

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 202-331 (SN 0000)

Drug Name: Edarbyclor

Indication(s): Hypertension

Applicant: Takeda

Date(s): Date of Document: 2/24/2011
PDUFA due date: 12/24/2011

Review Priority: Standard

Biometrics Division: Biometrics I, HFD-710

Statistical Reviewer: Jialu Zhang, Ph.D.

Concurring Reviewers: James Hung, Ph.D.

Medical Division: Division of Cardiovascular and Renal Products, HFD-110

Clinical Team: Khin U, M.D.

Project Manager: Quynh M. Nguyen, Pharm.D

Keywords:

Hypertension, Logistic regression, LOESS model, Goodness of Fit test

The sponsor had a face-to-face meeting with the Division on December 1, 2011. The labeling graphs were discussed during the meeting. The Division suggested that

- 1) The range of x-axis should not go below the target BP value
- 2) Each individual treatment group may use a different baseline range for the best model
- 3) The dots on the graph should change to smoothed curves and the treatment group corresponding to each line should be clearly marked
- 4) Excluding some outliers is influential to some logistic regression model, so additional leverage plots should be submitted.

The sponsor incorporated the suggestions from the Division during the meeting and submitted additional graphs and information.

Figure 1 Probability of achieving systolic blood pressure <140 mmHg at Week 8

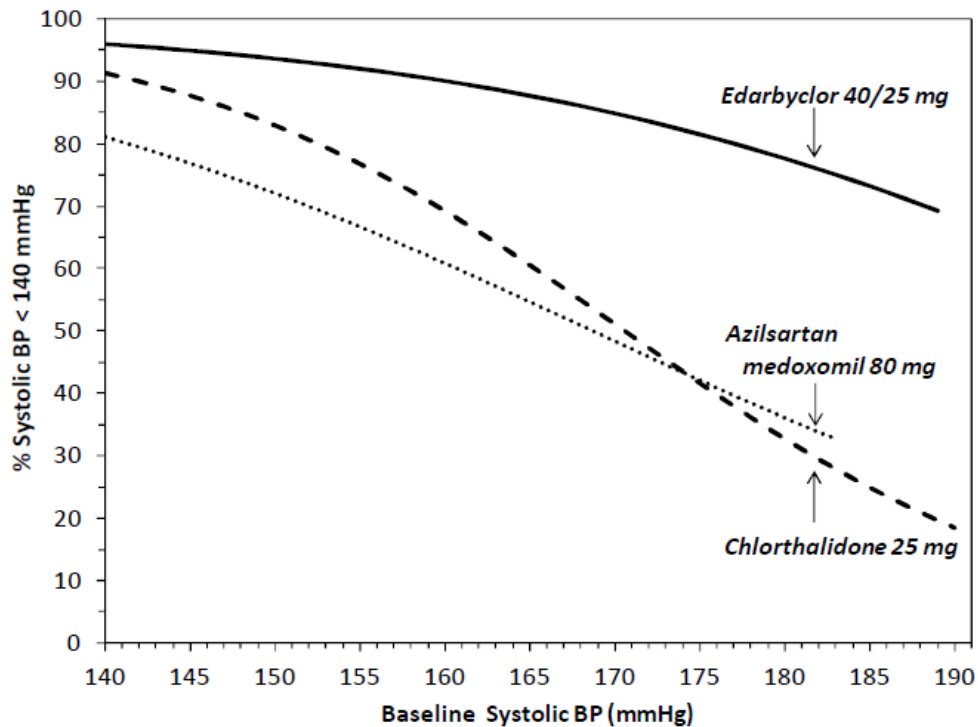


Figure 2 Probability of achieving systolic blood pressure <130 mmHg at Week 8

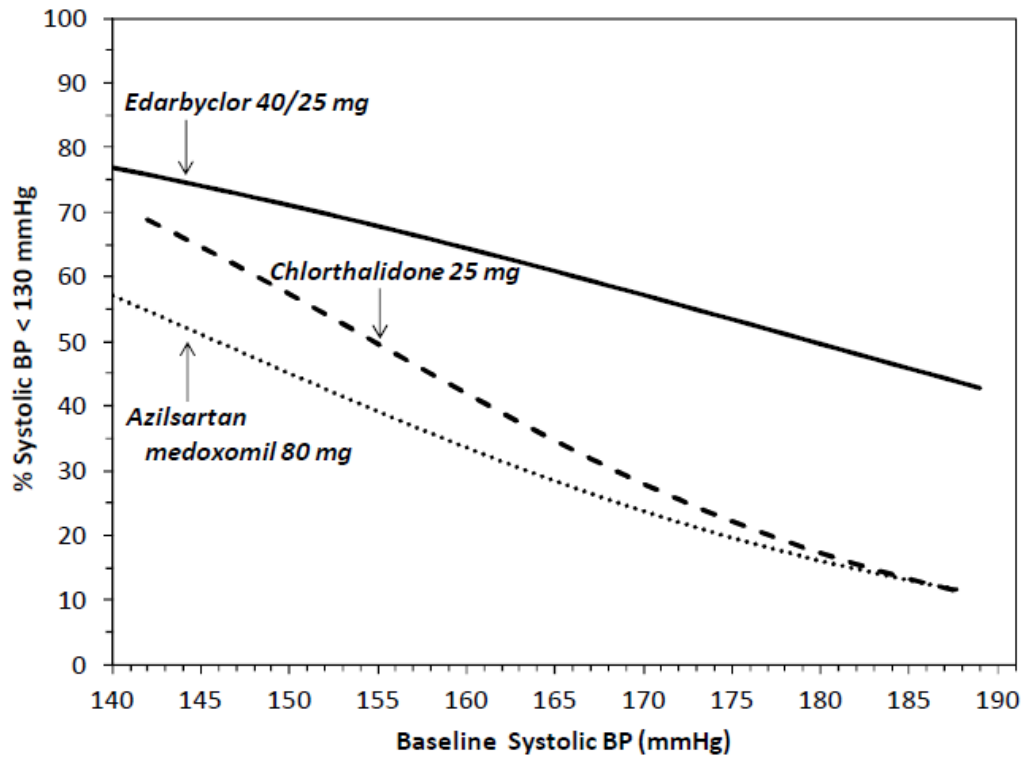


Figure 3 Probability of achieving diastolic blood pressure <90 mmHg at Week 8

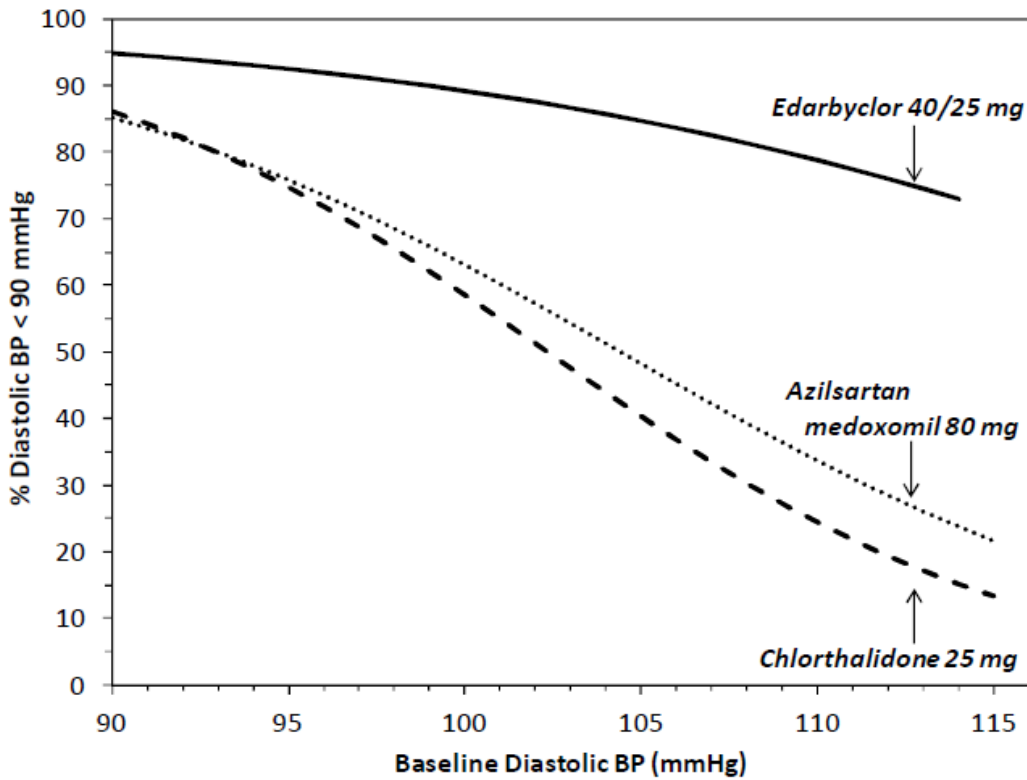


Figure 4 Probability of achieving diastolic blood pressure <80 mmHg at Week 8

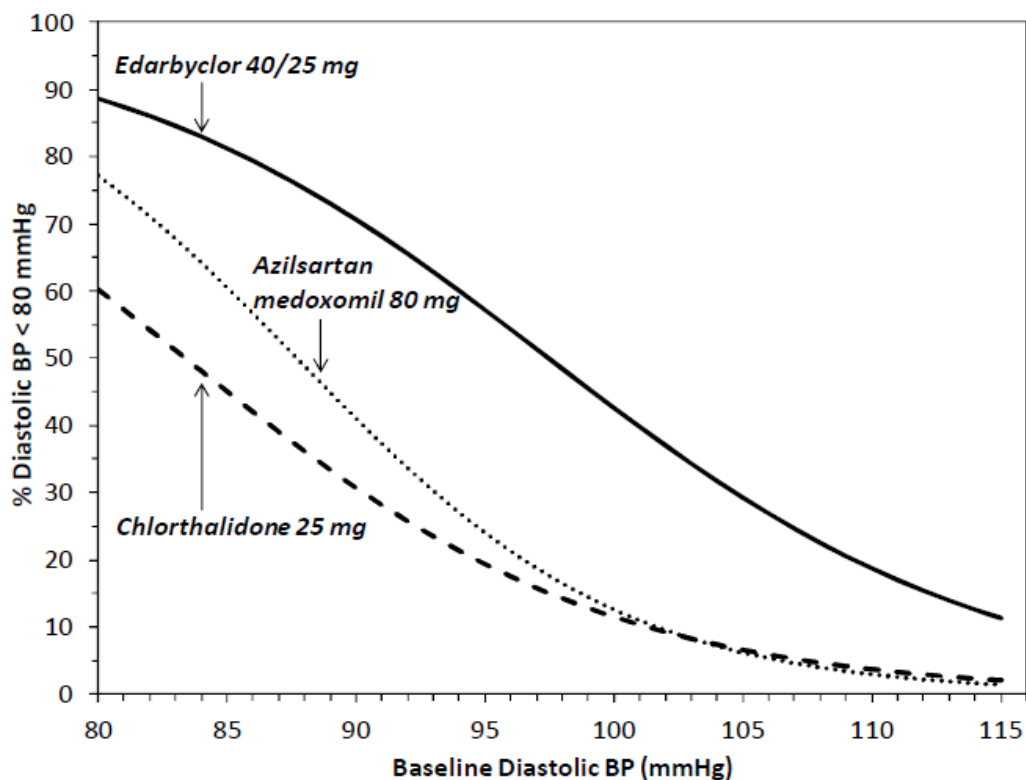


Table 1 Summary of labeling graphs

Graph	Treatment group	p-value of Hosmer-Lemeshow test	baseline range	# of outliers excluded
SBP<140 mmHg	Edarbyclor 40/25 mg	0.723	135mmHg<SBP<190mmHg	1
	azilsartan 80 mg	0.108	SBP<185mmHg	3
	Chlorthalidone 25 mg	0.06	all data	0
SBP<130mmHg	Edarbyclor 40/25 mg	0.91	135mmHg<SBP<190mmHg	1
	azilsartan 80 mg	0.09	all data	0
	Chlorthalidone 25 mg	0.728	140mmHg<SBP<190mmHg	3
DBP<90mmHg	Edarbyclor 40/25 mg	0.256	DBP<115mmHg	2
	azilsartan 80 mg	0.52	all data	0
	Chlorthalidone 25 mg	0.732	all data	0
DBP<80mmHg	Edarbyclor 40/25 mg	0.601	all data	0
	azilsartan 80 mg	0.288	all data	0
	Chlorthalidone 25 mg	0.188	all data	0

In the plot on probability of reaching target SBP<140 mmHg:

Although the Edarbyclor 40/25 mg model (using full data) has an insignificant p-value for goodness-of-fit, which indicates a reasonable fit, removing some extreme values in the Edarbyclor 40/25 mg model seems to affect the curve considerably (Figure 2.1.1 in 11/14 submission). The sponsor examined five different ranges (all data, baseline SBP 135-190 mmHg, 140-190 mmHg, 140-185 mmHg and <185 mmHg) by both the overlaid logistic regression curves and leverage plot (the diagonal of the hat matrix versus the predicted probability). Overlay plot suggests little difference between 135-190 mmHg range and 140-190 mmHg range. Removal of 1 observation below 135mmHg does have a noticeable change on the probability curve. In the end, the 135-190 mmHg range was selected. Similar conclusion also applies to the Edarbyclor 40/25 mg model for SBP<130 mmHg plot.

Removal of 3 observations with extreme baseline values (1 with baseline SBP below 140mmHg and 2 above baseline SBP 190 mmHg) also results in considerable improvement in the goodness-of-fit test score for chlorthalidone 25mg model. The three observations, however, do not have huge leverage. The logistic regression curves do not seem to be affected too much by removal of these three observations. The sponsor chose to retain all the data for the probability curve.

In conclusion, the reviewer found the proposed labeling graphs acceptable.

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/s/

JIALU ZHANG
12/15/2011

STEVE G BAI
12/15/2011



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1. EXECUTIVE SUMMARY

TAK-491CLD is a fixed-dose combination (FDC) tablet that is being developed for the treatment of hypertension. A review for the efficacy is prepared in a separate document. This review only focuses on the fixed-dose factorial study 302 and evaluates the efficacy data provided to support the approval of initial therapy indication, which mainly involves generation of graphs to show the probability of achieving certain blood pressure (BP) goals based on baseline blood pressure.

2. STATISTICAL EVALUATION

2.1 Considerations for initial therapy with combination indication

The document “points to consider in generating graphs for initial therapy with combination antihypertensive drugs” was issued by the agency to provide general guidance for use of graphs in drug labeling for initial therapy with combination antihypertensive drugs. The four graphs are generated to illustrate advantage of a combination drug over its component drugs in reaching blood pressure goals of 140 and 130 mmHg systolic and 90 and 80 mmHg diastolic for an initial therapy indication.

Each graph contains logistic regression curves for the probability of reaching a blood pressure target after treatment as a function of baseline blood pressure for the treatment groups.

In this application, the graphs displayed in the labeling were based on the factorial trial Study 302. There was no pooling of studies. The highest dose combination in the factorial trial was 80mg/25mg TAK-491/CLD. The highest dose that will be approved is 40mg/25mg TAK-491/CLD. The graphs that will be used in label are based on 40mg/25mg TAK-491/CLD, 80mg TAK-491 and 25mg CLD. The following has been reviewed to assess the goodness-of-fit of the regression curves:

- Comparison of regression curve with LOESS non-parametric curve
- Hosmer-Lemeshow test
- Residual plots (chi-square residual, deviance residual)

2.2.2.2 Estimated probability of msSBP and msDBP control

The graphs generated from data show that as baseline BP increases, the probability of achieving BP goals decreases in all groups. The probability of achieving systolic or diastolic BP goal was higher in TAK-491/CLD arm than in either monotherapy arm.

Figure 1 Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg in Patients at Week 8 Endpoint

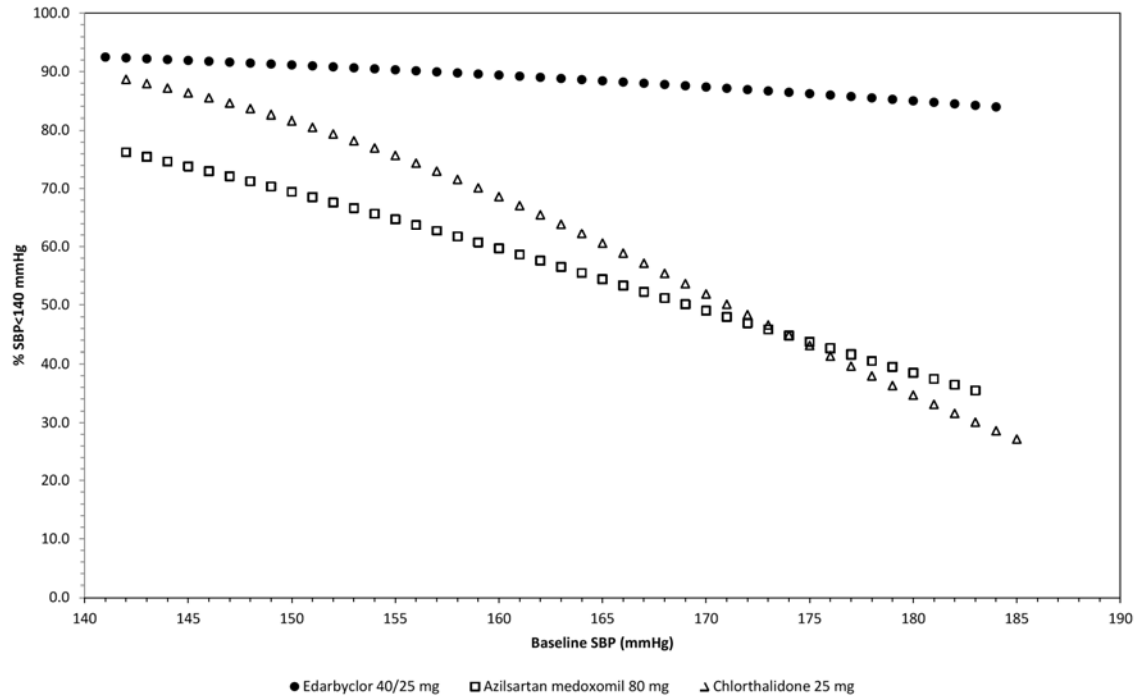


Figure 2 Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg in Patients at Week 8 Endpoint

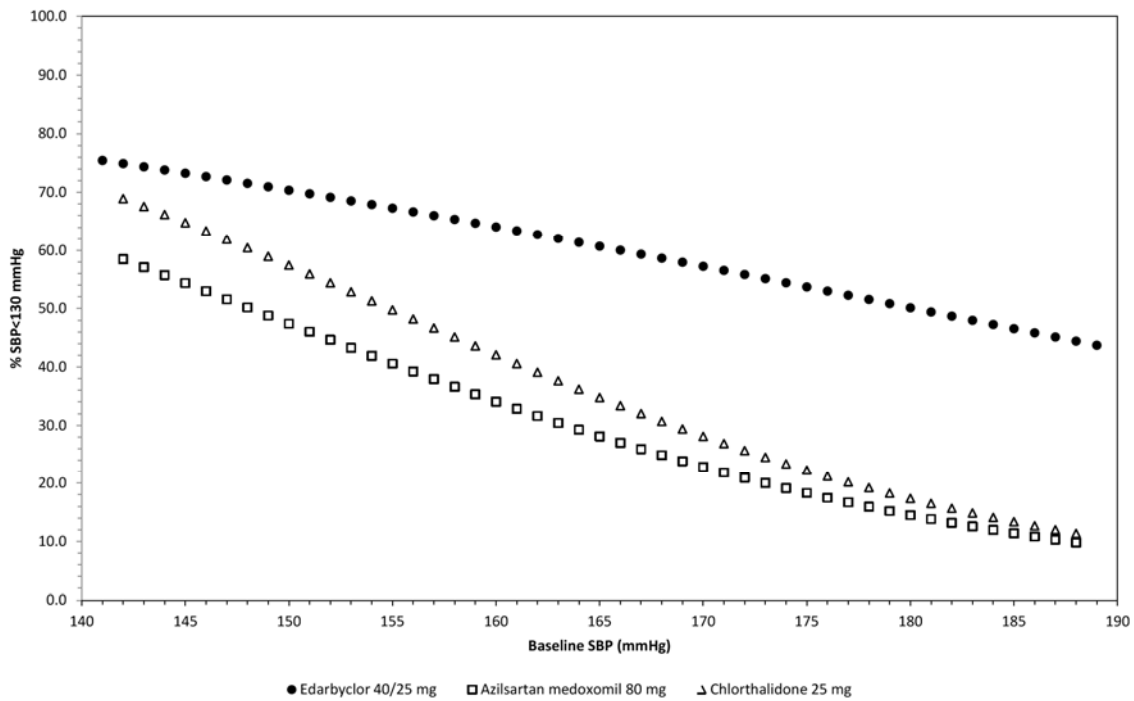


Figure 3 Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg in Patients at Week 8 Endpoint

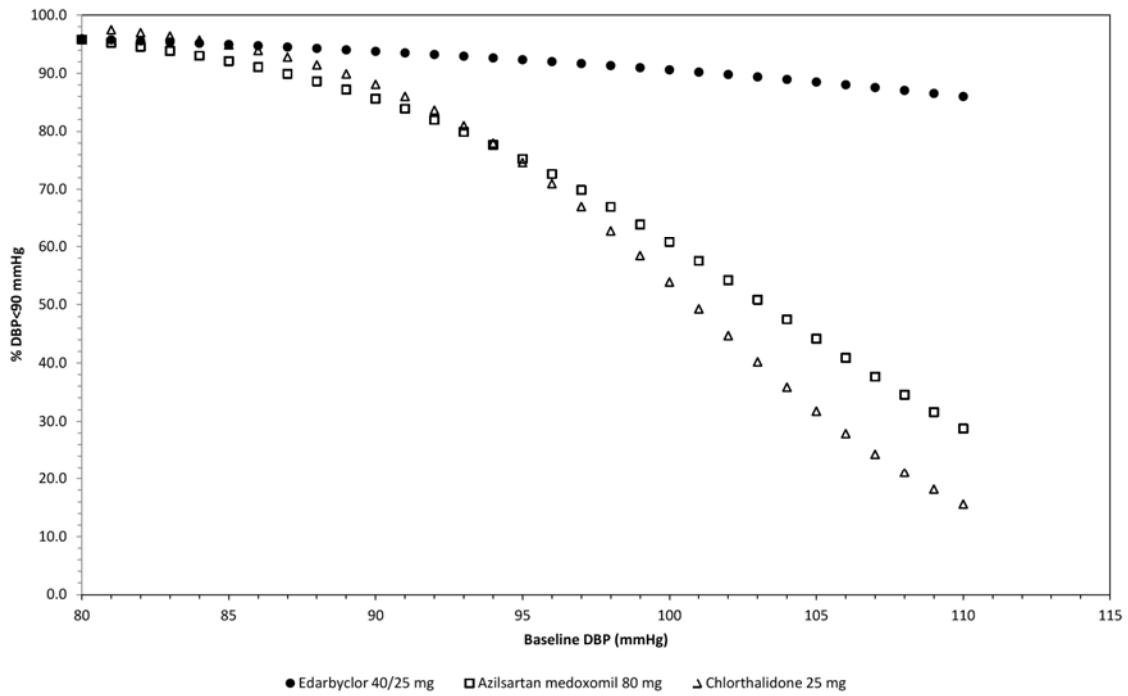
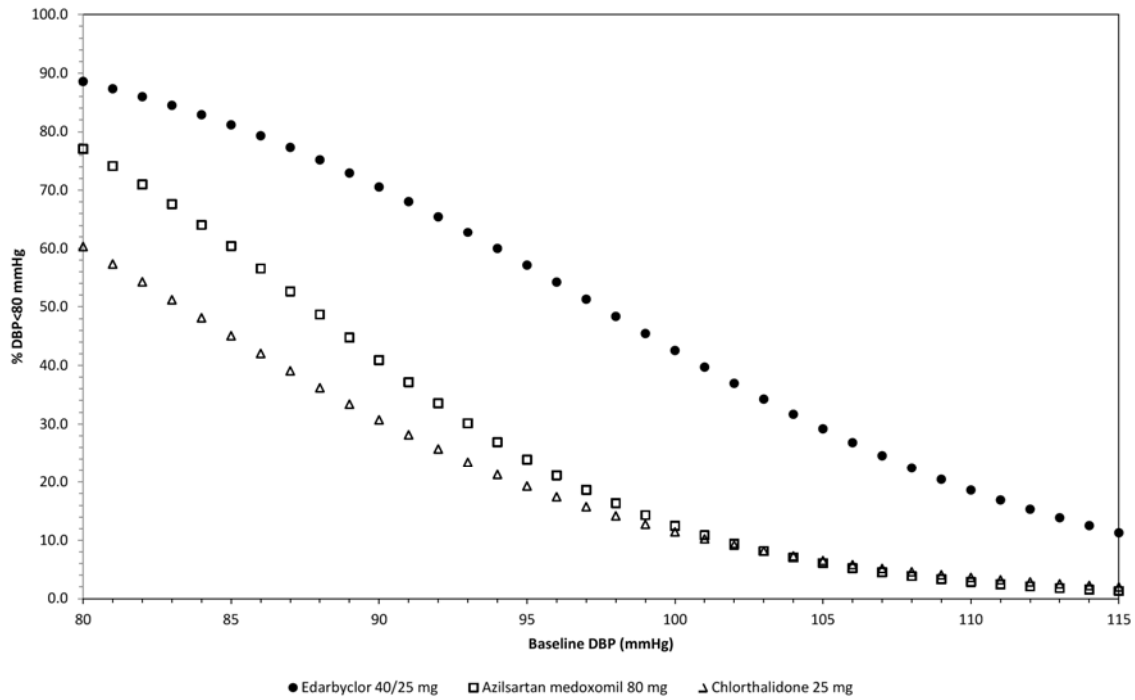


Figure 4 Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg in Patients at Week 8 Endpoint



2.3 2.3 Model diagnostics- Sponsor's analysis

2.3.1 Goodness-of-fit in logistic regression model

Hosmer-Lemeshow tests were applied as the goodness-of-fit assessments to check whether the overall logistic regression model was fitted adequately. A statistically insignificant p-value indicates that the overall fit using a logistic regression model is reasonable. Table 1 summarizes the test results.

Table 1 P-values from Hosmer-Lemeshow test to show overall goodness-of-fit

Treatment	Response Criteria	Dataset	LOF p-value
TAK-491CLD 40/25 mg	SBP <140 mmHg	All Data	0.864
		SBP: 140-190mmHg	0.707
		SBP: 140-185mmHg	0.627
	SBP<130 mmHg	All Data	0.613
		SBP: 140-190mmHg	0.887
		SBP: 140-185mmHg	0.919
	DBP<90 mmHg	All Data	0.022
		DBP: 80-115mmHg	0.037
		DBP: 80-110mmHg	0.285
	DBP<80 mmHg	All Data	0.601
		DBP: 80-115mmHg	0.744
		DBP: 80-110mmHg	0.767

Treatment	Response Criteria	Dataset	LOF p-value
TAK-491 80 mg	SBP <140 mmHg	All Data	0.035
		SBP: 140-190mmHg	0.024
		SBP: 140-185mmHg	0.074
	SBP<130 mmHg	All Data	0.093
		SBP: 140-190mmHg	0.081
		SBP: 140-185mmHg	0.023
	DBP<90 mmHg	All Data	0.520
		DBP: 80-115mmHg	0.191
		DBP: 80-110mmHg	0.495
	DBP<80 mmHg	All Data	0.288
		DBP: 80-115mmHg	0.301
		DBP: 80-110mmHg	0.187
CLD 25 mg	SBP<140 mmHg	All Data	0.058
		SBP: 140-190mmHg	0.571
		SBP: 140-185mmHg	0.531
	SBP<130 mmHg	All Data	0.043

		SBP: 140-190mmHg	0.728
		SBP: 140-185mmHg	0.741
	DBP<90 mmHg	All Data	0.732
		DBP: 80-115mmHg	0.894
		DBP: 80-110mmHg	0.978
	DBP<80 mmHg	All Data	0.188
		DBP: 80-115mmHg	0.350
		DBP: 80-110mmHg	0.301

[Source: Sponsor's analysis submitted on November 21, 2011]

The models that are lack of fit based on Hosmer-Lemeshow tests are highlighted. The sponsor tested the models using all data as well as data excluding some extreme baseline BP observations.

For SBP>140mmHg graph, the best model is the one with baseline SBP ranging from 140mmHg -185mmHg (Figure 1). This would exclude 13 observations in CLD 25mg arm, 7 observations in TAK-491 80mg arm and 7 observations in TAK-491/CLD 40mg/25mg arm.

For SBP>130mmHg graph, the best model is the one with baseline SBP ranging from 140mmHg -190mmHg (Figure 2). This would exclude 3 observations in CLD 25mg arm, 4 observations in TAK-491 80mg arm and 2 observations in TAK-491/CLD 40mg/25mg arm.

For DBP>90mmHg graph, model using baseline DBP ranging from 80mmHg -110mmHg seem to fit the best overall (Figure 3). This would exclude 19 observations in CLD 25mg arm, 17 observations in TAK-491 80mg arm and 17 observations in TAK-491/CLD 40mg/25mg arm. Quite a few observations are excluded in this model. Among these observations, about half have baseline DBP below 80mmHg.

For DBP>80mmHg graph, excluding extreme values in baseline BP does not seem to affect the model much (Figure 4). In fact, models with baseline DBP ranging from 80-115 mmHg, or baseline DBP ranging from 80-110 mmHg are very close to the model using all data. Therefore full data can be used in this graph.

2.3.2 Comparison of logistic regression model with LOESS model

Estimated probabilities of achieving blood pressure control from the logistic regression model (based on individual treatment groups) and LOESS estimates were plotted together to compare the model fitting as shown in Figure 5, Figure 6 and Figure 7. LOESS estimates are obtained from a weighted regression by using 50% of the neighboring data so extreme observations may affect the estimation. In some cases LOESS estimates are quite different from the logistic regression curve at both ends. In all cases, LOESS curves are reasonably close to the logistic regression curves in the middle range of baseline BP.

Figure 5 Non-parametric LOESS Curves for Achieving SBP <140 mm Hg at Week 8 by Baseline SBP (CLD 25mg)

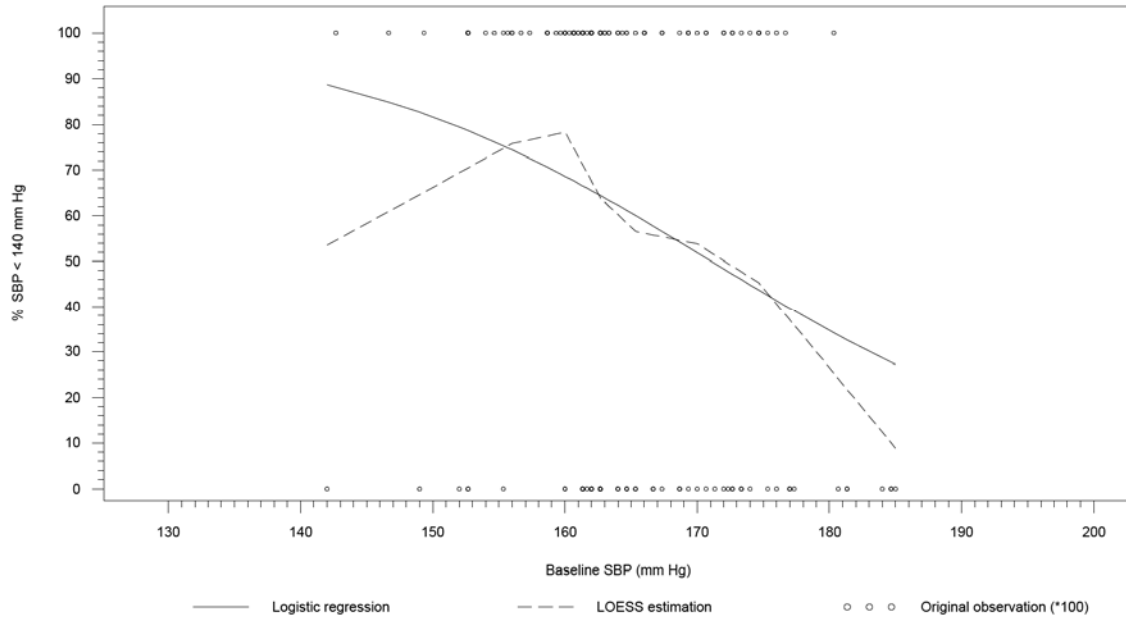


Figure 6 Non-parametric LOESS Curves for Achieving SBP <140 mm Hg at Week 8 by Baseline SBP (TAK-491 80mg)

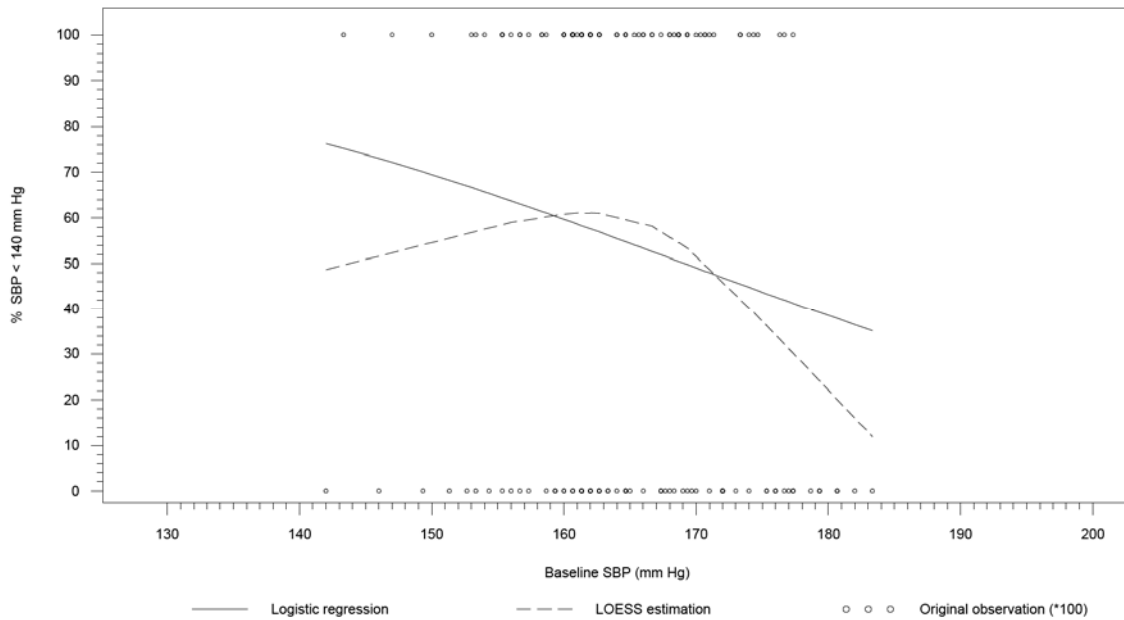
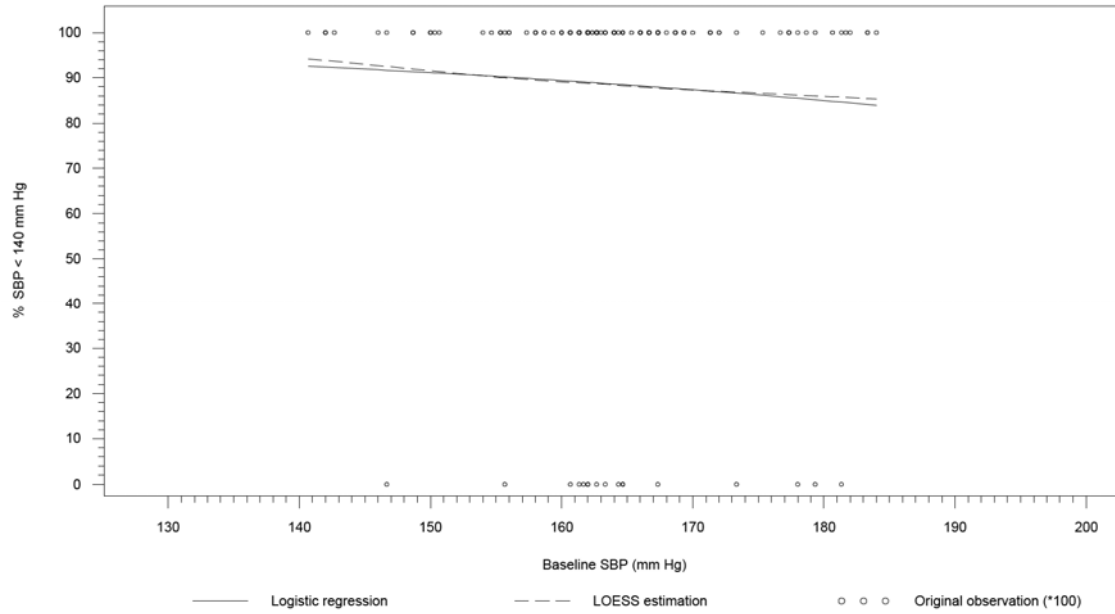


Figure 7 Non-parametric LOESS Curves for Achieving SBP <140 mm Hg at Week 8 by Baseline SBP (TAK-491/CLD 40mg/25mg)



2.3.3 Residual analysis

Figure 8, Figure 9 and Figure 10 below display the Pearson and Deviance residuals for the estimated probabilities of achieving SBP < 140 mmHg at Week 8 based the logistic regression model. The standardized values of the residuals were generally within ± 3 .

Figure 8 Residuals versus Estimated Probability (% SBP < 140 mm Hg) at Week 8 for CLD 25mg

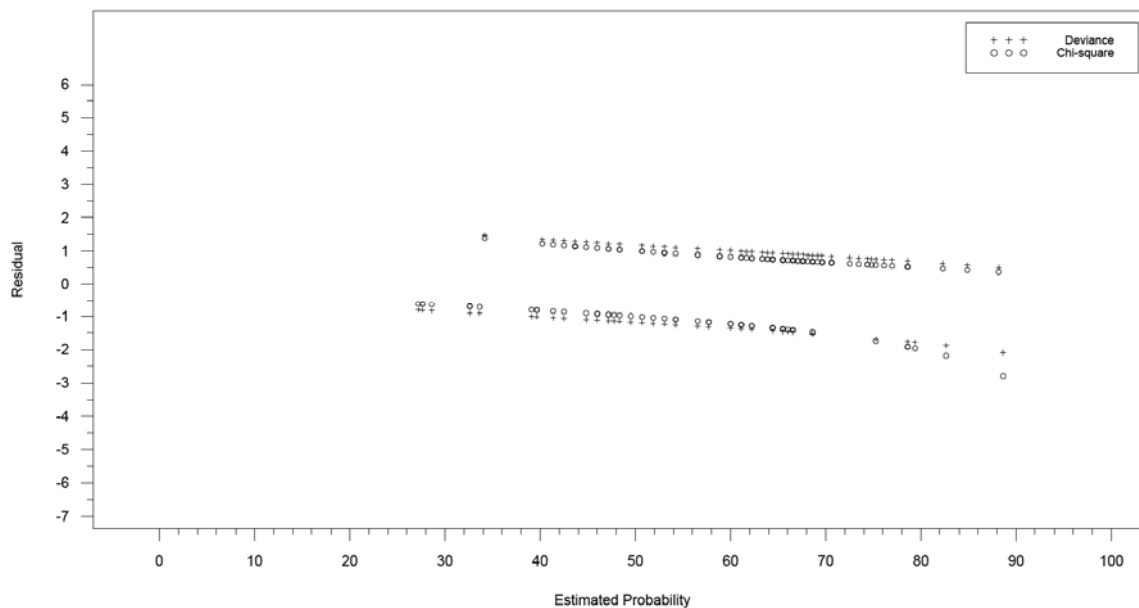


Figure 9 Residuals versus Estimated Probability (% SBP < 140 mm Hg) at Week 8 for TAK-491 80mg

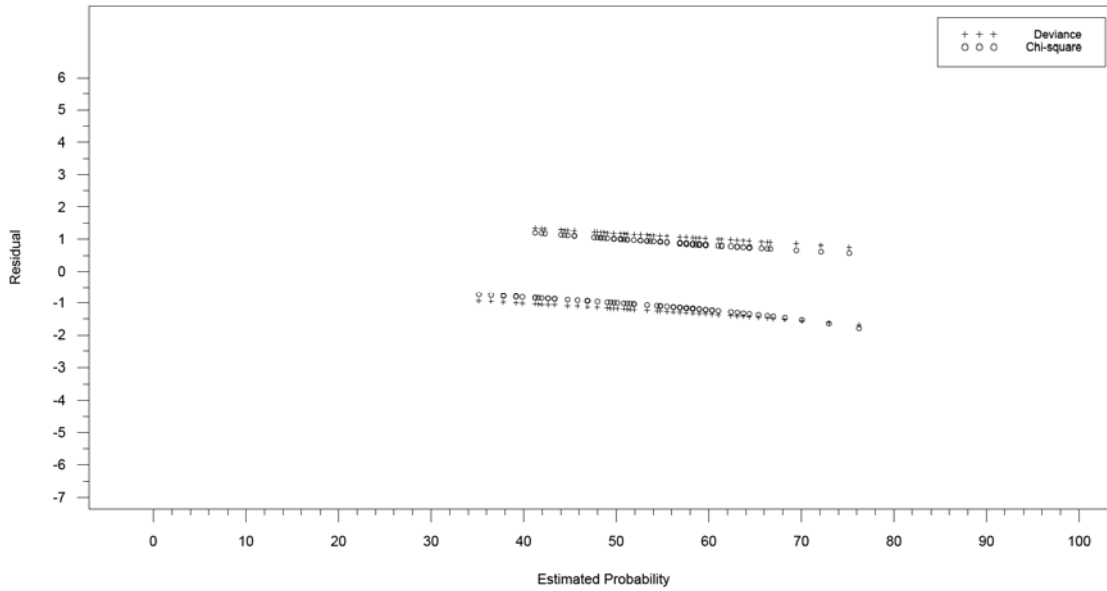
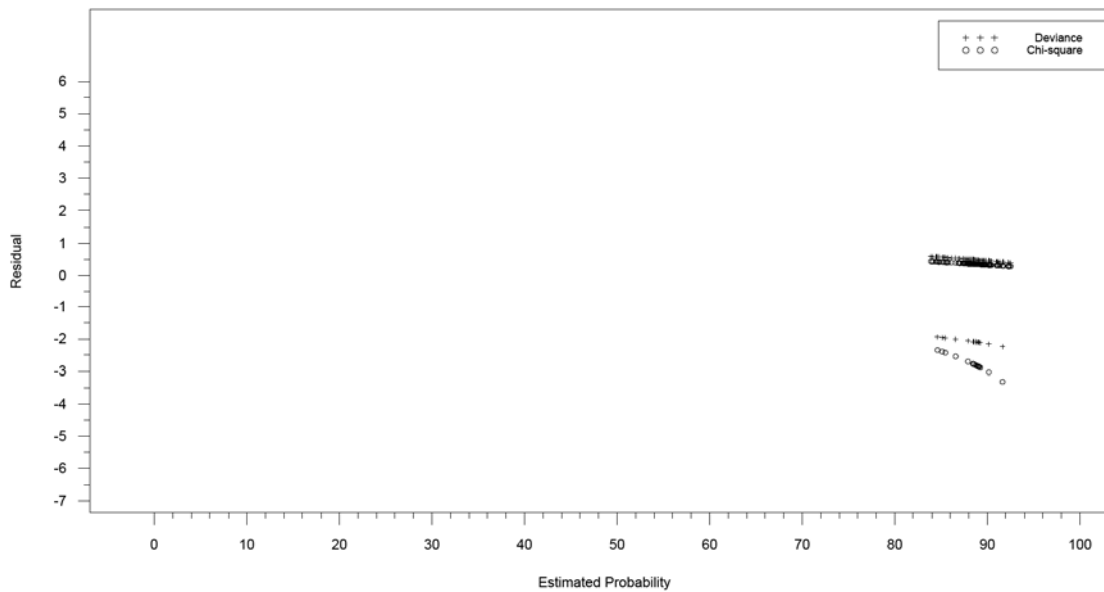


Figure 10 Residuals versus Estimated Probability (% SBP < 140 mm Hg) at Week 8 for TAK-491/CLD 40mg/25mg



2.3.4 Conclusion in modeling and diagnostics

In general, the goodness-of-fit assessment indicates that the logistic regression models fit the data reasonably well.

A number of potential outliers were excluded in order to improve the fitness of the models.

- For SBP>140mmHg graph, the best model is the one with baseline SBP ranging from 140mmHg -185mmHg.
- For SBP>130mmHg graph, the best model is the one with baseline SBP ranging from 140mmHg -190mmHg.
- For DBP>90mmHg graph, model using baseline DBP ranging from 80mmHg - 110mmHg fit the best overall.
- For DBP>80mmHg graph, the model using all data fits well.

The logistic regression curves and LOESS curves are reasonably close, except for the extreme baseline blood pressure values in some cases.

The standardized values of the Pearson and Deviance residuals were generally within ± 3 . There was no systematic departure of model assumption or indication of poor model fitting.

2.4 Conclusions

The estimated probabilities of achieving blood pressure goals based on logistic regression modeling appeared to be adequate. The graphs adequately represent the study data and support for the approval of initial therapy indication.

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/s/

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11/28/2011

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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Missing data, hypertension, fixed-dose combination

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1. EXECUTIVE SUMMARY

This review includes 4 placebo-controlled studies that compared the fixed-dose combination tablet TAK-491CLD with monotherapies or active-controls (OLM/HCTZ, or TAK-491+HCTZ).

In fixed-dose factorial study 302, the pooled TAK-491CLD 40/25 mg and 80/25 mg treatment groups (40/25+80/25 mg) reduced trough SBP by ABPM statistically significantly than TAK-491 80 mg and/or chlorthalidone 25 mg monotherapies.

In study 301, TAK-491CLD low-dose (40/25 mg) and high-dose (80/25 mg) treatments significantly reduced mean clinic SBP more than the OLM/HCTZ (40/25 mg) treatment.

In study 306, TAK-491CLD (40/25 mg) was significantly better than TAK-491+HCTZ (40mg + 25 mg) in reducing trough, sitting clinic SBP from Baseline to Week 6 and Week 10

In study 303, TAK-491CLD 40/25 and 80/25 mg titration groups significantly reduced mean clinic SBP more than the OLM/HCTZ titration group.

One concern in this application is that the dropout rate in the four trials is higher than typical hypertension trial. The primary analyses in all four trials used LOCF method. To address the missing data issue, a number of sensitivity analyses were performed, including multiple imputation, observed case analyses and analyses on per protocol population. The results based on LOCF method and other sensitivity analyses are consistent. Also the ABPM measurements and clinic measurements on SBP and DBP are consistent. Furthermore, if the dropouts were due to lack of treatment effect, the LOCF method tends to be conservative in the primary analysis. All the above analyses offer certain assurance that despite of the high dropout rate, the missing data unlikely would affect the conclusion of the studies.

2. INTRODUCTION

2.1 Overview

TAK-491CLD is a fixed-dose combination (FDC) tablet that is being developed for the treatment of hypertension. The components of TAK-491CLD are TAK-491 (azilsartan medoxomil) and chlorthalidone.

This review includes 4 placebo-controlled studies (Table 1). The pivotal study 302, was an 8-week, randomized, double-blind, controlled, fixed-dose, factorial study that evaluated the efficacy and safety of TAK-491CLD relative to TAK-491 and chlorthalidone monotherapies.

Study 301 (TAK-491CLD compared with OLM/HCTZ) and study 306 (TAK-491CLD compared with TAK-491+HCTZ) were short-term, randomized, double-blind studies designed to compare TAK-491CLD with active comparators. Study 303 was a 12-week, phase 3b, fixed-dose, double-blind study to compare TAK-491CLD with OLM/HCTZ using a forced titration design.

Table 1 List of all studies included in this review

Study	Phase and Design	Treatment Period	# of Subjects	Study Population
Study 302	Phase 3, fixed-dose factorial	8 weeks	1714 subjects randomized to 11 treatment arms	subjects with moderate to severe essential hypertension (SBP between 160 and 190 mm Hg)
Study 301	Phase 3, titrate-to-target	8 weeks	1085 patients randomized to 3 treatment arms	subjects with moderate to severe hypertension (SBP between 160 and 190 mm Hg)
Study 306	Phase 3, titrate-to-target	10 weeks	609 subjects randomized to 2 treatment arms	subjects with moderate to severe hypertension (SBP between 160 and 190 mm Hg)
Study 303	Phase 3b, forced titration	12 weeks	1071 subjects randomized to 3 treatment arms	subjects with moderate to severe hypertension (SBP between 160 and 190 mm Hg)

2.2 Data Sources

The sponsor's electronic data for Study 302, Study 301 and Study 306 are stored under the directory

<\\Cdsub1\evsprod\NDA202331\0000\m5\datasets\>.

The datasets for Study 303 were submitted later on April 22, 2011 and are stored under directory

<\\Cdsub1\evsprod\NDA202331\0009\m5\datasets\>

The sponsor also submitted SAS program for certain efficacy tables in the clinical study reports. These programs are stored under directory

<\\Cdsub1\evsprod\NDA202331\0006\m5\datasets\>,

<\\Cdsub1\evsprod\NDA202331\0017\m5\datasets\>, and

<\\Cdsub1\evsprod\NDA202331\0018\m5\datasets\>

3. STATISTICAL EVALUATION

This section will present the detailed review of the four studies.

3.1 Data and Analysis Quality

The reviewer was able to locate the variables needed from the datasets submitted by the sponsor to perform all the analyses.

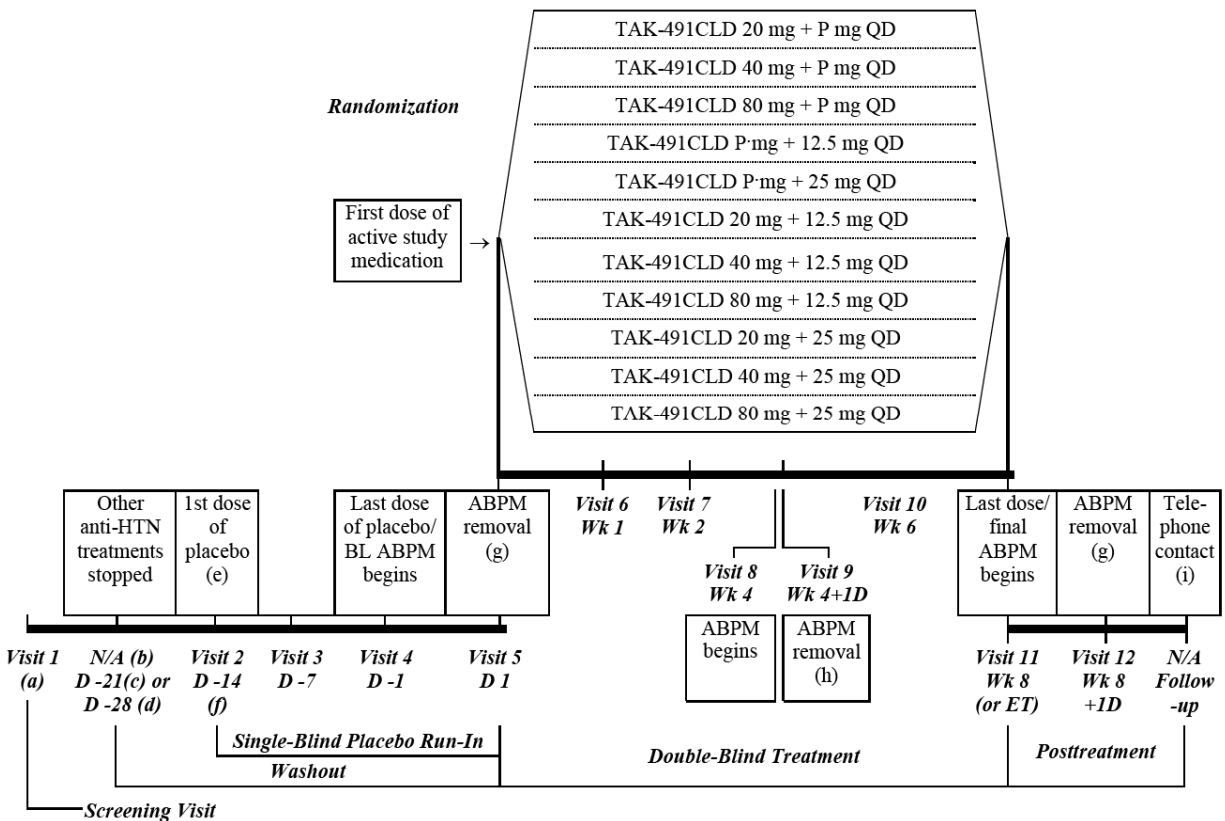
3.2 Evaluation of Efficacy

3.2.1 Study 302

3.2.1.1 Study Design and Endpoints

This was a phase 3, multicenter, double-blind, randomized, 3×4 factorial study (without a placebo only arm) in subjects with moderate to severe essential hypertension (SBP between 160 and 190 mm Hg) and compared the antihypertensive effect, safety, and tolerability of TAK-491CLD FDC with TAK-491 monotherapy and chlorthalidone monotherapy after 8 weeks of active treatment. Randomization was stratified by race: Black and non-Black.

Figure 1 Schematic of Study Design in Study 302



Before initiation of active treatment, all subjects participated in a 2-week, single-blind, placebo run-in period (Days -14 to -1). Subjects who had not received antihypertensive treatment within 28 days prior to Screening entered the Placebo Run-In Period as soon as all inclusion and exclusion criteria had been verified. Subjects taking previous antihypertensive agents were required to participate in a 3-week Washout Period (Days -21 to -1). Those subjects who were receiving antihypertensive treatment that included amlodipine or chlorthalidone had an extended Washout Period to 4 weeks (Days -28 to -1).

Subjects who were previously treated with antihypertensive agents were required to have a post washout mean sitting SBP measurement of 160 to 190 mm Hg, inclusive, on Day -1 to qualify for study entry. Subjects who had not received antihypertensive treatment within 28 days were required to meet this criterion during Screening and on Day -1 to qualify. Subject eligibility was determined by the mean of 3 sitting, trough, clinic blood pressure measurements. Subjects who met all entry criteria were treated for 8 weeks with 1 of 11 randomly assigned, double-blind treatment regimens.

The primary efficacy variable was trough (22 to 24 hours after dosing) SBP as measured by ABPM (hereafter referred to as trough SBP by ABPM). The primary efficacy endpoint was the change from Baseline to Week 8 in this variable using the last observation carried forward (LOCF).

There were 2 key secondary efficacy endpoints:

- Change from Baseline to Week 8 in sitting, trough, clinic SBP (hereafter referred to as clinic SBP).
- Change from Baseline to Week 8 in trough SBP by ABPM in Black subjects.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

1714 subjects at 165 sites were randomly assigned to 1 of 11 treatment groups during the Double-Blind Treatment Period. Overall, 1470 randomized subjects (85.7%) completed the study and 245 subjects (14.3%) prematurely withdrew. The lowest withdrawal rates were in the TAK-491 20 and 40 mg monotherapy treatment groups (9.0% and 9.2%, respectively), with a slightly higher withdrawal rate in the TAK-491 80 mg treatment group (12.3%)

Table 2 Patient Disposition by Treatment Arm (Study 302)

TAK-491	0	0	20	20	20	40	40	40	80	80	80
CLD	12.5	25	0	12.5	25	0	12.5	25	0	12.5	25
Full analysis set	156	159	155	156	154	153	146	156	162	153	161
completed	135	141	141	135	131	139	131	125	142	125	125
early terminated	21	18	14	21	23	14	15	31	20	28	36

Most subjects (63%) were enrolled at sites in the United States. The percentage of male (47%) and female (53%) subjects was similar. The majority of subjects were White, while Black

subjects represented 20% of all randomized subjects. Demographics and baseline characteristics were similar across pooled treatment groups in all randomized subjects.

Table 3 Demographic Characteristics by Treatment Arm (Study 302)

		CLD 25 mg	TAK-491 80 mg	TAK-491CLD 80/25 + 40/25mg pool
N		159	162	317
Age	Mean	56.2	57.3	57.5
	Std	10	10.9	11.1
Weight	Mean	86.7	86.3	88.3
	Std	20.3	20.4	21.3
Race	White (%)	111 (70%)	111 (69%)	219 (69%)
	Black (%)	29 (18%)	35 (22%)	64 (20%)
Gender	Male (%)	69 (43%)	78 (48%)	133 (42%)
Country	US (%)	105 (66%)	101 (62%)	202 (64%)

3.2.1.3 Statistical Methodologies

There were 3 analysis sets: FAS, PPS, and the safety analysis set. The FAS was the primary data set used for efficacy analyses.

The FAS was defined as all randomized subjects who received at least 1 dose of double-blind study medication. A subject was included in the analyses of a specific variable only when there was both a Baseline value and at least 1 value during the Double-Blind Treatment Period. Subjects were analyzed according to the treatment group to which they were randomized. The FAS included 1711 subjects. The PPS was defined as all subjects in the FAS except those identified as having major protocol violations. The PPS included 1582 subjects.

The primary efficacy endpoint was the change from Baseline to Week 8 in trough (22 to 24 hours after dosing) SBP as measured by ABPM using the last observation carried forward (LOCF).

There were 2 key secondary efficacy endpoints:

- Change from Baseline to Week 8 in sitting, trough, clinic SBP.
- Change from Baseline to Week 8 in trough SBP by ABPM in Black subjects.

Other Secondary Efficacy Endpoints included the following:

- Change from Baseline to Week 8 in trough, sitting, clinic DBP.
- Change from Baseline to Week 8 in the ABPM parameters:
- Proportion of responders at Week 8

The primary comparison will be the pooled TAK-491 CLD 80 mg + 25 mg group and TAK-491 CLD 40 mg + 25 mg group vs. the highest dose of each component using an appropriate contrast from the above ANCOVA model at the 5% significance level.

According to the SAP, if the primary comparison for the primary variable is statistically significant at 0.05, the key secondary endpoint, change from baseline to Week 8 in trough SBP by ABPM in black subjects will be analyzed similarly using as described above using a 2-sided type I error of 0.05. No multiplicity adjustment was mentioned for controlling the overall type I error.

In the meeting minutes dated May 17, 2010, the Division clarified “that the data would not result in a separate claim for use in the Black subgroup, but the label would describe qualitatively and quantitatively the effect in the Black population.” Also “even without a hypothesis test, the results from a pre-specified subgroup analysis of Black patients would be described in the labeling.” And “it was not necessary for the sponsor to control for Type 1 error for subgroup analyses of Black patients or any other subgroup”.

The primary analysis of change from Baseline for each variable was based on the LOCF method. In addition, sensitivity analyses for mean trough SBP and DBP by ABPM were performed on observed values and using a multiple imputation method for missing data to assess the impact of LOCF methodology and drop-outs. Similar sensitivity analyses were also conducted on clinic SBP and DBP.

3.2.1.4 Results and Conclusion

The primary efficacy endpoint was the change from Baseline in trough SBP by ABPM at Week 8 (LOCF). The pooled TAK-491CLD 40/25+80/25 mg were compared with the highest doses of TAK-491 (80 mg) or chlorthalidone (25 mg) monotherapy.

There were statistically significant reductions at Week 8 in trough SBP by ABPM in the groups receiving the highest doses of TAK-491CLD FDC (40/25+80/25 mg pool) compared with the groups receiving the highest dose of TAK-491 (80 mg) and chlorthalidone (25 mg) monotherapy.

Table 4 Analysis of Change from Baseline in Trough SBP by ABPM at Week 8 (LOCF, FAS, Study 302)

Trough SBP by ABPM	Treatment		
	TAK-491 80 mg N=162	CLD 25 mg N=159	TAK-491CLD 40/25+80/25 mg Pool (a) N=317
Baseline			
n	127	134	228
LS mean (SE)	151.1 (1.45)	151.2 (1.41)	152.2 (1.08)
Change from Baseline to Week 8 (Primary Endpoint)			
n	127	134	228
LS mean (SE)	-15.1 (1.19)	-15.9 (1.16)	-28.9 (0.89)
TAK-491CLD vs CLD			
<i>Primary analysis</i>			
LS mean difference (95% CI) (b)	--	--	-13.0 (-15.8, -10.1)
P-value (c)	--	--	<0.001
<i>Multiple imputation analysis</i>			
LS mean difference (95% CI) (b)	--	--	-12.7 (-15.8, -9.5)
P-value (c)	--	--	<0.001
TAK-491CLD vs TAK-491			
<i>Primary analysis</i>			
LS mean difference (95% CI) (b)	--	--	-13.8 (-16.7, -10.9)
P-value (c)	--	--	<0.001
<i>Multiple imputation analysis</i>			
LS mean difference (95% CI) (b)	--	--	-13.5 (-16.8, -10.1)
P-value (c)	--	--	<0.001

[Source: Sponsor's clinical study report TAK491CLD_302 Table 15.2.1.1.2.1, confirmed by the reviewer]

Table 5 Analysis of Change From Baseline in Clinic SBP at Week 8 (LOCF, FAS, Study 302)

Clinic SBP	Treatment		
	TAK-491 80 mg N=162	CLD 25 mg N=159	TAK-491CLD 40/25+80/25 mg Pool (a) N=317
Baseline			
n	162	156	313
LS mean (SE)	163.9 (0.80)	166.1 (0.82)	164.3 (0.58)
Change from Baseline to Week 8 (Key secondary Endpoint)			
LS mean (SE)	-24.2 (1.23)	-27.1 (1.25)	-39.8 (0.88)
TAK-491CLD vs CLD			
<i>Primary analysis</i>			
LS mean difference (95% CI) (b)	--	--	-12.7 (-15.7, -9.7)
P-value (c)	--	--	<0.001
<i>Multiple imputation analysis</i>			
LS mean difference (95% CI) (b)	--	--	-12.4 (-15.3, -9.5)
P-value (c)	--	--	<0.001
TAK-491CLD vs TAK-491			
<i>Primary analysis</i>			
LS mean difference (95% CI) (b)	--	--	-15.7 (-18.6, -12.7)
P-value (c)	--	--	<0.001
<i>Multiple imputation analysis</i>			
LS mean difference (95% CI) (b)	--	--	-15.1 (-18.2, -12.0)
P-value (c)	--	--	<0.001

[Source: Sponsor's clinical study report TAK491CLD_302 Table 15.2.3.1.2, confirmed by the reviewer]

Table 6 Analysis of Change From Baseline in Trough SBP by ABPM in Black Subjects at Week 8 (LOCF, FAS, Study 302)

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			
n	28	22	40
LS mean (SE)	153.9 (3.00)	151.4 (3.38)	154.2 (2.51)
Change from Baseline to Week 8 (Key Secondary Endpoint)			
n	28	22	40
LS mean (SE)	-9.9 (2.97)	-23.4 (3.36)	-28.2 (2.49)
TAK-491CLD vs CLD			
<i>Primary analysis</i>			
LS mean difference (95% CI) (b)	--	--	-4.8 (-13.0, 3.5)
P-value (c)	--	--	0.255
<i>Multiple imputation analysis</i>			
LS mean difference (95% CI) (b)	--	--	-6.1 (-16.6, 4.3)
P-value (c)	--	--	0.243
TAK-491CLD vs TAK-491			
<i>Primary analysis</i>			
LS mean difference (95% CI) (b)	--	--	-18.2 (-25.9, -10.6)
P-value (c)	--	--	<0.001
<i>Multiple imputation analysis</i>			
LS mean difference (95% CI) (b)	--	--	-19.2 (-28.5, -9.8)
P-value (c)	--	--	<0.001

[Source: Sponsor's clinical study report TAK491CLD_302 Table 15.2.1.3.2, confirmed by the reviewer]

Table 7 Analysis of Change From Baseline in Clinical SBP in Black Subjects at Week 8 (LOCF, FAS, Study 302)

Clinic SBP	Treatment		
	TAK-491 80 mg N=35	CLD 25 mg N=29	TAK-491CLD 40/25+80/25 mg Pool (a) N=64
Baseline			
n	35	29	63
LS mean (SE)	163.6 (1.75)	165.1 (1.92)	165.6 (1.31)
Change from Baseline to Week 8			
LS mean (SE)	-19.7 (2.71)	-31.3 (2.98)	-40.2 (2.02)
TAK-491CLD vs CLD			
LS mean difference (95% CI) (b)	--	--	-8.9 (-16.0, -1.8)
P-value (c)	--	--	0.014
TAK-491CLD vs TAK-491			
LS mean difference (95% CI) (b)	--	--	-20.5 (-27.1, -13.8)
P-value (c)	--	--	<0.001

[source: Sponsor's clinical study report Table 15.2.3.3.2, confirmed by the reviewer]

In summary, the pooled TAK-491CLD 40/25 mg and 80/25 mg treatment groups (40/25+80/25 mg) reduced SBP statistically significantly than TAK-491 80 mg and/or chlorthalidone 25 mg monotherapies in most measurements from Baseline to Week 8:

- Trough SBP by ABPM (LS mean difference vs TAK-491: 13.8 mm Hg [95% CI: 10.9, 16.7]; LS mean difference vs CLD: 13.0 mm Hg [95% CI: 10.1, 15.8])
- Trough SBP by clinic measurement (LS mean difference vs TAK-491: 15.7 mm Hg [95% CI: 12.7, 18.6]; LS mean difference vs CLD: 12.7 mm Hg [95% CI: 9.7, 15.7])
- Trough SBP by ABPM in Black subjects (LS mean difference vs TAK-491: 18.2 mm Hg [95% CI: 10.6, 25.9]; LS mean difference vs CLD: 4.8 mm Hg [95% CI: 13.0, -3.5])
- Trough SBP by clinic measurement in Black subjects (LS mean difference vs TAK-491: 20.5 mm Hg [95% CI: 27.1, 13.8]; LS mean difference vs CLD: 8.9 mm Hg [95% CI: 16.0, 1.8])

Similar results were observed in DBP measurements that the pooled TAK-491CLD 40/25 mg and 80/25 reduce both ABPM DBP and clinic DBP statistically significantly than TAK-491 80 mg and/or chlorthalidone 25 mg monotherapies from Baseline to Week 8.

The study has a higher dropout rate than a typical hypertension trial. In general, higher dose treatment groups in this trial tend to have more subjects terminated early. Table 8 shows the number of subjects with observed SBP values for each visit. On average, 14% subjects terminated early and did not complete the study. Therefore, clinic SBP measurements have about 14% data missing. Not all subjects who completed the study had ABPM measurements. Therefore, the ABPM measurement has even more missing data. The primary analysis of change from Baseline for each variable was based on the LOCF method. Sensitivity analyses were performed on observed values and using a multiple imputation method for missing data to assess the impact of LOCF methodology and drop-outs.

Table 8 Subjects with Observed Values (SBP) in Each Visit (Study 302)

	TAK-491 CLD	0	0	20	20	20	40	40	40	80	80	80
		12.5	25	0	12.5	25	0	12.5	25	0	12.5	25
ABPM	Full analysis set	156	159	155	156	154	153	146	156	162	153	161
	baseline	130	134	128	127	118	131	117	114	127	110	114
	Week 4	105	113	109	101	90	108	83	81	101	81	88
	Week 8	106	118	112	110	98	113	102	95	100	95	93
Clinic SBP	baseline	155	156	155	154	153	152	145	155	162	151	158
	Week1	147	147	146	147	142	136	130	142	147	136	145
	Week2	146	153	142	146	141	141	135	150	156	140	150
	Week4	136	148	141	144	130	140	132	133	144	136	140
	Week6	131	136	142	137	127	134	129	122	137	123	125
	Week8	133	143	140	134	131	138	130	124	136	123	131
	completed	135	141	141	135	131	139	130	125	142	125	125

It provides certain assurance that the results by LOCF method and sensitivity analysis using multiple imputations are consistent. The reviewer also did similar analyses based on observed values only and on PPS population that excluding subjects with major protocol violations. The results are also consistent. Also the ABPM measurements and clinic measurements on SBP and DBP are consistent. If the dropouts were due to lack of treatment effect, the LOCF method tends to be conservative in the primary analysis. Based on the number of dropouts in each treatment arm, it seems that tolerability rather than lack of treatment effect is more likely to be the cause of dropout. If it was due to lack of efficacy, the low dose treatment arms should have more dropouts than the high dose arms, which is not the case in this study.

In this study, the pre-specified ABPM SBP measurement in Black subjects wins on comparing the pooled TAK-491CLD 40/25 mg and 80/25 mg treatment groups to TAK-491 80 mg arm. However, the pooled TAK-491CLD 40/25 mg and 80/25 mg treatment groups did not demonstrate statistical significance in reducing trough SBP by ABPM when compared with CLD 25 mg arm in Black subjects. The clinic SBP measurement, on the other hand, did show that pooled TAK-491CLD 40/25 mg and 80/25 mg treatment groups are better than both monotherapies. Note that the SBP by ABPM had less Black subjects than the SBP by clinic measurement.

3.2.2 Study 301

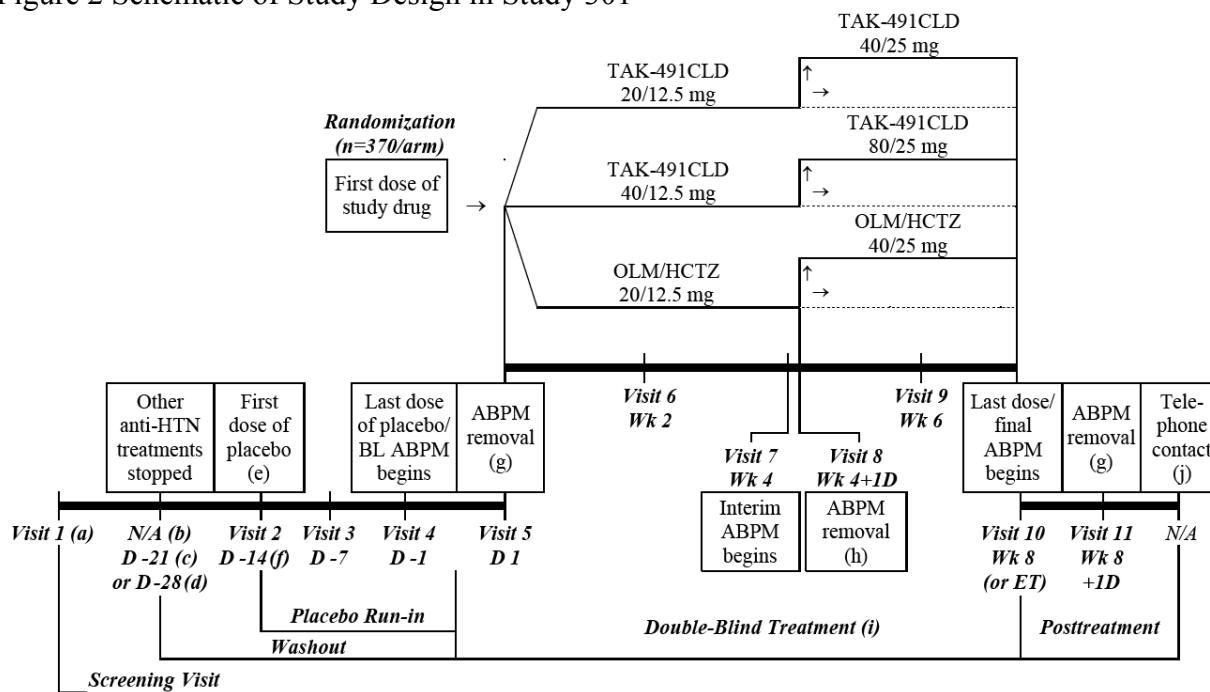
3.2.2.1 Study Design and Endpoints

This was a Phase 3, double-blind, randomized, parallel-group, 8-week efficacy and safety study comparing TAK-491CLD versus OLM/HCTZ in subjects with moderate to severe hypertension (defined as a SBP between 160 and 190 mm Hg).

Before initiation of treatment, all subjects participated in a 2-week, single-blind placebo Run-in Period (Days -14 to -1). Subjects who had not received antihypertensive treatment within 28 days before Screening were entered into the Run-in Period as soon as all inclusion and exclusion criteria were verified. Subjects taking previous antihypertensive agents were required to participate in a 3-week Washout Period (Days -21 to -1). If the subject's previous antihypertensive treatment included amlodipine or chlorthalidone, then the washout was extended to 4 weeks (Days -28 to -1).

Eligible subjects were randomly assigned to 8 weeks of treatment with 1 of the combination treatment regimens. For subjects who did not achieve target SBP and diastolic blood pressure (DBP) by Week 4, study drug was titrated to a higher dose. Subjects who achieved both blood pressure targets by Week 4 continued to receive their starting dose for the remainder of the study. The blood pressure target was defined as <140/90 mm Hg for subjects without diabetes or chronic kidney disease (CKD) versus <130/80 mm Hg for subjects with diabetes or CKD. The decision to titrate study drug at Week 4, as well as subject eligibility at the beginning of the study, was based on the mean of 3 clinic blood pressure measurements.

Figure 2 Schematic of Study Design in Study 301



3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

Of the 1085 patients randomized, 729 were randomized to TAK-491CLD: 372 in the low-dose (20/12.5 mg→40/25 mg) group and 357 in the high-dose (40/12.5 mg→80/25 mg) group; 356 patients were randomized to OLM/HCTZ (20/12.5 mg→40/25 mg). A total of 12.6% of subjects (137/1085) prematurely discontinued the study, including 55 subjects (14.8%) and 49 subjects (13.7%) in the TAK-491CLD low- and high-dose treatment groups, respectively, and 33 subjects (9.3%) in the OLM/HCTZ treatment group.

Table 9 Patient Disposition by Treatment Arm (Study 301)

	TAK-491CLD 40/25mg	TAK-491CLD 80/25mg	OLM/HCTZ 40/25mg
full analysis set	372	357	356
completed	317	308	323
early terminated	55	49	33

Only 38.4% of subjects in the low-dose treatment group titrated from 20/12.5 mg to 40/25 mg and 34.7% of subjects in the high-dose treatment group titrated from 40/12.5 mg to 80/25 mg. Subjects who achieved both SBP and DBP blood pressure targets by Week 4 continued to receive their starting dose for the remainder of the study.

Table 10 Study Drug Dose Titration by Treatment Group (Study 301)

	TAK-491CLD		OLM/HCTZ
	20/12.5 mg→ 40/25 mg N=372 n (%)	40/12.5 mg→ 80/25 mg N=357 n (%)	20/12.5 mg→ 40/25 mg N=356 n (%)
Subjects (%) received starting dose only	229 (61.6)	233 (65.3)	172 (48.3)
Subjects (%) titrated to higher dose	143 (38.4)	124 (34.7)	184 (51.7)

[source: Sponsor's clinical study report TAK491CLD_301 Table 15.1.4]

Table 11 Demographic Characteristics by Treatment Arm (Study 301)

		TAK-491CLD 40/25mg	TAK-491CLD 80/25mg	OLM/HCTZ 40/25mg
N		372	357	356
Age	Mean	55.5	56.7	55.7
	Std	10.5	10.8	9.8
Weight	Mean	89.3	89.9	90.7
	Std	21	21.3	20.7
Race	White (%)	235 (63%)	225 (63%)	220 (62%)
	Black (%)	95 (26%)	95 (27%)	100 (28%)
Gender	Male (%)	197 (53%)	183 (51%)	183 (51%)
Country	US (%)	302 (81%)	294 (82%)	295 (83%)

3.2.2.3 Statistical Methodologies

The FAS included all subjects who were randomized and received at least 1 dose of study medication (all 1085 randomized subjects). The PPS included all subjects in the FAS, excluding those identified as having major protocol deviations.

The primary endpoint is change from Baseline in clinic SBP at Weeks 8 and the key secondary endpoint is change from baseline in clinic SBP at Week 4.

Other secondary efficacy endpoints included:

- Change from Baseline to Weeks 4 and 8 in clinic DBP
- Change from Baseline to Weeks 4 and 8 in ABPM parameters
- Proportion of subjects at each study visit who reached their target clinic SBP, target clinic DBP, or target clinic SBP/DBP

The efficacy analysis for the clinic SBP and DBP was performed on last observation carried forward (LOCF) data set. Sensitivity analyses on clinic SBP and DBP were performed on observed values and using multiple imputations for missing clinic blood pressure data to assess the impact of LOCF methodology and drop-outs.

The latest version of SAP that sponsor submitted with this application was dated on July 15, 2009. In the SAP, the sponsor proposed to perform a test of non-inferiority by comparing the

upper-limit of the 95% CI of the treatment difference (ie, TAK-491CLD – OLM/HCTZ) to the value of 3.5 mm Hg. Both high dose and low dose groups would be tested for non-inferiority before proceeding to test superiority using a step-wise testing procedure to control the overall type I error.

In a correspondence to sponsor's SPA (dated September 8, 2009), the Division recommended that sponsor remove the non-inferiority test in Study 301 and Study 303. The clinical study report of Study 301 removed non-inferiority test, but this change was not reflected in the SAP. No multiplicity adjustment method was mentioned for controlling the overall type I error.

3.2.2.4 Results and Conclusion

51.7% of the subjects in the OLM/HCTZ treatment group did not achieve SBP and DBP targets by Week 4 and required titration from 20/12.5 mg to the higher dose of 40/25 mg, compared with 38.4% of subjects in the low-dose TAK-491CLD treatment group who required titration from 20/12.5 mg to 40/25 mg and 34.7% of subjects in the high-dose TAK-491CLD treatment group who required titration from 40/12.5 mg to 80/25 mg.

At Week 8, change from Baseline in clinic SBP was similar for the low- and high-dose TAK-491CLD treatment groups. Statistically significantly greater change from Baseline in clinic SBP were observed for both TAK-491CLD treatment groups compared with the OLM/HCTZ treatment group.

Table 12 Change From Baseline in Clinic SBP at Week 4 and Week 8 (LOCF, FAS, Study 301)

Study Visit	TAK-491CLD		OLM/HCTZ
	20/12.5 mg→ 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 vs OLM/HCTZ	0.503	0.870	
Week 4 (Key Secondary Endpoint) (b)			
n	360	347	352
LS mean Δ from BL (SE)	-33.0 (0.87)	-34.1 (0.88)	-26.9 (0.88)
LS mean difference vs OLM/HCTZ	-6.1	-7.2	
(95% CI)	(-8.5, -3.7)	(-9.6, -4.8)	
P-value	<0.001*†	<0.001*†	
Week 4: Sensitivity analysis using multiple imputation (b)			
LS mean difference	-6.2	-7.5	
(95% CI)	(-8.7, -3.8)	(-10.0, -5.0)	
P-value	<0.001*†	<0.001*†	
Week 8 (Primary Endpoint)			
n	363	350	353
LS mean Δ from BL (SE)	-37.6 (0.83)	-38.2 (0.85)	-31.5 (0.84)
LS mean difference vs OLM/HCTZ	-6.1	-6.7	
(95% CI)	(-8.4, -3.8)	(-9.1, -4.4)	
P-value	<0.001*†	<0.001*†	
Week 8: Sensitivity analysis using multiple imputation			
LS mean difference	-6.5	-7.2	
(95% CI)	(-8.8, -4.2)	(-9.5, -4.8)	
P-value	<0.001*†	<0.001*†	

[Source: sponsor's clinical study report TAK491CLD_301 Table 15.2.1.1.2, confirmed by the reviewer]

In addition,

- Change from Baseline to Week 8 in clinic DBP, TAK-491CLD low-dose and high-dose treatments reduced mean DBP more than the OLM/HCTZ treatment. Treatment differences and corresponding 95% CIs were:
 - Low-dose TAK-491CLD: -3.3 (CI: -4.6, -2.0) mm Hg (P<0.001).
 - High-dose TAK-491CLD: -3.7 (CI: -5.0, -2.4) mm Hg (P<0.001).
- Change from Baseline to Week 8 in trough SBP by ABPM, TAK-491CLD treatment reduced mean SBP statistically significantly more than OLM/HCTZ treatment. Treatment differences and corresponding 95% CIs were:
 - Low-dose TAK-491CLD: -5.3 (CI: -7.5, -3.0) mm Hg (P<0.001).
 - High-dose TAK-491CLD: -7.2 (CI: -9.4, -4.9) mm Hg (P<0.001).
- Change from Baseline to Week 8 in trough DBP by ABPM, TAK-491CLD treatment reduced mean SBP statistically significantly more than OLM/HCTZ treatment. Treatment differences and corresponding 95% CIs were:
 - Low-dose TAK-491CLD: -2.6 (CI: -4.2, -1.1) mm Hg (P=0.001).
 - High-dose TAK-491CLD: -3.9 (CI: -5.4, -2.3) mm Hg (P<0.001).

Again, missing data is a concern in this study. A total of 12.6% of subjects (137/1085) prematurely discontinued the study. **Table 13** shows the number of subjects in each treatment arm for each visit. Also the ABPM measurement has more missing than the clinic measurement.

Table 13 Subjects with Observed Values (SBP) in Each Visit (Study 301)

		TAK-491CLD 40/25mg	TAK-491CLD 80/25mg	OLM/HCTZ 40/25mg
full analysis set		372	357	356
completed		317	308	323
early terminated		55	49	33
Clinic SBP	baseline	372	357	356
	Week 2	343	334	345
	Week 4	327	323	333
	Week 6	319	309	327
	Week 8	314	305	321
ABPM SBP	baseline	371	353	356
	Week 4	223	227	219
	Week 8	242	238	249

The results by LOCF method and sensitivity analysis using multiple imputations are consistent. The reviewer did similar analyses based on observed values only and on PPS population that excluding subjects with major protocol violations. The results are consistent. Also the ABPM measurements and clinic measurements on SBP and DBP are consistent. All the analyses above provide certain assurance of robustness of the efficacy results despite of the missing data issue.

3.2.3 Study 306

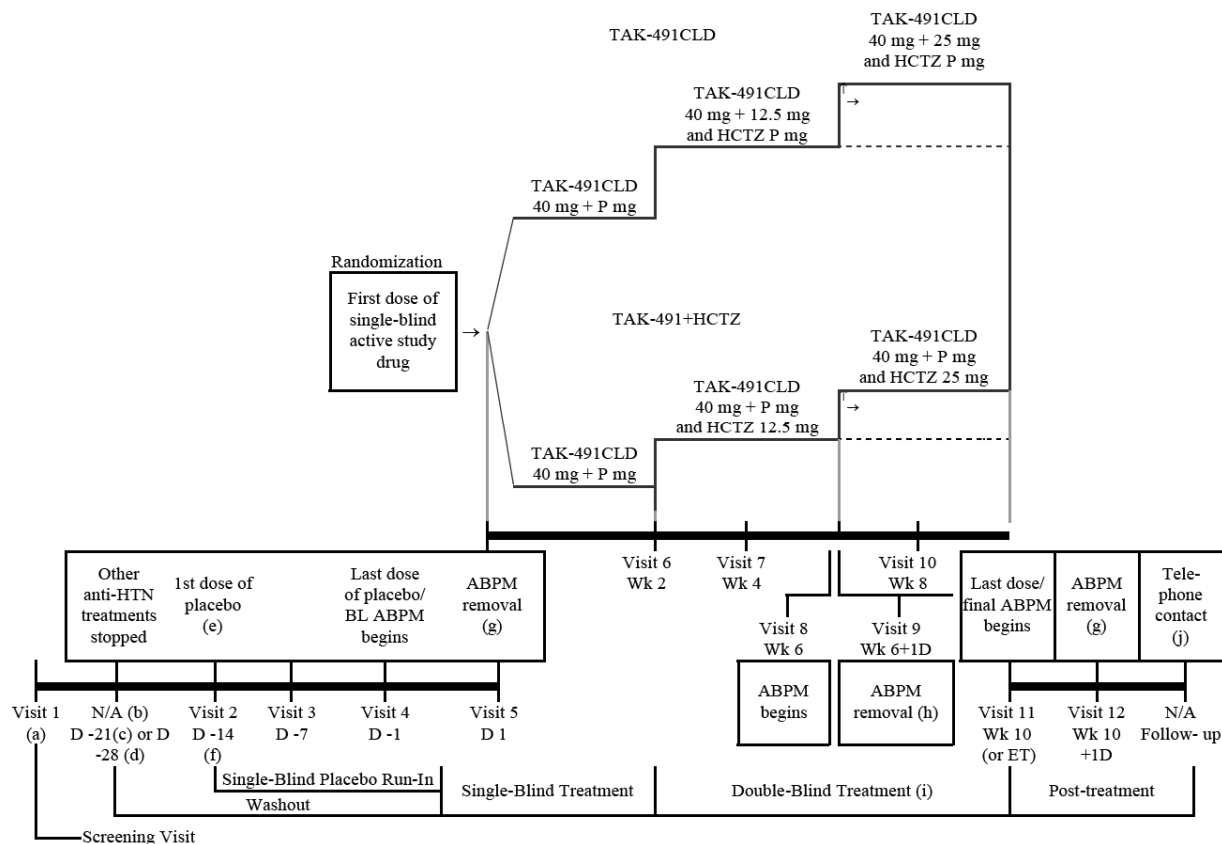
3.2.3.1 Study Design and Endpoints

This was a phase 3, multicenter, double-blind, randomized, parallel-group efficacy and safety study evaluating TAK-491 in FDC with chlorthalidone compared with TAK-491 co-administered with HCTZ over 10 weeks of treatment in subjects with moderate to severe essential hypertension (defined as SBP between 160 and 190 mm).

Eligible subjects were randomized to either the TAK-491CLD or TAK-491+HCTZ treatment group. All subjects initiated treatment with single-blind TAK-491 40 mg as monotherapy. Double-blind treatment began at the end of Week 2 and consisted of the FDC tablet of TAK-491 40 mg plus 12.5 mg of chlorthalidone (TAK-491CLD 40 mg/12.5 mg) or TAK-491 40 mg plus 12.5 mg HCTZ (TAK-491 40 mg + HCTZ 12.5 mg). If both target SBP and target diastolic blood pressure (DBP) were achieved by Week 6, the dose of chlorthalidone or HCTZ remained at 12.5 mg for the duration of the study. For subjects who did not achieve both target SBP and DBP by Week 6, the dose of chlorthalidone or HCTZ was titrated to 25 mg (TAK-491CLD 40 mg/25 mg or TAK-491 40 mg + HCTZ 25 mg, respectively). Target blood pressure was defined

as mean trough, sitting, clinic blood pressure <140/90 mm Hg for subjects without diabetes or chronic kidney disease (CKD) or <130/80 mm Hg for subjects with diabetes or CKD. The decision to titrate study drug at Week 6, as well as subject eligibility at the beginning of the study, was based on the mean of 3 sitting clinic blood pressure measurements.

Figure 3 Schematic of Study Design in Study 306



3.2.3.2 Patient Disposition, Demographic and Baseline Characteristics

1193 subjects entered the single-blind placebo run-in period, and 609 subjects were randomized to treatment at 63 sites in the United States and Russia; 303 and 306 subjects were randomized to the TAK-491CLD and TAK-491+HCTZ treatment groups, respectively. 84% of randomized subjects (512 of 609) completed 10 weeks of active treatment. 97 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.

Demographic and baseline characteristics were similar between treatment groups in all randomized subjects. The mean age of all randomized subjects was 56.4 years. The percentage of White subjects (84.9%) was higher than Black subjects (13.8%) and 70.1% of all subjects were from sites in the United States.

Table 14 Demographic Characteristics by Treatment Arm (Study 306)

		TAK-491CLD	TAK-491 + HCTZ
N		302	303
Age	Mean	56.8	55.9
	Std	10.8	11
Weight	Mean	87.6	90.8
	Std	19.2	19.8
Race	White (%)	251 (83%)	262 (86%)
	Black (%)	46 (15%)	38 (13%)
Gender	Male (%)	145 (48%)	149 (49%)
Country	US (%)	212 (70%)	214 (71%)

The FAS was defined as all randomized subjects who received at least 1 dose of active single-blind or double-blind study medication. The FAS included 605 subjects: 302 in the TAK-491CLD treatment group and 303 in the TAK-491+HCTZ treatment group.

The PPS was defined as all subjects in the FAS except those identified as having major protocol violations. The PPS included 576 subjects: 290 in the TAK-491CLD treatment group and 286 in the TAK-491+HCTZ treatment group.

For both the FAS and PPS analyses, data from all subjects in the population who had both a Baseline value and at least 1 post-baseline value for a specific variable were included in the analysis of that variable.

Table 15 Patient Disposition by Treatment Arm (Study 306)

	TAK-491CLD	TAK-491 + HCTZ
full analysis set	302	303
completed	252	260
early terminated	50	43

3.2.3.3 Statistical Methodologies

The primary efficacy variable was the change from baseline to Weeks 6 and 10 in trough, sitting, clinic SBP. The primary analyses will be an analysis of covariance (ANCOVA) model for change from baseline to Weeks 6 and 10 for the primary efficacy variable. The model will include treatment as a factor and its baseline measurement as covariate. Type I error will be controlled using a stepwise testing procedure.

Step 1: The first test will be done at Week 6. If it is statistically significant at a significance level of 5%, then proceed to Step 2.

Step 2: The treatment comparison at Week 10 will be performed at a significance level of 5%.

The rationale for conducting the first step of the testing procedure at Week 6 is because all subjects will be receiving the same 12.5 dose of CLD or HCTZ at that time point, whereas at Week 10, the proportion of subjects receiving the same dose of CLD or HCTZ will not necessarily be the same.

The secondary efficacy variables were the following:

- Change from Baseline to Weeks 6 and 10 in trough, sitting, clinic DBP.
- Change from Baseline to Weeks 6 and 10 in the following ABPM parameters for SBP and DBP:
 - Mean trough SBP and DBP (22 to 24 hours after dosing).
 - 24-hour mean SBP and DBP.
 - Mean daytime (6 AM to 10 PM) SBP and DBP.
 - Mean nighttime (12 AM to 6 AM) SBP and DBP.
 - Mean SBP and DBP at 0 to 12 hours after dosing.
- Proportion of subjects at each study visit who reached their target SBP, DBP, and SBP/DBP:

No specific multiplicity adjustment was mentioned for controlling type I error for testing the secondary endpoints.

The primary analysis of change from Baseline for each variable was based on the LOCF method. In the LOCF analysis, the last post-baseline observed values were carried forward and used for all subsequent, scheduled time points where data were missing (e.g., the subject had missing data or dropped out of the study). The efficacy analysis for the response criteria was also based on the LOCF data set.

In addition, sensitivity analyses on trough sitting clinic SBP and DBP were performed on observed values and using a multiple imputation method for missing trough sitting clinic blood pressure data to assess the impact of LOCF methodology and drop-outs. The sensitivity analyses on mean trough ABPM, SBP, and DBP were also conducted similarly.

3.2.3.4 Results and Conclusion

Table 16 Change from Baseline in Clinic SBP at Week 6 and Week 10 (LOCF, FAS, Study 306)

Study Visit	Treatment Group		P-Value
	TAK-491CLD N=302	TAK-491+HCTZ N=303	
Baseline (a)			
n	295	292	
LS mean (SE)	164.7 (0.55)	164.4 (0.56)	0.707
Week 6 (b)			
n	295	292	
LS mean change (SE)	-35.1 (0.97)	-29.5 (0.98)	
LS mean difference (c) (95% CI)	-5.6 (-8.3, -2.9)		<0.001*
Week 6: Sensitivity analysis using multiple imputation			
n	302	303	
LS mean difference (c) (95% CI)	-5.5 (-8.2, -2.8)		<0.001*
Week 10			
n	295	292	
LS mean change (SE)	-37.8 (0.91)	-32.8 (0.91)	
LS mean difference (c) (95% CI)	-5.0 (-7.5, -2.5)		<0.001*
Week 10: Sensitivity analysis using multiple imputation			
n	302	303	
LS mean difference (c) (95% CI)	-4.5 (-7.1, -2.0)		<0.001*

[Source: Sponsor's Clinical Study Report TAK-491 CLD 306 Table 11.a, confirmed by reviewer]

Table 17 Change from Baseline in Clinic DBP at Week 6 and Week 10 (LOCF, FAS, Study 306)

Study Visit	Treatment Group		P-Value
	TAK-491CLD N=302	TAK-491+HCTZ N=303	
Baseline (a)			
n	295	292	
LS mean (SE)	95.5 (0.54)	95.5 (0.55)	0.972
Week 6 (b)			
n	295	292	
LS mean change (SE)	-15.0 (0.55)	-11.2 (0.55)	
LS mean difference (c) (95% CI)	-3.7 (-5.2, -2.2)		<0.001*
Week 6: Sensitivity analysis using multiple imputation			
n	302	303	
LS mean difference (c) (95% CI)	-3.9 (-5.5, -2.3)		<0.001*
Week 10 (b)			
n	295	292	
LS mean change (SE)	-16.4 (0.50)	-13.7 (0.51)	
LS mean difference (c) (95% CI)	-2.7 (-4.1, -1.3)		<0.001*
Week 10: Sensitivity analysis using multiple imputation			
n	302	303	
LS mean difference (c) (95% CI)	-2.5 (-4.0, -1.1)		<0.001*

[Source: Sponsor's Clinical Study Report TAK-491 CLD 306 Table 11.b, confirmed by reviewer]

Table 18 Change from Baseline in ABPM SBP at Trough at Week 6 and Week 10 (LOCF, FAS, Study 306)

ABPM by Study Visit	Treatment Group		P-Value
	TAK-491CLD N=302	TAK-491+HCTZ N=303	
Trough SBP (22-24 hours)			
Baseline (a)			
n	227	230	
LS mean (SE)	149.5 (1.09)	148.8 (1.08)	
Week 6 (b)			
n	179	162	
LS mean change (SE)	-25.7 (1.11)	-18.4 (1.16)	
LS mean difference (c) (95% CI)	-7.3 (-10.5, -4.2)		<0.001*
Week 10 (b)			
n	227	230	
LS mean change (SE)	-25.6 (0.91)	-21.4 (0.90)	
LS mean difference (c) (95% CI)	-4.2 (-6.8, -1.7)		0.001*

[Source: Sponsor's Clinical Study Report TAK-491 CLD 306 Table 11.c, confirmed by reviewer]

In summary,

- A greater proportion of subjects in the TAK-491+HCTZ treatment group (45.9%) compared with the TAK-491CLD treatment group (30.8%) requiring titration of diuretic to the 25 mg dose at Week 6 to achieve target SBP/DBP.
- TAK-491CLD was significantly better than TAK-491+HCTZ in reducing mean trough clinic sitting SBP from Baseline to Week 6 and Week 10
- TAK-491CLD was significantly better than TAK-491+HCTZ in reducing mean trough clinic sitting DBP from Baseline to Weeks 6 and 10
- TAK-491CLD was significantly better than TAK-491+HCTZ in reducing mean trough SBP and DBP by ABPM from Baseline to Week 6 and Week 10.

Like other studies in this application, missing data is a concern. About 16% subjects prematurely discontinued the study. Table 19 shows the number of subjects in each treatment arm for each visit.

Table 19 Subjects with Observed Values (SBP) in Each Visit (Study 306)

		TAK-491CLD	TAK-491 + HCTZ
Clinic SBP	baseline	302	303
	Week 2	283	276
	Week 4	276	272
	Week 6	271	262
	Week 8	251	256
	Week 10	247	252
ABPM SBP	baseline	300	300
	Week 6	179	162
	Week 10	179	199

To assess the impact of missing data, the sponsor and the reviewer performed a number of analyses. The results by LOCF method and sensitivity analysis using multiple imputations are consistent. The reviewer did similar analyses based on observed values only and on PPS population that excluding subjects with major protocol violations. The results are consistent. The ABPM measurements and clinic measurements on SBP and DBP are consistent. All the analyses above provide certain assurance of robustness of the efficacy results despite of the missing data issue.

3.2.4 Study 303

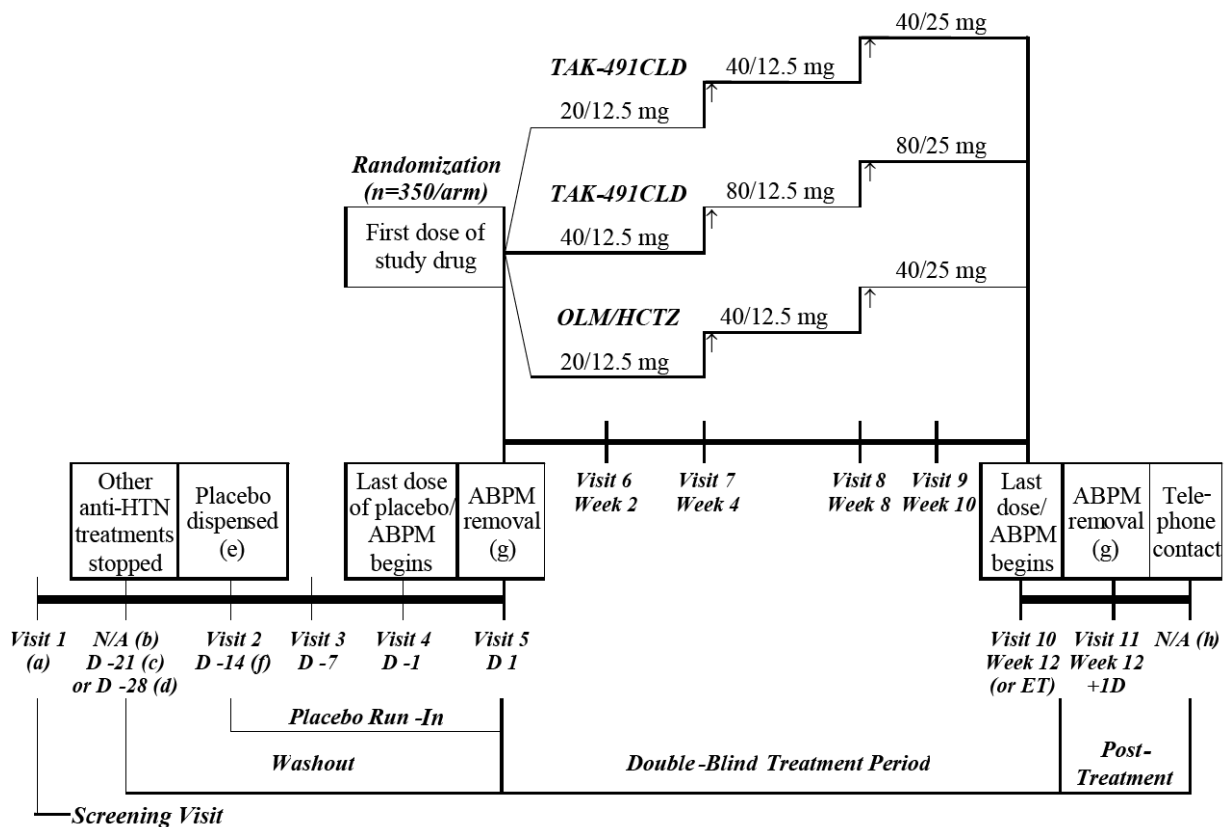
3.2.4.1 Study Design and Endpoints

This was a phase 3b, double-blind, randomized, parallel-group, 12-week efficacy and safety study of the TAK-491CLD FDC vs OLM/HCTZ FDC in subjects with moderate to severe

hypertension (SBP between 160 and 190 mm Hg). Randomization was stratified by subject's race: Black and non-Black.

Eligible subjects were randomly assigned to 12 weeks of treatment with 1 of the combination titration treatments (TAK-491CLD 40/25 mg, TAK-491CLD 80/25 mg, OLM/HCTZ 40/25 mg). Each subject's dose was force-titrated at the end of Weeks 4 and 8.

Figure 4 Schematic of Study Design in Study 303



3.2.4.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 1071 subjects were randomized to treatment and 892 (83.3%) subjects completed the study. Of the 1071 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).

The percentage of randomized subjects from sites within the United States totaled 78.2%. The majority of all randomized subjects were White (73.4%), followed by Black (22.4%).

Table 20 Demographic Characteristics by Treatment Arm (Study 303)

		TAK-491CLD 40/25mg	TAK-491CLD 80/25mg	OLM/HCTZ 40/25mg
N		355	352	364
Age	Mean	56.4	56.7	56.7
	Std	10.5	10.1	10.9
Weight	Mean	92.3	91.5	90.8
	Std	20.3	21	18.6
Race	White (%)	261 (74%)	258 (73%)	267 (73%)
	Black (%)	80 (23%)	80 (23%)	80 (22%)
Gender	Male (%)	223 (63%)	201 (57%)	205 (56%)
Country	US (%)	276 (78%)	277 (79%)	285 (78%)

The FAS included all subjects who were randomized and received at least 1 dose of study medication (all 1071 randomized subjects); subjects were included in the analyses of a specific variable only when there was both a baseline value and at least 1 value during the treatment period.

The PPS comprised all subjects in the FAS except those identified as having major protocol deviations. Approximately 89% of subjects were included in the PPS in all treatment groups.

Table 21 Patient Disposition by Treatment Arm (Study 303)

	TAK-491CLD 40/25mg	TAK-491CLD 80/25mg	OLM/HCTZ 40/25mg
full analysis set	355	352	364
completed	300	275	317
early terminated	55	77	47

3.2.4.3 Statistical Methodologies

The primary efficacy endpoint was the change from Baseline to Week 12 in mean clinic SBP. Secondary efficacy endpoints included:

- Change from Baseline to Weeks 4 and 8 in clinic SBP.
- Change from Baseline to Weeks 4, 8, and 12 in clinic DBP.
- Change from Baseline to Week 12 in the following ABPM parameters:
- Proportion of subjects at Weeks 4, 8, and 12 who reached their blood pressure target

The primary analysis of change from Baseline for each variable was based on the LOCF method. The primary analysis was based on an analysis of covariance (ANCOVA) model for change from Baseline to Week 12 or last on-treatment visit for the primary efficacy variable. The model included treatment as a factor and Baseline clinic SBP as a covariate.

The final version of SAP that sponsor submitted with this application was dated on July 20, 2009. Similar as Study 301, the sponsor proposed in the SAP to perform a test of non-inferiority. Both high dose and low dose groups would be tested for non-inferiority before proceeding to test superiority using a step-wise testing procedure to control the overall type I error.

In a correspondence to sponsor’s SPA (dated September 8, 2009), the Division recommended that sponsor remove the non-inferiority test in Study 301 and Study 303. The clinical study report removed non-inferiority test, but this change is not reflected in the SAP. To control the overall type I error, the clinical study report used a closed testing procedure for the primary analyses. The hypothesis of “all titration groups equal” was first tested at the 0.05 significance level. Upon rejection of this hypothesis, the 2 pairwise comparisons (TAK-491CLD 40/25 mg versus OLM/HCTZ and TAK-491CLD 80/25 mg versus OLM/HCTZ) were tested at the 0.05 level.

Sensitivity analyses on SBP and DBP were performed on observed values and using a multiple imputation method for missing trough blood pressure data to assess the impact of LOCF methodology and drop-outs for SBP and DBP.

3.2.4.4 Results and Conclusion

Statistically significantly greater changes from Baseline to Week 12 in mean clinic SBP were observed for both the TAK-491CLD 40/25 and 80/25 mg titration groups compared with the OLM/HCTZ titration group.

Table 22 Change From Baseline in Clinic SBP at Week 12 (mm Hg) (LOCF, FAS, Study 303)

Study Visit	TAK-491CLD		OLM/HCTZ
	20/12.5→ 40/12.5→ 40/25 mg N=355	40/12.5→ 80/12.5→ 80/25 mg N=352	20/12.5→ 40/12.5→ 40/25 mg N=364
Week 12 (Primary Endpoint)			
n	344	330	354
LS mean Δ from BL (SE)	-42.5 (0.81)	-44.0 (0.83)	-37.1 (0.80)
LS mean difference vs OLM/HCTZ	-5.3	-6.9	
(95% CI)	(-7.6, -3.1)	(-9.2, -4.6)	
P-value	<0.001*	<0.001*	
Week 12: Sensitivity analysis using multiple imputation			
LS mean difference	-5.6	-7.5	
(95% CI)	(-7.8, -3.4)	(-9.8, -5.1)	
P-value	<0.001*	<0.001*	

[Source: Sponsor’s Clinical Study Report TAK491-CLD-303 Table 11.b, confirmed by reviewer]

In addition,

For the secondary efficacy endpoint of change from Baseline to Week 4 in mean clinic SBP, TAK-491CLD 40/25 and 80/25 mg titration groups reduced mean SBP 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) mm Hg (P<0.001).
- TAK-491CLD 80/25 mg titration group: -7.0 (CI: -9.2, -4.8) mm Hg (P<0.001).

For the secondary efficacy endpoint of change from Baseline to Week 8 in mean clinic SBP, TAK-491CLD titration reduced mean SBP more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:

- TAK-491CLD 40/25 mg titration group: -5.6 (CI: -7.8, -3.5) mm Hg (P<0.001).
- TAK-491CLD 80/25 mg titration group: -5.9 (CI: -8.0, -3.7) mm Hg (P<0.001).

For the secondary efficacy endpoint of change from Baseline to Week 12 in clinic DBP, TAK-491CLD titration reduced mean DBP more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:

- TAK-491CLD 40/25 mg titration group: -2.3 (CI: -3.6, -1.0) mm Hg (P<0.001).
- TAK-491CLD 80/25 mg titration group: -4.1 (CI: -5.4, -2.8) mm Hg (P<0.001).

For the secondary efficacy endpoint of change from Baseline to Week 12 in trough SBP by ABPM, TAK-491CLD titration reduced SBP more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:

- TAK-491CLD 40/25 mg titration group: -7.0 (CI: -9.4, -4.7) mm Hg (P<0.001).
- TAK-491CLD 80/25 mg titration group: -9.0 (CI: -11.5, -6.6) mm Hg (P<0.001).

In Black subjects, change from Baseline to Week 12 in mean clinic SBP, TAK-491CLD titration reduced mean SBP more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:

- TAK-491CLD 40/25 mg titration group: -6.2 (CI: -11.7, -0.7) mm Hg (P=0.028).
- TAK-491CLD 80/25 mg titration group: -6.1 (CI: -11.7, -0.5) mm Hg (P=0.032).

In Black subjects, change from Baseline to Week 12 in trough SBP by ABPM, TAK-491CLD titration reduced SBP more than the OLM/HCTZ titration group. Treatment differences and corresponding 95% CIs were:

- TAK-491CLD 40/25 mg titration group: -5.8 (CI: -11.3, -0.3) mm Hg (P=0.040).
- TAK-491CLD 80/25 mg titration group: -7.2 (CI: -13.2, -1.3) mm Hg (P=0.018).

About 17% subjects prematurely discontinued the study. Table 23 shows the number of subjects in each treatment arm for each visit.

Table 23 Subjects with Observed Values (SBP) in Each Visit (Study 303)

		TAK-491CLD 40/25mg	TAK-491CLD 80/25mg	OLM/HCTZ 40/25mg
Clinic SBP	Baseline	355	352	364
	Week 2	339	324	346
	Week 4	333	320	340
	Week 8	308	288	326
	Week 10	309	283	314
	Week 12	296	273	317
ABPM SBP	Baseline	351	347	361
	Week 12	232	214	238

To assess the impact of missing data, the sponsor and the reviewer performed a number of analyses. The results by LOCF method and sensitivity analysis using multiple imputations are consistent. The reviewer did similar analyses based on observed values only and on PPS population that excluding subjects with major protocol violations. The results are consistent. The ABPM measurements and clinic measurements on SBP and DBP are consistent. This provides certain assurance of robustness of the efficacy results despite of the missing data issue.

3.3 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Overall, the treatment effect of TAK-491CLD appears consistent across various subgroup populations (gender, race, age and region) when compared with monotherapies or active-controls in the four studies (

Table 24, Table 25, Table 26, and

Table 27). In study 301, TAK-491CLD did not show any treatment effect when compared with OLM/HCTZ in races other than Caucasian and Black (marked in red). However, the sample sizes of treatment arms in this subgroup do appear to be small, so it could be due to chance.

Table 24 Subgroup Analysis on Changes in Clinical SBP in Study 302

	CLD 25 mg			TAK-491 80 mg			TAK-491CLD 80/25 + 40/25mg pool		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Age<65	123	-27.2	14.7	123	-25.9	16.5	232	-40.5	15.2
Age>65	33	-30	13.8	39	-17.9	20.1	81	-37.1	19.8
Male	67	-24.7	12.3	78	-22.6	17.3	131	-37.8	15.8
Female	89	-30	15.7	84	-25.2	18.1	182	-41	17
White	108	-26.3	14.6	111	-24.7	17.5	216	-38.9	17.1
Black	29	-31.5	15.3	35	-19.6	19.3	63	-40.5	16.5
Other	19	-30.3	12.2	16	-28.5	14.3	34	-42.4	13.1
US	102	-27.2	15	101	-22.6	19.5	198	-40.5	15.9
OUS	54	-28.9	13.8	61	-26.3	14.1	115	-38.1	17.6

Table 25 Subgroup Analysis on Changes in Clinical SBP in Study 301

	TAK-491CLD 40/25mg			TAK-491CLD 80/25mg			OLM/HCTZ 40/25mg		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Age<65	290	-38.9	16.7	276	-39.2	16.4	287	-31.5	17.3
Age>65	73	-33.1	16.5	74	-34.5	15.9	66	-30.9	14.1
Male	189	-34.9	18.5	178	-36	16	181	29.9	16.8
Female	174	-40.8	14.2	172	-40.4	16.4	172	-33	16.6
White	229	-38.2	16.2	220	-37.3	17.1	218	-30.5	15.8
Black	92	-34.9	19.2	93	-39.1	14.8	98	-28.7	18.6
Other	42	-41.6	13.9	37	-41.4	15.1	37	-43.9	10.2
US	293	-37	17.2	288	-37.8	16.5	292	-30.2	17.2
OUS	70	-40.9	14.6	62	-40	15.6	61	-37.1	13

Table 26 Subgroup Analysis on Changes in Clinical SBP in Study 306

	TAK-491CLD			TAK-491CLD + HCTZ		
	N	Mean	Std	N	Mean	Std
Age<65	226	-38	16.5	236	-32.8	16.9
Age>65	69	-37.6	14.5	56	-32.7	14.8
Male	142	-34.8	15	142	-30.2	16.9
Female	153	-40.9	16.4	150	-35.2	15.8
White	242	-38.5	15.2	252	-33.2	15.6

Black	46	-34.2	20.4	37	-28.7	21.2
Other	7	-42.5	11.6	3	-42	19.2
US	208	-37.5	17.2	206	-31.5	17.6
OUS	87	-39	12.8	86	-35.7	12.9

Table 27 Subgroup Analysis on Changes in Clinical SBP in Study 303

	TAK-491CLD 40/25mg			TAK-491CLD 80/25mg			OLM/HCTZ 40/25mg		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Age<65	271	-42.5	15.7	258	-44.8	15.9	272	-37.7	15.3
Age>65	73	-42.4	16.5	72	-42	17.9	82	-34.7	16.7
Male	218	-40.7	14.7	191	-42.3	17.1	199	-36	15.3
Female	126	-45.6	17.3	139	-46.7	14.9	155	-38.4	16.1
White	254	-42.9	14.2	243	-45.4	15	258	-38.4	14.9
Black	76	-40.4	20	72	-40.2	19	79	-33.3	16.5
Other	14	-46.8	18.1	15	-43.2	21.6	17	-33.7	20.8
US	268	-42.2	16	261	-43.9	16.3	276	-37.3	14.4
OUS	76	-43.4	15.6	69	-45	16.8	78	-36.2	19.7

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

One concern in this application is that the dropout rate in the four trials is higher than typical hypertension trial. The primary analyses in all four trials used LOCF method. To address the missing data issue, a number of sensitivity analyses were performed, including multiple imputation, observed case analyses and analyses on per protocol population. The results based on LOCF method and other sensitivity analyses are consistent. Also the ABPM measurements and clinic measurements on SBP and DBP are consistent. Furthermore, if the dropouts were due to lack of treatment effect, the LOCF method tends to be conservative in the primary analysis. All the above analyses offer certain assurance that despite of the high dropout rate, the missing data unlikely would affect the conclusion of the studies.

5.2 Conclusions and Recommendations

This review includes 4 placebo-controlled studies that compared the fixed-dose combination tablet TAK-491CLD with monotherapies or active-controls (OLM/HCTZ, or TAK-491+HCTZ).

Although missing data remains a concern for this application, the consistent results in various sensitivity analyses and in different blood pressure measurements offer certain assurance that missing data would unlikely affect the conclusion of the studies. The fixed-dose combination tablet TAK-491CLD is effective in treating moderate to severe essential hypertension.

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/s/

JIALU ZHANG
08/06/2011

HSIEN MING J J HUNG
08/06/2011
concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202-331

Applicant: Takeda

Stamp Date: 02/24/2011

Drug Name: TAK-491CLD

NDA/BLA Type: standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			x	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician

Date

Supervisor/Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIALU ZHANG
04/04/2011

HSIEN MING J J HUNG
04/04/2011