CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202331Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memo

NDA: 202331 Azilsartan medoxomil plus chlorthalidone (Edarbyclor) for hypertension.

Sponsor: Takeda

Review date: 16 December 2011

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

Distribution: NDA 202331
HFD-110/Nguyen/Targum

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

This application has been the subject of reviews of CMC (Shiromani; 11 July 2011), biopharmaceutics (Chen; 24 October 2011), pharmacology/toxicology (Gatti; 18 July 2011), clinical pharmacology (Menon-Andersen and McDowell; 4 April 2011), medical (U; 3 October 2011, 22 November 2011) and statistics (Zhang; 6 August 2011, 28 November 2011, 15 December 2011). There is a comprehensive CDTL memo (Targum, 10 November 2011) with which I am largely in agreement.

Azilsartan medoxamil is the most recently approved angiotensin receptor antagonist (2011) and the current submission is its first combination, and the first of any renin-angiotensin system antagonist with chlorthalidone.

There are no unresolved CMC, biopharmaceutics, pharmacology/toxicology, or clinical pharmacology issues. However, I note that there is a small effect of food on exposure to azilsartan in the combination product.

I note too that chlorthalidone used in this development program appears not to be a formulation commercially available in the US (and may have been manufactured from drug product explicitly for this study). That this formulation is an effective product seems clear enough from the monotherapy arms of study 302.

The main basis for approval is 8-week factorial study 302 with about 150 subjects per group. The main results for ABPM trough (average of hours 22-24) and withdrawals for adverse events are as follows:

		SBP/DBP				Withdrawal (%) for TEAE			
		Azilsartan							
		0	20	40	80	0	20	40	80
CLD	0	—	-12/-8	-13/-7	-15/-9	—	2	4	4
	12.5	-13/-7	-23/-13	-24/-14	-26/-17	2	6	3	9
	25	-16/-8	-26/-15	-30/-17	-28/-16	4	8	14	14

Although there is no placebo group, ABPM generally does not manifest a placebo effect (particularly when it is not used to screen subjects into a study), and the blood pressure effects of azilsartan monotherapy are similar to those reported in the Edarbi label.

Very nearly additive effects of the two drugs are achieved.

Once-daily dosing is well supported by ABPM profiles obtained in Study 302; see for example Figure 34, page 77 of Dr. U's first review.

Dr. U recommends approval of two [redacted] (b) (4) doses, 40/12.5 and 40/25, [redacted] (b) (4) I concur. Patients getting inadequate response to azilsartan 80 mg can reasonably go to 40/12.5 or 40/25. This continues a recent trend in antihypertensive drug development to have few dose titration steps, when the steps are smaller than the resolvable difference in casually measured BP in physicians' offices.

The sponsor sought a claim of similar effectiveness of the combination in Blacks and Caucasians. That claim appears to be adequately sustained. In this regard, the results are similar with other combinations of ACEI/ARB plus HCTZ.

The sponsor sought a claim of superiority over the combination of olmesartan and HCTZ. One such study was against the highest approved dose of olmesartan plus HCTZ and supports what I believe to be the first combination superiority claim we have acknowledged.

The sponsor seeks a claim for first-line use in patients far from blood pressure goals. Such a claim seems to be adequately supported by the demonstrated tolerability of initiating treatment with the combination. The sponsor performed modeling of the likelihood of getting to goal blood pressure on one or both drugs; these plots have been employed in previous labels to give healthcare providers a sense of the benefit of starting two drugs at once. The modeling was found satisfactory.

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/s/

NORMAN L STOCKBRIDGE
12/16/2011

Cross-Discipline Team Leader Review Memo

Date	November 10, 2011
From	Shari L. Targum, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA #202331 (IND 71,867)
Proprietary / Established (USAN) names	Edarbyclor/azilsartan medoxomil plus chlorthalidone
Proposed Dosage forms / strength	Oral tablets/ [redacted] (b) (4) 40/12.5, [redacted] (b) (4) 40/25 mg
Proposed Indication(s)	Treatment of hypertension; may be used as initial therapy if a patient is likely to need multiple drugs to help achieve blood pressure goals.
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.); ONDQA Biopharmaceutics (Tien-Mien Chen, Ph.D.); Pharmacology/Toxicology (Philip J. Gatti, Ph.D.); Clinical pharmacology (Divya Menon-Andersen, Ph.D.); Division of Medication Error Prevention and Analysis (Yelena Maslov, Pharm.D.), Statistical (Jailu Zhang, Ph.D.); and Clinical (Khin U, M.D.)

The following reviews are pending: DRISK; carton/container labels; and DMEPA repeat review of the proprietary name.

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

1. Introduction to Review

TAK-491CLD is a fixed-dose combination tablet containing TAK-491 (azilsartan medoxomil) and chlorthalidone (CLD). Azilsartan medoxomil (AZM) is a prodrug of azilsartan (AZ), an angiotensin II receptor blocker (ARB) approved on February 25, 2011 for the treatment of hypertension. Chlorthalidone (CLD) is a thiazide-type diuretic approved for treating hypertension. Note: Azilsartan medoxomil (AZM) is used interchangeably with the term TAK-491; azilsartan (AZ) is used interchangeably with TAK-536.

Several approved fixed-dose combination products utilize a renin-angiotensin-aldosterone system (RAAS)-blocking agent-diuretic combination (e.g., olmesartan- hydrochlorothiazide

(HCTZ), valsartan-HCTZ and aliskiren-HCTZ, lisinopril-HCTZ, captopril-HCTZ). CLD-containing combinations such as atenolol-CLD and clonidine-CLD are also approved for hypertension. This application, if approved, would be the first RAAS-blocking agent in combination with CLD.

The sponsor submitted one factorial (491CLD-302), one double-blind co-administration trial (491-009) and three active-controlled double-blind studies (491CLD-306, 491CLD 303, 491CLD-301) to support efficacy. Interim data from ongoing active-controlled safety trial 491CLD-308 were also provided in the submission.

Issues of interest include: dosing (section 7.1.6.1); comparative claim with olmesartan-HCTZ (section 7.1.4.3); efficacy in Black patients with hypertension (7.1.6.3) and creatinine elevations (7.2.2.3, 7.2.2.4, 7.2.2.5).

2. Background/Regulatory History

Date	Meeting type	Key Points/Comments
April 6, 2006	EOP1	Provided complete monotherapy characterization, a single factorial trial would be adequate to support a combination. Of interest were the placebo-subtracted differences between high-dose monotherapies and high-dose combination; one route to first-line therapy is to show that the low-dose combination has greater blood pressure effect and superior safety than either high-dose component. Rat embryo-fetal development studies should be conducted for TAK-491 and M-II and CLD in combination.
November 14, 2007	Pre-IND	Key factorial comparison is that at the high dose of each component, the second drug adds to the effect. Because of concern for "regression to the mean," subjects should qualify by cuff and ABPM serve as baseline. The usual primary endpoint is defined by effect at the inter-dosing interval.
May 19, 2009	Guidance	Sponsor should provide reassurance that creatinine elevations with combination are pharmacologic response to RAAS blockade, rather than toxicologic effect. Superiority claim between combinations is unusual. Principles of superiority for monotherapies: need robust demonstration (usually 2 studies); agents must be in the same class; comparison needs to be "fair" (comparator optimally dosed).
November 24, 2009	SPA Letter to sponsor (study 303)	If both TAK-491CLD doses were shown to be superior to OLM/HCTZ 40 mg/25 mg, a superiority claim would be supported even if only one TAK-491 CLD was marketed. Safety results need to be similar or better than OLM/HCTZ and withdrawal rates must not be substantially greater than OLM/HCTZ.
April 27, 2010	Type C guidance	In the factorial trial, a primary comparison could be individual or pooled treatment group data with combination vs. each of the high-dose monotherapies. The data would not result in a separate claim for use in the Black subgroup, but the label would describe qualitatively and quantitatively the effect in the Black population. Point estimates and confidence intervals for the combination effect in Black patients could be described in labeling provided that sufficient Black subjects were enrolled.
November 8, 2010	Pre-NDA	The clinical pharmacology program was adequate support for the NDA; the Agency agreed with the plan for population pharmacokinetics. The preliminary dose selections (20/12.5, 40/12.5, 80/12.5 and 40/25 mg) appeared reasonable.

3. CMC/Microbiology/Device

According to the reviewers, deficiencies in the submission have been resolved and there are no outstanding issues.

Following communications and teleconferences with the sponsor (8/5/11 and 10/13/11), the CMC and ONDQA Biopharmaceutics reviewer have recommended approval of this NDA with a postmarketing commitment (PMC) for the sponsor to provide dissolution data for all strengths of azilsartan medoxomil and chlorthalidone from the batches manufactured during the first year following the approval date (accepted by the sponsor).

4. Nonclinical Pharmacology/Toxicology

Dr. Gatti has concluded that the NDA was approvable without additional nonclinical recommendations. There are no outstanding or unresolved issues.

4.1. General nonclinical pharmacology/toxicology considerations

No new pharmacology data were submitted in this application.

4.1.1. Toxicology:

The potential toxicity of combination treatment with TAK-491 and CLD was evaluated in three studies:

a. Two-week oral toxicity study of rats dosed with vehicle (placebo), TAK-491 alone (1000 mg/kg/day), TAK-536 M-II (metabolite) alone (2000 mg/kg/day), CLD alone (100 and 300 mg/kg/day), TAK-491 plus CLD (100-1000 mg/kg/day of TAK-491 plus 100 or 300 mg/kg/day CLD), and TAK-536 M-II (2000 mg) plus 100 or 300 CLD.
b. Thirteen-week oral toxicity study of rats dosed with vehicle (placebo) or TAK-491 plus TAK-536 M-II plus CLD (triple combination) in rats;
c. Effect of CLD alone, TAK-491 plus TAK-536 (double combination) or TAK-491 plus TAK-536 M-II plus CLD (triple combination) on embryo-fetal development in rats.

The following was observed:

a. In the two-week study, plasma CLD levels were increased when dosed in combination with TAK-491. Increases in plasma urea nitrogen, water intake, urine output and plasma total cholesterol were observed in TAK-491/CLD combination groups. No clear combination effects were observed from dosing TAK-536 MII and CLD.
b. In the thirteen-week study, there was a decrease in weight gain and food consumption in rats receiving 1000 mg/kg TAK-491 and 2000 mg/kg of MII; this effect was enhanced in all groups receiving the triple combination. CLD 300 mg/kg was associated with an increase in BUN and adrenal weight, and an increased incidence and severity of background renal tubular regeneration; these effects were enhanced by administration with the double combination.

The increase in CLD levels, observed in the two-week study when CLD was dosed with TAK-491, was *not* observed in the clinical pharmacology program; the other effects were felt to be consistent with the pharmacologic properties of the administered drugs, enhanced with supratherapeutic doses.

Toxicologic studies of the metabolite TAK-536 M-II showed that this compound is relatively devoid of pharmacologic activity; in 13-week repeat-dose rat toxicity studies, no

renal/adrenal/stomach toxicities were observed with reported NOAELs in the 300 mg/kg/day (male) and 3000 mg/kg/day range.

4.2. Reproductive toxicology:

In the embryo-fetal study, severity of general toxicity in dams was increased, fetal growth was retarded and indices of visceral variations such as wavy ribs were increased by the triple combination. Increased fetal mortality or teratogenicity was not observed in the triple combination group in this study. TAK-491 remains contraindicated in pregnancy as are other drugs in this class.

4.3. Other notable issues: None.

Dr. Gatti has suggested that the increase in serum creatinine levels in the clinical program can be interpreted as a pharmacologic response to RAAS blockade in the setting of potent diuresis and extensive reductions in blood pressure and intra-glomerular pressure, rather than a toxicologic effect. In patients with chronic kidney disease treated with ACE inhibitors, acute increases of creatinine up to 30% are associated with improved long-term preservation of renal function without increased risk of hyperkalemia.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Menon-Andersen has recommended approval of the azilsartan medoxomil-chlorthalidone fixed dose combination. There are no outstanding or unresolved issues.

5.1. General clinical pharmacology/biopharmaceutics considerations:

The clinical pharmacology studies evaluated the 80/25 mg azilsartan-CLD combination only.

5.1.1. The relative AZ bioavailability of AZM tablet:

Following a single dose of the 80/25 mg tablet, the relative bioavailability of azilsartan and CLD was evaluated in TAK-CLD-103 and TAK-CLD-105. In both studies, total systemic exposures (AUC) to azilsartan and CLD were equivalent to exposures of each respective drug given alone; however, in each study the peak systemic exposure (Cmax) to CLD exceeded the upper bound of 90% CI when the combination product was administered. However, Dr. Menon-Andersen felt that the observed Cmax increase is not clinically relevant and no dose adjustment is required.

5.1.2. Food effect

Systemic exposure (AUC and C_{max}) to azilsartan was reduced to about 80% when the combination was given along with a standard high fat meal vs. fasted state. Peak plasma concentrations of CLD were also reduced to about 80% when the combination was administered with a standard high fat meal compared to fasting conditions. In contrast, food did not affect systemic exposure (AUC and C_{max}) to azilsartan or CLD when given as a free combination. However, the reduction in exposure is not clinically significant since the exposure-response for azilsartan is flat at doses above 10 mg, thus the observed pharmacokinetic fluctuation does not translate into a pharmacodynamic effect by ABPM data; CLD is a long-acting diuretic, and peak levels are not critical to its effect.

5.1.3. Pharmacokinetics: Following single-dose administration of azilsartan-CLD 80/25 combination, peak plasma azilsartan and CLD concentrations occurred at about 3 hours (range 1-6 hours) and 1 hour (range 0.5-3 hours), respectively. The mean (SD) half-lives of azilsartan and CLD were 12.9 (14.2) h and 44.5 (23.1) h, respectively. These findings are consistent with previous results for azilsartan and CLD.

5.1.4. Dose-ranging studies:

Exposure-response information was obtained from the clinical factorial trial (491CLD_302), where pharmacokinetic data were obtained via sparse sampling.

The results are consistent with concentration-dependent decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP).

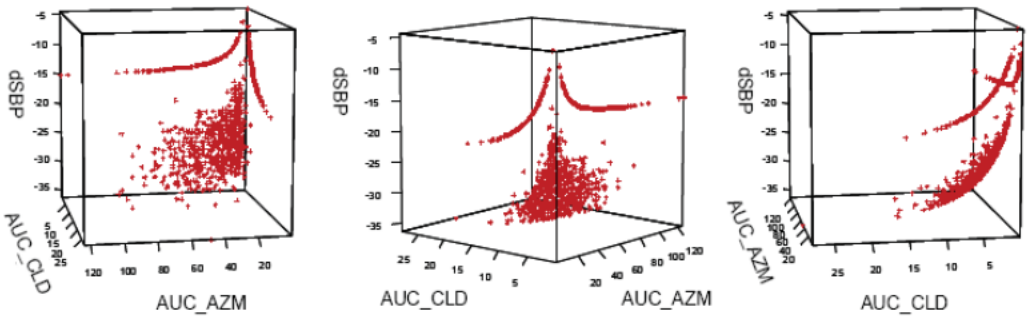


Figure 1. Exposure-response relationship for azilsartan-CLD ***Source: Divya Menon-Andersen, Ph.D. (clinical pharmacology review)***

Observed and predicted responses based on AUC model suggest that the blood pressure reductions with the combination represent additive effects of the two components.

Table 1. Observed and predicted response based on AUC model

	Observed [Predicted] (95%CI)					
	TAK-491 Placebo		**TAK-491 20 mg**	**TAK-491 40 mg**		**TAK-491 80 mg**
CLD Placebo	NA	[0] (NA)	(b) (4)	-12.8	[-13.4] (-16.0, -10.8)	(b) (4)
CLD 12.5 mg	-12.7	[-12.4] (-17.3, -7.5)		-24.4	[-25.8] (-31.3, -20.3)	
CLD 25 mg	-15.9	[-16.4] (-21.6, -11.2)		-29.8	[-29.8] (-35.6, -24.0)	

source: clinical pharmacology review and 491CLD 302 PPK/PD report

5.2. Drug-drug interactions, Metabolism and Elimination, Demographic interactions/special populations, Thorough QT study or other QT assessment: No new data were submitted.

6. Clinical Microbiology *Not applicable*

7. Clinical/Statistical

The primary medical reviewer, Dr. U, recommended approval of this NDA pending acceptance of labeling recommendations.

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The sponsor chose 12.5 mg and 25 mg doses of chlorthalidone (CLD) that are associated with improved outcomes (SHEP, ALLHAT); the sponsor did not explore higher CLD doses because of the flat dose-response BP curve along with dose-proportional decreases in potassium above 25 mg. The sponsor chose TAK-491 doses of 20, 40 and 80 mg that were evaluated in the phase 3 monotherapy program.

The sponsor has proposed (b) (4) 40/12.5 (b) (4) and 40/25 mg (b) (4) dose combinations for registration. (b) (4)

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

The phase 3 studies enrolled subjects with moderate to severe hypertension, defined as SBP 160-190 mm Hg, inclusive, after washout of previous antihypertensive medications. This review will focus on the factorial study 302, the main source of combination vs. monotherapy comparisons and identification of appropriate doses for therapy.

The other studies were, for the most part, active-controlled comparisons. Studies 301 and 303 were double-blind, active-controlled comparisons between TAK-491CLD and OLM/HCTZ, submitted to support a comparative claim; study 303 was a forced titration study and 301 was a "titrate to target" design. Study 306 was a "titrate to target" comparison of TAK-491CLD to TAK-491 co-administered with HCTZ. Study 308 ("titrate to target" TAK-491CLD vs. OLM/HCTZ) is an ongoing, 52-week, open-label safety study.

The application also includes studies 491-009 and 491-006, which were reviewed in the azilsartan medoxomil monotherapy NDA 200,796.

7.1.2.1. Study 302 was a double-blind randomized factorial study comparing 8 weeks of TAK-491-chlorthalidone (TAK-491CLD) fixed combinations with TAK-491 and CLD monotherapy; the trial did not include a placebo arm. Subjects qualified for inclusion by clinic SBP. Ambulatory blood pressure monitoring (ABPM) was performed at baseline and Weeks 4 and 8.

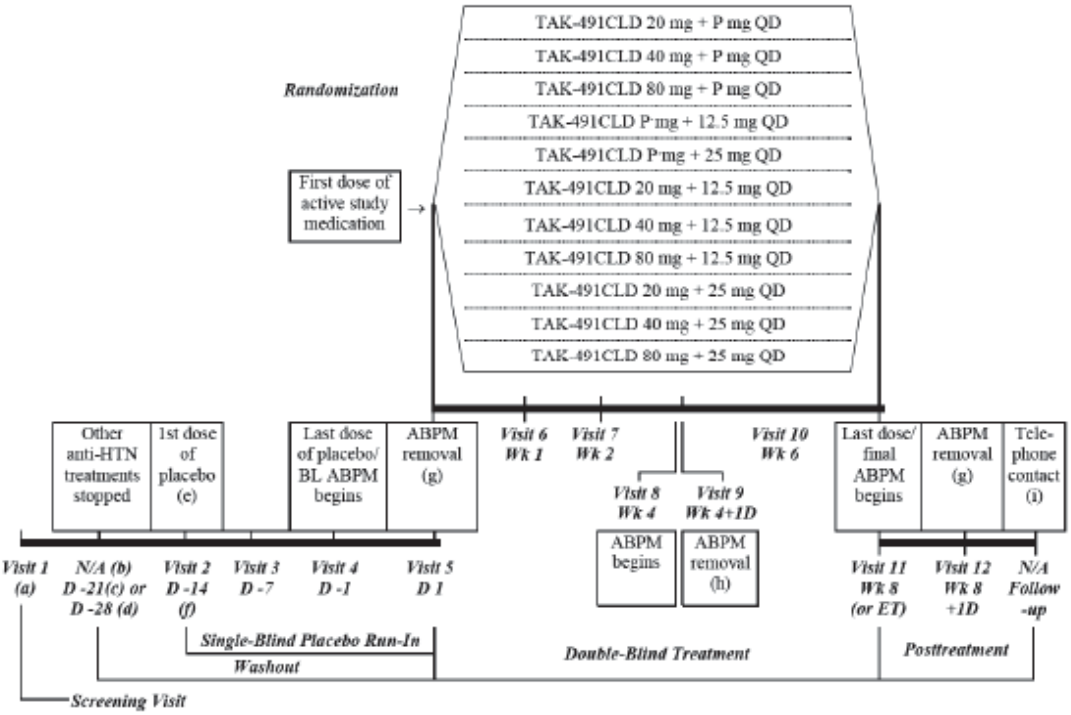


Figure 2; Study 302 scheme

There were about 150 subjects/treatment arm.

The primary efficacy endpoint was the change from baseline to Week 8 in trough ABPM SBP (22-24 hours post-dosing); key secondary endpoints were trough sitting cuff (or clinic) SBP and trough ABPM SBP in Black subjects; other secondary variables were trough DBP (clinic and ABPM); other ABPM SBP and DBP parameters; and proportion achieving BP response. The prespecified primary analysis compared pooled TAK-491CLD 40/25 + 80/25 with TAK-491 80 mg and CLD 25 mg monotherapy using ABPM SBP based on "last observation carried forward" (LOCF).

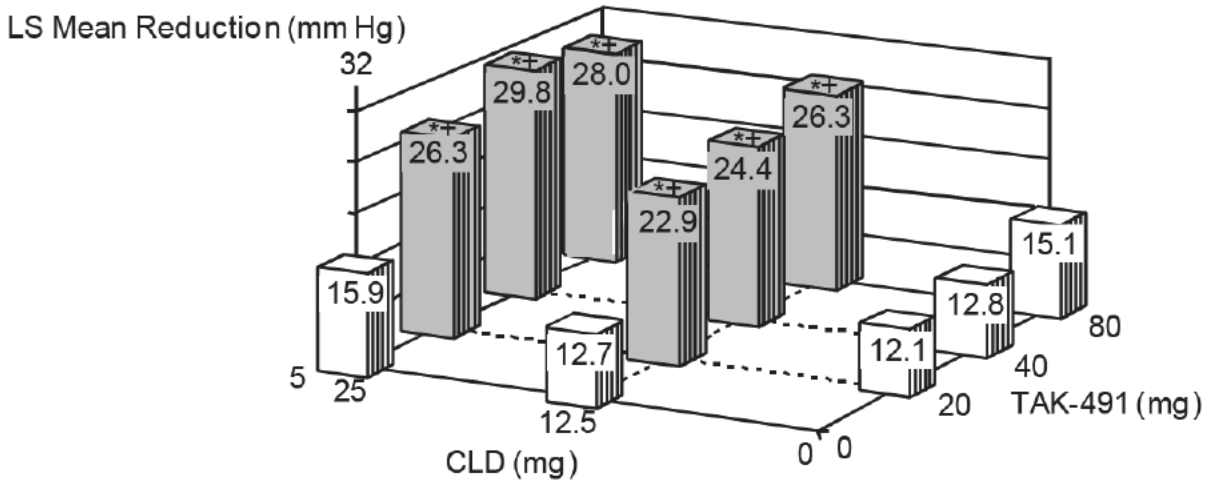
The study was conducted 1/29/2009-7/10/2010. There were a total of 13 protocol amendments; amendment 3 (1/7/2009) included subgroup analyses of Black subjects and amendment 10 (5/11/2010) changed the primary comparison to the pooled results for 40/25 and 80/25 mg groups vs. highest monotherapy doses (both topics discussed with the Agency). There were no interim analyses. The other protocol amendments do not appear to have impacted the study or results.

A total of 1714 subjects were randomized and 245 (14.3%) prematurely discontinued, with 6% due to adverse events and 1.6% due to lack of efficacy. A higher percentage (12.3%) withdrew from 80 mg TAK-491 than the 20 and 40 mg TAK-491 groups (9.0% and 9.2%, respectively). The highest percentage of premature discontinuations occurred in the TAK-491CLD 80/25 mg group (22.8%), where 13.6% of the total discontinued due to adverse events (and 5.6% due to voluntary withdrawal). The second highest discontinuations occurred

in the TAK-491CLD 40/25 mg (19.9% discontinuation, 12.2% due to AE and 5.1% due to voluntary withdrawals) and 80/12.5 mg (18.3% discontinuation, 7.2% due to AE and 7.8% due to voluntary withdrawal).

Dr. Zhang has suggested that tolerability, rather than lack of treatment effect, is more likely the cause of premature discontinuations, since the lowest withdrawal rates were in the TAK-491 20 and 40 mg monotherapy groups, with a slightly higher withdrawal rate in the TAK-491 80 mg group. Premature discontinuations due to lack of efficacy were low in the combination therapy arms (see primary medical review, Figure 14, page 44 of 112, not reproduced here, and section 7.2.2.3).

The mean age of the study population was about 57 years, about 50% female, and 25% were 65 and older. Mean BMI was 31 and almost 2/3 of the population came from US sites. About 20% of the study population was Black. No imbalances were observed.



*P < 0.05 for the TAK-491 CLD combination vs. CLD component dose
+P < 0.05 for the TAK-491CLD combination vs. TAK-491 component dose

Figure 3. Study 302: Primary endpoint: Change from baseline in trough SBP by ABPM at Week 8

The study met its primary endpoint, with statistically significant reductions in trough ABPM SBP in the pooled 40/25 + 80/25 mg group vs. 80 mg TAK-491 and 25 mg CLD.

Similar analyses for trough ABPM DBP and trough cuff SBP showed consistent results.

- Mean trough ABPM SBP and DBP reductions did not show greater efficacy of 80/25 mg compared to 40/25 mg.
- In addition, no efficacy advantage is observed for 80/12.5 mg vs. 40/25 mg.
- If one uses a minimum 5 mm Hg SBP difference between two dose-effect regimens, and preserves the 40/25 mg combination, with the largest SBP reduction, one can discern the following potential regimens for clinical use: (b) (4) 40/12.5 mg and 40/25 mg. Of note, the sponsor has proposed (b) (4) using 40/12.5 mg and 40/25 mg as potential doses.

- While there is no concurrent placebo group, there is literature evidence supporting lack of a significant placebo effect on trough BP by ABPM.[1]
- Results of trough SBP and DBP by ABPM and clinic (cuff) showed statistically significant reductions of each combination compared to its respective component monotherapies.

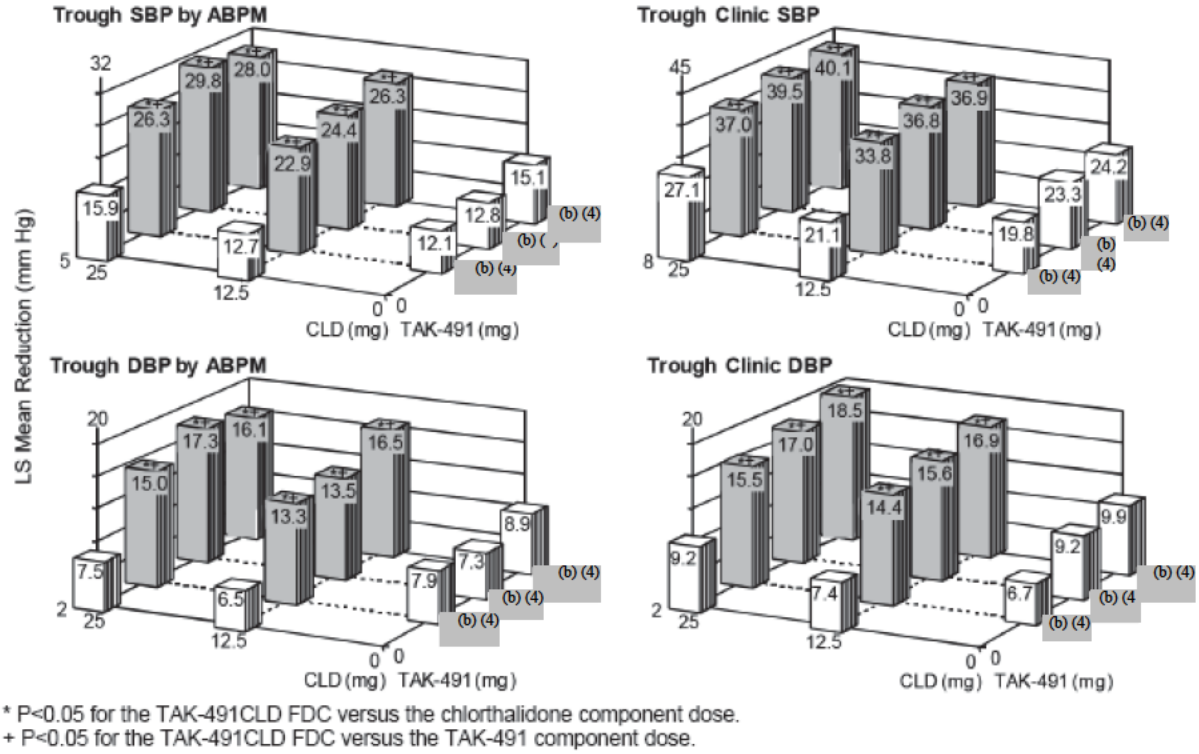


Figure 4. Change from baseline in trough SBP and DBP by ABPM and cuff measurements at Week 8 (study 302). Source: primary medical review and sponsor.

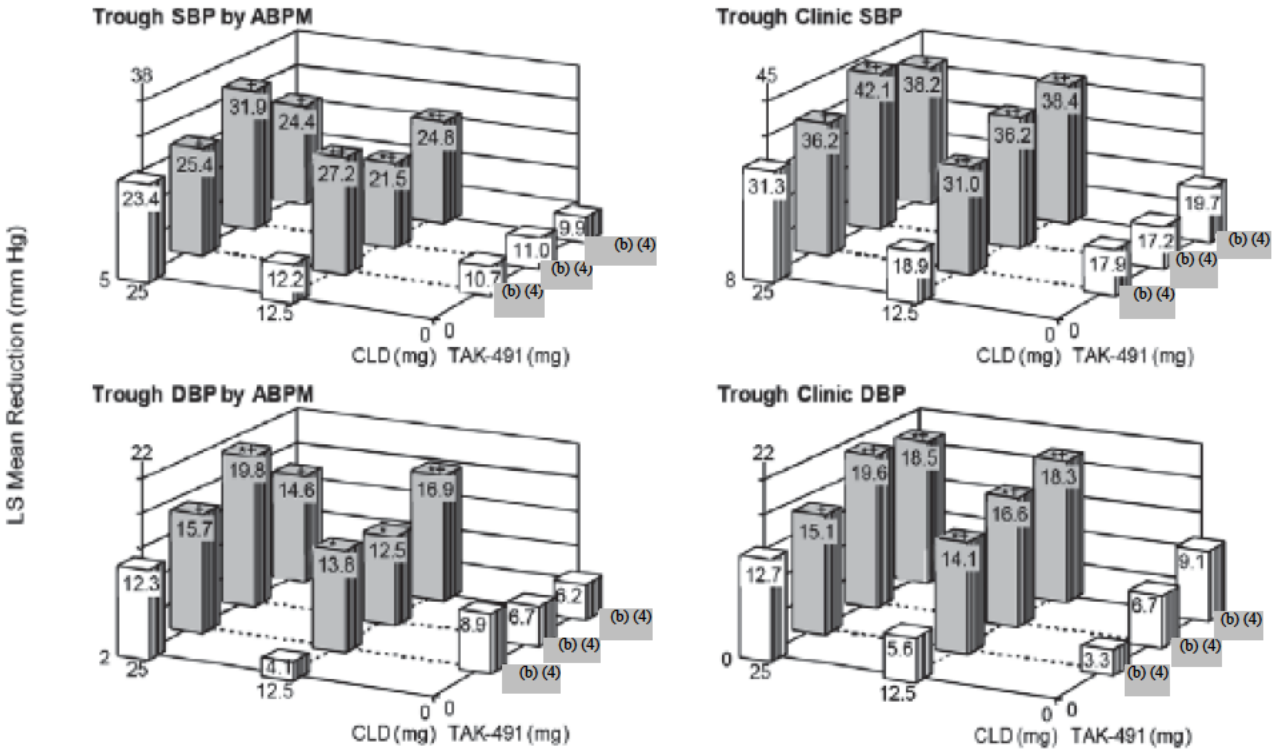
Dropouts/Missing data/sensitivity analyses: Dr. Zhang has commented on the 14% early termination from this study, a higher dropout rate than a typical hypertension trial; moreover, since not all subjects who completed the study had ABPM measurements, there are even more missing ABPM data. However, consistent results by LOCF method and sensitivity analysis using multiple imputations provide some reassurance. Similar analyses based on observed values only and on PP (per protocol) populations, excluding subjects with major protocol violations, are also consistent. The ABPM and clinic results for SBP and DBP are also consistent. If the dropouts were due to lack of treatment effect, the LOCF method tends to be conservative in the primary analysis.

Results in Black subjects:
In the subgroup of Black hypertensive subjects, the pre-specified measurement ABPM SBP in the pooled 40/25 and 80/25 mg groups (N=40) was not superior to CLD 25 mg monotherapy

[1] Mancia G et. al. Lack of Placebo Effect on Ambulatory Blood Pressure. *Am J Hypertension* 1995; 8:311-315.

(N=22). However, the pooled TAK-491CLD 40/25 and 80/25 was superior to both monotherapies by cuff SBP and the pooled group was superior to TAK-491 80 mg (N=28). Dr. Zhang has commented that there were fewer subjects in the pooled group for SBP via ABPM (N=40) than clinic measurement (N=63).

- The BP reduction from baseline for CLD 25 mg in this subgroup appears larger than the reduction for 80 mg TAK-491 at Weeks 4 and 8 (not shown).
- The mean reduction from baseline for CLD 25 mg in this subgroup appears larger (e.g., SBP ABPM reduction = 23.4 mm Hg) than the CLD 25 mg effect in the overall study population (SBP ABPM reduction = 15.9 mm Hg).
- There appears to be *no* increase in efficacy in 80/25 vs. 40/25; maximal effect in this population in the doses studied appears to be in the 40/25 mg group.
- 40/25 mg seems to have a larger treatment effect than 80/12.5 mg.



* P<0.05 for the TAK-491CLD FDC versus the chlorthalidone component dose.
\+ P<0.05 for the TAK-491CLD FDC versus the TAK-491 component dose.

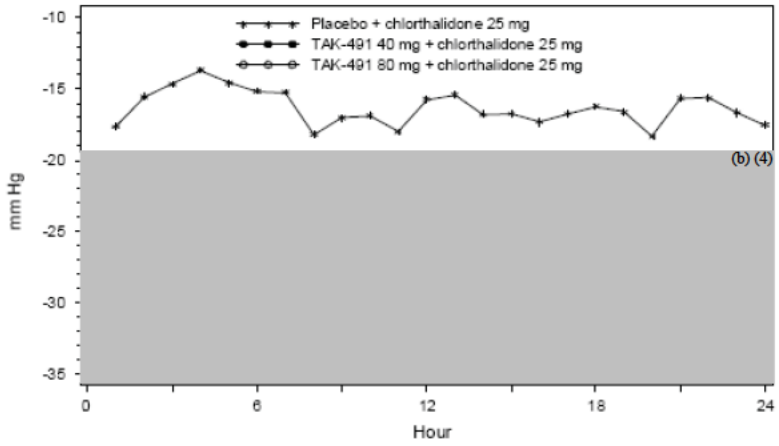
Figure 5. Study 302: results in Black subjects: Change from baseline in trough SBP and DBP by ABPM and cuff. Source: primary medical review and sponsor.

7.1.2.1.1. Study 491-009 (reviewed in the azilsartan monotherapy NDA) provides additional support that a significantly greater BP reduction can be observed with the TAK-491CLD combination versus CLD monotherapy: 551 eligible subjects (trough clinic SBP 160-190 mm Hg inclusive and 24-hour mean SBP 140-180 mm Hg inclusive) were

randomized to 40 mg TAK-491+ CLD 25 mg, TAK-491 80 mg + CLD 25 mg and placebo+ CLD 25 mg for 6 weeks of double-blind treatment. The primary endpoint was the change from baseline to Week 6 in 24-hour mean SBP via ABPM.

The study met its primary endpoint: the LS mean difference between TAK-491 40 mg + 25 mg CLD and TAK-491 80 mg + 25 mg CLD vs. 25 mg CLD were -15.86 and -15.45, respectively ($p < 0.001$ for both comparisons). Analyses of the changes from baseline in trough cuff SBP at weeks 2, 4 and 6 for both TAK-491 CLD combinations vs. CLD + placebo ($p < 0.001$) were consistent, as were analyses of DBP.

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



Source: Figure 15.2.1.5.3.

Figure 6. Hourly mean SBP by ABPM (study 491-009) from CDTL review for azilsartan medoxomil

The decision to pool 40/25 mg and 80/25 mg combinations was based on this study, since the 40/25 and 80/25 doses were not easily distinguishable.

7.1.2.2. Of the two comparative studies with olmesartan/HCTZ :

7.1.2.2.1. Study 301 was a 1085 subject, double-blind, parallel-group, "titrate to target"[2] study comparing 8 weeks of TAK-491CLD vs. OLM/HCTZ.

The primary endpoint was the change in trough cuff SBP at Week 8. A total of 51.7% of subjects in the OLM/HCTZ required up-titration, compared with 38.4% of subjects taking TAK-491CLD 20/12.5 mg and 34.7% of subjects taking TAK-491CLD 40/12.5 mg.

Statistically significant reductions from baseline to Week 8 in cuff SBP were shown in both TAK-491CLD groups vs. OLM/HCTZ (LS mean difference vs. OLM/HCTZ -6.1 mm Hg for low dose, -6.7 mm Hg for high dose, $p < 0.001$). Similar results were observed at Week 4,

[2] Target was defined by JNC7 goal BP: mean trough cuff BP < 140/90 mm Hg or < 130/80 mm Hg for subjects with diabetes or chronic kidney disease (CKD).

and sensitivity analyses using multiple imputations and other results (change in cuff BP and trough ABPM SBP and DBP) were consistent.

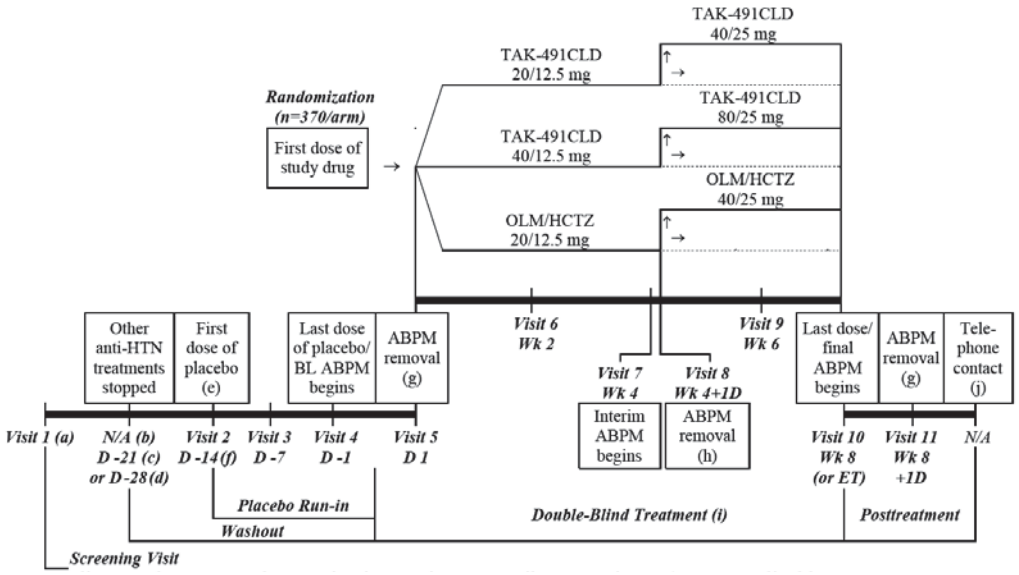


Figure 7. Study 301 scheme

However, TAK-491CLD was *not* being compared to the maximal doses of OLM/HCTZ, since a proportion of OLM/HCTZ subjects were not up-titrated. This study design, therefore, does not seem optimal to support a claim of superiority based on BP reductions.

7.1.2.2.2. In Study 303, a total of 1071 subjects were randomized to 12 weeks of double-blind treatment with TAK-491CLD 20/12.5 mg, TAK-491CLD 40/12.5 mg, or OLM/HCTZ 20/12.5 mg where each subject was force-titrated at Weeks 4 and 8. Subjects were stratified by race (Black, non-Black) upon randomization. Most subjects came from US sites (78.2%); about 22% of subjects were Black. The primary endpoint was the change from baseline to Week 12 in trough cuff SBP.

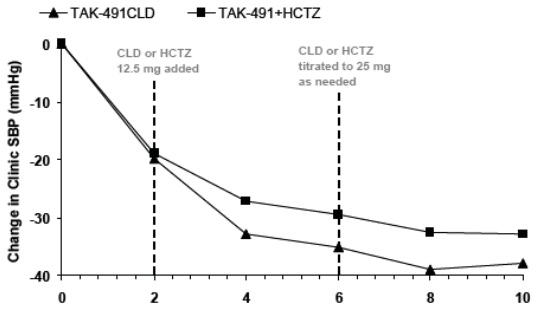
About 17% of subjects prematurely discontinued. There were about twice the number of AE-related discontinuations in the TAK-491CLD high-dose group (14.5%) compared to those on OLM/HCTZ (7.1%); AE-related discontinuations in the TAK-491CLD low-dose group (7.9%) appeared similar to OLM/HCTZ. The discontinuations due to lack of efficacy were similar between treatment groups.

Reductions from baseline to Week 12 in mean cuff SBP were greater in the TAK-CLD groups vs. OLM/HCTZ (LS mean difference vs. OLM/HCTZ -5.3 and -6.9 mm Hg, respectively, for low and high-dose groups, $p<0.001$). Secondary endpoints and sensitivity analyses were all consistent. In Black subjects, low and high-dose TAK-491CLD reduced trough SBP (ABPM and clinic) more than OLM/HCTZ (change at Week 12 $p < 0.05$); results were consistent with the overall population.

The most common AEs were increased blood creatinine (22% in the TAK-491CLD high-dose group, 18.6% in the TAK-491CLD low-dose group and 9.3% in OLM/HCTZ), followed by dizziness (highest, 16.5%, in the high-dose TAK-491CLD group and 8.0% with OLM/HCTZ) and fatigue (9.3% and 4.0% in the TAK-491CLD high and low-dose groups, respectively, and 4.4% in OLM/HCTZ). Please see section 7.2.2 for further safety discussion.

7.1.3. Other efficacy studies:

7.1.3.1. Study 306 was a 600 subject, double-blind, randomized, 2-arm parallel-group study of HCTZ vs. CLD, both co-administered with TAK-491. Subjects took single-blind 40 mg TAK-491 monotherapy for 2 weeks and 8 weeks of double-blind TAK-491 40 mg + 12.5 mg CLD or TAK-491 40 mg + 12.5 mg HCTZ. If the target SBP/ DBP[3] was achieved at Week 6, the diuretic dose remained at 12.5 mg for the rest of the study; otherwise, the respective diuretic dose was increased to 25 mg. The primary endpoint was the change from baseline to Weeks 6 and 10 in trough clinic SBP.



Source: Table 15.2.1.1.2, Figure 15.2.1.4.2.
NOTE: All subjects received TAK-491 40 mg; CLD 12.5 mg or HCTZ 12.5 mg was added after Week 2. CLD or HCTZ were titrated from 12.5 mg to 25 mg for subjects who had not achieved target SBP and DBP after Week 6.

Figure 8. 306: Change from baseline in clinic SBP at each study visit (LOCF)

7.1.3.2. Three open-label studies (308, 491-006, 491-016) were included in the integrated summary of efficacy as evidence supporting the pivotal results; one cannot exclude measurement or other bias in Studies 308 and 491-006, which were not designed to support efficacy, and but the results are consistent with the findings in the Phase 3 double-blind program.

7.1.3.3. Study 491-016 was a 26-week open-label "titrate to target" study that included a 6-week, double-blind, randomized, reversal period where subjects were given either TAK-491 (current dose) + CLD (if applicable) + other antihypertensive (if applicable) or placebo + CLD (if applicable) + other antihypertensive (if applicable) Subjects with DBP 95-119 mm Hg inclusive, or 85-109 mm Hg inclusive (if diabetes or CKD) were eligible; background anti-hypertensives, other than ARBs, were allowed. SBP and

[3] Target BP, per JNC7 criteria: mean trough sitting cuff BP < 140/90 mm Hg or < 130/80 mm Hg for subjects with diabetes or CKD

DBP increased after withdrawal of TAK-491 (12.97/7.92 mm Hg, respectively).

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

7.1.4.1. Dr. U concluded that the efficacy results support the combination TAK 491CLD as more effective compared with TAK-491 and CLD. Efficacy results of studies 303 and 308 support the claim that TAK-491CLD has a superior BP reduction compared with OLM/HCTZ. SBP in the subgroup of 40 Black subjects in pooled 40/25 + 80/25 mg TAK-491CLD was not significantly different from CLD 25 mg monotherapy. In study 303, which stratified subjects by race upon randomization, treatment with TAK-491CLD 40/25 mg or 80/25 mg led to significant reductions in SBP compared to OLM/HCTZ; however, the effect size was smaller in Black subjects (40 mm Hg) compared to Caucasian subjects (44 mm Hg). Dr. U felt that these findings do not support the claim that the combination is more effective than monotherapy in Blacks, or that the combination is as effective in Black subjects as in Caucasian subjects.

7.1.4.2. Dr. Zhang concluded that the fixed-dose combination tablet TAK-491CLD is effective in treating moderate to severe essential hypertension; overall, the treatment effect of TAK-491CLD appeared consistent across various subgroup populations (gender, race, age and region) when compared with monotherapies or active-controls in the four studies.

7.1.4.3. I concur with Drs. U and Zhang that the factorial study 302 supports the conclusion that the combination TAK-491CLD reduces BP to a greater extent than either high-dose monotherapy. I do not concur that superiority of TAK-491 CLD over OLM/HCTZ has been adequately demonstrated; while study 301 met its primary endpoint, the comparison is not against the highest dose of the comparator and the claim of "superior blood pressure reduction" is not fair. Study 308, cited as supportive by Dr. U, is an open-label safety study; one cannot exclude bias in the clinic SBP measurements used in to support superiority over OLM/HCTZ. I will discuss efficacy in Blacks in section 7.1.6.3.

7.1.5. Pediatric use/PREA waivers/deferrals

The Division, with concurrence from the Pediatric and Maternal Health Staff, has granted a waiver for this application, since this product does not represent a meaningful benefit and is not likely to be used in pediatric patients.

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

7.1.6.1. What dose (s) to approve: Dr. U has recommended a starting dose of 40/12.5 mg and top dose of 40/25 mg. I concur. The 40/12.5 mg and 40/25

mg combinations, based on the factorial study, appear to be reasonable doses that are distinguishable from each other. (b) (4) [redacted]

7.1.6.2. Superiority claim over OLM/HCTZ: Superiority over olmesartan/HCTZ, dosed maximally, has not been adequately demonstrated in two studies and I would not grant such a claim in labeling.

7.1.6.3. Efficacy in Black hypertensives: There are several efficacy-related questions concerning TAK-491CLD in Black hypertensives: whether the combination is more effective than monotherapy; whether the BP reductions are similar to those observed in non-Black subjects; and whether the TAK-491CLD combination is superior to olmesartan/HCTZ. Since I do not concur that there is adequate demonstration of superiority over olmesartan/HCTZ in the overall study population, I would not grant a superiority claim for TAK-491CLD over olmesartan/HCTZ in the subgroup of Black hypertensives.

The TAK-491CLD combination (pooled group) by ABPM SBP was superior to TAK-491 80 mg but not CLD 25 mg monotherapy and therefore is not superior to both combinations according to the prespecified analyses. Perhaps the ABPM sample was "underpowered," since the clinic BP sample (which won) was larger, and perhaps CLD 25 mg monotherapy had large effects in this particular subgroup.

When comparing trough SBP reductions (ABPM and clinic) between Black and White subjects in the factorial study, effects in the 40/12.5 and 40/25 mg groups appear similar, or higher, in Black subjects compared to White subjects (without any hypothesis testing for non-inferiority). In addition, results in the Black subgroup of study 303 were consistent with the overall study population, supporting a treatment effect regardless of race. Subgroup results by race in study 491-009 (24-hour mean ABPM SBP and trough clinic SBP reductions for TAK-491CLD 40/25 and 80/25 mg) showed BP reductions in Blacks that were similar to or numerically greater than reductions in the White subgroup (not shown). I therefore concur with Dr. Zhang that the TAK-491CLD combination was effective, regardless of race.

Table 2. SBP (ABPM and clinic) reductions by race subgroup (302)

Table 1.a Change From Baseline at Week 8 in Trough SBP by ABPM and Clinic SBP by Race (491CLD-302)

Study	Dose (mg)	Mean Reduction in SBP (mmHg) From Baseline			
		ABPM		Clinic	
		Black	White	Black	White
302	491 20	-10.7 (n=26)	-12.4 (n=91)	-17.9 (n=31)	-19.5 (n=113)
	491 40	-11.0 (n=27)	-13.8 (n=92)	-17.2 (n=35)	-24.8 (n=104)
	491 80	-9.9 (n=28)	-17.5 (n=85)	-19.7 (n=35)	-25.1 (n=111)
	CLD 12.5	-12.2 (n=24)	-12.6 (n=93	-18.9 (n=31)	-20.8 (n=109)
	CLD 25	-23.4 (n=22)	-15.0 (n=94)	-31.3 (n=29)	-25.3 (n=108)
	491CLD 20/12.5	(b) (4)			
	491CLD 40/12.5	-21.5*† (n=24)	-25.4*† (n=80)	-36.2*† (n=28)	-36.5*† (n=101)
	491CLD 80/12.5	(b) (4)			
	491CLD 20/25				
	491CLD 40/25	-31.9* (n=19)	-29.4*† (n=82)	-42.1*† (n=30)	-38.6*† (n=110)
	491CLD 80/25	(b) (4)			
	491CLD 40/25+80/25	-28.2* (n=40)	-29.2*† (n=158)	-40.2*† (n=63)	-39.4*† (n=216)

Source: 491CLD-302 Tables 15.2.1.3.2 and 15.2.3.3.2.
* Significant difference vs respective TAK-491 monotherapy component dose at 0.05 level.
† Significant difference vs respective CLD monotherapy component dose at 0.05 level.

7.2. Safety

7.2.1. General safety considerations

As of March 18, 2011, a total of 3082 subjects were exposed to at least one dose of the fixed-dose combination TAK-491CLD with a mean and median exposure of 86.1 and 59 days, respectively. In addition, 309 subjects were exposed to the TAK-491CLD combination for at least 24 weeks and 112 subjects were exposed to the combination for at least 52 weeks. Both TAK-491 and CLD are approved medications. 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 7 deaths in the phase 3 program, two occurred with OLM/HCTZ, one occurred in a subject taking TAK-491 40 mg monotherapy and 4 events occurred in subjects who received the TAK-491CLD combination. There were two cases of sudden death (one in TAK-491 40 mg monotherapy and one in TAK-491 40/12.5 mg) in at-risk hypertensive subjects (one with sleep apnea and obesity), but no obvious safety signal.

7.2.2.2. Serious adverse events (SAE, nonfatal):

Study 308, a long-term study, had a higher percentage of SAE. Otherwise, the incidence of SAE was low, and there was no signal of concern. In study 302, serum

creatinine increase as SAE occurred in only 1 subject (3118/015, TAK-491CLD 80/12.5 mg)

7.2.2.3. Discontinuations due to adverse events (AE)

In the pivotal factorial trial, there were more premature discontinuations (>15%) in the 80/12.5, 40/25, and 80/25 mg groups, with more discontinuations due to AE. Withdrawals from lack of efficacy appear to be low.

"Increased blood creatinine" was the most common event leading to temporary or permanent discontinuation in study 302. Since study 302 required investigators to report creatinine elevations ≥ 30% from baseline and >ULN and advised investigators to consider withdrawing subjects with creatinine elevations ≥ 50% from baseline and > ULN, this finding may reflect, in part, "heightened awareness" on the part of investigators. In studies 306, 301 and 308, increased creatinine was also the most common AE leading to discontinuation. Creatinine elevations appeared to be transient in most subjects who remained on treatment, with reversals toward baseline in about 96% of subjects; increases in serum creatinine appeared to parallel reductions in SBP in most subjects.

Dizziness was the second most frequent AE leading to discontinuation (incidence highest, 3.8% and 2.5%, respectively, in the 40/25 and 80/25 mg groups), followed by hypotension (highest incidence 1.9% in the 80/25 mg group) and vertigo (1.9% in the 80/25 mg group).

Table 3. Disposition in three Phase 3 studies

Table 1.k Subject Disposition: 491CLD-302 (FDC Only), 491CLD-306, and 491CLD-301

	Number (%) of Subjects										
	491CLD-302						491CLD-306		491CLD-301		
	TAK-491CLD						TAK-491 CLD	TAK-491 +HCTZ	TAK-491CLD		OLM/ HCTZ
Primary Reason for Discontinuation	20/12.5 N=156	40/12.5 N=147	80/12.5 N=153	20/25 N=154	40/25 N=156	80/25 N=161	40/12.5 → 40/25 N=303	40+12.5 → 40+25 N=306	20/12.5 → 40/25 N=372	40/12.5 → 80/25 N=357	20/12.5 → 40/25 N=356
Completed	135 (86.5)	131 (89.1)	125 (81.7)	131 (85.1)	125 (80.1)	125 (77.2)	252 (83.2)	260 (85.0)	317 (85.2)	308 (86.3)	323 (90.7)
Discontinued	21 (13.5)	16 (10.9)	28 (18.3)	23 (14.9)	31 (19.9)	37 (22.8)	51 (16.8)	46 (15.0)	55 (14.8)	49 (13.7)	33 (9.3)
Due to TEAE	10 (6.4)	6 (4.1)	11 (7.2)	10 (6.5)	19 (12.2)	22 (13.6)	28 (9.2)	19 (6.2)	20 (5.4)	30 (8.4)	11 (3.1)
Protocol deviation	2 (1.3)	2 (1.4)	1 (0.7)	1 (0.6)	1 (0.6)	1 (0.6)	2 (0.7)	2 (0.7)	5 (1.3)	4 (1.1)	0
Lost to follow-up	0	1 (0.7)	0	1 (0.6)	1 (0.6)	3 (1.9)	3 (1.0)	2 (0.7)	8 (2.2)	2 (0.6)	5 (1.4)
Voluntary withdrawal	5 (3.2)	3 (2.0)	12 (7.8)	5 (3.2)	8 (5.1)	9 (5.6)	16 (5.3)	14 (4.6)	11 (3.0)	11 (3.1)	9 (2.5)
Lack of efficacy	3 (1.9)	0	2 (1.3)	1 (0.6)	1 (0.6)	0	0	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.6)
Other	1 (0.6)	4 (2.7)	2 (1.3)	5 (3.2)	1 (0.6)	2 (1.2)	2 (0.7)	7 (2.3)	9 (2.4)	1 (0.3)	6 (1.7)
Pregnancy	0	0	0	0	0	0	0	0	1 (0.3)	0	0

Source: 491CLD-302 Table 15.1.4, 491CLD-306 Table 15.1.4, and 491CLD-301 Table 15.1.4.
Note: Primary reasons for discontinuation of study drug are mutually exclusive and exhaustive categories.

7.2.2.4.General adverse events (AEs)

Dose-related AEs are best evaluated in the factorial study 302. The most prominent dose-related event in 302 was "increased blood creatinine" (from 9.6% in the 20/12.5 mg group to 19.9% in the 80/25 mg group). In addition, a 6% spread (from lowest to highest dose) can be observed for "hyperuricemia," an expected dose-related AE with chlorthalidone; there is a separate category for "blood uric acid increased". Dose-related increases are also observed with respect to dizziness and increased blood urea. Increased creatinine was noted in the CLD co-administration study in the azilsartan monotherapy NDA. During review of the azilsartan monotherapy NDA, I was uncertain whether the creatinine elevations represented a pharmacologic effect, or a renal-related concern. It should be noted that in study 302, the sponsor prompted investigators to consider discontinuing from therapy subjects with creatinine elevations. However, the reversibility and lack of related renal AEs (e.g., renal impairment, renal failure) provides some short-term reassurance.
Therefore, AEs such as creatinine elevation and dizziness can be likely interpreted as consistent with pharmacologic effects of the drug or, in the case of increased uric acid, expected effects of thiazide-like diuretics.

One caveat is that subjects with severe renal disease (eGFR < 30 mL/min/1.73 m2) were excluded; consequently, the renal safety in this population cannot be evaluated. The sponsor is currently conducting a study in subjects with moderate renal impairment, and the results should be informative.

Table 4. Dose-related AEs (302)

Table 21 TEAEs in Study 302 in relation to dose of TAK-491CLD

	Study 302 TAK-491CLD doses					
MedDRA Preferred Term	**20/12.5 N=156**	**40/12.5 N=146**	**80/12.5 N=153**	**20/25 N=154**	**40/25 N=156**	**80/25 N=161**
Any TEAE	92 (59.0)	83 (56.8)	84 (54.9)	88 (57.1)	106 (67.9)	100 (62.1)
Blood creatinine increased	15 (9.6)	17 (11.6)	19 (12.4)	19 (12.3)	29 (18.6)	32 (19.9)
Dizziness	12 (7.7)	20 (13.7)	19 (12.4)	17 (11.0)	21 (13.5)	19 (11.8)
Headache	8 (5.1)	1 (0.7)	11 (7.2)	12 (7.8)	9 (5.8)	11 (6.8)
Hypokalemia	4 (2.6)	0	0	2 (1.3)	5 (3.2)	2 (1.2)
Blood CK increased	3 (1.9)	3 (2.1)	3 (2.0)	4 (2.6)	10 (6.4)	3 (1.9)
Blood uric acid increased	3 (1.9)	6 (4.1)	9 (5.9)	9 (5.8)	7 (4.5)	3 (1.9)
Blood urea increased	2 (1.3)	4 (2.7)	7 (4.6)	6 (3.9)	8 (5.1)	9 (5.6)
Diarrhea	5 (3.2)	3 (2.1)	6 (3.9)	5 (3.2)	5 (3.2)	7 (4.3)
Fatigue	6 (3.8)	2 (1.4)	6 (3.9)	4 (2.6)	6 (3.8)	7 (4.3)
Nasopharyngitis	8 (5.1)	2 (1.4)	2 (1.3)	5 (3.2)	7 (4.5)	3 (1.9)
Upper respiratory infection	1 (0.6)	0	0	0	7 (4.5)	2 (1.2)
Hyperuricemia	2 (1.3)	4 (2.7)	3 (2.0)	6 (3.9)	3 (1.9)	10 (6.2)
Blood potassium decreased	1 (0.6)	0	0	1 (0.6)	3 (1.9)	1 (0.6)

Source: primary medical review

7.2.2.5.Laboratory tests

7.2.2.5.1. Changes in creatinine:

In addition to the above discussion, the sponsor submitted an analysis of long-term study 308

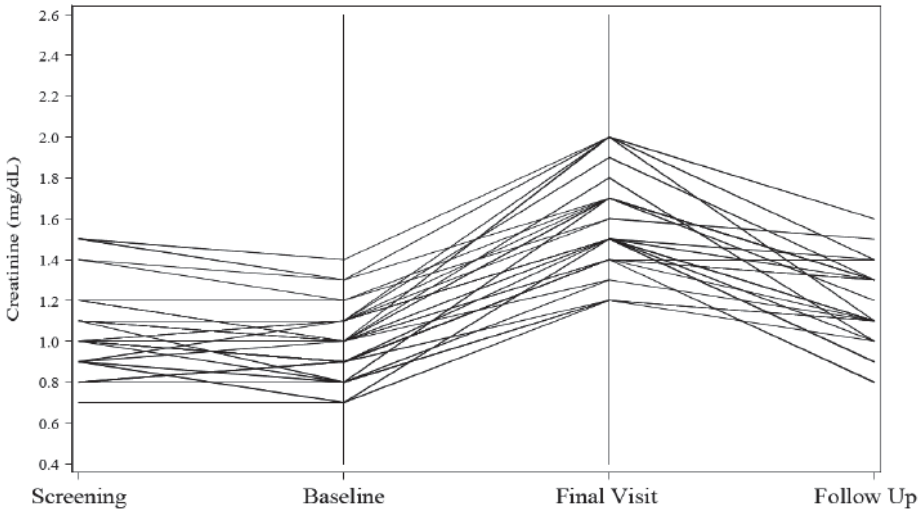
Table 5. Renal adverse event frequency in Study 308

MedDRA Preferred Term	Number (%) of subjects	
	TAK-491CLD N = 418	OLM/HCTZ N = 419
Subjects with ≥TEAE in Renal Cluster	86 (20.6)	41 (9.8)
Blood creatinine increased	85 (20.4)	36 (8.6)
Blood urea increased	12 (2.9)	6 (1.4)
GFR decreased	1 (0.2)	1 (0.2)
Fluid retention	1 (0.2)	0
Oliguria	0	1 (0.2)
Pyelonephritis	0	1 (0.2)
Renal failure acute	0	1 (0.2)
Renal impairment	1 (0.2)	0
Renal failure chronic	0	1 (0.2)

Source: Sponsor's 120-Day Update Table 2.4.4.4

It is worth noting that while "blood creatinine increased" is the most prominent signal, cases of renal impairment or renal failure were rare. It is also worth noting that, in ongoing study 308, many cases of creatinine elevation tend to decrease toward baseline during the follow-up visit.

Figure 39 Reversibility of creatinine elevations in subjects in TAK-491 CLD treatment group at Final Visit in Study 308



Source: 120 –Day Update Figure 7.4.4.1

Figure 9. Serum creatinine in TAK-491CLD at final visit (308)

Table 6. Reversibility of creatinine elevations across short-term studies

Table 33 Reversibility of creatinine elevations across Studies 301, 302, 303 and 306

		Study 301 N=1085	Study 302 N=1712	Study 303 N=1071	Study 306 N=605	Overall Total N=4473
Subjects with creatinine elevations ≥30% from Baseline and >ULN at Final Visit, n/N (%)						
Final Visit Elevations (a)		31/1070 (2.9)	44/1697 (2.6)	61/1049 (5.8)	19/595 (3.2)	155/4411 (3.5)
Reversibility of creatinine elevations ≥30% from Baseline and >ULN Present at Final Visit, n/N (%)						
Resolved (b)	All subjects	30/31 (96.8)	39/44 (88.6)	50/61 (82.0)	14/19 (73.7)	133/155 (88.6)
	Subjects with available followup(c)	30/30 (100)	39/41 (95.1)	50/52 (96.2)	14/15 (93.3)	133/138 (96.4)
Partially resolved (d)		0	2/44 (4.5)	2/61 (3.3)	0	4/155 (2.6)
Unresolved	In Follow-up (e)	0	0	0	1/19 (5.3)	1/155 (0.7)
	Lost to Follow-up (f)	0	0	2/61 (3.3)	1/19 (5.3)	3/155 (1.9)
No Follow-up (g)		1/31 (3.2)	3/44 (6.8)	7/61 (11.5)	3/19 (15.8)	14/155 (9.0)

Source: Study 301 CSR Table 12.p, Study 302 CSR Table 12.u, Study 303 CSR Table 12.t, Study 306 CSR Table 12.t

(a) Last observation carried forward, collected up to 7 days (inclusive) after the last dose of active study drug. A subject was counted as long as his/her value met the criterion according to either SI or CV units.

(b) Primarily subjects who resolved during follow-up but also includes subjects who were considered resolved at Final Visit relative to Screening values (i.e., resolved to ≤0.2 mg/dL above the Baseline or Screening value, and did not meet the ≥30% criterion).

(c) Does not include subjects who were considered Lost-to-Follow-up or who had no follow-up [(f) and (g) below].

(d) Subjects no longer met ≥30% from Baseline and >ULN criterion during follow-up but had not fully resolved to ≤0.2 mg/dL above the Baseline or Screening value. (e) Unresolved and follow-up is continuing. (f) Currently lost to follow-up, subjects had limited follow-up values reported and were considered unresolved at the last reported measurement.

(g) Lost-to-follow-up or Non-adverse event of special interest (AESI): Subjects for whom creatinine value elevated at Final Visit but no follow-up values available or subjects who had a Final Visit creatinine elevation that was not considered AESI (creatinine elevations for these subjects were <30% from Baseline based on unrounded, 3-digit laboratory values; therefore investigators did not receive flags for these values, and the sites did not record an AESI or obtain follow-up creatinine values for these subjects).

Besides elevations in serum creatinine, other laboratory abnormalities in long-term study 308 included elevated serum uric acid and cases of hypernatremia.

7.2.3. Discussion of primary reviewer's comments and conclusions

The primary medical reviewer felt that the safety profile was unremarkable at the doses studied, with the benefit-risk assessment favoring approval. The most frequent TEAE leading to discontinuation was creatinine elevation, followed by dizziness. The creatinine elevations were transient and tended to be inversely proportional to reductions in SBP. This reviewer concurs.

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

Study 309 is an ongoing study evaluating the use of TAK-491CLD in subjects with moderate renal insufficiency; results, when available, should be added to labeling.

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 Edarbyclor was acceptable per review by DMEPA (Yelena Masov, PharmD, 7/12/2011). DMEPA plans to re-review the proprietary name based on available dose combinations.

11.2. Physician labeling

11.2.1. Dosing: I concur with Dr. U in recommending an initial Edarbyclor dose of 40/12.5 mg and a maximal dose of 40/25 mg, taken once daily.

11.2.2. Initial Therapy: Based on the findings of study 302, as well as the safety database, Edarbyclor can be reasonably given to patients with moderate to severe hypertension likely to need multiple medications.

11.2.3. Comparative claim: As discussed, I would not grant a claim of superiority over OLM/HCTZ.

11.2.4. Effects in Blacks with hypertension:

A sampling of other labels for combination antihypertensive drugs describing effects by race revealed the following:

Table 7. Antihypertensive drug combinations: efficacy in Black patients

Drug	Package insert
Olmesartan-HCTZ	"The antihypertensive effect was independent of gender, but there were too few subjects to identify response differences based on race or age greater than or less than 65 years." (Clinical Trials, olmesartan medoxomil-hydrochlorothiazide)
Valsartan-HCTZ	"The antihypertensive effect is independent of age or gender. The overall response to the combination was similar for Black and non-Black patients." (section 14.2, Hypertension) "After 4 weeks of therapy, reductions in systolic and diastolic blood pressure were 9/5 mmHg greater in the group treated with Diovan HCT compared to valsartan. Similar trends were seen when the patients were grouped according to gender, race or age." (Section 14.2 Initial Therapy of Hypertension)
Aliskiren-HCTZ	"The antihypertensive effect was independent of age and gender. There were too few non-Caucasians to assess differences in blood pressure effects by race." (Section 14, Clinical studies)
Amlodipine-olmesartan	"Azor was effective in treating black patients (usually a low-renin population), and the magnitude of blood pressure reduction in black patients approached that observed for non-Black patients. This effect in black patients has been seen with ACE inhibitors, angiotensin receptor blockers, and beta-blockers." (Section 14.1, Clinical studies, Azor)
Clonidine-chlorthalidone	No labeling information regarding effects by race.
Atenolol-chlorthalidone	No labeling information regarding effects by race.

Based on the data from studies 302 and 303, labeling language can be crafted that Edarbyclor was effective regardless of race.

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

11.4 Patient labeling/Medication guide

A DRISK review is pending. The proposed routine safety monitoring by the sponsor appears adequate.

12. DSI Audits

Three sites (3019, 3026 and 3042) from study 302 and one site (2032) from study 301 were audited; (b) (4) (Contract Research Organization) was inspected in regard to use of the ABPM device and transmission of 24-hour BP readings to the sponsor. Only minor regulatory violations were found at sites 3019 and 2032; no regulatory violations were found in the (b) (4) inspection. It was noted at BP readings at site 3019 were not always taken at trough; however, ABPM measurements provide additional reassurance regarding effects at trough and over 24-hours.

13. Conclusions and Recommendations

13.1. Recommended regulatory action Edarbyclor (azilsartan medoxomil plus chlorthalidone) should be approved for the treatment of moderate to severe hypertension, with labeling recommendations as in section 11.2.

13.2. Safety concerns to be followed postmarketing
This reviewer recommends routine monitoring for any renal safety signals.

13.3. Postmarketing studies, voluntary or required

13.3.1. The ONDQA reviewer has asked for a PMC to collect dissolution data (see section 3).

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/s/

SHARI L TARGUM
11/10/2011