CENTER FOR DRUG EVALUATION AND RESEARCH

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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/Serial Number:	22217 / S_000
Drug Name:	ValturnaTM (aliskiren-valsartan) Tablets
Indication(s):	Treatment of Hypertension
Applicant:	Novartis
Date(s):	Date of Document: December, 26 2009 PDUFA Due Date: September, 26, 2008
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Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Xiao Shen, M.D, Norman Stockbridge, M.D., Ph.D.
Project Manager:	Lori Anne Wachter, RN, BSN
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1. EXECUTIVE SUMMARY

NDA 22207 for valturna is submitted to gain regulatory approval for indication of treatment of hypertension in patients not adequately controlled with monotherapy. Valturna may be substituted for titrated components and may be used as an initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals. Valturna is a combination of aliskiren and valsartan, a direct renin inhibitor and an angiotensin II receptor blocker/antagonist (ARB). Each of the two components has been approved for treatment of hypertension used as either monotherapy or in combination with other antihypertensive agents.

This NDA includes a pivotal efficacy study (Study 2327). A review for the efficacy is prepared in a separate document. This review only evaluates the efficacy data provided to support the approval of initial therapy indication, which mainly involves generation of graphs of the probability of achieving certain blood pressure goals based on baseline blood pressure values.

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 regression curves for the probability of reaching a blood pressure target after treatment as a function of baseline blood pressure for the treatment groups. The curves are often based on logistic regression modeling. Several statistical points for modeling are considered:

- Extensive model assessment of goodness-of-fit by Hosmer-Lemeshow test; comparison of fitted logistic regression curves with LOESS non-parametric curves; assessment of Pearson residuals for predicted probabilities of achieving blood pressure control.
- The model parameters of each treatment group should be estimated only from the data of this treatment group.
- In the case that there are multiple studies conduced, the pivotal trial with the largest sample size per treatment group should be first considered. The highest dose combination is first considered with its monotherapy doses if there are multiple dose combinations.

2.2 Predicted probability of msSBP and msDBP control

The highest dose aliskiren/valsartan 300/320 mg was used for the analyses to predict systolic BP and diastolic BP control rates at Week 8 endpoint versus its monotherapies and placebo, based on baseline BP. After evaluation of the data, it was decided that some of the extreme values on either or both ends of the baseline range needed to be removed because of only a few number of subjects available. There were total of six subjects with baseline SBP >180 mmHg excluded from the plots of probability of achieving SBP <140 mmHg (Figure 1) and probability achieving DBP <130 mmHg (Figure3). There were also total of six subjects with baseline DBP <90 mmHg or DBP>110 mmHg excluded from the plots of probability of achieving DBP <90 mmHg (Figure 2) and probability achieving DBP <80 mmHg (Figure 4). The graphs generated from data show that as baseline BP increases, the probability of achieving BP control decrease in all groups. However, at all levels of baseline BP, the probability of achieving systolic or diastolic goal was higher with the combination than with either monotherapy, see Figures 1-4.

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

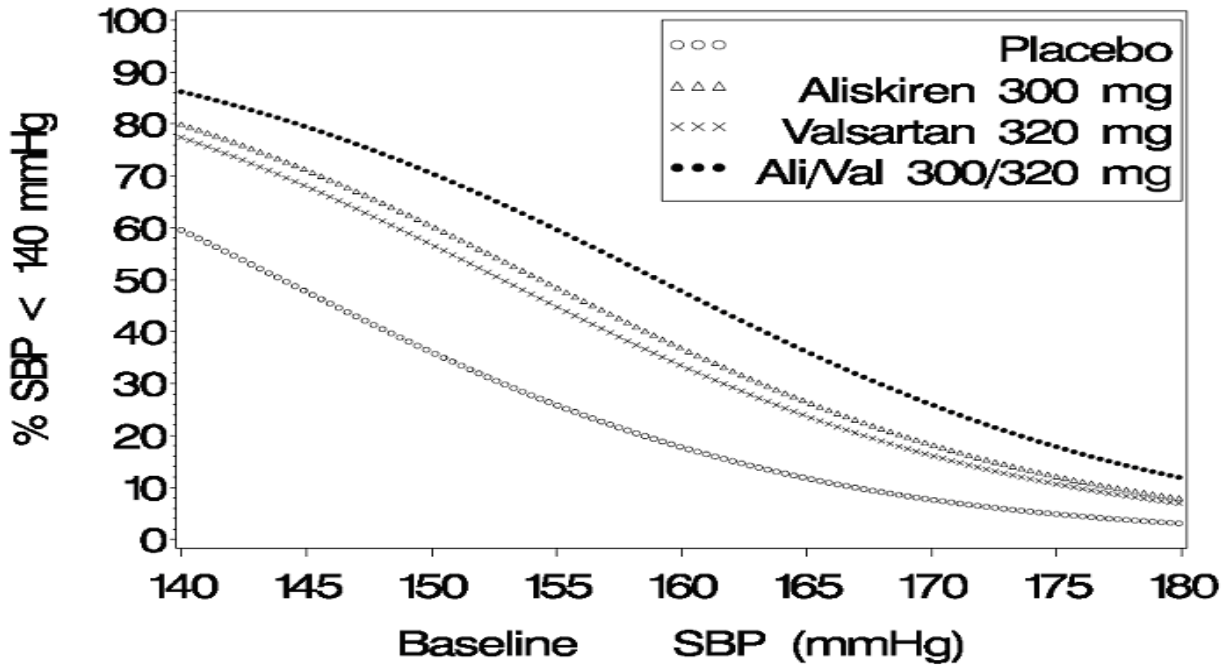


Figure 2 Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg in Patients at Week 8 Endpoint

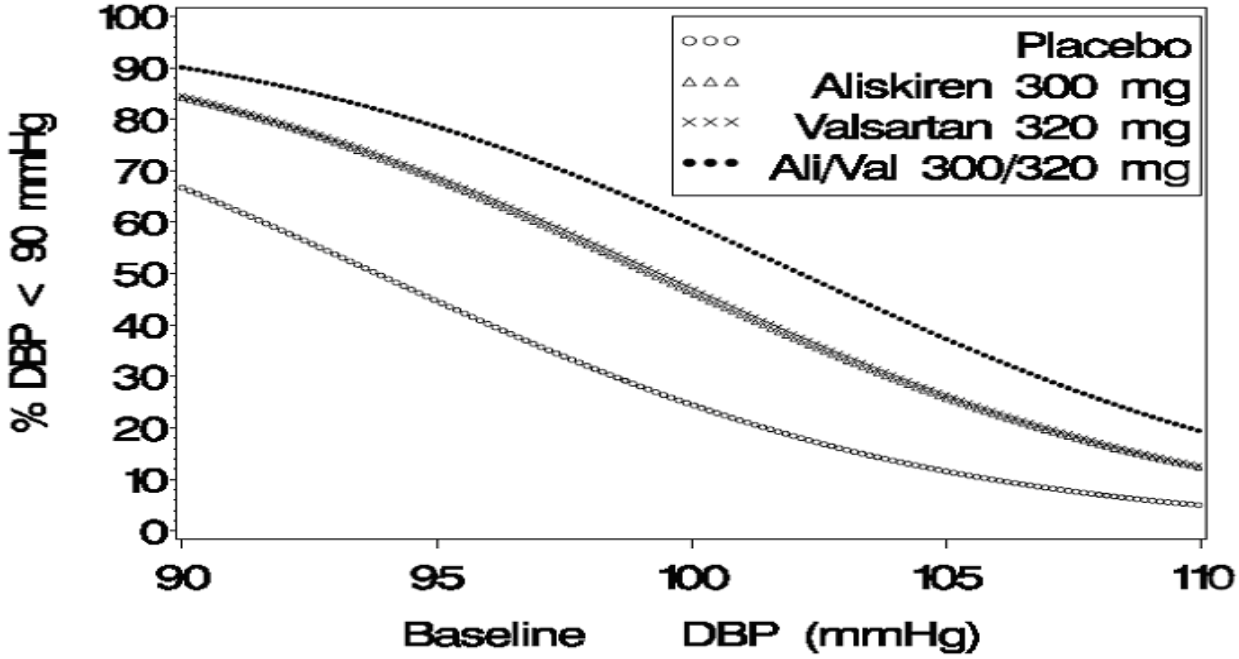


Figure 3 Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg in Patients at Week 8 Endpoint

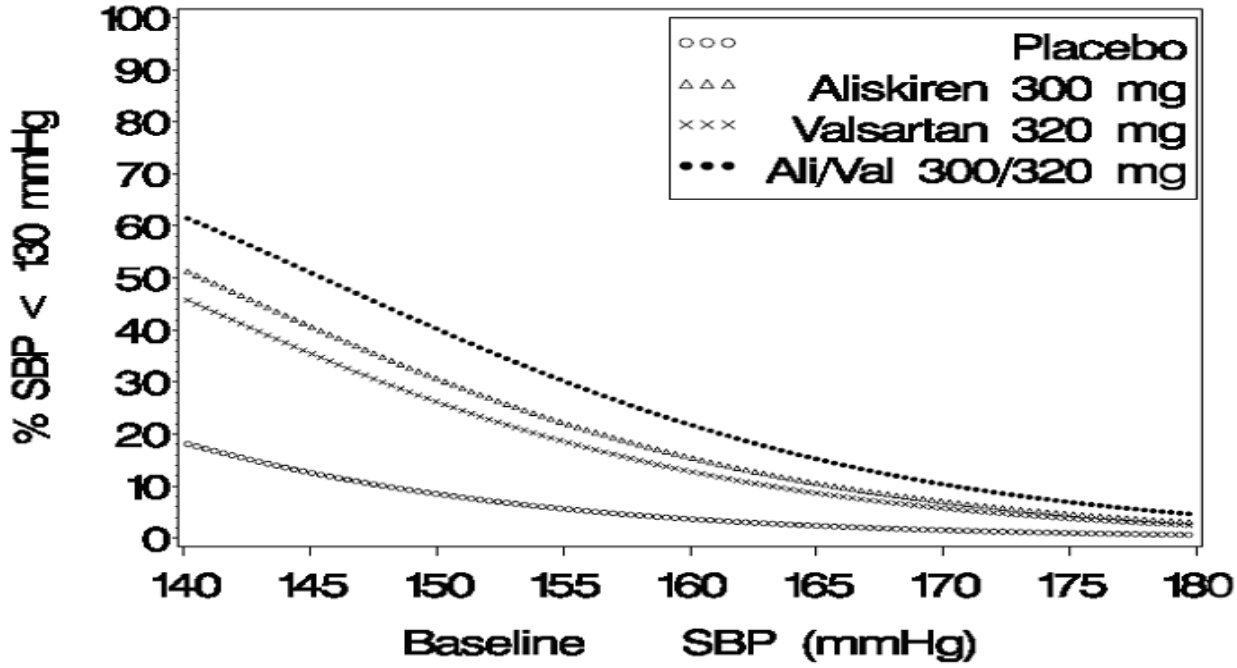
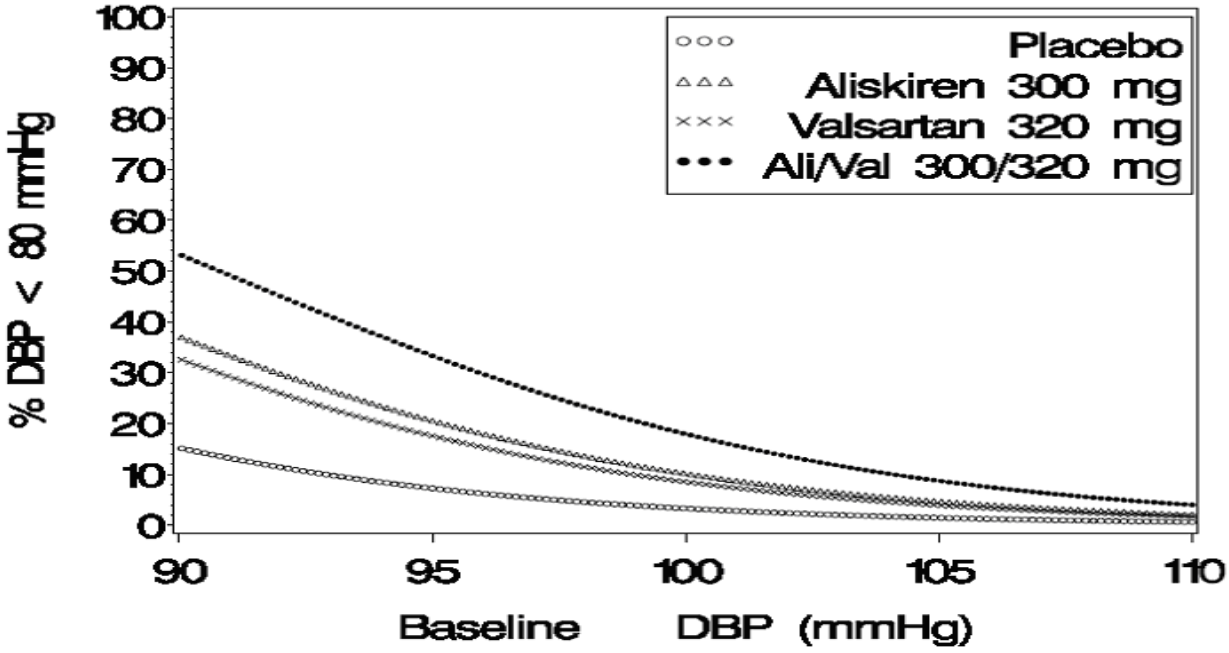


Figure 4 Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg in Patients at Week 8 Endpoint



2.3 Model diagnostics- Sponsor's analysis

2.3.1 Goodness-of-fit in logistic regression model

Hosmer-Lemeshow and Pearson tests were applied as the goodness-of-fit assessments to check whether the overall logistic regression model (either with or without treatment-by-baseline interaction) was fitted adequately. The statistically insignificant p-values for the goodness-of-fit tests indicate that the overall fit is considered reasonable for the logistic regression model either with or without the treatment by baseline interaction. Tables 1-2 below summarize the test results for DBP control rate (msDBP < 90 mmHg). The same conclusion can be made for other BP control rates with the exception of the logistic regression model without treatment-by-baseline interaction for SBP control rate (msSBP < 140 mmHg) which had a statistically significant p-value of 0.0349 in the Hosmer-Lemeshow test for valsartan 320 mg group and aggressive SBP control rate (msSBP < 130 mmHg) which had a statistically significant p-value of 0.0362 in the Pearson test for aliskiren 300 mg group.

Table 1 Logistic regression model overall goodness-of-fit by Hosmer-Lemeshow test for DBP control rate (msDBP < 90 mmHg) at Week 8 endpoint

Models	Chi-square	Degree of freedom	p-value
Model without interaction	2.981	8	0.9355
Model with each treatment alone			
Placebo	5.217	8	0.7342
Aliskiren 300 mg	10.134	7	0.1811
Valsartan 320 mg	8.058	8	0.4278
Aliskiren/valsartan 300/320 mg	10.478	7	0.1631

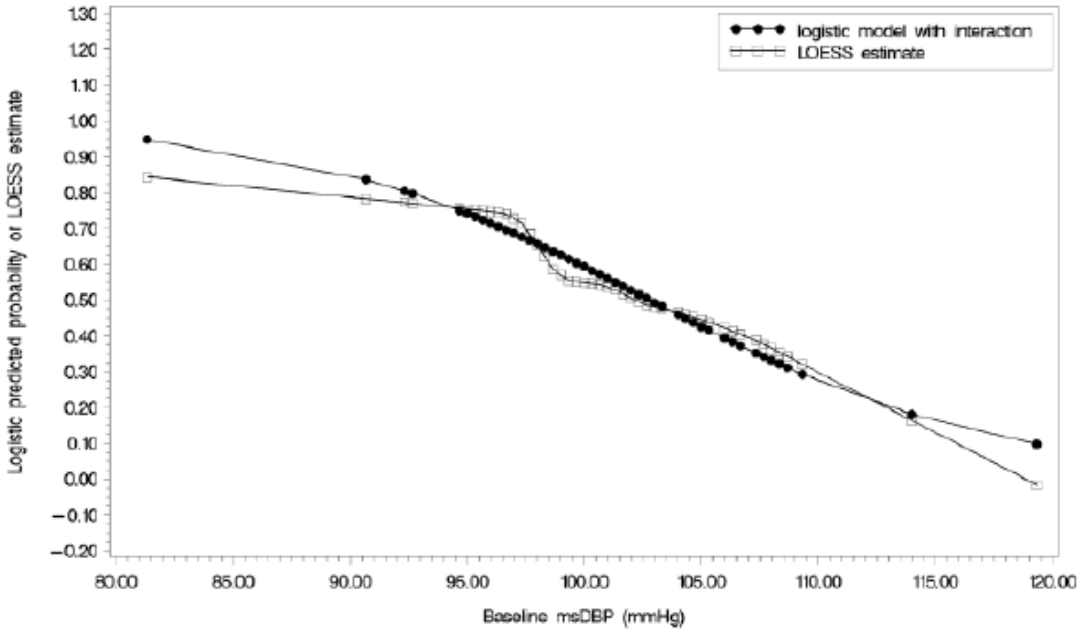
Table 2 Logistic regression model overall goodness-of-fit by Pearson test for DBP control rate (msDBP < 90 mmHg) at Week 8 endpoint

Models	Chi-square	Degree of freedom	p-value
Model without interaction	186.074	180	0.3626
Model with each treatment alone			
Placebo	45.565	49	0.6132
Aliskiren 300 mg	35.915	42	0.7341
Valsartan 320 mg	39.122	42	0.5980
Aliskiren/valsartan 300/320 mg	58.061	44	0.0759

2.3.2 Comparison of logistic regression model with LOESS model

Predicted probabilities of achieving blood pressure control from the logistic regression model (with interaction) and LOESS estimates were plotted together to compare the model fitting and to check whether there were influential points that might possibly have an unduly large impact on model fitting. The LOESS estimates were based on a locally weighted polynomial regression fitting with a smoothing parameter of 0.5. Figure 5 below displays the logistic regression (with interaction) predicted probability and LOESS estimate for DBP control rate (msDBP < 90 mmHg) at Week 8 endpoint by baseline BP for the aliskiren/valsartan 300/320 mg treatment group. Both curves were reasonably close. Because the LOESS method assigns more weight for closer observations and the LOESS estimates are obtained from a weighted regression by using 50% of the neighboring data; thus, extreme observations could dominate the estimation in some situations. Therefore, in some cases, the LOESS estimates may be less reliable at the left and right tails of the curve.

Figure 5 Predicted probability curves for DBP control rate (msDBP < 90 mmHg) at Week 8 endpoint by logistic regression model with treatment-by-baseline interaction and LOESS model for aliskiren/valsartan 300/320 mg treatment group

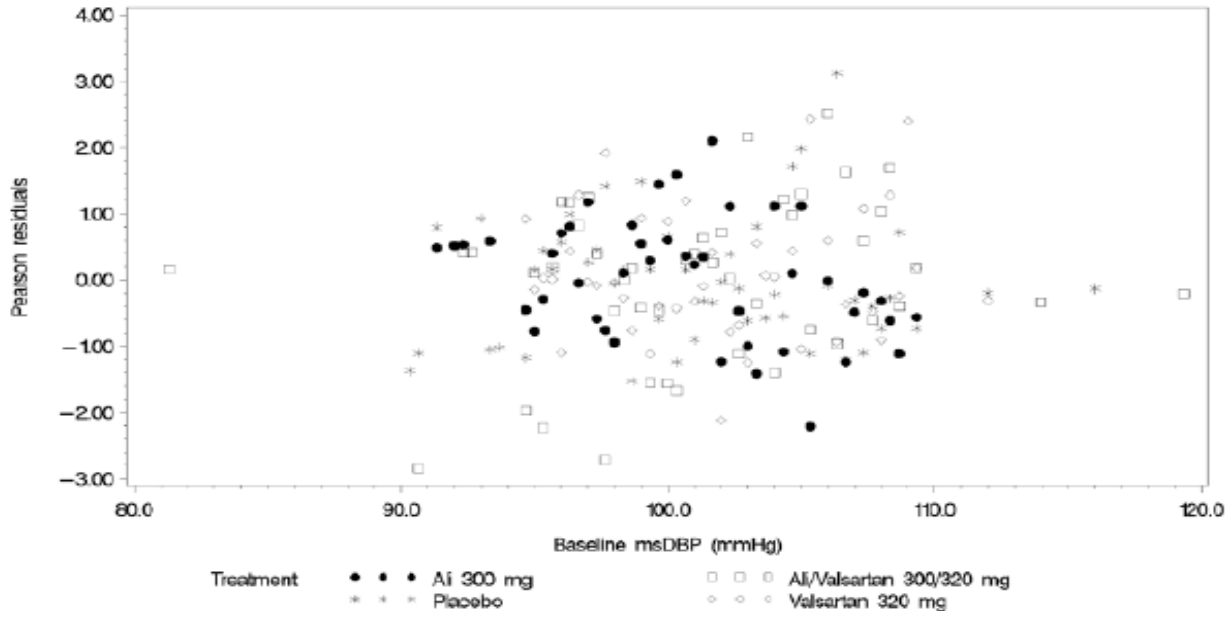


Note: The sponsor stated that the overall logistic regression model either with or without treatment-by-baseline interaction was fitted adequately. The FDA statistician also compared the curves generated by logistic regression model without treatment-by-baseline interaction and LOESS model. Both curves were still reasonably close, though they were more separate out comparing to the curves (above) including treatment-by-baseline interaction.

2.3.3 Residual analysis

Figure 6 below displays the Pearson residuals for the predicted probabilities of achieving DBP control (msDBP < 90 mmHg) at Week 8 endpoint obtained from the logistic regression model. The Pearson residuals appeared to be relatively random without particular patterns, except for a small number of potential outliers. The standardized values of the residuals were generally within ±3.

Figure 6 Pearson residuals plot for DBP control rate (msDBP < 90 mmHg) at Week 8 endpoint obtained from logistic regression model without treatment-by-baseline interaction for aliskiren/valsartan 300/320 mg, aliskiren 300 mg, valsartan 320 mg, and placebo treatment groups



2.3.4 Conclusion in modeling and diagnostics

In conclusion, the results from the model diagnostics assessments are summarized below:

- The goodness-of-fit assessment indicates that the logistic regression models (with and without treatment-by-baseline interaction) fit the data of blood pressure control rates reasonably well.

- In general, the predicted probabilities of achieving blood pressure control based on the logistic regression model and LOESS were reasonably close, except for the two tails of the curves with relatively low and high baseline blood pressures. The LOESS curves were generally more sensitive to a small number of observations with relatively low and high baseline blood pressures. In general, the predicted probabilities of achieving blood pressure control at the tails of both logistic regression and LOESS curves may be less robust due to a relatively small number of observations available.

- The Pearson residuals for predicted probabilities of achieving blood pressure control appeared to be relatively random without particular patterns. The standardized values of the Pearson residuals were generally within ±3 except a small number of points. Overall, there was no systematic departure of model assumption or indication of poor model fitting. The small number of extreme values has little impact on the predicted probabilities based on the logistic regression model fitting.

- Overall, the predicted probabilities of achieving blood pressure control obtained from the logistic regression modeling (without treatment-by-baseline interaction) with inclusion of all available data appeared to be adequate.

2.4 Conclusions

The graphs adequately represent the study data and support for the approval of initial therapy indication.

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/s/

Ququan Liu
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James Hung
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