CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200796Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review Memo

Date	January 21, 2011
From	Shari L. Targum, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	NDA #200,796
Proprietary / Established (USAN) names	Edarbi/Azilsartan medoxomil
Dosage forms / strength	Oral tablets/ 40 and 80 mg
Proposed Indication(s)	Treatment of hypertension
Recommended:	*Approval*

Purpose of Cross-Discipline Team Leader (CDTL) Review

The purpose of this CDTL review is to integrate the discipline reviews for this application and provide additional comments and recommendations.

This review is based, in part, on the following primary reviews:

Chemistry (Prafull Shiromani Ph.D. and Charles Jewell, Ph.D.); ONDQA Biopharmaceutics (Tien-Mien Chen, Ph.D.); Pharmacology/Toxicology (Philip J. Gatti, Ph.D. and William T. Link, Ph.D.); Clinical pharmacology (Divya Menon-Andersen, Ph.D.); and Clinical-statistical (Maryann Gordon, M.D. and John Lawrence, Ph.D.).

The cross-discipline team leader concurs with the medical, statistical and clinical pharmacology reviewers in recommending approval, pending resolution of dosing and agreement on labeling.

Note: Azilsartan medoxomil (AZM) is used interchangeably with the term TAK-491; azilsartan (AZ) is used interchangeably with TAK-536.

1. Introduction to Review

TAK-491, or azilsartan medoxomil (AZM), is a prodrug of azilsartan (AZ), an angiotensin II receptor blocker (ARB). After oral administration, the prodrug is rapidly converted to the active moiety, azilsartan (TAK-536), by ester hydrolysis in the gut and/or during the process of absorption.

Several ARBs, including olmesartan, losartan, candesartan and valsartan, have been approved for the treatment of hypertension. Olmesartan medoxomil, currently marketed, shares the same medoxomil side-chain.

In support of efficacy and safety, the sponsor submitted three double-blind, placebo-controlled Phase 3 studies; two active-controlled studies; dose-ranging studies of TAK-491 and TAK-536; a long-term randomized withdrawal study; and two co-administration studies (with chlorthalidone and amlodipine, respectively). These studies are summarized in Sections 5.1.3 and 7.1.2. Issues of interest include: dosing (sections 5.1.2, 7.1.2, 13.1); (b) (4) (b) (4) (section 7.1.2); and creatinine elevations (7.2.2).

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

An IND #71,867 for azilsartan was filed on 4/20/2005 and allowed to proceed. The Agency and the sponsor met on 4/6/2006 (End-of-Phase 1), 4/26/2007 (End-of-Phase 2), 6/16/2008 (CMC End-of-Phase 2), 5/19/2009 (Type C Guidance, related to creatinine elevations) and 10/27/2009 (pre-NDA). NDA #200796 was filed on 4/28/2010 as an electronic submission.

Azilsartan is not approved in any country.

3. CMC/Microbiology/Device

The Chemistry reviewers are recommending approval of NDA 200796 (proposed doses in labeling); all information requests have been addressed and issues resolved.

3.1. General product quality considerations

3.1.1. Drug Substance:

(b) (4)

According to the reviewers, the controls for all raw materials used in the manufacture have been adequately described and shown to produce consistent batches of drug substance within the sponsor's proposed specifications. (b) (4)

3.1.2. Drug Product:

The sponsor submitted data for the 20, 40 and 80 mg azilsartan medoxomil tablets; the different strengths are differentiated by size and debossing codes (b) (4) All manufacturing processes were shown to be controllable within the acceptable process ranges.

3.1.3. Stability and shelf-life:

The drug substance has been determined to be humidity and light-sensitive; so packaging requires protection from light and moisture.

Based on stability studies, an initial expiration dating period of 24 months for drug product was acceptable to the chemistry reviewers.

3.1.4. Facilities review/inspection:

Five sites involved in the manufacture of drug product were reviewed by the Office of Compliance and found to be acceptable. The Office of Compliance issued an Overall Recommendation of Acceptability on June 9, 2010.

3.2. Other notable issues *(resolved or outstanding)* None.

4. Nonclinical Pharmacology/Toxicology

According to the nonclinical pharmacology/toxicology reviewers, azilsartan medoxomil is approvable following recommended changes in the labeling sections on mutagenesis and reproductive toxicology.

The reviewers concluded that azilsartan medoxomil does not appear to have any major unique toxicities compared to other approved angiotensin receptor-antagonists. The observed toxicity targets were the kidney, adrenal gland and GI tract. Olmesartan medoxomil, the only other approved ARB with a medoxomil side chain, has similar toxicities. The renal and adrenal effects appear related to the primary pharmacology and are consistently seen with drugs affecting the renin-angiotensin-aldosterone system (RAAS).

4.1. General nonclinical pharmacology/toxicology considerations

Azilsartan medoxomil is a competitive reversible ARB (IC_{50} = 0.62-2.6 nmol/L). The drug produces a dose-dependent decrease in arterial blood pressure in a variety of hypertensive animal models such as spontaneously hypertensive rats and renal hypertensive dogs; it blocks the pressor effect of angiotensin II in rats.

4.1.1. Toxicology:

The toxicology program included assessment of the pro-drug (TAK-491) and active moiety (TAK-536) in single and repeat-dose toxicity studies in rats (up to 26 weeks, ≤ 2000 mg/kg) and dogs (up to 26 weeks with TAK-491 (≤ 60 mg/kg) and up to 52 weeks with TAK-536 (≤ 300 mg/kg), rodent carcinogenicity studies, genotoxicity studies, and reproduction and developmental toxicity studies. The major human metabolite, TAK-536 M-II, was examined in rat and dog repeat-dose toxicity studies (up to 13 weeks in duration), in 6-month transgenic

mouse and 2-year rat carcinogenicity assays, and in genotoxicity and reproduction/developmental studies.

The following toxicologic findings were observed with azilsartan medoxomil:

1. Dark red foci and stomach erosion (rats, 20-fold higher AUC than humans) and GI ulceration (dogs, 5-fold higher AUC than humans); olmesartan medoxomil produced similar findings.
2. Juxtaglomerular cell hypertrophy, consistent with chronic pharmacologic effects of angiotensin-receptor blockers and ACE inhibitors;
3. Minimal or mild atrophy of the adrenal zona glomerulosa. These effects appear in toxicology studies of other ARB and ACE inhibitors.

Toxicologic studies of the major metabolite TAK-536 M-II showed that this compound is relatively devoid of pharmacologic activity; in 13-week repeat-dose rat toxicity studies, renal/adrenal/stomach toxicities were not observed with reported NOAELs in the 300 mg/kg/day (male) and 3000 mg/kg/day range.

4.1.2. Genetic toxicology:

Structural chromosomal aberrations were observed in the Chinese Hamster Lung Cytogenetic Assay with the prodrug, azilsartan medoxomil (TAK-491) and the metabolite, TAK-536 MII without metabolic activation. The active moiety, azilsartan (TAK-536) was also positive in this assay both with and without metabolic activation. Other genetic toxicity assays were negative. The reviewers recommended that these findings be added to labeling.

4.2. Carcinogenicity:

4.2.1. Matthew Jackson, Ph.D. (Division of Biometrics 7) reviewed the carcinogenicity studies and observed a "significant trend" for hemolymphoreticular histiocytic sarcomas in the case of the pro-drug; however, he noted that the p-value was considered significant, after adjusting for multiplicity, only when such tumors are considered rare, and "a strong case could be made to consider them common." He also observed an increased incidence rate for adrenal cortical cell adenomas in treated female rats compared to the control group, but made a similar argument that the results depended on background incidence rate of the tumor. In the metabolite study, he reported three cases of nasal cavity hemangiosarcomas in high-dose female rats, which he considered significant if such tumors were considered to be rare.

4.2.2. The Executive Carcinogenicity Assessment Committee (CAC) (Sept. 2010) felt that these tumors should be assessed using common tumor criteria of α=0.005 for trend and α=0.01 for pairwise comparisons; consequently, the analyses did not reach statistical significance. In addition, the mode of action of azilsartan did not suggest that these tumors were pharmacologically related. The CAC concluded that there were no drug-related neoplasms; and that doses tested were adequate; the pharmacology reviewers concurred that the 2-year carcinogenicity studies were negative.

4.3. Reproductive toxicology:

In the rat and rabbit embryo-fetal developmental studies, there were minor variations in fetal development observed in both species at doses of 100 mg/kg/day [122 x MRHD[1]] in rats and 50 mg/kg/day [12 x MRHD in rabbits]. Maternal toxicity (decrease in food consumption and body weight) was observed at 1.2x MRHD in rats and 2.3X MRHD in rabbits.

There were adverse effects on pup viability in the peri- and postnatal rat development studies at a dose 1.2x the MRHD on a mg/m2 basis. In addition, delayed incisor eruption and renal pelvis dilatation with hydronephrosis were observed at the lowest (10 mg/kg/day) dose.

This reviewer concurs with the pharmacology-toxicology reviewers that TAK-491 should be contraindicated in pregnancy as are other drugs in this class.

4.4. Other notable issues: None

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics review team has recommended approval. Given azilsartan's flat dose-response relationship over the 10-80 mg dose range, the reviewers have recommended approval of azilsartan medoxomil 40 mg as the highest strength.

5.1. General clinical pharmacology/biopharmaceutics considerations:

The final to-be marketed formulation of azilsartan medoxomil (AZM) tablet was used in all Phase 3 studies, while AZM capsules or azilsartan (AZ) tablet was used in the Phase 1 and 2 studies.

5.1.1. The relative AZ bioavailability of AZM tablet and AZM capsule, compared to equal dose of AZ tablet (reference), was about 80% and 50%, respectively. The absolute bioavailability of AZ following administration of AZM tablet is 58%; peak AZ concentrations are achieved within 3 hours post-dose. Food did not affect systemic exposure to AZ following administration of AZM tablet. AZ is > 99% bound to plasma albumin and this is concentration independent. AZM inhibits the efflux transporter, p-glycoprotein. AZ does not inhibit or induce CYPs.

5.1.2. The pharmacokinetics of AZ following single and repeat doses of AZM tablet are dose-proportional in the range of 20 to 320 mg. Accumulation ratio for AZ following once daily administration for 10 days was ~ 1.2; mean CL/F was about 1.5 L/h and mean elimination half-life was ~ 12 hours. Peak to trough ratio at steady state was ~ 5.

5.1.3. Dose-ranging studies:

The sponsor submitted three randomized, double-blind, dose-ranging studies; of these, 491-005 utilized TAK-491 (AZM) capsules and the other two studies (536-002, 536-CCT-001) utilized TAK-536 (AZ) tablets.

[1] MRHD refers to Maximum Recommended Human Dose.

Study 491-005 randomized hypertensive subjects to TAK-491 5, 10, 20, 40 80 mg capsules, placebo, or olmesartan for 8 weeks. The primary endpoint was the change from baseline in cuff diastolic blood pressure (DBP). Secondary endpoints included ambulatory blood pressure monitoring (ABPM) systolic blood pressure (SBP) and DBP. Statistically significant SBP and DBP lowering vs. placebo were observed for all doses except for DBP reduction in the 5 mg group (p = 0.063). There was no further blood pressure (BP) lowering effect, by cuff or ABPM, observed with 80 mg.

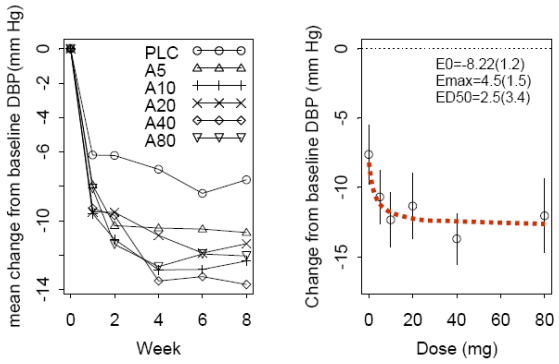

Figure 1. 491-005: Steady-state effect was reached by week 4 (left panel). Symbols represent mean DBP. There is no dose-dependent decrease in DBP in the 10-80 mg range (right panel). Model parameters are presented as mean (SE). Source: clinical pharmacology review

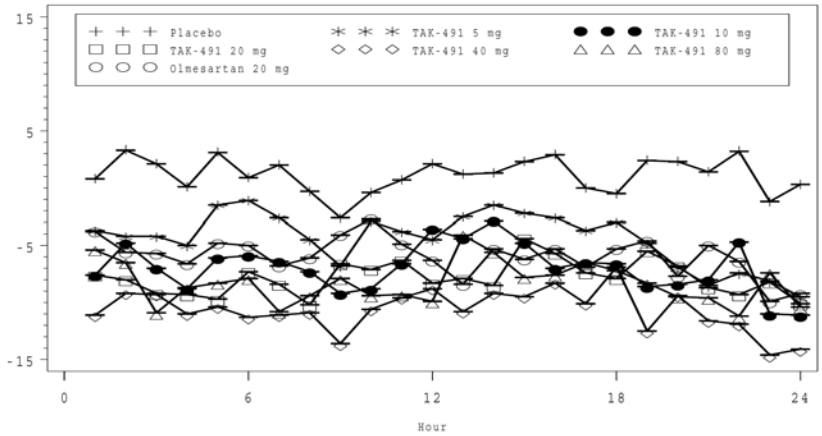

Figure 2. Study 491-005: change from baseline in mean hourly DBP (mm Hg). BP lowering appears maintained throughout the inter-dosing interval (source: clinical pharmacology review).

SBP and DBP treatment effects are maintained throughout the inter-dosing interval, with the largest effect size in subjects dosed with 40 mg. BP reduction corresponding to peak plasma AZ concentrations (1-3 h) was similar to trough (24 h), indicating a shallow exposure-response (E-R) relationship at steady state. Placebo-corrected peak (maximal effect post-dosing) to trough ratio ranged from 0.8 to 1.34 for the doses tested.

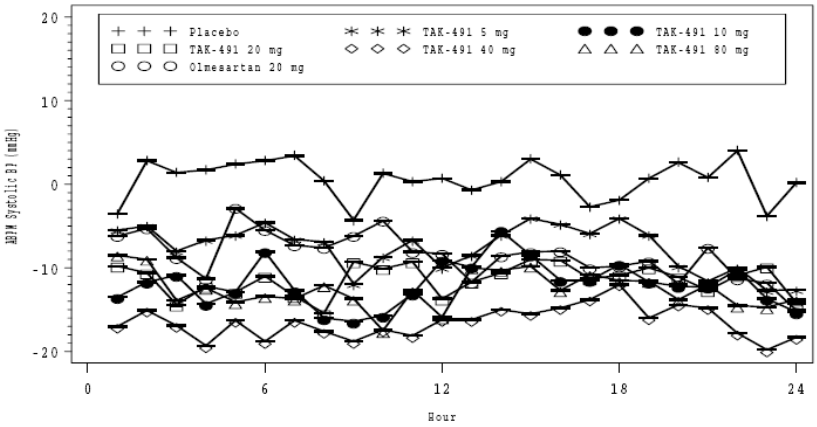

Figure 3. Study 491-005: ABPM Change from baseline in mean SBP (mm Hg) by hour

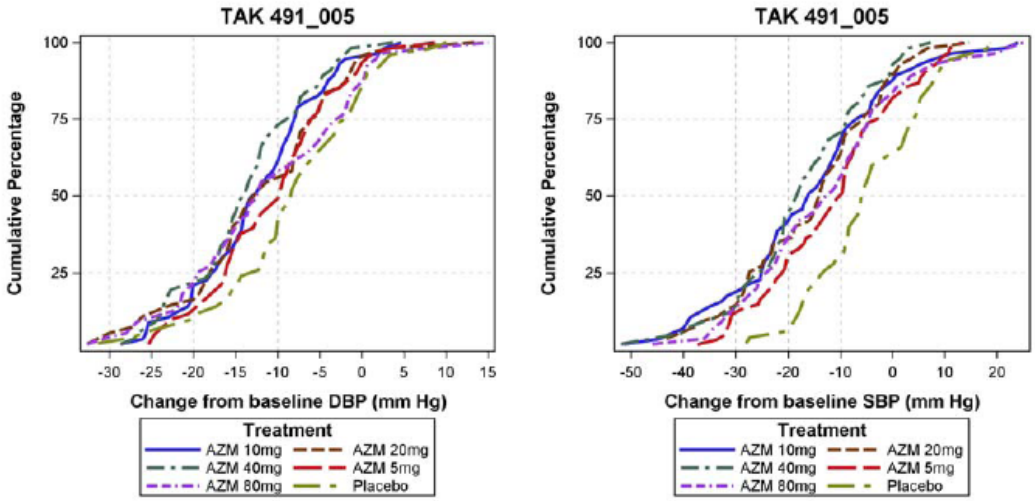

Figure 4. Study 491-005: Cumulative distribution for DBP and SBP change from baseline. The range of blood pressure reduction is similar across doses of AZM; there is no additional benefit of 80 mg (source: Dr. D. Menon-Andersen).

The sponsor also conducted a dose-ranging study for TAK-536 tablets, using doses of 2.5, 5 10, 20 and 40 mg once daily (QD) and including an olmesartan 20 mg QD arm for 8 weeks of treatment. Study 536-002 results are shown below because the sponsor based Phase 3 dosing on this study.

The primary efficacy endpoint was the change in cuff sitting DBP; the study also included ABPM measurements.

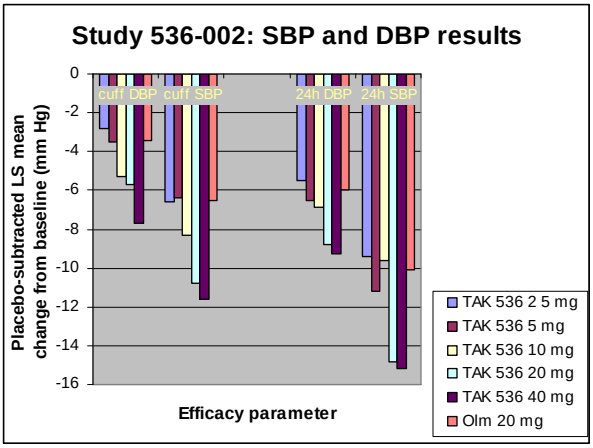

Figure 5. Placebo-subtracted LS mean change from baseline in SBP and DBP by cuff and mean 24-hr ABPM (source: CSR: 536-002).

All active treatments showed a statistically significant treatment effect for SBP and DBP ($p < 0.05$) except for cuff DBP at TAK 536 2.5 mg ($p=0.055$). The effect sizes for TAK-536 20 and 40 mg were similar for 24-hour mean SBP, DBP and the change in cuff SBP; an increase in effect size was observed for TAK-536 40 mg in the cuff DBP parameter.

5.2. Drug-drug interactions

5.2.1. Effect of co-administered drugs on AZ

There was no clinically significant change in systemic exposure to AZ when administered with CYP 2C9 inhibitor (fluconazole), p-gp inhibitor (ketoconazole), p-gp substrate (digoxin), antihypertensives (amlodipine, chlorthalidone), antidiabetics (metformin, pioglitazone) and antacids (Mylanta).

5.2.2. Effect of AZ on co-administered drugs

There was no clinically significant change in systemic exposure to midazolam (CYP 3A4/5 substrate), dextromethorphan (CYP 2D6 substrate), tolbutamide (CYP 2C9 substrate), caffeine (CYP 1A2 substrate), fexofenadine (P-gp substrate), warfarin, glyburide, metformin, chlorthalidone, digoxin (P-gp substrate), amlodipine, pioglitazone following repeat administration of AZM.
Although *in vitro* studies showed that AZM inhibited P-gp, systemic exposure to digoxin (p-gp substrate) was not altered following repeat once daily administration of 80 mg AZM.

5.3. Metabolism and Elimination

AZ is metabolized, mainly by CYP 2C9, to a lesser extent CYP 2C8 and CYP 2B6, to form two inactive metabolites. AZ is eliminated mostly in the urine as inactive metabolites; the mean half-life of AZ is about 12 hours.

5.3.1. Hepatic Impairment

Following repeat administration, peak and total AZ concentrations were ~ 20% and 75% higher in subjects with moderate hepatic impairment compared to those with normal hepatic

function; no dose adjustment was felt necessary in this group. Systemic exposure to AZ was not studied in subjects with severe hepatic impairment.

5.3.2. Renal Impairment

A single-dose study resulted in a 200% increase in peak and total AZ exposure in subjects with severe renal impairment vs. those with normal renal function. Given the shallow dose-response relationship for AZ and the absence of significant tolerability issues and adverse reactions, the clinical pharmacology reviewer felt that this increase in exposure was not of clinical significance.

A smaller increase of ~25% in total exposure to AZ was observed in subjects with mild or moderate renal impairment compared to subjects with normal renal function, and dose adjustments were not felt necessary in this population.

5.4. Demographic interactions/special populations

No dose adjustments are needed based on advanced age, gender, or race.

5.5. Thorough QT study or other QT assessment

No significant QT change was observed with AZM. The effect of a single dose of AZM 320 mg was assessed in a thorough QT study with adequate assay sensitivity and ΔΔQTcF 1.0 ms (90% CI: -1.3, 3.4).

5.6. Other notable issues *None.*

6. Clinical Microbiology *Not applicable*

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

In the End-of-Phase 2 meeting, the sponsor claimed that the commercial tablet formulation of TAK-491 was equivalent to TAK-536 tablet; therefore, dose selection was based on the TAK-536 dose ranging study (536-002) and supported by 491-005 (TAK-491 capsules). TAK-491 capsules and tablets were not bioequivalent.

The sponsor noted that BP reduction reached "a plateau of 20-40 mg" based on mean 24 hour SBP and DBP ABPM results and that "doses higher than 40-80 mg would not confer additional BP reduction." Based on the TAK-491 vs. TAK-536 tablet bioavailability analyses, the ratio between equal doses of TAK-491 and TAK-536 tablets for AUC was 0.62; thus, the TAK-491 equivalent dose based on TAK-536 exposure was about twice that of the TAK-536 tablet. During that meeting, the Agency agreed that doses of 20, 40 and 80 mg were reasonable in the Phase 3 program.

This application did not include a twice daily (BID) vs. QD study; however, the ABPM curves, as well as peak-trough analyses, suggest that once daily dosing is appropriate since the treatment effect is preserved throughout the inter-dosing interval.

7.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The sponsor submitted five phase 3 double-blind studies: three 6-week placebo-controlled (491-019, 491-008 and 491-011) trials and two 6-month, active-controlled (491-301 vs. valsartan 320 mg QD; and 491-020 vs. ramipril 10 mg[2] QD). Of the placebo-controlled studies, two (491-019 and 491-008) included an olmesartan 40 mg arm and one (491-019) included a valsartan 320 mg arm.

The placebo-controlled phase 3 studies utilized clinic SBP 150-180 mmHg, inclusive, and 24-hour SBP 130-170 mm Hg, inclusive, as entry criteria. The primary endpoint for these studies was the change from baseline in 24-hour mean ABPM SBP. Secondary endpoints included other ABPM and clinic measures of SBP and DBP.

During the End of Phase 2 meeting, the Agency accepted the 24-hour mean systolic BP by ABPM for the Phase 3 primary endpoint. (b) (4)

(b) (4)

7.1.2.1. Study 491-019 randomized 1291 subjects to TAK-491 20 or 40 mg, valsartan 160 mg, olmesartan 20 mg or placebo for 2 weeks, followed by up-titration to TAK-491 40 mg or 80 mg (respectively), valsartan 320 mg, olmesartan 40 mg or placebo (respectively) for the next 4 weeks. Type I error was controlled using a stepwise testing procedure.

About 90% of subjects completed the study, with the highest premature discontinuation rate in subjects taking TAK-491 80 mg (10.5%) and the lowest rate of discontinuations in subjects taking olmesartan 40 mg (7.4%). The most common reason for discontinuation in both groups was "voluntary withdrawal." The discontinuation rate due to adverse events was similar across groups (2-3%).

Significant decreases from baseline vs. placebo were observed for all treatment groups ($p < 0.001$) for the change in mean 24-hour ABPM SBP. In the context of sequential testing, TAK-491 80 mg was superior to olmesartan (treatment difference -2.54; $p = 0.009$) and valsartan (treatment difference -4.31 mm Hg; $p < 0.001$). However, the testing sequence was terminated at the comparison of TAK-491 40 mg vs. olmesartan (p= NS); thus, the ensuing comparison of TAK-491 40 mg vs. valsartan (treatment difference -3.20 mm Hg; $p = 0.001$) should be considered exploratory.

Results for mean 24-hour ABPM DBP was consistent, with statistically significant effects vs. placebo in all active treatment groups ($p< 0.001$).

[2] This is a submaximal daily dose; according to its label, ramipril is indicated for hypertension in a dose range up to 20 mg daily.

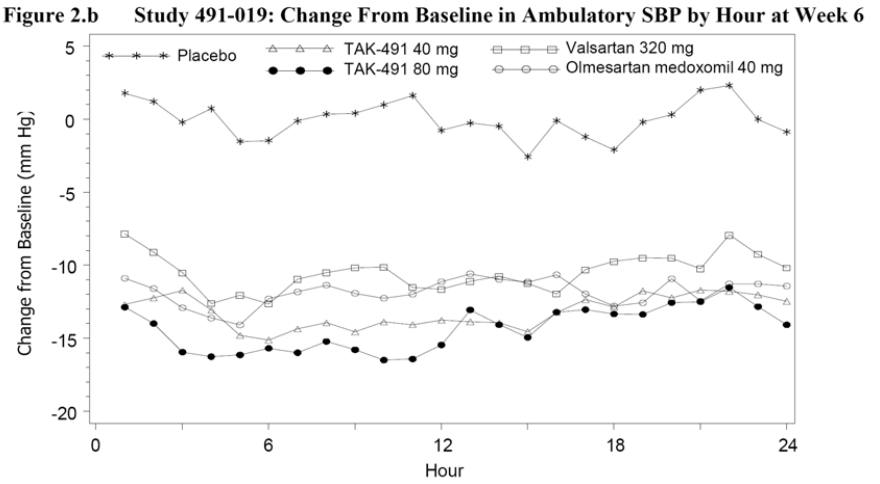

Figure 6. 491-019: Change from baseline in hourly SBP (source: medical-statistical review).

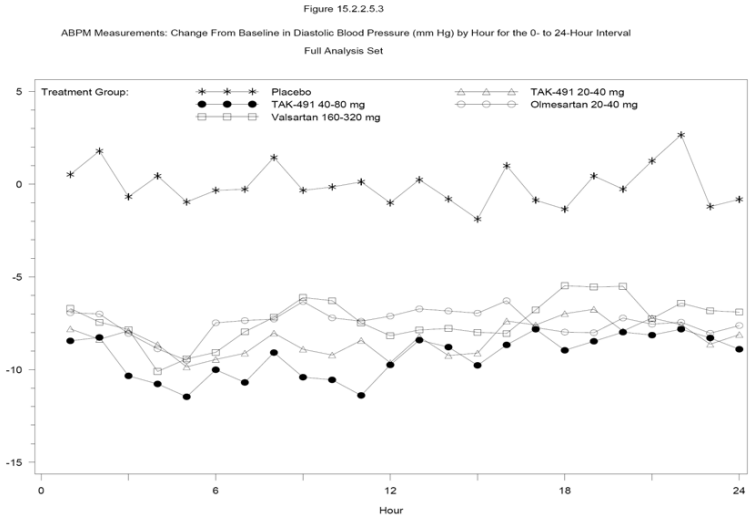

Figure 7. 491-019: Change from baseline in hourly DBP (source: medical-statistical review)

The mean hourly SBP and DBP ABPM curves show separation of all active treatments from placebo throughout the dosing interval. Olmesartan 40 mg and TAK-491 80 mg and 40 mg curves are not distinguishable at the 16 -24 hour time points; TAK-491 80 and 40 mg curves appear similar beyond 12 hours post-dosing. The placebo curve is clustered around zero, consistent with a lack of placebo effect in ABPM measurements.

At trough (Hours 22-24), all active treatments showed significant SBP reductions vs. placebo ($p < 0.001$) and neither TAK-491 dose was significantly different from olmesartan.

The statistical reviewer has commented on the lack of post-baseline ABPM data in about 20% of subjects. However, the sponsor's sensitivity analyses (with multiple imputations) were consistent in supporting efficacy; in addition, cuff BP results (ITT LOCF population about 95% of randomized patients) showed robust, consistent results. Mean changes in trough cuff SBP showed statistically significant treatment effects at Weeks 4 and 6 for all active treatments ($p < 0.001$) with little separation between the TAK-491 40 and 80 mg curves. The

change from baseline to Week 6 in trough cuff DBP was also consistent, with statistically significant reductions versus placebo for all active treatments ($p < 0.001$).

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

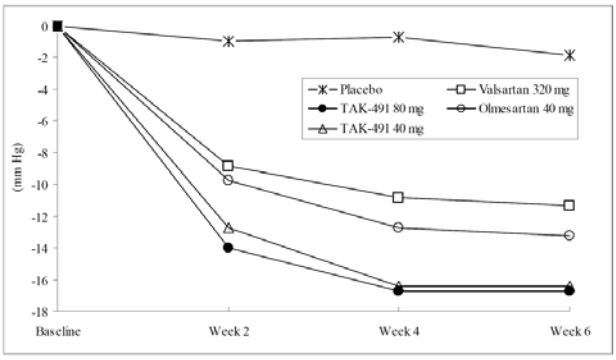

Figure 8. 491-019: Mean change in trough sitting SBP (source: medical-statistical review).

7.1.2.2. Study 491-008 randomized 1275 hypertensive subjects to TAK-491 20, 40 or 80 mg, olmesartan 40 mg or placebo for 6 weeks. All active treatments showed reductions in 24-hour mean SBP and DBP ($p < 0.001$). The change from baseline in SBP and DBP at Hours 22-24 (ABPM) were statistically significant vs. placebo ($p < 0.001$) for all treatment groups, supporting evidence of efficacy for TAK-491.

As in study 491-091, the TAK-491 80 mg SBP or DBP curves are not easily distinguishable from the TAK-491 40 mg or olmesartan treatment curves. While the primary endpoint was significant between TAK-491 80 mg and olmesartan (treatment effect -2.08; $p = 0.038$), trough (Hours 22-24) ABPM SBP or DBP treatment differences between TAK-491 80 mg and olmesartan were not statistically significant. The lack of curve separation and lack of consistency in other results, especially trough (Hour 22-24) comparisons between TAK-491 and olmesartan, (b) (4).
Changes in trough clinic (cuff) SBP and DBP showed significant reductions vs. placebo for all active treatments, supporting efficacy for TAK-491.

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

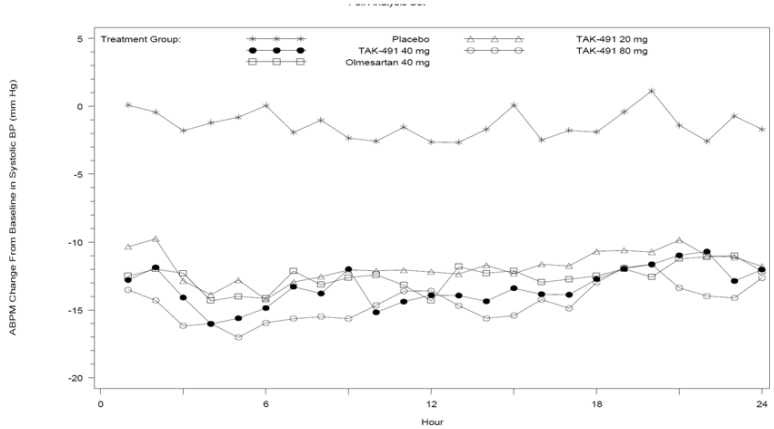

Figure 9. 491-008: Change from baseline to Week 6 in SBP by hourly ABPM and treatment

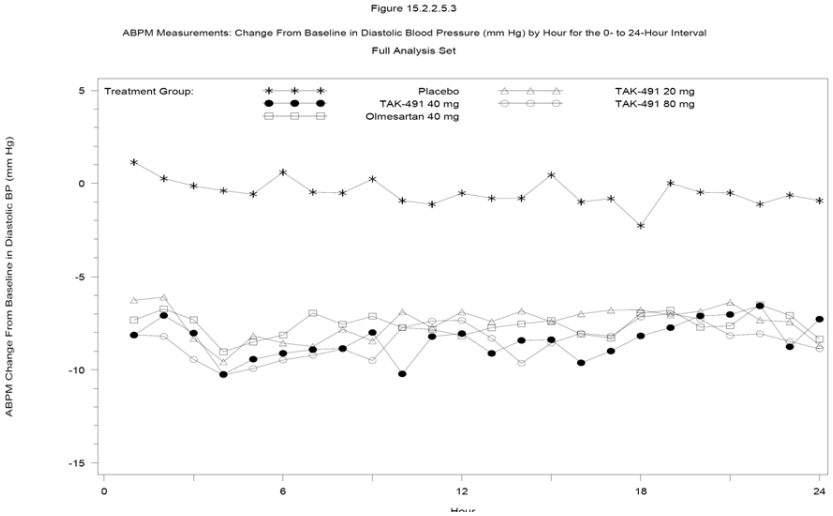

Figure 10. 491-008: Change from baseline to Week 6 in DBP by hourly ABPM and treatment

7.1.2.3. Study 491-011 randomized 413 Black subjects with hypertension (~140 /group) to placebo, TAK-491 40 or 80 mg for 6 weeks. Significant reductions vs. placebo were observed in both treatment groups for the change in 24 hour mean ABPM SBP. The DBP curves (not shown) were similar. The treatment effects were smaller than the effects in non-Black populations in other studies but were significantly different from placebo. Sensitivity analyses with multiple imputations were consistent.

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

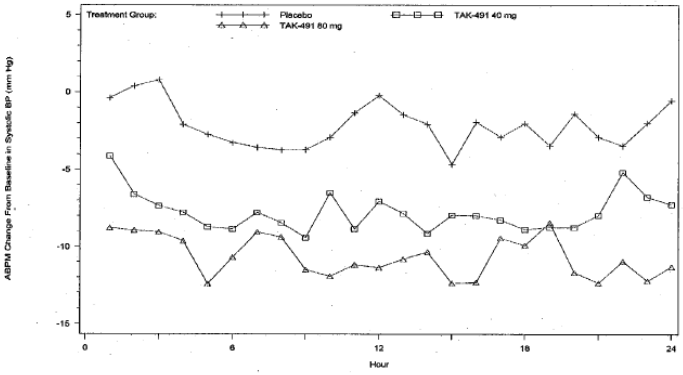

Figure 11. 491-011: Change from baseline in hourly mean SBP ABPM

Table 1. 491-011: Summary of efficacy results

	TAK-491 40 mg N=135	TAK-491 80 mg N=137
24 hour mean SBP/DBP (ABPM) N	94	101
Placebo-subtracted LS mean change from baseline SBP (95% CI)	-5.00 (-7.97, -2.04)	-7.78 (-10.69, -4.86)
p-value vs. placebo	0.001	< 0.001
24 hour mean DBP (ABPM) N	94	101
Placebo-subtracted LS mean change from baseline DBP (95% CI)	-3.44 (-5.47, -1.40)	-5.77 (-7.78, -3.77)
p-value	0.001	< 0.001

Subgroup analyses by race in studies 491-008 and 491-019 showed decreased effects in Black compared to non-Black populations but nonetheless statistically significant from placebo, supporting a treatment effect in Black subjects with hypertension.

Table 2. Pooled analyses by race: studies 491-008 and 491-019: SBP results

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.

7.1.2.4. Study 491-301 randomized 984 hypertensive[3] subjects to TAK-491 20 mg QD up- titrated to 40 mg after 2 weeks, TAK-491 40 mg QD up- titrated to 80 mg after 2 weeks, or valsartan 80 mg up- titrated to 320 mg QD after 2 weeks, with treatment for 6 months. The overall discontinuation rates were similar across groups (24-25%); subjects on valsartan showed a higher discontinuation rate for lack of efficacy (7.6%) than TAK-491 40 mg (4.9%) and 80 mg (2.7%). The discontinuation rate for AE was similar across groups (6-8%).

The changes from baseline in mean 24-hour ABPM SBP (primary endpoint) versus valsartan were -3.64 mm Hg ($p < 0.001$) and -4.03 mm Hg ($p < 0.001$) for TAK-491 40 and 80 mg, respectively. A similar analysis for ABPM DBP was consistent for both TAK-491 doses ($p < 0.001$). Change in trough sitting cuff SBP and DBP showed statistically significant reductions vs. valsartan for TAK-491 40 and 80 mg beginning at Week 2. In addition, SBP and DBP ABPM results at Hours 22-24 for the LS mean difference versus valsartan were statistically significant for both TAK-491 doses ($p < 0.01$).

The 24-hour ABPM TAK-491 40 and 80 mg curves are not easily distinguishable from each other; however, both TAK-491 curves are distinguishable from valsartan.

[3] Entry criteria included trough sitting SBP 150-180 mm Hg inclusive on Day -1 and 24 hour-mean SBP 130-170 mm Hg, inclusive, on Day 1.

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)

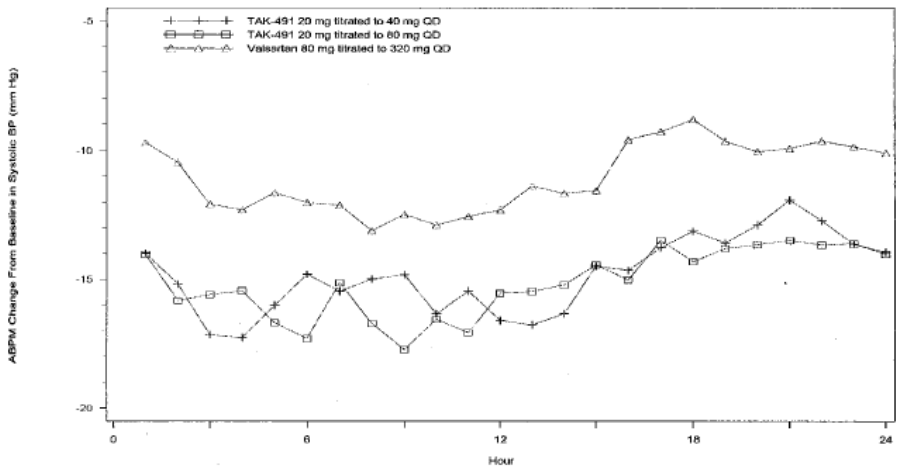

Figure 12. Change from baseline to Week 24 in mean hourly ABPM SBPM. The results for mean hourly DBP were similar (not shown).

These results are robust and consistent, (b) (4)

7.1.2.5. Study 491-020 randomized 884 hypertensive subjects to TAK-491 (20 up-titrated to 40 mg or 40 up-titrated to 80 mg) or ramipril 2.5 mg up-titrated to 10 mg) for 6 months. The primary endpoint, change in trough cuff SBP, showed a statistically significant reduction compared to a submaximal dose of ramipril.

7.1.3. Other efficacy studies

7.1.3.1. Study 491-009 randomized 551 subjects with uncontrolled hypertension (clinic SBP 160-190 mm Hg, inclusive and 24-hour mean SBP 140-180 mm Hg, inclusive), to TAK-491 40 or 80 mg or placebo co-administered with chlorthalidone 25 mg for six weeks. The primary endpoint was the change in 24-hour mean ABPM SBP. The overall premature discontinuation rate was about 13% for subjects on TAK-491 80 mg + chlorthalidone and about 9% for the other two groups (discontinuations for AE were about 5% for the two TAK-491 groups and 3% for placebo).

Assuming no ABPM placebo effect, one can observe an SBP reduction of about 16 mm Hg with chlorthalidone 25 mg, and an additional reduction of about 15 mm Hg with TAK-491 40 mg or 80 mg.

Table 3. 491-009: Primary endpoint

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

Study Visit	Treatment Group: Placebo + Chlorthalidone 25 mg N=181	TAK491 40 mg + Chlorthalidone 25 mg N=184	TAK491 80 mg + Chlorthalidone 25 mg N=182	Overall P-Value
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).

7.1.3.2. Study 491-010 randomized 562 hypertensive subjects[4] to amlodipine 5 mg QD co-administered with placebo, TAK-491 40 or 80 mg QD for six weeks. The primary endpoint was the change in 24-hour mean ABPM SBP. Overall discontinuation rates were similar across groups (5-7%). The primary endpoint showed a reduction from baseline of 13.6 mm Hg for placebo + amlodipine 5 mg; the treatment differences were -11.19 mm Hg ($p < 0.001$) and -10.91 mm Hg ($p < 0.001$) for TAK-491 40 mg + amlodipine 5 mg and TAK-491 80 mg + amlodipine 5 mg groups, respectively. Results for DBP were consistent.

7.1.3.3. Study 491-016 entered hypertensive subjects into a 26 week open-label phase (titration to target approach) followed by a double-blind placebo-controlled withdrawal; a total of 299 subjects were randomized to either TAK-491 at their final dose level or placebo, in addition to their other hypertensive medications. The primary efficacy variable was the change (Week 26 to Week 32) in tough clinic sitting DBP. The LS mean change from baseline was + 7.92 mm Hg in placebo and 0.14 mm Hg for TAK-491 ($p < 0.001$), supporting a long-term maintenance of efficacy. Results for SBP were consistent with the primary endpoint (treatment difference 12.38 mm Hg; $p < 0.001$).

7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary medical and statistical reviewers recommended approval of azilsartan medoxomil for the treatment of hypertension. The reviewers concluded that the drug's ability to lower blood pressure was adequately shown in blinded, placebo-controlled studies.

This reviewer concurs. There is ample evidence of azilsartan medoxomil's effectiveness in lowering SBP and DBP in placebo-controlled phase 3 studies and dose-ranging study. Maintenance of efficacy was adequately demonstrated in a randomized withdrawal study (491-016). Trough BP results by cuff were consistent with ABPM findings.

[4] SBP entry criteria were identical to study 491-009.

7.1.4.1. Dosing: Please see section 13.1 for a discussion of dosing.

7.1.4.2. Comparison with olmesartan and valsartan:

The medical and statistical reviewers felt that TAK-491 was not consistently superior to olmesartan and valsartan.

Two studies (491-019 and 491-008) resulted in ABPM curves that were not distinguishable between TAK-491 and olmesartan, especially at Hours 18-24, and trough (Hours 22-24) changes from baseline that were not significantly different between TAK-491 and olmesartan.

(b) (4)

Two studies, 491-301 and 491-019, included comparisons with maximally dosed valsartan. Study 491-301 showed statistically significant, robust reductions compared with valsartan ($p < 0.001$), significant SBP and DBP differences at trough ABPM and consistent results with cuff BP measurements.

The medical reviewer noted the higher baseline blood pressures in the valsartan group in study 491-019 compared to TAK-491 (difference about 2 mm Hg, $p < 0.05$ only for DBP, not for

(b) (4)

This conclusion was discussed with the medical and statistical reviewers.

7.1.5. Pediatric use/PREA waivers/deferrals

The sponsor has requested a deferral pending approval in adults. For premature and infants < 12 months, the sponsor has requested a waiver.

The sponsor has proposed (b) (4), one PK/safety/tolerability study, and two safety and efficacy studies (one in children 6-17 years, inclusive, with hypertension; one in children ≥ 12 months and < 25 kg with secondary hypertension). The pediatric program should be reviewed by the pediatric committee (PERC) with appropriate feedback to the sponsor.

7.1.6. Discussion of notable efficacy issues *(resolved or outstanding).*

An outstanding issue is what dose (s) to approve, with appropriate labeling.

7.2. Safety

7.2.1. General safety considerations

The Phase 3 program exposed 4814 subjects to 20, 40 or 80 mg TAK-491 with a mean and median exposure of 116 and 46 days, respectively. A total of 1254 subjects were exposed to TAK-491 80 mg daily for at least 24 weeks and 270 subjects were exposed to TAK-491 80 mg for at least 48 weeks. The exposure appears adequate for an antihypertensive drug.

7.2.2. Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

7.2.2.1. Deaths:

Of 9 fatal AEs in the 64 studies of TAK-491, three events occurred on TAK-491 and 1 occurred on TAK-536 + pioglitazone 45 mg. The 4 fatal AEs on TAK-491/TAK-536 were as follows:

7.2.2.1.1. GI bleeding, Day 31 (TAK-491 20 mg), 58 year-old white male with history of alcohol and GI bleeding;

7.2.2.1.2. Unwitnessed sudden death, Day 88 (TAK-491 40 mg), 37 year-old black male with history of alcohol, diabetes, and chronic renal failure. Autopsy diagnosis was hypertensive cardiovascular disease and arteriosclerotic cardiovascular disease; toxicology was positive for alcohol and quetiapine;

7.2.2.1.3. Suicide, Day 190 (TAK-491 80 mg), 47 year-old white male with major depressive disorder.

7.2.2.1.4. Sudden death, Day 36 (TAK-536 + pioglitazone), 64 year-old female with diabetes and past cerebrovascular accident; no autopsy.

These fatalities occurred in at-risk subjects and no signal for TAK-491 can be observed.

7.2.2.1.5. Serious adverse events (SAE):

In the Phase 3 placebo-controlled trials, SAE rates were low in all treatments and no safety signal was observed, except a potential increase in syncope (3 subjects on TAK-491 and 0 on placebo) in the Phase 3 placebo-controlled pool. Two of the syncope cases occurred on TAK-491+ chlorthalidone (one of these cases was associated with heart block and bradycardia). No SAE signal was observed in a review of pooled active-controlled and open-label studies.

7.2.2.1.6. Discontinuations due to AE

TAK-491 monotherapy appeared to be well tolerated. In the placebo-controlled studies, about 2.4% of patients discontinued TAK-491or placebo due to AEs. The most commonly reported AEs leading to discontinuation were hypotension (0.4%) and dizziness (0.3%); there was no change in frequency between 40 and 80 mg TAK-491.

In study 491-009 (180/group), where TAK-491 was co-administered with chlorthalidone, five subjects (~2.7%) discontinued TAK-491 40 mg + chlorthalidone and 3 subjects (1.6%) discontinued TAK-491 80 mg +chlorthalidone due to dizziness/hypotension/orthostatic hypotension; there were no similar discontinuations in placebo + chlorthalidone 25 mg subjects.

In the active-controlled studies, the safety-related overall discontinuation rate was similar between TAK-491 40 and 80 mg and comparators (3.5-4.0 %). The incidence of hypotension leading to discontinuation was low, slightly higher in TAK-491 80 mg (9 cases, 0.8%) than

with 40 mg (2 cases, 0.2%) or comparators (3 cases, 0.2%); the incidence of dizziness was 0.5% with either TAK-491 dose and 0.1% in the comparator group.

7.2.2.1.7. General adverse events (AEs)

The most common AEs in the Phase 3 placebo-controlled studies were diarrhea, dizziness and dyslipidemia (all with placebo-subtracted incidence < 1.7%). In the subgroup of Phase 3 placebo-controlled monotherapy trials, the most common AEs were dyslipidemia, dizziness, diarrhea, edema and fatigue, all with placebo-subtracted incidence < 2.0%. There were no dose-related AEs observed in the Phase 2 dose-ranging study 491-005 (with N= about 65/dose group).

The sponsor additionally conducted pooled analyses of hypotension and renal AEs. Statistically significant differences were observed between TAK-491 80 mg and placebo or comparator; most of the events appear to be dizziness and hypotension. The differences between TAK-491 80 mg and placebo/comparator appear to be on the order of 2-3%.

Table 4. The sponsor's pooled analysis of hypotension-related adverse events

Table 2.j Hypotension Cluster: Phase 3 Controlled-Study Pools

Study Pool / Preferred Term	Number (%) of Subjects			
Phase 3 Placebo-Controlled Pool (a)	**Placebo (N=801)**	**TAK-491 40 mg (N=1072)**	**TAK-491 80 mg (N=1074)**	**TAK-491 Total (N=2146)**
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.

The statistically significant increase in renal adverse events vs. placebo appears to be driven by "increased serum creatinine." The incidence of renal impairment or renal failure is low and not different between TAK-491 and placebo. In addition, in the placebo-controlled monotherapy trials (e.g., removing the two co-administration trials), the frequency of "renal cluster" events is lower (< 0.8%) and not dose-related.

Table 5. Sponsor's analysis of renal AE

Table 2.k Renal Cluster: Phase 3 Controlled-Study Pools

Study Pool / Preferred Term	Number (%) of Subjects			
Phase 3 Placebo-Controlled Pool (a)	**Placebo (N=801)**	**TAK-491 40 mg (N=1072)**	**TAK-491 80 mg (N=1074)**	**TAK-491 Total (N=2146)**
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.

7.2.2.1.8. Laboratory tests

7.2.2.1.8.1. Changes in creatinine:

Table 6. Sponsor's analysis of creatinine elevation: phase 3 placebo-controlled monotherapy 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 ≥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 ≥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.

In the placebo-controlled monotherapy studies, creatinine elevations were infrequent and unrelated to dose.

The frequency and dose relationship is more evident, however, in study 491-009, when TAK-491 is co-administered with chlorthalidone 25 mg, with some creatinine elevations observed at the final visit.

Table 7. Sponsor's analysis of creatinine elevations: study 491-009 (6 week study).

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 ≥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 ≥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.

Follow-up creatinine data in 14 of 18 subjects with elevated serum creatinine levels at the final visit (and available follow-up) showed that most, except for one subject, returned toward baseline.

One subject on TAK-491 80 mg + chlorthalidone was discontinued due to serious AEs of vasovagal syncope with elevated creatinine (1.1 mg/dL). Another subject (same regimen) was discontinued for renal impairment (serum creatinine 2.1 mg/dL) and increased uric acid (13.5 mg/dL); a subsequent serum creatinine was normal.

The frequency of creatinine elevations was increased in subjects with baseline renal impairment. The sponsor conducted additional analyses showing an increase in creatinine elevations with advanced age $\geq$ 75 years); however, these analyses were not adjusted for other potential baseline imbalances (e.g., renal function).

Table 8. Sponsor's analysis of creatinine elevations by baseline renal function

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).

Creatinine data from the randomized withdrawal study showed evidence of some reversibility, with a mean decrease in serum creatinine of 4.5 umol/L vs. small increase of 1.7 umol/L in the group remaining on TAK-491.

In summary, there appear to be treatment-related elevations in creatinine, most apparent when TAK-491 was co-administered with chlorthalidone. In a June 22, 2009 guidance meeting, the sponsor suggested that these creatinine elevations were reversible and due to a characteristic decrease of intraglomerular pressure associated with renin-angiotensin-aldosterone blockade, likely exaggerated by the decreased renal perfusion associated with potent BP reductions and diuretic effects of chlorthalidone 25 mg.
During this meeting, the Agency had "renal safety concerns about the TAK-491 + chlorthalidone product." The Agency made a number of recommendations for the development program (adding a long-term control group; including patients with eGFR < 50 mL/min, etc, renal biomarkers).

7.2.3. Safety update

A safety update (8/25/2010) included data from 3 open-label (491-016 completed, 491-006 and 491-301 ongoing) studies. Studies 491-006 and 491-301 included subjects taking TAK-491 + HCTZ 12. 5 mg or 25 mg in stepped care. About 67% of the study population reported "any treatment emergent adverse event," with the most common being dizziness (11.4%) and headache (9.0%), followed by urinary tract infection (5.6%), fatigue (5.4%) and upper respiratory tract infection (4.5%). The open-label pool incidence of serious adverse events was 5.1%. About 9% experienced an adverse event that led to study drug interruption or discontinuation.

This update also included data from 401CLD-306, which compared TAK-491CLD[5] (N=303) with TAK-491 + HCTZ (N=306) in subjects with moderate to severe hypertension (SBP 160-190 mm Hg inclusive). The primary endpoint was the change in trough sitting SBP at Weeks 6 and 10. The discontinuation rate due to adverse events was higher in the TAK-491CLD group (9.2%) than the TAK-491 + HCTZ group (6.2%). Over half of subjects had mild (59.8%) or moderate (7.7%) renal impairment by eGFR (MDRD). The incidences of dizziness and serum creatinine increased were higher in the TAK-491CLD group (12.3 and 12.9%, respectively) than in the TAK-491 + HCTZ group (10.6 and 8.9%, respectively).
Withdrawals due to elevated creatinine were higher in the TAK-491 CLD group (12, 4.0%) than TAK-491+ HCTZ (4, 1.3%) The withdrawal rate due to dizziness was low and similar between groups.

There were 2 sudden deaths (61 year old Black female, Day 6 of TAK-491 40 mg, history of obesity, sleep apnea and edema, also on furosemide 40 mg and potassium, baseline BP 191/104 mm Hg; and 67 year-old obese White male, Day 15 TAK-491CLD 40 mg/12.5 mg, last BP 131/82 mm Hg, no known concomitant medications); there were also 2 deaths during placebo run-in. While the number of deaths seems high for a short-term hypertension trial, the study population (moderate to severe hypertension, over half with renal impairment) likely represented a more vulnerable population; and the available exposure (and negative QT study) offer some reassurance of safety in a broader population.

[5] TAK-491CLD refers to the TAK-491-chlorthalidone combination.

Three TAK-491CLD and one TAK-491 + HCTZ discontinued due to renal-related AEs.

Table 9. Sponsor's analysis of study 491CLD-306: creatinine elevations: comparison of TAK-491 + chlorthalidone and TAK-491 + HCTZ

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.

7.2.4. Immunogenicity *Not applicable.*

7.2.5. Discussion of primary reviewer's comments and conclusions

The medical reviewer observed that the reporting rates for most adverse events were similar to or only slightly higher than those reported by the placebo groups and did not appear to be dose related. I concur.

The reviewer also stated, "As with other drugs that inhibit the renin-angiotensin-aldoseterone 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." I generally concur, but note that the creatinine elevations seen with chlorthalidone 25 mg were TAK-491 dose-related and more frequent than creatinine elevations seen with HCTZ.

7.2.6. Discussion of notable safety issues *(resolved or outstanding).*

An unresolved issue is the basis of dose-related creatinine elevations that occur more frequently with TAK-491 80 mg, especially when co-administered with chlorthalidone 25 mg QD. Data suggest that most of these creatinine elevations are reversible and renal impairment or renal adverse events were rare in this submission.

The sponsor has interpreted the creatinine elevations as transient or non-progressive while on treatment and associated with substantial reductions in blood pressure. However, not every blood pressure-lowering drug is associated with these frequencies of creatinine elevations. Co-administration with HCTZ did not produce similar creatinine elevations; perhaps one can argue that HCTZ does not produce the same level of BP reductions or RAAS effects. One is still left with the uncertainty as to whether the creatinine elevations represent any concern.

Information should be added to labeling that serum creatinine should be monitored when chlorthalidone is co-administered, and that lower doses (of either TAK-491, if approved, or diuretic) or alternative medications should be considered in the case of persistent creatinine elevations.

In considering a TAK-491-chlorthalidone combination, the sponsor should explore efficacy and safety of lower dose combinations for both products, in addition to long-term renal safety data.

8. **Advisory Committee Meeting**

This application was not presented at an advisory committee.

9. Other Relevant Regulatory Issues

There are no Application Integrity Policy, exclusivity or patent issues of concern.

10. Financial Disclosure

There are no financial disclosure issues.

11. Labeling

11.1. Proprietary name

The proposed proprietary name Edarbi was acceptable per review by DMEPA (Jibril Abdus-Samad, PharmD, 10/19/2010).

11.2. Physician labeling

11.2.1. Azilsartan should be contraindicated in pregnancy. Appropriate information concerning reproductive toxicology and mutagenicity should be labeled per recommendations of the pharmacology-toxicology reviewers.

11.2.2. Dosing: see section 13.1.1, below for discussion.

(b) (4)

11.3 Carton and immediate container labels (*if problems are noted*) Pending.

11.4 Patient labeling/Medication guide

According to a review by DRISK (Reema Jain, PharmD, MPH 10/26/10), the proposed routine safety monitoring by the sponsor was adequate and that additional strategies such as Medication Guide were not warranted.

12. DSI Audits

No sites were chosen for auditing, since the application included several large, multicenter placebo-controlled trials showing consistent results and few deaths or serious adverse events. These results were consistent with expected findings for an angiotensin II receptor-blocker.

13. Conclusions and Recommendations

13.1. Recommended regulatory action Azilsartan medoxomil should be approved.

The sponsor studied TAK-491 doses of 20, 40 and 80 mg in their placebo-controlled phase 3 program; based on proposed labeling, the sponsor plans to market the 40 and 80 mg doses.

The medical and statistical reviewers have recommended a starting dose of 5 or 10 mg once daily in subjects who are not volume contracted, up to 80 mg once daily. They noted that "there is little difference in effect among the doses 10-80 mg."

The clinical pharmacology reviewers have recommended a maximal dose of 40 mg daily, since there is no additional blood pressure lowering benefit over 40 mg.

Since the 40 and 80 mg doses appear indistinguishable in efficacy, one might approve the highest dose in the absence of any safety concerns. However, there appears to be an increased frequency of creatinine elevations that are mostly mild and reversible, but occur more frequently with TAK-491 80 mg, especially when the drug is co-administered with chlorthalidone 25 mg. Doses of 40 mg appeared to be associated with fewer and more transient creatinine elevations. Although other renal adverse events were rare, one cannot exclude a renal safety issue when this drug is administered in the larger community or vulnerable population (e.g., moderate renal insufficiency) or in a landscape of polypharmacy. Depending on the concern over creatinine, one might approve the 80 mg dose (if concluding that the creatinine increases are mild, reversible, related to hemodynamic effects of the drug, and similar to other ARBs in the class) or the 40 mg dose (if concluding that creatinine elevations might be a concern, but occur less frequently and are more likely to be transient with 40 mg dosing).

Because of the creatinine elevations, the cross-discipline team leader is recommending approval of TAK-491 40 mg; in addition, the sponsor should be encouraged to evaluate a lower daily dose, such as 5 mg, for use with diuretics such as chlorthalidone. Periodic monitoring of serum creatinine should be recommended when azilsartan is co-administered with diuretics, and the prescriber should consider a lower dose of diuretic, or alternative therapy, in the event of an increase in creatinine.

13.2. Safety concerns to be followed postmarketing
Therefore, routine monitoring should focus on renal-related adverse events.

13.3. Risk Minimization Action Plan, if any
At this point, there is no need for a risk minimization action plan.

13.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)
Pediatric studies are planned (section 7.1.5).

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/s/

SHARI L TARGUM
01/21/2011