CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202331Orig1s000

MEDICAL REVIEW(S)

Addendum to Clinical Review of NDA 202-331 (Edarbyclor®)

APPLICATION TYPE:	NDA 21202-331	SUBMISSION NUMBER:	N0027
ESTABLISHED NAME:	TAK-491CLD (azilsartan medoxomil plus chlorthalidone)		
PROPOSED NAME:	Edarbyclor®		
THERAPEUTIC CLASS:	Angiotensin II Receptor Blocker and thiazide-type diuretic in a fixed dose combination		
FORMULATIONS:	Two fixed dose combination tablets of TAK-491 and chlorthalidone: 40 mg / 12.5 mg and 40 mg / 25 mg.		
APPLICANT:	Takeda Global Research & Development Center, Inc.		
INTENDED POPULATION:	Patients with moderate hypertension (clinic SBP ≥160 and ≤190 mmHg) whose blood pressure is not controlled with monotherapy		
INDICATION:	Treatment of hypertension. May be used as initial therapy if a patient is likely to need multiple drugs to help achieve blood pressure goals.		
DATE SUBMITTED:	*04-Nov-2011*	DATE RECEIVED:	*04-Nov-2011*
DATE COMPLETED:	*22-Nov-2011*	PDUFA GOAL DATE:	*24-Dec-2011*
CLINICAL REVIEWER:	Khin Maung U, M.D.		

Submission: Sponsor's 04-Nov-2011 response to FDA Questions

Background:

Some of the sponsor's proposed doses and proposed labeling claims (discussed below) are not supported by the data submitted in the NDA. The Division forwarded questions to the sponsor on 24-Oct-2011 to provide the sponsor with an opportunity to provide additional data and/or analyses to support their claims and the proposed doses, and to provide the rationale/explanation for their claims.

On 04-Nov-2011, the sponsor submitted an electronic their response to the questions:

(b) (4)

Review Findings:

Claim related to effectiveness in Black subjects:

In my review, I found that the sponsor's claim that TAK-491CLD was more effective than monotherapy with TAK-491 or CLD in Black subjects, or that TAK-491CLD was as effective in Black subjects as in White subjects is not supported by the data in clinical trials:

- *In Study 302, the efficacy data in the subpopulation of Black subjects who had a*

baseline and a final ABPM (40 subjects for the TAK-491CLD 40/25+80/25 mg pool, and 28 and 22 subjects for the TAK-491 80 mg and CLD 25 mg monotherapy groups, respectively) showed statistically significant (P<0.001) larger reductions in trough SBP by ABPM at Week 8 in the treatment groups receiving the TAK-491CLD FDC (40/25 mg+80/25 mg pool) compared to monotherapy with TAK-491 80 mg, but not to monotherapy with CLD 25 mg. On the other than, the reductions in clinic SBP in the groups receiving the highest doses of TAk-491CLD (40/25 mg + 80/25 mg pool) were statistically significantly larger than the reductions in clinic SBP in the treatment groups receiving the highest doses of monotherapy with TAK-491 (80 mg) or CLD (25 mg).

- *In Study 303 which stratified subjects upon randomization as Black vs. non-Black, the Black subjects treated with TAK-491CLD 40/25 mg or 80/25 mg had statistically significant reductions in clinic SBP from Baseline to Week 12 compared to the OLM/HCTZ treatment group, but this SBP reduction in Black subjects was smaller (≈40 mmHg) compared to that observed in Caucasian subjects (≈44 mmHg).*

In their 11/04/11 response, the sponsor provided additional supportive data from Study 009 which compared TAK-491 (40 or 80 mg) plus CLD 25 mg (co-administered) versus CLD 25 mg monotherapy. This study showed (i) a statistically significant difference in reduction in 24-hour mean SBP by ABPM (protocol specified primary endpoint) in the TAK-491 (40 or 80 mg) plus CLD 25 mg coadministration treatment groups compared with the CLD 25 mg monotherapy group in both Black and White subgroups, and (ii) the absolute SBP reductions by ABPM were similar for Blacks (14.9 ~ 16.6 mmHg) and White (15.4 ~ 15.9 mmHg) subjects.

The sponsor also provided data on change from baseline in SBP by trough ABPM and clinic SBP for Black and White subjects in Studies 301, 303 and 306. For "titrate to target BP Studies (301 and 306), the sponsor evaluated the dose responses prior to titration, and observed similar absolute SBP reductions by ABPM in Blacks and Whites.

Reviewer's Comment: The additional data and analyses submitted by the sponsor provide persuasive evidence to support the labeling claim that the BP reduction effect of TAK-491CLD in Blacks is similar to that in non-Blacks.

Doses recommended for approval:

In my clinical review, I recommended approval of TAK-491CLD (Edarbyclor®) for the indication of treatment of hypertension at two doses: 40/12.5 mg (starting dose) and 40/25 mg (top dose). (b) (4)

(1) **80/25 mg dose**: The sponsor did not request approval for the highest dose of **80/25 mg** (b) (4)

(2) **20/25 mg dose**: The sponsor did not request approval for the **20/25 mg** dose. (b) (4)

[redacted] (b) (4)

(4) **40/12.5 mg dose**: This dose is recommended for approval as the initial dose. This **40/12.5 mg** dose had the same safety profile as the lower 20/12.5 mg dose, while producing a 3 mmHg greater reduction in clinic SBP. The logistic regression curves for the 40/12.5 mg dose relative to the individual TAK-491 and CLD monotherapies on the probability of achieving target systolic BP (<140 mmHg) and target diastolic BP (<90 mmHg) show that subjects randomized to the 40/12.5 mg dose had a greater probability of achieving SBP and DBP targets than subjects randomized to either monotherapy.

(5) **80/12.5 mg dose**: The [redacted] (b) (4) dose of **80/12.5 mg** produced BP reductions which are practically the same as the *starting* dose of 40 mg/12.5 mg, albeit with more adverse reactions. The sponsor argued in their response that this dose may be useful particularly for a patient who is not controlled with TAK-491 80 mg (to switch directly to 80/12.5 mg FDC). However, this dose produced the same magnitude of reduction in clinic SBP as the proposed initial dose of 40/12.5 mg. Also, the 80/12.5 mg dose was studied only in the factorial trial and not in any other clinical trial. I think that patients not achieving adequate BP reduction regardless of the antihypertensive medication they are receiving may be switched to the recommended starting dose of **40/12.5 mg**.

(6) **40/25 mg dose**: The **40/25 mg** dose produced the largest reduction in SBP by ABPM (29.8 mmHg) and by clinic measurement (39.5 mmHg). This is the reason for recommending the 40/25 mg as the top dose.

Reviewer's Comment: The additional data and analyses submitted by the sponsor in their response dated 11/04/11 do NOT provide any conclusive evidence to support the [redacted] (b) (4). There is no reason to change the current recommendation of the 40/12.5 mg as the initial dose, and the recommendation of the 40/25 mg as the top dose.

Other questions:

1. *The sponsor's claim that no initial dose adjustment is recommended for patients with mild-to-moderate renal impairment is not supported by the data in Study 302 in which subgroup analysis by baseline eGFR showed a greater response to monotherapies (TAK-491 80 mg and CLD 25 mg) and TAK-491CLD 40/25+80/25 mg pool in subjects with mild renal impairment compared with those with normal renal function*.

   The sponsor provided data related to (i) change in trough SBP by ABPM and (ii) clinic SBP from baseline to final visit stratified by renal status which suggested that the efficacy profiles appear to be similar in subjects with mild or moderate renal impairment and subjects with normal renal function in fixed-dose (Study 302), forced titration (Study 303) and titrate-to-target BP studies (301 and 306).

Reviewer's Comment: This additional data support the sponsor's claim that no initial dose adjustment is necessary for patients with mild-to-moderate renal impairment.

2. *The sponsor's claim that no initial dose adjustment is necessary in elderly patients is not supported by age specific data for patients ≥75 years.*

   The sponsor provided additional data in which the mean change from baseline in SBP by ABPM (Study 302) or clinic SBP (Study 306) stratified by age groups (<65, ≥65 and ≥75 years) appeared slightly less in subjects ≥65 years of aged compared to those <65 years. The safety profile in elderly subjects >75 years was roughly similar to those <75 years old.

   Reviewer's Comment: The additional data support the sponsor's claim that no initial dose adjustment is necessary in elderly subjects.

3. *The sponsor has not submitted data to support their statement that for "Chlorthalidone - Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma."*

   The sponsor provided case narratives of 18 subjects (0.3% of 5,857 subjects in the Edarbyclor program) who reported with hypersensitivity: 3 on Edarbi monotherapy, 1 on CLD monotherapy and 7 each on Edarbyclor and comparator groups. Also, of 1,095 subjects who had a history of allergy or asthma, only 6 (0.6%) subjects experienced asthma or worsening of asthma, and 3 (0.3%) experienced hypersensitivity events (eye swelling, urticaria and swelling of face).

   Reviewer's Comment: There is no evidence that patients with a history of allergy or bronchial asthma who receive Edarbyclor will be a greater risk of hypersensitivity reactions. (b) (4)

4. *The sponsor has no placebo-controlled data to show that the list of adverse reactions or the laboratory abnormalities reported in subjects with TAK-491CLD provide meaningful information.*

   The sponsor (b) (4) proposed to (b) (4) with the incidence of discontinuations due to adverse reactions. The sponsor also proposed to remove the (b) (4)

   Reviewer's Comment: The sponsor's proposal appears reasonable.

5. *The sponsor has not provided specific safety data related to chlorthalidone or the chlorthalidone component of TAK-491CLD other than copied the list of adverse reactions in the chlorthalidone label.*

   The sponsor provided safety data (list of adverse reactions) observed in subjects receiving CLD alone in the fixed-dose factorial trial, and in the CLD monotherapy

arm of Study 009.

Reviewer's Comment: The sponsor's proposal appears reasonable. In addition, I used the data in Dr. Karkowsky's review of NDA 19-574 (Thalitone™). (b) (4)

6. *The sponsor has not provided clinical information related to the finding of some patients who had hyponatremia (serum sodium <130 mmol/L, with values as low as 123 mmol/L) or hypernatremia (serum sodium >150 mmol/L, with maximum values of 153 mmol/L) to be able to determine their clinical importance.*

   The sponsor provided additional data related to patients who had hyponatremia or hypernatremia, including narratives of some subjects. Overall, these laboratory changes appeared to be transient, produced no clinical symptoms and were usually resolved by the next study visit, and appeared also to occur with comparators.

   Reviewer's Comment: The sponsor's proposal to retain the language (b) (4) appears reasonable.

7. *The sponsor claims that there is no information on overdosage with Edarbyclor; however, the 120 Day Safety Update mentions 5 reports of overdose (3 in Study 301 and 2 in Study 308).*

   The sponsor provided cases narratives of the 5 reported cases of overdose. It appears that the reports of overdose were based on compliance calculations (i.e., administration of study drug at a dose above the one tablet per day assigned to each subject). Case narratives show that subjects had taken one extra tablet (2 subjects) to three extra tablets (2 subjects) to five extra tablets (one subject) of study medication during a 14-day interval. None was associated with subject-reported AEs and none required intervention.

   Reviewer's Comment: (b) (4)

Conclusion:

My review of the sponsor's response does not reveal any mitigating information to require a change in recommendation of regulatory action from its current recommendation for "**approval**" status apart from appropriate amendments to the proposed label to the claim of efficacy in Black subjects, and minor changes to the label as discussed above.

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/s/

KHIN M U
11/22/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-331
Priority or Standard	Standard
Submit Date(s)	21-Feb-2011
Received Date(s)	24-Feb-2011
PDUFA Goal Date	24-Dec-2011
Division / Office	DCaRP/ODE 1/OND
Reviewer Name(s)	Khin Maung U, M.D.
Review Completion Date	03-Oct-2011
Established Name	TAK-491CLD (azilsartan medoxomil plus chlorthalidone)
(Proposed) Trade Name	Edarbyclor
Therapeutic Class	Angiotensin II Receptor Blocker and thiazide-type diuretic in a fixed dose combination
Applicant	Takeda Global Research & Development Center, Inc.
Formulation(s) recommended	Two fixed dose combination tablets of TAK-491 and chlorthalidone: 40 mg / 12.5 mg and 40 mg / 25 mg.
Dosing Regimen	One tablet once/day
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.
Intended Population(s)	Patients with moderate hypertension (clinic SBP ≥160 and ≤190 mmHg) whose blood pressure is not controlled with monotherapy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the data submitted in this NDA, the recommended regulatory action is **approval** (§21 CFR 314.105) for the indication for the treatment of hypertension, pending the sponsor's response to comply with making the changes as suggested in Section 9.2 Labeling Recommendations of this review.

1.2 Risk Benefit Assessment

TAK-491CLD (Edarbyclor®) is a fixed dose combination (FDC) of azilsartan medoxomil (TAK-491), an angiotensin II receptor blocker (ARB), and chlorthalidone (CLD), a thiazide-type diuretic. Each drug, on its own, has been approved by the Agency for the indication for treatment of hypertension.

The benefit of TAK-491CLD FDC is derived from its efficacy for more effective reduction of blood pressure (BP) compared to its respective monotherapies. The submission includes efficacy data in five Phase 3 clinical trials: the pivotal clinical trial (Study **302**) which was a randomized, double-blind, controlled factorial study that compared TAK-491CLD with TAK-491 and CLD monotherapies after 8 weeks of fixed dosed treatment, and four supportive FDC studies (3 short-term, randomized, double-blind, comparator-controlled studies (Study **306**, Study **301**, and Study **303**), and a 52-week, randomized, open-label, comparator-controlled, safety study, (Study **308**). The efficacy data in the 3 clinical trials in the TAK-491 monotherapy program in which TAK-491 and CLD were co-administered (one short-term, double blind, placebo-controlled Study **009**, and two long-term, open-label safety trials – Study **006** and Study **016)** were also evaluated.

Studies 302 and 009 are fixed dosage trials (the former used the FDC tablet, the latter used add-on tablets), Study 303 used fixed dosage by "forced titration," and Studies 301, 306, 308, 006 and 016 are "titrate-to-target-BP" trials (using JNC 7 criteria).

The subjects enrolled had mean sitting clinic systolic BP (SBP) of ≥160 to ≤190 mmHg after 2 to 4 weeks washout of previous antihypertensive therapy. Concurrent elevated diastolic BP (DBP) was permitted, but baseline DBP >119 mmHg was exclusionary. Patients were excluded if they had a history of (i) a CV event within 6 months, (ii) severe renal disease (eGFR <30mL/min/1.73m^2), (iii) unilateral or bilateral renal artery stenosis or presence of (iv) hyperkalemia, (v) hypokalemia, (vi) active liver disease, (vii) jaundice or (viii) ALT or AST > 2.5 ULN. In each study, the majority of subjects were enrolled in the United States, with additional enrollment in Latin America, Europe, and Russia.

The primary efficacy endpoint in Study 302 was the change from baseline at Week 8 in trough SBP by ABPM; the secondary endpoints were the change from baseline at Week 8 in trough SBP by ABPM in Black subjects, and in trough clinic SBP in all subjects. The other Phase 3 FDC trials (Studies 301, 306, and 303) used the change from baseline in clinic SBP for the primary efficacy endpoint. Study 009 used the 24-hour mean SBP by

ABPM for its primary efficacy endpoint. The open-label safety Studies 308, 006 and 016 used the incidence rate of AEs for their primary endpoint.

For the claim that the fixed-dose combination of TAK-491CLD is more effective compared to the respective monotherapies to reduce BP, the efficacy data came from the pivotal Study 302, and from Studies 306, 009, 006 and 016 (as supportive trials). In Study 302, the reductions in trough SBP by ABPM at Week 8 in all treatment groups were large enough to be clinically meaningful. The treatment differences between each TAK-491CLD and its TAK-491 component (-10.9 to -17mmHg) or its CLD component (-10.3 to -13.9 mmHg) were also large and statistically significant (P<0.001). Incremental dose-related reductions in trough SBP by ABPM were observed across the FDC dose range of 20/12.5, 40/12.5, 80/12.5, and 40/25 doses (with no further reduction in SBP with the 80/25 mg dose). This finding was supported by Study 306: after TAK-491 alone had produced SBP reduction at Week 2, the addition of 12.5 mg CLD at Week 2 showed statistically significant (P<0.05) incremental reductions in clinic SBP beginning at Week 4, and continuing to Weeks 6 and 8. The efficacy data in the Studies 009, 006 and 016 showed consistent findings.

For the claim of the superiority of the BP reduction effect of the TAK-491CLD FDC compared to the comparator OLM/HCTZ combination product, Study 301 showed that clinic SBP reductions at Weeks 4, 6 and 8 in the TAK-491CLD treatment groups (33 to 38 mmHg) were significantly (P<0.05) greater than in the OLM/HCTZ group (27 to 32 mmHg) at each visit. This was supported by Study 303 in which statistically significantly (P<0.001) larger reductions from Baseline to Week 12 in clinic SBP were observed for both the TAK-491CLD 40/25 (-42.5 mmHg) and 80/25 mg (44.0 mmHg) groups compared with the OLM/HCTZ group (-37.1 mmHg). In Study 308, too, the interim efficacy results (at Week 32) showed a larger reduction from baseline in clinic SBP at Week 32 in the TAK-491CLD treatment group (47.7 mmHg) compared to the OLM/HCTZ group (41.5 mmHg).

For the claim that the fixed-dose combination of TAK-491CLD is more effective than either component (TAK-491 or CLD monotherapy) in Black subjects, and that it is as effective in Black subjects as in White subjects, the efficacy data in the subpopulation of Black subjects in Study 302 who had a baseline and a final ABPM (40 subjects for the TAK-491CLD 40/25+80/25 mg pool, and 28 and 22 subjects for the TAK-491 80 mg and CLD 25 mg monotherapy groups, respectively) showed statistically significant (P<0.001) larger reductions in trough SBP by ABPM at Week 8 in the treatment groups receiving the TAK-491CLD FDC (40/25 mg+80/25 mg pool) compared to monotherapy with TAK-491 80 mg but not to monotherapy with CLD 25 mg. In Study 303 which stratified subjects upon randomization as Black vs. non-Black, the Black subjects treated with TAK-491CLD 40/25 mg or 80/25 mg had statistically significant reductions in clinic SBP from Baseline to Week 12 compared to the OLM/HCTZ treatment group, but this SBP reduction in Black subjects was smaller (≈40 mmHg) compared to that observed in Caucasian subjects (≈44 mmHg). *These findings do **not** support the claim that TAK-491CLD was more effective than TAK-491 or CLD monotherapy in Black subjects, or that TAK-491CLD was as effective in Black subjects as in White subjects*.

Subgroup analyses (by age (<65, ≥65, ≥75 years), sex, race (Black, White, Other), body

mass index (BMI) (<30, ≥30 kg/m2), renal function (estimated glomerular filtration rate [eGFR] ≥90, ≥60 to <90, ≥30 to <60mL/min/1.73m^2), diabetes status, and baseline hypertension severity) of the efficacy data in four Phase 3, short-term FDC studies showed no evidence of heterogeneity in response to treatment with TAK-491CLD.

Six doses of the TAK-491CLD FDC (20/12.5, 40/12.5, 80/12.5, 20/25, 40/25, and 80/25 mg) were evaluated in Study 302 and the titrate-to-target BP Studies 306 and 301. There were almost similar incremental dose-related BP reductions up to the 40/25 mg dose (≈40 mmHg in Study 302, and ≈38 mmHg in Studies 306 and 301), with no incremental BP reduction at the 80/25 mg dose, suggesting that the 40/25 mg dose may be the maximum effective and tolerated dose. Using a criterion of >2 mmHg in BP reduction as the "discernible difference," there was no discernible difference in BP reduction between the 20/12.5 mg and 40/12.5 mg doses, with no increase in adverse events (AEs) at 40/12.5 mg, suggesting that the 40/12.5 mg dose may be selected as the starting dose. The 80/12.5 mg and 20/25 mg doses showed no "discernible difference" in BP reduction from the selected low (40/12.5 mg) or high (40/25 mg) dose.

ABPM findings suggested that the administration of TAK-491CLD once daily produced clinically meaningful reductions in SBP and DBP throughout the 24-hour dosing interval.

Responder analyses (based on the achievement of target SBP of <140 mmHg or target DBP of <90 mmHg) in Study 302 showed that a larger proportion of subjects in the TAK-491CLD treatment groups (70~85%) achieved target BP at Week 8 compared to its respective TAK-491 component (30~52%) or CLD component (34~51%).

Regarding the risks of this FDC product, the safety profile of TAK-491CLD appears to be similar to other FDC products of ARBs and diuretics, with no new safety signals.

Safety data are derived mainly from (i) the randomized, long term (52 weeks), open-label Study **308** (ongoing) which used the TAK-491CLD FDC, and (ii) Study **006** (56 weeks) and Study **016** (26 weeks), both open-label, uncontrolled clinical trials which used co-administration of TAK-491 and CLD. All three studies used the titrate-to-target BP design. The primary safety endpoints were the incidences of AEs.

There appeared to be adequate exposure to TAK-491CLD. A total of 3,177 subjects with hypertension had received at least one dose of TAK-491 and CLD, 602 subjects had received treatment for ≥6months, and 171 subjects had received treatment for ≥1 year. For the FDC tablets, the median duration of treatment was calculated as 8.4 weeks (59 days), and the mean duration of treatment was 12.3 weeks (86 days).

In Study 302 and Study 009 in which of TAK-491 and CLD were administered in fixed doses, an increase in dose of TAK-491 or CLD was accompanied by a dose dependent increase in the incidences of (i) treatment emergent adverse events (TEAEs) overall, (ii) elevated levels of blood creatinine, urea and uric acid, and/or (iii) hypokalemia.

Seven deaths were reported: 4 of 2,358 patients who received the TAK-491CLD FDC, 1 of 470 subjects on TAK-491 40 mg monotherapy, and 2 of 759 patients on the OLM/HCTZ combination. Five deaths were associated with co-morbid or accidental conditions. The two sudden deaths were of unknown cause; no autopsies were done.

Serious AEs (SAEs) were observed more frequently in patients treated with the FDC

TAK-491CLD compared to monotherapy with TAK-491 or CLD. These SAEs also appear to be associated with co-morbid conditions.

"Increased blood creatinine" was the most frequent TEAE leading to temporary or permanent discontinuation of study drug in Study 302; of 40 patients who discontinued due to "increased blood creatinine," 37 received the fixed dose combination, 2 received TAK-491 monotherapy and 1 received CLD 25 mg. "Increased blood creatinine" was also the most common TEAE leading to discontinuation in Study 306, Study 301 and ongoing Study 308; more subjects discontinued study drug due to TEAEs in the TAK-491CLD treatment groups than in the TAK-491+HCTZ or OLM/HCTZ treatment groups.

The creatinine elevations were transient; in about 96% of subjects they returned to baseline levels (≤0.2 mg above the baseline). The changes in serum creatinine tended to be inversely related to changes in BP, with the serum creatinine increasing in parallel with reductions in SBP in most subjects.

Dizziness was the second most frequent TEAE leading to discontinuations (3.8% and 2.5% of patients in TAK-491CLD 40/25 and 80/25 mg treatment groups, respectively). Discontinuation for hypotension was most frequent (1.9%) in the highest dose (TAK-491CLD 80/25 mg) group. Discontinuations due to hypokalemia were found in 2 subjects in the CLD 25 mg group and 1 subject in the TAK-491CLD 20/12.5 mg group.

Among the common TEAEs, increased blood creatinine, dizziness, increased blood uric acid and back pain were more frequent in the TAK-491CLD group, whereas headache, upper respiratory tract infection and peripheral edema were observed more frequently in the OLM/HCTZ group. Orthostatic hypotension was rare (≤0.9% and <2.0% of subjects had a decrease in SBP (≥20 mmHg) or DBP (≥10 mmHg), respectively).

Subgroup analyses of age, sex, race, renal impairment and region based on most frequent TEAEs, TEAE clusters and laboratory parameters from the long-term safety Study 308 show minimal heterogeneity of the safety profile across these subgroups, and suggest that no initial dosing adjustment is required for any special population.

From a risk-benefit perspective, clinically meaningful and statistically significant reductions in BP were observed following treatment with TAK-491CLD in a milieu of an unremarkable safety profile at the doses studied. On the basis of the above findings, the risk-benefit profile of TAK-491CLD appears favorable to recommend approval of TAK-491CLD for the treatment of hypertension at the doses identified in this review (i.e., a starting dose of 40/12.5 mg and the top dose of 40/25 mg).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

2.1 Product Information

TAK-491/CLD is a FDC of azilsartan medoxomil (TAK-491), an angiotensin II receptor blocker (ARB), and chlorthalidone (CLD) a thiazide-type diuretic. TAK-491, with the proprietary name Edarbi®, was approved by FDA in February 2011 for treatment of hypertension. CLD is assumed to have a similar antihypertensive effect to the more widely used diuretic, hydrochlorothiazide (HCTZ), being 1.5 to 2 times as potent as HCTZ on a mg:mg basis; CLD has a longer half-life and extensive tissue distribution which may contribute to a prolonged diuretic effect.

2.2 Currently Available Similar Treatments for the Proposed Indications

There are many well established FDC products of ARBs and HCTZ: olmesartan/HCTZ, candesartan/HCTZ, losartan/HCTZ, and valsartan/HCTZ. ARBs counteract many of the adverse events associated with the use of thiazide diuretics and have been shown to reduce the occurrence of new-onset diabetes mellitus. Fixed combination ARB/HCTZ agents are used as initial therapy for patients in whom BP is >20/10 mmHg above goal.

2.3 Availability of Proposed Active Ingredient in the United States

Azilsartan medoxomil (Edarbi®) is marketed by the same sponsor (Takeda) in the U.S., and chlorthalidone (CLD) is a marketed product (Hygroton® and Thalitone®) in the U.S.

2.4 Important Safety Issues with Consideration to Related Drugs

The important safety issues associated with ARBs include the following:

- Pregnancy: injury and death to the developing fetus.
- Hypotension: in patients with volume or salt depletion (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur.
- Hyperkalemia: in patients with advanced renal impairment, heart failure, on renal replacement therapy, on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or drugs that increase potassium levels.
- Impaired Renal Function: changes in renal function in susceptible individuals may occur. Similar to the effect of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea could occur.

The important safety issues associated with CLD include the following:

- Decreases in fluid volume and cardiac output, hypotension, dizziness.
- Metabolic changes: hypokalemia, hypochloridemia, hyperuricemia (and acute gout attacks), increased blood sugar (diminish control of diabetes).
- Abnormal liver function tests.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following is a summary of the issues which were discussed during several pre-submission regulatory meetings between the Division and the sponsor:

Enrollment of subjects: The Division was concerned that using the qualifying BP measurement to enroll in a study as the baseline BP value would predispose to an inflated estimate of the treatment effect because of "regression to the mean." The Division suggested that subjects should either qualify by cuff BP measurements with the ambulatory BP data serving as the baseline measurement or that an additional ambulatory BP session be conducted that would not disqualify a subject should the BP for baseline not satisfy the original screening criteria.

Pivotal Study 302: The Division's position was that

- a single factorial study would be sufficient to establish the effectiveness of a FDC product relative to the individual components if the safety and efficacy of each of the components were well characterized, with the key comparison being that at the high dose of each component the second drug adds to the effect of the first drug.
- the upper and lower boundaries of the dose response curve should be fully represented for both TAK-491 and CLD in the factorial trial,
- the high dose combination should be compared to the high dose components, and,
- if Study 302 showed that TAK-491CLD FDC 80 mg/25 mg is significantly better than its monotherapy components, it would not be necessary to control type I error for other cell comparisons.

Dose of CLD: The Division noted that different formulations of CLD had different bioavailability, with the Thalitone® formulation of CLD having substantially greater bioavailability than the Hygroton® formulation.

The sponsor proposed to evaluate only relatively low doses of CLD (12.5 and 25 mg) which had been shown to have a good risk-benefit profile based on data from two outcome trials: (i) **S**ystolic **H**ypertension in the **E**lderly **P**rogram (SHEP)[1] and (ii) **A**ntihypertensive and **L**ipid-**L**owering to **P**revent **H**eart **A**ttack **T**rial (ALLHAT)[2].

First line indication: Following the November 14, 2007, Pre-IND Meeting, FDA provided the sponsor with a "Points to Consider Document for First Line Therapy." According to this guideline, if the low dose combination was found superior to either one of the high dose monotherapies with respect to efficacy and tolerability, the Division agreed that it could facilitate approval for a first line indication.

The sponsor agreed to include estimates of the probability of reaching a BP goal with TAK-491CLD 40/12.5 mg compared to TAK-491 40 mg and CLD 12.5 mg monotherapy, or other appropriate FDC dose strength in the clinical study report (CSR) for Study 302.

Pooling strategy: For Study 302, the Division agreed that it was acceptable to pool (i) the two high-dose monotherapy arms, or (ii) any combination of the arms that received both TAK491 and CLD, provided these pooled arms and the TAK-491CLD arms could be distinguished in efficacy from each of the two high-dose monotherapy arms.

The Division also agreed to the sponsor's proposal to not pool the combination arms at the patient level, but to combine the treatment estimates of the combination arms using a contrast statement in SAS and compare with the highest dose of the monotherapies.

Claim for Black patients: After review of the SAP and Request for Scientific Advice dated January 13, 2010, the Division clarified that the data would not result in a separate claim for use in the Black subgroup, but that the label would describe qualitatively and quantitatively the effect in the Black population. The sponsor confirmed that it was not their intent to seek an explicit claim for use in Black patients.

For the Black patient population, the sponsor would perform formal testing and control for overall study Type 1 error by using a step-wise testing procedure on the primary efficacy endpoint on TAK-491CLD FDC (80 mg/25 mg) and its respective monotherapy components in the overall patient population followed by the Black patient population. Statistical significance would only be tested in the Black patient population (dataset with only Black patients) if TAK-491CLD 80 mg/25 mg was significantly superior to both respective monotherapy components in the overall patient population first.

The Division agreed that the results (point estimates and confidence intervals) of the comparisons in Blacks of the 80 mg/25 mg combination to the high dose monotherapies could be included in labeling if sufficient numbers of Blacks were enrolled in Study 302 to have some confidence in the results, and that whether the results supported a simple claim of effectiveness in Blacks would depend upon the robustness of the results.

Superiority over Olmesartan/HCTZ combination (Benicar®): Following evaluation of the SPA for Study 303 in which two doses of TAK-491CLD would be studied, the Division agreed that (i) the trial design and the statistical analysis plan were adequate to support proof of replication, (ii) that if both doses of TAK-491CLD in Study 303 were superior to OLM/HCTZ 40/25 mg a superiority claim in the label would be supported (even if only one of the TAK-491CLD doses was approved), and (iii) that such language would be included in the Clinical Studies section of the label if no safety concerns were found.

Submission of the NDA: For the Clinical Summary of Efficacy, the Division agreed to the sponsor's plan to not pool the phase 3 studies due to differences in study designs.

The Division agreed that the sponsor's proposal to (i) re-submit phase 1 and 3 CSRs that included TAK-491 co-administered with CLD (Study 006, Study 009, and Study 016) and were submitted previously under the TAK-491 monotherapy NDA 200,796, and (ii) cross-reference the CSRs submitted previously under TAK-491 monotherapy NDA 200,796, would be sufficient for review of the TAK-491CLD FDC NDA.

For the Clinical Summary of Safety, the Division agreed to the sponsor (i) not pooling the safety data from the Phase 3 studies due to different study designs, (ii) not integrating safety data from the phase 1 studies, and (iii) including only descriptions of any deaths, SAEs, and discontinuations due to AEs from the phase 1 studies.

The Division agreed that the estimated safety exposures at the planned filing date appeared to be adequate: namely >3177 subjects with hypertension exposed to TAK-491CLD, including > 602 subjects exposed for 6 months and 171 subjects for 12 months. At the time of the 120-Day Safety Update, the sponsor anticipated that >3600

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subjects with hypertension would be exposed to TAK-491CLD, including >800 subjects exposed for 6 months and 300 subjects exposed for 12 months.

For the phase 3 studies, the Division agreed to the sponsor's proposal to submit (i) Council for International Organization of Medical Sciences (CIOMS) reports in place of text narratives for deaths and other SAEs and (ii) Programming Assisted Narratives (PANs) for premature discontinuations due to AEs and AEs of Special Interest (AESIs).

For phase 1 studies, the Division agreed to the sponsor's proposal to provide in-text narratives in the CSRs for deaths, other SAEs and discontinuations due to AEs.

For the 120-Day Safety Update, the Division agreed with the sponsor's proposal to:

(a) provide key safety information (deaths, other SAEs, discontinuation due to AEs, and lab values of interest) separately (datasets in support of them but not actual individual study datasets) for each of the studies that would be ongoing at the time of the initial NDA submission: namely,
   (i) the long-term, open-label safety Study 308,
   (ii) the phase 3 randomized controlled Study 303 to demonstrate superiority to OLM/HCTZ, and
   (iii) the phase 1 Bioavailability Study 106 to compare bioavailability of CLD from the FDC formulation with an EU-sourced CLD,
(b) to not pool the phase 3 studies in the Study Update because of differences in study design and treatment durations, and
(c) to submit an interim report for the open-label safety Study 308 in which only key safety data will be provided without an additional interim CSR.

Labeling: Per the draft "FDA Guidance for Industry for Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims," the sponsor proposed (i) to summarize the studies that demonstrated cardiovascular outcome benefit associated with CLD in the Clinical Studies section of the label using language consistent with the draft guidance, and (ii) that while there were no studies of TAK-491 demonstrating reductions in cardiovascular risk in patients with hypertension, at least one pharmacologically similar drug has demonstrated such benefits. The Division agreed to this proposal provided the FDA Guidance became finalized prior to NDA approval.

Reviewer's Comment: Outcome trials in patients with hypertension such as LIFE [**L**osartan **I**ntervention **F**or **E**ndpoint reduction in hypertension] [3], VALUE [**V**alsartan **A**ntihypertensive **L**ong-term **U**se **E**valuation][4], and SCOPE [**S**tudy on **CO**gnition and **P**rognosis in the **E**lderly][5], in which losartan, valsartan, and candesartan cilexetil, respectively, were used with HCTZ added as needed showed improvement in the primary clinical outcome measures.

The Division agreed to the sponsor's plans to present safety information from Study 302 for the recommended doses (b) (4) in the Adverse Reactions section of the label, and to present safety information from the TAK-491 monotherapy and CLD commercial label not be covered by TAK-491CLD information.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor conducted regular site monitoring to ensure the quality of the trial conduct and data integrity, and submitted audit certificates of clinical trial sites with the NDA.

3.2 Compliance with Good Clinical Practices

The Division requested the Office of Scientific Investigations (OSI) to inspect 3 sites for Study 302 and 2 sites for Study 301 (Table 1). These sites enrolled relatively large number of patients, showed large effect size (reduction in systolic BP (mmHg) compared to baseline and/or compared to the comparator), and had many AEs, discontinuations and protocol violations.

Table 1 Sites selected for OSI consult for GCP inspections

Trial #	Center #	Investigator Name & Address	Effect Size (↓mmHg)	Enrolled (Total)	Discon-tinued	AEs	Protocol Violations	COMMENTS
302	3019	**Gigi Lefebvre, MD** 4751 66th Street North **St. Petersburg, FL 33907**	**26 – 34***	**4* (43)**	**6***	**48* (1SAE)**	**31***	Large effect, large enrollment, many AEs and protocol violations
	3026	**Eli Roth, MD,** 2230 Auburn Ave, Level B **Cincinnati, OH 45219**	**17 – 44***	**8* (36)**	**3***	**50***	**22***	Large effect, large enrollment, many AEs and protocol violations
	3042	**Meera Dewan, MD, PC** 11912 Elm St., Suite 26, **Omaha, NE 68114**	**42 – 44***	**7* (38)**	**5***	**112***	**7***	Large effect, large enrollment, many AEs and protocol violations
301	2032	**Danilo Lopez, MD** 333 West 41st St, Suite 514, **Miami Beach, FL 33140**	**28 – 29§**	**33‡ (50)**	**4‡**	**14‡**	**6‡**	Large effect, large enrollment, many AEs, discontinuations, and protocol violations
	2074	**Jerry R. Mitchell, MD,PhD** Texas Center for Drug Development PA, 6550 Mapleridge St, Ste 201, **Houston, TX 77801**	**30 – 35§**	**50‡ (75)**	**8‡**	**27‡**	**34‡**	Large effect, large enrollment, many AEs, discontinuations, and protocol violations

*Data from patients in high effect treatment groups only; ‡patients in TAK 491-CLD group; §compared to olmesartan + HCTZ

OSI communicated on 09/12/2011 that no major data integrity issues were found during FDA inspection of these sites. A clinical inspection summary is not yet filed in DARRTS.

3.3 Financial Disclosures

The sponsor submitted financial disclosure information for clinical investigators in Studies 302, 301, 306 and 009; none of the investigators had disclosable financial interests. The sponsor stated that no financial disclosure information would be provided for open-label studies and Phase I studies. This arrangement had been agreed to by the Division per the pre-NDA meeting minutes dated 02-Nov-2010.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see CMC reviews by Albert Chen and Prafull Shiromani.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Please see Pharm-Tox review by Philip Gatti.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

TAK-536, the active moiety of TAK-491, has a selective affinity for the human AT_1 receptor (50% inhibitory concentration [IC_{50}] of 0.62 to 2.6 nmol/L) and dissociates from the receptor more slowly than other ARBs (valsartan, irbesartan, telmisartan and olmesartan). This AT_1 receptor blocking activity provides the anti-hypertensive effect.

CLD, similar to thiazide diuretics, inhibits sodium reabsorption in the distal convoluted tubule of the loop of Henle in the nephron, leading to increased water excretion. This diuresis decreases fluid volume and cardiac output, leading to a BP lowering effect.

TAK-491 and CLD co-administered together target two separate complementary mechanisms involved in BP regulation. The CLD-induced decrease in total body sodium by diuresis triggers compensatory release of renin and production of Angiotensin II. TAK-491 inhibition of RAAS renders this reactive increase in renin less effective, thus potentiating BP reduction. In addition, hypokalemia induced by CLD is counteracted by TAK-491 which tends to cause hyperkalemia.

4.4.2 Pharmacodynamics

Please see Clin-Pharm review by Divya Menon-Andersen.

4.4.3 Pharmacokinetics

Following administration of single and multiple doses of TAK-491 up to 320 mg, TAK-491 is rapidly hydrolyzed to TAK-536, the active moiety. TAK-536 is very highly plasma protein bound, and no selective uptake by red blood cells occurs.

TAK-536 is metabolized to TAK-536 M-I, a minor metabolite and TAK-536 M-II, a major metabolite in humans, which have relatively little activity. Radioactivity derived from [^{14}C]TAK-491 or [^{14}C]TAK-536 is excreted in similar proportions in the urine and feces; the urine contains predominantly TAK-536 and TAK-536 M-II, and the feces contain predominantly TAK-536 M-I.

CLD is moderately absorbed and undergoes little metabolism. The primary route of excretion (75% of the dose) is via the urine, with 90% of urinary radioactivity recovered as CLD. CLD binds extensively to carbonic anhydrase receptors in RBCs both *in vitro* and *in vivo*, which contributes to a large volume of distribution and long $T_{1/2}$ (45 hours) which could be associated with its long duration of antihypertensive effect.

Following oral administration of TAK-491CLD, the C_{max} values of TAK-536 and CLD were 3 hours and 1 hour, respectively, and $T_{1/2}$ values were approximately 12 and 45 hours, respectively.

Population PK showed that the systemic exposure to both TAK-536 and CLD was higher in subjects with hypertension than healthy subjects. These are not expected to have any clinically meaningful impact on safety or efficacy due to the relatively wide therapeutic indexes of both drugs.

The predicted maximum response to TAK-536 (major active metabolite) is greater in non-Black subjects than in Black subjects, and greater in subjects with higher baseline SBP and DBP by ABPM than in subjects with lower baseline SBP and DBP by ABPM. The predicted maximum response of CLD is greater in Black subjects than in non-Black subjects, and greater in subjects with higher baseline SBP by ABPM than in subjects with lower baseline SBP by ABPM.

5 Sources of Clinical Data

Efficacy data are submitted from five Phase 3 studies of TAK-491CLD FDC (Table 2):

(i) The pivotal study, 491CLD-302 (**Study 302**), was a randomized, double-blind, controlled, factorial study that compared TAK-491CLD with TAK-491 and CLD monotherapy after 8 weeks of treatment; study drug was administered at fixed-doses throughout the treatment period in this study.

(ii) The 4 supportive FDC studies include 3 short-term, randomized, double-blind, comparator-controlled studies, 491CLD-306 (**Study 306**), 491CLD-301 (**Study 301**), and 491-CLD 303 (**Study 303**), and a 52-week, randomized, open-label, comparator-controlled safety study, 491CLD-308 (**Study 308**).

Study 306 compared TAK-491CLD FDC with co-administration of TAK-491 plus HCTZ. Studies 308, 301 and 303 used olmesartan medoxomil plus HCTZ (OLM/HCTZ) as the comparator.

In Study 306, Study 301 and Study 308, up-titration of TAK-491CLD or the comparator proceeded according to a protocol-specified, titrate-to-target BP approach. Study 303 compared TAK-491CLD FDC vs. OLM/HCTZ in which the dose was forced-titrated.

The long-term safety study 308 is ongoing.

Supportive TAK-491 Plus Chlorthalidone Co-administration Studies (Table 2)

The submission also refers to the following 3 studies from the TAK-491 monotherapy program in which TAK-491 and CLD were co-administered (as separate tablets):

(a) one short-term, double-blind, placebo-controlled study [491CLD-009 (**Study 009**)], in which the combination of TAK-491 40 or 80 mg plus CLD 25 mg was compared with CLD 25 mg monotherapy, and

(b) two long-term, open-label safety studies in which CLD or HCTZ were added, if needed, to open-label treatment with TAK-491 to achieve target BP:
   (i) 491CLD-006 (**Study 006**) and
   (ii) 491CLD-016 (**Study 016**).

The design and primary endpoints of the above 8 clinical trials are discussed in detail in Section 5.3 below.

5.1 Tables of Studies/Clinical Trials

The clinical trials submitted in support of this NDA are shown in Table 2.

Table 2 List of clinical trials

Study #	# enrolled	Comparator	Design	Duration[a] and dose(s)	Patient selection criteria (BP)	Primary Endpoint
Fixed Dose Combination						
491CLD-302	1,714	Placebo	DB, R, 11-arm, factorial	8 wk – **fixed doses** TAK 20, 40 or 80; CLD 12.5 or 25, TAK-CLD 20/12.5, 40/12.5, 80/12.5, 20/25, 40/25, 80/25	Clinic SBP 160-190 mmHg (150/arm)	**Trough SBP by ABPM**
491CLD-301	1,085	OLM/HCTZ	DB, R, 3-arm	8 wk – **titrate to target BP** TAK-CLD 20/12.5 → 40/25; TAK-CLD 40/12.5 → 80/25; OLM/HCTZ 20/12.5 → 40/25	Clinic SBP 160-190 mmHg (370/arm)	Clinic SBP
491CLD-306	609	HCTZ	DB, R, 2-arm	10 wk – **titrate to target BP*** TAK 40 → TAK-CLD 40/12.5 → 40/25; TAK 40 → TAK 40+ HCTZ 12.5 → TAK40 +HCTZ 25	Clinic SBP 160-190 mmHg (300/arm)	Clinic SBP
491CLD-308	807 (ongoing)	OLM/HCTZ	OL, R, 2-arm,	52 wk – **titrate to target BP** TAK-CLD 40/12.5 → 80/12.5 →80/25; OLM/HCTZ 20/12.5 → 40/12.5 → 40/25	Clinic SBP 160-190 mmHg (400/arm)	**AEs (long-term safety study)**
491CLD-303	1,071	OLM/HCTZ	DB, R, 3-arm, fixed dose	12 wk – **forced titration**[c]	Clinic SBP 160-190 mmHg (350/arm)	Clinic SBP
Co-administration Studies						
491CLD-009	557	Placebo	R, 3-arm, PC	6 wk – **fixed doses** TAK 40 + CLD 25 TAK 80 + CLD 25 Placebo + CLD 25	Clinic SBP 160-190 mmHg and 24-hr SBP 140-180 mmHg (180/arm)	**24-hr mean SBP by ABPM**
491CLD-006	669	Add on CLD/HCTZ	OL, Uncontrolled, unrandomized, sequential enrollment	56 wk – **titrate to target BP** [d]Cohort 1: Step 1: TAK 40 → 80; Step 2: TAK + CLD 25 Step 3: TAK + CLD + others [d]Cohort 2: Step 1: TAK 40 → 80; Step 2: TAK + HCTZ 12.5 Step 3: TAK + HCTZ 25 Step 4: TAK + HCTZ 25 + others	Clinic DBP 95 – 119 mmHg	**Safety measures**
491CLD-016	418	Add on CLD/HCTZ	[b]OL, Uncontrolled, unrandomized	26 wk – **titrate to target BP** Step 1: TAK 40 → 80; Step 2: TAK + CLD 25 Step 3: TAK + CLD + others	Clinic DBP 95 – 119 mmHg	**Safety measures**
Long Term Safety Studies required by EMA						
491CLD-307					Patients with hypertension who did not achieve target BP with TAK-391 monotherapy	**Safety measures**
491CLD-309					Hypertensive subjects with moderate renal impairment	**Safety measures**

R=randomized, DB=double blind; OL=open-label; PC=placebo controlled; BP=blood pressure; SBP=systolic BP; DBP=diastolic BP
*initial titration from TAK-491 40 mg monotherapy to combination therapy was forced
(a) Duration of treatment only, does not include washout or run-in periods;
(b) Study 491-016 also included a double-blind, randomized, placebo-controlled reversal phase after completion of the open-label phase; existing background chlorthalidone use remained stable but was not a randomized study drug.
(c) All subjects had the initial dose of TAK-491 40 mg titrated to 80 mg, if tolerated.
(d) Enrollment in cohorts was sequential, not randomized (i.e., Cohort 2 was enrolled after Cohort 1 was complete).

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5.2 Review Strategy

Review of efficacy data: *To evaluate the sponsor's claim that TAK-491CLD FDC is more effective compared with the respective monotherapies to reduce BP*, I reviewed the efficacy data in the factorial Study 302 as the primary clinical trial, and the efficacy data in Study 306 and Study 009 as supportive trials. I made reference to the efficacy data in open-label safety Study 006 and Study 016 for consistency of the results (Figure 1).

To evaluate the claim of superiority of BP reduction effect (and AEs) of TAK-491CLD FDC compared to the OLM/HCTZ combination product, I reviewed Study 301 as the primary clinical trial, and Study 303 as the supportive trial (Figure 1), and made reference to the efficacy data in the ongoing safety Study 308 for conformity of results.

To evaluate the claim that TAK-491CLD is as effective in Black subjects as in White subjects, I reviewed the efficacy and safety data in Black subjects in Study 302 as the primary clinical trial, and the efficacy data in Study 303 (in which subjects were stratified at randomization as Black vs. non-Black) as the supportive trial (Figure 1).

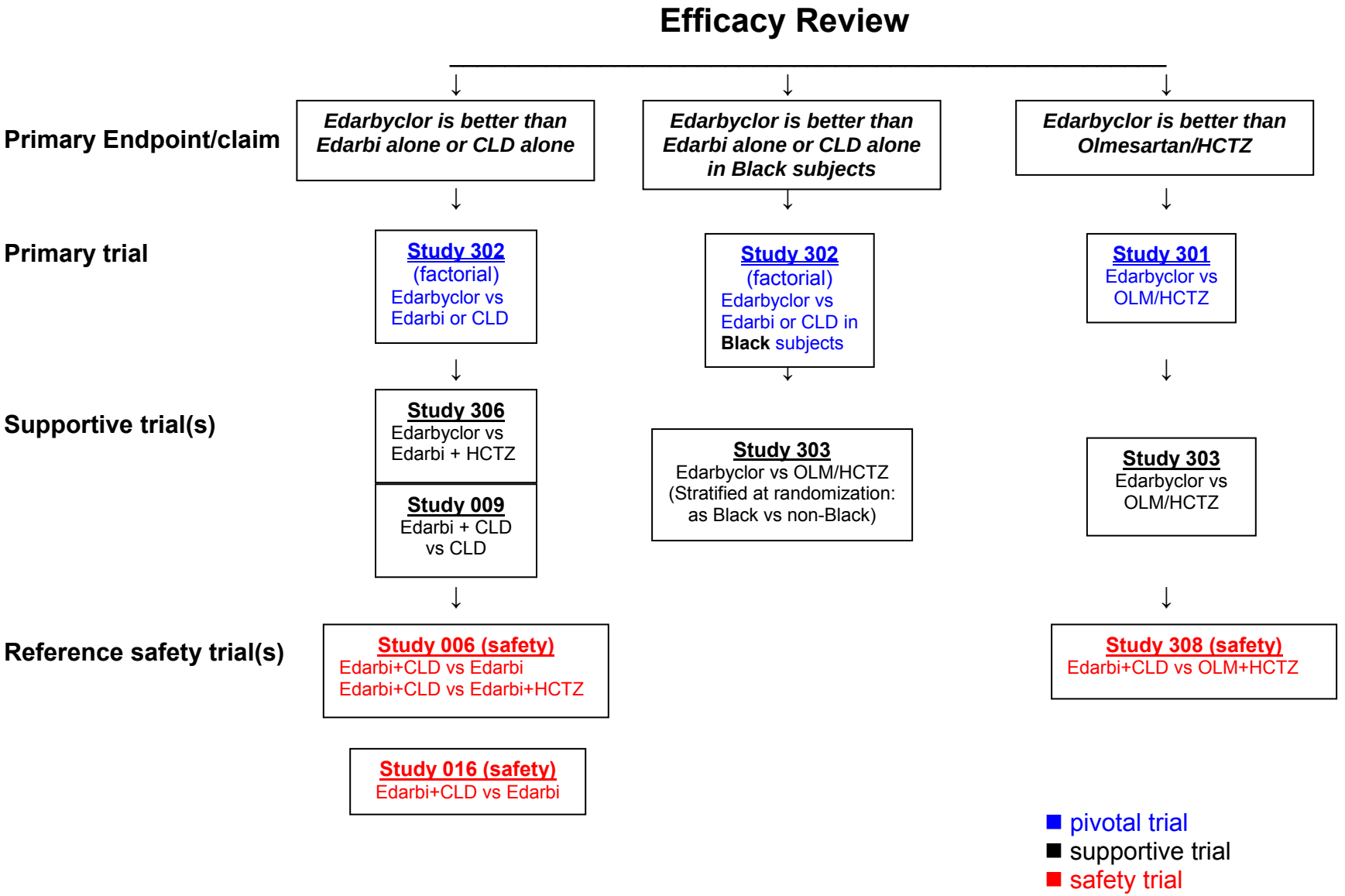
There were high frequencies of missing values in Study 302 – about 9% to 14% of subjects randomized to the lower doses of monotherapy with TAK-491 or CLD, and about 20% to 22% randomized to the two high-dose arms of the FDC which the sponsor pooled for their primary analyses. I queried the sponsor and evaluated the reasons for these drop outs.

To determine the dose to approve for marketing, I used a criterion of >2 mmHg in BP reduction as the "discernible difference" to separate the antihypertensive effect of the six doses of TAK-491CLD studied in the phase 3 clinical trials.

Review of safety data: I reviewed the safety data in the long term safety trials (Study 308, Study 006 and Study 016) of patients treated with TAK-491CLD compared to the safety data of patients administered (i) TAK-491 alone, (ii) CLD alone, and (iii) the OLM/HCTZ combination. I evaluated the frequencies of syncope, dizziness, fatigue (symptoms of hypotensive events) or orthostatic hypotension which are expected to increase in patients treated with dual drugs, and the frequencies of (i) electrolyte abnormalities, including hypokalemia, hypochloridemia, hyponatremia, (ii) metabolic abnormalities including increase in uric acid levels, and (ii) renal function test abnormalities (increased BUN, creatinine, and urinary albumin**:**creatinine ratio). I also checked the safety data in the short term trials for any signal of acute changes in these parameters. I reviewed the 120-Day Safety Update when it was submitted in June 2011.

I did not pool the data in my reviews, because (a) Studies 302 and 009 are fixed dosage trials (the former used the FDC tablet, the latter used add-on tablets), (b) Studies 301, 306, 308, 006 and 016 are "titrate-to-target-BP" trials (with variations in the time of titration and study duration), and (c) Study 303 used fixed dosage by "forced titration" (Table 2). Apart from Study 302 which used SBP by ABPM as the primary efficacy endpoint, the other Phase 3 FDC trials used clinic SBP for the primary efficacy endpoint, Study 009 used 24-hour mean SBP by ABPM, and the safety Studies 308, 006 and 016 used the incidences of AEs for their primary efficacy endpoint (Table 2).

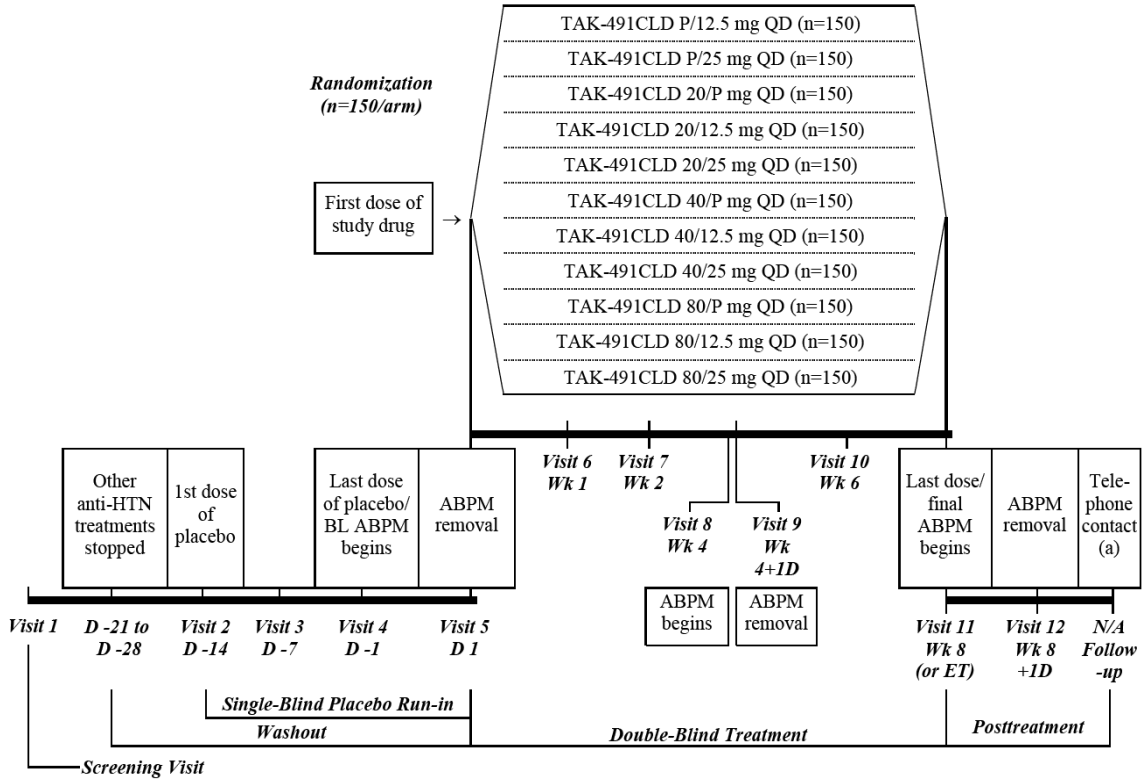
Figure 1 Strategy for Efficacy Review



5.3 Discussion of Individual Studies/Clinical Trials

Study-302 (Factorial study): Study 302 is the pivotal trial to evaluate the efficacy of TAK-491CLD vs. the TAK-491 and CLD monotherapy components after 8 weeks of treatment in a randomized, double-blind, 11 arm, factorial trial. Subjects with clinic SBP ≥160 and ≤190 mm Hg after washout of previous antihypertensive therapy were randomized to treatment for 8 weeks with 1 of the 11 double-blind treatments (Figure 2).

Figure 2 Study 302 Schematic



BL= baseline; D= day; ET= early termination; HTN= hypertension; P= placebo; QD= once daily. (a) Follow-up telephone contact was made approx 14 days after the last dose.

Subjects were enrolled at 175 sites in the United States, Latin America, Europe, and Russia, and randomized at 165 sites. On average, 10 subjects were randomized per site (range: 0 to 43). ABPM was performed on the last day of placebo run-in (Day -1), at Week 4, and after the last dose of treatment at Week 8. Clinic BP was measured at each visit.

The primary endpoint was the change from Baseline to Week 8 in trough SBP by ABPM. The protocol-specified primary analysis was to compare the TAK-491CLD 40/25+80/25 mg pool with each of the highest doses of monotherapy (TAK-491 80 mg and CLD 25 mg), using SBP by ABPM values based on the LOCF method. Pooling the TAK-491CLD 40/25 and 80/25 mg treatment groups was based on the results from

Study 009, which suggested that both of these dose combinations resulted in a similar BP reduction. Cell-by-cell analyses comparing each dose of TAK-491CLD to its respective components were also performed.

Key secondary endpoints of the study were:

(i) The change from baseline in trough clinic SBP (in all subjects), and

(ii) The change from baseline in trough SBP by ABPM in Black subjects (to be tested only if the test for the primary efficacy endpoint was significant).

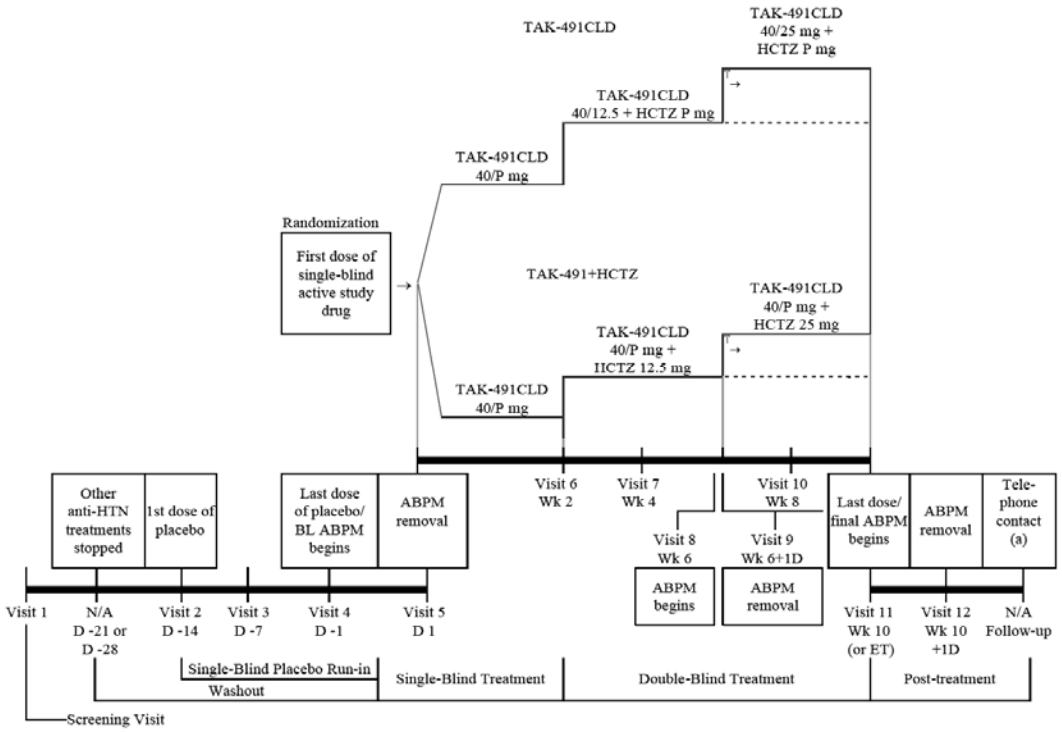
The primary efficacy analysis was based on the FAS population; similar analyses were also conducted using the PPS population. No interim analyses were performed.

Sensitivity analyses for mean trough SBP and DBP by ABPM, and also on clinic SBP and DBP, were performed using (ii) observed cases (which included data from only patients who had a post-baseline value), and (ii) a multiple imputation method (in which any subject with a baseline value – even without a post-baseline value – was included) to assess the impact of the missing values and dropouts on analyses using LOCF.

Study-306

Study 306 compared the efficacy of TAK-491CLD FDC vs. TAK-491 co-administered with HCTZ (TAK-491+HCTZ) in a 10-week, randomized, titrate-to-target-BP treatment, double-blind, two-arm, clinical trial (Figure 3), to evaluate the efficacy of CLD vs. HCTZ when used in combination with a RAAS-blocking agent.

Figure 3 Study-306: study schematic



BL=baseline, D=day, ET=Early Termination, HTN=hypertension, N/A=not applicable, P=Placebo.
(a) The follow-up telephone contact was to have been made approximately 14 days after the last dose.

The primary endpoint was the change from baseline to Week 6 and Week 10 in trough clinic SBP. A stepwise testing procedure was used in the analysis of the primary endpoint to control the type I error rate.

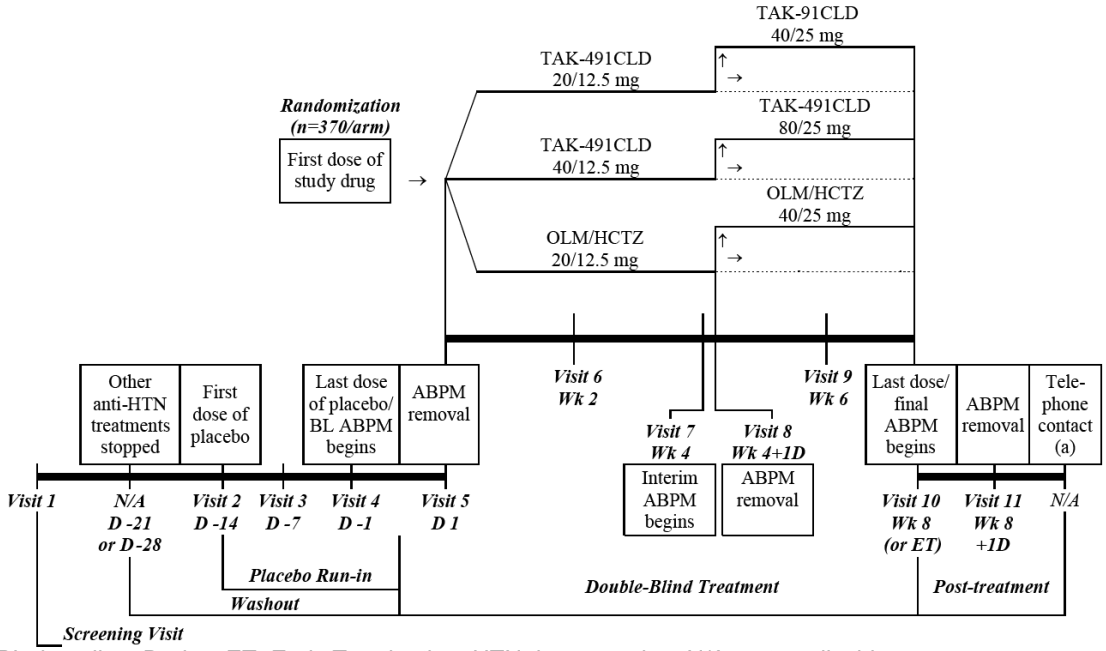
Secondary efficacy variables included trough clinic DBP and ABPM parameters of SBP and DBP. ABPM was performed on the last day of the placebo run-in, at Week 6, and after the last dose of treatment at Week 10.

Subjects were enrolled at sites in the United States and Russia, and were required to have trough clinic SBP ≥160 and ≤190 mmHg after the washout/run-in period, to be randomized to either the TAK-491CLD or the TAK-491+HCTZ treatment group. All subjects started treatment with single-blind TAK-491 40 mg as monotherapy. Double-blind treatment began at the end of Week 2 and consisted of treatment with an FDC tablet of TAK-491CLD 40/12.5 mg or coadministration of TAK-491 40 mg+HCTZ 12.5 mg. If both target SBP and target DBP (defined as trough clinic BP <140/90 mmHg for subjects without diabetes or CKD, and <130/80 mmHg for subjects with diabetes or CKD) were achieved by the end of Week 6, the dose of CLD or HCTZ remained at 12.5 mg for the duration of the study. For subjects who did not achieve both targets by Week 6, the dose of CLD or HCTZ was titrated to 25 mg (TAK-491CLD 40/25 mg or TAK-491 40 mg+HCTZ 25 mg, respectively).

Study 301

This study compared the efficacy of TAK-491CLD FDC vs. an OLM/HCTZ FDC tablet over an 8-week treatment period in a randomized, double-blind, 3-arm clinical trial (Figure 4). The sponsor submitted this study as the main clinical trial to support the claim that TAK-491CLD FDC is better than OLM/HCTZ FDC to lower BP.

Figure 4 Study 301: Study schematic



BL=baseline, D=day, ET=Early Termination, HTN=hypertension, N/A=not applicable.
(a) The follow-up telephone contact was to have been made approximately 14 days after the last dose.

Subjects were enrolled at sites in the United States and Latin America. After the washout/run-in period, eligible subjects with trough clinic SBP ≥160 and ≤190 mmHg were randomized to 8 weeks of treatment that initially consisted of TAK-491CLD 20/12.5 mg, TAK-491CLD 40/12.5 mg, or OLM/HCTZ 20/12.5 mg. If subjects achieved both target SBP and target DBP (<140/90 mmHg for subjects without diabetes or CKD or <130/80 mmHg for subjects with diabetes or CKD) by the end of Week 4, they continued to receive their starting dose for the duration of the study. For subjects who did not achieve both target SBP and DBP by Week 4, study drug was titrated to TAK-491CLD 40/25 mg, TAK-491CLD 80/25 mg, and OLM/HCTZ 40/25 mg (Figure 4). ABPM was performed on the last day of placebo run-in (Day -1), at Week 4, and after the last dose of treatment at Week 8. Clinic BP was measured at each visit.

The primary endpoint was the change from baseline to Week 8 in clinic SBP. The key secondary endpoint was change from baseline to Week 4 in clinic SBP. Other secondary efficacy variables included clinic DBP, and also SBP and DBP by ABPM.

A step-wise testing procedure was used to control the type I error rate for the analysis of the primary and key secondary efficacy endpoints. The analysis was first conducted with the TAK-491CLD high-dose group (40/12.5 → 80/25 mg) vs. OLM/HCTZ and then the TAK-491CLD low-dose group (20/12.5 → 40/25 mg) vs. the OLM/HCTZ group until the condition of a given step was not satisfied.

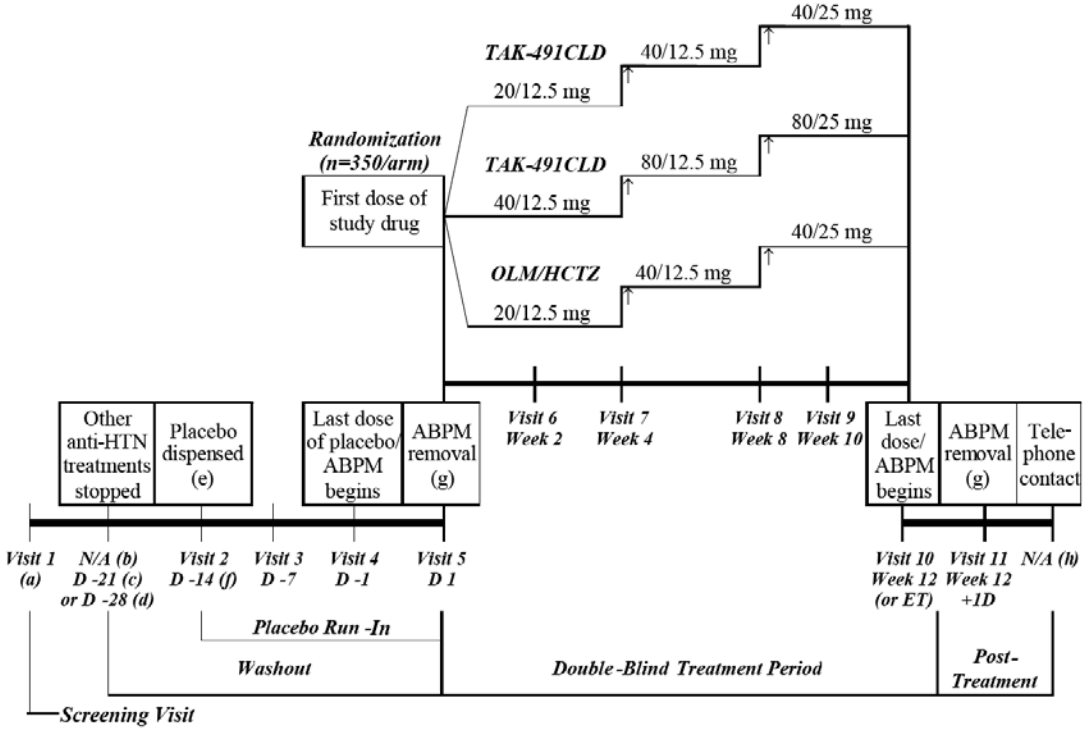
Study 303

Study 303 compared the efficacy of TAK-491CLD FDC vs. OLM/HCTZ in subjects with moderate to severe hypertension (baseline clinic SBP between 160 and 190 mmHg inclusive), in a 12-week, randomized, double-blind, parallel-group, 3-arm, fixed-dose, ***force-titration*** clinical trial, which was stratified by race (Black and non-Black).

Subjects were randomized to one of the combination titration treatments (Figure 5) and each subject's dose was force-titrated at the end of Week 4 and Week 8.

The primary efficacy endpoint was the change from Baseline to Week 12 in mean clinic SBP (previously defined as trough, sitting clinic SBP). Secondary efficacy endpoints included change from baseline to Weeks 4 and 8 in clinic SBP, and to Weeks 4, 8 and 12 in clinic DBP, and ABPM parameters.

Figure 5 Study 303: Study schematic



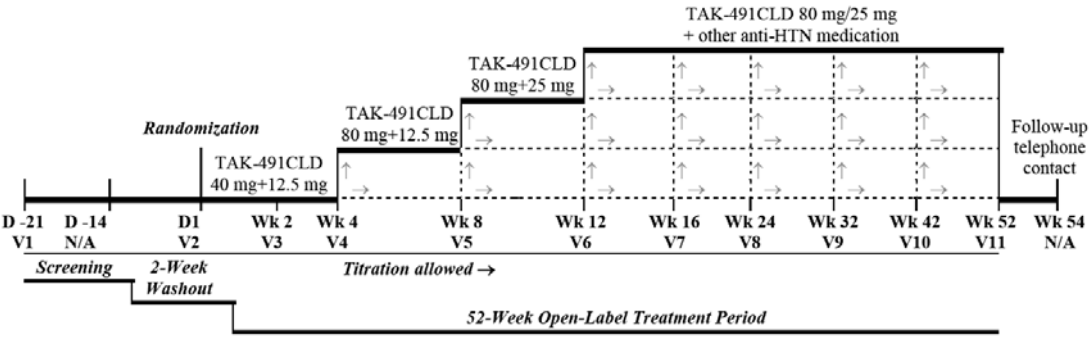
(a) The Screening Visit was scheduled before the Washout/Run-in Period began so that laboratory tests results could be reviewed and subject eligibility confirmed before other treatments were stopped or placebo was initiated.
(b) Subjects could have been notified by telephone to begin the Washout Period.
(c) Subjects taking previous antihypertensive agents participated in a 3-week Washout Period (Days -21 to -1).
(d) If the subject's previous antihypertensive treatment included amlodipine or chlorthalidone, then the washout was extended to 4 weeks (Days -28 to -1).
(e) The first dose of placebo was taken the morning following Visit 2 (i.e., on Day -13).
(f) Subjects who did not receive antihypertensive treatment within 28 days before Screening could be entered into the Run-in Period as soon as all inclusion and exclusion criteria, including laboratory results, were verified.
(g) If the baseline or final ABPM recording did not meet quality control criteria, it could be repeated once before moving on to the next study step; clinic vital signs and urine pregnancy test were also measured at the repeat ABPM visit. Urine pregnancy test was only repeated at Baseline, not at the final ABPM repeat visit.
(h) Follow-up contact was made by telephone approximately 14 days after the last dose.

Study 308 (ongoing):

Study 308 compared the efficacy of TAK-491CLD FDC vs. an OLM/HCTZ FDC tablet in a randomized, open-label, ***safety*** trial. I reviewed this study to determine if the efficacy results (change from baseline in trough clinic SBP and DBP) support the findings of Study 301 for the claim that TAK-491CLD is better than OLM/HCTZ to lower BP.

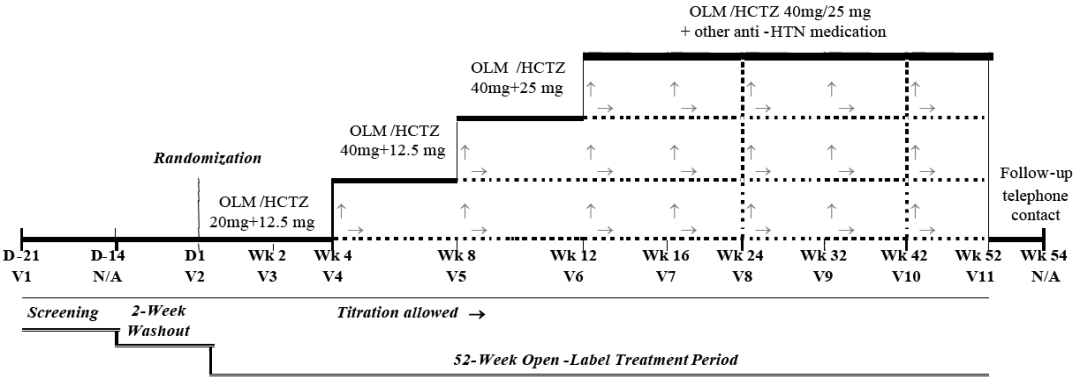
Subjects were enrolled at sites in the United States and Europe. After a 2-week washout, eligible subjects with trough clinic SBP ≥160 and ≤190 mmHg were randomized in a 1:1 ratio to receive open-label treatment with either TAK-491CLD or OLM/HCTZ for up to 52 weeks according to the titrate-to-target BP algorithms shown in Figure 6, Figure 7, and Figure 8. Differences in the available doses for OLM/HCTZ necessitated a region-specific titration schedule for subjects in US (Figure 7) and Europe (Figure 8) randomized to this treatment.

Figure 6 Study 308: study schematic for subjects randomized to TAK-491CLD



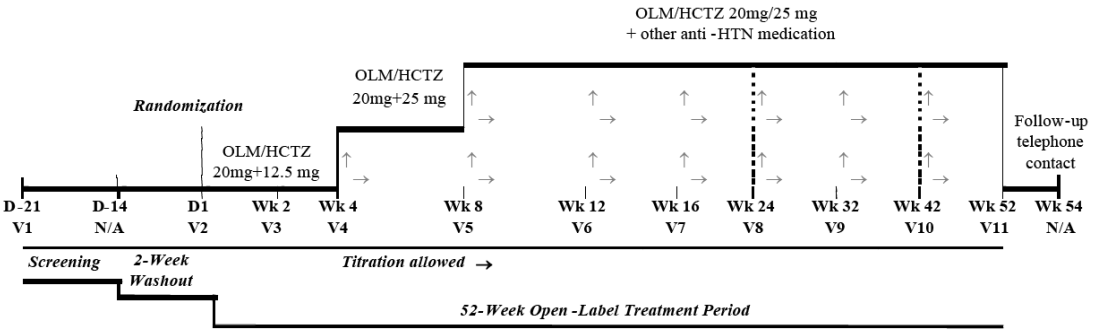
D=day, HTN=hypertension, N/A=not applicable, V=visit.

Figure 7 Study 308: study schematic for subjects randomized to OLM/HCTZ in US



D=day, HTN=hypertension, N/A=not applicable, V=visit.

Figure 8 Study 308: study schematic for subjects randomized to OLM/HCTZ in Europe



Note: Study drug was titrated according to a titrate-to-target approach.
D=day, HTN=hypertension, N/A=not applicable, V=visit.

During this study, if both target SBP and target DBP (defined as <140/90 mmHg for subjects without diabetes or CKD or <130/80 mmHg for subjects with diabetes or CKD) were achieved, subjects continued to receive their starting dose. The first opportunity for subjects to have their study drug titrated was after 4 weeks of treatment; thereafter, study drug was up-titrated (if BP was not controlled) or down-titrated (if experiencing

tolerability issues) at any study visit. The study drug was titrated by only 1 dose level per visit, and subjects must have been at the previous dose level for a minimum of 4 weeks before up-titration.

At the time of submission of the, this study is ongoing; interim data obtained through the cut-off date of 17-Sep-2010 were submitted in the CSR, which contained the change from Baseline in clinic SBP and DBP at each study visit as the efficacy variables. On 23-Jun-2011, a 12-Day Safety Update (for the safety variables of AEs, clinical safety laboratory tests, ECGs and vital signs) was submitted to this NDA.

Clinical trials from NDA 200-796 (TAK-491 monotherapy) applicable to this NDA

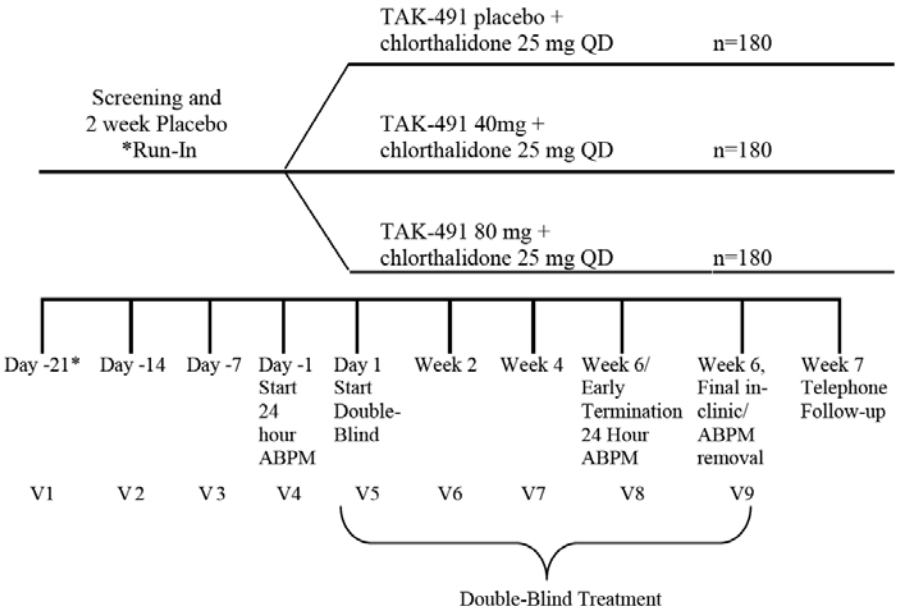
Study 009

Study 009 compared the efficacy of TAK-491 co-administered with CLD compared with CLD monotherapy in a 6-week, randomized, placebo-controlled, double-blind, 3-arm, fixed dose clinical trial (Figure 9). I reviewed this study to evaluate if the results here are consistent with the findings of Study 302.

Eligible subjects had trough clinic SBP ≥160 mmHg and ≤190 mmHg, and 24-hour mean SBP ≥140 mmHg and ≤180 mmHg after washout of previous antihypertensive therapy. After randomization, all subjects received CLD 25 mg plus one of the following: (i) placebo, (ii) TAK-491 40 mg or (iii) TAK-491 80 mg daily for 6 weeks. ABPM occurred 24 hours prior to first dose of double-blind study drug, and at Week 6 or Early Termination for 24 hours after the last dose. Clinic SBP and DBP were measured at screening, randomization (Day 1), Week 2, Week 4 and Week 6.

The primary efficacy endpoint was the change from Baseline to Week 6 in 24-hour mean SBP by ABPM. The key secondary efficacy endpoint was the change from Baseline to Week 6 in trough clinic SBP.

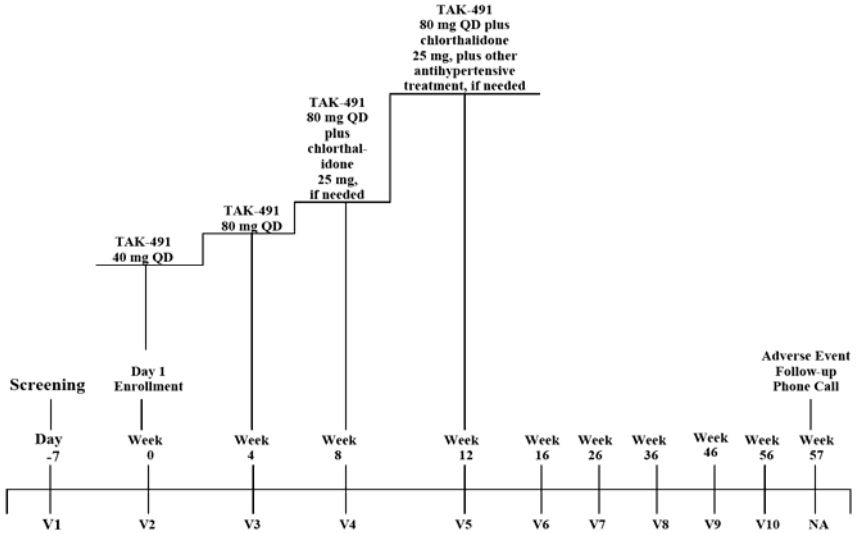
Figure 9 Study 009: study schematic



Study 006

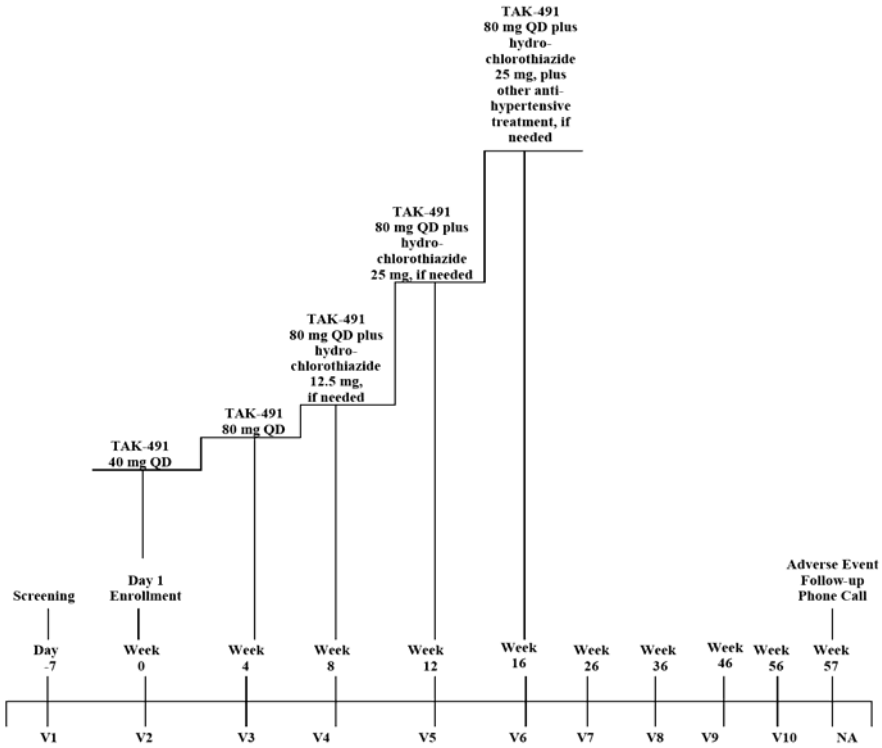
Study 006 was an open-label, multicenter ***safety*** study of treatment with TAK-491 for up to 56 weeks in patients with essential hypertension (trough clinic DBP ≥95 mmHg and ≤119 mmHg, or DBP ≥85 mmHg and ≤109 mmHg in subjects with diabetes or CKD).

Figure 10 Study 006: Study schematic for Cohort 1



Source: Study 006 CSR Figure 9.a

Figure 11 Study 006: Study schematic for Cohort 2



Source: Study 006 CSR Figure 9.b

Eligible subjects started treatment with TAK-491 40 mg on Day 1, which was added to existing treatments, if applicable. At Week 4, TAK-491 was titrated to 80 mg, if tolerated. Thereafter, subjects could have additional medications added, if needed, to reach target BP. The total duration of the study included a 7-day screening period, a 56-week, open-label period, and a 7-day post-treatment AE follow-up period. Vital signs were measured at every visit, included sitting clinic BP (average of 3 BP levels) and pulse.

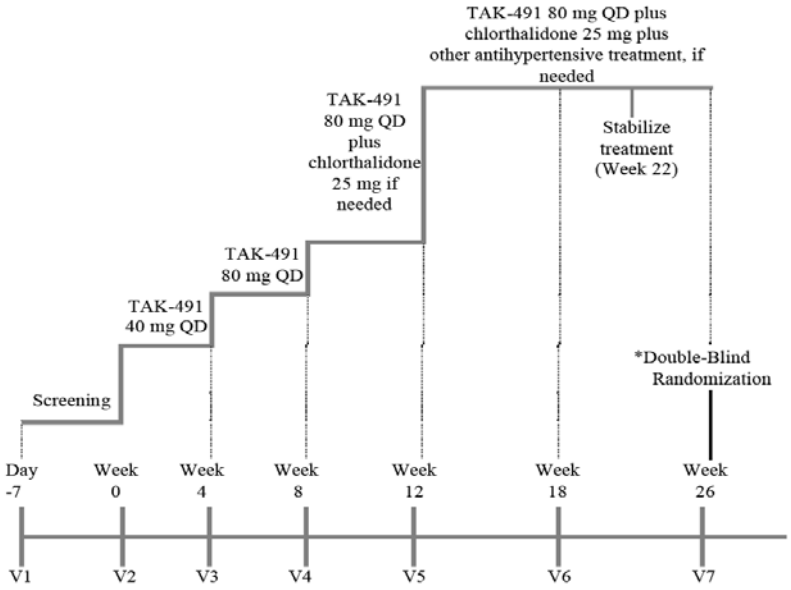
In the first cohort (Cohort 1, 350 subjects, Figure 10), CLD 25 mg was the initial add-on agent. The second cohort (Cohort 2, 300 subjects, Figure 11) – which was added 1.5 years after study initiation – received HCTZ as the initial add-on agent, if needed. This study was conducted at approximately 60 sites in the United States (both cohorts) and Latin America (Cohort 1 only).

The primary efficacy variable for Study 006 was the change in clinic SBP and DBP from baseline at each week of treatment for Cohort 1 and Cohort 2 separately and together.

Study 016

Study 006 was a multicenter, open-label, uncontrolled, unrandomized, titrate-to-target BP, ***safety*** study of treatment with TAK-491 with or without CLD for up to 26 weeks in patients with essential hypertension (trough clinic DBP ≥95 mmHg and ≤119 mmHg, or DBP ≥85 mmHg and ≤109 mmHg in subjects with diabetes or CKD), followed by a 6-week double-blind, placebo-controlled reversal phase.

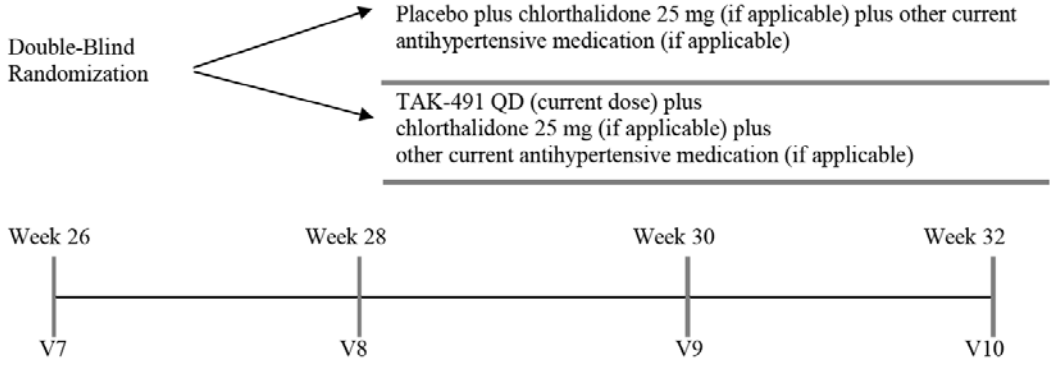
Figure 12 Study 016 – Study schematic of open-label phase



During the open-label phase (Figure 12), subjects were initiated at a dose of TAK-491 40 mg QD. At Week 4, if the initial dose of TAK-491 40 mg QD was deemed tolerable, the dose was increased to TAK-491 80 mg QD. At Week 8 through Week 22, subjects could receive CLD and other antihypertensive agents to achieve the target BP.

At Week 26, subjects discontinued open-label TAK-491 and entered double-blind reversal phase (Figure 13) in which subjects were randomized by IVRS to either double-blind TAK-491 at the final dose they received in the open-label phase, or placebo, in addition to their current other antihypertensive medications, including CLD, as applicable. Up- and down-titration of TAK-491 was not permitted during this phase.

Figure 13 Study 016 – Study schematic of double-blind reversal phase



The primary efficacy endpoint was the change in trough clinic sitting DBP from Double-Blind Baseline (Week 26) to Final Visit/Week 32 during the double-blind reversal phase (with the change in clinic sitting SBP from Double-Blind Baseline (Week 26) to Final Visit/ Week 32 during the double-blind reversal phase as the secondary efficacy endpoint).

6 Review of Efficacy

Efficacy Summary

Efficacy data are submitted from five Phase 3 studies of TAK-491CLD FDC (Table 2). The pivotal clinical trial (Study **302**) was a randomized, double-blind, controlled, factorial study that compared the antihypertensive effect of TAK-491CLD with TAK-491 and CLD monotherapy after 8 weeks of fixed-dose treatment. The four supportive FDC studies include three short-term, randomized, double-blind, comparator-controlled studies (Study **306**, Study **301**, and Study **303**), and a 52-week, randomized, open-label, comparator-controlled, safety study (Study **308**). The efficacy data from three clinical trials in the TAK-491 monotherapy program in which TAK-491 and CLD were co-administered (one short-term, double blind, placebo-controlled Study **009**, and two long-term, open-label safety trials – Study **006** and Study **016**) are also reviewed.

Studies 302 and 009 are fixed dosage trials (the former used the FDC tablet, the latter used add-on tablets), and Study 303 uses fixed dosage by "forced titration." Studies 301, 306, 308, 006 and 016 are "titrate-to-target-BP" trials (using JNC 7 criteria).

The subjects enrolled had mean sitting clinic SBP of ≥160 to ≤190 mmHg after 2 to 4 weeks wash out of previous antihypertensive therapy. Concurrent elevated DBP was permitted, but high baseline DBP (>119 mmHg) was exclusionary. Patients were excluded if they had a history of (i) a CV event within 6 months, (ii) severe renal disease (eGFR <30mL/min/1.73m^2), (iii) unilateral or bilateral renal artery stenosis, or presence of (iv) hyperkalemia, (v) hypokalemia, (vi) active liver disease, (vii) jaundice or (viii) ALT or AST > 2.5 ULN. In each study, the majority of subjects were enrolled in the United States, with additional enrollment in Latin America, Europe, and Russia.

Each short-term study assessed the efficacy of TAK-491CLD with both ambulatory and clinic measurements of BP; clinic BP was measured throughout the long-term studies. The primary efficacy endpoint in Study 302 was the change from baseline at Week 8 in trough SBP by ABPM; the secondary endpoints were the change from baseline at Week 8 in trough SBP by ABPM in Black subjects, and in trough clinic SBP in all subjects. The primary efficacy endpoint in Studies 301, 306, and 303 was the change from baseline in clinic SBP. Study 009 used 24-hour mean SBP by ABPM. The open-label safety Studies 308, 006 and 016 used the incidence rate of AEs for their primary endpoint.

The overall demographics including baseline BPs (by clinic and ABPM measurements), were similar across the efficacy studies. In Study 302, baseline mean clinic SBP and DBP ranged from 163.4 to 166.2 mmHg and 94.0 to 96.1 mmHg, respectively. The ranges for trough SBP and DBP by ABPM were 148.9 to 153.7 mmHg and 88.5 to 91.8 mmHg, respectively. Baseline BPs in the other Phase 3 studies fell within these ranges. Subjects enrolled in open-label safety Studies 308, 006 and 016 had a higher mean baseline clinic DBP (≈100 mmHg) and lower mean baseline clinic SBP (≈153 mmHg), consistent with the primary entry criterion being based on diastolic hypertension. Subjects enrolled in safety studies also tended to be younger (mean age ≈52 years).

There were relatively high frequencies of missing values in pivotal Study 302 (ranging

from 9% to 14% of subjects randomized to the lower doses of monotherapy with TAK-491 or CLD, to 20% to 22% of subjects randomized to the two high-dose arms of the FDC). The main reason was that subjects whose ABPM data were considered non-evaluable (due to failure to satisfy protocol-specified criteria) did not have post-baseline ABPM data for primary efficacy analysis. Sensitivity analyses performed using (i) LOCF, (ii) observed cases (data from only patients who had a post-baseline value) and (iii) multiple imputation method (data from any subject with a baseline value – even without any post-baseline value – was included) all showed consistent results.

For the claim that the fixed-dose combination of TAK-491CLD is more effective compared to the respective monotherapies to reduce BP, the efficacy data in Study 302 (as the primary clinical trial), and Studies 306, 009, 006 and 016 (as supportive trials) were evaluated. In Study 302, the reductions in trough SBP by ABPM at Week 8 in all treatment groups were large enough to be clinically significant (Table 5), and the treatment differences between each TAK-491CLD and its TAK-491 component (-10.9 to -17mmHg) or CLD component (-10.3 to -13.9 mmHg) were also large and statistically significant (P<0.001). Incremental dose-related reductions in trough SBP by ABPM were observed (Figure 15) across the FDC dose range of 20/12.5, 40/12.5, 80/12.5, and 40/25 doses (with no further reduction in SBP with 80/25 mg dose). This finding was supported by Study 306: after TAK-491 alone had produced SBP reduction at Week 2, the addition of 12.5 mg CLD at Week 2 showed statistically significant (P<0.05) incremental reductions in clinic SBP beginning at Week 4, and continuing to Weeks 6 and 8 (Figure 17). The efficacy data in Studies 009 (Table 8), 006 (Figure 19) and 016 (Figure 21) show consistent findings. *These efficacy results support the claim that TAK-491CLD is more effective to reduce BP compared with the respective monotherapies*.

For the claim of superiority of BP reduction effect of the TAK-491CLD FDC compared to the OLM/HCTZ combination drug product, the efficacy data in Study 301 (as the primary clinical trial), and Studies 303 and 308 (as supportive trials) are evaluated. Study 301 showed that clinic SBP reductions at Weeks 4, 6 and 8 in both TAK-491CLD treatment groups (33 to 38 mmHg) were significantly (P<0.05) greater than in the OLM/HCTZ group (27 to 32 mmHg) at each visit; (Table 9, Figure 23). This finding was supported by the finding of statistically significantly (P<0.001) larger reductions from Baseline to Week 12 in clinic SBP in Study 303 (Figure 24) for both the 40/25 mg and the 80/25 mg dose groups of TAK-491CLD (-42.5 and -44.0 mmHg, respectively) compared with the OLM/HCTZ group (-37.1 mmHg). In Study 308, too, the interim efficacy results (at Week 32) showed a greater reduction from baseline in clinic SBP at Week 32 (Figure 25) in the TAK-491CLD treatment group (47.7 mmHg) compared to the OLM/HCTZ treatment group (41.5 mmHg). *These efficacy results support the claim that TAK-491CLD has a superior BP reduction effect compared with the OLM/HCTZ combination drug product*.

For the claim that the fixed-dose combination of TAK-491CLD is more effective than either component (TAK-491 or CLD monotherapy) in Black subjects, and that it is as effective in Black subjects as in White subjects, the efficacy data in (i) the subgroup of Black subjects in Study 302 and (ii) in Study 303 in which subjects were stratified at randomization as Black vs. non-Black are reviewed. In Study 302, analysis of efficacy data in the relatively small subpopulation of Black subjects (40 subjects for the TAK-

491CLD 40/25+80/25 mg pool and 28 and 22 subjects for the TAK-491 80 mg and CLD 25 mg monotherapy groups, respectively, who had a baseline and final ABPM) showed statistically significantly (P<0.001) larger reductions in trough SBP by ABPM at Week 8 in the treatment groups receiving the pooled doses of the TAK-491CLD FDC (40/25 mg+80/25 mg pool) compared to monotherapy with TAK-491 80 mg but not to monotherapy with CLD 25 mg (Table 11). In Study 303 which stratified subjects upon randomization as Black vs. non-Black subjects, subgroup analysis by race (Table 12) showed that treatment with TAK-491CLD 40/25 mg or 80/25 mg led to clinically meaningful and statistically significant reductions in clinic SBP from Baseline to Week 12 compared to the OLM/HCTZ treatment group in both Blacks and Caucasian subjects. However, across subgroups and regardless of the treatment administered, there was a trend towards smaller clinic SBP reductions (mean change from baseline to Week 12 in clinic SBP, Table 12) among Black subjects (≈40 mmHg) compared to Caucasian subjects (≈44 mmHg). *These findings do **not** support the claim that TAK-491CLD was more effective than either TAK-491 or CLD monotherapy in Black subjects, or that TAK-491CLD is as effective in Black subjects as in White subjects*.

Subgroup analyses of efficacy data in the four Phase 3, short-term FDC studies (by age (<65, ≥65, ≥75 years), sex, race (Black, White, Other), body mass index (BMI) (<30, ≥30 kg/m2), renal function (estimated glomerular filtration rate [eGFR] ≥90, ≥60 to <90, ≥30 to <60mL/min/1.73m^2), diabetes status, and baseline hypertension severity) showed no evidence of heterogeneity in response to treatment with TAK-491CLD.

Six doses of the TAK-491CLD FDC (20/12.5, 40/12.5, 80/12.5, 20/25, 40/25, and 80/25 mg) were evaluated in the phase 3 clinical trials. The fixed-dose factorial Study 302, and the titrate-to-target BP Studies 306 and 301 showed almost similar incremental, dose-related BP reductions up to the 40/25 mg dose (≈40 mmHg in Study 302, ≈38 mmHg in Studies 306 and 301, Table 15), with no incremental BP reduction at the 80/25 mg dose, suggesting that the 40/25 mg may be the maximum effective and tolerated dose. Using a criterion of >2 mmHg in BP reduction as the "discernible difference," there was no discernible difference between the 20/12.5 mg and 40/12.5 mg doses, with no increase in AEs at 40/12.5 mg, suggesting that the 40/12.5 mg dose may be selected as the starting (low) dose. The 80/12.5 mg and 20/25 mg doses showed no "discernible difference" in BP reduction from the selected top (40/25 mg) or low (40/12.5 mg) dose.

ABPM findings (Figure 35) suggest that administration of TAK-491CLD once daily produced and maintained clinically meaningful reductions in SBP and DBP throughout the 24-hour dosing interval.

Interim BP data in the ongoing long term open-label Study 308 (Figure 37), replicated by BP data in the long term Study 006 (Figure 38), showed that the initial reduction in BP was observed around 2 ~ 4 weeks, with the maximal BP reduction effect observed at about 8 ~ 16 weeks, and that the BP reduction effect persisted throughout treatment.

Responder analyses (based on achievement of target SBP of <140 mmHg or target DBP of <90 mmHg) in Study 302 (Table 14) showed that a larger proportion of subjects in TAK-491CLD treatment groups (70~85%) achieved target BP at Week 8 compared to its respective TAK-491 component (30~52%) or CLD component (34~51%).

6.1 Indication

The labeled indication requested is as follows:

(b)(4)

[redacted]

6.1.1 Methods

As discussed under Section 5.2 Review Strategy (and Figure 1), to evaluate the sponsor's claims that TAK-491CLD FDC is more effective compared to monotherapies of the components to reduce BP, I

(i) reviewed the factorial Study 302 as the primary clinical trial,
(ii) evaluated the efficacy data in Studies 306 and 009 as supportive trials, and
(iii) made reference to the efficacy data in open label safety Studies 006 and 016.

To evaluate the claim of superiority of BP reduction effect of TAK-491CLD compared to that of the marketed OLM/HCTZ combination drug product, I

(i) reviewed Study 301 as the primary clinical trial,
(ii) evaluated the efficacy data in Study 303 as the supportive trial, and
(iii) made reference to the efficacy data in the ongoing open label safety Study 308.

I reviewed the efficacy data in Study 302 to evaluate the efficacy of TAK-491CLD in subpopulations of Blacks vs. non-Blacks, with supportive information from Study 303 (which stratified subjects at randomization as Black vs. non-Black).

For the ongoing Study 308, I reviewed the key *safety* data in the 120-Day Safety Update submitted 23-Jun-2011. Data on Study 307 and Study 309 to support registration in Europe based on EMA requirements, will not be submitted to FDA before the review goal date.

I did not plan to pool the data for efficacy analyses, because there were differences in study design, dosing and primary efficacy endpoints:

(a) Studies 302 and 009 are fixed dosage trials (the former uses the fixed dose combination tablet, the latter uses add on tablets),
(b) Studies 301, 306, 308, 006 and 016 are "titrate-to-target-BP" trials (with variations in the time of titration and duration of study), and
(c) Study 303 uses fixed dosage by "forced titration."
(d) For the primary efficacy endpoint,
- Study 302 used SBP by ABPM,
- Studies 301, 306 and 308 used clinic SBP,
- Study 303 used mean clinic SBP,
- Study 009 used 24-hour mean SBP by ABPM,
- Study 006 used clinic SBP and DBP, and
- Study 016 used trough clinic sitting DBP.

6.1.2 Demographics

The overall demographics of subjects enrolled in 3 short-term FDC studies (Studies 302, 306 and 301) are summarized (Table 3), followed by a description of demographic data for each phase 3 clinical trial.

Table 3 Summary of demographic and baseline characteristics in short-term FDC studies

Characteristic	Study 302	Study 306	Study 301
Age (years), mean (SD)	57.2 (10.8)	56.4 (10.9)	56.0 (10.4)
≥65 years, n (%)	422 (24.5)	132 (21.7)	214 (19.7)
Sex, n (%)			
Male	805 (47.0)	296 (48.6)	563 (51.9)
Female	909 (53.0)	313 (51.4)	522 (48.1)
Race (a), n (%)			
American Indian	142 (8.3)	7 (1.1)	106 (9.8)
Asian	34 (2.0)	5 (0.8)	17 (1.6)
Black	342 (20.0)	84 (13.8)	290 (26.7)
Native Hawaiian or other Pacific Islander	2 (0.1)	1 (0.2)	3 (0.3)
White	1210 (70.6)	517 (84.9)	680 (62.7)
Multiracial	15 (0.9)	5 (0.8)	11 (1.0)
Region, n (%)			
US	1074 (62.7)	427 (70.1)	891 (82.1)
Non-US (b)	640 (37.3)	182 (29.9)	194 (17.9)
BMI (kg/m^2), mean (SD)	31.4 (5.9)	31.2 (6.1)	31.8 (6.1)
eGFR (c) (mL/min/1.73 m^2), n (%)			
Severe impairment: ≥0 and <30	1 (0.1)	0	0
Moderate impairment: ≥30 and <60	108 (6.3)	47 (7.7)	76 (7.0)
Mild impairment: ≥60 and <90	1083 (63.2)	364 (59.8)	632 (58.2)
Normal: ≥90	521 (30.4)	198 (32.5)	377 (34.7)
Missing	1 (0.1)	0	0
CKD, n (%) (c)	ND	48 (7.9)	94 (8.7)
Diabetes, n (%) (d)	244 (14.3)	66 (10.8)	188 (17.3)

Source: Sponsor's CSR for Study 302 (Tables 15.1.7 and 15.2.1.3.14), Study 306 (Table 15.1.7), and Study 301 Table 15.1.7). ND=not determined. (a) Race categories not mutually exclusive.
(b) Non-US sites: Latin America and Russia for Study 302, Russia for Study 306, and Latin America for Study 301.
(c) Presence of diabetes and CKD determined at Screening in Studies 306 and 301 to facilitate determination of each subject's target BP; CKD defined as eGFR<60 mL/min/1.73 m^2 or UACR >200 mg/g. Presence of CKD not determined in Study 302 because this was not a titrate-to-target BP study.
(d) Diabetes status (yes/no) recorded at Screening in Studies 306 and 301 to facilitate determination of each subject's target BP; in Study 302, prevalence of diabetes was based on a MedDRA query (in the FAS) for medical history and concurrent medical condition terms compatible with diabetes mellitus.

Baseline BPs, including both clinic and ABPM measurements, were similar across the short-term FDC studies. Among subjects randomized in Study 302, baseline mean clinic SBP and DBP ranged from 163.4 to 166.2 mmHg and 94.0 to 96.1 mmHg, respectively. The ranges for trough SBP and DBP by ABPM were 148.9 to 153.7 mmHg and 88.5 to 91.8 mmHg, respectively. Baseline BPs in Studies 306 and 301 fell within these ranges.

Study-302: The demographics and baseline characteristics were similar across treatment groups in all randomized subjects (Table 4).

Table 4 Summary of Demographic and Baseline Characteristics by Treatment Group in Study-302 (All Randomized Subjects)

	TAK-491 (mg)			CLD (mg)		TAK-491CLD (mg)					
Characteristic	**20 N=155**	**40 N=153**	**80 N=162**	**12.5 N=157**	**25 N=159**	**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=162**
Age (years)											
	57.3 (11.04)	57.8 (10.28)	57.3 (10.87)	57.3 (11.30)	56.2 (10.04)	58.2 (10.57)	56.2 (10.50)	55.8 (11.22)	57.4 (11.13)	57.4 (11.07)	57.6 (11.04)
Sex, n (%)											
Male	68 (43.9)	85 (55.6)	78 (48.1)	83 (52.9)	69 (43.4)	70 (44.9)	71 (48.3)	71 (46.4)	77 (50.0)	71 (45.5)	62 (38.3)
Female	87 (56.1)	68 (44.4)	84 (51.9)	74 (47.1)	90 (56.6)	86 (55.1)	76 (51.7)	82 (53.6)	77 (50.0)	85 (54.5)	100 (61.7)
Race, n (%) (a)											
American Indian (b)	11 (7.1)	13 (8.5)	14 (8.6)	14 (8.9)	14 (8.8)	9 (5.8)	13 (8.8)	12 (7.8)	13 (8.4)	13 (8.3)	16 (9.9)
Asian	1 (0.6)	1 (0.7)	4 (2.5)	1 (0.6)	7 (4.4)	4 (2.6)	4 (2.7)	2 (1.3)	3 (1.9)	4 (2.6)	3 (1.9)
Black	31 (20.0)	35 (22.9)	35 (21.6)	31 (19.7)	29 (18.2)	34 (21.8)	29 (19.7)	26 (17.0)	28 (18.2)	30 (19.2)	34 (21.0)
White	113 (72.9)	105 (68.6)	111 (68.5)	111 (70.7)	111 (69.8)	111 (71.2)	102 (69.4)	114 (74.5)	112 (72.7)	111 (71.2)	109 (67.3)
Multiracial	1 (0.6)	1 (0.7)	2 (1.2)	1 (0.6)	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)	2 (1.3)	2 (1.3)	0
BMI (kg/m^2)											
Mean (SD)	31.3 (5.23)	31.0 (5.85)	30.8 (6.28)	31.2 (5.85)	31.2 (5.78)	32.2 (5.73)	31.8 (6.57)	31.4 (5.84)	31.0 (5.65)	32.2 (6.01)	31.5 (6.28)
eGFR (mL/min/1.73 m^2), n (%) (c)											
≥0 and <30	0	1 (0.7)	0	0	0	0	0	0	0	0	0
≥30 and <60	11 (7.1)	11 (7.2)	8 (4.9)	12 (7.6)	9 (5.7)	13 (8.3)	6 (4.1)	6 (3.9)	14 (9.1)	8 (5.1)	10 (6.2)
≥60 and <90	94 (60.6)	95 (62.1)	99 (61.1)	101 (64.3)	100 (62.9)	95 (60.9)	93 (63.3)	109 (71.2)	90 (58.4)	97 (62.2)	110 (67.9)
≥90	49 (31.6)	46 (30.1)	55 (34.0)	44 (28.0)	50 (31.4)	48 (30.8)	48 (32.7)	38 (24.8)	50 (32.5)	51 (32.7)	42 (25.9)
Missing	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Baseline blood pressure (mm Hg), Mean (SD) (d)											
Clinic SBP	163.4 (11.20)	164.1 (9.24)	163.9 (10.42)	164.3 (11.03)	166.2 (10.18)	165.3 (9.91)	165.1 (11.22)	164.6 (8.73)	164.7 (9.98)	164.1 (10.40)	164.2 (9.81)
Clinic DBP	95.1 (10.81)	95.2 (8.83)	94.6 (9.90)	95.9 (9.41)	95.6 (9.70)	95.3 (11.17)	96.1 (9.76)	94.3 (10.33)	95.6 (9.26)	94.0 (9.88)	94.2 (9.01)
Trough SBP by ABPM	151.1 (16.20)	153.7 (17.02)	150.5 (16.39)	151.9 (15.19)	151.0 (17.54)	151.3 (17.08)	152.6 (17.38)	149. 3 (18.67)	151.1 (16.83)	148.9 (15.57)	152.5 (17.14)
Trough DBP by ABPM	90.9 (11.81)	91.8 (11.89)	90.7 (12.98)	91.5 (12.21)	90.5 (12.87)	90.3 (13.66)	90.5 (12.49)	88.5 (12.92)	91.3 (12.32)	88.9 (12.62)	91.3 (12.75)

Source: Study 302 CSR Tables 15.1.7, 15.1.8.1, and 15.1.8.2.
(a) A subject could choose more than 1 category for race. Subjects who chose more than 1 race category were included in each category indicated and were also included in the multiracial category.
(b) The majority of subjects who self-identified as American Indian were enrolled at Latin American sites.
(c) eGFR, based on calculated creatinine clearance; ≥30 to <60 mL/min/1.73 m2=moderate renal impairment, ≥60 to <90 mL/min/1.73 m^2=mild renal impairment, ≥90 mL/min/1.73 m^2=normal renal function.
(d) Sample sizes for baseline BP by clinic and ABPM measurements are reported in Study 302 CSR Tables 15.1.8.1 and 15.1.8.2, respectively.

Most subjects (63%) were enrolled at sites in the US. The most commonly used antihypertensive agents before washout were ACE inhibitors and ARBs.

Study-306: The demographic and baseline characteristics were similar between treatment groups in randomized subjects (Table 3). By region, 70.1% of subjects were enrolled in the U.S., and 29.9% in Russia. At baseline, trough clinic SBP/DBP and trough SBP/DBP by ABPM were similar in each group. The most commonly used antihypertensive agents before washout were ACE inhibitors, ARBs, β-blockers, calcium channel blocker (amlodipine), and diuretic (HCTZ).

Study 301: The demographic and baseline characteristics were similar between treatment groups for the randomized subjects (Table 3). About 82% of all randomized subjects were from sites within the U.S. The mean BMI for all subjects was 31.8 kg/m^2. 17.3% of randomized subjects had diabetes, with a higher percentage in the OLM/HCTZ treatment group (19.9%) compared with the TAK-491CLD treatment groups overall (16.0%). At Baseline, mean clinic SBP/DBP and trough SBP/DBP by ABPM were similar in each group. The most commonly used antihypertensive agents before washout were ACE inhibitors and ARBs, β-blockers (metoprolol and atenolol), calcium channel blockers (nifedipine and amlodipine), and diuretics (HCTZ).

Study 308 (ongoing): 837 subjects have been randomized. There were no major differences in demographic and baseline characteristics between the 2 treatment groups in the randomized subjects. The mean age of randomized subjects was 58 years, with 61% of subjects ≥45 to <65 years of age, and 28% ≥65 years. A larger percentage of male subjects than female subjects were randomized: 56% and 44%, respectively. The majority of randomized subjects were White (~80%), followed by Black (~17.8%). About 62% of subjects were randomized at the US sites. About 65% of subjects had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2), 12% had moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2), and 6.1% had chronic kidney disease (CKD). About 15% of subjects were diabetic at baseline. This study population (for both treatment groups) had a higher clinic BP at baseline (≈168/96 mmHg) than the short-term studies. The most commonly used antihypertensive agents taken before washout were ACE inhibitors and ARBs, β-blockers (metoprolol and atenolol), calcium channel blockers (amlodipine and verapamil), and diuretics (HCTZ).

Study 303: The demographics and baseline characteristics were similar among the titration groups. The mean age of randomized subjects was 56.6 years (66.3% were between 45 and 64 years of age, and 22.0% of subjects were ≥ 65 years of age). 58.7% of subjects were male. 78.2% of randomized subjects were from sites within the United States. The majority of randomized subjects were White (73.4%, with 9% of Hispanic ethnicity), followed by Black (22.4%) and Asian (3.3%). The mean BMI of subjects was 31.6 kg/m^2. Baseline eGFR showed that 690 subjects (64.4%) had mild renal impairment, 80 subjects (7.5%) had moderate renal impairment, and 299 subjects (27.9%) had normal renal function. Clinic SBP and DBP and ABPM parameters for SBP and DBP at Baseline showed no significant differences among the titration groups.

There were no major differences in medical history across the titration groups. There was a higher percentage of subjects with renal and urinary disorders in the TAK-491CLD 40/25 mg titration group (11.5%) than in the TAK-491CLD 80/25 mg or the OLM/HCTZ titration groups (6.8% and 6.6%, respectively), and a higher percentage of

subjects with cardiac disorders in the TAK-491CLD 80/25 mg titration group (13.1%) than in the TAK-491CLD 40/25 mg or the OLM/HCTZ titration groups (8.5% and 7.7%, respectively).

The most common concomitant medications that started before study Baseline and continued during the active treatment period were aspirin, multivitamins, metformin, and simvastatin. The percentage of subjects taking these medications was similar among the titration groups.

Study 009: The demographic characteristics were similar across the treatment groups. The subject population was slightly older (59 years), with a higher proportion of subjects aged ≥65 years (27% to 31%) compared with the short-term FDC studies. Men and women were nearly equally represented. American-Indian subjects ranged from 20% to 28%, mostly from Latin American sites which enrolled approximately 30% of subjects. About 16.0% of subjects in each group were Black.

ABPM parameters for SBP and DBP (24-hour mean, mean daytime, mean nighttime, 12-hour mean, and trough) and trough clinic sitting SBP and DBP obtained at Baseline showed no significant differences among the treatment groups. In Study 009, Baseline SBP (≈166 mmHg) was similar to the FDC studies; baseline SBP by ABPM was higher (155-157 mmHg for trough SBP by ABPM), which is consistent with entry criteria that subjects must have systolic hypertension by both clinic and ABPM measurements.

There were no major differences in medical history across groups. The most common previous condition was myocardial infarction in the medical history of 9 (1.6%) subjects. The most common concurrent medical conditions were hypertension, metabolism and nutrition disorders (hyperlipidemia and hypercholesterolemia, and type 2 diabetes mellitus), and musculoskeletal/connective tissue disorders (osteoarthritis, back pain). The number of subjects with a medical condition was similar in the treatment groups.

The most common antihypertensive medications taken before the study were ACE inhibitors and ARBs, the diuretic HCTZ, the calcium channel blockers amlodipine and nifedipine, and the β-blocker atenolol.

Study 006: In Cohort 1, the mean age of enrolled subjects at Baseline was 53.0 years. The majority of subjects were White (63.0%) and from the United States (92.8%), with slightly more male subjects (52.2%) than female subjects (47.8%). The majority of subjects (64.4%) were aged 45 to 64 years, and 13.3% were ≥ 65 years of age. At Baseline, mean SBP and DBP were 151.2 and 99.4 mmHg, respectively.

In Cohort 2, the mean age of enrolled subjects at Baseline was 50.1 years. The majority of subjects were White (61.6%) and all were from the United States, with slightly more male subjects (53.1%) than female subjects (46.9%). The majority of subjects (62.9%) were aged 45 to 64 years and 7.8% were ≥ 65 years of age. At Baseline, mean SBP and DBP were 152.3 and 100.3 mmHg, respectively.

The 3-year difference in mean age between Cohort 1 and Cohort 2 was statistically significant.

More Black subjects and more male subjects required the addition of CLD (38.4% and

55.6%, respectively) or HCTZ (42.4% and 53.8%, respectively) to TAK-491, compared to subjects who received TAK-491 alone (25.7% and 49.4%, respectively). Baseline SBP and DBP were higher for subjects who received TAK-491 plus CLD or HCTZ compared with subjects who received TAK-491 alone.

Subjects who received TAK-491 plus CLD (mean age 53.9 years) were older than subjects who received TAK-491 alone (mean age 51.0 years) or TAK-491 plus HCTZ (mean age 49.9 years).

71.6% of subjects had ≥1 medical history findings, with 2.8% of subjects who entered the study having a history of cardiac disorders: angina pectoris (8 subjects, 1.2%), myocardial infarction (5 subjects, 0.7%) and atrial fibrillation (2 subjects, 0.3%).

88.6% of subjects reported previous medication use, the most common being aspirin (20.5%), ibuprofen (17.9%), , paracetamol (15.4%), metformin (9.6%), vicodin (7.9%), omeprazole (6.1%), simvastatin (5.7%), fish oil (5.4%), and naproxen (5.1%).

Study 016: *At Open-Label Baseline*, the mean age of all enrolled subjects was 52.1 years, with the majority of subjects aged 45 to 64 years, and 10.0% ≥65 years of age. The majority of subjects were White (68.7%) and from the United States (73.9%). Approximately half of the subjects were female (50.2%).

Subjects who additionally received CLD were older than those who did not (mean age 53.3 years and 50.4 years, respectively). There were also more Black subjects and more male subjects among those who received CLD. The mean BP among all subjects was 155.1/99.9 mmHg. Subjects who additionally received CLD in the open-label phase had a higher mean BP at Open-Label Baseline (158.3/101.2 mmHg) compared to subjects who did not receive CLD (150.8/98.2 mmHg).

57.9% of subjects had at least 1 medical history finding: 3.3% of subjects enrolled had a history of cardiac disorders (myocardial infarction in 6 subjects, (1.4%), and acute coronary syndrome and palpitations in 2 subjects (0.5%) each). 7.2% reported an ongoing cardiac condition or disease, the most common being left ventricular hypertrophy and palpitations (1.2% each).

In the double-blind reversal phase, no major differences were observed between the randomized treatment groups in demographic and Baseline characteristics, including the trough clinic sitting DBP and SBP values at Double-Blind Baseline.

Overall, 22.2% of subjects received concomitant medications that started and stopped prior to Open-Label Baseline. The most common medication was HCTZ (5.0%).

Overall, 13.6% of subjects received concomitant antihypertensive medications that started and stopped prior to Baseline, 39.7% continued use of prior antihypertensive medication use into the open-label phase, and 12.2% required additional antihypertensive medication after Open-Label Baseline. By Week 18 of the open-label phase, 9.0% (17/189) of subjects who were receiving TAK-491 plus CLD were prescribed additional antihypertensive medication.

6.1.3 Subject Disposition

Study 302: 5,145 subjects were screened at 175 sites, 3,607 subjects entered the single-blind placebo run-in period, 1,714 subjects were randomly assigned to double-blind treatment, and 1,470 subjects (86%) completed the study. Subject disposition is presented by treatment group in Figure 14.

Study-306: 1,652 subjects were screened at 66 sites, 1,193 subjects entered the single-blind placebo run-in period, and 609 subjects were randomized (303 and 306 subjects, respectively) to the TAK-491CLD and TAK-491+HCTZ treatment groups. Ninety-seven randomized subjects (15.9%) prematurely discontinued from the study: 51 subjects (16.8%) in the TAK-491CLD treatment group and 46 subjects (15.0%) in the TAK-491+HCTZ treatment group. The most common reasons leading to premature withdrawal included AEs (7.7%) and voluntary withdrawal (4.9%). The proportion of subjects who withdrew due to an AE was greater in the TAK-491CLD treatment group (9.2%) compared with the TAK-491+HCTZ treatment group (6.2%).

Approximately 31% of subjects treated with TAK-491CLD had their study medication up-titrated to 40/25 mg due to uncontrolled BP, compared to 46% of subjects randomized to TAK-491+HCTZ who required up-titration.

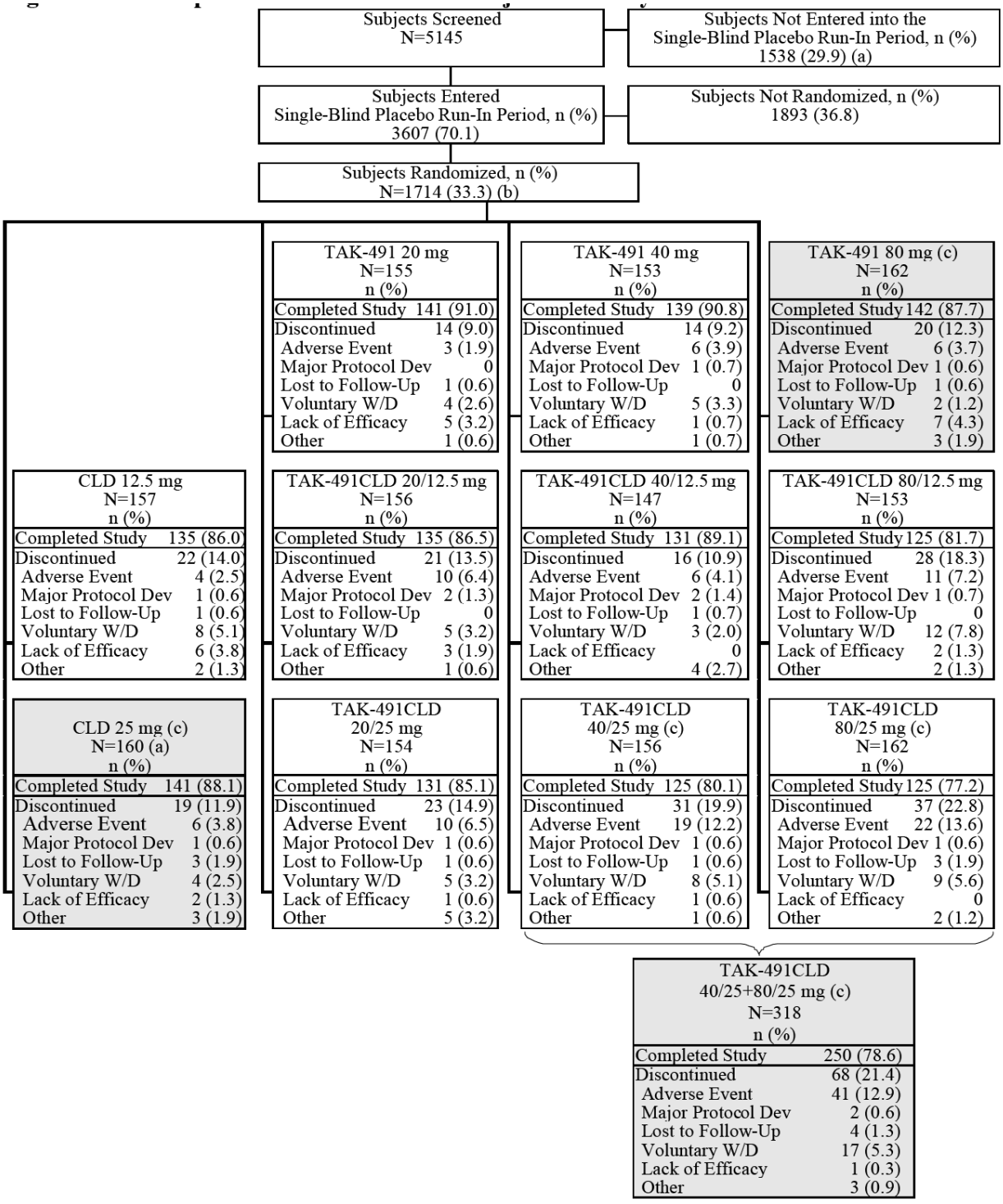
Study 301: 3,270 subjects were screened at 92 sites, 2,256 subjects entered the single-blind placebo run-in period, and 1,085 were randomized to treatment {729 to TAK-491CLD (372 to the 20/12.5→40/25 mg low-dose group, and 357 to the 40/12.5→80/25 mg high-dose group), and 356 patients to OLM/HCTZ 20/12.5→40/25 mg}.

Approximately 13% of subjects prematurely discontinued the study, including 15% and 14% in the TAK-491CLD low-dose and high-dose groups, respectively, and 9% in the OLM/HCTZ group. The most common reasons for premature withdrawal overall were AEs (5.6%) and voluntary withdrawal (2.9%). More subjects discontinued because of an AE in the TAK-491CLD high-dose group (8%) and TAK-491CLD low-dose group (5%) than in the OLM/HCTZ (3%) group.

Study 308 (Interim disposition): In the 120-Day PSUR (23-Jun-2011), 837 subjects were randomized (418 subjects to TAK-491CLD, and 419 subjects to OLM/HCTZ).

30.1% of subjects in the TAK-491CLD and 20.5% in the OLM/HCTZ treatment groups discontinued prematurely, the most common reasons being TEAEs and voluntary withdrawal, which were more frequent in the TAK-491CLD treatment group compared with the OLM/HCTZ treatment group (17.5% vs. 8.8% and 7.2% vs. 4.5%, respectively).

Figure 14 Disposition of randomized subjects in Study 302



Source: Sponsor's Figure 2.b in Summary of Clinical Efficacy. Dev=deviation, W/D=withdrawal.
(a) Includes Subject 3048/002, who was treated with double-blind study medication but not randomized.
(b) Excludes Subject 3048/002, who was treated with double-blind study medication but not randomized.
(c) Gray cells designate groups evaluated for the primary analysis in which pooled results from the TAK-491CLD 40/25 mg and TAK-491CLD 80/25 mg treatment groups (TAK-491CLD 40/25+80/25 mg pool) were compared to the highest monotherapy treatment groups (chlorthalidone 25 mg and TAK-491 80 mg).

Study 303: 2,933 subjects were screened at 130 sites in the US and Canada, 2,084 subjects entered the single-blind placebo Run-in Period, 1,071 subjects were randomized, and 892 (83.3%) subjects completed the study.

Of the 1,071 subjects randomized:

- 707 were randomized to TAK-491CLD:
  - 355 (33.1%) in the 40/25 mg titration group (20/12.5→40/12.5→40/25 mg) and
  - 352 (32.9%) in the 80/25 mg titration group (40/12.5→80/12.5→80/25 mg);
- 364 (34.0%) subjects were randomized to the OLM/HCTZ titration group (20/12.5→40/12.5→40/25 mg).

179 (16.7%) subjects prematurely discontinued (55 subjects [15.5%] and 77 subjects [21.9%] in the TAK-491CLD 40/25 and 80/25 mg titration groups, respectively, and 47 subjects [12.9%] in the OLM/HCTZ titration group). The most common reasons for withdrawal were AEs (105 subjects, 9.8%) and voluntary withdrawal (42 subjects, 3.9%). The percentage of subjects who discontinued treatment due to an AE was similar in the TAK-491CLD 40/25 mg titration group (28 subjects, 7.9%) and the OLM/HCTZ titration group (26 subjects, 7.1%), but higher in the TAK-491CLD 80/25 mg titration group (51 subjects, 14.5%).

Study 009: 1,786 subjects were screened, 1,344 subjects entered the single-blind placebo run-in period, and 551 subjects were randomized (184 to placebo plus CLD, 185 to TAK-491 40 mg plus CLD, and 182 to TAK-491 80 mg plus CLD). 495 (89.8%) subjects completed the double-blind period. 8.7% in CLD group, 8.6% in Tak-491 40 mg plus CLD group, and 13.2% (highest rate) in TAK-491 80 mg plus CLD group discontinued prematurely, the most common reasons being AEs (4.4%), voluntary withdrawal (1.8%), lost to follow up (1.1%) and other (1.1%).

Study 006: 1,039 subjects were screened at 39 sites in United States, Mexico, and Chile; 669 subjects entered the treatment phase.

Cohort 1: Of 362 subjects enrolled, 146 (40.3%) received TAK-491 alone and 216 (59.7%) received TAK-491 plus CLD 25 mg (with or without other non-ARB antihypertensive agents). 71.8% (260 subjects; 92 TAK-491 alone and 168 TAK-491 plus CLD) completed the study. 102 (28.2%) subjects discontinued: 37.0% (54/146) in subjects who received TAK-491 alone and 22.2% (48/216) in subjects who received TAK-491 plus CLD 25 mg.

Cohort 2: Of 307 subjects enrolled, 123 (40.1%) received TAK-491 alone and 184 (59.9%) received TAK-491 plus HCTZ (with or without other non-ARB antihypertensive agents). 66.1% (203 subjects; 69 TAK-491 alone, 134 TAK-491 plus HCTZ) completed the study. 104 (33.9%) subjects discontinued: 43.9% (54/123) in subjects who received TAK-491 alone and 27.2% (50/184) in subjects who received TAK-491 plus HCTZ.

Study 016:
During the open-label phase, 780 subjects were screened at 51 sites in United States,

Mexico, and Argentina, and 418 subjects entered the open-label phase and initiated treatment with TAK-491. 39.7% of subjects who entered the open-label phase were receiving other antihypertensive medications at Baseline. Of the 418 enrolled subjects, 299 (71.5%) completed the open-label phase and 119 subjects (28.5%) discontinued. The most frequent reasons for premature discontinuation from the open-label phase included voluntary withdrawal (8.9%), AEs (6.5%), and lost to follow-up (5.7%).

354 subjects were force-titrated to TAK-491 80 mg at Week 4, among which 239 subjects (68%) additionally received CLD during the open-label phase.

Sixty-four (15.3%) subjects were not force-titrated and remained on TAK-491 40 mg; of these, 15 (23.4%) subjects completed the study, and 49 (76.6%) subjects prematurely discontinued {reasons: protocol deviations (15 subjects); voluntary withdrawal (13 subjects); lost to follow-up (9 subjects); AEs (8 subjects); other (2 subjects [addition of third hypertensive drug and noncompliance]); lack of efficacy (1 subject); and investigator discretion (1 subject). Thirty of the premature withdrawals were prior to Week 4 (< Day 29), of which the main reasons were major protocol deviations (9 subjects) and AEs, voluntary withdrawal, and lost to follow up (6 subjects each).

During the double-blind reversal phase, 299 subjects were randomized at 48 sites: 148 to TAK-491 (at the final dose they received in the open-label phase) and 151 to placebo. All subjects continued taking CLD (and other antihypertensive medications, as applicable) at the doses taken during the open-label phase, independent of their randomized treatment group in the double-blind phase. 282 subjects (94.3%) completed the double-blind reversal phase, and 17 subjects (5.7%) prematurely discontinued (4.0% in the placebo group and 7.4% in the TAK-491 group). The most frequent reasons for premature discontinuation in the double-blind reversal phase included voluntary withdrawal (2.3%), AEs (1.3%), and lost to follow-up (1.0%).

6.1.4 Analysis of Primary Endpoint(s)

Primary efficacy endpoint analysis I: The following analysis of the primary efficacy endpoint pertains to the evaluation of the claim that the fixed-dose combination of TAK-491CLD was more effective than either component (TAK-491 or CLD monotherapy).

To evaluate the sponsor's claims that TAK-491CLD FDC is more effective compared with the respective monotherapies to (i) reduce BP, (ii) increase the likelihood of achieving target clinic SBP and clinic DBP (defined as <140 mmHg systolic and <90 mmHg diastolic), and (iii) allow a patient who experiences dose-limiting AEs on either component alone (e.g., hypokalemia with chlorthalidone) to achieve similar or greater BP reduction at a lower dose of that component, I reviewed the efficacy data in the factorial Study 302 as the primary clinical trial, evaluated the efficacy data in Studies 306 and 009 as supportive trials, and referred to the BP data in open label safety Studies 006 and 016 to determine if they also showed consistent results.

Study 302: The primary endpoint was the change from Baseline to Week 8 in trough SBP by ABPM. The protocol-specified primary analysis of this endpoint involved

comparison of pooled results from the 2 highest doses of the FDC vs. the highest doses of TAK-491 and CLD monotherapy. The sponsor's decision to pool TAK-491CLD 40/25 and 80/25 mg treatment groups was allegedly driven by results of Study 009 which showed that both of these dose combinations produced similar BP reduction; this approach also increased the statistical power for the primary and key secondary analyses. Analyses comparing each dose of TAK-491CLD to its respective components (cell-by-cell comparisons) were also reviewed.

Table 5 and Figure 15 show that the reductions in trough SBP by ABPM at Week 8 in all treatment groups were large enough to be *clinically significant*, and that the treatment differences (Table 5) between each TAK-491CLD FDC and its TAK-491 component (-10.9 to -17.0 mm Hg) or CLD component (-10.3 to -13.9 mm Hg) were also large and *statistically significant* (P<0.001).

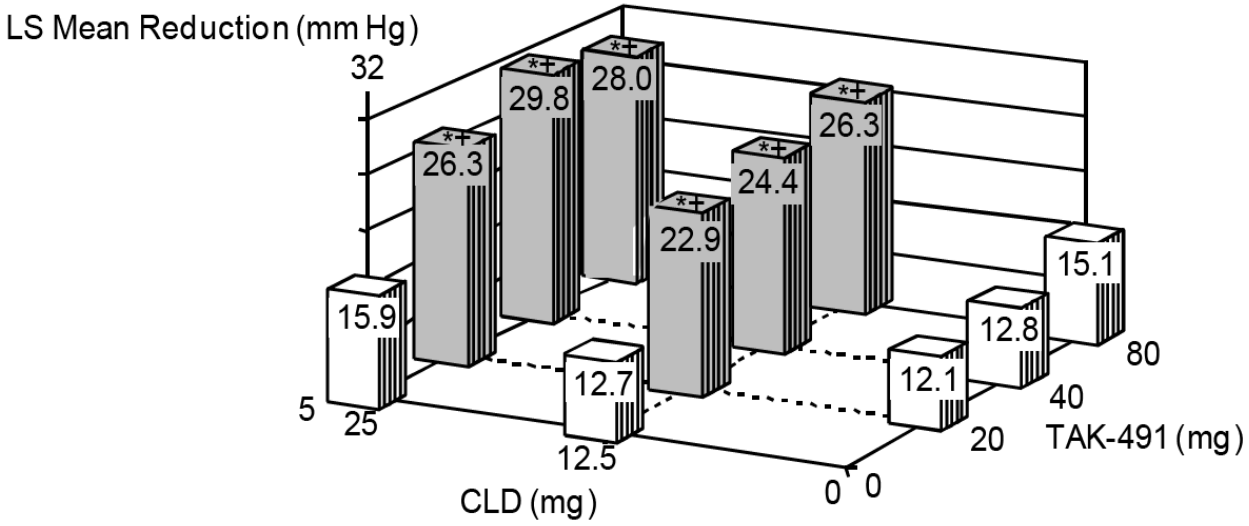
In the TAK-491CLD FDC treatment groups, incremental reductions were observed across the FDC dose range of 20/12.5, 40/12.5, and 80/12.5 mg (Figure 15); however, incremental reductions were observed only as the dose of TAK-491CLD increased from 20/25 mg to 40/25 mg (which produced the largest overall reduction in trough SBP by ABPM (29.8 mmHg) in this factorial study) with no additional reduction with the TAK-491CLD 80/25 mg dose compared with the 40/25 mg dose (Figure 15).

Table 5 Change from baseline in trough SBP by ABPM at Week 8 in Study 302

Trough SBP by ABPM (mmHg)				
		TAK-491 20 mg n=128	**TAK-491 40 mg n=131**	**TAK-491 80 mg** n=127
Baseline, LS Mean (SE)		151.0 (1.4)	153.3 (1.4)	151.1 (1.5)
LS Mean (SE) change from Baseline		-12.1 (1.2)	-12.8 (1.2)	-15.1 (1.2)
	CLD 12.5 mg n=130	**TAK-491CLD 20/12.5 mg n=127**	**TAK-491CLD 40/12.5 mg n=117**	**TAK-491CLD 80/12.5 mg n=110**
Baseline, LS Mean (SE)	152.3 (1.4)	152.4 (1.5)	153.6 (1.5)	151.6 (1.6)
LS Mean (SE) change from Baseline	-12.7 (1.2)	-22.9 (1.2)	-24.4 (1.2)	-26.3 (1.3)
LS mean difference (95% CI)				
TAK-491CLD vs. CLD component	---	-10.3* (-13.6, -7.0)	-11.8* (-15.1, -8.4)	-13.7* (-17.1, -10.3)
TAK-491CLD vs TAK-491 component	---	-10.9* (-14.2, -7.6)	-11.6* (-15.0, -8.3)	-11.2* (-14.7, -7.8)
	CLD 25 mg n=134	**TAK-491CLD 20/25 mg n=118**	**TAK-491CLD 40/25 mg n=114**	**TAK-491CLD 80/25 mg n=114**
Baseline, LS Mean (SE)	151.2 (1.4)	151.8 (1.5)	150.1 (1.5)	154.3 (1.5)
LS Mean (SE) change from Baseline	-15.9 (1.2)	-26.3 (1.2)	-29.8 (1.3)	-28.0 (1.3)
LS mean difference (95% CI)				
TAK-491CLD vs. CLD component	---	-10.4* (-13.7, -7.0)	-13.9* (-17.3, -10.6)	-12.0* (-15.4, -8.7)
TAK-491CLD vs TAK-491 component	---	-14.2* (-17.6, -10.9)	-17.0* (-20.4, -13.6)	-12.8* (-16.2, -9.4)

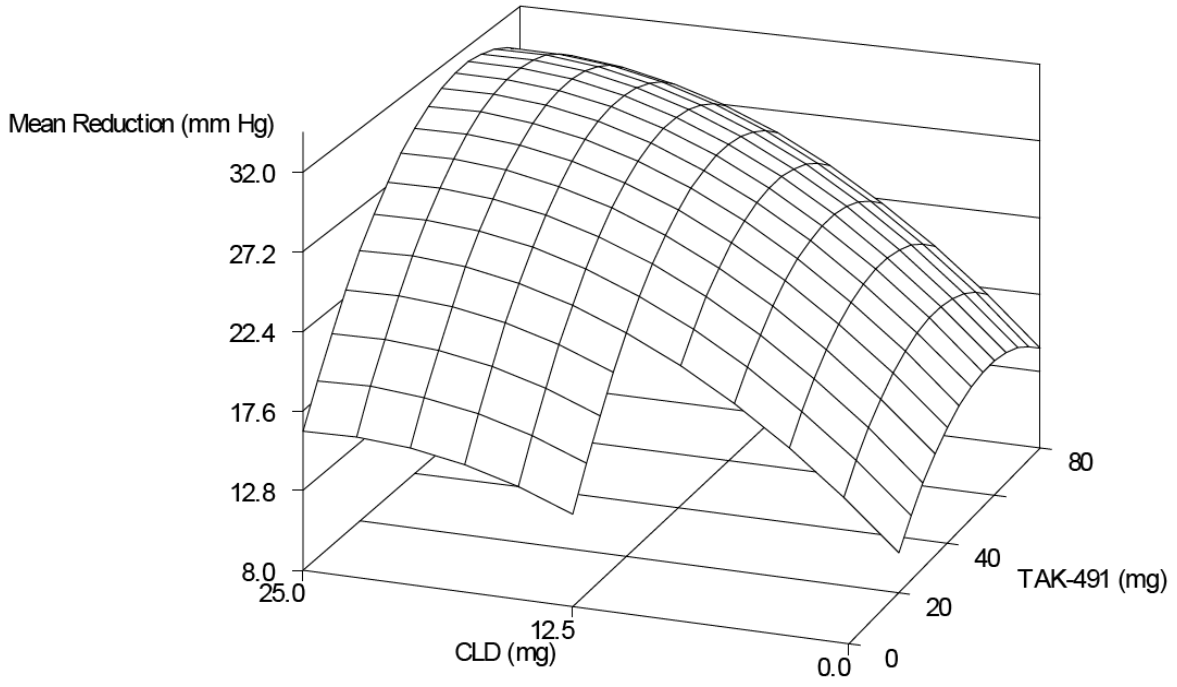
LS mean differences are between each dose of TAK-491CLD and individual chlorthalidone or TAK-491 component.
*P<0.001 for the comparison between TAK-491CLD and the individual chlorthalidone or TAK-491 component.

Figure 15 Change from baseline in trough SBP by ABPM at Week 8 in Study 302



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

Figure 16 Response surface plot for change from baseline in trough SBP by ABPM at Week 8 in all treatment groups in Study 302



Source: Sponsor's Figure 11.m in CSR Study 302.

A response surface method (Figure 16) was used to obtain dose response information. Both the linear and quadratic response surface models were tested. The response surface analysis suggests that the reduction in trough SBP by ABPM from baseline to Week 8 for the FDC increases as the dose of TAK-491 increases (P<0.001) or as the

dose of CLD increases (P<0.001); this increase in the reduction in trough SBP by ABPM for the FDC reached plateau towards the higher end of the study FDC dose ranges for TAK-491 and CLD. The data suggest a curvature in the response surface with a significant quadratic term of TAK-491 dose (P<0.001) as well as a significant quadratic term of the CLD dose (P<0.001). The response surface plot (Figure 16) suggests that the maximum mean reduction is predicted toward the high end of the FDC doses (between 40 to 80 mg of TAK-491, and close to 25 mg of CLD).

Lack of fit tests indicated that the linear model was inadequate (P-value< 0.001) and that the quadratic model was adequate (P-value=0.247). The final response surface derived from the quadratic models is obtained by the following formula by the sponsor:

Δ= -2.50628+ {-0.47909× **X**} + {-1.20558× **Y**} + {0.00416× $\mathbf{X^2}$} + {0.02608× $\mathbf{Y^2}$} + {-0.00058× **XY**}
Where Δ = Mean Change from Baseline to Week 8 in trough SBP (mmHg) by ABPM,
X = TAK-491 dose, and **Y** = CLD dose.

I substituted X and Y in the above quadratic formula with the TAK-491 and CLD doses in the factorial trial dose groups, and obtained the *calculated values* of the mean change from baseline to Week 8 in trough SBP by ABPM as shown in column #3 in Table 6. My calculated values of the mean change from baseline to Week 8 in trough SBP by ABPM are not very different from the *observed values* shown in Figure 15 and Table 5.

Table 6 Comparison of observed and calculated values of mean change from baseline to Week 8 in trough SBP (mmHg) by ABPM

X = TAK-491 dose	Y = CLD dose	Calculated Δ	Observed Δ
80	25	29.2	28.0
40	25	29.4	29.8
20	25	24.6	26.3
80	12.5	25.8	26.3
40	12.5	26.3	24.4
20	12.5	21.6	22.9
80	-	14.2	15.1
40	-	15.0	12.8
20	-	10.4	12.1
-	25	16.3	15.9
-	12.5	13.5	12.7

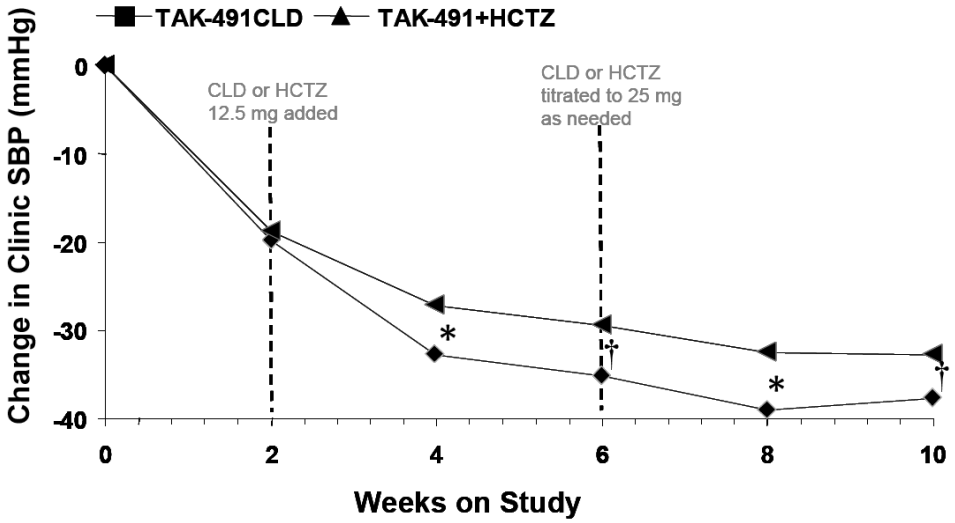
Δ = Mean Change from Baseline to Week 8 in trough SBP (mmHg) by ABPM; TAK-491CLD doses intended for marketing are highlighted.

Study 306

Figure 17 shows the change from baseline in clinic SBP at all visits in this study. Large reductions in clinic SBP were observed by Week 2 of the single-blind period after treatment with **TAK-491 40 mg monotherapy**. The BP reductions were similar in both treatment groups.

Beginning at Week 4, after 2 weeks of treatment with either TAK-491CLD 40/12.5 mg or TAK-491 40 mg+HCTZ 12.5 mg, further incremental reductions in clinic SBP were observed in both groups relative to TAK-491 monotherapy.

Figure 17 Change from baseline in SBP at each visit in Study 306



Source: Study 306 CSR Figure 15.2.1.4.2. All subjects received TAK-491 40 mg. CLD 12.5 mg or HCTZ 12.5 mg was added after Week 2. CLD and HCTZ were titrated from 12.5 mg to 25 mg for subjects who had not achieved target SBP and DBP after Week 6. *P< 0.05 level. †Significant difference at the 0.05 level by step-wise analysis.

Table 7 Change from baseline in clinic SBP (mmHg) at each visit in Study 306

Study Visit	Treatment Group	
	TAK-491CLD 40/12.5 →40/25 mg N=302	**TAK-491+HCTZ 40+12.5 →40+25 mg N=303**
Baseline (a)		
n	295	292
LS mean (SE)	164.7 (0.6)	164.4 (0.6)
P-value	0.707	--
Week 4		
n	292	289
LS mean (SE)	**-32.9 (0.9)**	**-27.2 (0.9)**
LS mean treatment difference (b)	-5.7	--
(95% CI)	(-8.3, -3.2)	--
P-value	**<0.001***	--
Week 6: Primary Endpoint (b)		
n	295	292
LS mean (SE)	**-35.1 (1.0)**	**-29.5 (1.0)**
LS mean treatment difference (b)	-5.6	--
(95% CI)	(-8.3, -2.9)	--
P-value	**<0.001†**	--
Week 8:		
n	295	292
LS mean (SE)	**-39.0 (0.9)**	**-32.5 (0.9)**
LS mean treatment difference (b)	-6.4	--
(95% CI)	(-9.0, -3.9)	--
P-value	**<0.001***	--
Week 10		
n	295	292
LS mean (SE)	**-37.8 (0.9)**	**-32.8 (0.9)**
LS mean treatment difference (b)	-5.0	--
(95% CI)	(-7.5, -2.5)	--
P-value	**<0.001†**	--

Note: Subjects took TAK-491 40 mg throughout the study, with addition of 12.5 mg chlorthalidone or HCTZ at Week 2 and then, if needed, titration to 25 mg chlorthalidone or HCTZ, if needed, at Week 6 for subjects with uncontrolled BP.
*Significant difference (P<0.05). † Significant difference (P< 0.05) within the framework of the step-wise analysis.
(a) Baseline value is the last observation before the first dose of active single-blind study drug.
(b) LS mean treatment difference=LS mean change of the TAK-491CLD group – LS mean change of TAK-491+HCTZ group. (Source: Study 306 CSR Table 15.2.1.1.2)

In the TAK-491CLD group, a statistically significant reduction (-35.1 mmHg) from baseline in clinic SBP was observed at Week 6 after treatment with TAK-491CLD 40mg/12.5 mg. At Week 10, 8 weeks after treatment with TAK-491CLD, the decrease from baseline in clinic SBP improved further by -37.8 mmHg. This finding supports the finding in the pivotal factorial trial (Study 302) that addition of CLD to TAK-491 increases the reduction in clinic SBP in a dose-dependent manner.

For the primary endpoint of the change in clinic SBP from Baseline to Week 6, TAK-491CLD led to statistically significantly greater reductions in clinic SBP (P<0.001) compared withTAK-491+HCTZ, with a treatment difference and corresponding 95% CI of -5.6 (-8.3, -2.9) mmHg (Table 7).

The reductions in clinic SBP from baseline were statistically significantly greater in the TAK-491CLD treatment group compared with the TAK-491+HCTZ group, and this finding was maintained to Week 8. Qualitatively similar results were observed for change from baseline in clinic DBP.

TAK-491CLD also led to significantly (P<0.001) greater reductions in mean clinic SBP at Week 10 compared with TAK-491+HCTZ, with a treatment difference and 95% CI of -5.0 (-7.5, -2.5) mm Hg. This occurred despite a larger proportion of subjects having the study drug up-titrated in the TAK-491+HCTZ treatment group (46% of subjects who received TAK-491+HCTZ 40+12.5 mg did not achieve SBP and DBP targets by Week 6, and required to be up-titrated to the higher dose of 40+25 mg). In the TAK-491CLD treatment group, less (31%) subjects required titration from 40/12.5 to 40/25 mg.

Study 009:
At Baseline, the 24-hour mean SBP was similar in the CLD monotherapy and TAK-491 plus CLD co-administration groups (Table 8).

Table 8 Change from baseline to Week 6 in 24-hour Mean SBP by ABPM in Study 009

	Treatment Group			Overall P-value
	Placebo+ CLD 25mg	**TAK491 40mg+ CLD 25mg**	**TAK491 80mg+CLD 25mg**	
N	181	184	182	
Baseline BP Mean (SE)	153.4 (0.8)	152.0 (0.8)	(b) (4)	
Week 6				
LS mean change (SE)	-15.9 (1.0)	-31.7 (1.0)		<0.001
LS mean difference (95% CI)		-15.9 (-18.5, -13.2)		
P value vs. Placebo + CLD		<0.001		
Week 6 (Sensitivity analysis)				
LS mean difference (95% CI)		-15.9 (-18.6, -13.1)		
P value vs. Placebo + CLD		<0.001		

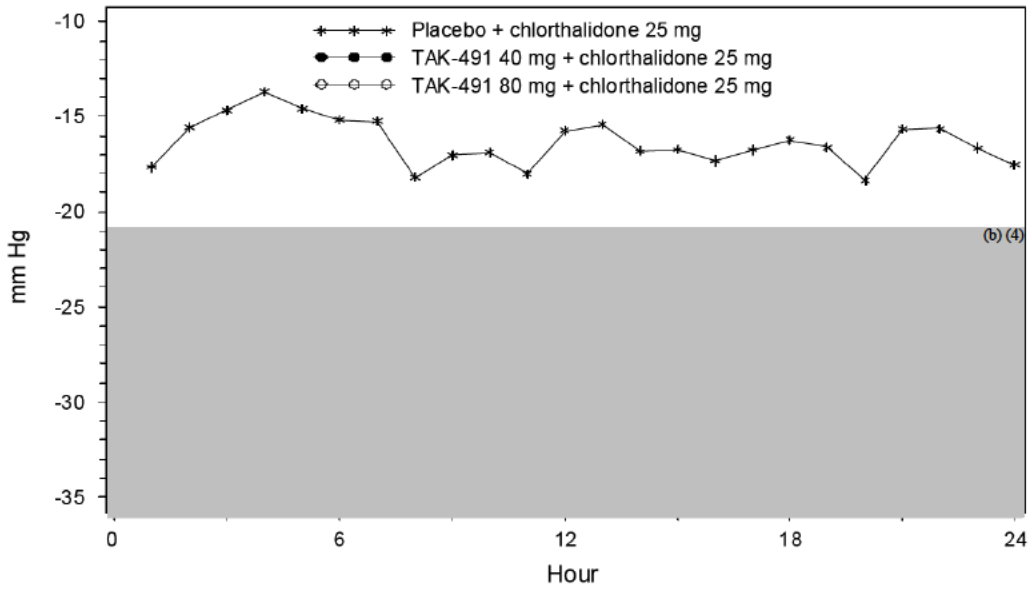
* Significance difference at 0.05 level. Source: Sponsor's Table 15.2.1.1.2 in CSR for Study 009.
(a) LS mean difference=LS mean change of each active treatment (TAK-491 plus chlorthalidone co-administration group) – LS mean change of placebo group (chlorthalidone monotherapy group).

After the 6-week treatment period, a statistically significant reduction from baseline in the 24-hr mean SBP was observed across groups (P<0.001 for overall comparison). The changes observed in the TAK-491 40 mg and 80 mg plus CLD co-administration groups were similar in magnitude (-31.7 (b) (4) mmHg, respectively), and greater than (almost twice) that in the CLD monotherapy group (-15.9 mmHg). Each co-

administration group was associated with an incremental statistically significant (P<0.001) reduction in the 24-hr mean SBP by 15.9 mmHg (95% CI: -18.54, -13.19) and 15.5 mmHg (95% CI: -18.13, -12.76), relative to the CLD monotherapy group.

Figure 18 shows that consistent changes from baseline in mean SBP were generally maintained in all groups during the 24-hour interval following study drug administration, with greater reductions observed with TAK-491 plus CLD co-administration groups throughout the interval.

Figure 18 Change from baseline to Week 6 in Mean SBP by ABPM for 0 to 24 hour – Study 009



Source: Study 009 CSR Figure 15.2.1.5.3.

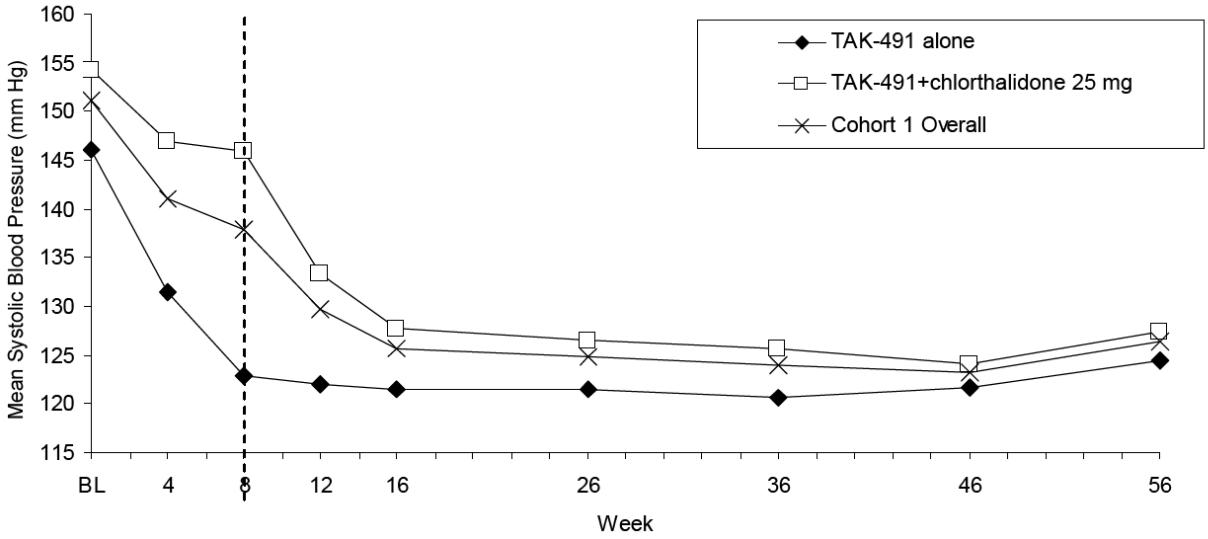
Study 006

For both Cohort 1 (Figure 19) and Cohort 2 (Figure 20), the overall reduction in clinic SBP was -10.1 to -14.4 mmHg after 4 weeks of treatment with TAK-491 40 mg; the reduction in clinic SBP increased to -13.1 to (b) (4) mmHg after an additional 4 weeks of treatment with 80 mg (but before add-on CLD or HCTZ was initiated). The reduction in SBP observed at these visits was greater for subjects who continued to receive TAK-491 alone compared with those who required add-on CLD or HCTZ.

I note that the mean baseline SBP was higher for the patients who required add-on CLD and HCTZ. In these subjects, the response to TAK-491 monotherapy was much less at 2 weeks (40 mg) and, there was practically no further reduction at 8 weeks (after up-titration to 80 mg TAK). Addition of 12.5 mg CLD at Week 8 produced a reduction in clinic SBP at week 12, and further up-titration with 25 mg CLD produce a further small incremental reduction in clinic SBP at week 16 which was maintained to Week 56.

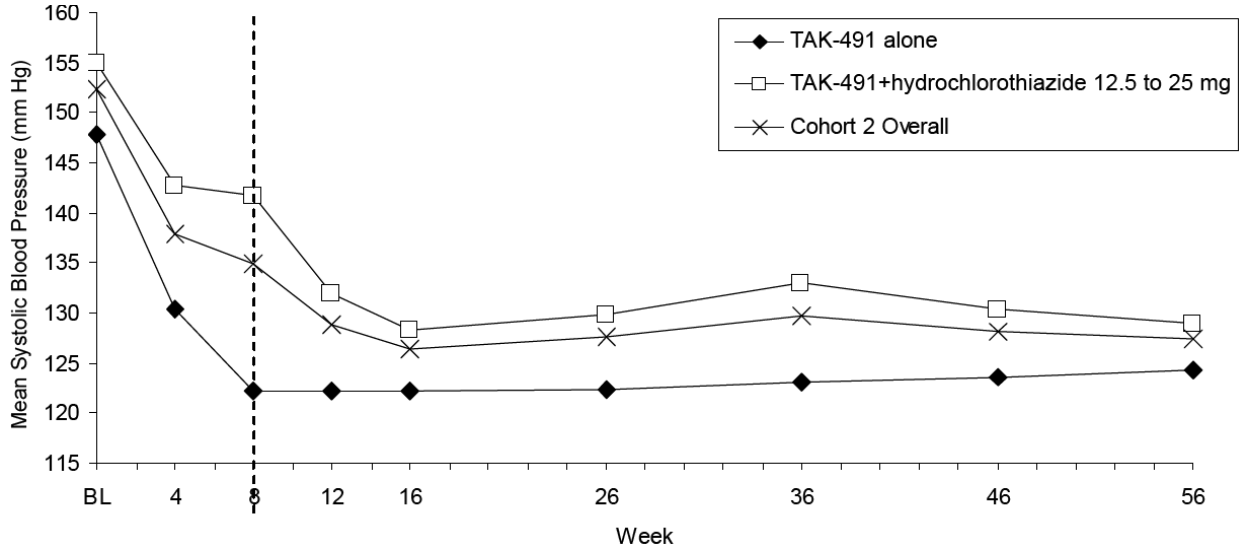
For subjects who continued to receive TAK-491 alone, the change in clinic SBP observed at Week 8 was maintained throughout the study to Week 56.

Figure 19 Study 006 - Mean clinic sitting SBP for Cohort 1 by Study Visit



Source: Study 006 CSR Figure 11.a The dashed line at Week 8 represents the first visit at which subjects in Cohort 1 could additionally receive CLD and subjects in Cohort 2 could receive HCTZ.

Figure 20 Study 006 - Mean clinic sitting SBP for Cohort 2 by Study Visit



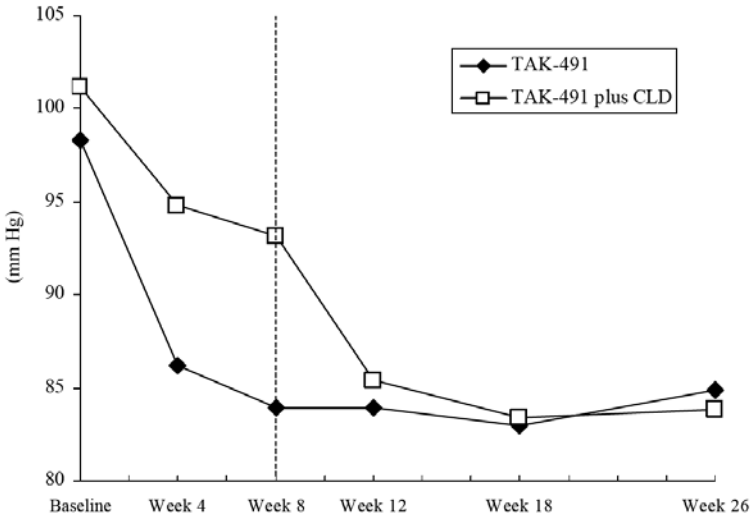
Source: Study 006 CSR Figure 11.b. The dashed line at Week 8 represents the first visit at which subjects in Cohort 1 could additionally receive CLD and subjects in Cohort 2 could receive HCTZ.

When clinic SBP baseline data were analyzed by cohort, no statistically significant difference was observed between Cohort 1 and Cohort 2. However, interpretation of comparisons of BP changes among subjects who received (i) TAK-491 alone, (ii) TAK-491 plus CLD, and (iii) TAK-491 plus HCTZ is limited by the open-label design of the study, lack of randomization, treat-to-target-BP approach, differences in enrollment time of the 2 cohorts, and variations in length of exposure to study drugs.

Study 016:

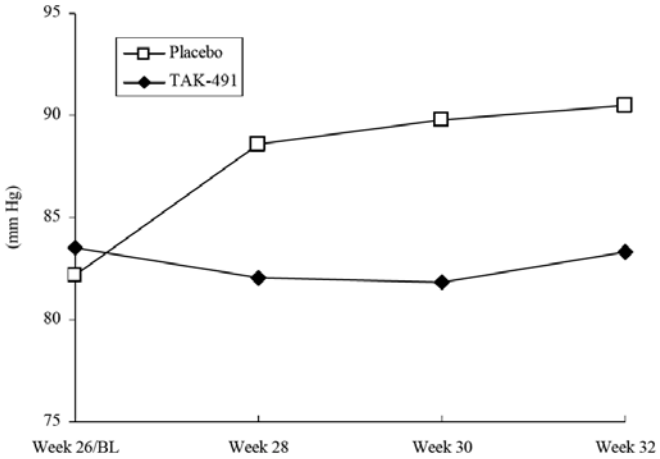
Mean clinic DBP at open-label baseline was higher among subjects who received CLD plus TAK-491 compared to those who received TAK-491 alone (101.20 mmHg and 98.29 mmHg, respectively) (Figure 21).

Figure 21 Study 016 – Mean trough clinic sitting DBP in open-label phase



These subjects with higher baseline DBP had small reductions in clinic DBP at Week 4 and Week 8 compared to subjects with lower baseline DBP who responded with larger reductions in DBP when treated with TAK-491 alone up to Week 8. Following addition of CLD at Week 8 to subjects with high mean baseline DBP, the mean clinic DBP was similar at subsequent visits (i.e., Weeks 12, 18, and 26) between subjects who received TAK-491 alone and those who additionally received CLD. 51 subjects (12.2%) initiated use of other concomitant antihypertensive medication during the open-label phase.

Figure 22 Study 016 – Mean trough clinic sitting DBP in double-blind reversal phase



At double-blind reversal phase baseline (Figure 22), the mean clinic DBP was similar in both treatment groups (82.25 mm Hg and 83.50 mm Hg). At Week 26, following the randomization into the double-blind reversal phase, when subjects either (i) continued on TAK-491 (at the dose they were on) plus other antihypertensive drugs including CLD or (ii) received placebo in addition to their current other antihypertensive medication, the mean DBP was maintained in subjects who received TAK-491 from Week 28 through Week 32, whereas in subjects randomized to placebo, the mean DBP increased demonstrating a loss of efficacy after discontinuation of TAK-491. This increase in DBP in the placebo group was mostly observed within the first 2 weeks of the double-blind phase. The LS mean changes in clinic DBP from Double-Blind Baseline to the Final Visit were +7.92 and +0.14 mmHg in the placebo and TAK-491 treatment groups, respectively ($p<0.001$).

Reviewer's comments: The efficacy results in the clinical trials above (Studies 302, 306, 009, 006 and 016) support the claim that TAK-491CLD is more effective to reduce BP than monotherapy with either component (TAK-491 or CLD).

Primary efficacy endpoint analysis II: The following analysis of the primary efficacy endpoint pertains to the evaluation of the claim that fixed-dose combination of TAK-491CLD is more effective than the marketed combination product OLM/HCTZ.

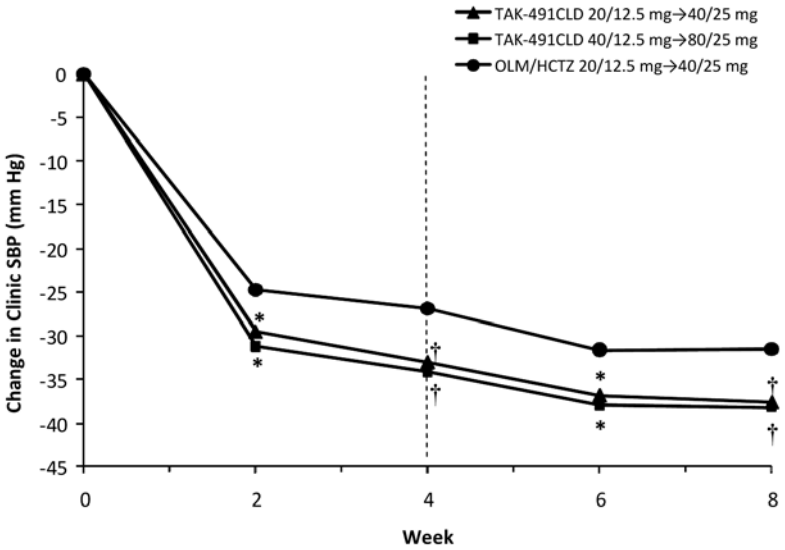
To evaluate the claim of superiority of BP reduction effect (and AEs) of the FDC of TAK-491CLD compared to that of the marketed OLM/HCTZ combination product, I reviewed the efficacy data in Study 301 as the primary clinical trial, evaluated the efficacy data in Study 303 as the supportive trial, and referred to the efficacy data in the ongoing open label safety Study 308 to determine consistency of the efficacy results (Please also see the review Section 5.2 – Review Strategy and Figure 1).

Study 301:
As shown in Figure 23, most of the reduction in clinic BP was observed by Week 2 in each treatment group; incremental BP reduction was observed within each group from Week 4 to Week 6, consistent with titration to higher doses in uncontrolled subjects.

For the primary efficacy endpoint of change in clinic SBP from baseline to Week 8, both TAK-491CLD treatment groups led to statistically significantly greater reductions compared with OLM/HCTZ within the stepwise testing scheme (Table 9).

In Study 301, approximately one-third of subjects treated with TAK-491CLD had study medication up-titrated to 40/25 or 80/25 mg due to uncontrolled BP, whereas 52% of subjects randomized to OLM/HCTZ required titration. The statistically significant differences observed at Week 8 occurred despite a higher proportion of subjects being titrated at Week 4 for inadequate BP control in the OLM/HCTZ treatment group (52%) compared with the TAK-491CLD low-dose (38%) and high-dose (35%) groups.

Figure 23 Change from baseline in clinic SBP at each visit in Study 301



Source: Study 301 CSR Table 15.2.1.1.2. Note: At Week 4, subjects with uncontrolled blood pressure were titrated to the higher dose (shown with dashed line). *Significant difference vs. OLM/HCTZ at the 0.05 level.
† Significant difference at the 0.05 level within the framework of the step-wise analysis.

Table 9 Change from baseline in clinic SBP (mmHg) at Weeks 4 and 8 in Study 301

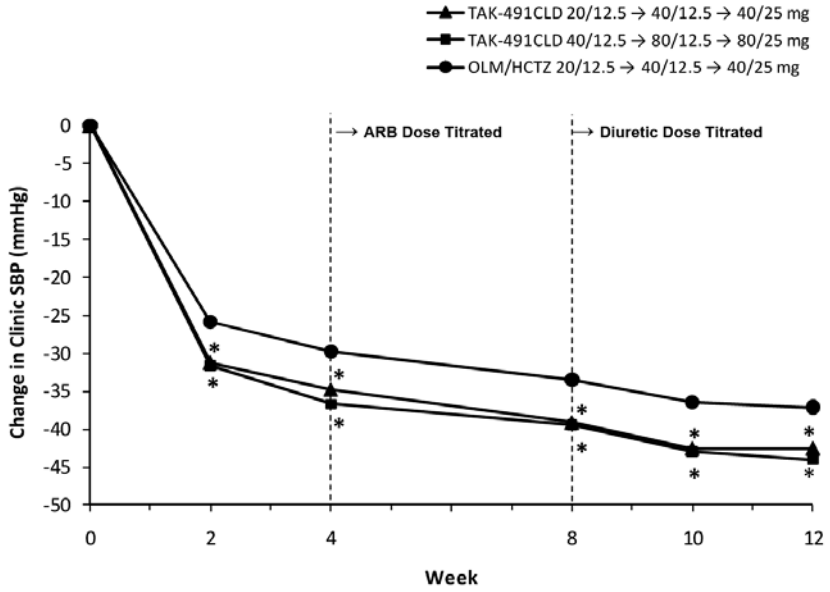
Study Visit	TAK-491CLD		OLM/HCTZ
	20/12.5 →40/25 mg N=372	**40/12.5 →80/25 mg N=357**	**20/12.5→40/25 mg N=356**
Baseline (a)			
n	363	350	353
LS mean (SE)	165.2 (0.6)	164.8 (0.6)	164.7 (0.6)
P-value	0.503	0.870	--
Week 2			
n	343	334	345
LS mean change (SE)	**-29.5 (0.9)**	**-31.2 (0.9)**	**-24.7 (0.9)**
LS mean treatment difference (b)	-4.8	-6.5	--
(95% CI)	(-7.2, -2.4)	(-8.9, -4.1)	--
P-value	<0.001*	<0.001*	--
Week 4: Key Secondary Endpoint			
n	360	347	352
LS mean change (SE)	**-33.9 (0.9)**	**-34.1 (0.9)**	**-26.9 (0.9)**
LS mean treatment difference (b)	-6.1	-7.2	--
(95% CI)	(-8.5, -3.7)	(-9.6, -4.8)	--
P-value	<0.001†	<0.001†	--
Week 6			
n	362	350	353
LS mean change (SE)	**-36.8 (0.8)**	**-37.9 (0.8)**	**-31.6 (0.8)**
LS mean treatment difference (b)	-5.2	-6.3	--
(95% CI)	(-7.4, -3.0)	(-8.5, -4.1)	--
P-value	<0.001*	<0.001*	--
Week 8:			
n	363	350	353
LS mean change (SE)	**-37.6 (0.8)**	**-38.2 (0.9)**	**-31.5 (0.8)**
LS mean treatment difference (b)	-6.1	-6.7	--
(95% CI)	(-8.4, -3.8)	(-9.1, -4.4)	--
P-value	<0.001†	<0.001†	--

Source: Study 301 CSR Table 15.2.1.1.2. At Week 4, subjects with uncontrolled BP were titrated to the higher dose.
*Significant difference at 0.05 level. †Significant difference at 0.05 level within the framework of step-wise analysis.
(a) Baseline value is the last observation before the first dose of double-blind study drug.
(b) LS mean treatment difference=LS mean change of each TAK-491CLD treatment group – LS mean change of OLM/HCTZ treatment group.

Study 303:

The primary efficacy endpoint of change in mean clinic SBP from Baseline to Week 12 and at each visit is shown in Figure 24. Statistically significantly larger reductions from Baseline to Week 12 in clinic SBP were observed for both the TAK-491CLD 40/25 and 80/25 mg titration groups (-42.5 and -44.0 mmHg, respectively) compared with the OLM/HCTZ titration group (-37.1 mmHg). The largest part of the BP reduction effect of TAK-491CLD or OLM/HCTZ was observed at Week 2; further incremental reductions continued after the Week 4 and Week 8 titrations. Plateau or near-plateau of BP reduction was observed between Weeks 10 and 12 for all treatment groups.

Figure 24 Change from baseline in clinic SBP at each study visit in Study 303



Source: Study 303 CSR Table 15.2.1.1.2

In Study 303, subjects with moderate to severe hypertension treated for 12 weeks by forced-titration with TAK-491CLD 40/25 mg (20/12.5→40/12.5→40/25 mg), TAK-491 CLD 80/25 mg (40/12.5→80/12.5→80/25 mg), or OLM/HCTZ (20/12.5→40/12.5→40/25 mg), showed the following findings:

- For the primary efficacy endpoint of change from Baseline to Week 12 in clinic SBP, TAK-491CLD 40/25 and 80/25 mg titration groups reduced mean SBP statistically significantly more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:
  – TAK-491CLD 40/25 mg titration group: -5.3 (CI: -7.6, -3.1) mmHg (P<0.001).
  – TAK-491CLD 80/25 mg titration group: -6.9 (CI: -9.2, -4.6) mmHg (P<0.001).
- For the secondary efficacy endpoint of change from Baseline to Week 4 in clinic SBP, at which time all subjects had received 4 weeks of treatment with the initial dose of study drug in each treatment group, TAK-491CLD 40/25 and 80/25 mg titration groups reduced mean SBP statistically significantly more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:

– TAK-491CLD 40/25 mg titration group: -5.0 (CI: -7.1, -2.9) mmHg (P<0.001).
– TAK-491CLD 80/25 mg titration group: -7.0 (CI: -9.2, -4.8) mmHg (P<0.001).

- For the secondary efficacy endpoint of change from Baseline to Week 8 in clinic SBP, at which time all subjects had received 4 weeks of treatment with the initial dose of study drug and 4 weeks of treatment with the first forced-titration dose of study drug (TAK-491CLD 40/12.5 mg, TAK-491CLD 80/12.5 mg, or OLM/HCTZ 40/12.5 mg), TAK-491CLD titration reduced the mean SBP statistically significantly more than OLM/HCTZ titration. Treatment differences (95% CIs) were:
  – TAK-491CLD 40/25 mg titration group: -5.6 (CI: -7.8, -3.5) mmHg (P<0.001).
  – TAK-491CLD 80/25 mg titration group: -5.9 (CI: -8.0, -3.7) mmHg (P<0.001).
- Consistent with the primary endpoint analysis, both TAK-491CLD titration groups reduced the clinic DBP statistically significantly more at each visit than the OLM/HCTZ titration group.
- Both TAK-491CLD titration groups had statistically significant larger reductions in the ambulatory SBP and DBP parameters (trough [22- to 24-hours after dosing], daytime [6 AM-10 PM], nighttime [12 AM-6 AM], 0- to 12-hour, and 24-hour) than the OLM/HCTZ titration group at Week 12.
- Statistically significant or numerically greater percentages of subjects achieved the BP responder criteria and absolute BP targets in the TAK-491CLD 40/25 and 80/25 mg titration groups compared with the OLM/HCTZ titration group.
- In each subgroup, treatment with TAK-491CLD led to large, clinically significant reductions in all BP parameters with minimal heterogeneity, and for most of the subgroups, treatment with either TAK-491CLD 40/25 or 80/25 mg titration led to numerically greater or statistically significant decreases in BP compared with titration with OLM/HCTZ.

Study 308 (Interim efficacy results):
The primary and secondary endpoints of this long-term safety study were safety related; clinic SBP and DBP were measured at each visit to evaluate BP response and to determine the need for titration due to uncontrolled BP. Changes in BP were also summarized for the following subgroups in Study-308: race (Black, non-Black), baseline clinic DBP, and region (US, non-US).

The presentation of interim efficacy data is focused on the change from baseline to Week 32, as a substantial number of subjects (173 [43.1%] in the TAK-491CLD treatment group and 203 [50.4%] in the OLM/HCTZ treatment group) had BP data at that visit at the time of the interim data cut.

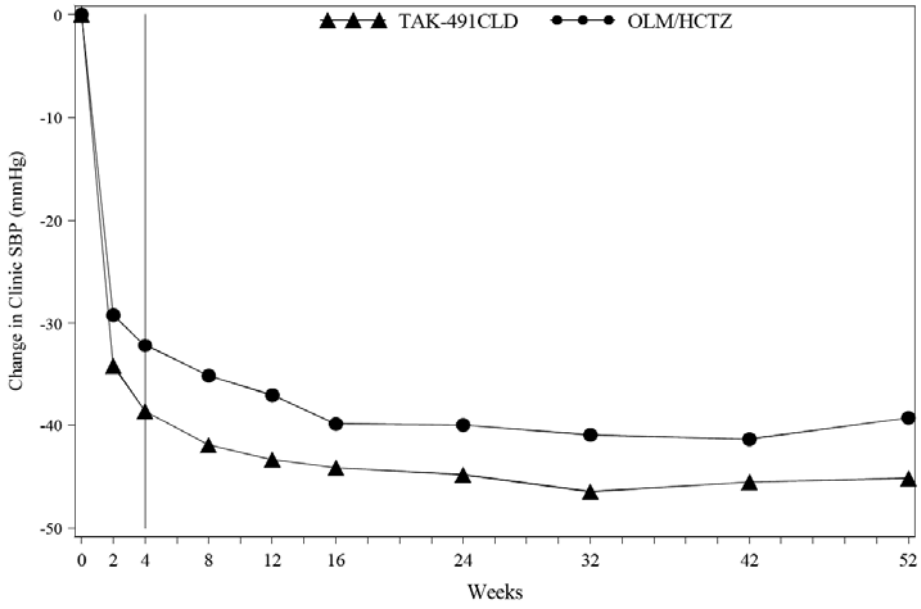
Table 10 shows the cumulative percentage of titration in each treatment group. More subjects in the OLM/HCTZ treatment group (42.9%) required at least 1 dose titration during the study compared with the TAK-491CLD treatment group (26.9%) due to uncontrolled blood pressure. The titration regimen for subjects in the OLM/HCTZ treatment group varied in Europe and in the United States due to the available dose strengths in Europe at the time the study was initiated.

Table 10 Cumulative percentage of dose titrations in Study 308

	Number of subjects (%)	
	TAK-491CLD N=401	**OLM/HCTZ N=403**
Initial dose (a)	401 (100.0)	403 (100.0)
1st titration (b)	108 (26.9)	173 (42.9
2nd titration (c)	51 (12.7)	94 (23.3)
3rd titration (d)	16 (4.0)	33 (8.2)

Source: Study 308 CSR Table 15.1.15.
(a) Initial dose for TAK-491CLD: 40/12.5 mg; for OLM/HCTZ: 20/12.5 mg.
(b) 1st titration for TAK-491CLD: 80/12.5 mg; for OLM/HCTZ in US: 40/12.5 mg; for OLM/HCTZ in Europe: 20/25 mg.
(c) 2nd titration for TAK-491CLD: 80/25 mg: for OLM/HCTZ in US: 40/25 mg; for OLM/HCTZ in Europe: 20/25 mg + other antihypertensive.
(d) 3rd titration for TAK-491CLD: 80/25 mg + other antihypertensive; for OLM/HCTZ in US: 40/25 mg + other antihypertensive; for OLM/HCTZ in Europe: no additional titration allowed.

Figure 25 Mean change from baseline in clinic SBP (mmHg) at each study visit in Study 308



Number of Subjects

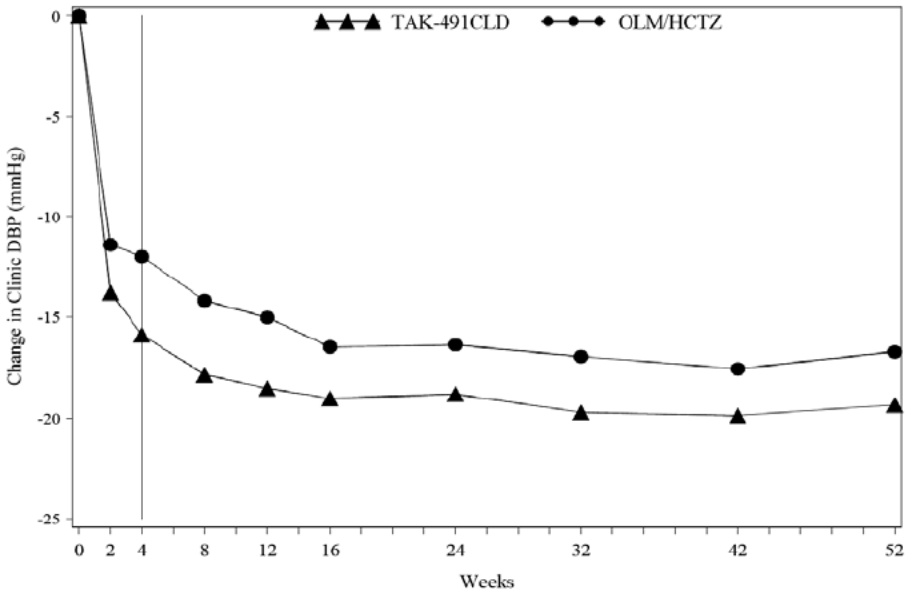
TAK-491CLD	418	405	400	371	359	343	312	266	199	169
OLM/HCTZ	419	413	398	386	376	372	355	304	236	197

Source: 120-Day PSUR Figure 7.4.5.1. Vertical line at Week 4 denotes first possible titration.

At baseline, the mean clinic SBP was similar in the TAK-491CLD and OLM/HCTZ treatment groups (168.2 mm Hg and 167.7 mmHg, respectively). At each post baseline visit, the mean SBP decreased in both treatment groups (Figure 25). The reductions in SBP at Weeks 2 and 4, before titration was allowed, were greater in the TAK-491CLD group than the OLM/HCTZ group. After Week 4, incremental reductions in BP continued in both treatment groups at each study visit; greater reductions in SBP were achieved in the TAK-491CLD treatment group compared with the OLM/HCTZ treatment group at each visit, despite the ability to titrate the study drug as needed to achieve the target BP. The mean (SD) reduction from baseline in clinic SBP at Week 52 was 42.8 (14.5) mmHg in the TAK-491CLD treatment group and 38.2 (15.3) mmHg in the OLM/HCTZ treatment group.

As with clinic SBP, reductions from baseline in the mean (SD) clinic DBP at Week 52 (Figure 26) were also greater in the TAK-491CLD group (18.7 (9.3) mmHg) than the OLM/HCTZ group (15.9 (9.8) mmHg).

Figure 26 Mean change from baseline in clinic DBP (mmHg) at each study visit in Study 308



Number of Subjects										
TAK-491CLD	418	405	400	371	359	343	312	266	199	169
OLM/HCTZ	419	413	398	386	376	372	355	304	236	197

Source: 120-Day PSUR Figure 7.4.5.2. Vertical line at Week 4 denotes first possible titration.

Reviewer's comments: *The efficacy results in the clinical trials above (Studies 301, 303 and 308) support the claim that TAK-491CLD has a superior BP reduction effect compared with the OLM/HCTZ combination drug product).*

6.1.5 Analysis of Secondary Endpoints(s)

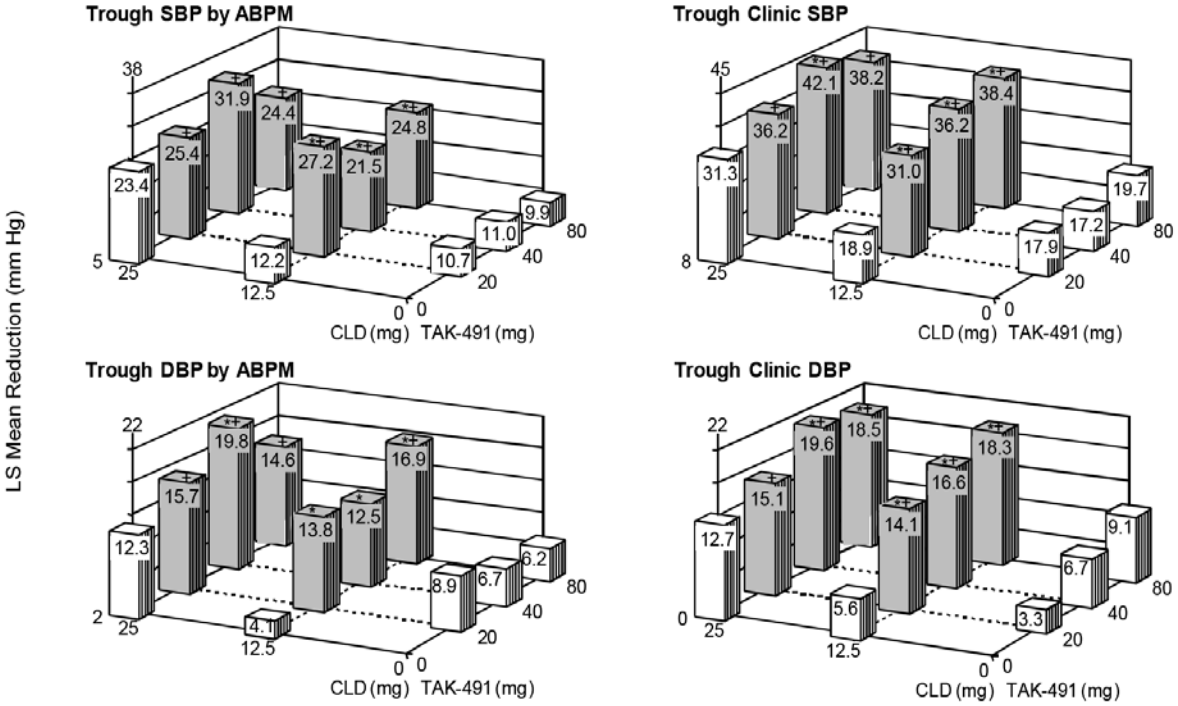
Efficacy endpoint analysis III: The following analysis of the secondary efficacy endpoint pertains to the evaluation of the claim that (b) (4)

Study 302 - Secondary endpoints: The key secondary endpoints were change in trough clinic SBP (all subjects) and change in trough SBP by ABPM in Black subjects. Analysis of the latter endpoint proceeded only if there was a statistically significant result for the primary endpoint in the full study population.

Trough SBP by ABPM in Black Subjects: There were relatively few Black subjects in each of the groups evaluated (40 subjects for the TAK-491CLD 40/25+80/25 pool and 28 and 22 subjects for the TAK-491 80 mg and chlorthalidone 25 mg monotherapy

groups, respectively, with a baseline and final Week 8 ABPM). Clinically significant reductions in trough SBP by ABPM were observed for Black subjects in all treatment groups. The reductions observed with each dose of TAK-491CLD were greater than those observed with its respective TAK-491 or CLD components (Figure 27, Table 11).

Figure 27 Change from baseline in trough SBP and DBP by ABPM and clinic measurements at Week 8 in Black Subjects in Study 302



* 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.

Clinically significant and dose-related reductions in *clinic* SBP and DBP in Black subjects were observed also for all treatment groups (Figure 27); these reductions in clinic SBP and DBP in Black subjects were larger with each dose of TAK-491CLD than those observed with its respective TAK-491 or CLD component.

Table 11 shows that there was a statistically significantly (P<0.001) larger reduction in the trough SBP by ABPM at Week 8 (key secondary endpoint) in the treatment groups receiving the pooled doses of the TAK-491CLD FDC (40/25 mg+80/25 mg pool) compared with the treatment group receiving monotherapy with the highest dose of TAK-491 (80 mg). However, this reduction in trough SBP by ABPM at Week 8 in the TAK-491CLD treatment group is *not* statistically significantly different (P= 0.243 ~ 0.255) from that in the CLD 25 mg treatment group. Sensitivity analyses using multiple imputation methodology also showed consistent results (Table 11).

Table 11 Change from baseline in trough SBP by ABPM in Black subjects at Week 4 and Week 8 – Study 302 (TAK-491CLD 40/25 + 80/25 mg Pool vs. TAK-491 80 mg and CLD 25 mg monotherapies)

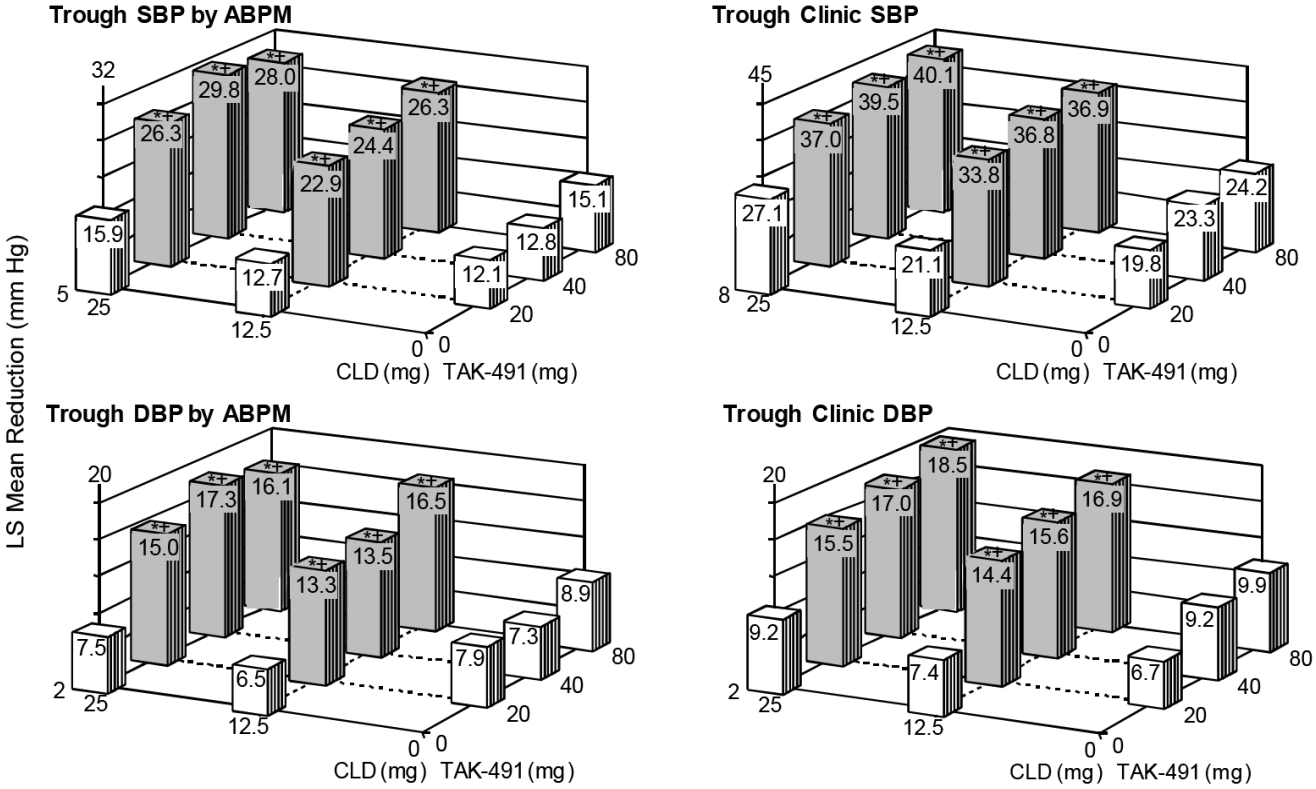
Trough SBP by ABPM	Treatment		
	TAK-491 80 mg N=34	CLD 25 mg N=29	TAK-491CLD 40/25+80/25 mg Pool(a) N=64
Baseline (a)			
n	28	22	40
LS mean (SE)	153.9 (3.0)	151.4 (3.4)	154.2 (2.5)
Change from Baseline to Week 4			
n	25	17	32
LS mean (SE)	-9.8 (3.1)	-21.8 (3.8)	-24.6 (2.8)
TAK-491CLD vs. CLD			
LS mean difference (95% CI)(b)	--	--	-2.8 (-12.2, 6.5)
P-value (c)	--	--	0.550
TAK-491CLD vs. TAK-491			
LS mean difference (95% CI)(b)	--	--	-14.8 (-23.1, -6.5)
P-value (c)	--	--	**<0.001**
Change from Baseline to Week 8: *(Key Secondary Endpoint)*			
n	28	22	40
LS mean (SE)	-9.9 (3.0)	-23.4 (3.4)	-28.2 (2.5)
TAK-491CLD vs. CLD			
Primary analysis			
LS mean difference (95% CI)(b)	--	--	-4.8 (-13.0, 3.5)
P-value (c)	--	--	0.255
Multiple imputation analysis			
LS mean difference (95% CI)(b)	--	--	-6.1 (-16.6, 4.3)
P-value (c)	--	--	0.243
TAK-491CLD vs. TAK-491			
Primary analysis			
LS mean difference (95% CI)(b)	--	--	-18.2 (-25.9, -10.6)
P-value (c)	--	--	**<0.001**
Multiple imputation analysis			
LS mean difference (95% CI)(b)	--	--	-19.2 (-28.5, -9.8)
P-value (c)	--	--[†]	**<0.001**

Source: Sponsor's Table 15.2.1.3.2 in CSR Study 302.
Note: Only subjects with both a Baseline and at least 1 post Baseline value were included; multiple imputation analysis performed on all FAS subjects with a Baseline value without LOCF.
(a) Results for TAK-491CLD 40/25+80/25 mg pool were obtained using contrast with coefficients of 0.5 for TAK-491CLD 40/25 mg and 0.5 for TAK-491CLD 80/25 mg from the respective model.
(b) LS mean difference=LS mean change in the TAK-491CLD 40/25+80/25 mg pool-LS mean change in the CLD 25 mg group or the TAK-491 80 mg group.
(c) P-value from an ANCOVA model using treatment as a fixed effect and baseline as a covariate.

Reviewer's comments: *These findings do **not** support the claim that the* (b) (4) [redacted]

Clinic SBP: The change in clinic SBP from baseline to Week 8 in the overall factorial trial population (Figure 28) shows statistically significant reductions in clinic SBP in the groups receiving the highest doses of TAK-491CLD (40/25 mg+80/25 mg pool) compared with the treatment groups receiving the highest doses of TAK-491 (80 mg) or chlorthalidone (25 mg) monotherapy. The reduction in clinic SBP at Week 8 in the TAK-491CLD 40/25+80/25 mg pool was 39.8 mmHg, which was 15.7 mmHg greater than with TAK-491 80 mg (95% CI: 12.7, 18.6) and 12.7 mmHg greater than with chlorthalidone 25 mg (95% CI: 9.7, 15.7).

Figure 28 Change from baseline in trough SBP and DBP by ABPM and clinic measurements at Week 8 in Study 302



* 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.

Trough DBP by ABPM and Clinic DBP: The change from baseline in trough DBP at Week 8 by ABPM and clinic DBP (Figure 28) shows statistically significant reductions for both in all treatment groups. The groups receiving the highest doses of TAK-491CLD (40/25 mg+80/25 mg pool) had significantly (P<0.001) larger reductions in trough DBP by ABPM or clinic DBP compared with the treatment groups receiving the highest doses of TAK-491 (80 mg) or chlorthalidone (25 mg) monotherapy.

Other ABPM Parameters: Changes in other ABPM parameters of SBP and DBP (i.e., 24-hour mean, mean daytime, mean nighttime, and mean 0 to 12 hours after dosing) were consistent with the results observed for trough SBP and DBP by ABPM.

Study 303:
Study 303 stratified subjects upon randomization as Black vs. non-Black. In subgroup analysis by race (Table 12), titration with TAK-491CLD led to large, clinically significant reductions in all BP parameters in both Black and Caucasian subgroups; also, titration with either TAK-491CLD 40/25 or 80/25 mg led to statistically significantly greater decreases in clinic SBP from Baseline to Week 12 compared with OLM/HCTZ (Table 12). However, across subgroups and regardless of treatment administered, there was a trend towards *a smaller clinic SBP reduction* (mean change from baseline to Week 12 in clinic SBP) *among Black subjects compared with Caucasian subjects* (Table 12).

Table 12 Change from baseline to Week 12 in clinic SBP in Blacks and non-Blacks in Study 303

Subgroup		TAK-491CLD		OLM/HCTZ
		20/12.5 mg → 40/12.5 mg → 40/25 mg	40/12.5 mg → 80/12.5 mg → 80/25 mg	20/12.5 mg → 40/12.5 mg → 40/25 mg
Black subjects	N =	76	72	79
LS Mean BP (SE) at baseline		166.8 (1.2)	166.5 (1.2)	165.4 (1.1)
LS Mean (SE) from baseline		-40.1 (2.0)	-40.0 (2.0)	-33.9 (2.0)
LS Mean difference vs. OLM/HCTZ (95% CI)		-6.2 (-11.7, -0.7)	-6.1 (-11.7, -0.5)	---
P-value		0.028*	0.031*	
Caucasian subjects	N =	254	243	259
LS Mean BP (SE) at baseline		164.0 (0.6)	164.5 (0.7)	164.2 (0.6)
LS Mean (SE) from baseline		-43.0 (0.9)	-45.2 (0.9)	-38.3 (0.9)
LS Mean difference vs. OLM/HCTZ (95% CI)		-4.7 (-7.1, -2.3)	-7.0 (-9.4, -4.6)	---
P-value		<0.00*1	<0.001*	

Source: CSR 303: Table 11.i. * Indicates statistically significant difference versus OLM/HCTZ at the 0.05 level.
Note: Post baseline P-values are obtained from an ANCOVA model with treatment as a factor and Baseline as a covariate. [(a)] Baseline value is the last observation before the first dose of double-blind study drug.

*Reviewer's comments: The findings in Study 302 and Study 303 do **not** support the claim that* [redacted] (b) (4)

Study 306:
Treatment with TAK-491CLD compared with TAK-491+HCTZ:

(a) led to statistically significantly greater reductions in
   (i) clinic DBP from baseline to Weeks 6 and 10, with treatment differences (95% CI) of -3.7 (-5.2, -2.2) mmHg and -2.7 (-4.1, -1.3) mmHg, respectively, and
   (ii) in trough SBP, DBP, mean SBP and mean DBP by ABPM from Baseline to Week 6 and Week 10.

(b) was associated with a significantly greater proportion of responders
   (i) at Week 6 based on changes in clinic SBP (71.9% and 58.2%, respectively), DBP (76.6% and 59.2%, respectively), and joint SBP and DBP (64.1% and 45.9%, respectively), and
   (ii) at Week 10 based on changes in clinic SBP (76.9% and 69.9%, respectively), DBP (82.7% and 75.0%, respectively), and joint SBP and DBP (71.5% and 62.3%, respectively).

Study 301:
For the key secondary efficacy endpoint of the change from baseline to Week 4 in clinic SBP, both TAK-491CLD treatment groups led to statistically significantly greater reductions in clinic SBP compared with OLM/HCTZ. Most of the reduction in clinic SBP was observed by Week 2 in each treatment group (Figure 23), and incremental BP reduction was observed within each group from Week 4 to Week 6, consistent with titration to higher doses in uncontrolled subjects.

BP reductions at each visit in both TAK-491CLD treatment groups were greater than in the OLM/HCTZ group; at the end of the study, the reductions observed in both the low-dose and high-dose TAK-491CLD treatment groups were similar in magnitude.

The results of other secondary endpoints showed the following:

At Week 4, a statistically significantly greater reduction from baseline in clinic DBP was observed for both TAK-491CLD treatment groups compared with the OLM/HCTZ treatment group; the treatment difference and corresponding 95% CI were -3.2 (-4.6, -1.9) mmHg (P<0.001) in favor of TAK-491CLD low-dose group and -3.8 (-5.2, -2.5) mmHg (P<0.001) in favor of TAK-491CLD high-dose group (Table 9).

At Week 8, statistically significant differences of a similar magnitude were maintained in both TAK-491CLD treatment groups despite the greater proportion of subjects requiring titration in the OLM/HCTZ group.

Both the TAK-491CLD low-dose and high-dose groups were associated with statistically significantly greater reductions in mean SBP and DBP by ABPM at Week 4 and Week 8 for the 24-hour, daytime (6 AM to 10 PM), nighttime (12 AM to 6 AM), and 0- to 12-hour.

6.1.6 Other Endpoints

Responder analyses: For the responder analyses based on changes in clinic BP, the responder rate definitions and additional endpoints or analyses across studies are shown in Table 13.

Table 13 Responder analyses in phase 3 clinical trials of TAK-491CLD

Study	Analysis of Response or Achievement of Target BP (mmHg) (a)	Additional Analyses	Exploratory Analyses
302	**SBP response**: Reduction in clinic SBP to <140 and/or a ≥20 decrease **DBP response**: Reduction in clinic DBP to <90 and/or a ≥10 decrease **SBP/DBP response**: Reductions meeting both above criteria	• Logistic regression curves (probability of reaching target BP as a function of baseline BP) • Response surface analysis • Population PK (b)	• Biomarkers
306	**Achievement of target SBP/DBP**: Reduction in clinic SBP/ DBP to <140/90 or <130/80 for subjects with diabetes or CKD **Achievement of target SBP**: Reduction in clinic SBP to <140 or <130 for subjects with diabetes or CKD **Achievement of target DBP**: Reduction in clinic DBP to <90 or <80 for subjects with diabetes or CKD		• Time to first target BP • Biomarkers
301	**Same as Study 306**		• Time to first target BP • Biomarkers
009	**Same as Study 302**		• Biomarkers

BP=blood pressure, PK=pharmacokinetics. (a) Analyses in the table were pre-specified secondary endpoints. For study 302, analyses were also completed based on achievement of target BP only (i.e., SBP <140, DBP <90 mm Hg, or both).
(b) Source: Module 2.7.2 Section 2.2.4.

In Study 302, subjects were considered responders if they achieved a target BP of <140 mmHg for SBP and <90 mmHg for DBP and/or had a corresponding decrease from baseline of ≥20 mmHg for SBP or ≥10 mmHg for DBP; analyses were completed based on SBP, DBP, and joint SBP/DBP reductions. Because a high proportion of subjects in each treatment group were considered responders based on these criteria, additional

responder analyses based on achievement of target BP only were also completed.

For the titrate-to-target Studies 306 and 301, responder rates were based exclusively on achievement of target BP, as the decision to titrate study drug after 4 weeks of FDC treatment in these studies was also based only on achievement of target BP.

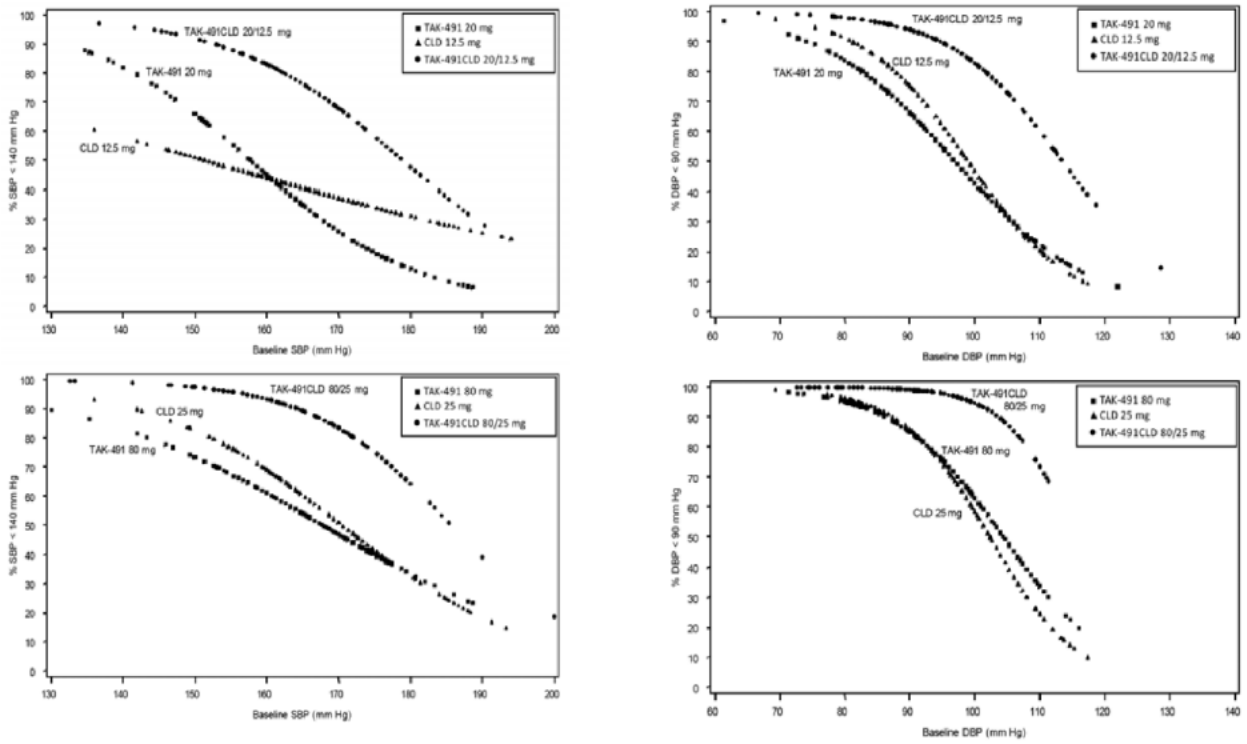
Study 302: *Proportion of Responders and Subjects Who Achieved Target BP*: The responder rate analyses show that a higher proportion of subjects in each TAK-491CLD FDC treatment group met the response criteria or achieved target BP at Week 8 compared with its respective TAK-491 or CLD component (Table 14).

Table 14 Proportion of subjects achieving target SBP and DBP at Week 8 in Study 302

Subjects Achieving Target, n (%)	TAK-491 20 mg n=155 46 (**29.7**)	TAK-491 40 mg n=152 55 (**36.2**)	TAK-491 80 mg n=162 84 (**51.9**)
CLD 12.5 mg n=155 53 (**34.2**)	**TAK-491CLD 20/12.5 mg** n=154 107 (**69.5**)*	**TAK-491CLD 40/12.5 mg** n=145 106 (**73.1**)*	**TAK-491CLD 80/12.5 mg** n=151 115 (**76.2**)*
CLD 25 mg n=156 80 (**51.3**)	**TAK-491CLD 20/25 mg** n=153 112 (**73.2**)*	**TAK-491CLD 40/25 mg** n=155 126 (**81.3**)*	**TAK-491CLD 80/25 mg** n=158 135 (**85.4**)*

Source: Sponsor's Study 302 CSR. Table 15.2.5.4.3. Target blood pressure was defined as trough clinic SBP <140 mmHg and trough clinic DBP <90 mmHg for all subjects (including those with CKD or diabetes).
*P<0.001 for the comparison of odds ratios between TAK-491CLD FDC and both of the individual components.

Figure 29 Probability of achieving target SBP (<140 mmHg) and target DBP (<90 mmHg) at Week 8 by baseline SBP and DBP, respectively, in Study 302



Following the FDA guideline on "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs," the sponsor submitted curves (Figure 29) that depict the probability of achieving target SBP and DBP as a function of respective baseline BPs for the lowest and highest doses of TAK-491CLD studied (i.e., 20/12.5 mg and 80/25 mg) to achieve the SBP target of <140 mmHg and the DBP target of <90 mmHg.

Figure 29 shows that subjects randomized to treatment with the TAK-491CLD FDC had a greater likelihood of achieving SBP and DBP control than subjects randomized to monotherapy with either TAK-491 or CLD, with the advantage of the FDC over the individual monotherapies being maintained over the observed range of baseline BPs.

Study 301: At Week 4, both the TAK-491CLD low-dose and high-dose groups were associated with a statistically significantly greater proportion of responders compared with the OLM/HCTZ treatment group based on changes in clinic SBP (66.1%, 68.9%, and 52.3%, respectively), DBP (71.4%, 73.8%, and 58.2%, respectively), and joint SBP and DBP (58.1%, 61.4%, and 44.6%, respectively).

At Week 8 also, significant differences in responder rates were observed with the TAK-491CLD low-dose and high-dose groups compared with the OLM/HCTZ treatment group based on changes in clinic SBP (76.0%, 76.0%, and 64.6%, respectively), DBP (79.9%, 79.1%, and 66.0%, respectively), and joint SBP and DBP (69.4%, 68.9%, and 54.7%, respectively).

6.1.7 Subpopulations

Subgroup analyses in Study 302:

Within each subgroup in Study 302, treatment with the TAK-491CLD FDC (40/25+80/25 mg pool) resulted in greater LS mean reductions in trough SBP by ABPM compared with both TAK-491 80 mg monotherapy and CLD 25 mg monotherapy for each subgroup, and the differences were statistically significant ($P<0.05$ to $P<0.001$) for all comparisons with the exception of:

(i) the analysis between the FDC pool and CLD 25 mg monotherapy in black subjects, and
(ii) subjects with Grade 3 hypertension (SBP >180 mmHg) at baseline. These subgroups were too small to draw statistical inferences.

Across subgroups, there was no evidence of heterogeneity in response to treatment with the TAK-491CLD FDC by age (<65 and ≥65 years), sex, or BMI (there were too few subjects (4 to 14 per group) to make a meaningful comparison for the age category of ≥75 years). There was a greater response to treatment with CLD 25 mg monotherapy among female subjects compared with males.

In the subgroup analysis by race, treatment response to TAK-491 80 mg monotherapy was lower in Black subjects than Caucasian subjects, whereas the response to CLD 25 mg monotherapy was higher in Black subjects than Caucasian subjects. In the treatment groups that received the highest doses of the FDC (TAK-491CLD 40/25+80/25 mg pool) all race subgroups shared a similar reduction in trough SBP by

ABPM, ranging from 28.2 to 29.6 mm Hg.

In the subgroup analysis by baseline trough SBP by ABPM, treatment response to both the monotherapies (TAK-491 80 mg and chlorthalidone 25 mg) and the TAK-491CLD 40/25+80/25 mg pool were greater among subjects whose baseline trough SBP by ABPM was greater than or equal to the median (151.5 mmHg).

In the subgroup analysis by baseline hypertension severity, too, treatment response increased with severity grade (Grade 1: ≥140 to <160, Grade 2: ≥160 to <180, and Grade 3: ≥180 mmHg) for both monotherapies (TAK-491 80 mg and CLD 25 mg) and the TAK-491CLD 40/25+80/25 mg pool. However, the majority of subjects were Grade 2 (95 to 158 per group) with notably fewer Grade 1 (26 to 44 per group) and Grade 3 (4 to 22 per group) subjects.

In the subgroup of subjects who had both systolic and diastolic hypertension (i.e., DBP ≥90 mmHg), there was a higher mean trough SBP by ABPM at Baseline and a trend of greater reduction in this variable during treatment with TAK-491CLD, compared with those who had isolated systolic hypertension (i.e., DBP <90 mmHg).

In the subgroup analysis by baseline diabetes status, treatment response to the TAK-491CLD 40/25+80/25 mg pool and to both monotherapies (TAK-491 80 mg and CLD 25 mg) was similar in normal and diabetic subjects. However, the diabetic subgroups were relatively small (16 to 41 per group).

In the subgroup analysis by baseline eGFR, a greater response to both monotherapies (TAK-491 80 mg and CLD 25 mg) was observed in subjects with mild renal impairment compared with those with normal renal function. A similar response was observed in the normal and mildly impaired subjects for the TAK-491CLD 40/25+80/25 mg pool. The sample sizes were relatively small in subjects with moderate renal impairment to draw statistical inferences (the responses were not substantially different than subjects with normal renal function).

For trough DBP by ABPM, similar results were observed for the TAK-491CLD FDC 40/25+80/25 mg pool versus monotherapy with TAK-491 80 mg chlorthalidone 25 mg. However, greater reduction in DBP with the TAK-491CLD 40/25+80/25 mg pool was greater among subjects <65 years compared with those ≥65 years, and in subjects with both systolic and diastolic hypertension (i.e., DBP ≥90 mmHg) at baseline compared with subjects with isolated diastolic hypertension (i.e., DBP <90 mmHg).

For clinic SBP and DBP, reductions in BP were statistically significantly greater with the TAK-491CLD 40/25+80/25 mg pool than either monotherapy (TAK-491 80 mg and CLD 25 mg) for all races, including Black subjects, and in most other subgroups, with exceptions of clinic SBP in subjects with eGFR 30 to 60 mL/min/1.73m^2 or subjects with diabetes, where the size of samples was small.

Subgroup analyses in Study 306:

In Study 306, subgroup analyses for the primary endpoint of change from baseline in clinic SBP at Week 6 showed the following:

Within subgroups, treatment with TAK-491CLD led to numerically or statistically significant greater decreases in clinic SBP compared with TAK-491+HCTZ. (Exceptions were the small subgroups (n≤15) of subjects ≥75 years old, and in the "Other" racial category primarily composed of American Indian subjects).

Across subgroups, there were no major differences in response to TAK-491CLD compared with TAK-491+HCTZ by renal function, diabetes status or age (<65, ≥65 years). However, there was a trend for

- reduced response among subjects ≥75 years (small subgroup)
- greater SBP reductions in female subjects compared with male subjects,
- greater SBP reductions in White subjects compared with Black subjects,
- greater SBP reductions in subjects with BMI <30 kg/m^2 compared with those with BMI ≥30 kg/m^2.
- greater reductions in clinic SBP in subjects with higher baseline SBP, subjects with isolated systolic hypertension (i.e., DBP <90 mm Hg) and subjects with both systolic and diastolic hypertension (i.e., DBP ≥90 mm Hg) at baseline (although there were greater DBP reduction in subjects with diastolic hypertension), and
- greater reductions in clinic SBP in Russian subjects compared with subjects in the United States.

Subgroup analyses in Study 301:
Subgroup analyses of change from baseline in clinic SBP at Week 4, before titration to higher doses occurred, showed the following:

Within subgroups, treatment with TAK-491CLD led to numerically or statistically significantly greater reduction in clinic SBP compared with OLM/HCTZ. (Exceptions were subjects in the "Other" race subgroup, subjects ≥75 years of age, and subjects with diabetes).

Across subgroups, there were no consistent differences in response to treatment with TAK-491CLD by BMI, race, or baseline renal function with respect to reductions in clinic SBP. There was a trend for less SBP reduction with increasing age and in diabetics compared with non-diabetics. There was a trend for greater clinic SBP reductions in

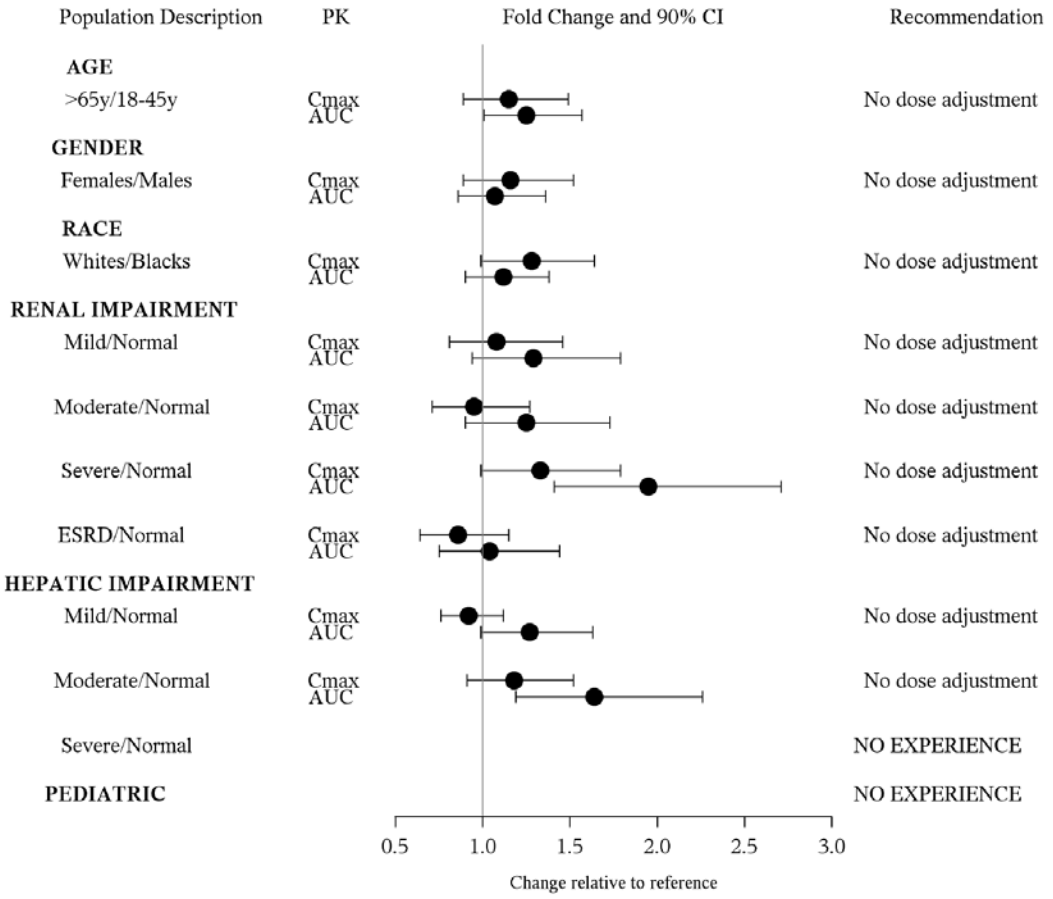
- female compared with male subjects
- subjects with higher baseline SBP;
- subjects with isolated systolic hypertension (i.e., DBP <90 mmHg),
- subjects with both systolic and diastolic hypertension (i.e., DBP ≥90 mmHg) at baseline (although there were greater DBP reduction in subjects with diastolic hypertension).

For most subgroups, incremental reductions in clinic SBP were observed at Week 8 after titration had occurred; however, the treatment differences between TAK-491CLD and OLM/HCTZ were similar to those at Week 4.

Subgroup analyses in Study 308:
Subgroup analyses conducted by region (US and non-US), race (Black and non-Black), and baseline DBP (<90 mm Hg and ≥90 mmHg) indicated the following:

- For all subgroups, treatment with TAK-491CLD led to greater mean reductions in SBP than OLM/HCTZ at each study visit, as observed in the overall population.
- No heterogeneity was observed in blood pressure responses by region. However, due non-US sites being initiated later than US sites, there is less data at each study visit in the non-US subgroup at the time of the interim data cut.
- No heterogeneity in SBP and DBP reductions was observed in response to treatment with TAK-491CLD by Black vs. non-Black subgroups. In the OLM/HCTZ group, SBP reduction in the Black subgroup tended to be less than that in the non-Black subgroup through Week 12.
- Reductions in SBP were similar in the subgroups with baseline DBP <90 and ≥90 mmHg, while reductions in DBP were greater in subjects with higher baseline DBP.

Figure 30 Impact of intrinsic factors on the pharmacokinetics of azilsartan



The effect of demographic and functional factors on the pharmacokinetics of azilsartan was studied in single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of the effect on azilsartan are presented in Figure 30 as change relative to reference (test/reference). Effects are modest and do not call for dosage adjustment, except where indicated based on no experience in patients treated with azilsartan medoxomil.

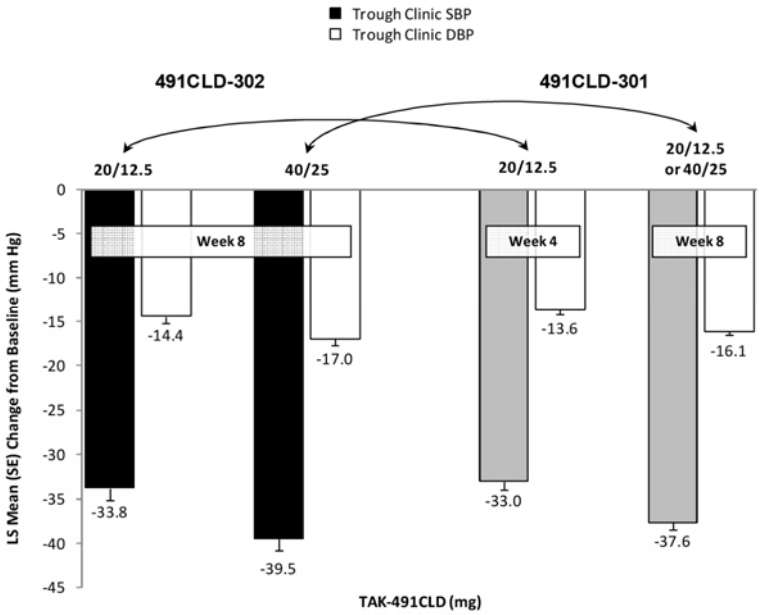
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Six doses of the TAK-491CLD FDC (20/12.5, 40/12.5, 80/12.5, 20/25, 40/25, and 80/25 mg) were evaluated in the phase 3 clinical trials.

In the factorial Study 302, the trough SBP/DBP reductions by both ABPM and clinic measurements generally were dose-related in the TAK-491CLD groups; greater BP reductions were observed as the dose of TAK-491 increased, or as the dose of CLD increased (Figure 28). This dose-response relationship was observed for SBP and/or DBP by ABPM as well as by clinic measurements across the TAK-491CLD FDC dose range, with the exception of the 80/25 mg dose, which did not confer an incremental SBP or DBP reduction compared with the 40/25 mg dose. Modeling results from response-surface analyses were consistent with the observed dose-response.

Dose-response information was also evaluated in the titrate-to-target BP Studies 306 and 301, in which incremental reductions in BP were observed and achievement of target BP increased after dose escalation to TAK-491CLD 40/25 or 80/25 mg. Consistent with the plateau of BP reduction observed at the 40/25 and 80/25 mg strengths in Study 302, similar BP reductions (37.6 ≈ 38.2 mmHg) were observed at the end of both titrate-to-target Studies 306 (Table 7) and 301 (Table 9) regardless of whether 40/25 or 80/25 mg was the high-dose option. These reductions in clinic SBP at the end of both titrate-to-target studies (≈38 mm Hg) approached the same magnitude of BP reduction among subjects who were randomized directly to fixed-dose treatment with TAK-491CLD 40/25 or 80/25 mg in the factorial Study 302 (≈40 mm Hg).

Figure 31 Change from baseline in clinic SBP/DBP at Week 8 in Studies 302 and 301



Source: Sponsor's Study 301 CSR (Table 15.2.3/4.1.2) and Study 302 CSR (Tables 15.2.1.1.2.1 and 15.2.2.1.2)

While the above across-study comparisons have limitations, they share identical inclusion criteria, had study populations with similar baseline characteristics and

demographics, and showed consistent BP reductions in the fixed-dose segments of each study (302, 306 and 301). For example, in Figure 31:

(a) the reductions in clinic SBP and DBP observed at Week 8 in study 301 (which reflects use of the 40/25 mg dose by a subset of subjects) were greater than the reductions observed at Week 4 within this study 301, and approached the same magnitude as the reductions seen in Study 302 among subjects who received the 40/25 mg dose exclusively for 8 weeks;

(b) similar reductions in BP were seen with the 20/12.5 mg dose at Week 4 in Study 301 and at Week 8 in the factorial Study 302.

This same pattern was also observed when the high-dose group of Study 301 (40/12.5 → 80/25 mg) and the TAK-491CLD dose group of Study 306 (40/12.5 → 40/25 mg) were compared with the corresponding dose groups of the factorial Study 302.

Study-009 indicated that no additional BP reduction was observed with TAK-491 80 mg compared with TAK-491 40 mg when each was co-administered with CLD 25 mg.

These observations suggest that the TAK-491CLD dose of 40/25 mg is an effective dose option for patients who have not achieved target BP with lower doses.

Proposed Commercial Doses

Figure 32 shows the reductions in trough SBP/DBP by ABPM in the factorial Study 302 for the proposed doses (b) (4) of TAK-491CLD.

Figure 32 Change from baseline in trough SBP/DBP by ABPM at Week 8 in Study-302 (proposed doses)

A dose-response relationship was observed for SBP and/or DBP across the TAK-491CLD dose range in the factorial Study 302, with the exception of the 80/25 mg dose (not shown), which did not confer incremental SBP or DBP reduction compared with the

40/25 mg dose. The BP reductions observed at the end of the titrate-to-target BP Study 301 were similar among subjects randomized to either the high-dose (TAK-491CLD 40/12.5 → 80/25 mg) or low-dose regimen (TAK-491CLD 20/12.5 → 40/25 mg).

The sponsor's contention is that the range of [redacted] (b) (4) doses allows the option to up-titrate either the TAK-491 component to the dose of TAK-491CLD 80/12.5 mg or the CLD component to the dose of TAK-491CLD 40/25 mg, and that it allows individualization of dose titration based not only on the need for additional BP reduction, but also on whether a reason exists to increase the dose of one component vs. the other (e.g., a patient at risk for hypo- or hyperkalemia).

In the clinical review of TAK-491 monotherapy (Review by Maryann Gordon and John Lawrence), the efficacy analyses showed that little added efficacy was observed above TAK-491 40 mg. I find it doubtful, too, whether [redacted] (b) (4) 80/12.5 mg is useful.

I tabulated the magnitude of BP reductions by different doses of TAK-491CLD in the five randomized, double-blind, controlled, clinical trials submitted in the NDA (Table 15).

Table 15 Mean BP reduction from baseline by dose in TAK-491CLD clinical studies

Study	Dose (mg) of TAK-491/CLD	Mean reduction in BP (mmHg) from baseline			
		By ABPM		By clinic	
		SBP	DBP	SBP	DBP
302*	20/12.5	22.9	13.3	33.8	14.4
	40/12.5	24.4	13.5	36.8	15.6
	80/12.5	26.3	16.5	36.9	16.9
	20/25	26.3	15.0	37.0	15.5
	40/25	29.8	17.3	39.5	17.0
	80/25	28.0	16.1	40.1	18.5
009	40/25	31.7	18.3	36.2	16.2
	80/25	31.3	18.5	34.4	16.0
306†	40/12.5 – 40/25	25.7†	15.2†	35.1†	15.0†
		25.6‡	15.1‡	39.0‡	16.1‡
301	20/12.5→ 40/25	26.4	15.1	37.6	16.1
	40/12.5→ 80/25	27.9	16.4	38.2	16.5
303§	20/12.5→ 40/25	32.9	19.8	42.5	18.8
	40/12.5→ 80/25	34.9	20.2	44.0	20.5

*Week 8 data for the proposed doses; †Week 6 data; ‡Week 8 data; §Week 12 data

I used a difference of **>2 mmHg** as the "discernible difference" in BP reduction effect between the different dose groups. While meta-analyses of BP treatment trials show that reductions in SBP of about 10 -12 mmHg and in DBP of 5 - 6 mmHg conferred relative risk reductions in (i) stroke of 38% and (ii) coronary heart disease of 16% - 20% within a few years of beginning treatment[6,7,8], a meta-analysis of the relevance of age-specific BP data to vascular mortality for one million adults in 61 prospective studies suggested that a 2 mmHg lower SBP would cause about 10% lower stroke mortality and about 7% lower mortality from CHD or other vascular causes in patients in middle age[9].

[redacted] (b) (4)

(b) (4) The 40/12.5 mg dose appears to be a more appropriate dose for marketing approval as the lower dose.

(b) (4) This further strengthens the notion that the 40/12.5 mg dose is an appropriate dose for marketing approval, which will provide the BP reduction effect in SBP and DBP by ABPM seen with (b) (4) and the BP reduction effect in clinic SBP and DBP seen with (b) (4)

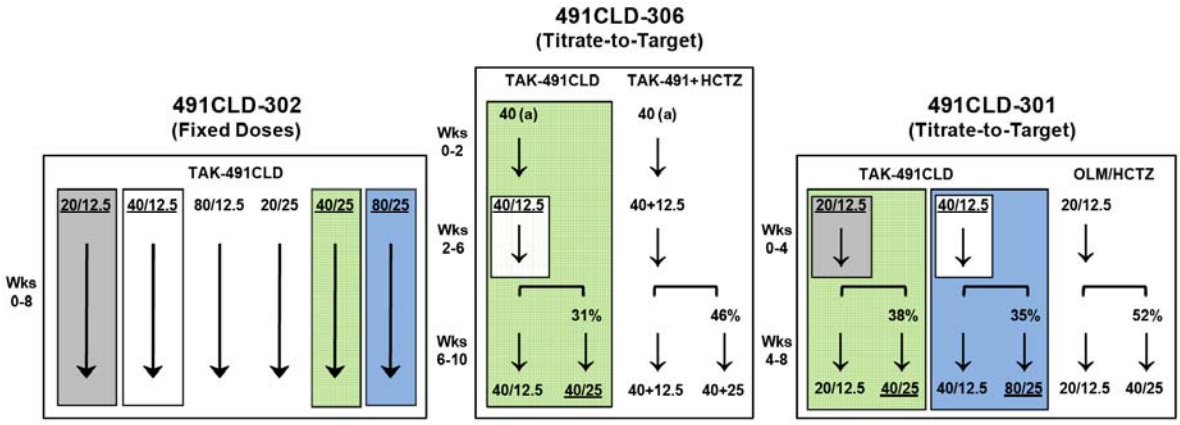
(b) (4) Thus, the 40/25 mg dose appears to be an appropriate dose for marketing approval as the top dose.

Reviewer's comment: Only the doses of 40/12.5 and 40/25 appear to demonstrate clear differences in BP reduction in the parameters that were evaluated, and therefore, I recommend these doses for approval – should this product be approved by FDA.

There is also some support for the above comment from BP reductions observed in other clinical trials in the Phase 3 program:

- (b) (4) the 40/25 mg dose is the appropriate maximum dose for approval.
- In the titrate-to-target BP trial Study 306, there was no "discernible difference" in the reduction of SBP and DBP by ABPM or clinic DBP (Table 15) from baseline between the 40/12.5 mg dose group (measured at Week 6) and the 31% of patients (Figure 33) who were titrated up to the 40/25 mg dose for 2 more weeks (measured at Week 8).
- (b) (4)
- (b) (4)

Figure 33 Schematic of Study Drug Administration in Short-term FDC Studies and Proportion of Subjects Receiving High Doses in the Titrate-to-Target Studies



Source: Sponsor's Figure 3.a in Summary of Clinical Efficacy, page 93.
Note: Treatments shown as dose (mg/mg) of individual components. Percents indicate proportion of subjects who had study drug titrated to high dose in studies 306 and 301 at Week 6 and Week 4, respectively.
Gray and white boxes identify treatment arms in which stable treatment with TAK-491CLD was administered at comparable identical fixed doses (i.e., 20/12.5 and 40/12.5 mg) in all subjects; green and blue boxes designate treatment arms in which high doses of TAK-491CLD (i.e., 40/25 and 80/25 mg) were administered either as a stable fixed dose or as the high dose option in a titrate-to-target blood pressure treatment algorithm.
(a) All subjects received monotherapy with TAK-491 40 mg for the first 2 weeks of study 491CLD-306.

*Reviewer's comment: From the perspective of the magnitude of SBP reduction, the **40/12.5 mg** and the **40/25 mg** doses appear to show clinically discernible separate BP reduction effects.*

Safety data in relation to the above dose recommendation:

For the selection of the starting dose between the (b) (4) 40/12.5 mg doses: discontinuations due to AEs and TEAEs in relation to dose show that the AEs and TEAEs did *not* increase with the higher dose of 40/12.5 mg compared to (b) (4) (Table 26), and also that the most frequent TEAEs leading to discontinuation (namely, blood creatinine increased and dizziness), too, did *not* increase with the higher starting dose of 40/12.5 mg compared to (b) (4) (Table 27). This supports the selection of 40/12.5 mg dose as the starting dose, which can be anticipated to produce a clinically significant reduction in SBP (Table 15) by ABPM (24.4 mmHg) or clinic measurement (36.8 mmHg) for a patient who does not respond to the 80 mg dose of TAK-491.

For the selection of the high end dose,

(i) The highest dose of (b) (4) is associated with the highest frequency of discontinuations (Table 26) due to AEs (13.6%) and TEAEs (14.3%). Thus, the selection is narrowed to choose between 40/25 mg and (b) (4) doses, with the possibility of starting from 40/12.5 with the option of titrating TAK-491 dose up to (b) (4) or titrating CLD dose up to 40/25 mg.

(ii) The 40/25 mg dose produced the largest reduction in SBP by ABPM (29.8 mmHg) and by clinic measurement (39.5 mmHg) , but was associated with a higher frequency of discontinuations (Table 26) due to AEs (12.2%) and TEAEs (14.1%).

(iii) The (b) (4) dose produced a relatively smaller reduction in SBP (Table 15) by ABPM (26.3 mmHg) or by clinic measurement (36.9 mmHg), but was associated with less discontinuations due to AEs (7.2%) and TEAEs (9.2%). The (b) (4) dose produced a reduction in SBP by clinic measurement (36.9 mmHg) which is practically the same as that produced by the starting dose of 40/12.5 mg (36.8 mmHg), and a reduction in SBP by ABPM (26.3 mmHg) which is <2 mmHg (the discernible difference) higher than that produced by the 40/12.5 mg dose (24.4 mmHg). The (b) (4) dose showed a larger reduction in DBP by ABPM (16.5 mmHg) over the 40/12.5 mg dose (13.5 mmHg), but the difference in DBP by clinic measurement (16.9 mmHg vs. 15.6 mmHg) is <2 mmHg (the discernible difference).

Thus, I think that 40/25 mg dose is appropriate to be selected as the maximally effective upper dose.

Reviewer's comment: The selection of the 40/12.5 mg dose as the starting dose and the 40/25 mg dose as the high dose provides the simplicity of two dose choices, and the titration of the CLD dose only.

The other two doses (20/12.5 mg and 80/12.5 mg) (b) (4) do not produce a discernible advantage in BP reduction, and can confuse physicians prescribing the combination, pharmacists dispensing the prescription and patients taking the medication.

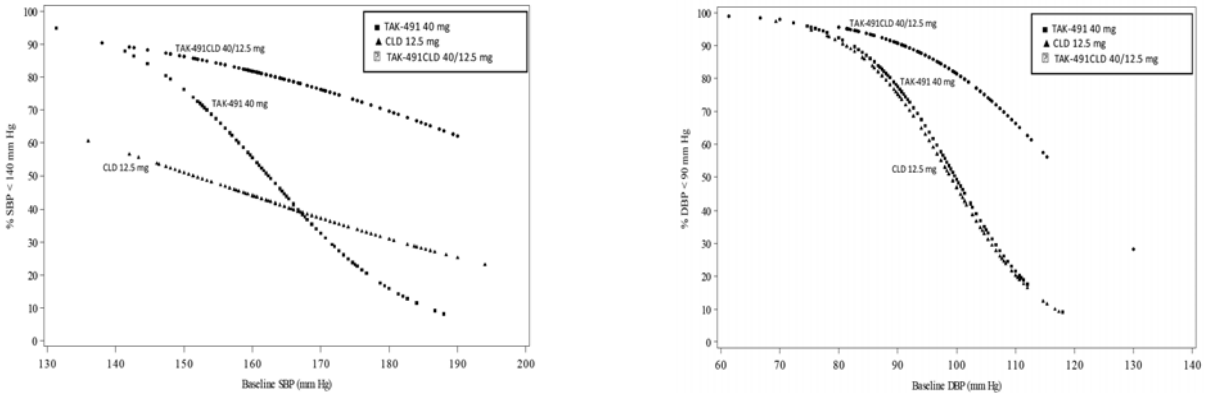
(b) (4) doses for use as initial therapy:

The (b) (4) 20/12.5 mg and 40/12.5 mg doses of TAK-491CLD as the starting doses with the contention that these doses confer clinically meaningful and robust reduction in BP (Table 5, and Figure 15) compared with the monotherapy high doses of (b) (4) while providing RAAS inhibition by TAK-491 to mitigate the hypokalemia associated with CLD 25 mg.

Logistic regression curves for the 40/12.5 mg dose relative to the individual TAK-491 and chlorthalidone monotherapies (Figure 34) on the probability of achieving SBP target (<140 mmHg) and DBP target (<90 mmHg) show that subjects randomized to treatment with the TAK-491CLD 40/12.5 mg had a greater probability of achieving SBP and DBP targets than subjects randomized to either monotherapy, and that the 40/12.5 mg dose is an appropriate starting dose.

For patients who require additional BP reduction TAK-491CLD may be titrated up to a dose of 40/25 mg. TAK-491CLD was administered once-daily in the morning in all phase 3 clinical trials. Administration of the FDC with food (in phase 1 Study 104) did not have a clinically significant effect on exposure to TAK-536 (the active moiety of TAK-491) or CLD.

Figure 34 Probability of achieving target SBP (<140 mmHg) and target DBP (<90 mmHg) at Week 8 by baseline SBP for TAK-491CLD 40/12.5 mg dose and its individual components (Study-302)

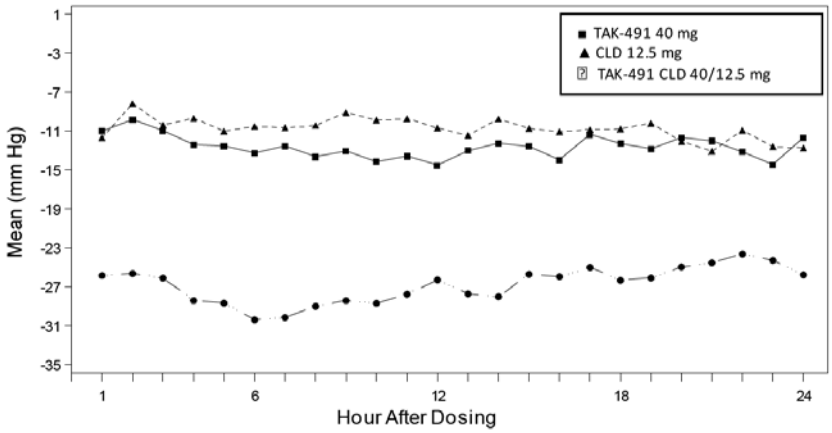


Source: Study-302 CSR Figures 15.2.6.1.1 and 15.2.6.1.3

Evaluation of the dosing interval:

Use of ABPM allowed evaluation of treatment response for the 24-hour period following dosing. The change from baseline in SBP by ABPM at the Final Visit is shown by hour for the 24-hour period following dosing at 40/12.5 mg of the FDC in Figure 35.

Figure 35 Change in SBP during 24-hour post-dose interval at final visit in Study 302 (Tak-491/CLD 40/12.5 mg and individual components)



Source: Study-302 CSR Figure 15.2.1.5.3

Similar findings were observed with the other proposed doses, suggesting that once-daily administration of TAK-491CLD produced clinically meaningful BP reductions throughout the 24-hour dosing interval, and also that greater mean BP reductions were maintained with TAK-491CLD compared to the constituent monotherapy treatments throughout this dosing interval.

Onset of antihypertensive effect:

Most of the antihypertensive effect of TAK-491CLD occurs within 1-2 weeks of dosing in Study 302 (Figure 36) with fixed dose treatment, and in titrate-to-target BP doses in Study 308 (Figure 37) and Study 006 (Figure 38).

Figure 36 Mean change from baseline in clinic SBP (mmHg) at each week in Study 302

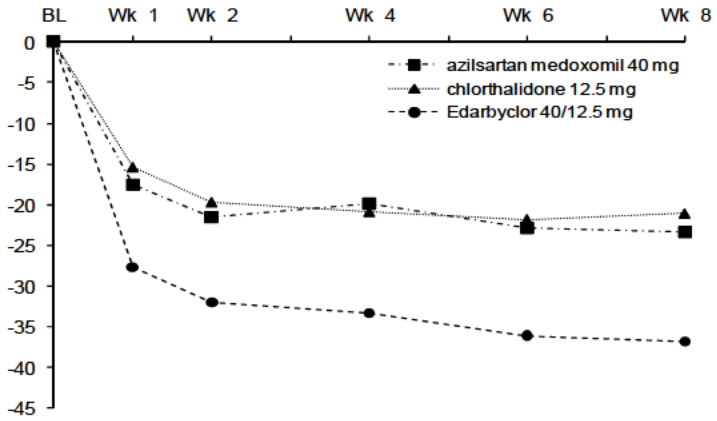
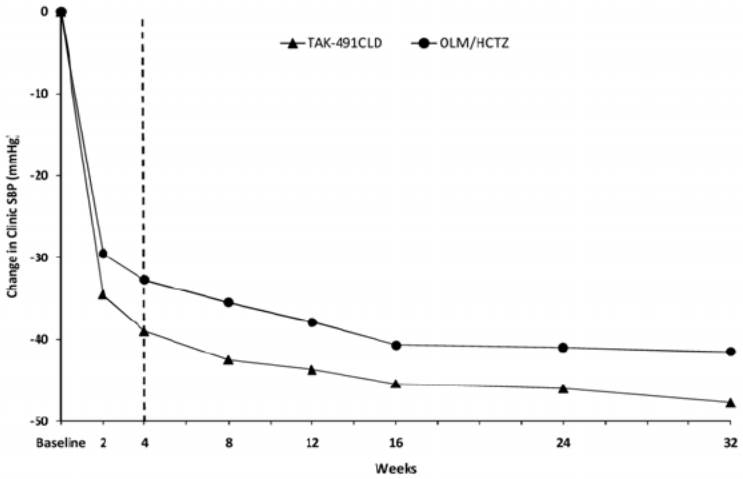
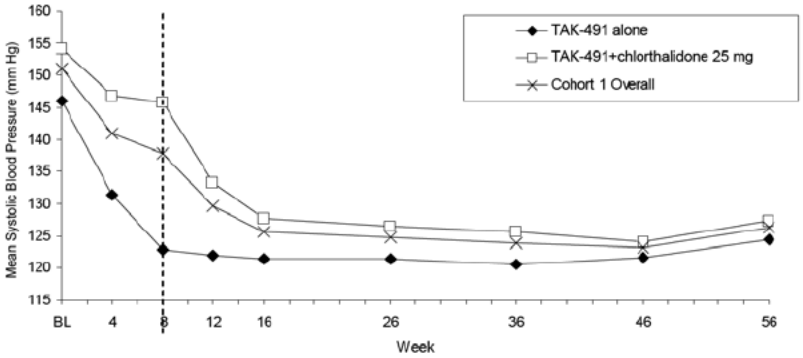


Figure 37 Mean change from baseline in clinic SBP by study visit in Study 308



Source: Study 308 Interim CSR Table 15.2.1. Dashed line at Week 4 denotes first possible titration.

Figure 38 Study 006: change from baseline in clinic SBP by Visit



Source: Study 006 CSR Table 15.2.1.1.1 and Table 15.2.3.1.
Note: Dashed line indicates the first study visit when add-on diuretic treatment was allowed.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Measurement of clinic BP throughout the treatment period of Study 308 allowed for evaluation of BP changes associated with TAK-491CLD during chronic dosing.

In the ongoing 52-week, randomized, open-label Study 308 in which subjects received initial doses of either TAK-491CLD (40/12.5 mg) or OLM/HCTZ (20/12.5 mg) which was titrated or additional antihypertensive medications were added, the interim data related to the time course of the change from baseline in clinic SBP through Week 32 (completed: n=173 for TAK-491CLD; n=203 for OLM/HCTZ) are shown in Figure 37.

SBP reductions at Weeks 2 and 4, before titration was allowed, were greater in the TAK-491CLD group than the OLM/HCTZ group. Incremental BP reductions continued at each study visit in both treatment groups, with greater reductions in SBP observed at each visit in the TAK-491CLD treatment group compared with the OLM/HCTZ treatment group. The reductions from baseline in clinic SBP at Week 32 were 47.7 mmHg in the TAK-491CLD treatment group (n=173) and 41.5 mmHg in the OLM/HCTZ treatment group (n=203). The interim results of Study 308 suggest that treatment with TAK-491CLD results in sustained BP reduction over a treatment period up to 32 weeks.

Additional results from the uncontrolled, titrate-to-target, long-term, open-label safety Study 006 support the maintenance of efficacy for TAK-491 plus CLD treatment. In this 56-week study, subjects were enrolled into 1 of 2 cohorts; in both cohorts, all subjects received a starting dose of TAK-491 40 mg, which was titrated to 80 mg at Week 4, if tolerated. Subjects could be receiving up to 2 existing antihypertensive treatments at baseline, and if additional BP reduction was required, investigators added CLD 25 mg (Cohort 1) or HCTZ 12.5 to 25 mg (Cohort 2) as the initial add-on agent beginning at Week 8. In both cohorts, other antihypertensive medications were added thereafter.

Reductions in SBP by visit observed in Study 006 are shown for Cohort 1 in Figure 38; results are shown by treatment received (i.e., TAK-491 alone throughout the study or TAK-491 plus CLD 25 mg) and for the overall cohort. Among subjects who received TAK-491 alone throughout the treatment period, the Week 8 reduction in clinic SBP/DBP was 23.5/17.2 mmHg, and similar reductions were maintained throughout the remainder of the study (21.3/17.9 mmHg at Week 56). Clinically meaningful BP reductions were also observed at Week 8 visit among subjects who subsequently received add-on diuretic, but the BP reductions were smaller; for subjects who subsequently received TAK-491 plus CLD, the reductions in clinic SBP/DBP at Week 8 with TAK-491 alone were 8.4/7.7 mmHg. These findings suggest that coadministration of TAK-491 and CLD results in sustained BP reduction over a prolonged treatment period up to 56 weeks.

A similar pattern of BP reduction was observed in a second open-label Study 016.

6.1.10 Additional Efficacy Issues/Analyses

Missing subjects in primary efficacy endpoint analysis
In Table 16, the numbers in row 2 (who completed the study) and row 3 (who were

analyzed for the primary efficacy endpoint) are different. There is a deficiency of 5 to 15 patients in the number of patients analyzed for efficacy compared to those who completed the study {shown in the row 5 [Discrepancy (Row 3 – Row 2)]}. The actual total number of missing patients becomes larger (shown in row 5, particularly in cells in column 80/12.5 and 80.25 which approached 30% of patients randomized).

Table 16 Missing subjects in primary efficacy endpoint analysis (SBP by ABPM) in Study 302

Drug	CLD		TAK-491			TAK/CLD					
Dose (mg)	12.5	25	20	40	80	20/12.5	20/25	40/12.5	40/25	80/12.5	80/25
Total randomized	157	160	155	153	162	156	154	147	156	153	162
Completed Study*	135 (86.0%)	141 (88.1%)	141 (91.0%)	139 (90.8%)	142 (87.7%)	135 (86.5%)	131 (85.1%)	131 (89.1%)	125 (80.1%)	125 (81.7%)	125 (77.2%)
Number for Primary Endpoint	130 (82.8%)	134 (83.8%)	128 (82.6%)	131 (85.6%)	127 (78.4%)	127 (81.4%)	118 (76.6%)	117 (79.6%)	114 (73.1%)	110 (71.9%)	114 (72.2%)
Discontinued (Row 1-2)*	22 (14.0%)	19 (11.9%)	14 (9.0%)	14 (9.2%)	20 (12.3%)	21 (13.5)	23 (14.9)	16 (10.9)	31 (19.9)	28 (18.3)	37 (22.8)
Discrepancy (Row 3-2)	-5 (3.2%)	-7 (4.4%)	-13 (8.4%)	-8 (5.2%)	-15 (9.3%)	-8 (5.1%)	-13 (8.4%)	-14 (15.0%)	-11 (7.1%)	-15 (9.8%)	-11 (6.8%)
Actual Missing in Analysis (Row 1-3)	27 (17.2%)	26 (16.3%)	27 (17.4%)	22 (14.4%)	35 (21.6%)	29 (18.6%)	36 (23.4%)	30 (20.4%)	42 (26.9%)	43 (28.1%)	48 (29.6%)

Source: Sponsor's table 15.2.1.1.2.1 in Study 302 CSR; *Data from Disposition of subjects

Missing patients in clinic SBP (secondary efficacy endpoint) analysis:
In Table 17 for the secondary efficacy endpoint analysis, the numbers in Row 2 (who completed the study) and Row 3 (who are analyzed for the secondary efficacy endpoint) are different. There are an additional 13 to 33 patients in the number of patients who were analyzed for the secondary efficacy endpoint {shown in the row 5 [Discrepancy (Row 3 – Row 2)]} compared to the number of patients who completed the study.

Table 17 Missing subjects in secondary efficacy endpoint analysis (clinic SBP) in Study 302

Drug	CLD		TAK-491			TAK/CLD					
Dose (mg)	12.5	25	20	40	80	20/12.5	20/25	40/12.5	40/25	80/12.5	80/25
Total randomized	157	160	155	153	162	156	154	147	156	153	162
Completed Study*	135 (86.0%)	141 (88.1%)	141 (91.0%)	139 (90.8%)	142 (87.7%)	135 (86.5%)	131 (85.1%)	131 (89.1%)	125 (80.1%)	125 (81.7%)	125 (77.2%)
Number for Secondary Endpoint	155 (98.7%)	156 (97.5%)	155 (100%)	152 (99.3%)	162 (100%)	154 (98.7%)	153 (99.4%)	145 (98.6%)	155 (99.4%)	151 (98.7%)	158 (97.5%)
Discontinued (Row 1-2)*	22 (14.0%)	19 (11.9%)	14 (9.0%)	14 (9.2%)	20 (12.3%)	21 (13.5)	23 (14.9)	16 (10.9)	31 (19.9)	28 (18.3)	37 (22.8)
Discrepancy (Row 3-2)	+20 (3.2%)	+15 (4.4%)	+14 (8.4%)	+13 (5.2%)	+20 (9.3%)	+19 (5.1%)	+22 (8.4%)	+14 (15.0%)	+30 (7.1%)	+26 (9.8%)	+33 (6.8%)
Actual Missing in Analysis (Row 1-3)	2 (1.3%)	4 (2.5%)	0	1 (0.7%)	0	2 (1.3%)	1 (0.6%)	2 (1.4%)	1 (0.6%)	2 (1.3%)	4 (2.5%)

Source: Sponsor's table 15.2.3.1.2 in Study 302 CSR; *Data from Disposition of subjects

I queried the sponsor to explain the above discrepancies.

The sponsor submitted the following explanation on 28-Jul-2011 to my query regarding why these discrepant patients were dropped from the primary or secondary efficacy analysis, and at what point in time in the clinical trial they were dropped.

For the primary efficacy analysis (Table 16):

(i) Subjects whose ABPM data were considered non-evaluable due to failure to satisfy protocol-specified criteria did not have valid post-baseline ABPM data for analysis; therefore, they were not included in Row 3 (Table 16) for lack of a valid post-baseline ABPM value.

(ii) The number of subjects included in primary endpoint analysis (Row 2, Table 16) included data from subjects whose last ABPM occurred at Week 4 and were carried forward for analysis based on the principle of LOCF.

For the secondary efficacy analysis (Table 17):

(i) The number of subjects included in the secondary endpoint analysis (Row 3) included data from subjects whose last clinic SBP measurement occurred at a visit prior to the Week 8 window, and were included in the analysis based on the principle of LOCF.

These explanations appear reasonable. Sensitivity analyses performed using

(a) LOCF,

(b) observed cases (OC) which included data from only patients who had a post-baseline value, and

(c) multiple imputation method in which any subject with a baseline value (even without any post-baseline values) were included,

all showed consistent results for both the primary and the secondary efficacy endpoints.

7 Review of Safety

Safety Summary

The safety data in this population of hypertensive patients are derived mainly from a randomized, long term, open-label Study **308** (ongoing) which used the TAK-491CLD FDC. The intended duration of treatment in Study 308 is 52 weeks. The two supportive safety studies are: (i) Study **006** (56 weeks duration), and (ii) Study **016** (26 weeks duration), both open-label, unrandomized, uncontrolled clinical trials which used co-administration of TAK-491 and CLD. All three studies used the titrate-to-target BP design. The primary endpoint for all three studies was the incidence of AEs.

The safety data from the short-term, randomized controlled trials (Study 302, Study 301, Study 306, Study 303 and Study 009) were also reviewed.

All patients enrolled had, on admission, clinic SBP 160-190 mmHg or clinic DBP 95-119 mmHg. Patients were excluded from the above trials if they had a history of (i) a CV event within 6 months, (ii) severe renal disease (eGFR <30mL/min/1.73m^2), (iii) unilateral or bilateral renal artery stenosis, or presence of (iv) hyperkalemia, (v) hypokalemia, (vi) active liver disease, (vii) jaundice or (viii) ALT or AST > 2.5 ULN.

There appeared to be adequate exposure to TAK-491CLD. A total of 3,177 subjects with hypertension had received at least one dose of TAK-491 and CLD (2,358 received the FDC tablet and 819 received TAK-491 co-administered with CLD), 602 subjects had received treatment for ≥6months (≥24 weeks), and 171 had received treatment for at ≥1 year (≥52 weeks). For the FDC tablets, the median duration of treatment was calculated as 8.4 weeks (59 days), and the mean duration of treatment was 12.3 weeks (86 days).

In the factorial Study 302 and the supportive Study 009 in which fixed doses of TAK-491 and CLD were administered, an increase in dose of TAK-491 or CLD was accompanied by an increase in the incidence of (i) treatment emergent adverse events (TEAEs), (ii) elevated levels of blood creatinine, urea and uric acid, and/or (iii) hypokalemia.

Seven deaths were reported among patients receiving active treatment: 4 of 2,358 patients who received the TAK-491CLD combination, 1 of 470 subjects who received TAK-491 40 mg monotherapy, and 2 of 759 patients who received the OLM/HCTZ combination. Five of these deaths appear to be associated with co-morbid or accidental conditions. The two sudden deaths are of unknown cause; no autopsies were done.

Serious adverse events (SAEs) were observed more frequently in patients treated with the FDC TAK-491CLD compared to monotherapy with TAK-491 or CLD. These SAEs also appear to be associated with co-morbid conditions.

“Increased blood creatinine” was the most frequent TEAE leading to temporary or permanent discontinuation of study drug in Study 302. Of 40 patients who discontinued due to increased blood creatinine, 37 received the FDC, 2 received TAK-491 monotherapy and 1 received CLD 25 mg. In Studies 306, 301 and ongoing 308, too, “increased blood creatinine” was the most common TEAE leading to discontinuation,

and more subjects discontinued study drug due to TEAEs in the TAK-491CLD treatment groups than in the TAK-491+HCTZ or OLM/HCTZ treatment groups.

The creatinine elevations were transient for most subjects who remained on treatment, and about 96% of the subjects tended to reverse towards baseline levels (≤0.2 mg above the baseline or screening value). The changes in serum creatinine tended to be inversely related to changes in BP, with the mean serum creatinine increasing in parallel with reductions in SBP in most subjects.

"Dizziness" was the second most frequent TEAE leading to discontinuations in 3.8% and 2.5% of patients in the TAK-491CLD 40/25 and 80/25 mg treatment groups, respectively. Discontinuations for "hypotension" were most frequent (1.9%) in the TAK-491CLD 80/25 mg dose group. Discontinuations due to "hypokalemia" occurred in 2 subjects in the CLD 25 mg group and 1 subject in the TAK-491CLD 20/12.5 mg group.

Among the common TEAEs, the frequencies of "increased blood creatinine," "dizziness," "increased blood uric acid" and "back pain" were greater in the TAK-491CLD group than in the OLM/HCTZ group, whereas "headache," "upper respiratory tract infection" and "peripheral edema" were observed more frequently in the OLM/HCTZ group than in the TAK-491CLD group. "Orthostatic hypotension" was infrequent (≤0.9% and <2.0% of subjects experienced a decrease in SBP (≥20 mmHg) or DBP (≥10 mmHg), respectively).

Subgroup analyses of age, sex, race, renal impairment, and region based on most frequent TEAEs, TEAE clusters and laboratory parameters from the long-term safety Study 308 show minimal heterogeneity of safety profile across these subgroups, and suggest no initial dosing adjustment is required for any special population.

While an observational study reported that ARBs may be associated with a modestly increased risk of new cancer occurrences, evaluation of a list of neoplasm events in the long-term safety Study 308 suggests no signal for increased risk of new cancers.

The review found that the safety profile of TAK-491CLD appeared to be similar to other FDC products of ARBs and diuretics, with no new safety signals.

7.1 Methods

For safety review, I used JReview software to analyze the safety data of patients in the long term clinical trials (Study 308, Study 006 and Study 016) who received TAK-491 and CLD (as fixed dose combination or co-administration of TAK-491 and CLD) compared to the safety data of patients administered (i) TAK491 alone, (ii) CLD alone, (iii) placebo, and (iv) OLM/HCTZ combination, and also reviewed the safety data in the short term trials for any signal of acute changes in the safety parameters.

I evaluated the frequencies of syncope, dizziness or fatigue (symptoms of hypotensive events) which are expected to increase in patients treated with dual drugs, and the frequencies of (i) electrolyte abnormalities, including hypokalemia, hypochloridemia, hyponatremia, (ii) metabolic abnormalities including increase in uric acid levels, and (ii)

renal function test abnormalities (increased BUN, creatinine, and the urinary albumin : creatinine ratio). The data in the 120-Day PSUR of the ongoing Study 308 which was submitted on 23-Jun-2011 is also reviewed. Table 18 shows the clinical trials from which the safety data are derived.

Table 18 Studies, Treatment/doses/duration, selection criteria & primary endpoints

Study #	# enrolled	Comparator	Design	Duration and dose(s)	Patient selection criteria (BP)	Primary Endpoint
Fixed Dose Combination						
491CLD-302	1,714	Placebo	DB, R, 11-arm, factorial	**8 wk – fixed doses** TAK 20, 40 or 80; CLD 12.5 or 25, TAK-CLD 20/12.5, 40/12.5, 80/12.5, 20/25, 40/25, 80/25	Clinic SBP 160-190 mmHg (150/arm)	**Trough SBP by ABPM**
491CLD-301	1,085	OLM/HCTZ	DB, R, 3-arm	**8 wk – titrate to target BP** TAK-CLD 20/12.5 → 40/25; TAK-CLD 40/12.5 → 80/25; OLM/HCTZ 20/12.5 → 40/25	Clinic SBP 160-190 mmHg (370/arm)	Clinic SBP
491CLD-306	609	HCTZ	DB, R, 2-arm	**10 wk– titrate to target BP*** TAK 40 → TAK-CLD 40/12.5 → 40/25; TAK 40 → TAK 40+ HCTZ 12.5 → TAK40 +HCTZ 25	Clinic SBP 160-190 mmHg (300/arm)	Clinic SBP
491CLD-308	807 (ongoing)	OLM/HCTZ	OL, R, 2-arm,	**52 wk – titrate to target BP** TAK-CLD 40/12.5 → 80/12.5 →80/25; OLM/HCTZ (N.America) 20/12.5 → 40/12.5 → 40/25 OLM/HCTZ (Europe) 20/12.5 → 20/25	Clinic SBP 160-190 mmHg (400/arm)	**AEs (long-term safety study)**
491CLD-303	1,071	OLM/HCTZ	DB, R, 3-arm, fixed dose	**12 wk – forced titration**	Clinic SBP 160-190 mmHg (350/arm)	Clinic SBP
Co-administration Studies						
491CLD-009	557	Placebo	R, 3-arm, PC	6 wk – **fixed doses** TAK 40 + CLD 25 TAK 80 + CLD 25 Placebo + CLD 25	Clinic SBP 160-190 mmHg & 24-hr SBP 140-180 mmHg (180/arm)	**24-hr mean SBP by ABPM**
491CLD-006	669	Add on CLD/HCTZ	OL, Uncontrolled, unrandomized, sequential enrollment	**56 wk – titrate to target BP** Cohort 1: Step 1: TAK 40 → 80; Step 2: TAK + CLD 25 Step 3: TAK + CLD + others Cohort 2: Step 1: TAK 40 → 80; Step 2: TAK + HCTZ 12.5 Step 3: TAK + HCTZ 25 Step 4: TAK+HCTZ 25+others	Clinic DBP 95 – 119 mmHg	**Safety measures**
491CLD-016	418	Add on CLD/HCTZ	OL, Uncontrolled, unrandomized	**26 wk – titrate to target BP** Step 1: TAK 40 → 80; Step 2: TAK + CLD 25 Step 3: TAK + CLD + others	Clinic DBP 95 – 119 mmHg	**Safety measures**
Long Term Safety Studies required by EMA						
491CLD-307					Hypertensive subjects who did not achieve target BP on TAK-491 monotherapy	**Safety measures**
491CLD-309					Hypertensive subjects with moderate renal impairment	**Safety measures**

R= randomized, DB= double blind; OL= open-label; PC= placebo controlled;
* initial titration from TAK-491 40 mg monotherapy to combination therapy was forced

When reviewing the MedDRA Preferred Terms (PTs), I checked them against the verbatim reports to ensure that the PTs are coded appropriately.

In addition to the frequencies of syncope or hypotensive events expected to be increased in patients treated with dual drugs, I explored the frequencies of (i) electrolyte abnormalities, including hypokalemia, hypochloridemia, hyponatremia, (ii) cancers, (iii) worsening of renal function tests (BUN, creatinine, and urinary albumin:creatinine ratio), which have been identified as a class effect for ARBs (keeping in mind that patients in the clinical trials in this NDA had received the ARBs for a relatively short duration, unlike the long term clinical outcomes trials of ARBs such as ONTARGET, PROGRESS, etc., in which these class effect AEs have been reported).

The sponsor indicated that two additional studies will be submitted to EMA to support registration in Europe:

(i) Study 491CLD-307, (the FDC in subjects with hypertension who have not achieved target blood pressure while receiving TAK-491 monotherapy), and
(ii) Study 491CLD-309, (a long-term safety study in hypertensive subjects with moderate renal impairment).

The safety data from these two studies are not yet submitted to this NDA.

I reviewed also the safety data in Study 106 (a phase 1 bioavailability study which was recently completed) which was submitted with the 120-day PSUR on 23-Jun-2011.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

I evaluated the safety data of patients in the clinical trials as shown in Table 18.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) in the clinical trials in support of this NDA are categorized by intensity as mild, moderate or severe, and by relation to treatment (TEAEs or treatment emergent adverse events). AEs are also categorized as deaths, serious AEs (SAEs), treatment-related SAEs and discontinuations.

The protocol required investigators to report creatinine elevations ≥30% from baseline and >ULN as an adverse event of special interest (AESI), and advised investigators to consider withdrawing subjects with consecutive creatinine elevations ≥50% from baseline and >ULN. This may partly account for the finding that “blood creatinine increased” was the most frequently reported treatment emergent adverse event (TEAE) and also the most frequently reported TEAE leading to discontinuation of study drug. In the earlier monotherapy program which did not have this protocol requirement or guidance, a relatively lower incidence of “blood creatinine increased” was reported.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

I did not pool the data, because (a) Studies 302 and 009 are fixed dosage trials (the former used the FDC tablet, the latter used add-on tablets), (b) Studies 301, 306, 308, 006 and 016 are "titrate-to-target-BP" trials (with variations in the time of titration and duration of study), and (c) Study 303 used fixed dosage by "forced titration" (Table 2). Apart from Study 302 which used SBP by ABPM as the primary efficacy endpoint, the other Phase 3 FDC trials used clinic SBP for the primary efficacy endpoint, Study 009 used 24-hour mean SBP by ABPM, and open-label safety Studies 308, 006 and 016 used safety measures for their primary efficacy endpoint (Table 18).

7.2 Adequacy of Safety Assessments

The overall exposure to TAK491-CLD fixed dose combination and co-administration studies appears to support the adequacy of safety assessments in this NDA.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to different doses varies with different clinical trials. Table 19 shows the pooled duration of exposure of patients treatment groups in the Phase 3 TAK-491CLD trials (Studies 302, 301, 306 and 308) in which the fixed dose combination was used. It includes the safety data in the 120-day PSUR submitted on 23-Jun-2011.

Table 19 Duration of exposure in Phase 3 TAK-491 CLD fixed dose combination studies

Duration of Exposure (Days)	TAK-491 N = 470	CLD N = 316	TAK-491CLD N = 3082*	OLM/HCTZ N = 1139*	TAK-491+ HCTZ N = 303
Mean (SD)	53.5 (11.8)	52.7 (13.7)	86.1 (81.4)	144.8 (122.2)	65.4 (16.2)
Median	56.0	56.0	59.0	84.0	71.0
Min – Max	1 - 69	1 – 72	1 – 393	1 – 392	1 – 84
Cumulative Exposure (Number of Subjects)					
≥ 1 day	470	316	3082	1139	303
> 2 weeks	453	300	2954	1113	291
> 4 weeks	438	289	2834	1087	288
> 8 weeks	357	235	2447	984	265
> 12 weeks	0	0	847	640	1
> 24 weeks	0	0	309	355	0
> 48 weeks	0	0	180	208	0
> 52 weeks	0	0	112	135	0

Studies included: 491CLD-302, 306, 301, and 308 (Source: Sponsor's Module 2.7.4 Table 1.6.1, and 120-day PSUR Table 1.8.1)
*Data from 120 day PSUR; TAK-491 denotes the total of TAK-491 20, 40, and 80 mg treatment groups in study 491CLD-302. CLD denotes the total of CLD 12.5 and 25 mg treatment groups in study 491CLD-302. TAK-491CLD denotes the total of TAK-491CLD 20/12.5 mg through 80/25 mg, TAK-491 40 mg titrated to TAK-491CLD 40/25 mg, TAK-491CLD 20/12.5 mg titrated to 40/25 mg and 40/12.5 mg titrated up to 80/25 mg (+other antihypertensive drugs except ARBs). OLM/HCTZ denotes the total of OLM/HCTZ 20/12.5 mg titrated up to 40/25 mg (+other) and 20/12.5 mg titrated up to 20/25 mg (+other). The majority of OLM/HCTZ subjects are in the long-term study, 491CLD-308. TAK-491+HCTZ denotes TAK-491 40 mg titrated up to TAK-491+HCTZ 40/25 mg.

3,082 patients had received at least one dose of the TAK-491CLD FDC (20/12.5, through 80/25), with 309 of them treated for ≥24 weeks (≥6 months), and 112 subjects had cumulative exposure to TAK-491CLD or ≥52 weeks. The median duration of treatment was calculated as 8.4 weeks (59 days), and the mean duration of treatment was 12.3 weeks (86 days). The exposure of OLM/HCTZ is relatively lower due to lack of OLM/HCTZ treatment arms in the short-term Studies 302 and 306.

Table 20 shows the pooled duration of exposure of patients who received TAK-491 plus CLD coadministration (studies 009, 006 and 016).

Table 20 Duration of exposure in Phase 3 TAK-491 Coadministration studies

Duration of exposure (days)	TAK-491+CLD (a) N=819
Mean (SD)	165.5 (137.9)
Median	135.0
Min – Max	1 – 425
Cumulative Exposure (Number of Subjects)	
≥ 1 day	819
≥ 2 weeks	803
≥ 4 weeks	789
≥ 8 weeks	453
≥ 12 weeks	440
≥ 24 weeks	406
≥ 48 weeks	174
≥ 52 weeks	171

Source: Sponsor's Table 1.7.1. (a) Subjects took at least one dose of TAK-491 + CLD.

From the two tables above, a total of 3,177 patients with hypertension had received at least one dose of TAK-491 and CLD (2,358 received the fixed dose combination tablet and 819 received TAK-491 co-administered with CLD), with 602 subjects having received treatment for ≥6months (≥24 weeks) and 171 having received treatment for at ≥1 year (≥52 weeks).

7.2.2 Explorations for Dose Response

Dose-relationships were not evaluated for clinical trials in which the dose of the study drug was titrated to target BP.

Dose-relationship were explored for the factorial trial which studied FDC tablets administered for 8 weeks, and for the supportive trial Study 009 in which fixed dose co-administration of TAK and CLD at 40/25 and 80/25 was compared to placebo/25 administered for 6 weeks.

For the TEAEs, a dose relationship was found with an increase in the dose of TAK-491 for the TAK-491CLD fixed dose groups containing CLD 12.5 mg or CLD 25 mg, and also when the CLD dose was increased from 12.5 to 25 mg (e.g., from TAK-491 CLD 40/12.5 to 40/25) – for "blood creatinine," "blood urea increased," and "blood uric acid increased," and for "fatigue" in the CLD 25 dose groups (Table 21).

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)

Table 22 TEAEs by preferred term in ≥2% of all subjects (Study 009).

	Number (%) of Subjects		
Preferred Term	**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 any TEAE	94 (51.9)	96 (52.2)	94 (51.6)
Dizziness	6 (3.3)	16 (8.7)	19 (10.4)
Headache	13 (7.2)	8 (4.3)	9 (4.9)
Plasminogen activator inh bitor increased	3 (1.7)	12 (6.5)	4 (2.2)
Hypokalemia	11 (6.1)	2 (1.1)	4 (2.2)
Dyslipidemia	4 (2.2)	7 (3.8)	5 (2.7)
Blood creatinine increased	0	5 (2.7)	9 (4.9)
Asthenia	2 (1.1)	6 (3.3)	5 (2.7)
Urinary tract infection	3 (1.7)	3 (1.6)	7 (3.8)
Back pain	2 (1.1)	7 (3.8)	3 (1.6)
Fatigue	5 (2.8)	6 (3.3)	0
Diarrhea	0	4 (2.2)	6 (3.3)
Blood uric acid increased	2 (1.1)	4 (2.2)	3 (1.6)
Muscle spasms	1 (0.6)	5 (2.7)	3 (1.6)
Peripheral edema	4 (2.2)	4 (2.2)	1 (0.5)
Upper respiratory tract infection	2 (1.1)	4 (2.2)	3 (1.6)
Blood creatinine phosphokinase increased	3 (1.7)	1 (0.5)	4 (2.2)
C-reactive protein increased	0	4 (2.2)	4 (2.2)
Hypotension	0	4 (2.2)	4 (2.2)
Palpitations	4 (2.2)	3 (1.6)	1 (0.5)
Hematuria	1 (0.6)	3 (1.6)	3 (1.6)
Hypertriglyceridemia	2 (1.1)	1 (0.5)	4 (2.2)
Blood potassium decreased (a)	3 (1.7)	0	0
Edema (b)	1 (0.6)	0	1 (0.5)

Source: Sponsor's Table 15.3.1.4.

In Study 009, too, a dose relationship was found with an increase in dose of TAK-491 from 0 mg (placebo) to 40 mg to 80 mg (while receiving also CLD 25 mg) for "dizziness," "increased blood creatinine," "and diarrhea," but no dose relationship was found for other AEs (Table 22).

In general the incidence rates of mechanism-based AEs such as "increased blood

creatinine," "increased blood urea," "increased blood uric acid" and "hypokalemia" were similar between the factorial clinical trial (Study 302) in which patients received relatively lower doses, and Study 301 and Study 306 in which patients received titrate-to-target BP treatment, approximately 30% of subjects being titrated to higher dose strengths.

7.2.3 Special Animal and/or In Vitro Testing

Repeat dose toxicity studies in the monotherapy NDA 200,796 provided adequate exposure and safety profiles for the high dose (80 mg) of TAK-491 used, with the NOAEL in the 26-week being 1.2 times in female dogs (endpoint = observation of renal tubular dilatation and basophilia) and 4.3 times in the male dogs.

In a 13-week toxicity study in rats treated with CLD alone, TAK-491/TAK-536 M-II or the combination TAK-491/TAK-536 M-II/CLD, there were no deaths and no abnormal clinical signs at doses up to 1000/2000/300 mg/kg/day of TAK-491/TAK-536 M-II/CLD with the exception of decrease in body weight gain and food consumption in the TAK-491/TAK-536 M-II groups which was enhanced by CLD. Also, WBC and lymphocyte counts, and BUN and creatinine values (attributed to decreased GFR secondary to changes in renal perfusion) were increased in the TAK-491/TAK-536 M-II alone, and were increased further when CLD was added. The study did not find kidney lesions consisted with severe or acute injury to renal tubules or glomeruli.

Another dose-finding study in rats to evaluate maternal toxicity and fetal development of CLD alone, TAK-491/TAK-536 M-II or the combination TAK-491/TAK-536 M-II/CLD found no adverse on embryo-fetal mortality or teratogenicity at maternally toxic doses although some degree of fetal growth retardation and increased incidence of morphological variations were found (which would be covered by a black box warning in the label against the use in pregnant women of all currently marketed ARBs).

7.2.4 Routine Clinical Testing

Clinical laboratory abnormalities commonly seen with ARBs and diuretics such as increases in BUN and creatinine from baseline values, were among the most frequent TEAEs leading to temporary or permanent discontinuation of study drug in Study 302, 306, 301 or 308 (Table 25, Table 27 and Table 28).

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

Seven deaths were reported as of 30-Nov-2010 among patients receiving active treatment: 1 of 470 subjects receiving TAK-491 40 mg monotherapy, 4 of 2358 patients who received TAK-491CLD combination treatment, and 2 of 759 patients who received OLM/HCTZ combination treatment (Table 23).

Table 23 Deaths in TAK-491CLD clinical research program

Study	Site/Subject # Sex/Age/Race	Most Recent Treatment	Day of Last Dose	Preferred Term (Onset Study Day)
302	3300 / 006 Female/72/White	**TAK-491CLD** 80/25 mg	31	Multi-organ failure / bacterial endocarditis (32)
306	1023 / 024 Female/61/Black	TAK-491 40 mg	6	Sudden death (6)
	1047 / 002 Male/67/White	**TAK-491CLD** 40/12.5 mg	14	Sudden death (14)
308	2112 / 014 Female/40/White	**TAK-491CLD** 40/12.5 mg	216	Accidental drowning (217)
	2047 / 011 Male/58/White	**TAK-491CLD** 80/12.5 mg	72	Septic shock (74)
	2090 / 012 Female/49/White	OLM/HCTZ 20/12.5 mg	183	Gunshot wound (183)
	2075 / 019 Male/64/White	OLM/HCTZ 40/12.5 mg	168	Arteriosclerosis (191)

Source: Sponsor's Table 2.h in Module 2.7.4

Five of these deaths appear to be associated with co-morbid or accidental conditions. Of the two sudden deaths, one (61 year old black female) died on day 6 of treatment; the death certificate recorded "sudden death with unknown cause." The other death (67 year old white male) occurred on day 15 of treatment; the death certificate recorded the cause of death as "acute cardiovascular insufficiency." Autopsies were not done.

There were also four additional deaths (three appear to be sudden deaths) prior to randomization:

- Subject 3002/043 (in Study 302), died suddenly 5 days after the Screening Visit.
- Subject 1023/018 (in Study 306) died on Day 6, due to cardiac arrest as a result of complications of spontaneous hemothorax and arterial occlusion.
- Subject 1016/006 (in Study 306) died due to cardiac arrest 42 days after the last (13^{th}) dose of single-blind placebo treatment.
- Subject 2112/008 (in Study 301) died suddenly 8 days after starting single-blind placebo run-in. Cause of death was unknown.

In the 120-day Update, no additional deaths were reported for Study 308 (as of 01-May-2011 data cut). There were also no deaths reported for Study 303 during active treatment, but two deaths occurred following screening and prior to randomization:

- Subject 1051/025 (67 yr, black male), after the screening visit and being instructed to discontinue his medications (verapamil and lisinopril), was found unresponsive at home. His BP at the ER was 241/95 mmHg. He died on transfer to hospital for neurosurgery. The cause of death was subarachnoid hemorrhage.
- Subject 1015/002 (50 yr, white male) with history of alcohol dependence, alcohol related seizures, and palpitations, on atenolol 50 mg qd, was in placebo run-in, and deemed a screen-fail because of drug abuse. He was re-started on atenolol, and found 10 days later to have BP 161/90 mmHg and a withdrawal seizure. He was admitted to a hospitalized, transferred to a rehabilitation facility, and died 2 days later. The cause of death was alcohol withdrawal.

7.3.2 Nonfatal Serious Adverse Events

Table 24 shows that a higher frequency of nonfatal SAEs associated with TAK-491CLD were reported with in the long-term Study 308 (as expected from the longer exposure to TAK-491CLD). There was a higher frequency of SAEs overall in patients treated with the combination TAK-491CLD compared to monotherapy with TAK-491 or CLD.

For patients treated with OLM/HCTZ combination, too, a higher frequency of nonfatal SAEs was reported in the long-term Study 308, probably due to a longer exposure.

Table 24 Nonfatal SAEs in TAK-491CLD clinical research program

	n/N (%)				
Study	**TAK-491 N = 1078**	**CLD N = 316**	**TAK-491CLD N = 2375**	**TAK-491+ HCTZ N = 303**	**OLM/HCTZ N = 775**
Study 302	7/470 (1.5)	2/316 (0.6)	10/926 (1.1)	NA	NA
Study 306(a)	2/608 (0.3)	NA	5/302 (1.7)	4/303 (1.3)	NA
Study 301	NA	NA	12/729 (1.6)	NA	6/356 (1.7)
Study 308	NA	NA	17/418 (4.1)	NA	23/419 (5.5)
Total	9/1078 (0.8)	3/216 (0.6)	44/2375 (1.9)	4/303 (1.3)	29/775 (3.7)

Source: Sponsor's Table 2.i in Module 2.7.4; NA= not applicable; (a) SAE counts are assigned to treatment at time of the event. All subjects in 491CLD-306 received TAK-491 40 mg during the 2-week, single-blind period. In the double-blind treatment period, 302 subjects were treated with TAK-491CLD and 303 subjects were treated with TAK-491+HCTZ.

The safety report mentions CIOMS reports for 11 SAEs (6 subjects in the TAK-491CLD group and 5 in the OLM/HCTZ group) that were received after the cutoff dates of 17-Sep-2010 to 30-Nov-2010, which were not included in Table 24. Four CIOMS reports for SAEs were submitted in an Appendix to the 120-day PSUR (received after data close).

These include the following:

- A 75-year-old white female on TAK-491CLD 40/12.5 mg, was hospitalized for *rectocele repair, including vaginal repair and vaginal hysterectomy* on Study Days 235 to 238. The study drug was unchanged and the subject continued in the study.
- A 69-year-old white female on TAK-491CLD 40/12.5 mg experienced *atrial fibrillation* (Study Days 153 to 155). The subject had a history of an unspecific arrhythmia. The

study drug was unchanged and the subject continued in the study.

- A 64-year-old white male on TAK-491CLD 80/25 mg experienced *septicemia from suspected endocarditis on a degenerated mitral valve* (Study Day 195 to ongoing); it was not resolved at the time of reporting. The subject discontinued the study drug.
- A 63-year-old white male on TAK-491CLD 40/12.5 mg was hospitalized for *hydrocele resection* on (Study Days 218 to 219). The subject continued in the study.

The following SAEs were reported by >1 subject:

- 4 SAEs of pulmonary embolism (2 in TAK-491CLD, 1 in TAK-491+HCTZ, and 1 in OLM/HCTZ group).

7.3.3 Dropouts and/or Discontinuations

In Study 302, "blood creatinine increased" was the most frequent TEAE leading to temporary or permanent discontinuation of the study drug (Table 25). Of 40 patients who discontinued due to "blood creatinine increased," 37 received the FDC, 2 received TAK-491 monotherapy and 1 received CLD 25 mg monotherapy.

Table 25 Most frequent TEAEs leading to temporary or permanent discontinuation of study drug (≥2 subjects in any pooled treatment group) in Study TAK-491CLD -302

	Number (%) of Subjects										
	TAK-491			CLD		TAK-491 CLD					
MedDRA Preferred Term	20 N=155	40 N=153	80 N=162	12.5 N=156	25 N=160	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
Discontinuations due to any TEAE	3 (1.0)	6 (3.9)	7 (4.3)	3 (1.9)*	6 (3.8)	10 (6.4)	5 (3.4)†	14 (9.2)§	12 (7.8)	22 (14.1)	23 (14.3)
Blood creatinine increased	0	1 (0.7)	1 (0.6)	0	1 (0.6)	4 (2.6)	1 (0.7)	5 (3.3)	8 (5.2)	10 (6.4)	9 (5.6)
Dizziness	0	0	1 (0.6)	0	0	1 (0.6)	1 (0.7)	1 (0.7)	0	6 (3.8)	4 (2.5)
Hypotension	0	0	1 (0.6)	0	0	0	2 (1.4)	1 (0.7)	1 (0.6)	1 (0.6)	3 (1.9)
Blood urea increased	0	0	0	0	1 (0.6)	1 (0.6)	0	2 (1.3)	2 (1.3)	1 (0.6)	1 (0.6)
Headache	0	1 (0.7)	1 (0.6)	2 (1.3)	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)	0
Fatigue	0	0	1 (0.6)	0	0	0	0	1 (0.7)	2 (1.3)	1 (0.6)	0
Vertigo	0	0	0	0	0	0	0	1 (0.7)	1 (0.6)	0	3 (1.9)
Diarrhea	0	0	0	0	0	0	1 (0.7)	1 (0.7)	0	1 (0.6)	0
Hypokalemia	0	0	0	0	2 (1.3)	1 (0.6)	0	0	0	0	0
Nausea	0	1 (0.7)	0	0	0	1 (0.6)	0	0	0	0	1 (0.6)

Source: Sponsor's Table 15.3.1.10 in Study 302 CSR.
*Excludes Subject 3216/011, who was withdrawn from the study on Day 20 due to an AE, as counted in disposition. However, the AEs of headache (Day -29 to Day 1), abdominal pain upper (Day -12 to Day 42), and vertigo (Day -10 to ongoing) that resulted in discontinuation were not treatment emergent, but pretreatment events.
†Excludes Subject 3046/001, who was withdrawn due to TEAEs of ankle pain (Days 5-6) and BP increased; the events were not noted as leading to discontinuation of study medication on the adverse event CRF page.
§Includes Subject 3204/003, who had study medication withdrawn due to a TEAE but was counted in the disposition summary as having withdrawn voluntarily.

Of the 37 on the FDC who discontinued, 7 patients had additional renal-related TEAEs

which led to discontinuation: 3 had increased blood urea, 1 had "increased blood urea nitrogen," 1 had "increased blood urea" and "fatigue," 1 had "increased blood uric acid" and 1 had "renal impairment." There were also 2 permanent discontinuations due to other renal-related TEAEs: 1 due to "renal impairment," and 1 due to "increased blood urea," "hyperkalemia" and "increased hepatic enzymes."

"Dizziness" was the second most frequent TEAE which led to discontinuations in 3.8% and 2.5% of patients in the TAK-491CLD 40/25 and 80/25 mg treatment groups, respectively.

Discontinuations for "hypotension" was found with highest frequency (1.9%) in the highest dose (TAK-491CLD 80/25 mg) group.

Discontinuations due to "hypokalemia" were found in 2 subjects in CLD 25 mg group and 1 subject in TAK-491CLD 20/12.5 mg group.

For discontinuations due to AEs in Study 302 (Table 26), there are a few discrepancies between the number of discontinuations submitted in the Disposition tables in the efficacy analyses, and the number of discontinuations submitted in the Safety tables. For discontinuations where the reasons are known, the explanations are provided in the footnotes. The sponsor's explanations for the remaining discrepancies (highlighted in bold and yellow background in Table 26) are as follows:

(i) the disposition table (in efficacy analyses) includes only permanent study drug discontinuations due to AEs, whereas the safety table for discontinuations includes both temporary and permanent study drug discontinuations due to AEs, and therefore reflects a higher overall number of discontinuations/

(ii) nine subjects who discontinued subsequently restarted study medication and completed the study (and are not included in the disposition table). These nine subjects plus subject 3204/003 (who was withdrawn due to TEAE but included in disposition summary as voluntary withdrawal) accounted for the differences observed in Table 26.

Table 26 Discontinuations due to AEs by dose in Study 302

Drug	CLD		TAK-491			TAK/CLD					
Dose (mg)	12.5	25	20	40	80	20/12.5	20/25	40/12.5	40/25	80/12.5	80/25
Total enrolled	157	160	155	153	162	156	154	147	156	153	162
Discontinuations due to AEs*	4 (2.5%)	6 (3.8%)	3 (1.9%)	6 (3.9%)	6 (3.7%)	10 (6.4%)	10 (6.5%)	6 (4.1%)	19 (12.2%)	11 (7.2%)	22 (13.6%)
Discontinuations due to TEAEs†	3 (1.9%)[a]	6 (3.8%)	3 (1.9%)	6 (3.9%)	**7 (4.3%)**	10 (6.4%)	**12 (7.8%)**	5 (3.4%)[b]	**22 (14.1%)**	**14 (9.2%)[c]**	**23 (14.3%)**

*From disposition table; †From safety table; [a] Exclude subject 3216/011 who was withdrawn on Day 30 due to AEs of headache and vertigo which were pre-treatment symptoms; [b]Excludes subject 3046/001 who was withdrawn due to ankle pain and BP increased; [c]Includes subject 3204/003 who was withdrawn due to TEAE but was in disposition summary as voluntary withdrawal.

In Studies 306 and 301, more subjects temporarily or permanently discontinued the study drug due to TEAEs in the TAK-491CLD treatment groups than in the TAK-491 + HCTZ or the OLM/HCTZ treatment groups. "Blood creatinine increased" was the most common TEAE leading to discontinuation in both of these short-term titration studies, consistent with results in the factorial Study 302 (Table 27).

Table 27 Most frequent TEAEs leading to temporary or permanent discontinuation of study drug across Study 302, Study 306 and Study 301

	Number (%) of Subjects										
	Study 302						Study 306		Study 301		
	TAK-491CLD						TAK-491CLD	TAK-491 +HCTZ	TAK-491CLD		OLM/ HCTZ
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**	**40/12.5 →40/25 N=302**	**40+12.5 →40+25 N=303**	**20/12.5 →40/25 N=372**	**40/12.5 →80/25 N=357**	**20/12.5 →40/25 N=356**
Discontinuations due to any TEAE	10 (6.4)	5 (3.4)†	14 (9.2)§	12 (7.8)	22 (14.1)	23 (14.3)	28 (9.3)	22 (7.3)	23 (6.2)	34 (9.5)	11 (3.1)
Blood creatinine increased	4 (2.6)	1 (0.7)	5 (3.3)	8 (5.2)	10 (6.4)	9 (5.6)	12 (4.0)	6 (2.0)	2 (0.5)	9 (2.5)	2 (0.6)
Dizziness	1 (0.6)	1 (0.7)	1 (0.7)	0	6 (3.8)	4 (2.5)	3 (1.0)	5 (1.7)	4 (1.1)	2 (0.6)	1 (0.3)
Hypotension	0	2 (1.4)	1 (0.7)	1 (0.6)	1 (0.6)	3 (1.9)	2 (0.7)	2 (0.7)	3 (0.8)	4 (1.1)	1 (0.3)
Blood urea increased	1 (0.6)	0	2 (1.3)	2 (1.3)	1 (0.6)	1 (0.6)	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)	0
Headache	0	0	0	1 (0.6)	1 (0.6)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0
Fatigue	0	0	1 (0.7)	2 (1.3)	1 (0.6)	0	1 (0.3)	0	0	3 (3.8)	1 (0.3)
Vertigo	0	0	1 (0.7)	1 (0.6)	0	3 (1.9)	0	0	0	0	0
Diarrhea	0	1 (0.7)	1 (0.7)	0	1 (0.6)	0	0	0	0	1 (0.3)	0
Hypokalemia	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Nausea	1 (0.6)	0	0	0	0	1 (0.6)	1 (0.3)	0	0	1 (0.3)	1 (0.3)

Source: Sponsor's 491CLD-302 Table 15.3.1.10, 491CLD-306 Table 15.3.1.10, 491CLD-301 Table 15.3.1.10.

In a cross-study comparison of Studies 302, 306 and 301, the discontinuation rates due to TEAEs ("blood creatinine increased," "dizziness," and "hypotension") were relatively similar between study 302 (were relatively low fixed doses were administered) compared to Studies 306 and 301 where >30% of patients in TAD-491CLD group were titrated to higher doses (Table 27).

In the ongoing open-label Study 308, too, the incidence of discontinuation due to TEAEs was higher in the TAK-491CLD treatment group (17.5%) compared with the OLM/HCTZ treatment group (8.8) (Table 28).

Table 28 Most frequent TEAEs leading to temporary or permanent discontinuation of study drug in Study 308

Reason for Discontinuation	Number (%) of subjects	
	TAK-491CLD N = 418	OLM/HCTZ N = 419
Total discontinued	126 (30.1)	86 (20.5)
Due to TEAE	73 (17.5)	37 (8.8)
Protocol deviation	6 (1.4)	6 (1.4)
Lost to follow-up	13 (3.1)	16 (3.8)
Voluntary withdrawal	30 (7.2)	19 (4.5)
Lack of efficacy	0	2 (0.5)
Other	4 (1.0)	6 (1.4)

Source: Sponsor's 120-Day Update Table 1.4.2

Voluntary withdrawals were also higher in the TAK-491CLD group (7.2%) compared to the OLM/HCTZ group (4.5%); the data showed that the reason for premature discontinuations due to voluntary withdrawal were not associated with TEAEs, but were due to “moving out of the area,” “change in work hours,” “subject felt the drug was not working,” “withdrew consent” or “for personal reasons.”

7.3.4 Significant Adverse Events

Significant AEs associated most frequently with TAK-491CLD are in the following clusters of TEAEs: Cardiovascular, MACE (Major Adverse Cardiovascular Events), Renal, Hypersensitivity, Hypertension and Hypotension.

7.3.5 Submission Specific Primary Safety Concerns

For TAK-491CLD, the safety concerns specific to this drug are related to changes in renal function (increased BUN, increased creatinine), serum electrolytes (hypokalemia, hyperkalemia, hyponatremia) and hypotension.

The Hypotension Cluster, reported as dizziness, hypotension, postural dizziness, etc., which were observed in Study 308, occurred more frequently in the TAK-491CLD group (Table 29).

Table 29 Frequency of AEs in Hypotension Cluster in Study 308

MedDRA Preferred Term	Number (%) of subjects	
	TAK-491CLD N = 418	OLM/HCTZ N = 419
Subjects with ≥TEAE in Hypotension Cluster	98 (23.4)	69 (16.5)
Dizziness	67 (16.0)	51 (12.2)
Hypotension	12 (2.9)	9 (2.1)
Dizziness postural	12 (2.9)	8 (1.9)
Orthostatic hypotension	5 (1.2)	4 (1.0)
Presyncope	3 (0.7)	2 (0.5)
Syncope	4 (1.0)	1 (0.2)
Dizziness exertional	2 (0.5)	1 (0.2)
BP decreased	1 (0.2)	0
Cardiovascular insufficiency	1 (0.2)	0

Source: Sponsor’s 120-Day Update Table 2.4.4.6

Table 30 lists the AEs in the Renal Cluster in Study 308 which were reported as increased blood creatinine, increased BUN, etc. Elevated blood creatinine was the most frequent TEAE in this cluster, and was observed more frequently in the TAK-491CLD group. Increased BUN was also observed more frequently in the TAK-491CLD group.

Table 30 Frequency of AEs in Renal Cluster 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

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Among the common TEAEs, the frequencies of "blood creatinine increased," "dizziness," "blood uric acid increased" and "back pain" were greater in the TAK-491CLD group than in the OLM/HCTZ group (Table 31) whereas "headache," "upper respiratory tract infection" and "edema peripheral" were observed more frequently in the OLM/HCTZ group than in the TAK-491CLD group. The differences in frequencies for other TEAEs were smaller.

Table 31 Top 12 common TEAEs (≥2% incidence) in 120-Day Update for Study 308 (preferred term)

MedDRA Preferred Term	Number (%) of subjects	
	TAK-491CLD N = 418	OLM/HCTZ N = 419
Subjects with any TEAE	319 (76.3)	314 (74.9)
Blood creatinine increased	83 (19.9)	35 (8.4)
Dizziness	67 (16.0)	51 (12.2)
Nasopharyngitis	45 (10.8)	41 (9.8)
Headache	27 (6.5)	42 (10.0)
Upper respiratory tract infection	20 (4.8)	26 (6.2)
Fatigue	20 (4.8)	17 (4.1)
Diarrhea	19 (4.5)	19 (4.5)
Nausea	19 (4.5)	19 (4.5)
Blood uric acid increased	17 (4.1)	9 (2.1)
Edema peripheral	7 (1.7)	16 (3.8)
Back pain	15 (3.6)	10 (2.4)

Source: 120-Day Update Table 2.4.2.3.

The increase in blood creatinine appears to drive the HLT (high level term) of "renal

function analyses" to be the highest incidence (≥5%) of any HLT for TAK-491CLD treatment group.

7.4.2 Laboratory Findings

In the long-term safety Study 308, small increases or decreases from baseline were observed for hematology parameters at some visits, which showed no trends. No subject discontinued the study and none experienced an SAE as a result of a markedly abnormal hematology lab value.

Table 32 Frequency of subjects with ≥1 markedly abnormal lab value at any visit in Study 308

MedDRA Preferred Term		Number (%) of subjects	
		TAK-491CLD N = 418	OLM/HCTZ N = 419
Electrolyte parameters			
Sodium	<130 mmol/L	10/407 (2.5)	7/414 (1.7)
	>150 mmol/L	23/407 (5.7)	27/414 (6.5)
Potassium	<3.0 mmol/L	2/407 (0.5)	0/413
	>6.0 mmol/L	2/407 (0.5)	1/413 (0.2)
Calcium	>1.2 x ULN	1/405 (0.2)	0/408
Metabolic parameters			
Uric	M: >650 μmol/L	66/405 (16.3)	41/408 (10.0)
	F: >506 μmol/L		
CK, total	>10 x ULN	0/405	1/408 (0.2)
Renal parameters			
Serum creatinine	>1.5 x baseline	69/408 (16.9)	25/414 (6.0)

Source: Sponsor's 120-Day Update Table 3.4.1

The frequencies of subjects with markedly abnormal lab values are shown in Table 32. The frequencies of subjects with high levels of serum creatinine and serum uric acid are greater in the TAK-491CLD group; the frequencies of subjects with high sodium values are greater in the OLM/HCTZ group.

The frequencies of subjects with elevated liver enzymes were low in both treatment groups. None had elevated ALT or AST with concurrent elevations in total bilirubin or alkaline phosphatase.

Reversibility of creatinine elevations in Study 308:

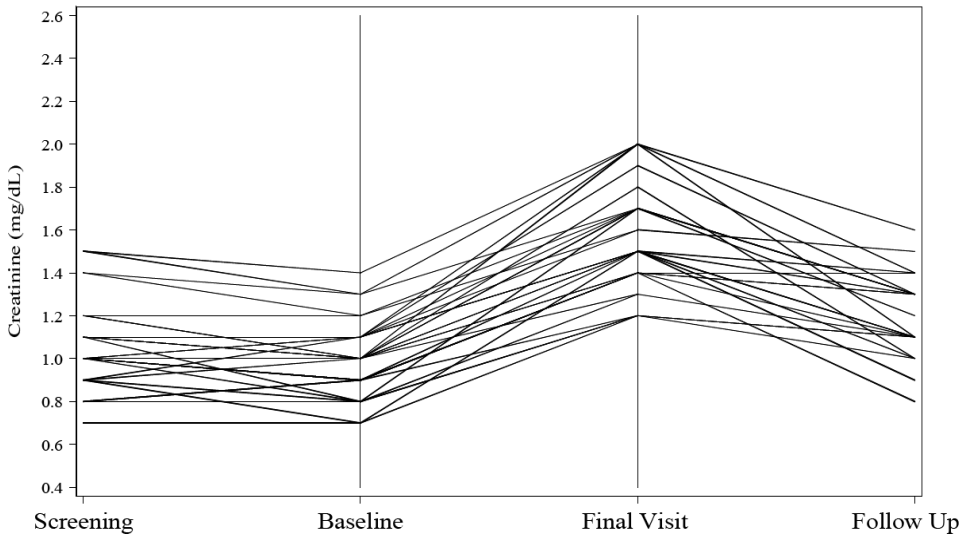
Subjects with elevations based on 2 criteria: (i) ≥30% change from Baseline and >ULN and (ii) ≥50% change from Baseline and >ULN were analyzed for elevations that occurred at any post-baseline visit (defined as any visit after the first dose of the study drug) and at the Final Visit (defined in the protocol as the last observed value within 7 days of the last dose of the study drug or the last value obtained as of the 18-Mar-2010 data cut).

The cumulative data for both the ≥30% and ≥50% criteria demonstrates that the percentage of subjects meeting these criteria at the Final Visit was substantially less

than at any post-baseline visit, suggesting that creatinine elevations were transient for most subjects who remained on treatment.

Although the reversibility of creatinine elevations cannot be fully assessed because Study 308 is still ongoing, the line plot presented in Figure 39 shows that the creatinine levels for the subjects who met the ≥30% criterion during treatment at the Final Visit tended to reverse toward the baseline levels.

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

Reversibility of creatinine elevations across Studies 301, 302, 303 and 306: Subjects with creatinine values that met ≥30% criterion at the final visit/early termination visit who were followed until 2 consecutive creatinine values were ≤0.2 mg/dL above the baseline or screening value.

In Table 33, apart from the 6 subjects with elevated creatinine who were not flagged for follow up, and the 8 subjects who were lost to follow-up with no post-study values, follow-up data available on 138 subjects show that:

- 133 subjects (96.4%) resolved to ≤0.2 mg/dL above the Baseline or Screening value.
- 2 subjects (1.4%) in 491CLD-303 were below the 30% criterion but were >0.2 mg/dL above the Baseline or Screening value.
- 2 subjects (1.4%) in 491CLD-302 were below the 30% criterion and no longer >ULN but were >0.2 mg/dL above the Baseline or Screening value.
- 1 subject (0.7%) remained unresolved. For this female subject with a history of CKD Stage II/III followed for 11 months, her serum creatinine eventually came down from a high of 5.0 to 1.85 mg/dL; her baseline was 1.27 mg/dL. Her BP remained controlled.

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).

7.4.3 Vital Signs

No clinically relevant changes were observed for physical examinations or vital signs including heart rate, weight and orthostasis.

Orthostatic hypotension (defined as decreases from sitting to standing SBP and DBP of ≥20 mmHg or 10 mmHg, respectively) was infrequent (≤0.9% and ≤2.0% of subjects experienced SBP or DBP decrease, respectively, meeting the definition of orthostatic hypotension at the Final Visit) and not different from Baseline.

7.4.4 Electrocardiograms (ECGs)

No clinically important effect on any ECG parameter was reported across the Studies using the FDC.

7.4.5 Special Safety Studies/Clinical Trials

The following two safety studies are being conducted to be submitted to EMA to support registration in Europe:

(i) Study 491CLD-307 is conducted in subjects with hypertension who have not achieved target BP while receiving TAK-491 monotherapy, and

(ii) Study 491CLD-309 is being conducted as a long-term safety study in hypertensive

subjects with moderate renal impairment.

These studies are ongoing, and safety data will be submitted to EMA; the safety data are not yet available to submit to this NDA.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The incidence of TEAEs was comparable across the 12.5 mg CLD containing FDC doses (20/12.5, 40/12.5, and 80/12.5 mg TAK-491CLD) with a higher incidence observed with the 40/25 mg TAK-491CLD dose. In terms of discontinuations due to AEs, the lowest incidences were observed at the 20/12.5 and 40/12.5 mg TAK-491CLD dose levels, an intermediate incidence was observed at the 80/12.5 mg TAK-491CLD dose level, and the highest incidence was observed at the 40/25 mg TAK-491CLD dose-level. These differences were primarily driven by the common mechanism-based TEAEs of “blood creatinine increased” and “dizziness.” Please also see section 7.2.2 Explorations for Dose Response.

7.5.2 Time Dependency for Adverse Events

In the ongoing Study 308, AEs were accounted according to the 3-month interval in which they started, and were not carried over into the subsequent interval.

The 120-Day PSUR showed that the proportion of subjects with at least 1 TEAE decreased over time (e.g., from 61.7% during the first 3-month interval to 36.9% during the second 3-month interval in the TAK-491CLD group, and from 57.8% during the first 3-month interval to 35.6% during the second 3-month interval in the OLM/HCTZ group).

The incidence of blood creatinine elevations decreased substantially in the TAK-491CLD and OLM/HCTZ groups from the first 3-month interval (10.2% and 4.2%, respectively) to the second 3-month interval (5.3% and 1.4%, respectively). The incidence of most other common preferred terms decreased over time. It appears that that increased exposure is not associated with an increase in the incidence of AEs.

However, these data may be somewhat confounded due to potential period effects related to discontinuation of subjects, reporting biases during the first 3-month interval, and differences in the number of visits during different titration intervals.

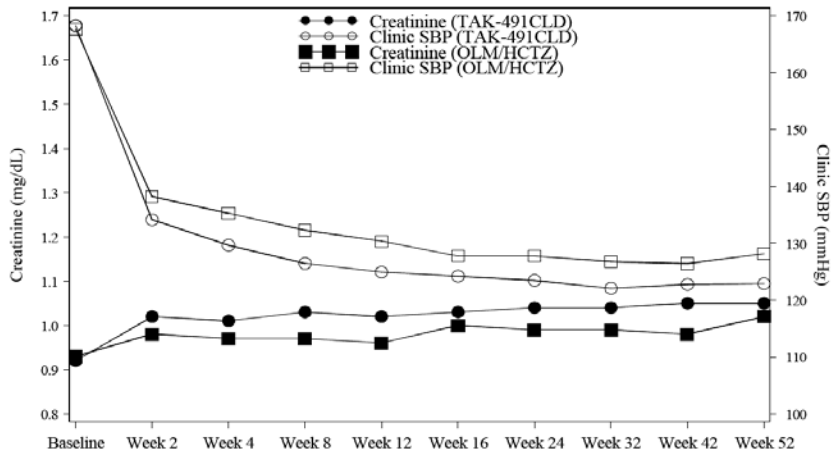
7.5.3 Drug-Demographic Interactions

Subgroup analyses of age, sex, race, renal impairment, region and other subgroups based on most frequent TEAEs, TEAE clusters and laboratory parameters from Study 308 show minimal heterogeneity of safety and tolerability profile observed across these subgroups. No initial dosing adjustment is recommended for any special population.

7.5.4 Drug-Disease Interactions

Relationship between serum creatinine elevations and BP reductions:
The changes in serum creatinine tended to be inversely related to the changes in BP. The relationship between mean SBP and mean creatinine increases for each treatment group in the ongoing 491CLD-308 study is shown in Figure 40. The greatest mean SBP reduction (and mean increase in serum creatinine levels) appear at Week 2. Titration was allowed at the Week-4 Visit. After Week 4, small increases in mean creatinine occurred in both treatment groups and mean SBP in this group is further reduced. After the initial increase, the mean serum creatinine levels in both treatment groups remained relatively stable.

Figure 40 Mean creatinine and clinic SBP values by treatment group in Study 308



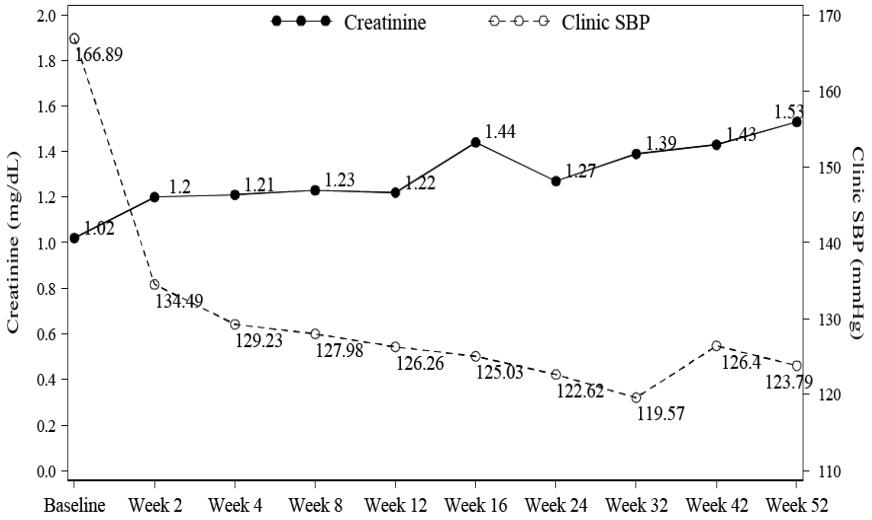
Number of Subjects

Creatinine (TAK-491CLD)	408	384	396	368	356	341	312	266	192	167
Clinic SBP (TAK-491CLD)	408	382	396	368	356	341	311	263	192	167
Creatinine (OLM/HCTZ)	414	399	391	379	374	368	355	302	235	196
Clinic SBP (OLM/HCTZ)	414	399	391	379	374	368	354	301	233	196

This relationship was evaluated further for subgroups of subjects with (Figure 41) and without (Figure 42) creatinine elevations, defined by the ≥30% criterion. At the Final Visit, subjects with creatinine elevations had a SBP mean decrease from Baseline of 43.1 mmHg, compared with subjects without creatinine elevations (42.2 mmHg).

These plots suggest that the mean serum creatinine increased in parallel with the reductions in SBP in the subjects who have creatinine elevations as defined by the ≥30% criterion (Figure 41).

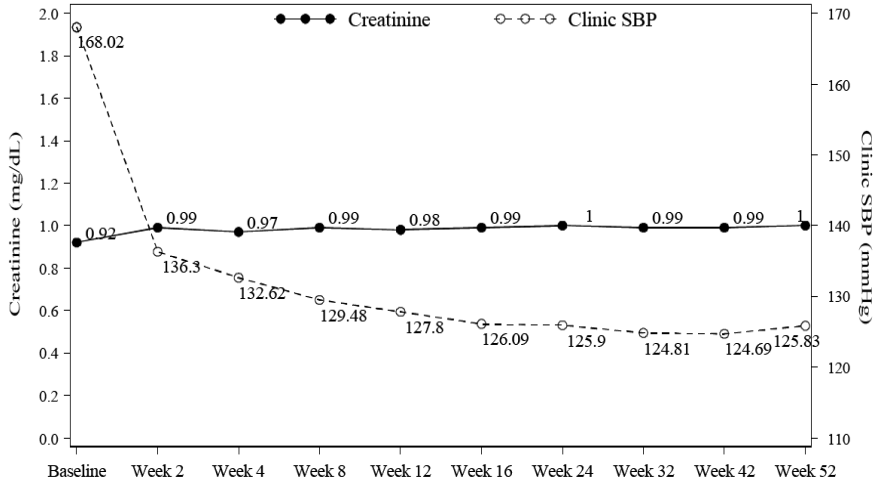
Figure 41 Mean creatinine and SBP in Study 308 –subjects with creatinine elevation at Final Visit



Number of Subjects										
Creatinine	44	43	43	40	39	38	34	29	20	19
Clinic SBP	44	43	43	40	39	38	34	28	20	19

Source: 120-Day Update Figure 7.4.3.3

Figure 42 Mean creatinine and SBP in Study 308 –subjects without creatinine elevation at Final Visit



Number of Subjects										
Creatinine	778	740	744	707	691	671	633	539	407	344
Clinic SBP	778	738	744	707	691	671	631	536	405	344

Source: 120-Day Update Figure 7.4.3.4

7.5.5 Drug-Drug Interactions

There is no clinically important pharmacokinetic interaction between TAK-536 (active metabolite derived from TAK-491) and CLD when they are co-administered.

There was no PK interaction between TAK-491 and other co-administered drugs such as amlodipine, antacids, chlorthalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, pioglitazone, and warfarin [in NDA 200,796 Module 2.7.2 Section 2.2.4].

CLD reduced lithium renal clearance increasing the risk of lithium toxicity.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Following the publication of an observational study which reported that ARBs may be associated with a modestly increased risk of new cancer occurrences, the sponsor submitted a list of neoplasm events (by preferred term) in the long-term safety Study 308 (Table 34). There appears to be no signal for increased risk of new cancers.

Table 34 Benign, malignant or unspecified neoplasms in Study 308

	Number (%) of Subjects			
	Module 2.7.4		120-Day Update	
Neoplasms Preferred Terms	TAK-491CLD N=401	OLM/HCTZ N=403	TAK-491CLD N=418	OLM/HCTZ N=419
Any neoplasm	1 (0.2)	3 (0.7)	4 (1.0)	4 (1.0)
Bladder transitional cell cancer	0	1 (0.2)	0	1 (0.2)
Breast cancer stage II	0	1 (0.2)	0	1 (0.2)
Hemangioma	0	1 (0.2)	0	1 (0.2)
Renal cancer	1 (0.2)	0	1 (0.2)	0
Lung cancer	0	0	0	1 (0.2)
Malignant melanoma	0	0	1 (0.2)	0
Melanocyte naevus	0	0	1 (0.2)	0
Neoplasm skin	0	0	1 (0.2)	0

Source: Study 308 CSR Table 15.3.1.10 and 120-Day Update Table 2.4.2.1.

7.6.2 Human Reproduction and Pregnancy Data

Female subjects of child-bearing potential were required to have a serum pregnancy test done at baseline and to use adequate contraception. However, one pregnancy was reported during Study 301. The subject was a 39 year-old black female who stated using condoms as the birth control method. She had been administered the study drug (20/12.5 mg of FDC) for 6 days. The fetal exposure (date from last negative pregnancy test or last menstrual period to the last dose of drug) was not known. She underwent an elective abortion at 6 weeks gestation.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. The drug product was not administered to pediatric subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: There were 5 reports of overdose: 3 in Study 301, and 2 in Study 308. None reported AEs, 4 completed the study and one was lost to follow-up.

Drug Abuse Potential: Clinical studies to evaluate this were not done.

Withdrawal and Rebound: Study 016 evaluated the effect of treatment withdrawal after a 26-week open-label treatment period. In the 6-week double-blind reversal phase (subjects were randomized to continue open-label regimen or switch to placebo plus CLD and current other antihypertensive medications, as required), no pattern of TEAEs was observed in the group randomized to placebo with the exception of 1 subject who had a hypertensive crisis after 13 days on placebo. It appears that TAK-491 and TAK-491CLD can be withdrawn without a rebound increase in BP.

7.7 Additional Submissions / Safety Issues

On 23-Jun-2011, the sponsor submitted a 120-Day Periodic Safety Update Report which includes (i) a summary of the safety and efficacy information contained in the Study 303 CSR, (ii) additional safety data obtained from the ongoing open-label Study 308, and (iii) the safety data from the recently completed phase 1 bioavailability (BA) Study 106 (which compared the relative bioavailability of TAK-491 CLD FDC tablets compared with co-administration of individual TAK-491 tablets and CLD tablets sourced in the European Union). These data are integrated into the clinical safety review in section 7.1 to 7.5 above.

8 Postmarket Experience

Not applicable. The TAK-491CLD FDC is not marketed in any country.

9 Appendices

9.1 Literature Review/References

Need for combination antihypertensive therapy: According to the US Agency for Healthcare Research and Quality news release dated 28-Sep-2011, 55.1 million Americans (one-quarter of the American adult population) received treatment for high BP in 2008. The Agency also noted that 25% of women received treatment for high BP in 2008 compared to 23% of men[10].

The research based on the Medical Expenditure Panel Survey also revealed that 25% of white adults were treated for high BP in 2008, compared to 15% Hispanics and 20% of people of other races. Treatment for high BP in 2008 were most frequent in patients 65 years or older (60%), followed by patients 45 to 64 years (32%) and those 18 to 44 years (5%).

Despite a wide range of effective antihypertensive medications, the BP remains inadequately controlled in nearly half of the patient population and in approximately one-third of the treated patient population in the United States[11,12]. For most patients, the achievement of the BP targets requires at least two antihypertensive medications from different drug classes[13,14,15].

Choice of chlorthalidone (CLD): CLD 25 mg and 50 mg dose strengths (and therapeutic equivalents) have been commercially available since 1959; however, lower doses (12.5 and 25 mg) also reduce the BP very effectively, are better tolerated than the higher doses, and are associated with favorable cardiovascular outcomes[16,17,18]. On the other hand, low doses of HCTZ (12.5 and 25 mg) typically used in antihypertensive FDCs have been shown to be less potent than CLD and less effective than other drug classes[19], and there are no outcomes trials demonstrating the cardiovascular protective effect of low-dose HCTZ[20]. Based on this information, the sponsor chose CLD 12.5 and 25 mg doses to administer in combination with TAK-491 20, 40, and 80 mg doses in the TAK-491CLD clinical development program.

Use of systolic BP in endpoints: In the clinical trials, measures of SBP were selected as the primary and key secondary endpoints because SBP is more predictive of adverse CV outcomes than DBP, particularly in individuals older than 50 years of age[21,22,23].

Proposed doses for marketing: Based on the aggregate efficacy data and safety profile submitted, the sponsor proposed the TAK-491CLD dose range of (b) (4) 40/12.5, (b) (4) and 40/25 mg for marketing. The sponsor contended that incremental BP reductions observed across this dose range represent clinically meaningful effects, as the association of decreased BP and risk reduction for stroke and ischemic heart disease is continuous[24,25,26,27].

However, analysis of BP data in the Phase 3 study shows that only the **40/12.5 mg** and the **40/25 mg** doses appear to be clinically useful doses. The other (b) (4) will confuse the physicians prescribing the combination, the

pharmacists dispensing the prescription and the patients taking the medication.

Adverse events – increased serum creatinine: The most common TEAEs appear to be mechanism-based events, such as blood creatinine increased, dizziness, and headache. Blood creatinine increased and dizziness TEAEs are commonly associated with the combined use of RAAS-blocking and diuretic agents resulting from large magnitude BP reductions[28]. It was not unexpected that these mechanism-based TEAEs were observed more frequently in TAK-491CLD treatment groups compared with the monotherapy and combination comparator treatment groups, with the highest incidence observed at the TAK-491CLD 80/25 mg dose level.

Increases in serum creatinine attributed to decreases of intraglomerular pressure are not uncommon during treatment with ARBs and ACE inhibitors and may be potentiated by the intravascular volume contraction and large decreases in BP associated with potent diuresis[28]. Serum creatinine elevations and associated AESIs were observed in all treatment groups in the TAK-491CLD phase 3 studies, although they occurred more frequently in subjects treated with the higher doses of TAK-491CLD. These elevations appear to be generally transient (few subjects experienced consecutive elevations or had elevations present at Final Visit) or non-progressive (while subjects continued treatment) or reversible (following discontinuation of treatment) and were associated with large BP reductions. In addition, these elevations were asymptomatic and were associated with reductions of albuminuria.

The frequency at which blood creatinine increased was reported as a TEAE in the TAK-491CLD phase 3 program was probably influenced by the study protocol which instructed investigators to report as an AE any serum creatinine elevation ≥30% above Baseline and >ULN, regardless of symptoms. This is supported by the coadministration data from the TAK-491 monotherapy program where this guidance was not fully implemented and the "blood creatinine increased" TEAE reporting rates were substantially lower. Across studies, few renal-related SAEs were reported and few subjects prematurely discontinued treatment due to renal AEs (other than the AEs of "blood creatinine increased").

This creatinine elevation profile associated with TAK-491CLD treatment may be attributed to the changes in renal hemodynamics associated with the mechanisms of action of TAK-491 and CLD, as has been well described with other RAAS-blocking agents when used in combination with diuretics,[28] rather than to renal injury. In addition, treatment with ACE inhibitors and ARBs has been shown to slow the decline in renal function over time, despite acute increases in serum creatinine[29,30], and long-term treatment with CLD had not been associated with worse renal outcomes compared with amlodipine or lisinopril or compared with placebo in the ALLHAT trial[16].

Changes in laboratory parameters: Clinically important changes in other laboratory parameters were uncommon with TAK-491CLD, despite the electrolyte and metabolic alterations associated with thiazide-type diuretic therapy[31,32]. Consistent with these effects, small mean decreases in serum sodium, and mean increases in serum uric acid, triglycerides, and glucose were observed although reports of gout and new or worsening diabetes were infrequent. There were no clinically significant changes in HDL and LDL cholesterol, liver enzyme parameters, or in magnesium and calcium. Small

mean decreases from Baseline in hematocrit, hemoglobin levels, and RBC count were observed in the TAK-491CLD and the TAK-491 monotherapy treatment groups, consistent with the known effects of RAAS blockade on these parameters.

9.2 Labeling Recommendations

Black-boxed warning: The heading should be changed to be consistent with other ARB FDC labels as: WARNING: (b) (4) FETAL TOXICITY.

1. INDICATIONS AND USAGE: The following changes are added:

Edarbyclor may be used in patients whose blood pressure is not adequately controlled on monotherapy.

Edarbyclor may be used as initial therapy if a patient is likely to need multiple drugs to help achieve blood pressure goals.

The figures in the label on page 4 (Figures 1.a – 1.d) depict the responder analyses for Edarbyclor (b) (4)

2. DOSAGE AND ADMINISTRATION
This section should be modified to reflect the doses recommended in this review as follows:

(b) (4)

3. DOSAGE FORMS AND STRENGTHS
As discussed in Section 6.1.8 of this review, this section should be modified as follows:
(i) delete the proposed doses of (b) (4) and
(ii) keep only the dose of 40mg/12.5 mg as the starting dose and 40mg/25 mg as the maximum effective and tolerated dose.

4. CONTRAINDICATIONS
An additional sentence is added to specify the information: (b) (4)

5. WARNINGS AND PRECAUTIONS:
(b) (4)

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following corrections are made to reflect the data in the 120-Day Safety Update:

- The number of patients with hypertension exposed to Edarbyclor
- In Table 1, the incidences of dizziness and fatigue observed with Edarbyclor
- Hypertension and syncope incidences in patients treated with Edarbyclor
- Discontinuations because of AEs

(b) (4)

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. This section will need to be amended, after class labeling is published, to upgrade to a BOXED warning for all three trimesters.

10. OVERDOSAGE

The information is corrected with the data reported in Study 301 and Study 308 as follows:

(b) (4)

14. CLINICAL STUDIES

The following information regarding dose selection, effect in Black subjects, and outcome trials of angiotensin II receptor blockers are added to the label on page 20:

(b) (4)

(b) (4)

[redacted]

9.3 Advisory Committee Meeting

None planned.

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/s/

KHIN M U

10/03/2011

Clinical review of NDA for a fixed-dosed combination of azilsartan medoxomil and chlorthalidone. Based on the data submitted which shows clinically meaningful and statistically significant BP reductions with an unremarkable safety profile, this reviewer's recommendation of the NDA is approval pending the sponsor's response to comply with making the labeling changes.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-331 | **Applicant: Takeda Global Research and Development Center, Inc** | **Stamp Date: 24-Feb-2011**

Drug Name: TAK-491CLD (azilsartan medoxomil plus chlorthalidone) | **NDA/BLA Type: NDA** | **New NDA for fixed-dose combination tablet**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			√	**505(b)(1)**
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	√			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 491CLD-302:Factorial Indication: Hypertension Pivotal Study #2 ---------- Indication:	√			One pivotal and three supportive studies of FDC are submitted.

File name: 5_Clinical Filing Checklist for NDA_202-331 (TAK-491 CLD) azilsartan medoxomil plus chlorthalidone

Reference ID: 2927547

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	√			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			√	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	√			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			√	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_202-331 (TAK-491 CLD) azilsartan medoxomil plus chlorthalidone

Reference ID: 2927547

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	√			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Filed in DARRTS 04-Apr-2011

Reviewing Medical Officer: Khin Maung U, M.D. Date: 04-Apr-2011

Clinical Team Leader: Shari Targum, M.D. Date

File name: 5_Clinical Filing Checklist for NDA_202-331 (TAK-491 CLD) azilsartan medoxomil plus chlorthalidone

Reference ID: 2927547

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/s/

KHIN M U
04/04/2011

SHARI L TARGUM
04/04/2011

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA #:	202,331	DOCUMENT TYPE:	Request for Priority Review
DRUG NAME:	TAK-491CLD (azilsartan medoxomil plus chlorthalidone) tablets		
SD#:	155	SPONSOR:	Takeda Global Research & Development
DATE SUBMITTED:	09-Mar-2011	DATE RECEIVED:	09-Mar-2011
DATE ASSIGNED:	09-Mar-2011	DATE COMPLETED:	11-Mar-2011
MEDICAL OFFICER:	Khin Maung U, M.D.		

SUBMISSION

The submission is a Request for Priority Review in eCTD format.

Pharmacologic Category Azilsartan medoxomil (Edarbi)® is an Angiotensin II Receptor Blocker. Chlorthalidone is a thiazide diuretic.

Approved Indications Both azilsartan and chlorthalidone are approved for the treatment of hypertension, alone or in combination with other antihypertensive agents.

Review of Submission: The submission includes a statement form Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) that over 2/3^{rds} of patients with hypertension require ≥2 antihypertensive medications, and that combination treatment be considered as initial therapy for patients whose BP is ≥20/10 mmHg above target. JNC7 also recommended chlorthalidone over HCTZ to be used in combination with a RAAS inhibitor because chlorthalidone consistently reduces CV morbidity and mortality in high-risk patients with hypertension (MRFIT trial), including Blacks and diabetic patients.

My premise is that the Priority Review *is considered for an NDA/BLA of a product that (i) addresses an unmet medical need or (ii) has a significantly increased effectiveness over marketed products.*

For increased effectiveness, the sponsor submitted a comparison of their combination product with the olmesartan medoxomil-HCTZ combination in study 491CLD-301, an 8-week, titrate-to-target BP study of 1,066 patients with hypertension (Mean baseline clinic SBP 164-165 (SE0.55-0.56)). The primary endpoint was change in clinic SBP at Week 8, and a secondary endpoint was change in clinic SBP at Week 4. The sponsor claimed to have achieved statistically significant greater reductions in SBP for both the primary (Wee 8) and secondary (Week 4) endpoints (Table 1).

Table 1 Change from baseline in clinic SBP (mmHg) at Weeks 4 and 8 (Study 491CLD-301)

	TAK-491CLD		OLM/ HCTZ
Study Visit	20/12.5→ 40/25 mg N=372	40/12.5 mg→ 80/25 mg N=357	20/12.5 mg→ 40/25 mg N=356
Baseline (a)			
n	363	350	353
LS mean (SE)	165.2 (0.55)	164.8 (0.56)	164.7 (0.56)
P-value	0.503	0.870	--
Week 4: Key Secondary Endpoint			
n	360	347	352
LS mean change (SE)	-33.0 (0.87)	-34.1 (0.88)	-26.9 (0.88)
LS mean treatment difference (b)	-6.1	-7.2	--
(95% CI)	(-8.5, -3.7)	(-9.6, -4.8)	--
P-value	<0.001†	<0.001†	--
Week 8: Primary Endpoint			
n	363	350	353
LS mean change (SE)	-37.6 (0.83)	-38.2 (0.85)	-31.5 (0.84)
LS mean treatment difference (b)	-6.1	-6.7	--
(95% CI)	(-8.4, -3.8)	(-9.1, -4.4)	--
P-value	<0.001†	<0.001†	--

† P<0.05 (step-wise analysis); (a) baseline is the last observation before the first dose of double-blind study drug; (b) LS mean treatment difference = LS mean change of each TAK-491CLD treatment group – LS mean change of OLM/HCTZ treatment group.

The sponsor alluded to safety and increased effectiveness of their combination TAK-491CLD (azilsartan medoxomil plus chlorthalidone) in Black patients by showing in study 491CLD-302 that the BP reduction with this combination in Blacks is comparable to that observed in non-Blacks (Table 2).

Table 2 Change from baseline in trough sitting clinic SBP by Race (LOCF, FAS) in study 491CLD-302.

	491CLD-302			491CLD-306				491CLD-301					
	TAK-491 80 mg N=162	CLD 25 mg N=160	TAK-491CLD 40/25+ 80/25 mg Pool N=318	TAK-491CLD 40/12.5→ 40/25 mg N=302		TAK-491+HCTZ 40+12.5→ 40+25 mg N=303		TAK-491CLD 20/12.5→ 40/25 mg N=372		TAK-491CLD 40/12.5→ 80/25 mg N=357		OLM/ HCTZ 20/12.5→ 40/25 mg N=356	
Black													
Baseline	n=35	n=29	n=63	n=46		n=37		n=92		n=93		n=98	
LS Mean (SE)	163.6 (1.75)	165.1 (1.92)	165.6 (1.31)	165.2 (1.56)		163.3 (1.74)		165.6 (1.03)		164.9 (1.02)		165.9 (0.99)	
Study Visit	**Final**	**Final**	**Final**	**Wk 6**	**Final**	**Wk 6**	**Final**	**Wk 4**	**Final**	**Wk 4**	**Final**	**Wk 4**	**Final**
LS mean change (SE)	-19.7 (2.71)	-31.3 (2.98)	-40.2* (2.02)	-30.3 (2.67)	-33.6 (2.86)	-23.1 (2.97)	-29.5 (3.20)	-28.0† (1.92)	-34.9† (1.82)	-33.6† (1.89)	-39.3† (1.81)	-21.1 (1.85)	-28.5 (1.76)
White													
Baseline	n=111	n=108	n=216	n=244		n=252		n=229		n=220		n=219	
LS Mean (SE)	163.1 (0.97)	166.3 (0.98)	163.2** (0.70)	164.8 (0.60)		164.6 (0.59)		164.7 (0.73)		164.4 (0.74)		163.5 (0.75)	
Study Visit	**Final**	**Final**	**Final**	**Wk 6**	**Final**	**Wk 6**	**Final**	**Wk 4**	**Final**	**Wk 4**	**Final**	**Wk 4**	**Final**
LS mean change (SE)	-25.1 (1.49)	-25.3 (1.51)	-39.4* (1.07)	-35.9‡ (1.04)	-38.5‡ (0.95)	-30.2 (1.02)	-33.3 (0.93)	-34.6† (1.04)	-37.9† (1.02)	-34.8† (1.07)	-37.2† (1.04)	-27.7 (1.07)	-30.9 (1.04)
Other													
Baseline	n=18	n=20	n=36	n=10		n=3		n=46		n=39		n=40	
LS Mean (SE)	169.4 (2.04)	166.6 (1.94)	168.5 (1.44)	167.1 (3.12)		162.4 (5.70)		166.9 (1.28)		167.1 (1.39)		167.9 (1.37)	
Study Visit	**Final**	**Final**	**Final**	**Wk 6**	**Final**	**Wk 6**	**Final**	**Wk 4**	**Final**	**Wk 4**	**Final**	**Wk 4**	**Final**
LS mean change (SE)	-27.0 (3.22)	-30.9 (3.06)	-42.7* (2.28)	-39.7 (4.16)	-41.7 (4.43)	-54.0 (7.68)	-43.1 (8.20)	-33.7 (2.02)	-41.1 (1.95)	-31.5 (2.19)	-40.7 (2.12)	-36.8 (2.17)	-43.0 (2.09)

Final=Final Visit (LOCF); * Significant difference vs respective TAK-491 and CLD monotherapy component doses at 0.05 level.
** Significant difference vs respective CLD monotherapy component dose at 0.05 level.
† Significant difference vs OLM/HCTZ at 0.05 level; ‡ Significant difference vs TAK-491+HCTZ at 0.05 level.

However,

(i) there is no head-to-head comparison of the two combinations in blacks on ***clinical endpoints***,

(ii) the reduction in SBP with TAK-491CLD in study 491-CLD-302 (LS mean change of 39.3±1.8 (80/25 mg) and 34.9±1.8 (40/25 mg) in the final week) is not replicated in study 491CLD-306 (LS mean change of 33.6±2.9 (40/25 mg) in final week), and

(iii) there is no comparison with other combination antihypertensives in blacks to enable making a generalized assumption that their combination TAK-491CLD (azilsartan medoxomil plus chlorthalidone) is more effective than other combination antihypertensives in the treatment of hypertension in Blacks.

As for addressing an unmet medical need, I do not think that the combination TAK-491CLD (azilsartan medoxomil plus chlorthalidone) tablets addresses an unmet medical need because there are many marketed combination products of ACE-inhibitors with HCTZ, ARBs with HCTZ and other combination products which are as effective to treat patients (including blacks) with hypertension.

Conclusion: The submission does not demonstrate the combination TAL-491CLD represents a significantly increased effectiveness over current antihypertensive therapy, and does not address an unmet medical need.

Recommendation: This reviewer's opinion is that the submission does not support a Priority Review designation for this NDA supplement.

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cc: orig.
DCaRP / Quynh Nguyen / Thomas Marciniak / Shari Targum / K.M.U

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/s/

KHIN M U
03/11/2011