1 (0.4)
Cholelithiasis	1 (0.4)	0	0
Infections and infestations			
Pneumonia	1 (0.4)	0	0
Pyelonephritis acute	0	0	1 (0.4)
Tooth abscess	0	0	1 (0.4)
Injury, poisoning, and procedural complications			
Femur fracture	0	0	1 (0.4)
Lower limb fracture	0	1 (0.4)	0
Metabolism and nutrition disorders			
Hypoglycemia	1 (0.4)	2 (0.9)	1 (0.4)
Musculoskeletal and connective tissue disorders			
Spondylolisthesis acquired	1 (0.4)	0	0
Nervous system disorders			
Cerebrovascular accident	0	1 (0.4)	1 (0.4)
Hemorrhagic stroke	1 (0.4)	0	0
Syncope	1 (0.4)	0	0
Reproductive system and breast disorders			
Breast microcalcification	0	1 (0.4)	0
Dysfunctional uterine bleeding	0	1 (0.4)	0
Vascular disorders			
Hypertension	1 (0.4)	0	0
Hypertensive emergency	1 (0.4)	0	0

Source: Table 14.3.1.7.

PIO= pioglitazone (15 and 45 mg pooled).

Data represent number (%) of subjects.

The treatment groups, shown above, are similar to one another in regards to the reporting of serious adverse events.

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/s/

MARYANN GORDON
01/03/2011

JOHN P LAWRENCE
01/03/2011

Clinical Review

Application Type NDA# 200796

Submission Type; Code: N_000, original

Letter Date April 22, 2010

Stamp Date April 27, 2010

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Medical Reviewer Maryann Gordon, M.D.

Statistical Reviewer John Lawrence, PhD. (efficacy only)

Review Completion Date December 16, 2010

Established Name Azilsartan medoxomil

(Proposed) Trade Name Edarbi

Therapeutic Class Angiotensin II receptor blocker

Applicant Takeda Pharmaceuticals America, Inc

Priority Designation S

Formulation Tablets

Dosing Regimen Once daily

Indication Treatment of hypertension

Intended Population Hypertensive adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The primary medical and statistical reviewers of the new drug application (NDA) #200796 pertaining to the use of TAK-491, also known as azilsartan medoxomil, in the treatment of patients with essential hypertension, are recommending approval. This drug is an angiotensin II receptor blocker (ARB).

Azilsartan has shown the ability to lower blood pressure in numerous randomized, double blind, placebo controlled trials and the adverse event profile is similar to that reported in clinical trials with other ARBs.

The most commonly reported adverse events in the placebo controlled trials included headache, dizziness, dyslipidemia, and urinary tract infections. The reporting rates for most adverse events were similar to or only slightly higher than those reported by the placebo groups and there did not appear to be dose related.

As with other drugs that inhibit the renin-angiotensin-aldosterone system, increases in serum creatinine were more common in the TAK-491 groups compared to placebo. Most were mild and transient and rarely resulted in study discontinuation. There were few reports of adverse renal events. Those subjects with moderate or severe renal impairment at baseline were more likely to report greater elevations of serum creatinine.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None recommended

1.2.2 Required Phase 4 Commitments

None recommended

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

TAK-491 (azilsartan medoxomil) is the prodrug of an angiotensin receptor blocker. In vivo, TAK-491 is rapidly hydrolyzed to its active moiety, TAK-536 (azilsartan). The TAK-491 development program includes studies in which TAK-491 was evaluated alone or in combination with other antihypertensive agents. TAK-491 is also being evaluated as a fixed-dose combination product with chlorthalidone (TAK-491CLD) in an ongoing program under (b) (4). TAK-536, the active moiety of TAK-491, is under development in Japan and has been evaluated in both a monotherapy program and as a fixed dose combination with pioglitazone (TAK-536OPI).

This application for TAK-491 use in hypertension is based on data from the studies listed in the tables below.

Table 1.a Phase 3: Randomized, Double-Blind, Controlled Studies

Study Design and Study Number (Regions)	BP Entry Criteria Planned Sample Size	Duration of Double-Blind Treatment, Dose/Regimen (a)	1° Endpoint (Key 2° Endpoint)
Monotherapy			
TAK-491 vs Placebo, Olmesartan Medoxomil, and Valsartan 491-019 (US, Lat Am)	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=1305 (active=290/group; placebo=145)	6 weeks (2 wks→4 wks) • TAK-491 20→40 mg • TAK-491 40→80 mg • OLM-M 20→40 mg • Valsartan 160→320 mg • Placebo	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 vs Placebo and Olmesartan Medoxomil 491-008 (US, Lat Am)	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=1260 (active=280/group; placebo=140)	6 weeks • TAK-491 20 mg • TAK-491 40 mg • TAK-491 80 mg • OLM-M 40 mg • Placebo	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 vs Valsartan 491-301 (US, Lat Am)	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=972 (324/group)	6 months (2 wks→22 wks) • TAK-491 20→40 mg • TAK-491 20→80 mg • Valsartan 80→320 mg	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 vs Ramipril 491-020 (Europe, Russia)	Clinic SBP 150-180 mm Hg N=890 (270/group)	6 months (2 wks→22 wks) • TAK-491 20→40 mg • TAK-491 20→80 mg • Ramipril 2.5→10 mg	Clinic SBP (N/A)
Black Population (TAK-491 vs Placebo) 491-011 (US, Puerto Rico)	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=411 (137/group)	6 weeks • TAK-491 40 mg • TAK-491 80 mg • Placebo	24-hr mean SBP by ABPM (Clinic SBP)
Coadministration			
TAK-491 + Diuretic 491-009 (US, Lat Am)	Clinic SBP 160-190 and 24-hr SBP 140-180 mm Hg N=540 (180/group)	6 weeks • TAK-491 40 mg + CLD 25 mg • TAK-491 80 mg + CLD 25 mg • Placebo + CLD 25 mg	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 + CCB 491-010 (US, Lat Am)	Clinic SBP 160-190 and 24-hr SBP 140-180 mm Hg N=540 (180/group)	6 weeks • TAK-491 40 mg + AML 5 mg • TAK-491 80 mg + AML 5 mg • Placebo + AML 5 mg	24-hr mean SBP by ABPM (Clinic SBP)

BP=blood pressure, CCB=calcium channel blocker, AML=amlodipine, CLD=chlorthalidone, Lat Am=Latin America, OLM-M=olmesartan medoxomil, US=United States.

(a) All study drugs were administered QD.

(b) Forced-titration at Week 2.

A total of 5941 subjects were enrolled into these studies (3672 received TAK-491). Other than study 491-020 which was conducted in Russia and Europe, the efficacy trials enrolled subjects residing in the U.S. or Latin America.

The dose ranging studies (with TAK-491 or TAK-536) are listed below.

Table 1.c Phase 2: Randomized, Double-Blind, Controlled Dose-Ranging Studies

Study Design and Study Number (Regions)	Population Planned Sample Size	Duration of Double-blind Treatment Dose/Regimen	Endpoints
TAK-491 (Capsules) vs Placebo and Olmesartan medoxomil			
491-005 (US, Lat Am)	Clinic DBP 95-114 mm Hg N=420 (60/group)	8 weeks • TAK-491 5 mg • TAK-491 10 mg • TAK-491 20 mg	Clinic DBP • TAK-491 40 mg • TAK-491 80 mg • OLM-M 20 mg • Placebo
TAK-536 (Tablets) vs Placebo and Olmesartan medoxomil			
536-002 (US, Lat Am)	Clinic DBP 95-114 mm Hg N=525 (75/group)	8 weeks • TAK-536 2.5 mg • TAK-536 5 mg • TAK-536 10 mg	Clinic DBP • TAK-536 20 mg • TAK-536 40 mg • OLM-M 20 mg • Placebo
TAK-536 (Tablets) vs Placebo and Candesartan			
536-CCT-001 (Japan)	Clinic DBP 95-109 and SBP 150-179 mm Hg N=518 (74/group)	12 weeks • TAK-536 5 mg • TAK-536 10 mg • TAK-536 20 mg	Clinic DBP • TAK-536 40 mg • TAK-536 80 mg • Cand. 8 mg→12 mg • Placebo

Lat Am=Latin America, OLM-M=olmesartan medoxomil, US=United States, Cand.=candesartan.

The open label studies are listed below.

Table 1.b Phase 3: Long-term Open-Label Safety Studies and Randomized, Double-Blind, Placebo-Controlled Reversal Period

Study Design and Study Number (Regions)	BP Entry Criteria Planned Sample Size	Treatment Duration and Dose/Regimen (a)	Endpoints
Open-label safety study with reversal period			
<i>Open-label Phase</i>			
491-016 (US, Lat Am)	Clinic DBP 95-119 mm Hg N=400	26 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)
<i>Reversal Period</i>			
	Subjects who completed the open-label phase	6 weeks • Continue current dose of TAK-491; maintain stable dose(s) of background BP medication • Substitute placebo for TAK-491; maintain stable dose(s) of background BP medication	Clinic BP (automated) Safety measures
Open-label safety study with 2 cohorts			
<i>Cohort 1</i>			
491-006 (b) (US, Lat Am)	Clinic DBP 95-119 mm Hg N=350	56 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated or manual)
<i>Cohort 2</i>			
	Clinic DBP 95-119 mm Hg N=300	56 weeks (Ongoing) Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + HCTZ 12.5 Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated or manual)
Open-label extension following a randomized, double-blind, controlled study			
491-301 (US, Lat Am)	Subjects who completed the double-blind phase (see Table 1.a) N=170	28 weeks (Ongoing) Step 1: TAK-491 40 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)

BP=blood pressure, CLD=chlorthalidone, US=United States, Lat Am=Latin America, HCTZ=hydrochlorothiazide.

(a) All study drugs were administered QD.

(b) Subjects were not randomized; enrollment of Cohort 2 was initiated after enrollment of Cohort 1 was complete.

Two additional TAK-536 studies are listed below.

Table 1.d Other Phase 2 TAK-536 Studies

Study Design and Study Number (Region)	Population Planned Sample Size	Duration of Double-blind Treatment Dose/Regimen	Endpoints
TAK-536 vs Placebo			
	Clinic DBP 100-114 mm Hg	8 weeks	
536-GHBA-590 (US)	• 5-arm • Placebo-controlled N=225 (45/group)	• TAK-536 0.5 mg • TAK-536 1 mg • TAK-536 2.5 mg • TAK-536 5 mg • Placebo	Clinic DBP
TAK-536 vs Placebo			
	Clinic DBP 100-114 mm Hg	8 weeks (4 wks→4 wks)	
536-GHBA-774 (US)	• 2-arm, crossover • Placebo-controlled N=48	• TAK-536 10 mg→Placebo • Placebo→TAK-536 10 mg	Clinic DBP

For completeness, a list of all primary and supportive clinical pharmacology studies is shown below.

Table 1.b Clinical Studies

Study Number (Country/Region)	Description (a)	P	S
Single-Dose Studies			
491-012 (US)	ADME	X	
536-014 (US)	ADME	X	
491-001 (US)	Ascending dose: pharmacokinetics with pharmacodynamics and food effect	X	
491-007 (US)	QTc	X	
491-015 (US) (b)	Relative bioavailability of TAK-536 derived from the TAK-491 capsule and TAK-491 tablet, and food effect of TAK-491 tablet	X	
491-CPH-001 (Japan)	Ascending dose: pharmacokinetics with pharmacodynamics and food effect		X
491-CPH-005 (Japan)	Ascending dose: pharmacokinetics with pharmacodynamics and food effect		X
536-007 (US)	Food effect		X
536-016 (US) (b)	Absolute bioavailability of TAK-536 and relative bioavailability of TAK-536 derived from TAK-536 IV administration and TAK-491 capsule	X	
536-CPH-001 (Japan)	Ascending dose: pharmacokinetics with pharmacodynamics and food effect	X	
536-CPH-009 (Japan)	Relative bioavailability among 3 dose strengths		X
536-316 (US)	Ascending dose: pharmacokinetics with pharmacodynamics		X
536-GHBA-328 (EU)	Ascending dose: pharmacokinetics with pharmacodynamics	X	
536-661 (US)	Food effect		X
Multiple-Dose Studies			
491-002 (US)	Ascending dose: pharmacokinetics with pharmacodynamics	X	
491-101 (US)	Ascending dose: pharmacokinetics	X	
491-017 (US)	Ascending dose: pharmacokinetics and relative bioavailability	X	
536-CPH-002 (Japan)	Ascending dose: pharmacokinetics with pharmacodynamics	X	
536-317 (US)	Ascending dose: pharmacokinetics with pharmacodynamics		X
536-EC101 (EU)	Ascending dose: pharmacokinetics	X	

Study Number (Country/Region)	Description (a)	P	S
Effects of Intrinsic Factors			
491-003 (US)	Age, sex, and race: pharmacokinetics	X	
536-008 (US)	Age, sex, and race: pharmacokinetics		X
491-102 (US)	Hepatic impairment	X	
491-103 (US)	Renal impairment	X	
536-CPH-005 (Japan)	Renal impairment in subjects with hypertension (phase 2)		X
Effects of Extrinsic Factors (Drug-Interaction Studies)			
Effect of an Antacid on TAK-491			
491-107 (US)	Aluminum-magnesium hydroxide	X	
Effect of Other Drugs on TAK-536 (Derived From TAK-536)			
536-005 (US)	Ketoconazole and fluconazole	X	
Effect of TAK-536 (Derived From TAK-491 or TAK-536) on Other Drugs			
536-009 (US)	Warfarin	X	
536-010 (US)	Glyburide	X	
491-013 (US)	Caffeine, tolbutamide, dextromethorphan, midazolam, fexofenadine (drug cocktail)	X	
536-004 (US)	Caffeine, tolbutamide, dextromethorphan, midazolam, fexofenadine (drug cocktail)		X
Effect of TAK-536 (Derived From TAK-491 or TAK-536) on Other Drugs and Effect of Other Drugs on TAK-536 (Derived From TAK-491 or TAK-536)			
491-004 (US)	Chlorthalidone	X	
491-104 (US)	Digoxin	X	
491-110 (EU)	Amlodipine	X	
536-006 (US)	Pioglitazone	X	
536-011 (US)	Metformin	X	
Population Pharmacokinetics			
536-CCT-001 (Japan)	Dose-ranging in subjects with hypertension (phase 2)	X	
FDC Studies			
491CCB-101 (EU)	Relative bioavailability of TAK-491 + amlodipine		X
491CLD-102 (EU)	Relative bioavailability of TAK-491 + chlorthalidone		X
491CLD-103 (US)	Relative bioavailability of TAK-491 + chlorthalidone		X
491CLD-104 (US)	Food-effect with TAK-491 + chlorthalidone		X
491CLD-105 (US)	Relative bioavailability of TAK-491 + chlorthalidone		X
536OPI-001 (US)	Relative bioavailability of TAK-536 + pioglitazone		X
536OPI-002 (US)	Relative bioavailability of TAK-536 + pioglitazone		X

ADME=absorption, distribution, metabolism, and excretion, EU=Europe, P=primary study, S=supportive study, US=United States.

(a) Subjects in all studies were healthy, and all studies were phase 1 unless otherwise stated.

1.3.2. Efficacy

Four studies (-019, -008, -011, -005) using a randomized, double blind, placebo controlled trial design demonstrated that TAK-491 lowers blood pressure in subjects with mild to moderate hypertension. Most of the double blind treatment phases of these studies were up to 8 weeks in duration.

Another study (-016) was a withdrawal trial. Subjects were treated for 26 weeks with open labeled TAK-491. They were then randomized in a double blind fashion to placebo or TAK-491 and treated for 6 weeks. Compared to placebo group which saw a rise in blood pressure, the blood pressure remained at approximately baseline level in the group that remained on TAK-491.

The blood pressure responses for the four placebo controlled trials are shown below.

Trough clinic blood pressure

Study id	Approx number per group	Placebo response mmHg	Placebo subtracted SBP/DBP change from baseline mmHg				
			5 mg	10 mg	20 mg	40 mg	80 mg
TAK-491 019	290	-2/-1	-	-	-	-14/-6	-15/-8
008	280	-2/0	-	-	-12/-7	-12/-7	-15/-8
011^	137	-3/-2	-	-	-	-5/-3	-6/-3
005	60	-5/-8	-6/-3	-11/-5	-10/-4	-12/-6	-9/-4

^black subjects only

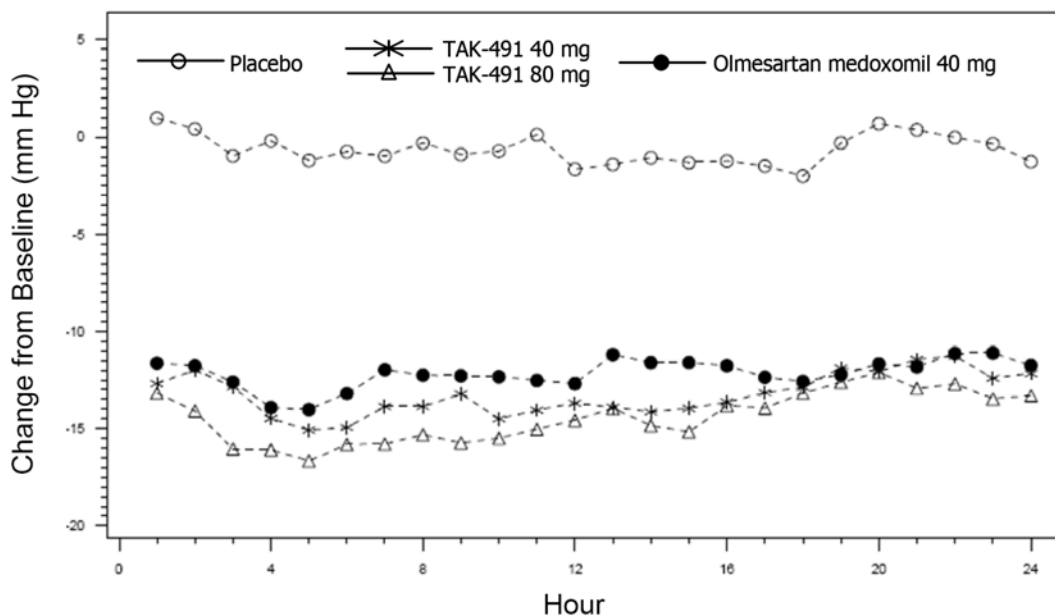
Doses of TAK-491 5 mg and above are superior to placebo in lowering blood pressure. There is little difference in effect among the doses 10-80 mg.

Dosing interval

The entire SBP 24-hour period ABPM monitoring following one dose is shown below for the pooled analyses of studies 491-008 and 491-019.

SBP: change from baseline by hour post dose at Week 6 for TAK-401 40 mg and 80 mg and olmesartan.

Figure 4.d Pooled Analyses of 491-008 and 491-019: Change from Baseline in Ambulatory SBP by Hour at Week 6



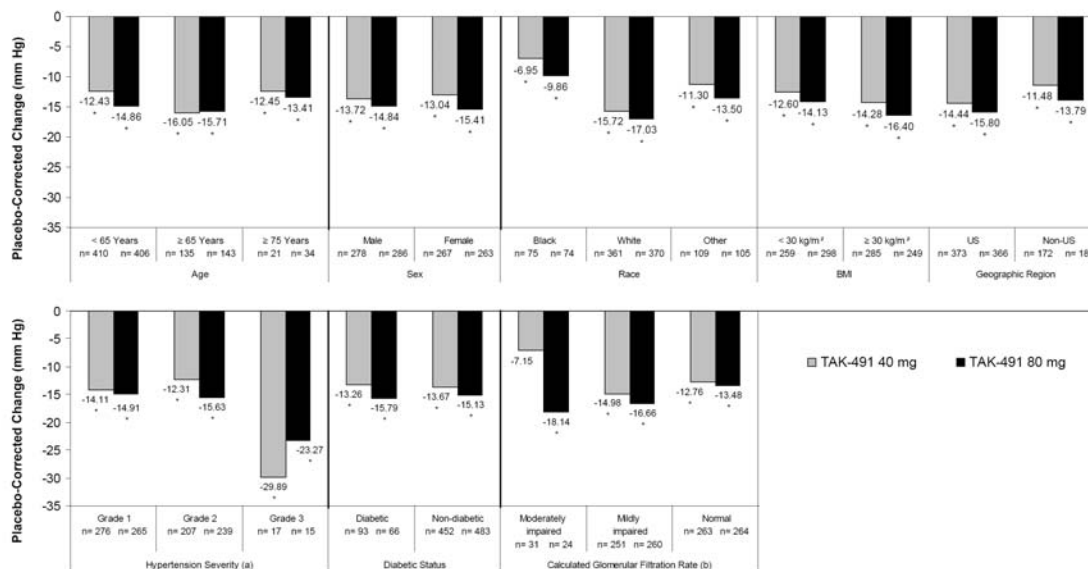
The ratio of the placebo-corrected blood pressure reductions observed at trough (22 to 24 hours post dose) vs peak response (i.e., the trough-to-peak ratios) were >0.85 for both SBP and DBP in these pooled analyses for TAK-491.

Subgroups

The following subgroups were examined for difference in blood pressure effect by age, sex, race, BMI, geographic region, hypertensive grade, and diabetic status

The figure below shows placebo subtracted change from baseline at week 6 for mean clinic SBP. The data are from studies 491-008 and 019 by subgroup

Figure 3.f Overview of Pooled Subgroup Analyses in Studies 491-008 and 491-019: Placebo-Corrected Change From Baseline in Clinic SBP—TAK-491 vs Placebo



Source: Table 1.8.3, Table 1.8.4, Table 1.8.5, Table 1.8.6, Table 1.8.7, Table 1.8.8, Table 1.8.9, and Table 1.8.10.

*Significant difference vs placebo.

(a) Grade 1: Baseline clinic SBP ≥ 140 to < 160 mm Hg; Grade 2: SBP ≥ 160 to < 180 mm Hg; Grade 3: SBP ≥ 180 mm Hg.

(b) Moderately impaired: Baseline GFR ≥ 30 to < 60 ml/min/1.73 m²; Mildly impaired: ≥ 60 to < 90 ml/min/1.73 m²; Normal: ≥ 90 ml/min/1.73 m².

There was a reduced response in the subjects ≥ 75 years of age (probably because of a small sample size) and black subjects. There were greater blood pressure reduction as hypertension severity increased and as calculated GFR decreased, although the sample sizes were small in the subgroups of subjects with Grade 3 hypertension and moderately impaired renal function (based on calculated GFR).

Comparators

TAK-491 was not consistently superior in lowering blood pressure compared to other ARBs (olmesartan medoxomil and valsartan).

1.3.3. Safety

TAK-491, an angiotensin II receptor blocker (ARB), has a safety profile similar to other drugs in this class. The most commonly reported adverse events in the placebo controlled trials included headache, dizziness, dyslipidemia, and urinary tract infections. The reporting rates for most adverse events were similar to or only slightly higher than those reported by the placebo groups and there did not appear to be dose related.

As with other drugs that inhibit the renin-angiotensin-aldosterone system, increases in serum creatinine were more common in the TAK-491 groups compared to placebo. Most were mild and transient and rarely resulted in study discontinuation. There were few reports of adverse renal events. Those subjects with moderate or severe renal impairment at baseline were more likely to report greater elevations of serum creatinine.

1.3.4. Dosing Regimen and Administration

The usual recommended starting dose should be 5 mg or 10 mg once daily in subjects who are not volume contracted. Doses may be increased up to 80 mg once daily.

1.3.5. Drug-Drug Interactions

Please see Clinical Pharmacology review by Divya Menon-Andersen, PhD.

Preliminary analyses show no significant drug interactions with digoxin or warfarin in healthy volunteers. Azilsartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.

1.3.6. Special Populations

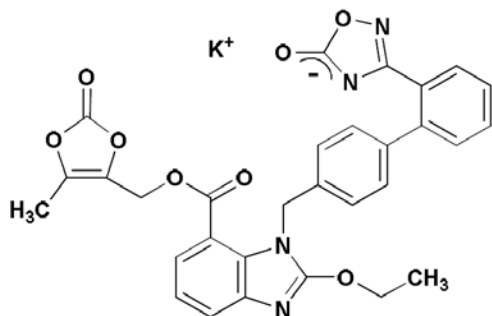
- Nursing mothers
- In patients with an activated renin-angiotensin system, such as volume- or salt-depletion, renin-angiotensin-aldosterone system blockers such as azilsartan medoxomil can cause excessive hypotension. In susceptible patients, e.g., with renal artery stenosis, RAAS blockers can cause renal failure.
- Geriatrics: No overall difference in efficacy or safety vs. younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

2 INTRODUCTION AND BACKGROUND

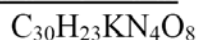
2.1 Product information

TAK-536 (azilsartan medoxomil) is an antagonist of human angiotensin II type 1 (AT1) receptors developed by Takeda Global Research & Development Center, Inc.

Figure 1.a Structural Formula of TAK-491



Molecular Formula:



Molecular Weight:

606.62

TAK-491 is a prodrug of the active moiety, TAK-536 (azilsartan). TAK-491 was selected for US development rather than TAK-536 because of a different pharmacokinetic profile for TAK-491 capsules.

2.2 Currently Available Treatment for Indication

There are many well established drugs including numerous angiotensin receptor blockers (ARBs) for the treatment of hypertension.

2.3 Availability of Proposed Active Ingredient in the United States

Azilsartan medoxomil is not currently marketed in this country.

2.4 Important Issues with Pharmacologically Related Products

Pregnancy: drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

Hypotension: in patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with ARBs

Hyperkalemia: may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels.

Impaired Renal Function: as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function in susceptible individuals may occur. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of ARBs in

patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors could occur.

Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) require close monitoring of renal function.

2.5 Pre-submission Regulatory Activity

The Agency met with the sponsor for a pre NDA meeting on December 10, 2009, a type C guidance meeting on June 22, 2009, and an end of phase 2 meeting on April 26, 2007.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Please see individual reviews

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor has submitted electronic submissions to the electronic document room dated April 28, 21010.

4.2 Tables of Clinical Studies

See section 1.3.1

4.3 Review Strategy

This review is a joint clinical-statistical review. Since there were numerous trials, the following table shows the depth of review for the individual studies. The individual study reviews are found in the appendix.

Complete efficacy/safety	Brief efficacy/safety reviews	Safety only
008	009	TAK-536 studies
019	010	006
011	016	
005	301	
	020	

4.4 Data Quality and Integrity

The Division did not require an inspection for NDA 200796 because there were many placebo controlled trials with large sample sizes and with large number of investigators all showing consistent efficacy results (and results the Division expected for a drug that is an angiotensin II receptor blocker). In addition, there were very few reported deaths or serious adverse events. ARBs, in general, have found to be reasonably safe and effective drugs for hypertension.

4.5 Compliance with Good Clinical Practices

Each protocol used to support this new indication stated that the study was to be conducted in compliance with Good Clinical Practices. With the exception of minor protocol violations, there is no indication that good clinical practices were not followed by any investigator.

4.6 Financial Disclosures

The sponsor submitted the following statement and table:

1.3.4.1.1 In accordance with 21 CFR §314.50(k), a financial disclosure certification summary is provided for all studies that meet the definition of “covered study” as stated in 21 CFR 54.2(e). As agreed at the [Pre-NDA meeting on October 27, 2009 \(question 1\)](#), financial disclosure information would be provided for the studies listed in the table below and would not be provided for TAK-491 Phase 1 studies, open-label studies, and TAK-536 studies.

Study Number	Study Title
01-05-TL-491-005	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Dose-Ranging Study of the Efficacy, Safety and Tolerability of TAK-491 in Subjects With Mild to Moderate Uncomplicated Essential Hypertension
01-05-TL-491-008	A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 in Subjects with Essential Hypertension
01-05-TL-491-009	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 When Co-Administered with Chlorthalidone in Subjects with Essential Hypertension
01-05-TL-491-010	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 when Co-Administered with Amlodipine 5 mg in Subjects with Essential Hypertension
01-06-TL-491-011	A Double-Blind, Randomized, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of TAK-491 in Black Subjects with Essential Hypertension.
01-06-TL-491-019	A Double-Blind, Randomized, Placebo-Controlled, 5-Arm Titration Study to Evaluate the Efficacy and Safety of TAK-491 When Compared With Valsartan and Olmesartan in Subjects with Essential Hypertension
01-06-TL-491-020	A Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 With Ramipril in Subjects With Essential Hypertension
TAK-491_301 [Interim CSR]	A Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 with Valsartan in Subjects with Essential Hypertension

5 CLINICAL PHARMACOLOGY

Please see review by Dr. Divy Menon-Andersen

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Azlisartan medoxomil is indicated for mild to moderate essential hypertension

The phase 3 program of TAK-491 was designed to characterize the efficacy of TAK-491: (1) vs placebo, (2) vs active comparators, (3) in subpopulations, (4) during long-term administration (maintenance of effect), and (5) when co administered with other antihypertensive agents.

Placebo controlled

The efficacy of TAK-491 was evaluated in placebo controlled studies 491-005, 491-008 and TAK-491-019 (and others). These studies enrolled subjects with mild-to-moderate hypertension¹ for a duration of 6-8 weeks and the primary endpoint was either blood pressure measured by ABPM or manually (referred to as clinic blood pressure). All dosing was once daily. The TAK-491-005 study evaluated doses (capsules) 5, 10, 20, 40 and 80 mg, the TAK-491-008 study

¹ BP around 150-180/90-114 mmHg

evaluated doses (tablets) 20, 40, and 80 mg, and the TAK-491-019 study evaluated doses (tablets) 40 mg and 80 mg after forced-titration from lower doses (20 and 40 mg, respectively). The efficacy results of these three studies are discussed below.

Results

Study 491-005

After a 2-week, single-blind placebo run-in period, subjects who met entry criteria were randomized to receive (capsule formulation) TAK-491 5, 10, 20, 40, 80 mg, placebo, or olmesartan 20 mg QD for 8 weeks. Clinical DBP and SBP were measured at Screening (Day -21, Day -14 and Day -7), Randomization (Day 1), Week 1, Week 2, Week 4, Week 6, and Week 8. ABPM occurred at Day 1 and Week 8 or Early Termination.

Efficacy endpoints:

Primary endpoint was the change from baseline at final visit in the sitting clinic DBP. The secondary efficacy variables were the change from baseline at final visit in sitting clinic SBP, standing SBP and DBP, as well as SBP and DBP measured by ABPM.

Results

A total of 449 subjects were randomized and 404 subjects completed the study. The blood pressures as baseline and endpoint and change from baseline at endpoint are shown below by treatment group.

Study Visit	Placebo N=61	TAK-491 5 mg N=65	TAK-491 10 mg N=63	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	OLM 20 mg N=63
<u>Sitting Clinic DBP</u>							
Baseline (a)							
N	61	65	63	64	62	64	63
LS mean (SE)	100.1 (0.56)	99.8 (0.55)	99.4 (0.55)	99.7 (0.55)	99.7 (0.56)	100.3 (0.55)	99.8 (0.55)
Week 8							
N	58	63	63	63	61	63	63
LS mean (SE)	-7.9 (1.12)	-10.8 (1.08)	-13.1 (1.08)	-11.5 (1.08)	-13.6 (1.10)	-11.6 (1.08)	-11.0 (1.08)
LS mean difference from Placebo (SE) (b)		-2.9	-5.3	-3.7	-5.7	-3.7	-3.2
95% CI of difference		(-5.96, 0.16)	(-8.33, -2.20)	(-6.73, -0.61)	(-8.80, -2.63)	(-6.77, -0.65)	(-6.24, -0.12)
P-value		0.063	<0.001*	0.019*	<0.001*	0.018*	0.042*
<u>Sitting Clinic SBP</u>							
Baseline (a)							
N	61	65	63	64	62	64	63
LS mean (SE)	150.8 (1.59)	150.2 (1.54)	152.4 (1.56)	149.1 (1.55)	150.6 (1.57)	151.2 (1.55)	150.3 (1.56)
Week 8							
N	58	63	63	63	61	63	63
LS mean (SE)	-4.9 (1.73)	-11.0 (1.66)	-15.7 (1.66)	-14.7 (1.66)	-17.1 (1.69)	-13.3 (1.66)	-13.5 (1.66)
LS mean difference from placebo (SE) (b)		-6.1	-10.8	-9.8	-12.3	-8.5	-8.7
95% CI of difference		(-10.84, -1.41)	(-15.51, -6.08)	(-14.53, -5.10)	(-17.02, -7.52)	(-13.19, -3.76)	(-13.39, -3.96)
P-value		0.011*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

All post-baseline P-values were determined by ANCOVA with terms for treatment (as a factor) and baseline value (as a covariate).

CI=confidence interval.

* Significant difference at 0.05 level.

(a) Baseline value is the last observation before the first dose of double-blind study medication.

(b) LS mean difference=LS mean change of each active group (TAK-491 dose group or olmesartan) – LS mean change of placebo group.

Baseline blood pressures were fairly similar across treatment groups (around 150/100 mmHg). At week 8, there were substantial decreases in blood pressure in all doses of TAK-491 compared to placebo, although the lowest dose was not significantly different from placebo for DBP.

The placebo subtracted blood pressure effects on SBP and DBP for all doses of TAK-491 on SBP and DBP are show below.

Blood pressure (mmHg): change from baseline at week 8 minus placebo

	TAK-491 5 mg N=63	TAK-491 10 mg N=63	TAK-491 20 mg N=63	TAK-491 40 mg N=61	TAK-491 80 mg N=63
Clinic SBP	-6	-11	-10	-12	-9
Clinic DBP	-3	-5	-4	-6	-4

The lowest tested dose TAK-491 5 mg produced a treatment effect of 6/3 mmHg compared to 9/4 mmHg for the 80 mg dose. There is no convincing evidence that doses of TAK-491 above 40 mg are necessary.

Study 491-019

Subjects were enrolled at sites in the United States and Latin America and were required to have a clinic SBP ≥ 150 and ≤ 180 mm Hg and 24-hour mean SBP ≥ 130 and ≤ 170 mm Hg. Those who met the entry criteria were randomized to receive TAK-491 20 mg, TAK-491 40 mg, valsartan 160 mg, olmesartan 20 mg, or placebo for 2 weeks. At the end of 2 weeks, subjects were force-titrated to the higher dose: TAK-491 40 mg or 80 mg, valsartan 320 mg, olmesartan 40 mg, or remained on placebo, respectively. Subjects remained at the higher dosage for the remainder of the study. Ambulatory blood pressure monitoring (ABPM) occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 or Early Termination for 24 hours following the last administration of study medication. Clinic DBP (diastolic blood pressure) and SBP were measured at Screening, randomization, Week 2, Week 4, and Week 6.

Efficacy endpoint

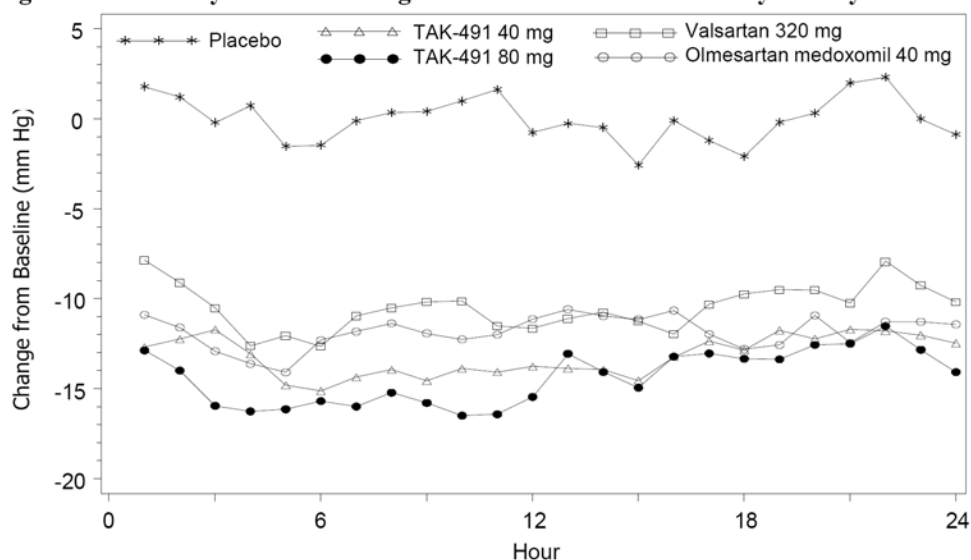
Primary endpoint was change from baseline at final visit in mean 24 hour SBP as measured by ABPM.

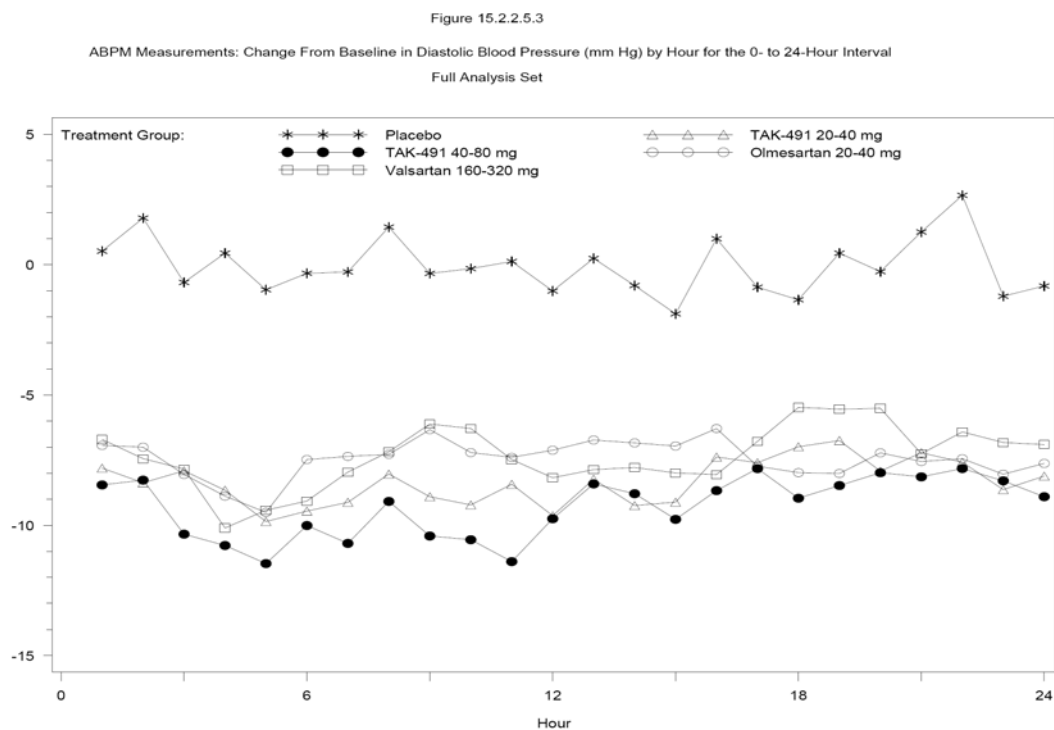
Results

A total of 1291 subjects were randomized (154 placebo, 280 to 290 in the active treatment groups) and 90% completed the study.

The subjects randomized to TAK-491 or placebo had similar baseline SBP and DBP throughout the 24 hour profile (approximately 144/88 mmHg). At week 6, there were statistically significantly greater reductions in 24 hour SBP and DBP as measured by ABPM for subjects randomized to TAK-491 40 mg and 80 mg compared to those randomized to placebo. The figures below shows the change from baseline for SBP followed by DBP at week 6 for all treatment arms.

Figure 2.b Study 491-019: Change From Baseline in Ambulatory SBP by Hour at Week 6





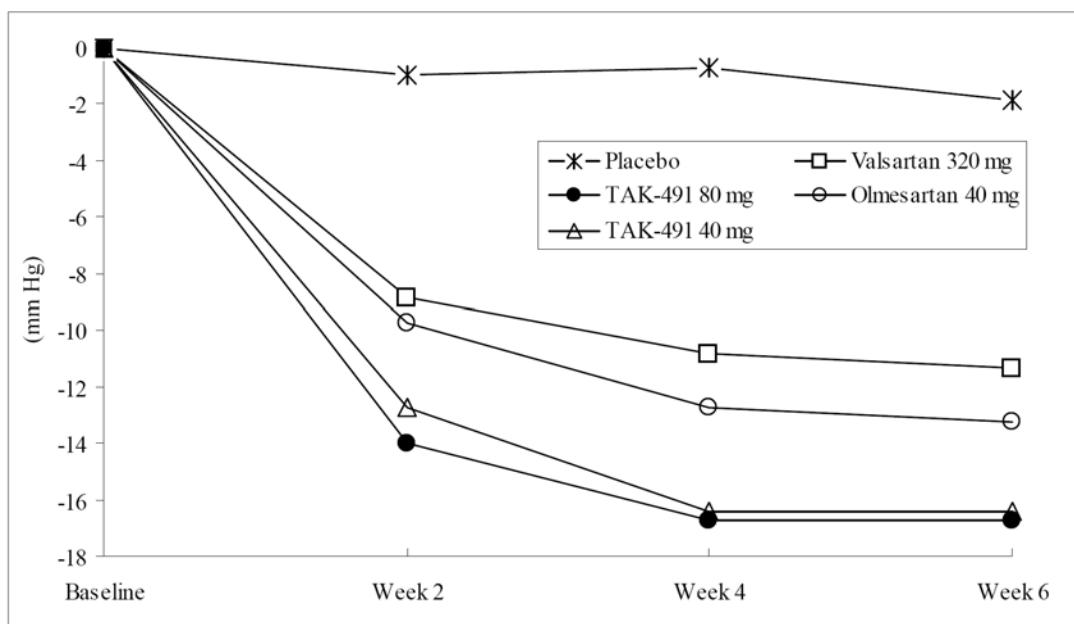
Dose effect

The two doses of TAK-491 (40 mg and 80 mg) are similar to one another in lowering both SBP and DBP. The treatment effects for 24 hour mean for TAK-491 40 mg and 80 mg were 13/9 mmHg and 14/9 mmHg, respectively.

Time course of effect (manual BP measurements)

The doses of the study drugs were forcibly doubled at week 2. There was further SBP decline with the increased doses in all active treatment groups at week 4. SBP between weeks 4 and 6 were similar for all groups. The effects of the two doses of TAK 491 are similar. This is shown in the figure below.

Figure 11.d Mean Change in Trough Clinic Sitting SBP by Study Visit (LOCF, FAS)



Study 491-008

Subjects were enrolled at sites in the United States and Latin America and were required to have a clinic SBP ≥ 150 and ≤ 180 mm Hg and 24-hour mean SBP ≥ 130 and ≤ 170 mm Hg. Those who met the entry criteria were randomized to receive TAK-491 20 mg, TAK-491 40 mg, TAK-491 80 mg, olmesartan 40 mg, or placebo for 6 weeks. ABPM was obtained on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 or Early Termination for 24 hours following the last administration of study medication. Clinic DBP and SBP were measured at screening, randomization, Week 2, Week 4, and Week 6.

Efficacy endpoint

Primary efficacy endpoint was change from baseline at week 6 in 24-hour mean SBP as measured by ABPM.

Results

A total of 1275 subjects were randomized (142 placebo, 282 to 285 in the active treatment groups) with 92% completing the study.

The subjects randomized to TAK-491 or placebo had similar baseline SBP and DBP throughout the 24 hour profile (approximately 146/87 mmHg). At week 6, statistically significantly greater reductions in 24-hour mean SBP were observed at Week 6 with each active treatment compared to placebo. The three doses of TAK 491 tended to produce similar blood pressure lowering effects. The figures below shows the change from baseline for SBP followed by DBP at week 6 for all treatment arms.

Figure 11.a Change From Baseline to Week 6 in SBP by ABPM by Hour for the 0- to 24-Hour Interval (FAS)

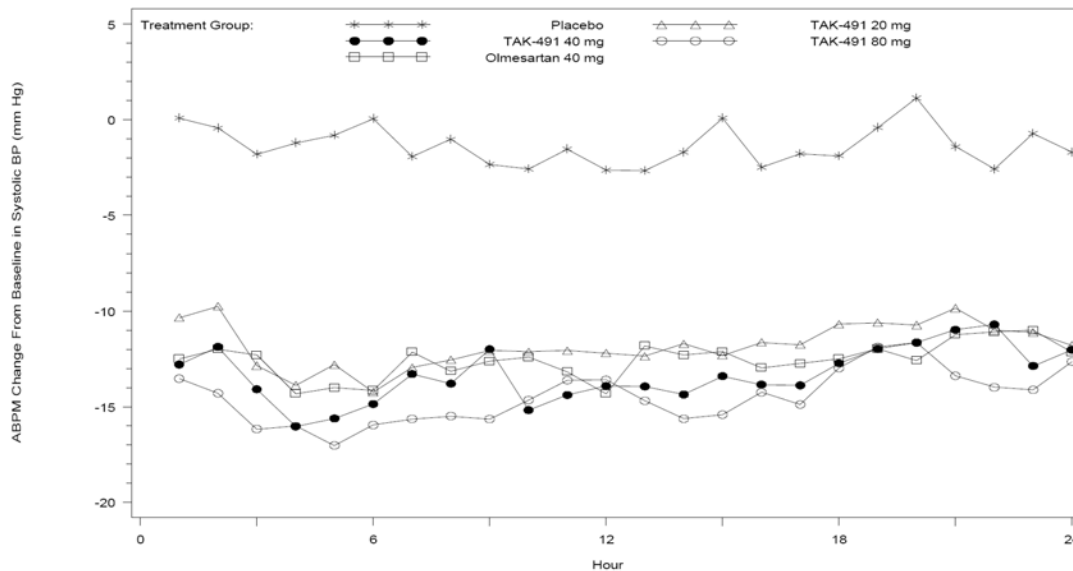
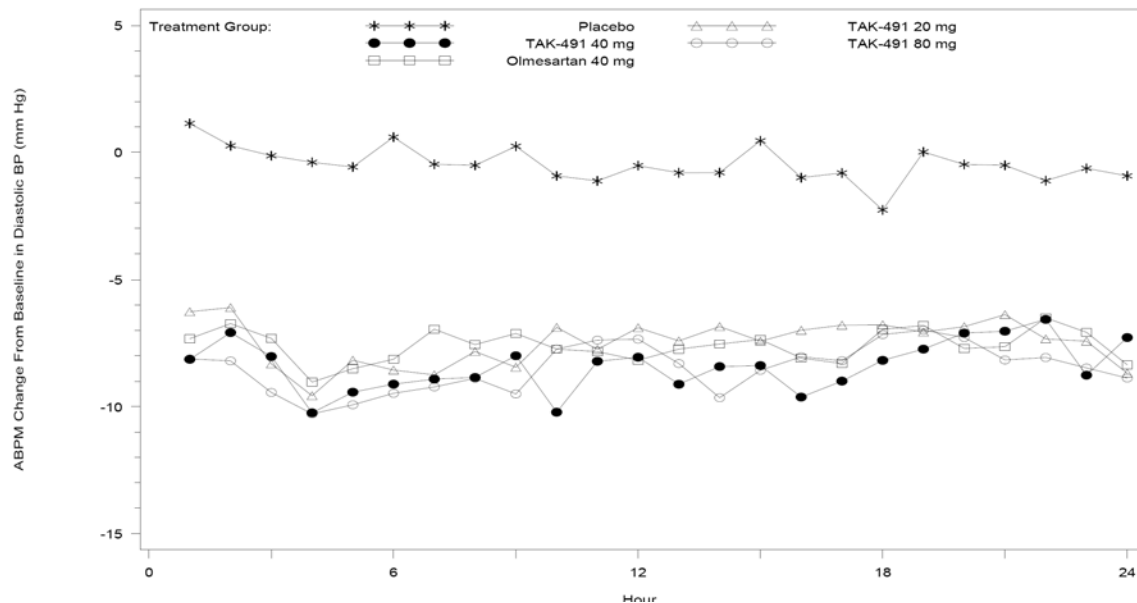


Figure 15.2.2.5.3

ABPM Measurements: Change From Baseline in Diastolic Blood Pressure (mm Hg) by Hour for the 0- to 24-Hour Interval
Full Analysis Set



The three doses of TAK 491 produced similar blood pressure lowering effect. The treatment effects for 24 hour mean for TAK-491 20 mg, 40 mg and 80 mg were 11/7 mmHg, 12/7 mmHg and 13/8 mmHg, respectively. There is little added efficacy with dose above TAK-491 40 mg.

Active Comparators

vs. Olmesartan

The two studies that included a treatment arm with olmesartan were 491-008 and 491-019. The study designs of the trials were discussed previously. The pooled BP results are shown below.

Table 3.e Pooled Analyses of Studies 491-008 and 491-019: Change in 24-hour Mean and Clinic SBP and DBP—TAK-491 vs Olmesartan Medoxomil

	TAK-491 40 mg N=561	TAK-491 80 mg N=567	OLM-M 40 mg N=572
24-Hour Mean SBP: LS Mean Change from Baseline at Week 6 (mm Hg)			
n	481	472	504
BL (SE)	145.17 (0.464)	145.34 (0.466)	145.41 (0.453)
Change from BL (SE)	-13.78 (0.501)	-14.87 (0.504)	-12.60 (0.489)
PBO-corrected (a)	-12.65	-13.74	-11.47
(95% CI)	(-14.29, -11.01)	(-15.38, -12.09)	(-13.09, -9.84)
Difference vs OLM-M (b)	-1.18	-2.27	--
(95% CI)	(-2.53, 0.16)	(-3.62, -0.92)	--
P-value vs OLM-M	0.085	0.001†	--
Clinic SBP: LS Mean Change from Baseline at Week 6 (mm Hg) (LOCF)			
n	545	549	563
BL (SE)	157.93 (0.536)	158.77 (0.533)	158.64 (0.527)
Change from BL (SE)	-16.09 (0.685)	-17.75 (0.681)	-14.64 (0.673)
PBO-corrected (a)	-13.50	-15.17	-12.05
(95% CI)	(-15.73, -11.26)	(-17.40, -12.93)	(-14.27, -9.82)
Difference vs OLM-M (b)	-1.45	-3.12	--
(95% CI)	(-3.29, 0.40)	(-4.96, -1.28)	--
P-value vs OLM-M	0.124	<0.001†	--
24-Hour Mean DBP: LS Mean Change from Baseline at Week 6 (mm Hg)			
n	481	472	504
BL (SE)	87.62 (0.434)	87.87 (0.436)	87.40 (0.424)
Change from BL (SE)	-8.59 (0.333)	-9.07 (0.335)	-7.82 (0.326)
PBO-corrected (a)	-8.17	-8.65	-7.39
(95% CI)	(-9.26, -7.08)	(-9.74, -7.56)	(-8.48, -6.31)
Difference vs OLM-M (b)	-0.77	-1.26	--
(95% CI)	(-1.67, 0.12)	(-2.16, -0.36)	--
P-value vs OLM-M	0.091	0.006*	--
Clinic DBP: LS Mean Change from Baseline at Week 6 (mm Hg) (LOCF)			
n	545	549	563
BL (SE)	91.39 (0.455)	91.45 (0.451)	91.01 (0.446)
Change from BL (SE)	-7.36 (0.385)	-8.74 (0.382)	-6.91 (0.378)
PBO-corrected (a)	-6.67	-8.06	-6.23
(95% CI)	(-7.93, -5.42)	(-9.31, -6.80)	(-7.48, -4.98)
Difference vs OLM-M (b)	-0.45	-1.83	--
(95% CI)	(-1.48, 0.59)	(-2.86, -0.79)	--
P-value vs OLM-M	0.399	<0.001*	--

Source: Table 1.6.1, Table 1.7.1, 1.8.1, and Table 1.9.1.

BL=Baseline; PBO=placebo; OLM-M=olmesartan medoxomil.

(a) Placebo-corrected=LS mean change of each active treatment (TAK-491 dose group or olmesartan medoxomil) – LS mean change of placebo group.

(b) LS mean difference=LS mean change of each TAK-491 dose group – LS mean change of olmesartan medoxomil.

* Significant difference vs olmesartan medoxomil.

† Significant difference vs olmesartan medoxomil within the step-wise analysis.

TAK-491 40 mg was not consistently better in lowering blood pressure compared to olmesartan medoxomil 40 mg. The blood pressure differences between TAK 491 and olmesartan were small (between 1 and 3 mmHg).

The table below shows the disposition of subjects in the pooled trials.

Table 3.b Pooled Analyses of Studies 491-008 and 491-019: Summary of Disposition of Subjects

	Placebo	TAK-491 40 mg	TAK-491 80 mg	OLM-M 40 mg
Randomized Subjects	296	563	570	572
Discontinued Study	25 (8.4)	45 (8.0)	54 (9.5)	36 (6.3)
Adverse Event	9 (3.0)	10 (1.8)	15 (2.6)	10 (1.7)
Major Protocol Deviation	4 (1.4)	4 (0.7)	4 (0.7)	0
Lost to Follow-up	3 (1.0)	5 (0.9)	7 (1.2)	6 (1.0)
Voluntary Withdrawal	1 (0.3)	12 (2.1)	17 (3.0)	8 (1.4)
Lack of Efficacy	7 (2.4)	8 (1.4)	5 (0.9)	7 (1.2)
Other	1 (0.3)	6 (1.1)	5 (0.9)	5 (0.9)
Reason Missing	0	0	1 (0.2)	0

OLM-M=olmesartan medoxomil.

Source: [Table 1.1](#)

There were more study discontinuations, indicating more intolerance, in the TAK-491 80 mg group compared to olmesartan medoxomil 40 mg group.

vs. Valsartan

The efficacy of TAK-491 compared to valsartan 320 mg was evaluated in studies 491-019 and 491-301. Both studies were similar in terms of subject population enrolled. However, they varied in duration (6 weeks and 24 weeks, respectively) and study 491-301 did not include a placebo arm.

In study 419-019, the valsartan group had significantly higher baseline values compared to the other treatment arms. This is shown in the table below.

Table 10.b Summary of ABPM SBP and DBP (mm Hg) at Baseline (Randomized Subjects)

Characteristic	Treatment Group					P-value (a)
	Placebo N=154	TAK-491 40 mg N=280	TAK-491 80 mg N=285	Valsartan 320 mg N=282	Olmesartan 40 mg N=290	
Number of Subjects with Blood Pressure by ABPM at Baseline	153	277	280	278	289	
0- to 24-hour mean SBP						0.096
Mean (SD)	144.2 (10.57)	144.3 (9.87)	145.0 (9.54)	146.3 (10.45)	144.5 (9.52)	
Mean daytime (6 AM - 10 PM) SBP						0.150
Mean (SD)	147.5 (10.70)	147.7 (10.05)	148.6 (9.89)	149.6 (10.84)	148.1 (9.75)	
Mean nighttime (12 AM - 6 AM) SBP						0.209
Mean (SD)	134.1 (12.87)	134.3 (12.65)	134.3 (12.65)	136.2 (12.95)	133.8 (12.79)	
0- to 12-hour mean SBP						0.146
Mean (SD)	148.1 (11.28)	148.3 (10.45)	149.2 (10.54)	150.3 (11.24)	148.9 (10.08)	
Trough 22- to 24-hour mean SBP						0.566
Mean (SD)	148.1 (12.93)	147.7 (12.51)	149.1 (11.82)	149.2 (13.38)	148.1 (12.36)	
0- to 24-hour mean DBP						0.029*
Mean (SD)	88.7 (9.44)	87.9 (9.57)	88.6 (9.58)	90.2 (8.91)	87.9 (9.08)	
Mean daytime (6 AM - 10 PM) DBP						0.027*
Mean (SD)	91.9 (9.99)	91.2 (9.95)	91.8 (10.19)	93.6 (9.48)	91.2 (9.51)	
Mean nighttime (12 AM - 6 AM) DBP						0.355
Mean (SD)	79.5 (9.74)	79.0 (10.80)	79.5 (10.18)	80.5 (10.00)	78.9 (10.55)	
0- to 12-hour mean DBP						0.042*
Mean (SD)	92.4 (10.52)	91.8 (10.47)	92.4 (10.81)	94.2 (9.81)	91.8 (9.92)	
Trough 22- to 24-hour mean DBP						0.142
Mean (SD)	93.9 (10.92)	92.4 (10.80)	93.7 (10.91)	94.7 (11.26)	93.0 (10.65)	

Source: [Table 15.1.8.1](#).

Note: Baseline was the last observation before the first dose of double-blind study drug.

* Significant difference at 0.05 level.

(a) The treatment groups were compared using a 1-way analysis of variance with effects for treatment.

As a result of baseline imbalance, the blood pressure differences at endpoint between TAK 491 and valsartan, therefore, are uninformative.

Subgroups

The effect of TAK-491 on blood pressure by subgroup (race, age, sex, BMI, and geographic region, hypertension severity, diabetic status, and renal function status) were evaluated in pooled studies shown below.

Table 1.f Description of Pooled Analyses of Phase 3, Controlled Studies

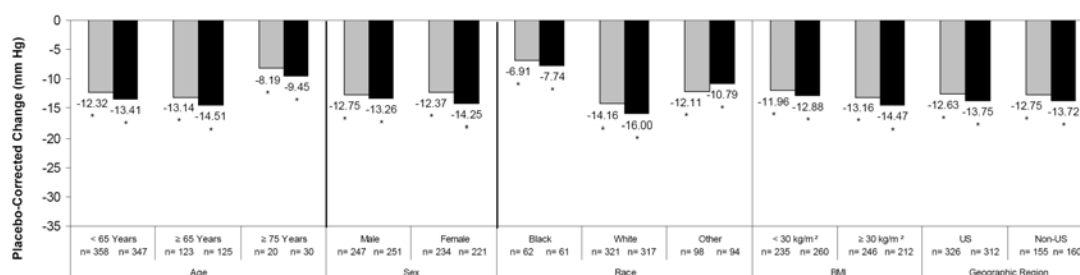
Pool, Studies (Duration)	Dose Groups	Description
TAK-491 vs Placebo and Olmesartan medoxomil 491-008 (6 weeks) 491-019 (6 weeks)	<ul style="list-style-type: none"> • Placebo • TAK-491 40 mg • TAK-491 80 mg • OLM-M 40 mg 	Both studies were 6-weeks in duration and enrolled a general population; both were conducted in the US and Latin America.
TAK-491 vs Valsartan 491-019 (6 weeks) 491-301 (6 months)	<ul style="list-style-type: none"> • TAK-491 40 mg • TAK-491 80 mg • Valsartan 320 mg 	Pool incorporates data through Week 6 of 491-019 and Week 8 of 491-301; both studies enrolled a general population and were conducted in the US and Latin America.
Long-term: TAK-491 vs Active Comparator 491-020 (6 months) 491-301 (6 months)	<ul style="list-style-type: none"> • TAK-491 40 mg • TAK-491 80 mg • Active comparator (a) 	Both studies were 6-months in duration and enrolled a general population. 491-020 (ramipril comparator) was conducted in Europe and Russia; 491-301 (valsartan comparator) was conducted in US and Latin America.
Black Population: TAK-491 vs Placebo 491-008 (6 weeks) 491-019 (6 weeks) 491-011 (6 weeks)	<ul style="list-style-type: none"> • Placebo • TAK-491 40 mg • TAK-491 80 mg 	Pool incorporates data only from Black subjects enrolled in these studies. All subjects were enrolled in the US and Latin America.

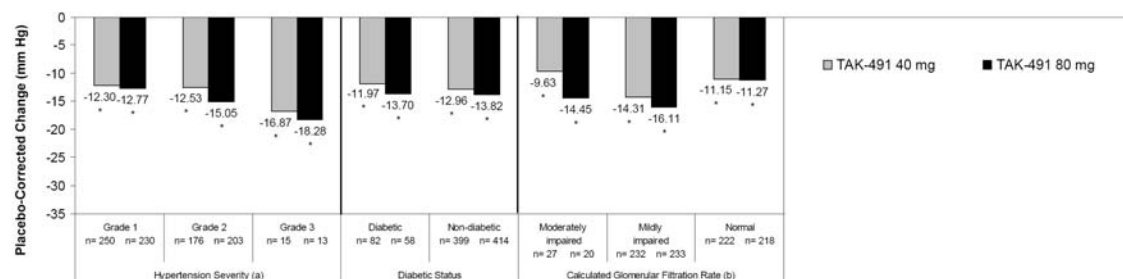
OLM-M=olmesartan medoxomil, US=United States.

(a) Data from subjects who received ramipril 10 mg (491-020) and valsartan 320 mg (491-301) were combined into a single "active comparator" group.

There was no evidence of heterogeneity in response as measured by 24-hour mean SBP by sex, BMI, geographic region, diabetic status, or age (<65 or ≥65), although there was a reduced response in the small subset of subjects ≥75 years of age. Regarding race, black subjects had a substantially reduced response compared to white subjects (differences by race are discussed further). Results measure by clinic BP were similar to the mean 24 hour data.

Figure 3.e Overview of Pooled Subgroup Analyses in Studies 491-008 and 491-019: Placebo-Corrected Change From Baseline in 24-Hour Mean SBP—TAK-491 vs Placebo





Source: Table 1.6.3, Table 1.6.4, Table 1.6.5, Table 1.6.6, Table 1.6.7, Table 1.6.8, Table 1.6.9, and Table 1.6.10.

*Significant difference vs placebo.

(a) Grade 1: Baseline clinic SBP ≥ 140 to < 160 mm Hg; Grade 2: SBP ≥ 160 to < 180 mm Hg; Grade 3: SBP ≥ 180 mm Hg.

(b) Moderately impaired: Baseline GFR ≥ 30 to < 60 ml/min/1.73 m²; Mildly impaired: ≥ 60 to < 90 ml/min/1.73 m²; Normal: > 90 ml/min/1.73 m².

A trend of greater reduction in 24-hour mean SBP was observed as hypertension severity increased (discussed further below), although the sample sizes were small in some of the subgroups.

Race

Change from baseline to Week 6 for 24-hour mean SBP and clinic SBP is summarized by race in the table below. These pooled analyses include data from the 6-week studies 491-008 and 491-019.

Table 3.n Pooled Subgroup Analyses of Studies 491-008 and 491-019: Change in 24-Hour Mean SBP and Clinic SBP by Race—TAK-491 vs Placebo

	Black			White			Other		
	PBO	40 mg	80 mg	PBO	40 mg	80 mg	PBO	40 mg	80 mg
24-Hour SBP:LS Mean Change from Baseline to Week 6 (mm Hg)									
n	38	62	61	158	321	317	58	98	94
BL	147.10	145.06	145.99	145.69	145.42	145.82	142.92	144.71	143.55
Change from BL	-0.42	-7.33	-8.17	-0.13	-14.29	-16.13	-2.10	-14.21	-12.89
PBO-corrected (a)	--	-6.91	-7.74	--	-14.16	-16.00	--	-12.11	-10.79
(95% CI)	--	(-11.00, -2.81)	(-11.86, -3.63)	--	(-16.19, -12.14)	(-18.03, -13.97)	--	(-15.53, -8.69)	(-14.23, -7.34)
P-value vs PBO	--	0.001*	<0.001*	--	<0.001*	<0.001*	--	<0.001*	<0.001*
Clinic SBP:LS Mean Change from Baseline to Week 6 (mm Hg) (LOCF)									
n	43	75	74	181	361	370	64	109	105
BL	155.21	157.78	158.39	158.14	157.74	158.74	156.47	157.35	157.82
Change from BL	-2.47	-9.42	-12.33	-0.88	-16.60	-17.91	-5.25	-16.55	-18.75
PBO-corrected (a)	--	-6.95	-9.86	--	-15.72	-17.03	--	-11.30	-13.50
(95% CI)	--	(-12.45, -1.45)	(-15.39, -4.33)	--	(-18.51, -12.92)	(-19.81, -14.25)	--	(-16.20, -6.40)	(-18.44, -8.57)
P-value vs PBO	--	0.014*	<0.001*	--	<0.001*	<0.001*	--	<0.001*	<0.001*

Source: Table 1.6.5 and Table 1.8.5.

BL=baseline, PBO=placebo.

* Significant difference vs placebo.

(a) Placebo-corrected=LS mean change of each TAK-491 dose group – LS mean change of placebo group.

The placebo corrected SBP effects were approximately twice as great for the white subjects compared to the black subjects.

Hypertension severity

Change from baseline to Week 6 for 24-hour mean SBP and clinic SBP by hypertension severity (Grades 1, 2, and 3) are shown below. These pooled analyses include data from the placebo-controlled, 6-week studies 491-008 and 491-019. There were very few subjects with baseline SBP ≥ 180 mmHg.

Table 3.r Pooled Subgroup Analyses of Studies 491-008 and 491-019: Change in 24-Hour Mean SBP and Clinic SBP by Hypertension Severity—TAK-491 vs Placebo

	SBP ≥140 to <160 mm Hg [Grade 1]			SBP ≥160 to <180 mm Hg [Grade 2]			SBP ≥180 mm Hg [Grade 3]		
	PBO	40 mg	80 mg	PBO	40 mg	80 mg	PBO	40 mg	80 mg
24-Hour Mean SBP:LS Mean Change from Baseline to Week 6 (mm Hg)									
n	134	250	230	92	176	203	8	15	13
BL	141.92	142.35	142.65	151.16	149.74	148.45	152.43	154.62	156.38
Change from BL	-1.29	-13.60	-14.06	-0.86	-13.39	-15.91	0.76	-16.11	-17.52
PBO-corrected (a)	--	-12.30	-12.77	--	-12.53	-15.05	--	-16.87	-18.28
(95% CI)		(-14.48, -10.13)	(-14.98, -10.57)		(-15.37, -9.70)	(-17.83, -12.28)		(-29.17, -4.57)	(-31.09, -5.47)
P-value vs PBO	--	<0.001*	<0.001*	--	<0.001*	<0.001*	--	0.008*	0.006*
Clinic SBP:LS Mean Change from Baseline to Week 6 (mm Hg) (LOCF)									
n	155	276	265	102	207	239	9	17	15
BL	152.04	151.88	151.53	168.31	168.51	167.86	185.95	185.77	186.55
Change from BL	-0.22	-14.33	-15.13	-6.68	-18.99	-22.31	-6.50	-36.39	-29.76
PBO-corrected (a)	--	-14.11	-14.91	--	-12.31	-15.63	--	-29.89	-23.27
(95% CI)		(-17.05, -11.18)	(-17.86, -11.95)		(-16.19, -8.43)	(-19.43, -11.84)		(-48.42, -11.37)	(-42.21, -4.32)
P-value vs PBO	--	<0.001*	<0.001*	--	<0.001*	<0.001*	--	0.002*	0.017*

Source: Table 1.6.6 and Table 1.8.6.

BL=baseline, PBO=placebo.

(a) Placebo-corrected=LS mean change of each TAK-491 dose group – LS mean change of placebo group.

* Significant difference vs placebo.

The subjects with the highest baseline SBP (grade 3) tended to have the largest response to TAK-491.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Extent of exposure

There were 64 studies used for the safety evaluation of this drug. The sponsor pooled 24 studies that they considered to have similar characteristics and left the remaining 40 studies unpooled.

The 64 studies divided into pooled and unpooled groups are listed below.

Table 1.a Clinical Studies Overview

POOLED STUDIES			
TAK-491 Phase 3 Studies (3 study pools)			
491-008	Monotherapy (vs placebo, OLM-M)	491-019	Monotherapy (vs placebo, OLM-M, valsartan)
491-009	Chlorthalidone coadministration	491-301 (a)	Monotherapy (vs valsartan)
491-010	Amlodipine coadministration	491-006 (a)	OL long-term safety (1 year)
491-011	Monotherapy in Black population (vs placebo)	491-016	OL long-term safety (6 months) with DB reversal
491-020	Monotherapy (vs ramipril)		
TAK-491 Phase 1 Studies (1 study pool)			
491-001	SRD PK, PD, food effect (capsule)	491-017	Relative bioavailability, SRD, MRD
491-002	MRD PK, PD (capsule)	491-101	MRD PK
491-003	Sex, age, race (capsule)	491-102	Hepatic impairment
491-004	Chlorthalidone (capsule) DDi	491-103	Renal impairment
491-007	QTc	491-104	Digoxin DDi
491-012	ADME	491-107	Antacid DDi
491-013	Drug cocktail (capsule) DDi	491-110	Amlodipine DDi
491-015	Relative bioavailability, food effect		
UNPOOLED STUDIES			
Dose-Ranging Studies (phase 2)			
491-005	Dose-ranging (capsule)	536-002	Dose-ranging
		536-CCT-001	Dose-ranging (Japan)
Other TAK-536 Studies (phase 1 except where indicated)			
536-004	Drug cocktail DDi	536-CPH-001	SRD PK, PD, food effect (Japan)
536-005	Ketoconazole, fluconazole DDi	536-CPH-002	MRD PK, PD (Japan)
536-006	Pioglitazone DDi	536-CPH-005	Renal impairment (Japan) (phase 2)
536-007	Food effect	536-CPH-009	Relative bioavailability (Japan)
536-008	Sex, age, race	536-EC101	MRD PK
536-009	Warfarin DDi	536-GHBA-328	SRD PK, PD
536-010	Glyburide DDi	536-GHBA-590	Dose-ranging (phase 2)
536-011	Metformin DDi	536-GHBA-774	PK in patients (phase 2)
536-014	ADME	536-CCT-005 (a)	Comparator (Japan) (phase 3)
536-016	Absolute, relative bioavailability	536-OCT-006 (a)	OL hypertension (Japan) (phase 3)
536-316	SRD PK, PD	536-OCT-003 (a)	OL severe hypertension (Japan) (phase 3)
536-317	MRD PK, PD	536-OCT-002 (a)	OL renal patients (Japan) (phase 3)
536-661	Food effect		
TAK-491 Japanese Studies (phase 1)			
491-CPH-001	SRD PK, PD, food effect (capsule) (Japan)	491-CPH-005	SRD PK, PD, food effect (capsule) (Japan)
TAK-491 or TAK-536 FDC Studies (phase 1 except where indicated)			
491CCB-101	Formulation bioavailability	536OPI-001	Formulation bioavailability capsule
491CLD-102	Formulation bioavailability	536OPI-002	Formulation bioavailability tablet
491CLD-103	Formulation bioavailability	536OPI-525	Proof of concept in diabetes patients (phase 2)
491CLD-104	Food effect	536OPI-003	Efficacy in diabetes patients (phase 3)
491CLD-105	Formulation bioavailability	536OPI-005	Long-term safety in diabetes patients (phase 3)

Footnotes for Table 1.a are on the following page

ADME=absorption, distribution, metabolism, excretion, DB=double-blind, DDi=drug-drug interaction, MRD=multiple-rising dose, OL=open-label, OLM-M=olmesartan medoxomil, PD=pharmacodynamic, PK=pharmacokinetic, QTc=corrected QT interval, SRD=single-rising dose.

Except where indicated, all studies were conducted with the tablet formulation.

(a) Ongoing studies, with interim data cut of 30 October 2009 and serious adverse event data cut of 03 February 2010.

The focus of the safety review is on the nine phase 3 studies. These studies used multiple doses 20 mg, 40, 80 mg given once daily for between 6 and 24 weeks.

The following table shows the extent of exposure for the 4814 subjects who were randomized to TAK 491 in these nine studies.

Table 1.e Exposure Overview: All TAK-491 Phase 3 Studies

Exposure	Placebo(a) (N=801)	Comparator(b) (N=1468)	TAK-491 20 mg(c) (N=283)	TAK-491 40 mg(d) (N=1808)	TAK-491 80 mg(d) (N=2783)	TAK-491 All Doses(e) (N=4814)
Days of exposure						
Mean (SD)	41.3 (7.43)	86.4 (61.21)	41.2 (7.45)	90.9 (72.43)	137.1 (112.02)	115.8 (102.65)
Median (min-max)	42 (1-63)	44 (1-190)	43 (1-57)	44 (1-410)	134 (1-427)	46 (1-427)
Cumulative exposure (n)						
≥1 day	801	1468	283	1808	2783	4814
≥2 weeks	782	1438	276	1777	2690	4683
≥4 weeks	758	1394	269	1734	2609	4552
≥8 weeks	3	556	2	692	1539	2173
≥12 weeks	0	532	0	649	1472	2071
≥24 weeks	0	386	0	456	1254	1688
≥48 weeks	0	0	0	25	270	327

Source: ISS Table 1.5.

Studies included 491- 006 (interim), 008, 009, 010, 011, 016, 019, 020, and 301 (interim).

(a) Placebo group combines subjects who received placebo alone, with amlodipine, or with chlorthalidone.

(b) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(c) Includes only 491-008 20 mg group.

(d) TAK-491 40 and 80 mg dose groups combined subjects who received TAK-491 alone, with amlodipine, or with chlorthalidone or HCTZ and includes initiating 2-week 20 mg dose prior to titration.

(e) TAK-491 All Doses group combines unique subjects who received TAK-491 20, 40, or 80 mg.

Placebo controlled pool

The placebo controlled pool of five studies (3 monotherapy and 2 coadministration studies) is shown below. These studies were all six weeks in duration.

Table 1.b Study Design Summary: Phase 3 Placebo-Controlled Pool

Study Design and Study Number (Regions)	Entry Criteria Planned Sample Size	Duration of Double-Blind Treatment and Dose/Regimen (a)	1° Endpoint (Key 2° Endpoint)
Monotherapy			
TAK-491 vs placebo and olmesartan medoxomil 491-008 (US, Lat Am)	Clinic SBP 150-180 mm Hg and 24-hr SBP 130-170 mm Hg N=1260 (active=280/group; placebo=140)	6 weeks • TAK-491 20 mg • TAK-491 40 mg • TAK-491 80 mg • OLM-M 40 mg • Placebo	24-hr mean SBP by ABPM (clinic SBP)
TAK-491 vs placebo, olmesartan medoxomil, and valsartan 491-019 (US, Lat Am)	Clinic SBP 150-180 mm Hg and 24-hr SBP 130-170 mm Hg N=1305 (active=290/group; placebo=145)	6 weeks (2 weeks→4 weeks) • TAK-491 20→40 mg • TAK-491 40→80 mg • Valsartan 160→320 mg • OLM-M 20→40 mg • Placebo	24-hr mean SBP by ABPM (clinic SBP)
Black population (TAK-491 vs placebo) 491-011 (US, Puerto Rico)	Clinic SBP 150-180 mm Hg and 24-hr SBP 130-170 mm Hg N=411 (137/group)	6 weeks • TAK-491 40 mg • TAK-491 80 mg • Placebo	24-hr mean SBP by ABPM (clinic SBP)
Coadministration			
TAK-491 + diuretic 491-009 (US, Lat Am)	Clinic SBP 160-190 mm Hg and 24-hr SBP 140-180 mm Hg N=540 (180/group)	6 weeks • TAK-491 40 mg + CLD 25 mg • TAK-491 80 mg + CLD 25 mg • Placebo + CLD 25 mg	24-hr mean SBP by ABPM (clinic SBP)
TAK-491 + CCB 491-010 (US, Lat Am)	Clinic SBP 160-190 mm Hg and 24-hr SBP 140-180 mm Hg N=540 (180/group)	6 weeks • TAK-491 40 mg + AML 5 mg • TAK-491 80 mg + AML 5 mg • Placebo + AML 5 mg	24-hr mean SBP by ABPM (clinic SBP)

ABPM=ambulatory blood pressure monitoring, AML=amlodipine, CLD=chlorthalidone, Lat Am=Latin America, OLM-M=olmesartan medoxomil, US=United States.

(a) All study drugs were administered once daily.

The subject disposition for the five studies making up the placebo controlled pool is shown below.

Table 1.2.2
Primary Reasons for Which Subjects Prematurely Discontinued Study Drug
in Phase 3 Randomized Placebo-Controlled Studies

	Placebo (N= 801)	TAK-491 40 mg (N = 1072)	TAK-491 80 mg (N = 1074)	TAK-491 40/80 mg (N = 2146)
Number of Subjects Prematurely Discontinued	65 (8.1%)	78 (7.3%)	107 (10.0%)	185 (8.6%)
Primary Reason for Premature Discontinuation				
Adverse Event	19 (2.4%)	24 (2.2%)	29 (2.7%)	53 (2.5%)
Protocol Deviation	7 (0.9%)	8 (0.7%)	8 (0.7%)	16 (0.7%)
Lost to Follow-up	3 (0.4%)	8 (0.7%)	16 (1.5%)	24 (1.1%)
Voluntary Withdrawal	15 (1.9%)	19 (1.8%)	31 (2.9%)	50 (2.3%)
Study Termination	0	0	0	0
Pregnancy	0	0	0	0
Lack of Efficacy	12 (1.5%)	10 (0.9%)	9 (0.8%)	19 (0.9%)
Investigator Discretion	0	0	0	0
Other	9 (1.1%)	9 (0.8%)	14 (1.3%)	23 (1.1%)

Compared to placebo (8%) and TAK-491 40 mg (7%), a higher percentage of subjects randomized to TAK-491 80 mg (10%) had been discontinued early. The difference between the groups is mostly the percents of subjects who voluntarily withdrew or were lost to follow up, categories that suggest subjects were unable to tolerate the study drug. Placebo had more withdrawals because of lack of effect compared to active treatment groups.

The subject disposition for the 3 monotherapy studies is shown below.

Table 8.4
Primary Reasons for Which Subjects Prematurely Discontinued Study Drug
in Phase 3 Randomized Placebo-Controlled Monotherapy Studies

	Placebo (N= 435)	TAK-491 40 mg (N = 698)	TAK-491 80 mg (N = 704)
Number of Subjects Prematurely Discontinued	41 (9.4%)	54 (7.7%)	72 (10.2%)
Primary Reason for Premature Discontinuation			
Adverse Event	10 (2.3%)	13 (1.9%)	18 (2.6%)
Protocol Deviation	7 (1.6%)	6 (0.9%)	5 (0.7%)
Lost to Follow-up	3 (0.7%)	7 (1.0%)	11 (1.6%)
Voluntary Withdrawal	7 (1.6%)	11 (1.6%)	24 (3.4%)
Study Termination	0	0	0
Pregnancy	0	0	0
Lack of Efficacy	10 (2.3%)	9 (1.3%)	5 (0.7%)
Investigator Discretion	0	0	0
Other	4 (0.9%)	8 (1.1%)	9 (1.3%)

There were slightly more premature discontinuations in the TAK-491 80 mg group (10%) compared to the lower dose of TAK-491 (8%) and placebo (9%). Overall, the withdrawal rate for adverse events and voluntary withdrawal combined was 6% for TAK-491 80 mg compared to 4% for the other two groups.

Selected demographics for the subjects in the placebo controlled trials are shown below.

Table 1.h Demographic and Baseline Characteristics: Phase 3 Placebo-Controlled Pool

Characteristic	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	TAK-491 Total(a) (N=2146)
Number (%) of Subjects (except where noted)				
Age (yrs), mean (SD)	57.4 (11.36)	56.7 (10.97)	56.8 (11.45)	56.8 (11.21)
65-<75 years	158 (19.7)	216 (20.1)	207 (19.3)	423 (19.7)
≥75 years	57 (7.1)	48 (4.5)	67 (6.2)	115 (5.4)
American Indian/Alaskan Native	134 (16.7)	154 (14.4)	171 (15.9)	325 (15.1)
Black/African American	237 (29.6)	276 (25.7)	272 (25.3)	548 (25.5)
White	400 (49.9)	594 (55.4)	595 (55.4)	1189 (55.4)
BMI, mean (SD)	30.73 (5.735)	31.04 (6.04)	30.52 (5.881)	30.78 (5.965)
SBP (mm Hg), mean (SD)	161.4 (13.66)	160.6 (13.43)	161.2 (13.35)	160.9 (13.39)
DBP (mm Hg), mean (SD)	93.6 (11.4)	93.8 (11.28)	93.3 (11.02)	93.6 (11.15)
SBP <140 mm Hg	41 (5.1)	64 (6.0)	49 (4.6)	113 (5.3)
SBP 140-<160 mm Hg	321 (40.1)	452 (42.2)	437 (40.7)	889 (41.4)
SBP 160-<180 mm Hg	358 (44.7)	473 (44.1)	502 (46.7)	975 (45.4)
SBP ≥180 mm Hg	81 (10.1)	83 (7.7)	86 (8.0)	169 (7.9)
eGFR (mL/min/1.73 m ²), mean (SD)	90.2 (22.76)	89.4 (20.53)	89.8 (21.22)	89.6 (20.87)
eGFR ≥90 mL/min/1.73 m ²	376 (46.9)	528 (49.3)	515 (48.0)	1043 (48.6)
eGFR 60-<90 mL/min/1.73 m ²	383 (47.8)	484 (45.1)	499 (46.5)	983 (45.8)
eGFR 30-<60 mL/min/1.73 m ²	42 (5.2)	60 (5.6)	57 (5.3)	117 (5.5)
eGFR <30 mL/min/1.73 m ²	0	0	1 (<0.1)	1 (<0.1)

Source: ISS Table 1.2.3.

eGFR=estimated glomerular filtration rate.

Study pool included monotherapy (491- 008, 011, and 019) and coadministration (491- 009 and 010) studies.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The groups were reasonably well balanced. The mean age was approximately 57 years. Somewhat more elderly subjects (≥75 years of age) had been randomized to the placebo group compared to the other groups. About half of the study population was white.

Approximately half of subjects had a BMI ≥30 and less than a quarter of subjects were current smokers. The majority of subjects had no history of cardiovascular disease (an exclusion criterion for 3 of 5 studies) or diabetes, and reported no use of lipid-modifying or diabetes.

Most subjects had normal renal function or mild renal impairment at baseline. At baseline, the majority of subjects had clinic SBP of 160 to <180 mm Hg or 140 to <160 mm Hg. There were slightly more placebo subjects (10%) compared with TAK-491 subjects (8%) with SBP ≥180 mm Hg.

The active controlled pool

The active controlled pool of four studies is shown below. These studies were either 6 or 24 weeks in duration.

Table 1.c Study Design Summary: Phase 3 Active-Controlled Pool

Study Design and Study Number (Regions)	Entry Criteria Planned Sample Size	Duration of Double-Blind Treatment and Dose/Regimen (a)	1° Endpoint (Key 2° Endpoint)
Monotherapy			
TAK-491 vs placebo and olmesartan medoxomil 491-008 (US, Lat Am)	Clinic SBP 150-180 mm Hg and 24-hr SBP 130-170 mm Hg N=1260 (active=280/group; placebo=140)	6 weeks • TAK-491 20 mg • TAK-491 40 mg • TAK-491 80 mg • OLM-M 40 mg • Placebo	24-hr mean SBP by ABPM (clinic SBP)
TAK-491 vs placebo, olmesartan medoxomil, and valsartan 491-019 (US, Lat Am)	Clinic SBP 150-180 mm Hg and 24-hr SBP 130-170 mm Hg N=1305 (active=290/group; placebo=145)	6 weeks (2 weeks→4 weeks) • TAK-491 20→40 mg • TAK-491 40→80 mg • Valsartan 160→320 mg • OLM-M 20→40 mg • Placebo	24-hr mean SBP by ABPM (clinic SBP)
TAK-491 vs valsartan 491-301(DB) (US, Lat Am)	Clinic SBP 150-180 mm Hg and 24-hr SBP 130-170 mm Hg N=972 (324/group)	6 months (2 weeks→24 weeks) • TAK-491 20→40 mg • TAK-491 20→80 mg • Valsartan 80→320 mg	24-hr mean SBP by ABPM (clinic SBP)
TAK-491 vs ramipril 491-020 (Europe, Russia)	Clinic SBP 150-180 mm Hg N=890 (270/group)	6 months (2 weeks→24 weeks) • TAK-491 20→40 mg • TAK-491 20→80 mg • Ramipril 2.5→10 mg	Clinic SBP (N/A)

ABPM=ambulatory blood pressure monitoring, Lat Am=Latin America, N/A=not applicable, OLM-M=olmesartan medoxomil, US=United States.

(a) All study drugs were administered once daily.

The subject disposition for the four studies making up the active controlled pool is shown below.

Table 1.3.2
Primary Reasons for Which Subjects Prematurely Discontinued Study Drug
in Phase 3 Randomized Active-Controlled Studies

	TAK-491 40 mg (N = 1182)	TAK-491 80 mg (N = 1189)	TAK-491 40/80 mg (N = 2371)	Comparator (N= 1468)
Number of Subjects Prematurely Discontinued	150 (12.7%)	160 (13.5%)	310 (13.1%)	179 (12.2%)
Primary Reason for Premature Discontinuation				
Adverse Event	38 (3.2%)	50 (4.2%)	88 (3.7%)	49 (3.3%)
Protocol Deviation	10 (0.8%)	5 (0.4%)	15 (0.6%)	6 (0.4%)
Lost to Follow-up	17 (1.4%)	19 (1.6%)	36 (1.5%)	20 (1.4%)
Voluntary Withdrawal	45 (3.8%)	53 (4.5%)	98 (4.1%)	48 (3.3%)
Study Termination	0	0	0	0
Pregnancy	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Lack of Efficacy	27 (2.3%)	16 (1.3%)	43 (1.8%)	41 (2.8%)
Investigator Discretion	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Other	11 (0.9%)	16 (1.3%)	27 (1.1%)	13 (0.9%)

Compared to the lower dose TAK-491 group and the comparator group, a higher percentage of subjects randomized to TAK-491 80 mg discontinued prematurely because of an adverse event or had voluntarily withdrawn from the study. The differences in incidence rates among the treatment groups for withdrawal, however, were not large.

Selected demographics for the subjects in the active controlled trials are shown below.

Table 1.i Demographic and Baseline Characteristics: Phase 3 Active-Controlled Pool

Characteristic	Comparator (a) (N=1468)	TAK-491 40 mg (N=1182)	TAK-491 80 mg (N=1189)	TAK-491 Total (b) (N=2371)
Number (%) of Subjects (except where noted)				
Age (yrs), mean (SD)	57.0 (11.03)	57.2 (11.27)	56.9 (11.17)	57.1 (11.22)
65-<75 years	305 (20.8)	266 (22.5)	251 (21.1)	517 (21.8)
≥75 years	71 (4.8)	61 (5.2)	61 (5.1)	122 (5.1)
American Indian/Alaskan Native	140 (9.5)	109 (9.2)	100 (8.4)	209 (8.8)
Black/African American	181 (12.3)	130 (11.0)	125 (10.5)	255 (10.8)
White	1111 (75.7)	905 (76.6)	934 (78.6)	1839 (77.6)
BMI, mean (SD)	30.55 (5.409)	30.65 (5.661)	30.24 (5.358)	30.45 (5.514)
SBP (mm Hg), mean (SD)	158.5 (12.26)	158.7 (12.09)	158.7 (11.39)	158.7 (11.74)
DBP (mm Hg), mean (SD)	92.4 (10.23)	92.6 (10.72)	92.8 (10.19)	92.7 (10.45)
SBP <140 mm Hg	96 (6.5)	75 (6.3)	59 (5.0)	134 (5.7)
SBP 140-<160 mm Hg	686 (46.7)	568 (48.1)	581 (48.9)	1149 (48.5)
SBP 160-<180 mm Hg	637 (43.4)	499 (42.2)	518 (43.6)	1017 (42.9)
SBP ≥180 mm Hg	49 (3.3)	40 (3.4)	31 (2.6)	71 (3.0)
eGFR (mL/min/1.73 m ²), mean (SD)	86.8 (19.62)	85.7 (18.84)	86.5 (19.95)	86.1 (19.41)
eGFR ≥90 mL/min/1.73 m ²	595 (40.5)	481 (40.7)	483 (40.6)	964 (40.7)
eGFR 60-<90 mL/min/1.73 m ²	795 (54.2)	624 (52.8)	640 (53.8)	1264 (53.3)
eGFR 30-<60 mL/min/1.73 m ²	78 (5.3)	76 (6.4)	64 (5.4)	140 (5.9)
eGFR <30 mL/min/1.73 m ²	0	1 (<0.1)	2 (0.2)	3 (0.1)

Source: ISS Table 1.3.3.

Study pool included 491- 008, 019, 020, and 301(DB).

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Demographic and baseline characteristics were fairly well balanced in all categories. The mean age was around 57 years and the subjects were mostly white.

Approximately half of subjects had a BMI ≥30 and less than a quarter of subjects were current smokers. The majority of subjects had no history of cardiovascular disease (recent history of major cardiovascular events was an exclusion criterion) or diabetes, and reported no use of lipid-modifying or diabetes medications.

Most subjects had normal renal function or mild renal impairment at baseline and the majority of subjects had baseline clinic SBP of 140 to <180 mm Hg. Less than 4% of subjects in any dose group had SBP ≥180 mm Hg.

The open label pool

The open label pool of three studies is shown below.

Table 1.d Study Design Summary: Phase 3 Open-Label Pool

Study Design and Study Number (Regions)	Study Entry Criteria Planned Sample Size	Treatment Duration and Dose/Regimen (a)	Endpoints
Open-label safety study with reversal phase			
491-016 (US, Lat Am)	<i>Open-label phase</i> • Uncontrolled • Forced-titration • Treat-to-target BP	26 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)
	<i>Reversal phase</i> • Double-blind • Randomized • Placebo-controlled	6 weeks • Continue current dose of TAK-491; maintain stable dose(s) of background BP medication including CLD • Substitute placebo for TAK-491; maintain stable dose(s) of background BP medication including CLD	Clinic BP (automated) Safety measures
Open-label safety study with 2 cohorts			
491-006 (b,c) (US, Lat Am)	<i>Cohort 1</i> • Uncontrolled • Forced-titration • Treat-to-target BP	56 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated and manual)
	<i>Cohort 2</i> • Uncontrolled • Forced-titration • Treat-to-target BP	56 weeks Step 1: TAK-491 40→80 mg (same as Cohort 1) Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated and manual)
Open-label extension of a randomized, double-blind, controlled study			
491-301(OL) (c) (US, Lat Am)	Subjects who completed double-blind phase (see Table 1.c) N=170 • Uncontrolled • Treat-to-target BP	28 weeks Step 1: TAK-491 40 mg Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)

BP=blood pressure, CLD=chlorthalidone, Lat Am=Latin America, US=United States.

(a) All study drugs were administered once daily.

(b) Ongoing; Cohort 1 is complete; enrollment of Cohort 2 was initiated after enrollment of Cohort 1 was completed.

(c) Ongoing; interim data cut occurred on 30 October 2009 and SAE data cut occurred on 03 February 2010.

Phase 1 pool

The Phase 1 Pool integrates data from 15 studies (491- 001, 002, 003, 004, 007, 012, 013, 015, 017, 101, 102, 103, 104, 107, and 110).

7.1.1 Deaths

As of February 3, 2010, a total of 9 fatal serious adverse events were reported during the 64 studies investigating the use of TAK-491. Details regarding these deaths are shown in the table below.

Table 2.d Summary of Fatal SAEs

Treatment (a)	Study/Site-Subject No.	Sex, Age (yrs)	Exposure Days (b)	Days Postdose (c)	Preferred Term (d)
Placebo					
Placebo	536-CCT-005/0019-026	Female, 34	12	0	Cardiac failure
Placebo+ pioglitazone 15 mg	536OPI-525/10182	Female, 65	42	0	Haemorrhagic stroke
Placebo+ CLD 25 mg	491-009/7090-008	Female, 62	9	9	Cardiogenic shock
TAK-491					
TAK-491 20 mg	491-008/6021-004	Male, 58	31	2	Gastrointestinal haemorrhage and shock
TAK-491 40 mg	491-301/1061-043	Male, 37	88	9	Arteriosclerosis and hypertensive cardiovascular disease
TAK-491 80 mg	491-006/1026-016	Male, 46	190	21	Completed suicide
TAK-536					
TAK-536 5 mg+ pioglitazone 45 mg	536OPI-525/10033	Female, 64	36	0	Sudden cardiac death
Comparator					
Olmesartan medoxomil 20 mg	491-005/5083-003	Male, 51	26	0	Cardiac arrest and hypertensive heart disease
Valsartan 320 mg	491-301/1030-001	Male, 61	58	0	Arteriosclerosis

Source: Primary (ie, CSRs).

CLD=chlorthalidone.

(a) Dose at time of death or last dose before death if the subject withdrew from the study earlier.

(b) Number of days on study drug at time of death or time of premature discontinuation from study.

(c) Number of days after the last dose of study drug that death occurred (0=death occurred same day as last dose).

(d) Medical Dictionary for Regulatory Activities (MedDRA) versions varied (536OPI-525 used 7.0, 491-005 used 9.0, and 491-006, 491-008, 491-009, and 491-301 used 12.0). MedDRA version is undecided for ongoing study 536-CCT-005.

Of the nine reports of death, three subjects had been randomized to TAK-491 and one had been randomized to TAK-536. These subjects are discussed below.

-Subject 491-008/6021-004 (TAK-491 20 mg) was a 58-year-old, white male with a history of anemia, peptic ulcer, and alcoholism, who experienced gastrointestinal hemorrhage and shock. On Study Day 31, the subject was admitted to the ICU with nausea, vomiting blood, and feeling weak, and study drug was stopped. Medical history on hospital admission revealed liver cirrhosis, ethanol abuse (for 20 years, denied at screening), hepatitis C (not reported at screening), anemia, peptic ulcer disease, and a gastrointestinal bleed the previous year. Bleeding could not be stopped and the subject was pronounced dead two days later.

-Subject 491-301/1061-043 (TAK-491 40 mg) was a 37-year-old black male with a medical history of alcohol abuse, pancreatitis, hypothyroidism, hypercholesterolemia, type 2 diabetes mellitus, and chronic renal failure. He apparently experienced an unwitnessed sudden death around 9 days after the last known dose of study drug. The cause of death as determined by autopsy was hypertensive cardiovascular disease and arteriosclerotic cardiovascular disease. Toxicology was positive for alcohol and quetiapine.

-Subject 491-006/1026-016 (TAK-491 80 mg) was a 47-year-old white male with no known relevant medical history who committed suicide on study day 211. The subject presented to his primary care physician with irritability, insomnia, feelings of worthlessness, and impaired concentration several weeks prior to the fatal event. He was diagnosed with major depressive disorder, prescribed duloxetine hydrochloride and clonazepam for anxiety and advised to withdraw from the study.

-Subject 536OPI-525/10033 (TAK-536 5 mg and pioglitazone 45 mg) was a 64-year-old white female with a history of type 2 diabetes mellitus, polio, cerebral vascular accident, and hyperlipidemia. The subject received pioglitazone 15 mg for 7 days during screening and pioglitazone 45 mg with TAK-536 5 mg for 28 days. On study day 36, the subject was seen for a routine clinic visit. She was without complaints and her examination was unremarkable. She was found dead the evening of that day. No autopsy was performed.

All four deaths appear to be unremarkable.

7.1.2. Serious adverse events

Phase 3 placebo-controlled pool

The table shows the total number of subjects reporting at least one serious adverse event in these studies.

Table 2.f SAE Summary (≥2 Subjects in Any Group by HLT): Phase 3 Placebo-Controlled Pool

HLT Preferred Term	Number (%) of Subjects			
	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	T I (N)
Overall (any SAE)	7 (0.9)	9 (0.8)	10 (0.9)	1
Pain and discomfort NEC	2 (0.2)	1 (<0.1)	0	
Chest discomfort	0	1 (<0.1)	0	
Chest pain	2 (0.2)	0	0	
Urinary tract infections	0	0	2 (0.2)	
Urinary tract infection	0	0	2 (0.2)	
Central nervous system haemorrhages and cerebrovascular accidents	0	1 (<0.1)	1 (<0.1)	
Cerebral haemorrhage	0	1 (<0.1)	0	
Lacunar infarction	0	0	1 (<0.1)	
Disturbances in consciousness NEC	0	2 (0.2)	1 (<0.1)	
Syncope	0	2 (0.2)	1 (<0.1)	

Source: ISS Table 2.2.11.1.

Study pool included monotherapy (491- 008, 011, and 019) and coadministration (491- 009 and 010) studies. Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone. Events sorted by SOC.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The rate of subjects reporting a serious adverse event was about 10% regardless of treatment group. There is no reported serious adverse event, other than probably syncope, that is obviously linked to the use of TAK-491.

Phase 3 active-controlled pool

The table shows the total number of subjects reporting at least one serious adverse event in these studies.

Table 2.g SAE Summary (≥2 Subjects in Any Group by HLT): Phase 3 Active-Controlled Pool

HLT Preferred Term	Number (%) of Subjects			Total (N=1189)
	Comparator (a) (N=1468)	TAK-491 40 mg (N=1182)	TAK-491 80 mg (N=1189)	
Overall (any SAE)	23 (1.6)	18 (1.5)	21 (1.8)	3
Ischaemic coronary artery disorders	2 (0.1)	0	3 (0.3)	
Acute coronary syndrome	1 (<0.1)	0	0	
Angina pectoris	0	0	1 (<0.1)	
Myocardial infarction	0	0	1 (<0.1)	
Silent myocardial infarction	1 (<0.1)	0	1 (<0.1)	
Supraventricular arrhythmias	0	1 (<0.1)	1 (<0.1)	
Atrial fibrillation	0	1 (<0.1)	1 (<0.1)	
Cholecystitis and cholelithiasis	1 (<0.1)	2 (0.2)	0	
Cholecystitis	0	1 (<0.1)	0	
Cholecystitis acute	0	1 (<0.1)	0	
Cholecystitis chronic	1 (<0.1)	0	0	
Cholelithiasis	0	1 (<0.1)	0	
Abdominal and gastrointestinal infections	1 (<0.1)	1 (<0.1)	1 (<0.1)	
Appendicitis	1 (<0.1)	1 (<0.1)	0	
Diverticulitis	0	0	1 (<0.1)	
Hepatitis viral infections	1 (<0.1)	2 (0.2)	0	
Hepatitis A	0	1 (<0.1)	0	
Hepatitis C	1 (<0.1)	1 (<0.1)	0	
Non-site specific injuries NEC	3 (0.2)	0	1 (<0.1)	
Fall	3 (0.2)	0	0	
Road traffic accident	0	0	1 (<0.1)	
Central nervous system haemorrhages and cerebrovascular accidents	0	0	2 (0.2)	
Cerebral ischaemia	0	0	1 (<0.1)	
Ischaemic stroke	0	0	1 (<0.1)	
Seizures and seizure disorders NEC	2 (0.1)	0	0	
Epilepsy	1 (<0.1)	0	0	
Partial seizures	1 (<0.1)	0	0	

Source: ISS Table 2.3.11.1.

Study pool included 491-008, 019, 020, and 301(DB).

Events sorted by SOC.

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The reporting rates of serious adverse events were low in all treatment groups (2%).

Phase 3 open-label pool

The incidence rate of reporting serious adverse events in the open label trials was 4.9%. The most frequently reported events included chest pain (4 subjects, 0.3%), syncope and hypotension (3 subjects, 0.2%, each).

Phase 1 pool

No serious adverse event was reported in any study comprising this pool of studies.

Unpooled studies

There were 17 serious adverse events reported by 13 subjects enrolled in one of the two 8-week phase dose-ranging studies (491-005 and 536-002). There was one reported death (olmesartan medoxomil).

There were six subjects (5 TAK-536 subjects and 1 candesartan subject) reporting serious adverse events in the 12-week phase dose-ranging study (536-CCT-001). The events reported by the TAK-536- subjects were fall, road traffic accident, rectal cancer, gastric ulcer hemorrhage, and chest pain.

Enrollment is continuing in the TAK-536 phase 3 Japanese studies (536- CCT-005, OCT-006, OCT-003, and OCT-002). A total of nine serious adverse events have been reported as of February 3, 2010. These include death resulting from cardiac failure (placebo), road traffic accident, fall, cerebral infarction, and duodenal ulcer (all placebo). The remaining four were in TAK-536- or candesartan cilexetil groups (treatment remains blinded) and include foot fracture resulting from a fall, concussion resulting from a traffic accident, intervertebral disc protrusion aggravated condition, and basal cell carcinoma.

There were two serious adverse events reported in the other 8-week phase 2 studies (536-GHBA-590 and 536-GHBA-774). These included cerebrovascular accident (placebo) and atrial fibrillation (TAK-536 0.5 mg).

There were two serious adverse events reported in the open-label study 536-CPH-005. These included headache/blood pressure increased and ECG ST segment depression.

No serious adverse events were reported in any of the 18 TAK-536 phase 1 studies (536- 004, 005, 006, 007, 008, 009, 010, 011, 014, 016, 316, 317, 661, CPH-001, CPH-002, CPH-009, EC101, and GHBA-328) or in the TAK-491 Japanese phase 1 studies (491-CPH-001 and 491-CPH-005).

There were two SAEs were reported (scrotal abscess and infective cholecystitis) in the TAK-536/pioglitazone study 536OPI-003. There were no SAEs in study 536OPI-005.

There were two deaths reported in study 536OPI-525 (sudden cardiac death, TAK-536 5 mg+pioglitazone 45 mg, and hemorrhagic stroke, placebo+pioglitazone 15 mg). Twenty-four subjects reported serious adverse events.

The seven phase 1 fixed dose combination (FDC) studies (491CCB-101; 491CLD- 102, 103, 104, and 105; and 536OPI- 001 and 002) had no reported serious adverse events.

7.1.3 Discontinuations for adverse events

Phase 3 Placebo-Controlled Pool

The table below shows the number and percent of subjects who withdrew from a clinical trial because of an adverse event by treatment group. (The adverse events shown below are those that were reported by at least 2 subjects in any group.)

Table 2.h Study Drug Interruption or Premature Discontinuation TEAE Summary by HLT (≥ 2 Subjects in Any Group): Phase 3 Placebo-Controlled Pool

HLT	Number (%) of Subjects			
	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	TAK-491 Total (a) (N=2146)
Overall (any discontinuation TEAE)	19 (2.4)	25 (2.3)	26 (2.4)	51 (2.4)
Cardiac signs and symptoms NEC	2 (0.2)	1 (<0.1)	0	1 (<0.1)
Nausea and vomiting symptoms	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Asthenic conditions	0	1 (<0.1)	2 (0.2)	3 (0.1)
Oedema NEC	2 (0.2)	1 (<0.1)	0	1 (<0.1)
Abdominal and gastrointestinal infections	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Liver function analyses	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)
Renal function analyses	0	0	2 (0.2)	2 (<0.1)
Headaches NEC	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)
Neurological signs and symptoms NEC	1 (0.1)	4 (0.4)	3 (0.3)	7 (0.3)
Ovarian and fallopian tube cysts and neoplasms	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Accelerated and malignant hypertension	0	1 (<0.1)	2 (0.2)	3 (0.1)
Vascular hypertensive disorders NEC	3 (0.4)	2 (0.2)	0	2 (<0.1)
Vascular hypotensive disorders	0	4 (0.4)	4 (0.4)	8 (0.4)

Source: ISS Table 2.2.9.1.

Study pool included monotherapy (491- 008, 011, and 019) and coadministration (491- 009 and 010) studies.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

ALT=alanine aminotransferase, GGT= γ -glutamyl-transferase.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The incidence rates of subjects discontinued prematurely (temporarily or permanently) from study drug because of an adverse event were similar across the treatment groups (approximately 2.4%).

Table 2.p Study Drug Interruption or Premature Discontinuation TEAE Summary by HLT (≥2 Subjects in Any Group): Phase 3 Placebo-Controlled Pool

HLT Preferred Term	Number (%) of Subjects			
	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	TAK-491 Total (a) (N=2146)
Overall (any discontinuation TEAE)	19 (2.4)	25 (2.3)	26 (2.4)	51 (2.4)
Cardiac signs and symptoms NEC	2 (0.2)	1 (<0.1)	0	1 (<0.1)
Palpitations	2 (0.2)	1 (<0.1)	0	1 (<0.1)
Nausea and vomiting symptoms	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Nausea	0	1 (<0.1)	0	1 (<0.1)
Vomiting	0	0	1 (<0.1)	1 (<0.1)
Asthenic conditions	0	1 (<0.1)	2 (0.2)	3 (0.1)
Asthenia	0	0	2 (0.2)	2 (<0.1)
Fatigue	0	1 (<0.1)	0	1 (<0.1)
Oedema NEC	2 (0.2)	1 (<0.1)	0	1 (<0.1)
Oedema	1 (0.1)	0	0	0
Oedema peripheral	1 (0.1)	1 (<0.1)	0	1 (<0.1)
Abdominal and gastrointestinal infections	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Diverticulitis	0	0	1 (<0.1)	1 (<0.1)
Gastroenteritis	0	1 (<0.1)	0	1 (<0.1)
Liver function analyses	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)
ALT increased	1 (0.1)	0	0	0
GGT increased	1 (0.1)	0	0	0
Hepatic enzyme increased	0	2 (0.2)	1 (<0.1)	3 (0.1)
Transaminases increased	0	0	1 (<0.1)	1 (<0.1)
Renal function analyses	0	0	2 (0.2)	2 (<0.1)
Blood creatinine increased	0	0	2 (0.2)	2 (<0.1)
Headaches NEC	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)
Headache	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)
Neurological signs and symptoms NEC	1 (0.1)	4 (0.4)	3 (0.3)	7 (0.3)
Dizziness	1 (0.1)	4 (0.4)	3 (0.3)	7 (0.3)
Ovarian and fallopian tube cysts and neoplasms	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Ovarian cyst torsion	0	0	1 (<0.1)	1 (<0.1)
Polycystic ovaries	0	1 (<0.1)	0	1 (<0.1)
Accelerated and malignant hypertension	0	1 (<0.1)	2 (0.2)	3 (0.1)
Hypertensive crisis	0	1 (<0.1)	2 (0.2)	3 (0.1)
Vascular hypertensive disorders NEC	3 (0.4)	2 (0.2)	0	2 (<0.1)
Hypertension	3 (0.4)	2 (0.2)	0	2 (<0.1)
Vascular hypotensive disorders	0	4 (0.4)	4 (0.4)	8 (0.4)
Hypotension	0	3 (0.3)	4 (0.4)	7 (0.3)
Orthostatic hypotension	0	1 (<0.1)	0	1 (<0.1)

Source: Table 2.2.9.1.

Study pool included monotherapy (491- 008, 011, and 019) and coadministration (491- 009 and 010) studies.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

Events sorted by SOC.

ALT=alanine aminotransferase, GGT=γ-glutamyl-transferase.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Overall, the most frequently reported adverse events leading to discontinuation by subjects randomized to TAK- 491 40 mg plus 80 mg were dizziness (0.3% vs. 0.1% placebo) and hypotension (0.3% vs. 0 placebo). There was little difference in reporting rates between the 40 mg and 80 mg doses.

Adverse events of note leading to study discontinuation only by subjects randomized to TAK- 491 80 mg include hypertensive crisis (3) asthenia (2) and blood creatinine increased (2).

Phase 3 Active-Controlled Pool

The table below shows the number and percent of subjects who reported temporary or permanent drug discontinuations because of an adverse event by treatment group (reported by at least 2 subjects in one or more groups).

Table 2.q Study Drug Interruption or Premature Discontinuation TEAE Summary by HLT (≥ 2 Subjects in Any Group): Phase 3 Active-Controlled Pool

HLT Preferred Term	Number (%) of Subjects			TAK-491 Total (b) (N=2371)
	Comparator (a) (N=1468)	TAK-491 40 mg (N=1182)	TAK-491 80 mg (N=1189)	
Overall (any discontinuation TEAE)	51 (3.5)	40 (3.4)	50 (4.2)	90 (3.8)
Cardiac signs and symptoms NEC	0	2 (0.2)	0	2 (<0.1)
Palpitations	0	2 (0.2)	0	2 (<0.1)
Ischaemic coronary artery disorders	1 (<0.1)	0	3 (0.3)	3 (0.1)
Acute coronary syndrome	1 (<0.1)	0	0	0
Angina pectoris	0	0	1 (<0.1)	1 (<0.1)
Myocardial infarction	0	0	1 (<0.1)	1 (<0.1)
Silent myocardial infarction	0	0	1 (<0.1)	1 (<0.1)
Diarrhoea (excl infective)	2 (0.1)	0	2 (0.2)	2 (<0.1)
Diarrhoea	2 (0.1)	0	2 (0.2)	2 (<0.1)
Gastrointestinal and abdominal pains (excl oral and throat)	2 (0.1)	0	0	0
Abdominal pain	1 (<0.1)	0	0	0
Abdominal pain upper	1 (<0.1)	0	0	0
Nausea and vomiting symptoms	0	2 (0.2)	1 (<0.1)	3 (0.1)
Nausea	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Vomiting	0	1 (<0.1)	0	1 (<0.1)
Non-site specific gastrointestinal haemorrhages	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Gastrointestinal haemorrhage	0	0	1 (<0.1)	1 (<0.1)
Haematochezia	0	1 (<0.1)	0	1 (<0.1)
Asthenic conditions	4 (0.3)	2 (0.2)	1 (<0.1)	3 (0.1)
Asthenia	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Fatigue	3 (0.2)	2 (0.2)	0	2 (<0.1)
Oedema NEC	3 (0.2)	0	0	0
Oedema peripheral	3 (0.2)	0	0	0
Pain and discomfort NEC	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Chest discomfort	0	1 (<0.1)	0	1 (<0.1)
Chest pain	0	0	1 (<0.1)	1 (<0.1)
Liver function analyses	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
ALT increased	1 (<0.1)	0	0	0
Hepatic enzyme increased	0	1 (<0.1)	0	1 (<0.1)
Transaminases increased	0	0	1 (<0.1)	1 (<0.1)
Vascular tests NEC (incl blood pressure)	2 (0.1)	2 (0.2)	0	2 (<0.1)
Blood pressure increased	2 (0.1)	2 (0.2)	0	2 (<0.1)
Disturbances in consciousness NEC	3 (0.2)	0	1 (<0.1)	1 (<0.1)
Lethargy	2 (0.1)	0	0	0
Syncope	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Headaches NEC	7 (0.5)	4 (0.3)	6 (0.5)	10 (0.4)
Headache	7 (0.5)	4 (0.3)	6 (0.5)	10 (0.4)

Neurological signs and symptoms	2 (0.1)	6 (0.5)	8 (0.7)	14 (0.6)
NEC				
Dizziness	2 (0.1)	6 (0.5)	6 (0.5)	12 (0.5)
Dizziness postural	0	0	2 (0.2)	2 (<0.1)
Seizures and seizure disorders NEC	2 (0.1)	0	0	0
Epilepsy	1 (<0.1)	0	0	0
Partial seizures	1 (<0.1)	0	0	0
Coughing and associated symptoms	4 (0.3)	0	0	0
Cough	4 (0.3)	0	0	0
Dermatitis and eczema	1 (<0.1)	0	2 (0.2)	2 (<0.1)
Dermatitis	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Dermatitis allergic	0	0	1 (<0.1)	1 (<0.1)
Pruritus NEC	0	0	2 (0.2)	2 (<0.1)
Pruritus	0	0	1 (<0.1)	1 (<0.1)
Pruritus generalized	0	0	1 (<0.1)	1 (<0.1)
Urticarias	2 (0.1)	0	0	0
Urticaria	2 (0.1)	0	0	0
Accelerated and malignant hypertension	0	0	2 (0.2)	2 (<0.1)
Hypertensive crisis	0	0	2 (0.2)	2 (<0.1)
Vascular hypertensive disorders	3 (0.2)	4 (0.3)	3 (0.3)	7 (0.3)
NEC				
Hypertension	3 (0.2)	4 (0.3)	3 (0.3)	7 (0.3)
Vascular hypotensive disorders NEC	3 (0.2)	2 (0.2)	9 (0.8)	11 (0.5)
Hypotension	3 (0.2)	2 (0.2)	9 (0.8)	11 (0.5)

Source: Table 2.3.9.1.

Study pool included 491-008, 019, 020, and 301(DB).

Events sorted by SOC.

ALT=alanine aminotransferase, excl=excluding, incl=including.

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The incidence of adverse events leading to study drug interruption or premature discontinuation was higher in the TAK-491 80 mg group compared with the other groups.

The adverse events of note leading to discontinuation or study interruptions that were reported more often in the TAK-491 group included dizziness (0.5% for both TAK-491 doses vs. 0.1% for the comparators), hypotension (0.8% for the TAK-491 80 mg dose vs. 0.2% for the lower dose of TAK-491 and comparators), and hypertensive crisis (0.2% for TAK-491 80 mg vs. 0% for the other 2 groups).

Phase 3 Open-Label Pool

The overall incidence of adverse events that led to study drug interruption or premature discontinuation was 8.7% with dizziness (1.6%), fatigue (1.4%), headache (0.9%), and hypotension (0.7%) being the most commonly reported.

Phase 1 Pool

Two adverse events leading to prematurely discontinuation in the Phase 1 pool included conjunctivitis and headache (reported by one subject each).

Unpooled Studies

There was a study discontinuation because of headache with blood pressure increased (study 536-CPH-005).

In the phase 3 study 536OPI-003, adverse events that led to premature discontinuation included hyperglycaemia and blood glucose increased, dizziness and erectile dysfunction, tremor, and heart rate increased.

7.1.5 Common adverse events

The sponsor stated that the common adverse events (referred to as treatment emergent adverse event, TEAE) presented in this section occurred after the first dose of study drug and within 30 days of the last dose of study drug, unless otherwise noted.

The most common TEAEs were defined as those reported by $\geq 5\%$ of subjects in any group and other common TEAEs were defined as those reported by $\geq 2\%$ of subjects in any group, regardless of investigators' opinion on causality.

Placebo controlled pool

The table below displays the adverse events reported by at least 2% in any treatment group in this pool.

Table 2.2.4.1
Most Frequently Reported Treatment-Emergent Adverse Events by PT
in Phase 3 Randomized Placebo-Controlled Studies

MedDRA Preferred Term	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)
HEADACHE	50 (6.2%)	52 (4.9%)	56 (5.2%)
DIZZINESS	19 (2.4%)	39 (3.6%)	42 (3.9%)
DYSLIPIDAEMIA	17 (2.1%)	35 (3.3%)	35 (3.3%)
URINARY TRACT INFECTION	18 (2.2%)	24 (2.2%)	29 (2.7%)
PLASMINOGEN ACTIVATOR INHIBITOR INCREASED	15 (1.9%)	27 (2.5%)	22 (2.0%)
DIARRHOEA	4 (0.5%)	21 (2.0%)	23 (2.1%)
NASOPHARYNGITIS	12 (1.5%)	15 (1.4%)	23 (2.1%)
OEDEMA PERIPHERAL	17 (2.1%)	20 (1.9%)	17 (1.6%)

Studies included: 491-008, 491-009, 491-010, 491-011 and 491-019.
Adverse events summarized were reported after the first dose of study drug and within 30 days after the last dose of study drug.
Subjects with one or more adverse events within a level of the MedDRA term are counted only once in that level.
Most frequent events are those Preferred Terms occurring in at least 2% (prior to rounding) of subjects in any treatment group.
Preferred Terms are sorted in descending order based on incidence in any treatment group.

The placebo subtracted rates for the most commonly events reported by the TAK-491 subjects are shown below.

Percents-placebo subtracted

	TAK-491 40 mg N=1072	TAK-491 80 mg N=1074
Diarrhea	1.5	1.6
Dizziness	1.2	1.5
Dyslipidemia	1.2	1.2
Plasminogen activator inhibitor increased	<1	<1

Overall, the adverse event reporting by TAK-491 subjects was uncommon and not greatly different from the reporting by placebo subjects.

Common adverse events in study 005 (placebo controlled, dose response TAK-491 5 mg to 80 mg).

Table 12.c Treatment-Emergent AEs Presented by Preferred Term with Incidence of at Least 5 Subjects Total Among All Treatment Groups – Safety Set

Preferred Term	Placebo N=63	TAK-491 5 mg N=65	TAK-491 10 mg N=64	TAK-491 20 mg N=64	TAK-491 40 mg N=62	TAK-491 80 mg N=64	Olmesartan 20 mg N=63
Headache	3 (4.8)	2 (3.1)	2 (3.1)	7 (10.9)	3 (4.8)	3 (4.7)	5 (7.9)
Nasopharyngitis	4 (6.3)	0	3 (4.7)	3 (4.7)	1 (1.6)	3 (4.7)	1 (1.6)
Dizziness	2 (3.2)	1 (1.5)	3 (4.7)	4 (6.3)	2 (3.2)	1 (1.6)	1 (1.6)
Diarrhea	1 (1.6)	1 (1.5)	1 (1.6)	2 (3.1)	2 (3.2)	2 (3.1)	1 (1.6)
Dyslipidemia	1 (1.6)	2 (3.1)	1 (1.6)	1 (1.6)	1 (1.6)	0	0
Fatigue	0	0	2 (3.1)	0	2 (3.2)	1 (1.6)	1 (1.6)
Upper respiratory tract infection	0	4 (6.2)	0	0	2 (3.2)	0	0
Cough	1 (1.6)	1 (1.5)	0	1 (1.6)	1 (1.6)	1 (1.6)	0
Vomiting	0	0	2 (3.1)	0	1 (1.6)	1 (1.6)	1 (1.6)

Source: [Table 15.3.1.3](#).

Note: Data represent number (percentage) of subjects.

None of these adverse events appears to be dose related.

Adverse events reported by at least 1% of subjects and with higher rates in both the TAK-491 dose groups compared to placebo in the placebo controlled monotherapy studies are shown below.

Percent of subjects

	Placebo N=435	TAK 40 mg N=698	TAK-80 mg N=704
Dyslipidemia	1.4	2.7	3.3
Dizziness	2.1	2.9	3.0
Diarrhea	0.5	1.6	2.4

Edema	0.9	1.7	1.7
Fatigue	0.5	0.9	1.4

Table 8.6 sent 10-18-2010

The rates are fairly low for all dose groups.

Active controlled pool

A summary of adverse events reported by at least 2% of subjects in any group is shown below.

Table 2.c Common TEAEs (≥2% Incidence in Any Group): Phase 3 Active-Controlled Pool

Preferred Term	Number (%) of Subjects			
	Comparator (a) (N=1468)	TAK-491 40 mg (N=1182)	TAK-491 80 mg (N=1189)	TAK-491 Total (b) (N=2371)
Overall (any TEAE)	695 (47.3)	560 (47.4)	605 (50.9)	1165 (49.1)
Headache	95 (6.5)	71 (6.0)	67 (5.6)	138 (5.8)
Dizziness	43 (2.9)	51 (4.3)	54 (4.5)*	105 (4.4)
Urinary tract infection	34 (2.3)	42 (3.6)	41 (3.4)	83 (3.5)
Nasopharyngitis	49 (3.3)	39 (3.3)	34 (2.9)	73 (3.1)
Dyslipidaemia	32 (2.2)	23 (1.9)	31 (2.6)	54 (2.3)
Cough	38 (2.6)	9 (0.8)***	10 (0.8)***	19 (0.8)
Blood creatine phosphokinase increased	25 (1.7)	24 (2.0)	30 (2.5)	54 (2.3)
Back pain	23 (1.6)	19 (1.6)	27 (2.3)	46 (1.9)
Diarrhoea	21 (1.4)	20 (1.7)	27 (2.3)	47 (2.0)
Fatigue	33 (2.2)	22 (1.9)	19 (1.6)	41 (1.7)
Oedema peripheral	31 (2.1)	15 (1.3)	16 (1.3)	31 (1.3)

Source: ISS Tables 2.3.1 and 2.3.4.1.

Study pool included 491-008, 019, 020, and 301(DB).

*P≤0.05 vs comparator, ***P≤0.001 vs comparator (Fisher exact test).

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The reporting rates for dizziness, urinary tract infection and increased blood creatinine phosphokinase were higher for TAK-491 40 mg and 80 mg compared to the active comparators combined. There was more cough in the active comparator group (because of the inclusion of subjects taking ramipril).

The adverse events reported in the ARB comparison studies were also pooled. Events reported more often with TAK-491 compared with olmesartan medoxomil (studies 491-008 and 491-019) were dyslipidemia, diarrhea, and UTI. Events reported more often with TAK-491 compared with valsartan were diarrhea, dizziness, UTI, and fatigue in the short-term study (491-019) and headache, dizziness, UTI, fatigue, blood CK increased, back pain, pain in extremity, and bronchitis in the long-term study (491-301).

Phase 1 Pool

In the phase 1 pool, dizziness, headache, and nausea were the most commonly reported adverse events. Other commonly reported adverse events included oropharyngeal pain, diarrhea, fatigue, feeling hot, syncope, tremor, nasopharyngitis, and contact dermatitis.

Unpooled Studies

In study 536-002, nasopharyngitis was the most frequently reported adverse event.

In the 12-week phase 2 dose-ranging study (536-CCT-001), adverse event incidences were higher in all TAK-536 groups compared with placebo and candesartan cilexetil. Nasopharyngitis was the most frequently reported adverse event which was higher in TAK-536 treatment groups compared with the placebo and candesartan cilexetil groups.

In other 8-week phase 2 studies (536-GHBA-590 and 536-GHBA-774), TEAE incidences were 55.0% to 72.5% (536-GHBA-590) and 60.5% to 69.8% (536-GHBA-774). For each study, incidences were similar across treatment groups except for placebo (72.5%) compared with TAK-536 groups (55.0%-65.1%). Five subjects (22.7%) experienced at least 1 TEAE in the open-label study 536-CPH-005.

Adverse event reporting rates among the 18 TAK-536 phase 1 studies were variable, ranging from zero to 87.5% across treatment groups. The most frequently reported adverse events were headache and dizziness.

Adverse event reporting rates were zero to 33.3% and 20.0% to 40.0%, respectively, across treatment groups in the 491-CPH-001 and 491-CPH-005 studies. Postural dizziness was the only adverse event that was reported by at least 2 subjects in both studies.

In the TAK-536/pioglitazone phase 3 study 536OPI-003, adverse event reporting rates ranged from 51.5% to 56.3% and was similar across treatment groups. In 536OPI-005, adverse events reporting rates ranged from zero to 66.7%, with wide differences among groups. UTI was the most commonly reported adverse event in 536OPI-003. In 536OPI-005, only diarrhea and edema were reported by 2 subjects, though in different treatment groups. In the single phase 2 study (536OPI-525), dizziness and hypotension were the only frequently reported adverse events with incidences higher in TAK-536 groups compared with the placebo groups.

Adverse event reporting rates ranged from 4.2% to 41.7% across treatment groups among the 7 phase 1 FDC studies (491CCB-101; 491CLD- 102, 103, 104, and 105; and 536OPI- 001 and 002). The most frequently reported TEAEs were headache and dizziness.

Hypotension

The reporting rates of adverse events of hypotension or suggestive of hypotension in the Phase 3 study pools are shown below.

Table 2.j Hypotension Cluster: Phase 3 Controlled-Study Pools

Study Pool Preferred Term	Number (%) of Subjects			
	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	TAK-491 Total (N=2146)
Phase 3 Placebo-Controlled Pool (a)				
Overall (any cluster event)	23 (2.9)	49 (4.6)	52 (4.8)*	101 (4.7)
Cardiogenic shock	1 (0.1)	0	0	0
Dizziness	19 (2.4)	39 (3.6)	42 (3.9)	81 (3.8)
Dizziness postural	1 (0.1)	1 (<0.1)	0	1 (<0.1)
Hypotension	1 (0.1)	5 (0.5)	8 (0.7)	13 (0.6)
Orthostatic hypotension	2 (0.2)	3 (0.3)	1 (<0.1)	4 (0.2)
Syncope	0	2 (0.2)	3 (0.3)	5 (0.2)
Phase 3 Active-Controlled Pool (b)	Comparator (N=1468)	TAK-491 40 mg (N=1182)	TAK-491 80 mg (N=1189)	TAK-491 Total (N=2371)
Overall (any cluster event)	52 (3.5)	64 (5.4)*	74 (6.2)**	138 (5.8)
Dizziness	43 (2.9)	51 (4.3)	54 (4.5)	105 (4.4)
Dizziness postural	0	4 (0.3)	7 (0.6)	11 (0.5)
Hypotension	7 (0.5)	10 (0.8)	16 (1.3)	26 (1.1)
Orthostatic hypotension	0	1 (<0.1)	2 (0.2)	3 (0.1)
Presyncope	0	2 (0.2)	1 (<0.1)	3 (0.1)
Syncope	3 (0.2)	1 (<0.1)	3 (0.3)	4 (0.2)

Source: ISS Tables 2.2.14.6 and 2.3.14.6.

*P≤0.05 vs placebo or active comparator (Fisher exact test); **P<0.01 vs active comparator (Fisher exact test).

(a) Study pool included 491- 008, 009, 010, 011, and 019. Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone. TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

(b) Study pool included 491- 008, 019, 020, and 301(DB). Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril. TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Overall, more adverse events suggestive of hypotension were reported by subjects randomized to TAK-491 80 mg (4.8% and 6.2%) compared to subjects randomized to placebo (2.9%) or one of the comparator groups (3.5%). The subjects randomized to TAK-491 40 mg reported an adverse event suggestive of hypotension less often compared to subjects in the TAK-491 80 mg dose group. Syncope was reported by 0.3% of subjects in TAK-491 80 mg group compared to 0.2% in the TAK-491 40 mg group and 0% in the placebo group. The reporting rate of syncope in the comparator group was 0.2%, slightly less than that reported by TAK-491 80 mg (0.3%). The TAK-491 40 mg group had the lowest reporting rate (<1%). In addition, dizziness tended to be reported more often by the TAK-491 80 mg group compared to placebo or the comparators.

Renal events

N.B. The majority of renal adverse events were based on the investigator assessment of clinical significance and not all abnormalities were reported as adverse events. Further discussion regarding reported creatinine elevations is provided in chemistry laboratory evaluations.

Renal events reported by subjects in the phase 3 pools are shown below.

Table 2.k Renal Cluster: Phase 3 Controlled-Study Pools

Study Pool Preferred Term	Number (%) of Subjects			
	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	TAK-491 Total (N=2146)
Phase 3 Placebo-Controlled Pool (a)				
Overall (any cluster event)	3 (0.4)	14 (1.3)*	16 (1.5)*	30 (1.4)
Blood creatinine increased	1 (0.1)	10 (0.9)	12 (1.1)	22 (1.0)
Blood urea increased	0	5 (0.5)	3 (0.3)	8 (0.4)
Fluid retention	1 (0.1)	0	0	0
Glomerular filtration rate decreased	0	2 (0.2)	0	2 (<0.1)
Renal failure	0	1 (<0.1)	0	1 (<0.1)
Urine albumin/creatinine ratio abnormal	0	0	1 (<0.1)	1 (<0.1)
Urine albumin/creatinine ratio increased	1 (0.1)	3 (0.3)	1 (<0.1)	4 (0.2)
Phase 3 Active-Controlled Pool (b)	Comparator (N=1468)	TAK-491 40 mg (N=1182)	TAK-491 80 mg (N=1189)	TAK-491 Total (N=2371)
Overall (any cluster event)	12 (0.8)	12 (1.0)	17 (1.4)	29 (1.2)
Blood creatine increased	1 (<0.1)	0	0	0
Blood creatinine increased	1 (<0.1)	8 (0.7)	10 (0.8)	18 (0.8)
Blood urea increased	0	6 (0.5)	5 (0.4)	11 (0.5)
Fluid retention	1 (<0.1)	0	0	0
Glomerular filtration rate decreased	1 (<0.1)	3 (0.3)	4 (0.3)	7 (0.3)
Pyelonephritis acute	1 (<0.1)	0	0	0
Renal disorder	1 (<0.1)	0	0	0
Renal failure	0	0	1 (<0.1)	1 (<0.1)
Renal failure chronic	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Renal impairment	2 (0.1)	2 (0.2)	0	2 (<0.1)
Urine albumin/creatinine ratio increased	5 (0.3)	2 (0.2)	1 (<0.1)	3 (0.1)

Source: ISS Tables 2.2.14.4 and 2.3.14.4.

*P≤0.05 vs placebo (Fisher exact test).

(a) Study pool included 491-008, 009, 010, 011, and 019. Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone. TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

(b) Study pool included 491-008, 019, 020, and 301(DB). Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril. TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Overall, renal events were reported more often by subjects randomized to a TAK-491 group compared to subjects randomized to placebo or a comparative agent. In addition, TAK-491 80 mg had a higher reporting rate compared to the lower TAK-491 dose. The majority of reported events were increased serum creatinine, increased blood urea nitrogen (BUN), or decreased GFR, all with higher reporting rates in the TAK-491 groups (with and without diuretic co-administration).

The reporting rates of renal failure, renal failure chronic, and renal impairment as adverse events were low for all treatment groups.

The reporting rates for renal events from the placebo-controlled monotherapy studies (excluded co-administration of chlorthalidone and amlodipine) are shown below.

Table 2.1 Renal Cluster: Phase 3 Placebo-Controlled Monotherapy Studies Group

Preferred Term	Number (%) of Subjects			
	Placebo (N=435)	TAK-491 40 mg (N=698)	TAK-491 80 mg (N=704)	TAK-491 Total (a) (N=1402)
Overall (any cluster event)	2 (0.5)	5 (0.7)	4 (0.6)	9 (0.6)
Blood creatinine increased	1 (0.2)	4 (0.6)	3 (0.4)	7 (0.5)
Blood urea increased	0	4 (0.6)	1 (0.1)	5 (0.4)
Glomerular filtration rate decreased	0	1 (0.1)	0	1 (<0.1)
Urine albumin/creatinine ratio increased	1 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)

Source: ISS Table 2.5.3.

Studies included 491- 008, 011, and 019.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

These events were slightly higher in the TAK-491 groups compared to placebo with increased blood creatinine and increased blood urea increased being the most common. In this comparison, the doses of TAK-491 look similar.

Adverse events by subgroups

By gender: adverse events tended to be similar in frequency and type between male and female subjects. UTI was reported more frequently in female subjects in all treatment groups. Headache was reported more frequently in female subjects in all active treatments. Dizziness was reported more frequently for male subjects with TAK-491 80 mg and back pain was reported more often by female subjects with TAK-491 80 mg. Overall, there were no consistently significant differences between sexes in reporting adverse events.

By age: there were no differences in the incidence of the most frequent adverse events between the <65 years and ≥65 years subjects. Hypotension was not uncommonly reported but the differences between the ages was negligible.

There were few subjects 75 years or older.

Table 5.2.1.3.13
Overall Summary of Adverse Event Clusters by Age (< 75 vs ≥ 75)
in Phase 3 Randomized Placebo-Controlled Studies

	Placebo (N=801)		TAK-491 40 mg (N=1072)	
	<75 (years)	≥75 (years)	<75 (years)	≥75 (years)
Number of Subjects with Non-missing Factor	744	57	1024	48
Cardiovascular Adverse Events	1 (0.1%)	1 (1.8%)	2 (0.2%)	0
Custom Major Adverse Cardiovascular Events	1 (0.1%)	0	0	0
Hypertension Adverse Events	4 (0.5%)	0	5 (0.5%)	0
Renal Adverse Events	2 (0.3%)	1 (1.8%)	10 (1.0%)	4 (8.3%)
Hypersensitivity Adverse Events	0	1 (1.8%)	1 (<0.1%)	1 (2.1%)
Hypotension Adverse Events	21 (2.8%)	2 (3.5%)	46 (4.5%)	3 (6.3%)

	TAK-491 80 mg (N=1074)		TAK-491 40/80 mg (N=2146)	
	<75 (years)	≥75 (years)	<75 (years)	≥75 (years)
Number of Subjects with Non-missing Factor	1007	67	2031	115
Cardiovascular Adverse Events	3 (0.3%)	1 (1.5%)	5 (0.2%)	1 (0.9%)
Custom Major Adverse Cardiovascular Events	1 (<0.1%)	0	1 (<0.1%)	0
Hypertension Adverse Events	3 (0.3%)	2 (3.0%)	8 (0.4%)	2 (1.7%)
Renal Adverse Events	13 (1.3%)	3 (4.5%)	23 (1.1%)	7 (6.1%)
Hypersensitivity Adverse Events	2 (0.2%)	0	3 (0.1%)	1 (0.9%)
Hypotension Adverse Events	49 (4.9%)	3 (4.5%)	95 (4.7%)	6 (5.2%)

Hypertension and renal events were reported slightly more frequently with TAK-491 in the ≥75 years subgroup compared with the placebo group.

By race: study 491-011 evaluated the efficacy and safety of TAK-491 40 mg and 80 mg in more than 400 black subjects with essential hypertension. Headache was more common among subjects taking TAK-491 40 mg and 80 mg (4.4% and 6.6%, respectively) compared with placebo subjects (2.2%) and appeared to show a trend toward a dose response between the 2 TAK-491 doses. Additionally, dizziness and peripheral edema were more common in the TAK-491 40 mg and 80 mg treatment groups (2.9% and 2.2%, respectively) compared with placebo (0.7%).

In the Phase 3 Placebo-Controlled Pool, 27% of the subjects were black, 54% were white, and 19% were other. Only adverse events associated with hypotension showed a difference in reporting rates. These events were reported more by white subjects randomized to TAK-491 80 mg in the Phase 3 Placebo-Controlled Pool and with both TAK-491 40 mg and 80 mg in the Phase 3 Active-Controlled Pool.

Table 5.o Summary of TEAE Clusters by Race: Phase 3 Placebo-Controlled Pool

TEAE Clusters	Placebo (a) N=801 n (%)			TAK-491 40 mg N=1072 n (%)			TAK-491 80 mg N=1074 n (%)			TAK-491 Total (b) N=2146 n (%)		
	Black	White	All Other	Black	White	All Other	Black	White	All Other	Black	White	All Other
Number of subjects	237	400	163	276	594	202	272	595	207	548	1189	409
Cardiovascular	0*	0	2 (1.2)	1 (0.4)	0	1 (0.5)	0	3 (0.5)	1 (0.5)	1 (0.2)	3 (0.3)	2 (0.5)
MACE	0	0	1 (0.6)	0	0	0	0	0	1 (0.5)	0	0	1 (0.2)
Hypertension	1 (0.4)	2 (0.5)	1 (0.6)	1 (0.4)	2 (0.3)	2 (1.0)	1 (0.4)	2 (0.3)	2 (1.0)	2 (0.4)	4 (0.3)	4 (1.0)
Renal	0	2 (0.5)	1 (0.6)	3 (1.1)	8 (1.3)	3 (1.5)	0*	9 (1.5)	7 (3.4)	3 (0.5)	17 (1.4)	10 (2.4)
Hypersensitivity	0	0	1 (0.6)	0	2 (0.3)	0	1 (0.4)	0	1 (0.5)	1 (0.2)	2 (0.2)	1 (0.2)
Hypotension	3 (1.3)	14 (3.5)	6 (3.7)	8 (2.9)	35 (5.9)	6 (3.0)	9 (3.3)*	38 (6.4)	5 (2.4)	17 (3.1)	73 (6.1)	11 (2.7)

Source: Table 5.2.1.3.3.

Study pool included monotherapy (491-008, 011, and 019) and coadministration (491-009 and 010) studies.

* P≤0.05, ** P≤0.01 within treatment comparisons by race (Fisher exact test).

(a) Placebo group combines all subjects who received placebo alone, with amlodipine, or with chlorthalidone.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg alone, with amlodipine, or with chlorthalidone.

By hepatic function: there is no evidence that dose adjustment of TAK-491 is required for patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). Subjects with severe hepatic impairment (Child-Pugh score >9) were not evaluated.

By renal function: total exposure to TAK-536 was higher in subjects with renal impairment than in healthy subjects in the Phase 1 study 491-103, with increases of 30%, 25%, 96%, and 5% in subjects with mild, moderate, and severe renal impairment, and ESRD, respectively.

The overall number of subjects in the moderate/severe renal function subgroup was low for both the Phase 3 Placebo-Controlled Pool and Phase 3 Active-Controlled Pool. Three baseline renal function categories were defined by eGFR for the subgroup analyses: Normal (eGFR ≥ 90 mL/min/1.73 m²), mild impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m²), and moderate/severe impairment (eGFR < 60 mL/min/1.73 m²). Subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m²) were uncommon in both pools because this was an exclusion criterion in all phase 3 studies.

The table below shows the incidence of adverse events by baseline renal function, phase 3 placebo controlled pool.

Table 5.q Incidence of TEAEs by Baseline Renal Function: Phase 3 Placebo-Controlled Pool

	Placebo (a) N=801 n (%)			TAK-491 40 mg N=1072 n (%)			TAK-491 80 mg N=1074 n (%)		
	Normal	Mild	Moderate/ Severe	Normal	Mild	Moderate/ Severe	Normal	Mild	Moderate/ Severe
Number of subjects	376	383	42	528	484	60	515	499	58
TEAEs	167 (44.4)	172 (44.9)	15 (35.7)	228 (43.2)	219 (45.2)	26 (43.3)	221 (42.9) ^{***}	215 (43.1)	38 (65.5)
Discontinuation TEAEs (c)	5 (1.3)	13 (3.4)	1 (2.4)	9 (1.7)	14 (2.9)	2 (3.3)	11 (2.1) ^{***}	8 (1.6)	7 (12.1)
SAEs	2 (0.5)	4 (1.0)	1 (2.4)	4 (0.8)	5 (1.0)	0	3 (0.6)	7 (1.4)	0

Source: Table 5.2.1.1.6.

Study pool included monotherapy (491- 008, 011, and 019) and coadministration (491- 009 and 010) studies.

^{***} P \leq 0.01, ^{****} P \leq 0.001 within treatment comparisons by baseline renal function categories (Fisher exact test).

(a) Placebo group combines all subjects who received placebo alone, with amlodipine, or with chlorthalidone.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg alone, with amlodipine, or with chlorthalidone.

(c) TEAEs that led to study drug interruption or premature discontinuation.

The overall incidence rates of reported adverse events and adverse events that led to study discontinuation were much higher in the TAK-491 80 mg (65.5% and 12.1%) in the moderate/severe subgroup, respectively, compared to the same renal group randomized to TAK-491 40 mg (43.3% and 3.3%, respectively) and placebo (35.7% and 2.4%, respectively).

7.1.7 Clinical Laboratory

Clinical laboratory samples were collected at Screening, Baseline, Final Visit, and at least 1 visit during the treatment period in phase 3 studies. For the phase 1 pooled and phase 2 unpooled studies, clinical laboratory samples were collected at protocol-specified intervals.

Clinical chemistry

Individual subject changes

Individual subject changes are summarized by treatment group and were evaluated based on (1) shifts in laboratory values from Baseline at any visit relative to reference ranges, (2) markedly abnormal values, and (3) selected other laboratory measurements.

Phase 3 placebo controlled pool

The table below shows the percentages of subjects with shifts from Baseline to Week 2 and Final Visit in renal, hepatic, and potassium laboratory parameters.

Table 3.d Shifts From Baseline in Renal, Hepatic, and Potassium Laboratory Values Relative to Normal Ranges at Week 2 and Final Visit: Phase 3 Placebo-Controlled Pool

Laboratory Test	Visit	Placebo N=801	TAK-491 40 mg N=1072	TAK-491 80 mg N=1074	TAK-491 Total (a) N=2146
n/N (%) Shift to High					
BUN	Week 2	15/723 (2.1)	54/990 (5.5)	58/995 (5.8)	112/1985 (5.6)
	Final Visit	19/770 (2.5)	64/1040 (6.2)	80/1023 (7.8)	144/2063 (7.0)
Creatinine	Week 2	15/705 (2.1)	36/965 (3.7)	34/972 (3.5)	70/1937 (3.6)
	Final Visit	12/751 (1.6)	37/1015 (3.6)	39/1000 (3.9)	76/2015 (3.8)
AST	Week 2	23/675 (3.4)	37/912 (4.1)	41/939 (4.4)	78/1851 (4.2)
	Final Visit	28/721 (3.9)	27/961 (2.8)	41/970 (4.2)	68/1931 (3.5)
ALT	Week 2	28/677 (4.1)	37/909 (4.1)	45/924 (4.9)	82/1833 (4.5)
	Final Visit	29/723 (4.0)	40/960 (4.2)	47/954 (4.9)	87/1914 (4.5)
Total bilirubin	Week 2	7/721 (1.0)	10/981 (1.0)	16/984 (1.6)	26/1965 (1.3)
	Final Visit	7/767 (0.9)	12/1032 (1.2)	9/1014 (0.9)	21/2046 (1.0)
ALP	Week 2	11/714 (1.5)	16/962 (1.7)	11/977 (1.1)	27/1939 (1.4)
	Final Visit	10/762 (1.3)	10/1013 (1.0)	9/1005 (0.9)	19/2018 (0.9)
GGT	Week 2	33/569 (5.8)	42/773 (5.4)	50/795 (6.3)	92/1568 (5.9)
	Final Visit	33/608 (5.4)	45/812 (5.5)	61/818 (7.5)	106/1630 (6.5)
Potassium	Week 2	11/728 (1.5)	19/998 (1.9)	20/1000 (2.0)	39/1998 (2.0)
	Final Visit	9/778 (1.2)	22/1050 (2.1)	17/1033 (1.6)	39/2083 (1.9)
n/N (%) Shift to Low					
Potassium	Week 2	73/713 (10.2)	25/975 (2.6)	26/975 (2.7)	51/1950 (2.6)
	Final Visit	70/760 (9.2)	30/1024 (2.9)	21/1007 (2.1)	51/2031 (2.5)

Source: Table 3.2.6.

Study pool included 491-008, 009, 010, 011, and 019.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Renal: there were more abnormal increases in BUN and creatinine at week 2 and final visit for subjects randomized to TAK-491 compared to placebo. The higher dose of TAK-491 tended to have greater percentages of abnormal shifts compared to the lower dose.

Hepatic: there were similar abnormal increases in AST, ALT, total bilirubin, ALP, and GGT at week 2 and final visit for the subjects randomized to TAK-491 compared to placebo except there were slightly more abnormal increases in GGT at final visit in the TAK-491 80 mg group compared to the other groups.

Potassium: there were slightly more increases in potassium in the TAK-491 groups compared to the placebo group.

The table below shows the percentages of subjects with markedly abnormal values of serum chemistries and LFTs observed at any time during treatment.

Table 3.e Subjects With at Least 1 Markedly Abnormal Serum Chemistry Value During Treatment: Phase 3 Placebo-Controlled Pool

Laboratory Test and Criteria	n/N (%)			
	Placebo N=801	TAK-491 40 mg N=1072	TAK-491 80 mg N=1074	TAK-491 Total (a) N=2146
Creatinine >1.5×BL and >ULN	2/789 (0.3)	14/1058 (1.3)*	12/1046 (1.1)*	26/2104 (1.2)
Sodium				
>150 mEq/L	0/789	0/1058	1/1048 (<0.1)	1/2106 (<0.1)
<130 mEq/L	4/789 (0.5)	5/1058 (0.5)	2/1048 (0.2)	7/2106 (0.3)
Potassium				
>6.0 mEq/L	1/789 (0.1)	3/1058 (0.3)	1/1048 (<0.1)	4/2106 (0.2)
<3.0 mEq/L	11/789 (1.4)	1/1058 (<0.1)***	5/1048 (0.5)*	6/2106 (0.3)
Total protein				
>1.2×ULN	0/789	0/1058	0/1048	0/2106
<0.8×LLN	0/789	0/1058	0/1048	0/2106
Albumin <2.5 g/dL	0/789	0/1058	0/1048	0/2106
BUN >3×ULN	0/789	0/1058	0/1048	0/2106
Total bilirubin >2×ULN	2/789 (0.3)	2/1058 (0.2)	0/1048	2/2106 (<0.1)
ALP >3×ULN	0/789	2/1058 (0.2)	1/1048 (<0.1)	3/2106 (0.1)
AST >3×ULN	4/789(0.5)	6/1058 (0.6)	6/1048 (0.6)	12/2106 (0.6)
ALT >3×ULN	2/789 (0.3)	6/1058 (0.6)	7/1048 (0.7)	13/2106 (0.6)
GGT >3×ULN	24/789 (3.0)	27/1058 (2.6)	33/1048 (3.1)	60/2106 (2.8)
Triglycerides >2.5×ULN	23/767 (3.0)	35/1034 (3.4)	44/1018 (4.3)	79/2052 (3.8)
Calcium				
>1.2×ULN	0/789	0/1058	0/1048	0/2106
<0.8×LLN	1/789 (0.1)	0/1058	0/1048	0/2106
Uric acid	17/789 (2.2)	30/1058 (2.8)	31/1048 (3.0)	61/2106 (2.9)
M: >10.5 mg/dL; F: >8.5 mg/dL				
CK >10×ULN	2/789 (0.3)	3/1058 (0.3)	4/1048 (0.4)	7/2106 (0.3)

Source: Tables 3.0.1, 3.2.1.

Study pool included 491- 008, 009, 010, 011, and 019.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

BL=baseline, F=female, M=male.

*P≤0.05 vs placebo, ***P≤0.001 vs placebo (Fisher exact test).

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Renal: the percentages of subjects with markedly abnormal increases in creatinine were higher in the TAK-491 40 mg and 80 mg groups (1.3% and 1.1% respectively) compared with the placebo group (0.3%). Marked BUN abnormalities were not reported in any of the treatment groups.

Hepatic: there were more subjects reporting markedly abnormal ALT in the TAK-491 groups compared to placebo but this did not occur for AST and GGT.

Other: there were slightly higher percentages of subjects reporting markedly abnormal levels of triglycerides and uric acid compared with placebo.

The table below shows the number and percent of subjects reporting elevated liver transaminases.

Table 3.f Summary of Subjects With Elevations of LFTs: Phase 3 Placebo-Controlled Pool

Hepatic Chemistry Parameter Evaluation Criterion	n/N (%)			
	Placebo N=801	TAK -491 40 mg N=1072	TAK-491 80 mg N=1074	TAK-491 Total (a) N=2146
ALT				
>3×ULN	2/789 (0.3)	6/1058 (0.6)	7/1048 (0.7)	13/2106 (0.6)
>5×ULN	0/789	1/1058 (<0.1)	1/1048 (<0.1)	2/2106 (<0.1)
>10×ULN	0/789	0/1058	0/1048	0/2106
AST				
>3×ULN	4/789 (0.5)	6/1058 (0.6)	6/1048 (0.6)	12/2106 (0.6)
>5×ULN	0/789	3/1058 (0.3)	2/1048 (0.2)	5/2106 (0.2)
>10×ULN	0/789	0/1058	1/1048 (<0.1)	1/2106 (<0.1)
ALT and AST concurrently Both ALT and AST >3×ULN	2/789 (0.3)	5/1058 (0.5)	3/1048 (0.3)	8/2106 (0.4)
ALT and total bilirubin concurrently ALT>3×ULN and T.Bil.>2×ULN	1/789 (0.1)	0/1058	0/1048	0/2106
AST and total bilirubin concurrently AST>3×ULN and T.Bil.>2×ULN	1/789 (0.1)	0/1058	0/1048	0/2106
ALT or AST, and total bilirubin concurrently ALT or AST >3×ULN and T.Bil.>2×ULN	1/789 (0.1)	0/1058	0/1048	0/2106

Source: Table 3.2.3.

Study pool included 491- 008, 009, 010, 011, and 019.

T.Bil.=total bilirubin.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

There were higher percentages of TAK-491 subjects with elevated ALT (>3xULN) values compared to placebo (TAK-491 40, 80 mg and placebo: 0.6%, 0.7%, and 0.3%, respectively). However, the other parameter were similar across treatment groups. There is no evidence that TAK-491 had a deleterious effect on the liver.

Subjects with elevated liver enzymes are discussed below:

Subject 491-008/6120-008 (TAK-491 40 mg) prematurely discontinued because of elevated LFTs. She was a 61 year-old, white female who had elevated liver enzymes at baseline² as well as mild renal impairment, hypothyroidism, and dyslipidemia reported elevated hepatic enzymes on Study Day 15 (ALT 206 U/L, AST 130 U/L, and GGT=88 U/L. Both total bilirubin and ALP values were reported as within normal limits throughout the study. Previous medications included metoprolol 25 and 50 mg. Concomitant medication included levothyroxine 175 µg. The subject was prematurely discontinued on Study Day 28 and the event resolved about 2 weeks later.

Subject 491-019/1019-027 (TAK-491 80 mg) had an AST >10×ULN (AST=526 U/L) and ALT=206 U/L on Study Day 5³ as well as an increase in CK >33000 U/L (ULN=195). Follow-up AST and ALT values obtained on Study Day 9 were less than >3×ULN threshold; AST was normal at Study Day 13 and ALT was normal at Study Day 27. By Study Day 41, AST=29 U/L, ALT=33 U/L, and total bilirubin=0.4 mg/dL. The subject continued in the study.

² At Baseline, ALT=100 U/L, AST=102 U/L, and GGT=61 U/L.

³ At Baseline Total bilirubin=0.4 mg/dL, AST=39 U/L, and ALT=40U/L

Subject 491-008/6060-002 (TAK-491 40 mg) had an ALT=368 U/L and AST 280 U/L that were $>5 \times \text{ULN}$ and an ALP of 1976 U/L that was $>10 \times \text{ULN}$ at Final Visit on Study Day 42. Baseline values for total bilirubin=0.5 mg/dL, AST=50 U/L, ALT=26 U/L, and ALP=131 U/L. Follow-up values for ALT and AST on Day 490 were within normal limits and ALP=194 U/L.

Individual Subject Changes in the Phase 3 Active-Controlled Pool

A summary of shifts from Baseline to Week 2 and Final Visit in the Phase 3 Active-Controlled Phase 3 Active-Controlled Pool in renal, hepatic, and potassium laboratory parameters shown in the table below.

Table 3.g Shifts From Baseline in Renal, Hepatic, and Other Laboratory Parameters of Interest Relative to Normal Ranges at Week 2 and Final Visit: Phase 3 Active-Controlled Pool

Laboratory Test	Visit	Comparator(a) N=1468	TAK-491 40 mg N=1182	TAK-491 80 mg N=1189	TAK-491 Total (b) N=2371
n/N (%) Shift to High					
BUN	Week 2	32/1409 (2.3)	40/1126 (3.6)	31/1127 (2.8)	71/2253 (3.2)
	Final Visit	43/1426 (3.0)	53/1146 (4.6)	52/1143 (4.5)	105/2289 (4.6)
Creatinine	Week 2	22/1390 (1.6)	27/1113 (2.4)	13/1117 (1.2)	40/2230 (1.8)
	Final Visit	22/1408 (1.6)	24/1135 (2.1)	37/1135 (3.3)	61/2270 (2.7)
AST	Week 2	48/1328 (3.6)	39/1060 (3.7)	45/1076 (4.2)	84/2136 (3.9)
	Final Visit	56/1352 (4.1)	31/1083 (2.9)	45/1095 (4.1)	76/2178 (3.5)
ALT	Week 2	44/1287 (3.4)	38/1034 (3.7)	44/1041 (4.2)	82/2075 (4.0)
	Final Visit	59/1307 (4.5)	46/1058 (4.3)	63/1060 (5.9)	109/2188 (5.1)
Total bilirubin	Week 2	16/1408 (1.1)	16/1122 (1.4)	15/1107 (1.4)	31/2229 (1.4)
	Final Visit	12/1428 (0.8)	14/1144 (1.2)	13/1126 (1.2)	27/2270 (1.2)
ALP	Week 2	18/1393 (1.3)	13/1100 (1.2)	13/1100 (1.2)	26/2200 (1.2)
	Final Visit	23/1410 (1.6)	10/1121 (0.9)	15/1116 (1.3)	25/2237 (1.1)
GGT	Week 2	36/1114 (3.2)	34/908 (3.7)	41/907 (4.5)	75/1815 (4.1)
	Final Visit	56/1127 (5.0)	52/924 (5.6)	65/923 (7.0)	117/1847 (6.3)
Potassium	Week 2	23/1410 (1.6)	23/1132 (2.0)	24/1128 (2.1)	47/2260 (2.1)
	Final Visit	25/1432 (1.7)	33/1155 (2.9)	30/1147 (2.6)	63/2302 (2.7)
n/N (%) Shift to Low					
Potassium	Week 2	23/1392 (1.7)	14/1125 (1.2)	16/1118 (1.4)	30/2243 (1.3)
	Final Visit	17/1414 (1.2)	10/1147 (0.9)	13/1137 (1.1)	23/2284 (1.0)

Source: Table 3.3.6.

Study pool included 491- 008, 019, 020, and 301(DB).

(a) Comparator group combines all subjects who received olmesartan, medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Renal: the percentages of subjects with shifts to high for BUN were larger in the TAK-491 40 and 80 mg than for the comparator groups at week 2 and final visit. The percentages of subjects with shifts to high in creatinine values at final visit were higher in the TAK-491 40 and 80 mg groups compared with the comparator group. The percentages of shifts in creatinine at last visit were higher for TAK-491 80 mg (3.3%) compared to TAK-491 40 mg (2.1%). The percentage for the comparator group was 1.6%.

Hepatic: the percentage of shifts in the hepatic laboratory parameters tended to be small and variable. However, compared to the active controls, the percentage of ALT increases was higher for TAK-491 80 at final visit. Both TAK-491 groups reported higher percentages of subjects with increased total bilirubin at final visit, and both TAK-491 had higher percentages of subjects with increased GGT at both visit 2 and final visit. In the latter case, TAK-491 80 mg was worse than the lower dose. The percentages were small and probably not associated with use of TAK-491

Potassium: the percentages of subjects with shift-to-high values in the TAK-491 40 and 80 mg groups were slightly higher than the comparator group at both visit 2 and final visit.

The table below shows the percentages of subjects with markedly abnormal values of serum chemistries and LFTs observed at any time during treatment.

Table 3.h Subjects With at Least 1 Markedly Abnormal Serum Chemistry Value During Treatment: Phase 3 Active-Controlled Pool

Laboratory Test	n/N (%)			
	Comparator (a) N=1468	TAK-491 40 mg N=1182	TAK-491 80 mg N=1189	TAK-491 Total (b) N=2371
Creatinine >1.5 × BL and >ULN	3/1452 (0.2)	13/1170 (1.1)**	14/1163 (1.2)**	27/2333 (1.2)
Sodium				
>150 mEq/L	4/1452 (0.3)	9/1170 (0.8)	7/1163 (0.6)	16/2333 (0.7)
<130 mEq/L	10/1452 (0.7)	10/1170 (0.9)	2/1163 (0.2)†	12/2333 (0.5)
Potassium				
>6.0 mEq/L	7/1452 (0.5)	16/1170 (1.4)*	12/1163 (1.0)	28/2333 (1.2)
<3.0 mEq/L	2/1452 (0.1)	1/1170 (<0.1)	1/1163 (<0.1)	2/2333 (<0.1)
Total protein				
>1.2×ULN	0/1452	0/1170	0/1163	0/2333
<0.8×LLN	1/1452 (<0.1)	0/1170	0/1163	0/2333
Albumin <2.5 g/dL	1/1452 (<0.1)	0/1170	0/1163	0/2333
BUN >3×ULN	0/1452	0/1170	1/1163 (<0.1)	1/2333 (<0.1)
Total bilirubin >2×ULN	3/1452 (0.2)	3/1170 (0.3)	1/1163 (<0.1)	4/2333 (0.2)
ALP >3×ULN	0/1452	1/1170 (<0.1)	1/1163 (<0.1)	2/2333 (<0.1)
AST >3×ULN	14/1452 (1.0)	11/1170 (0.9)	6/1163 (0.5)	17/2333 (0.7)
ALT >3×ULN	9/1452 (0.6)	12/1170 (1.0)	8/1163 (0.7)	20/2333 (0.9)
GGT >3×ULN	60/1452 (4.1)	42/1170 (3.6)	49/1163 (4.2)	91/2333 (3.9)
Triglycerides >2.5×ULN	40/1365 (2.9)	36/1111 (3.2)	42/1109 (3.8)	78/2220 (3.5)
Calcium				
>1.2×ULN	0/1452	1/1170 (<0.1)	0/1163	1/2333 (<0.1)
<0.8×LLN	2/1452 (0.1)	4/1170 (0.3)	1/1163 (<0.1)	5/2333 (0.2)
Uric acid	19/1452 (1.3)	27/1170 (2.3)	24/1163 (2.1)	51/2333 (2.2)
M >10.5 mg/dL; F >8.5 mg/dL				
CK >10×ULN	5/1452 (0.3)	7/1170 (0.6)	3/1163 (0.3)	10/2333 (0.4)

Source: Table 3.0.1 and Table 3.3.1.

Study pool included 491-008, 019, 020, and 301(DB).

BL=baseline, F=female, M=male.

*P≤0.05 vs placebo, **P≤0.01 vs placebo, and †P≤0.05 vs TAK-491 40 mg (Fisher exact test).

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

The parameters with more markedly abnormal values in the TAK-491 groups compared to the comparator group include creatinine, elevated sodium, elevated potassium, triglycerides, and uric acid. Only the serum creatinine increases are particularly noteworthy.

The percentages of subjects with markedly abnormal values of high creatinine in the TAK-491 40 and 80 mg groups were 1.1% and 1.2% respectively. The percentage for the comparator group was 0.2%.

The percentage of subjects with markedly abnormal values of high potassium was larger in both the TAK-491 40 mg (1.4%) and TAK-491 80 mg (1.0%) groups compared with the comparator group (0.5%).

The table below shows the number and percent of subjects with elevated LFTs in the Phase 3 Active-Controlled Pool by treatment group.

Table 3.i Summary of Subjects With Elevations of LFTs: Phase 3 Active-Controlled Pool

Hepatic Chemistry Parameter Evaluation Criterion	n/N (%)			
	Comparator (a) N=1468	TAK-491 40 mg N=1182	TAK-491 80 mg N=1189	TAK-491 Total (b) N=2371
ALT				
>3×ULN	9/1452 (0.6)	12/1170 (1.0)	8/1163 (0.7)	20/2333 (0.9)
>5×ULN	1/1452 (<0.1)	4/1170 (0.3)	1/1163 (<0.1)	5/2333 (0.2)
>10×ULN	0/1452	1/1170 (<0.1)	0/1163	1/2333 (<0.1)
AST				
>3×ULN	14/1452 (1.0)	11/1170 (0.9)	6/1163 (0.5)	17/2333 (0.7)
>5×ULN	3/1452 (0.2)	6/1170 (0.5)	1/1163 (<0.1)	7/2333 (0.3)
>10×ULN	1/1452 (<0.1)	1/1170 (<0.1)	1/1163 (<0.1)	2/2333 (<0.1)
ALT and AST concurrently				
Both ALT and AST >3×ULN	5/1452 (0.3)	9/1170 (0.8)	3/1163 (0.3)	12/2333 (0.5)
ALT and total bilirubin concurrently				
ALT>3×ULN and T.Bil.>2×ULN	0/1452	0/1170	0/1163	0/2333
AST and total bilirubin concurrently				
AST>3×ULN and T.Bil.>2×ULN	0/1452	0/1170	0/1163	0/2333
ALT or AST, and total bilirubin concurrently				
ALT or AST >3×ULN and T.Bil.>2×ULN	0/1452	0/1170	0/1163	0/2333

Source: Table 3.3.3.

Study pool included 491- 008, 019, 020, and 301(DB).

T.Bil.=total bilirubin.

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Overall, the treatment groups look similar for the percentages of subjects with elevated LFTs.

Subject 491-301/1013-060 (TAK-491 80 mg) with ALT and AST >5×ULN had high ALT and AST at follow-up visits. This subject had reported metastatic liver cancer and was prematurely discontinued as a result of postural dizziness.

Subject 491-020/0017-003 (TAK-491 40 mg), had an AST=490 U/L and ALT=936 U/L on Study Day 117. The subject was prematurely discontinued on Study Day 117 with a because of hepatitis C. Follow-up values obtained 28 days post treatment had returned to near normal values.

Subject 491-019/1019-027 (TAK-491 80 mg) had AST >10×ULN, which was transient and was within normal limits at subsequent visits. On Study Day 5, the subject had an AST=526 U/L, ALT=206 U/L, total bilirubin=0.3 mg/dL, and CK >33,000 U/L on Study Day 5. This subject had been in training for a marathon and CK values varied throughout the study (1000 U/L at Baseline, 655 U/L at Week 2, and 164 U/L at Week 4). Baseline AST=39 U/L, ALT=40 U/L, and total bilirubin=0.4 mg/dL. The ALT, AST and total bilirubin values were normal by Study Day 27.

Individual Subject Changes in the Phase 3 Open-Label Pool

A summary of the percentages of subjects with shifts from Baseline to Week 4 and Final Visit in the Phase 3 Open-Label Pool in renal, hepatic, and potassium laboratory parameters are shown in the table below.

Table 3.j Shifts From Baseline in Renal, Hepatic, and Other Laboratory Parameters of Interest Relative to Normal Ranges at Week 4 and Final Visit: Phase 3 Open-Label Pool

Laboratory Test	Visit	TAK-491 All (a) N=1257 n/N (%)
		n/N (%) Shift to High
BUN	Week 4	56/1181 (4.7)
	Final Visit	133/1193 (11.1)
Creatinine	Week 4	41/1154 (3.6)
	Final Visit	106/1166 (9.1)
AST	Week 4	46/1093 (4.2)
	Final Visit	60/1105 (5.4)
ALT	Week 4	56/1071 (5.2)
	Final Visit	79/1083 (7.3)
Total bilirubin	Week4	6/1183 (0.5)
	Final Visit	10/1198 (0.8)
ALP	Week 4	14/1174 (1.2)
	Final Visit	8/1186 (0.7)
GGT	Week 4	56/875 (6.4)
	Final Visit	82/886 (9.3)
Potassium	Week 4	30/1188 (2.5)
	Final Visit	25/1204 (2.1)
		n/N (%) Shift to Low
Potassium	Week 4	23/1146 (2.0)
	Final Visit	64/1162 (5.5)

Source: Table 3.4.6.

Study pool included 491-006 (interim), 016, and 301(OL) (interim).

(a) TAK-491 All combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The percentages of subjects with markedly abnormal serum chemistries in the Phase 3 Open-Label Pool observed at any time during treatment are shown below.

Table 3.k Subjects With at Least 1 Markedly Abnormal Serum Chemistry Value During Treatment: Phase 3 Open-Label Pool

Laboratory Test	n/N (%)
	TAK-491 All (a) N=1257
Creatinine >1.5×BL and >ULN	91/1218 (7.5)
Sodium	
>150 mEq/L	2/1218 (0.2)
<130 mEq/L	18/1218 (1.5)
Potassium	
>6.0 mEq/L	4/1218 (0.3)
<3.0 mEq/L	4/1218 (0.3)
Total protein	
>1.2×ULN	0/1218
<0.8×LLN	5/1218 (0.4)
Albumin <2.5 g/dL	1/1218 (<0.1)
Total bilirubin >2×ULN	1/1218 (<0.1)
AST >3×ULN	13/1218 (1.1)
ALT >3×ULN	11/1218 (0.9)
GGT >3×ULN	72/1218 (5.9)
Triglycerides >2.5×ULN	83/1127 (7.4)
Calcium	
>1.2×ULN	0/1218
<0.8×LLN	1/1218 (<0.1)
Uric acid (M >10.5 mg/dL; F >8.5 mg/dL)	137/1218 (11.2)
CK (>10×ULN)	6/1217 (0.5)

Source: Tables 3.0.1, 3.4.1.

Study pool included 491-006 (interim), 016, and 301(OL) (interim).

BL=baseline, F=female, M=male.

(a) TAK-491 All combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

A summary of elevated LFTs in the Phase 3 Open-Label Pool is shown in the table below.

Table 3.1 Summary of Elevations of LFTs: Phase 3 Open-label Pool

Hepatic Chemistry Parameter Evaluation Criterion	n/N (%)
	TAK-491 All (a) N=1257
ALT	
>3×ULN	11/1218 (0.9)
>5×ULN	3/1218 (0.2)
>10×ULN	0/1218
AST	
>3×ULN	13/1218 (1.1)
>5×ULN	5/1218 (0.4)
>10×ULN	0/1218
ALT and AST concurrently	
Both ALT and AST >3×ULN	8/1218 (0.7)
ALT and total bilirubin concurrently	
ALT>3×ULN and T.Bil.>2×ULN	0/1218
AST and total bilirubin concurrently	
AST>3×ULN and T.Bil.>2×ULN	0/1218
ALT or AST, and total bilirubin concurrently	
ALT or AST >3×ULN and T.Bil.>2×ULN	0/1218

Source: Table 3.4.3.

Study pool included 491-006 (interim), 016, and 301(OL) (interim).

T. Bil.=total bilirubin, ULN=upper limit of normal.

(a) TAK-491 All combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

Without control groups, it is difficult to draw any conclusions about these findings.

Individual Clinically Significant Chemistry Abnormalities

Individual clinically significant chemistry abnormalities were those changes in clinical chemistry laboratory values that were considered to be a serious adverse event or resulted in the permanent premature discontinuation of the subject from the study. Subjects who prematurely discontinued as a result of a clinically significant renal laboratory parameters are presented separately.

Phase 3 Placebo-Controlled Pool

No subjects reported a serious adverse event related to chemistry abnormalities in this pool. The TAK-491 subjects presented below experienced adverse events associated with abnormal chemistry values that resulted in premature discontinuation. There were 2 placebo subjects who were discontinued: one for increased transaminases and one for hyperkalemia.

Subject 491-008/6120-008 (TAK-491 40 mg) with hepatic enzyme increase on Study Day 15, with ALT=206 U/L, AST=130 U/L, and GGT=88 U/L. Both total bilirubin and ALP values were within normal limits throughout the study. At Baseline, ALT=100 U/L, AST=102 U/L, and GGT=61 U/L. Previous medications included metoprolol 25 and 50 mg. Concomitant medication included levothyroxine 175 µg. On Study Day 28, the subject's ALT=124 U/L, AST=84 U/L, and GGT 88 U/L, and the subject was prematurely discontinued on Study Day 28. The event resolved on Study Day 51.

Subject 491-009/7067-017 (TAK-491 40 mg plus chlorthalidone 25 mg) with hepatic enzyme increase on Study Day 2, with Study Day 1 (Baseline) ALT=132 U/L, AST=110 U/L, and GGT=71 U/L. Both total bilirubin and ALP values were within normal limits throughout the study. Concomitant medication included ranitidine 300 mg. The subject was prematurely discontinued on Study Day 14 and on Study Day 15, the values were ALT=98 U/L, AST=64 U/L, and GGT=63 U/L.

Subject 491-008/6147-012 (TAK-491 80 mg) reported transaminases increased on Study Day 15, with ALT=132 U/L and AST=171 U/L. ALT and AST at Baseline were 107 U/L and 137 U/L, respectively. Total bilirubin was normal throughout the study. The subject was prematurely discontinued on Study Day 44.

Subject 491-011/0023-002 (TAK-491 80 mg) reported hepatic enzyme increased and prematurely discontinued on Study Day 21, as the Study Day 14 ALT, AST, and GGT values were 465 U/L, 180 U/L, and 48 U/L, respectively. Both total bilirubin and ALP values were within normal limits throughout the study. Concomitant medications included paracetamol 500 mg from Study Day 19 to 24. On Study Day 19, the subject also reported an episode of viral infection, which resolved on Study Day 26. Baseline values were within normal limits and at a follow-up visit on Study Day 35, they were ALT=84 U/L, AST=28 U/L, and GGT=38 U/L.

Subject 491-009/7057-042 (TAK-491 80 mg plus chlorthalidone 25 mg) had a history of gout and moderate renal impairment and reported blood creatinine increased of >50% on Study Day 14, with a creatinine=1.8 mg/dL and a BUN=38 mg/dL. Baseline creatinine=1.1 mg/dL and BUN=16 mg/dL; eGFR was normal throughout the study. Concomitant medications include allopurinol 100 mg. The subject was prematurely discontinued on Study Day 23, and the event was considered resolved on Study Day 36.

Subject 491-009/7068-045 (TAK-491 80 mg plus chlorthalidone 25 mg) had a history of hyperlipidaemia and obesity reported blood creatinine increased on Study Day 29, with a creatinine=1.2 mg/dL and a BUN=32 mg/dL. Baseline creatinine=0.7 mg/dL and BUN=12 mg/dL, with BUN=26 mg/dL by Study Day 15; eGFR was normal throughout the study. Other events on Study Day 29 included hyperkalaemia (potassium=5.5 mEq/L) and increased uric acid=9.2 mg/dL. The subject was prematurely discontinued because of the elevated blood creatinine and the events was considered resolved on Study Day 43 (creatinine=0.8 mg/dL).

Subject 491-010/8001-031 (TAK-491 80 mg plus amlodipine 5 mg) had a history of moderate renal impairment and hyperlipidemia and reported hypokalemia on Study Day 1, with a potassium=2.3 mEq/L. Screening potassium values on Study Days -22 and -15 were 2.7 and 3.0 mEq/L, respectively and baseline potassium values were 2.3 mEq/L. Potassium values continued to decline and the subject was prematurely discontinued on Study Day 25. On Study Day 26, potassium=2.1 mEq/L.

Individual Abnormalities in the Phase 3 Active-Controlled

The subjects presented below reported adverse events associated with abnormal chemistry values that were considered to be serious or resulted in premature discontinuation in the Phase 3 Active-

Controlled Pool, TAK-491 subjects only. Subjects who prematurely discontinued as a result of a clinically significant renal laboratory parameters are presented separately.

Subject 491-301/1013-052 (TAK-491 80 mg) reported elevated BUN on Study Day 112, with a BUN (48 mg/dL), creatinine (2.0 mg/dL) and potassium (5.4 mEq/L). Baseline BUN=17 mg/dL, creatinine=1.0 mg/dL, and potassium=4.2 mEq/L. Estimated GFR was normal throughout the study. Concomitant medications included low-dose aspirin, Avodart (dutasteride), Cetacaine (benzocaine, aminobenzoate and tetracaine) topical, dutasteride 0.5 mg, ibuprofen 400 mg, solifenacin succinate 5 mg, Vytorin (ezetimibe and simvastatin) 1 tablet, and calcium supplement. Both BUN and creatinine continued to be elevated and on Study Day 168, the subject was withdrawn from treatment with an increased BUN=40 mg/dL; corresponding creatinine=1.6 mg/dL. Potassium values were normal. The subject continued into the open label phase of 491-301 and the event was resolved on Study Day 339.

Subject 491-020/0027-014 (TAK-491 40 mg) had a history of moderate renal impairment and hyperlipidaemia and reported azotaemia on Study Day 83, with BUN=53.0 mg/dL and creatinine=1.7 mg/dL. Baseline values for BUN=17.0 mg/dL and creatinine=1.3 mg/dL. The subject was referred to a nephrologist and ultra sound examination showed diffuse sclerotic changes on both renal arteries. The subject prematurely discontinued on Study Day 121. The subject did not return for follow-up.

Subject 491-301/1085-015 (TAK-491 40 mg) reported renal impairment on Study Day 169. ???

Subject 491-301/1134-022 (TAK-491 40 mg) who had a history of chronic renal failure reported worsening chronic renal failure on Study Day 87, with BUN=22 mg/dL and creatinine=1.9 mg/dL. The subject's baseline BUN=25 mg/dL and creatinine=1.6 mg/dL, which continued to be elevated throughout the study. At the time of premature discontinuation on Study Day 93, values were BUN=23 mg/dL and creatinine=1.8 mg/dL.

Subject 491-301/1064-015 (TAK-491 40 mg) reported blood CK increased on Study Day 85, with CK=1223 U/L. On Study Day -21 (Baseline) CK=87 U/L. On Study Day 87, CK=1633 U/L. It was considered resolved (CK=105 U/L) on Study Day 92.

Subject 491-020/0045-005 (TAK-491 80 mg), who had a history of moderate renal impairment (Screening creatinine=1.34 mg/dL reported hyperkalaemia on Study Day 109, with a potassium=5.9 mEq/L. Baseline potassium=5.0 mEq/L and creatinine=1.38 mg/dL). Concomitant medications included furosemide 40 mg IV, sodium chloride IV, simvastatin 20 mg, aspirin 100 mg. The subject also reported renal failure on Study Day 112 which was considered resolving at discontinuation on Study Day 172, with creatinine=1.76 mg/dL (ULN=1.3), BUN=43 mg/dL (ULN=23), and potassium=5.9 mEq/L.

Subject 491-301/1047-020 (TAK-491 80 mg) reported hyperkalaemia on Study Day 62, with a potassium=5.7 mEq/L. The Baseline potassium=5.0 mEq/L. On Study Day 71, potassium=5.9 mEq/L and the subject was prematurely discontinued on Study Day 76. The event was considered resolved (potassium=4.8 mEq/L) on Study Day 84.

Serum creatinine changes

RAAS blockade has been shown to cause reversible decreases in GFR that correspond to transient or nonprogressive increases in serum creatinine levels that are reversible. Creatinine elevations of up to 30% that stabilize within the first 2 months after treatment initiation are considered within the range of normal pharmacological response⁴.

As discussed at the May 19, 2009 Type C Meeting, creatinine elevations consistent with the above pharmacodynamic effects have been observed in subjects in the TAK-491 clinical program, especially in subjects concomitantly receiving chlorthalidone treatment. The sponsor conducted comprehensive evaluation of renal safety with emphasis placed on changes in serum creatinine.

Creatinine Elevations in Phase 3 Placebo-Controlled Studies

The Phase 3 Placebo-Controlled Pool contains both monotherapy (491-008, 011, and 019) and coadministration studies (491-009 and 010), all of which were of 6-week duration. The 3 monotherapy studies evaluated TAK-491 alone vs placebo, while the 2 coadministration studies evaluated TAK-491 vs placebo taken concomitantly with chlorthalidone 25 mg (491-009) or amlodipine 5 mg (491-010). In each study, 2 serum creatinine measurements were scheduled postbaseline, at Week 2 and Week 6. The table below shows the percentage of subjects with a creatinine elevation $\geq 30\%$ or $\geq 50\%$ from baseline and $>ULN$ at any postbaseline visit or at final visit in the Phase 3 placebo-controlled pool.

Table 3.m Summary of Subjects With a Creatinine Elevation: Phase 3 Placebo-Controlled Pool

	n/N (%)			
	Placebo N=801	TAK-491 40 mg N=1072	TAK-491 80 mg N=1074	TAK-491 Total (a) N=2146
Subjects with $\geq 30\%$ from BL and $>ULN$ creatinine elevations				
Any postbaseline visit	7/789 (0.9)	28/1058 (2.6)**	38/1046 (3.6)***	66/2104 (3.1)
Final Visit	4/789 (0.5)	20/1058 (1.9)*	25/1046 (2.4)***	45/2104 (2.1)
Subjects with $\geq 50\%$ from BL and $>ULN$ creatinine elevations				
Any postbaseline visit	2/789 (0.3)	15/1058 (1.4)*	18/1046 (1.7)**	33/2104 (1.6)
Final Visit	1/789 (0.1)	10/1058 (0.9)*	11/1046 (1.1)*	21/2104 (1.0)

Source: Table 3.2.7 and Table 3.2.9.

Study pool included monotherapy (491-008, 011, and 019) and coadministration (491-009 and 010) studies.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

* $P \leq 0.05$ vs placebo, ** $P \leq 0.01$ vs placebo, and *** $P \leq 0.001$ vs placebo (Fisher exact test).

The incidence of subjects with creatinine elevations $\geq 30\%$ or $\geq 50\%$ from Baseline and $>ULN$ was greater in both the TAK-491 40 and 80 mg groups compared with the placebo group at any postbaseline visit and at final visit. The higher dose of TAK-491 had higher incidence rates compared to the lower dose. The incidence rate was lower at final visit for all groups suggesting a transient effect for some of the subjects.

⁴ Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160(5):685-93.

The table below shows results for the monotherapy only placebo controlled studies.

Table 3.n Summary of Subjects With a Creatinine Elevation: Phase 3 Placebo-Controlled Monotherapy Studies Group

	n/N (%)			
	Placebo N=435	TAK-491 40 mg N=698	TAK-491 80 mg N=704	TAK-491 Total N=1402
Subjects with $\geq 30\%$ from BL and $>ULN$ creatinine elevations				
Any postbaseline visit	4/429 (0.9)	8/689 (1.2)	9/686 (1.3)	17/1375 (1.2)
Final Visit	2/429 (0.5)	4/689 (0.6)	5/686 (0.7)	9/1375 (0.7)
Subjects with $\geq 50\%$ from BL and $>ULN$ creatinine elevations				
Any postbaseline visit	1/429 (0.2)	4/689 (0.6)	2/686 (0.3)	6/1375 (0.4)
Final Visit	0/429	2/689 (0.3)	2/686 (0.3)	4/1375 (0.3)

Source: Table 3.5.1 and Table 3.8.1.

Studies included 491- 008, 011, and 019.

TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

BL=Baseline.

The incidence rates are higher for the TAK-491 dose groups compared to placebo, but the difference is less, particularly at final visit.

Coadministration with Chlorthalidone: the table below shows the percentage of subjects with a creatinine elevation $\geq 30\%$ or $\geq 50\%$ from baseline and $>ULN$ at any postbaseline visit or at Final visit obtained from the chlorthalidone 25 mg coadministration study 491-009.

Table 3.o Summary of Subjects With Creatinine Elevations: 491-009

	n/N (%)		
	Placebo + CLD 25 mg N=181	TAK-491 40 mg + CLD 25 mg N=184	TAK-491 80 mg + CLD 25 mg N=182
Subjects with $\geq 30\%$ from BL and $>ULN$ creatinine elevations			
Any postbaseline visit	3/180 (1.7)	18/181 (9.9)	26/176 (14.8)
Final Visit	2/180 (1.1)	15/181 (8.3)	19/176 (10.8)
Subjects with $\geq 50\%$ from BL and $>ULN$ creatinine elevations			
Any postbaseline visit	1/180 (0.6)	10/181 (5.5)	15/176 (8.5)
Final Visit	1/180 (0.6)	8/181 (4.4)	9/176 (5.1)

Source: 491-009 Table 12.1.

Note: statistical analyses were not performed on individual study-level creatinine elevations.

BL=baseline, CLD=chlorthalidone.

The incidences of creatinine elevations were substantially higher in the TAK-491 plus chlorthalidone groups compared with the placebo plus chlorthalidone group. The TAK-491 80 mg plus chlorthalidone group had higher rates compared to the lower combination dose.

The incidence at final visit tended to be somewhat lower for all treatment groups compared to the incidence at any post baseline visit suggesting a transient creatinine elevation in some subjects.

Creatinine Elevations in Active-Controlled Studies

Data in the Active-Controlled pool were derived from both short-term studies (6 weeks: 491-008 olmesartan medoxomil and 491-019 olmesartan medoxomil and valsartan) and long-term studies (6 months: 491-020 ramipril 10 mg and 491-301 valsartan 320 mg).

Compared to valsartan: The table below shows the percentage of subjects with a creatinine elevation $\geq 30\%$ or $\geq 50\%$ from Baseline and $>ULN$ at any postbaseline visit or at Final Visit in 491-301.

Table 3.q Summary of Subjects With Creatinine Elevations: Double-Blind Treatment Phase of 491-301

	n/N (%)		
	Valsartan 320 mg N=326	TAK-491 40 mg N=327	TAK-491 80 mg N=329
Subjects with $\geq 30\%$ from BL and $>ULN$ creatinine elevations			
Any postbaseline visit	3/323 (0.9)	20/326 (6.1)	26/319 (8.2)
Final Visit	0/323	2/325 (0.6)	10/316 (3.2)
Subjects with $\geq 50\%$ from BL and $>ULN$ creatinine elevations			
Any postbaseline visit	0/323	9/326 (3.8)	13/319 (4.1)
Final Visit	0/323	1/325 (0.3)	7/316 (2.2)

Source: 491-301 Table 12.z.

Note: statistical analyses were not performed on individual study-level creatinine elevations.

BL=baseline.

In this study, the proportion of TAK-491 subjects with creatinine elevations of $\geq 30\%$ from baseline and $>ULN$ at any postbaseline visit in the TAK-491 40 and 80 mg groups (6.1% and 8.2%, respectively) were much greater than in the valsartan group (0.9%). This was also the situation for the subjects with creatinine elevations $\geq 50\%$.

By final visit there were few elevations but the TAK-491 80 mg group had worse results compared to the valsartan and TAK-491 40 mg dose groups.

Comparison with olmesartan medoxomil: the table below shows the creatinine elevations in the study 008 for the placebo and active treatment groups.

Table 12.l Summary of Subjects With a Creatinine Elevation —Safety Analysis Set

	Subjects (%)				
	Placebo N=142	TAK-491 20 mg N=283	TAK-491 40 mg N=281	TAK-491 80 mg N=284	Olmesartan 40 mg N=282
Subjects with Creatinine Elevations at Any Postbaseline Visit					
≥30% from BL and >ULN	0/140	2/277 (0.7)	3/276 (1.1)	2/280 (0.7)	7/280 (2.5)
Subjects with Creatinine Elevations at Final Visit (a)					
≥30% from BL and >ULN	0/140	1/277 (0.4)	2/276 (0.7)	1/280 (0.4)	4/280 (1.4)
≥50% from BL and >ULN	0/140	1/277 (0.4)	0/276	1/280 (0.4)	2/280 (0.7)

Source: Table 15.3.4.9 and Appendix 16.2.8.3.3.

(a) LOCF. Narratives are provided in Section 15.3.3.4.

Creatinine increases ≥30% from baseline and >ULN at any postbaseline visit were higher in the active treatment groups compared to placebo and a lower frequency of reports in the TAK-491 treatment groups compared to the olmesartan treatment group. The frequency of reports of subjects with creatinine increases at final visit was reduced in all active treatment groups.

Comparison with ramipril: the table below shows the creatinine elevations in the study 020 for the active treatment groups.

Table 3.r Summary of Subjects With Creatinine Elevations: 491-020

	n/N (%)		
	Ramipril 10 mg N=293	TAK-491 40 mg N=294	TAK-491 80 mg N=293
Subjects with ≥30% from BL and >ULN creatinine elevations			
Any postbaseline visit	1/290 (0.3)	7/290 (2.4) (a)	9/289 (3.1)
Final Visit	0/287	2/290 (0.7)	1/289 (0.3)
Subjects with ≥50% from BL and >ULN creatinine elevations			
Any postbaseline visit	0/290	4/290 (1.4)	4/289 (1.4)
Final Visit	0/287	1/290 (0.3)	0/289

Source: 491-020 Table 12.k.

Note: statistical analyses were not performed on individual study-level creatinine elevations.

BL=baseline.

(a) Includes 1 subject (491-020/0042-010) with a medically impossible elevation due to data entry error in the database.

The proportion of TAK-491 subjects with creatinine elevations of ≥30% and ≥ 50% from baseline and >ULN at any postbaseline visit in the TAK-491 40 and 80 mg groups and at final visit was higher than in ramipril group.

Creatinine Elevations in Open-Label Studies

Phase 3 Open-Label Pool studies employed forced titration of TAK-491 followed by addition of other therapies in treat-to-target blood pressure study designs. These designs specified addition of a diuretic as first rescue medication (primarily chlorthalidone but also HCTZ), followed by non-ARB antihypertensives, if needed. Subjects in these studies were not required to wash out any non-ARB antihypertensive medications prior to enrollment.

The table summarizes the percentage of subjects with creatinine elevations of $\geq 30\%$ or $\geq 50\%$ from baseline and $>ULN$ at any postbaseline visit or at final visit in the Phase 3 Open-Label pool.

Table 3.s Summary of Subjects With Creatinine Elevations: Phase 3 Open-Label Pool

	n/N (%)
	All TAK-491(a) N=1257
Subjects with $\geq 30\%$ from BL and $>ULN$ creatinine elevations	
Any postbaseline visit	177/1218 (14.5)
Final Visit	69/1218 (5.7)
Subjects with $\geq 50\%$ from BL and $>ULN$ creatinine elevations	
Any postbaseline visit	106/1218 (8.7)
Final Visit	41/1218 (3.4)

Source: Tables 3.4.7 and 3.4.9.

Study pool included 491-006 (interim), 016, and 301(OL) (interim).

BL=baseline.

(a) All TAK-491 combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent. Exposure to HCTZ is limited as studies are ongoing.

Elevations of serum creatinine, BUN, and uric acid were more common in subjects who received TAK-491 plus chlorthalidone. Serum creatinine generally returned to baseline or near baseline levels either during treatment or after discontinuing study medication.

Study 016: withdrawal study

Following open label treatment for 26 weeks subjects were randomized to either stay on TAK-491 or go onto placebo. At week 8, investigators could have added chlorthalidone and other antihypertensive agents to achieve the subject's target blood pressure, defined as $<140/90$ mm Hg for subjects without diabetes or chronic kidney disease (CKD) and $<130/80$ mm Hg for subjects with diabetes or CKD.

The table below shows the mean changes from open label baseline to week 26 for serum creatinine.

Table 12.o Serum Chemistry: Mean Changes From Open-Label Baseline to Week 26 Visit During the Open-Label Phase (Safety Analysis Set)

Serum Chemistry Parameter (unit)	TAK-491 N=179		TAK-491 plus CLD N=239		Total N=418	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Creatinine (umol/L)						
Open-Label Baseline (a)	179	78.7 (18.75)	239	83.7 (20.44)	418	81.5 (19.87)
Week 26	101	81.4 (19.79)	205	94.3 (23.96)	306	90.0 (23.44)
Change	101	3.1 (12.98)	205	11.0 (16.53)	306	8.4 (15.86)

Mean creatinine was higher at open-label baseline in subjects who additionally received chlorthalidone (83.7 umol/L) than for subjects who received TAK-491 alone (78.7 umol/L). At Week 26, the mean increase from Open-Label Baseline in creatinine was 3.1 umol/L for subjects who received TAK-491 alone and 11.9 umol/L for subjects who additionally received chlorthalidone. There were no reported study discontinuations for elevated serum creatinine or renal impairment.

The mean change from double blind baseline to final visit for serum creatinine for placebo and TAK-491 groups is shown below for the randomized groups.

Table 12.q Serum Chemistry: Mean Changes From Double-Blind Baseline to Final Visit During the Double-Blind Reversal Phase (FAS) (Continued)

		Treatment Group			
		Placebo		TAK-491	
Creatinine (umol/L)					
S	Double-Blind Baseline	151	90.6 (22.76)	146	89.1 (24.05)
	Final Visit	146	86.5 (19.19)	142	89.4 (24.93)
	Change	146	-4.5 (12.42)	142	1.7 (19.13)

The group randomized to placebo had a drop in serum creatinine level of 4.5 umol/L compared to a small increase of 1.7 umol/L in the group remaining on TAK-491.

There were two subjects who withdrew from the double blind treatment phase because of renal adverse events.

Serious Adverse Events relating to renal effects

Across the phase 3 pools, there were three subjects who reported a serious adverse renal event associated with abnormal laboratory values.

-subject 491-301/1085-015 (TAK-491 40 mg) reported renal impairment based on a serum creatinine=2.8 mg/dL that was obtained during a scheduled visit. This abnormal value returned to normal within a week of retesting. The subject continued in the study and the event resolved.

-subject 491-006/1017-001 (TAK-491 80 mg plus chlorthalidone 25 mg) prematurely discontinued from the study because of the serious adverse event vasovagal syncopal episode on study day 116. Elevated blood creatinine (1.1 mg/dL) was also reported as a serious event on the same study day.

-subject 491-006/1025-008 (TAK-491 80 mg plus chlorthalidone 25 mg) reported a serious adverse event renal impairment based on elevated serum creatinine elevation (2.1 mg/dL) and uric acid (13.5 mg/dL). The subject was prematurely discontinued from the study after failure to appear for a scheduled visit. A follow-up serum creatinine indicated a return to within normal limits.

Premature Discontinuation Associated With Abnormal Laboratory Values

There were 29 TAK-491 and 3 placebo subjects who experienced an adverse event associated with renal laboratory parameters in the phase 3 placebo controlled pool. Of these, two subjects (491-009/7057-042 and 491-009/7068-045; both TAK 80 mg plus chlorthalidone 25 mg) prematurely discontinued because of increased blood creatinine.

There were 27 TAK-491 and 7 active comparator subjects who experienced a renal adverse event associated with abnormal laboratory values in the phase 3 active-controlled pool, 2 subjects (491-301/1013-052, TAK-491 80 mg; 491-301/1011-044, valsartan 320 mg) prematurely discontinued because of increased BUN and increased urine albumin/creatinine ratio, respectively.

Of the 2 TAK-491 and 2 active comparator subjects reporting renal impairment adverse events and 3 TAK-491 subjects reporting renal failure, only 2 subjects (491-301/1134-022 TAK-491 40 mg (worsening chronic renal failure) and 491-020/0059-001, ramipril 10 mg (renal impairment) prematurely discontinued from the study.

In addition, there was a premature discontinuation as a result of azotaemia (491-020/0027-014; TAK-491 40 mg) reported in the Phase 3 Active-Controlled Pool.

In the Phase 3 Open-Label Pool, 7 of the 34 subjects who experienced a renal adverse event associated with abnormal laboratory values prematurely discontinued (491-006HCTZ/1002-518 [TAK-491 20 mg], 491-301/1008-046 [TAK-491 40 mg], 491-006/1017-001 [TAK-491 80 mg plus chlorthalidone 25 mg], 491-006HCTZ/1009-502 [TAK-491 80 mg plus HCTZ 12.5 mg], 491-006HCTZ/1009/512 [TAK-491 80 mg plus HCTZ 25 mg], 491-006HCTZ1028-504 [TAK-491 80 mg plus HCTZ 25 mg], 491-301/1153-041 [TAK-491 40 mg plus HCTZ 12.5 mg]) or BUN increased (491-006HCZT/1028-504 [TAK-491 80 mg plus HCTZ 25 mg]).

Of the 13 open-label subjects who reported renal impairment, 3 subjects (491-016/0021015 [TAK-491 80 mg], 491-006/1050-037 [TAK-491 80 mg plus chlorthalidone 25 mg], 491-016/0022-004 [TAK-491 80 mg plus chlorthalidone 25 mg]) prematurely discontinued.

It appears that the majority of subjects who reported a renal-laboratory associated adverse event EAE resulting in premature discontinuation, the renal laboratory values returned to normal and the event was considered resolved.

Creatinine Elevations in Special Populations

Subgroups analyses of creatinine elevations meeting the $\geq 30\%$ or $\geq 50\%$ from baseline and $>ULN$ criteria were conducted in the following subgroups: baseline renal status (cGFR), age (≥ 75), and race (black vs other).

Renal impairment at baseline: the number of subjects in the phase 3 pools with moderate to severe renal impairment was small. The table below shows the creatinine elevations by baseline renal function and treatment group in this study pool.

Table 3.w Creatinine Elevations by Baseline Renal Function: Phase 3 Placebo-Controlled Pool

	Placebo N=801 n (%)			TAK-491 Total (a) N=2146 n (%)		
	Renal Function (b)					
	Normal	Mild	Moderate/ Severe	Normal	Mild	Moderate/ Severe
Number of subjects	369	378	42	1020	968	116
Subjects with ≥30% from BL and >ULN creatinine elevations						
Any postbaseline visit	2 (0.5)	4 (1.1)	1 (2.4)	14 (1.4)	42 (4.3)	10 (8.6)
Final Visit	1 (0.3)	2 (0.5)	1 (2.4)	11 (1.1)	26 (2.7)	8 (6.9)
Subjects with ≥50% from BL and >ULN creatinine elevations						
Any postbaseline visit	1 (0.3)	0	1 (2.4)	13 (1.3)	17 (1.8)	3 (2.6)
Final Visit	0	0	1 (2.4)	9 (0.9)	12 (1.2)	0

Source: Tables 5.4.1.1.1, 5.4.2.1.1.

Study pool included 491-008, 009, 010, 011, and 019.

BL=baseline; ULN=upper limit of normal.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

(b) Baseline renal function categories were: Normal (eGFR ≥ 90 mL/min/1.73 m²), Mild Impairment (eGFR ≥ 60 to <90 mL/min/1.73 m²), and Moderate/Severe Impairment (eGFR <60 mL/min/1.73 m²).

In the Phase 3 Placebo-Controlled Pool, the frequency of any postbaseline creatinine elevation and final visit elevation $\geq 30\%$ from Baseline and $>ULN$ regardless of renal function at baseline was higher with TAK-491 (dose 40 mg and 80 mg combined) compared to placebo. This phenomenon was most pronounce for the moderate/severe group any post baseline visit. There were fewer increases at final visit but the percentages were still higher in the TAK-491 group.

By age: there were no subjects ≥ 75 years in the placebo group of the Phase 3 placebo controlled study pool. Therefore, the results for the phase 3 active controlled pool are shown below.

Table 3.z Creatinine Elevations by Age: Phase 3 Active-Controlled Pool

	Comparator (a) N=1468 n (%)		TAK-491 Total (b) N=2371 N=(%)	
	Age Category			
	<75 Years	≥75 Years	<75 Years	≥75 Years
Number of subjects	1384	68	2212	121
Subjects with ≥30% from BL and >ULN creatinine elevations				
Any postbaseline visit	14 (1.0)	1 (1.5)	66 (3.0)	8 (6.6)
Final Visit	6 (0.4)	0	21 (0.9)	1 (0.8)
Subjects with ≥50% from BL and >ULN creatinine elevations				
Any postbaseline visit	4 (0.3)	1 (1.5)	33 (1.5)	1 (0.8)
Final Visit	3 (0.2)	0	12 (0.5)	0

Source [Tables 5.4.1.3.2, 5.4.2.3.2](#).

Study pool included 491-008, 019, 020, and 301(DB).

BL=baseline; ULN=upper limit of normal.

(a) Comparator group combines all subjects who received olmesartan medoxomil, valsartan, or ramipril.

(b) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

Elderly subjects ≥75 years randomized to TAK-491 reported a higher incidence of creatinine elevations following TAK-491 treatment (6.6%) compared with elderly subjects randomized to a comparator (3.0%). The incidence of elevations at final visit in this population was similar to that observed with the active comparators.

By race: there were no trends that would indicate a higher frequency in the black population for creatinine elevations ≥30% or ≥50% from Baseline and >ULN criteria at any visit compared subjects of other races.

Reviewer's conclusions:

Treatment with TAK-491 tends to increase serum creatinine levels, particularly in subjects
--receiving a diuretic (chlorthalidone, HCTZ),
-with impaired renal function at baseline,
-are > 75 years of age.

There were few subjects who reported serious adverse events related to renal impairment or discontinued treatment because of it. There was also a tendency for fewer elevations in serum creatinine to be reported at final visit, indicating that the increased values were fleeting in most subjects.

Clinical Hematology

The numbers and percents of subjects with markedly abnormal hematology value reported during a phase 3 placebo controlled trial are shown below.

Table 3.a Subjects With at Least 1 Markedly Abnormal Hematology Value During Treatment: Phase 3 Placebo-Controlled Pool

Laboratory Test and Criteria	n/N (%)			
	Placebo N=801	TAK-491 40 mg N=1072	TAK-491 80 mg N=1074	TAK-491 Total (a) N=2146
Hemoglobin	0/785	3/1059 (0.3)	1/1047 (<0.1)	4/2106 (0.2)
>3 g/dL decrease from BL and <LLN				
Hematocrit/PCV	0/785	4/1059 (0.4)	5/1047 (0.5)	9/2106 (0.4)
<0.8×BL and <LLN				
Platelet count				
≥700×10 ⁹ /L	1/786 (0.1)	0/1055	1/1044 (<0.1)	1/2099 (<0.1)
<50×10 ⁹ /L	0/786	0/1055	0/1044	0/2099
RBC	0/785	3/1059 (0.3)	4/1047 (0.4)	7/2106 (0.3)
<0.8×BL and <LLN				
WBC				
>20.0×10 ¹² /L	1/788 (0.1)	1/1059 (<0.1)	0/1049	1/2108 (<0.1)
<2.0×10 ¹² /L	0/788	0/1059	1/1049 (<0.1)	1/2108 (<0.1)

Source: Tables 3.0.1, 3.2.1.

Study pool included 491-008, 009, 010, 011, and 019.

BL=baseline, LLN=lower limit of normal.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

These types of abnormalities were rarely reported regardless of treatment group. Markedly abnormal hematology values were uncommon; low hemoglobin, hematocrit, and RBC counts were observed in 1.7%, 3.2%, and 2.4% of subjects, respectively. Low and high markedly abnormal platelet and WBC counts were observed in <0.2% of subjects.

Individual Clinically Significant Hematology Abnormalities

A hematology value was considered clinically significant if it resulted in a serious adverse event or premature discontinuation. No abnormal hematology values were reported as serious in the Phase 3 Placebo-Controlled, Active-Controlled, or Open-Label Pools.

There were 3 subjects who discontinued prematurely because of a hematology value:

- Subject 491-008/6152-018 (TAK-491 40 mg) discontinued because of basophilia. (The relative basophil values at Baseline and day 37 were 1.0% and 3%, respectively.)
- Subject 491-019/1213-006 (TAK-491 80 mg) discontinued because of eosinophilia. (The relative eosinophil value at Baseline and day 34 were 10.9% and 26.1%, respectively.) Reported adverse events included pruritus on Study Day 31 and rash on Study Day 33.
- Subject 491-016/0022-003 (TAK-491 80 mg plus chlorthalidone 25 mg) discontinued because of leucopenia. The subject entered the study with a Baseline WBC count of 4.06 x10⁹/L. The subject's WBC count was 3.46x10⁹/L at Study Day 25 (TAK-491 40 mg) and 2.60x10⁹/L on Study Day 53 (TAK-491 80 mg). The event was considered resolved on Study Day 67 (WBC count was 4.33x10⁹/L).

Urinalysis Evaluations

Changes from baseline in urinalysis parameters of pH and specific gravity for all treatment groups tended to be small and variable.

Vital signs

There is no evidence that TAK-491 changes heart rate.

ECG finding

A summary of ECG results for the Phase 3 Placebo-Controlled Pool is shown in the table below.

Table 4.a Summary of ECG Results: Phase 3 Placebo-Controlled Pool

Variable	n/N (%)			
	Placebo (N=801)	TAK-491 40 mg (N=1072)	TAK-491 80 mg (N=1074)	TAK-491 Total (a) (N=2146)
Heart rate (bpm)				
<50	8/763 (1)	16/1034 (2)	22/1016 (2)	38/2050 (2)
>120	0	0	0	0
QT interval (msec)				
≥450–<480	35/764 (5)	23/1034 (2)**	25/1015 (2)*	48/2049 (2)
≥480–<500	7/764 (<1)	5/1034 (<1)	4/1015 (<1)	9/2049 (<1)
≥500	0	1/1034 (<1)	3/1015 (<1)	4/2049 (<1)
≥30–<60 CFB	77/764 (10)	69/1034 (7)*	75/1015 (7)*	144/2049 (7)
≥60 CFB	16/764 (2)	15/1034 (1)	12/1015 (1)	27/2049 (1)
≥500 and ≥60 CFB	0	0	2/1015 (<1)	2/2049 (<1)
QTcF interval (msec)				
≥450–<480	40/763 (5)	32/1034 (3)*	33/1015 (3)*	65/2049 (3)
≥480–<500	4/763 (<1)	7/1034 (<1)	5/1015 (<1)	12/2049 (<1)
≥500	0	0	1/1015 (<1)	1/2049 (<1)
≥30–<60 CFB	53/763 (7)	51/1034 (5)	51/1015 (5)	102/2049 (5)
≥60 CFB	9/763 (1)	9/1034 (<1)	7/1015 (<1)	16/2049 (<1)
≥500 and ≥60 CFB	0	0	1/1015 (<1)	1/2049 (<1)

Source: Table 4.2.2.1.

Study pool included monotherapy (491- 008, 011, and 019) and coadministration (491- 009 and 010) studies.

Each dose group combines subjects who received study drug alone, with amlodipine, or with chlorthalidone.

(a) TAK-491 Total combines all subjects who received TAK-491 40 or 80 mg.

CFB=change from Baseline, QTcF=QT interval with Fridericia correction method.

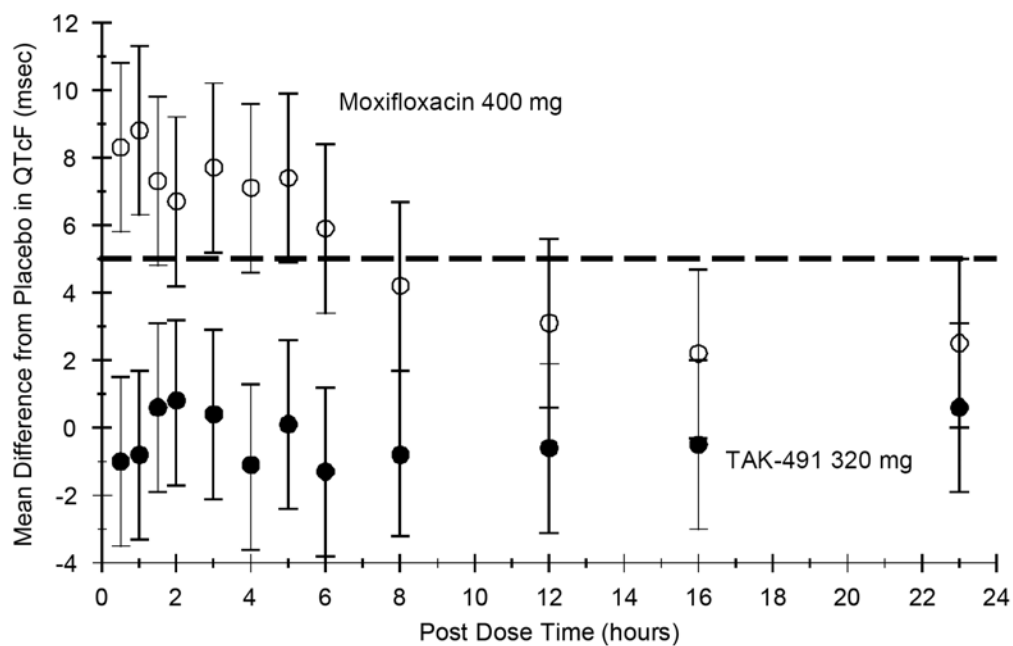
*P≤0.05 vs placebo, **P≤0.01 vs placebo (Fisher exact test).

Incidences of abnormal changes from baseline were similar for all ECG categories in the TAK-491 treatment groups. There is no evidence that TAK-491 has a deleterious effect as determined by changes in ECG.

In the thorough QT/QTc study (491-007), no effect on QTc prolongation was observed following TAK-491 320 mg tablet administration.

The figure below shows the comparison of change from Baseline QTcF interval by scheduled time and treatment.

Figure 4.a Mean Difference from Placebo in Change from Baseline: QTcF Interval and 90% CI



Reviewer's conclusions: TAK-491 appears to have no clinically meaningful effect on pulse, weight, or ECG parameters and a single dose of TAK-491 320 mg did not prolong QTc intervals in healthy subjects.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
12/16/2010

JOHN P LAWRENCE
12/16/2010

HSIEN MING J J HUNG
12/16/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Applicant: Takeda Global

Stamp Date: 4/27/10

Drug Name: azilsartan medoxomil **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?		X		
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number:01-05-TL-491-005 Study Title: Sample Size: 449 Arms: 7 Location in submission: clinical efficacy	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 01-05-TL-491-008 : Indication HYPERTENSION	X			

File name: 5 Clinical Filing Checklist for NDA BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #01-06-TL-491-019 Indication: hypertension				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?				WAIVE
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				SEE STATISTICS
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES X

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

MARYANN GORDON, MD

06-08-2010

Reviewing Medical Officer

Date

Clinical Team Leader

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	azilsartan medoxomil

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
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**Clinical Review
Safety Update**

Application Type NDA# 200796

Submission Type; Code: N_000, original
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Medical Reviewer Maryann Gordon, M.D.
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Established Name Azilsartan medoxomil

(Proposed) Trade Name Edarbi
Therapeutic Class Angiotensin II receptor blocker

Applicant Takeda Pharmaceuticals America, Inc
Priority Designation S

Formulation Tablets
Dosing Regimen Once daily
Indication Treatment of hypertension
Intended Population Hypertensive adults

Conclusions

There is a higher incidence rate of increased blood creatinine values in the subjects taking TAK-491 chlorthalidone combination compared to those taking TAK-491 HCTZ combination. There are no other safety conclusions that differ from the ones based on review of the ISS.

Background

The following safety information was added:

- Phase 3 Open-Label Pool: The ISS Phase 3 Open-Label Pool comprised integrated data from 1 completed (491-016) and 2 ongoing (491-006 and 491-301) phase 3 open-label studies.

- TAK-536 Program (under development in Japan): Updated SAE reports as of 01 June 2010 from these supportive phase 3 studies (536- CCT-005, OCT-002, OCT-003, and OCT-006).

- TAK-491CLD Program [REDACTED] (b) (4): TAK-491 is also being evaluated as a fixed-dose combination (FDC) product with chlorthalidone.

Phase 3 open label pool

The following studies are included:

Table 2.a Study Design Summary: Phase 3 Open-Label Pool

Study Design and Study Number (Regions)		Study Entry Criteria Planned Sample Size	Treatment Duration and Dose/Regimen (a)	Endpoints
Open-label safety study with reversal phase (study completed and reported in the ISS)				
491-016 (US, Lat Am)	Open-label phase	Clinic DBP 95-119 mm Hg N=400	26 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)
	Reversal phase Double-blind Randomized Placebo-controlled	Subjects who completed the open-label phase	6 weeks Continue current dose of TAK-491; maintain stable dose(s) of background BP medication including CLD Substitute placebo for TAK-491; maintain stable dose(s) of background BP medication including CLD	Clinic BP (automated) Safety measures
Open-label safety study with 2 cohorts (additional interim data provided in this Safety Update)				
491-006 (b) (US, Lat Am)	Cohort 1	Clinic DBP 95-119 mm Hg N=350	56 weeks Step 1: TAK-491 40→80 mg TAK-491 + other medications if needed as follows: Step 2: Step 1 + CLD 25 mg Step 3: Step 2 + other antihypertensive agent(s)	Safety measures Clinic BP (automated and manual)
	Cohort 2 Uncontrolled Forced-titration Treat-to-target BP	Clinic DBP 95-119 mm Hg N=300	56 weeks Step 1: TAK-491 40→80 mg (same as Cohort 1) Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated and manual)
Open-label extension of a randomized, double-blind, controlled study (final data provided in this Safety Update)				
491-301 (OL) (US, Lat Am)	Uncontrolled Treat-to-target BP	Subjects who completed double-blind phase N=170	28 weeks Step 1: TAK-491 40 mg Step 2: Step 1 + HCTZ 12.5 mg Step 3: Step 1 + HCTZ 25 mg Step 4: Step 3 + other antihypertensive agent(s)	Safety measures Clinic BP (automated)

BP=blood pressure, CLD=chlorthalidone, DBP=diastolic blood pressure, Lat Am=Latin America, OL=open label, US=United States.

(a) All study drugs were administered QD.

(b) Cohort 1 is complete; Cohort 2 (initiated after enrollment of Cohort 1 was completed) is ongoing. Interim data cut occurred on 30 April 2010 (clinical database) and SAE data cut occurred on 01 June 2010 (pharmacovigilance database).

There were no new subjects added. However, the mean duration of exposure increased from a 215 days to 247 days. The subjects who were treated for at least 48 weeks increased from 270 in the ISS to 482 in the update.

Table 2.b Exposure Duration: Phase 3 Open-Label Pool

Exposure	ISS (a) N=1257	Update (a) N=1257
Days of exposure		
Mean (SD)	215.1 (113.64)	247.2 (127.91)
Median (min-max)	204.0 (1-427)	222.0 (1-427)
Cumulative exposure (n)		
≥1 day	1257	1257
≥2 weeks	1216	1216
≥4 weeks	1200	1200
≥8 weeks	1143	1143
≥12 weeks	1072	1087
≥24 weeks	943	1007
≥48 weeks	270	482

Source: Table 1.4.1.

Study pool included 491- 006 (interim), 016, and 301(OL).

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The subject disposition is shown below for the ISS as well as the update.

Table 2.c Subject Disposition: Phase 3 Open-Label Pool

Discontinuation Reason	Number (%) of Subjects (a)	
	ISS N=1257	Update N=1257
Overall (any discontinuation)	314 (25.0)	353 (28.1)
TEAE	84 (6.7)	88 (7.0)
Protocol deviation	24 (1.9)	25 (2.0)
Lost to follow-up	73 (5.8)	97 (7.7)
Voluntary withdrawal	90 (7.2)	98 (7.8)
Pregnancy	1 (<0.1)	1 (<0.1)
Lack of efficacy	10 (0.8)	11 (0.9)
Investigator discretion	6 (0.5)	6 (0.5)
Other	26 (2.1)	27 (2.1)

Source: Table 1.4.2.

TEAE=treatment-emergent adverse event.

Study pool included 491- 006 (interim), 016, and 301(OL).

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The percent of discontinuations for any reason increased from 25 % in the ISS to 28% in the update. The reason that had the largest change was “lost to follow up.”

Discontinuations for adverse events increased slightly.

Adverse events reported by at least 2% of subjects are shown below.

Table 2.d Common TEAEs (≥2% Incidence): Phase 3 Open-Label Pool

Preferred Term	Number (%) of Subjects (a)	
	ISS N=1257	Update N=1257
Overall (any TEAE)	795 (63.2)	838 (66.7)
Dizziness	136 (10.8)	143 (11.4)
Headache	108 (8.6)	113 (9.0)
Urinary tract infection	62 (4.9)	70 (5.6)
Fatigue	66 (5.3)	68 (5.4)
Upper respiratory tract infection	53 (4.2)	56 (4.5)
Back pain	30 (2.4)	37 (2.9)
Cough	31 (2.5)	37 (2.9)
Blood creatinine increased	29 (2.3)	36 (2.9)
Diarrhoea	35 (2.8)	36 (2.9)
Hypotension	36 (2.9)	36 (2.9)
Nasopharyngitis	25 (2.0)	35 (2.8)
Arthralgia	27 (2.1)	32 (2.5)
Nausea	30 (2.4)	30 (2.4)
Muscle spasms	27 (2.1)	28 (2.2)
Sinusitis	21 (1.7)	28 (2.2)
Oedema peripheral	23 (1.8)	27 (2.1)
Blood CK increased	26 (2.1)	26 (2.1)
Influenza	20 (1.6)	26 (2.1)

Source: [Tables 2.4.1](#) and [2.4.4.1](#).

Study pool included 491- 006 (interim), 016, and 301(OL).

CK=creatinine phosphokinase.

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

The overall reporting rate increased from 63% in the ISS to 67% in the update. The events that increased by at least 1% include dizziness and urinary tract infection.

Common adverse events by time interval are shown below.

Table 2.e Common TEAEs by Time Interval: Phase 3 Open-Label Pool

Preferred Term	Number (%) of Subjects (a)							
	1-3 Months		>3-6 Months		>6-9 Months		>9 Months	
	ISS N=1257	Update N=1257	ISS N=1040	Update N=1070	ISS N=918	Update N=979	ISS N=291	Update N=497
Overall (any TEAE)	632 (50.3)	639 (50.8)	334 (32.1)	346 (32.3)	149 (16.2)	198 (20.2)	77 (26.5)	131 (26.4)
Dizziness	96 (7.6)	98 (7.8)	29 (2.8)	30 (2.8)	9 (1.0)	12 (1.2)	6 (2.1)	8 (1.6)
Headache	80 (6.4)	80 (6.4)	20 (1.9)	21 (2.0)	8 (0.9)	11 (1.1)	4 (1.4)	7 (1.4)
UTI	37 (2.9)	37 (2.9)	13 (1.3)	14 (1.3)	10 (1.1)	13 (1.3)	2 (0.7)	6 (1.2)
Fatigue	53 (4.2)	53 (4.2)	5 (0.5)	6 (0.6)	2 (0.2)	3 (0.3)	2 (0.7)	1 (0.2)
URI	25 (2.0)	25 (2.0)	20 (1.9)	20 (1.9)	4 (0.4)	5 (0.5)	5 (1.7)	8 (1.6)
Back pain	17 (1.4)	17 (1.4)	8 (0.8)	9 (0.8)	4 (0.4)	6 (0.6)	1 (0.3)	5 (1.0)
Cough	14 (1.1)	14 (1.1)	12 (1.2)	12 (1.1)	2 (0.2)	5 (0.5)	2 (0.7)	5 (1.0)
Blood creatinine increased	13 (1.0)	15 (1.2)	8 (0.8)	8 (0.7)	4 (0.4)	6 (0.6)	0	3 (0.6)
Diarrhoea	22 (1.8)	22 (1.8)	8 (0.8)	9 (0.8)	3 (0.3)	3 (0.3)	0	0
Hypotension	21 (1.7)	21 (1.7)	16 (1.5)	16 (1.5)	4 (0.4)	4 (0.4)	1 (0.3)	1 (0.2)
Nasopharyngitis	10 (0.8)	11 (0.9)	9 (0.9)	10 (0.9)	5 (0.5)	8 (0.8)	3 (1.0)	7 (1.4)
Arthralgia	18 (1.4)	19 (1.5)	5 (0.5)	5 (0.5)	4 (0.4)	5 (0.5)	0	3 (0.6)
Nausea	26 (2.1)	26 (2.1)	2 (0.2)	2 (0.2)	3 (0.3)	3 (0.3)	0	0
Muscle spasms	17 (1.4)	17 (1.4)	7 (0.7)	7 (0.7)	2 (0.2)	3 (0.3)	1 (0.3)	2 (0.4)
Sinusitis	18 (1.4)	18 (1.4)	3 (0.3)	3 (0.3)	0	5 (0.5)	0	2 (0.4)
Oedema peripheral	12 (1.0)	12 (1.0)	5 (0.5)	6 (0.6)	2 (0.2)	4 (0.4)	1 (0.3)	2 (0.4)
Blood CK increased	19 (1.5)	19 (1.5)	1 (<0.1)	1 (<0.1)	2 (0.2)	2 (0.2)	3 (1.0)	3 (0.6)
Influenza	9 (0.7)	9 (0.7)	6 (0.6)	6 (0.6)	4 (0.4)	6 (0.6)	1 (0.3)	5 (1.0)

Source: Table 2.4.15.

Study pool included 491- 006 (interim), 016, and 301(OL).

CK=creatinine phosphokinase, URI=upper respiratory tract infection.

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

Half of the adverse events were reported in the first three months of the study. The reports for most adverse events tended to decreased with increasing length of study duration except for nasopharyngitis and influenza.

There were no additional deaths reported in the open label pool. There were 3 subjects (all taking 80 mg of TAK-491) with serious adverse events that were reported after the completion of the ISS: 47 year old female with anemia, 47 year old female with viral gastroenteritis, and 55 year old female with depression, psychotic disorder, post-traumatic stress disorder.

The discontinuation rate for adverse events was 9% for both the ISS and the safety update. There were 2 subjects who discontinued since the completion of the ISS: 59 year old female with chest pain that resolved and 41 year old male with hyperkalemia that also resolved.

Serum creatinine elevations, shown in the table below, were similar in both the ISS and the safety update.

Table 2.j Categorical Analyses of Creatinine Elevations: Phase 3 Open-Label Pool

Criterion Visit	n/N (%) (a)	
	ISS (N=1257)	Update (N=1257)
Subjects with $\geq 30\%$ change from Baseline and $>ULN$		
Any postbaseline visit	177/1218 (14.5)	185/1218 (15.2)
Final Visit	69/1218 (5.7)	70/1218 (5.7)
Subjects with $\geq 50\%$ change from Baseline and $>ULN$		
Any postbaseline visit	106/1218 (8.7)	112/1218 (9.2)
Final Visit	41/1218 (3.4)	45/1218 (3.7)

Source: Tables 3.4.7 and 3.4.9.

Study pool included 491- 006 (interim), 016, and 301(OL).

(a) Combines all subjects who received TAK-491 40 or 80 mg alone, with chlorthalidone or HCTZ, or with chlorthalidone or HCTZ plus another non-ARB antihypertensive agent.

Overall, there is no change in the interpretation of the safety of TAK-491 with the addition of safety update data.

TAK-491CLD PHASE 3 STUDIES

TAK-491 is also being evaluated as a fixed dose product with chlorthalidone (TAK-491CLD) in the ongoing clinical development program being conducted under (b) (4). To date, TAK-491CLD has been evaluated in 4 phase 1 studies (491CLD- 102, 103, 104, and 105), all of which were included in the TAK-491 NDA to provide supportive safety information. In addition, there are 4 phase 3 studies (491CLD- 301, 302, 303, and 308) that are ongoing and 1 phase 3 study (491CLD-306) that was recently completed.

Study 491-306 was a randomized, double-blind, parallel-group study comparing the efficacy and safety of TAK-491CLD fixed dose combination (FDC) with coadministration of TAK-491 and HCTZ in subjects with moderate to severe hypertension (SBP 160-190 mm Hg inclusive). All subjects initiated treatment with single-blind TAK-491 40 mg (2-week single-blind period), followed by the addition of chlorthalidone or HCTZ (8-week double-blind period) in the form of an FDC tablet (TAK-491 40 mg plus 12.5 mg of chlorthalidone) or coadministered TAK-491 40 mg plus 12.5 mg HCTZ. After 4 weeks of double-blind treatment (Week 6), subjects who did not reach their target blood pressure had their dose of chlorthalidone or HCTZ titrated to 25 mg, while subjects who did reach their target blood pressure continued chlorthalidone or HCTZ 12.5 mg for the duration of the study. Target blood pressure was defined as $<140/90$ mm Hg ($<130/80$ mm Hg for subjects with diabetes or chronic kidney disease), and dose titration at Week 6 was based on the mean of 3 sitting clinic blood pressure measurements.

There were 609 randomized subjects (303 on TAK-401 plus CLD and 306 on TAK-491 plus HCTZ). The incidence of withdrawals from study for adverse events was higher in the CLD combination (9%) compared to the HCTZ combination (6%).

	Number of Subjects (%)		
	TAK-491CLD (N = 303)	TAK-491+HCTZ (N = 306)	Total (N = 609)
Randomized But Not Treated	1 (0.3)	3 (1.0)	4 (0.7)
Completed Study Drug	252 (83.2)	260 (85.0)	512 (84.1)
Prematurely Discontinued Study Drug	51 (16.8)	46 (15.0)	97 (15.9)
Primary Reason for Discontinuation of Study Drug			
Adverse Event	28 (9.2)	19 (6.2)	47 (7.7)
Major Protocol Deviation	2 (0.7)	2 (0.7)	4 (0.7)
Lost to Follow-Up	3 (1.0)	2 (0.7)	5 (0.8)
Voluntary Withdrawal	16 (5.3)	14 (4.6)	30 (4.9)
Study Termination	0	0	0
Pregnancy	0	0	0
Lack of Efficacy	0	2 (0.7)	2 (0.3)
Other	2 (0.7)	7 (2.3)	9 (1.5)

Treated=treated with active single-blind/double-blind study drug.

Note 1: Subjects take TAK-491 40 mg in the study, with titration to 12.5 mg (Chlorthalidone [CLD] or Hydrochlorothiazide [HCTZ]) at Week 2, and then to 25 mg (CLD and HCTZ) at Week 6, if needed.

Note 2: Primary reasons for discontinuation of study drug are mutually exclusive and exhaustive categories.

Note 3: Subjects who are randomized but not treated will also be counted as prematurely discontinued study drug.
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The table below shows the adverse events reported by at least 2% of subjects in the CLD combination.

Table 15.3.1.4.1
Treatment-Emergent Adverse Events by Preferred Term
Safety Analysis Set

Preferred Term	Number of Subjects (%)		
	TAK-491CLD (N=302)	TAK-491+HCTZ (N=303)	Total (N=605)
Subjects With Any Treatment-Emergent AEs	158 (52.3)	144 (47.5)	302 (49.9)
Dizziness	37 (12.3)	32 (10.6)	69 (11.4)
Blood creatinine increased	39 (12.9)	27 (8.9)	66 (10.9)
Headache	16 (5.3)	16 (5.3)	32 (5.3)
Fatigue	11 (3.6)	10 (3.3)	21 (3.5)
Asthenia	9 (3.0)	6 (2.0)	15 (2.5)
Hypotension	7 (2.3)	3 (1.0)	10 (1.7)

There were a few more reports of dizziness, increased blood creatinine, asthenia and hypotension in the CLD combination compared to the HCTZ combination.

Two additional deaths were reported in the update:

-subject 1023/024 (TAK-491 40 mg), a 61-year-old, Black female had sudden death on Day 6 of the active treatment period. An autopsy was not performed and circumstances surrounding the death are unknown. The subject's relevant medical history included sleep apnea, obesity, and lower extremity pitting edema. The subject's baseline blood pressure was 191/104 mm Hg.

-Subject 1047/002 (TAK-491CLD 40 mg/12.5 mg), a 67-year-old, White male had sudden death on Day 15 of the active treatment period, when he did not wake from an afternoon nap. The subject had received single-blind TAK-491 40 mg for 2 weeks and a

single dose of double-blind TAK-491CLD 40 mg/12.5 mg. His blood pressure was 162/91 mm Hg at baseline and 131/82 mm Hg at the study visit on the day prior to his death. The subject's relevant medical history included obesity (body mass index >32). Acute cardiovascular insufficiency was provided as cause of death on the death certificate; an autopsy was not performed.

These types death are not unexpected in subjects with moderate to severe hypertension.

The table below shows the serious adverse events reported in this study.

Table 3.a Nonfatal SAEs by Treatment Group: 491CLD-306

Site/Subject Sex/Age	Most Recent Treatment	Preferred Term	Onset Day	Relationship to Drug (a)	Action/ Outcome
TAK-491CLD Treatment Group					
1010/019 Male/52	TAK-491 40 mg	Unstable angina	6	Not related	Drug withdrawn/ Resolved
		Coronary artery occlusion	6	Not related	Drug withdrawn/ Resolved
		Coronary artery stenosis	10	Not related	Not applicable (b)/ Resolved
1017/037 Female/72	TAK-491CLD 40 mg/12.5 mg	Blood creatinine increased	15	Definite	Drug withdrawn/ Not resolved
	TAK-491CLD 40 mg/12.5 mg	Renal failure chronic	21	Probable	Drug withdrawn/ Not resolved
1023/022 Female/57	TAK-491CLD 40 mg/12.5 mg	Chest discomfort	43	Not related	Drug withdrawn/ Resolved
1026/026 Female/68	TAK-491CLD 40 mg/12.5 mg	Gastrointestinal haemorrhage	48	Possible	Drug withdrawn/ Resolved
1032/002 Female/64	TAK-491CLD 40 mg/12.5 mg	Breast cancer	23	Not related	Not applicable (b)/ Not resolved
TAK-491+HCTZ Treatment Group					
1014/004 Male/71	TAK-491+HCTZ 40 mg+12.5 mg	Cerebrovascular accident	31	Possible	Drug withdrawn/ Resolved with sequelae
1021/003 Female/70	TAK-491+HCTZ 40 mg+12.5 mg	Pneumonia	61	Not related	Dose not changed/ Resolved
1022/039 Male/40	TAK-491+HCTZ 40 mg+12.5 mg	Chest pain (gastrointestinal etiology)	24	Not related	Drug withdrawn/ Resolved
1025/010 Female/70	TAK-491+HCTZ 40 mg+12.5 mg	Syncope	27	Possible	Drug withdrawn/ Resolved
		Renal failure acute	27	Possible	Drug withdrawn/ Resolved
		Pulmonary embolism	34	Not related	Not applicable (b)/ Resolved

Source: [Appendix E Table 15.3.2.2.](#)

(a) As judged by the investigator.

(b) Not applicable, as study drug had previously been withdrawn.

There were two reports of renal failure and one report of syncope.

The adverse events leading to discontinuation are shown below.

Table 3.b Permanent Study Withdrawal TEAEs (≥2 Subjects): 491CLD-306

Preferred Term	Number (%) of Subjects		
	TAK-491CLD N=302	TAK-491+HCTZ N=303	Total N=605
Blood creatinine increased	12 (4.0)	4 (1.3)	16 (2.6)
Dizziness	3 (1.0)	4 (1.3)	7 (1.2)
Hypotension	2 (0.7)	2 (0.7)	4 (0.7)
Blood urea increased	2 (0.7)	2 (0.7)	4 (0.7)
Blood sodium decreased	2 (0.7)	1 (0.3)	3 (0.5)
Syncope	1 (0.3)	1 (0.3)	2 (0.3)
Tachycardia	0	2 (0.7)	2 (0.3)
Hyperhidrosis	1 (0.3)	1 (0.3)	2 (0.3)
Headache	1 (0.3)	1 (0.3)	2 (0.3)

Source: [Appendix E Tables 15.3.1.10 and 15.3.2.1](#) and [Appendices 16.2.1.2 and 16.2.7.1](#).

There were more withdrawals for increased blood creatinine in the CLD combination (4%) compared to the HCTZ combination (1%). The other events were reported at similar rates.

Incidence rates of abnormal elevations of blood creatinine by study drug are shown below.

Table 3.c Categorical Analyses of Creatinine Elevations: 491CLD-306

	n/N (%)	
	TAK-491CLD N=302	TAK-491+HCTZ N=303
Subjects with Creatinine Elevations ≥30% above Baseline and >ULN		
Any postbaseline visit (a)	41/297 (13.8)	25/298 (8.4)
Final Visit (b)	15/297 (5.1)	4/298 (1.3)
Subjects with Creatinine Elevations ≥50% above Baseline and >ULN		
Any postbaseline visit (a)	26/297 (8.8)	14/298 (4.7)
Final Visit (b)	8/297 (2.7)	3/298 (1.0)

Source: [Appendix E Table 15.3.4.9](#).

(a) Experienced at least one creatinine increase with prespecified percentage above Baseline and > ULN.

(b) Last observation carried forward; the last observation collected up to 7 days (inclusive) after the last dose of active study medication.

There were more creatinine elevations (both ≥ 30% and ≥ 50%) in the CLD combination, any time post base as well as at final visit, compared to the HCTZ combination. Both drug groups had fewer elevations at final visit, implying that the abnormality resolves in most (but not all) subjects even with continued treatment.

TAK-536 studies

To date, TAK-536, the active moiety of TAK-491, has been evaluated in 18 phase 1 studies, 5 phase 2 studies, and 5 FDC studies (TAK-536 with pioglitazone), all of which were included in the TAK-491 NDA to provide supportive safety information.

Additionally, SAE reports as of 03 February 2010 were provided in the NDA for 4 ongoing phase 3 studies in Japan.

There were seven additional subjects with reports of serious adverse events. These are shown below.

Table 4.a SAEs as of 01 June 2010 by Treatment Group: TAK-536 Phase 3 Studies

Subject Sex/Age	Treatment	Preferred Term	Onset Day	Relationship to Drug (a)	Action/Outcome
536-OCT-002/0015-005 Female/61	Placebo	Cholelithiasis, pancreatitis acute	8	Not related	Drug withdrawn/ Resolved
536-OCT-002/0001-007 Male/67	TAK-536 10 mg	Cardiac failure	7	Not related	Drug withdrawn/ Resolved
536-OCT-002/0016-002 Male/61	TAK-536 10 mg	Subdural haematoma	8	Not related	Drug withdrawn/ Resolved with sequelae
536-OCT-006/0006-012 Female/78	TAK-536 40 mg	Aggravated cataract	82	Not related	Dose not changed/ Resolved
536-OCT-006/0021-011 Male/57	TAK-536 40 mg	Road traffic accident, ankle fracture	90	Not related	Drug withdrawn/ Resolved
536-OCT-006/0001-001 Male/71	TAK-536 40 mg	Hepatic neoplasm malignant	198	Not related	Drug withdrawn/ Not resolved
536-CCT-005/0032-016 Female/51	Blinded (b)	Breast cancer female	83	Not related	Drug withdrawn/ Not resolved

Source: [Appendix C](#).

(a) As judged by the investigator.

(b) TAK-536 40 mg or candesartan 12 mg.

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/s/

MARYANN GORDON

02/02/2011