CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205003Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 205-003
Drug Name:	Prestalia (Perindopril arginine/amlodipine besylate)
Indication(s):	hypertension
Applicant:	Symplmed Pharmaceuticals
Date(s):	Date of Document: 03/21/2014
	PDUFA due date: 01/21/2015
Review Priority:	Standard
Biometrics Division:	HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
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Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
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Keywords:

Logistic regression curves, Hosmer-Lemeshow Test, goodness-of-fit,

LIST OF TABLES

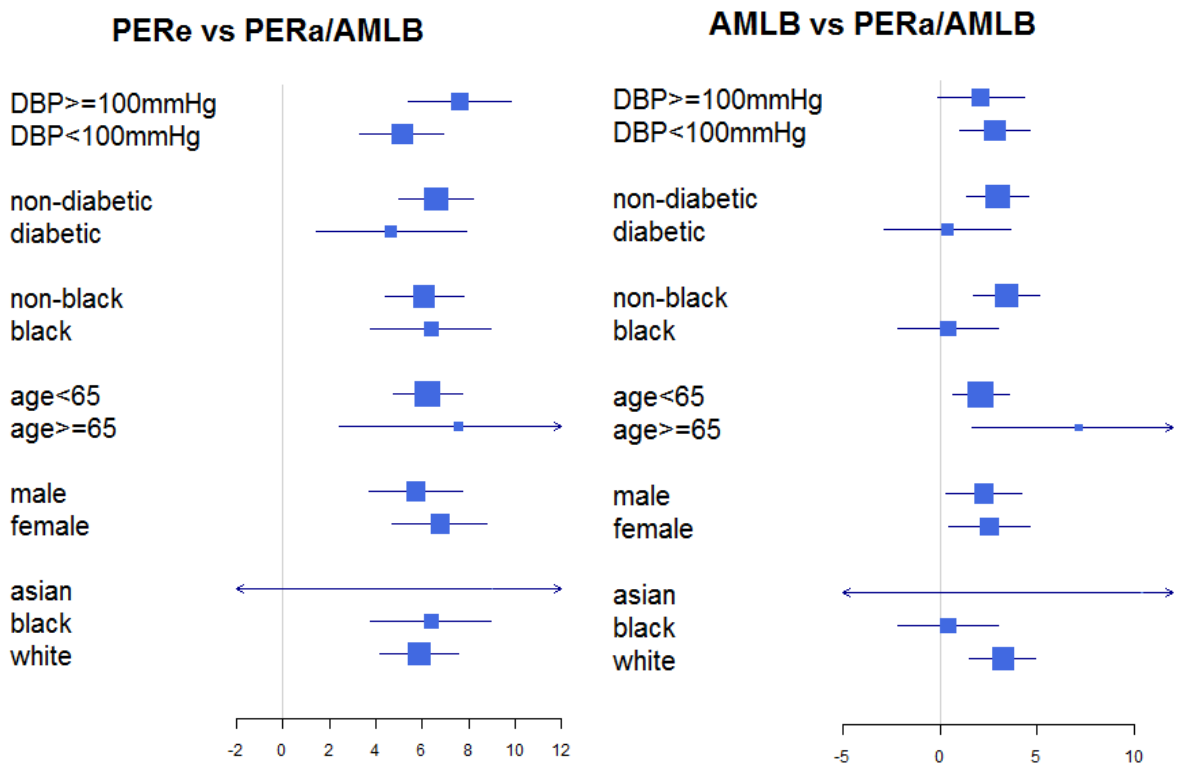
LIST OF FIGURES (Optional)

This addendum makes corrections to the forest plots included in the statistical review dated November 6, 2014, in which some subgroups were mislabeled. In addition, for the initial therapy indication, this addendum evaluates the graphs that show the probability of achieving certain blood pressure (BP) goals as a function of baseline blood pressure.

1. Corrections on Forest Plots

A few subgroups in the forest plots were mislabeled in the statistical review dated November 6, 2014. The corrected version is shown below.

Figure 1: Subgroup Analyses in PATH trial



2. Graphs for Initial Therapy Indication

To support the initial therapy indication, the sponsor submitted the required graphs to illustrate the advantage of the combination drug over its component drugs in reaching blood pressure goals of 140 and 130 mmHg systolic and 90 and 80 mmHg diastolic (SDN 0031 on 11/15/2014, SDN 0033 on 12/10/2014, and SDN 0036 on 12/19/2014). This reviewer examined the graphs in both

PATH trial and the factorial trial CL2-05985-005. There was no pooling of studies. Logistic regression curves were plotted to show the probability of reaching a blood pressure target after treatment as a function of baseline blood pressure for the treatment groups. 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
- Pearson residual plots

PATH trial

The logistic regression curves using all data for each blood pressure goal were displayed below.

Figure 2: Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg in PATH trial

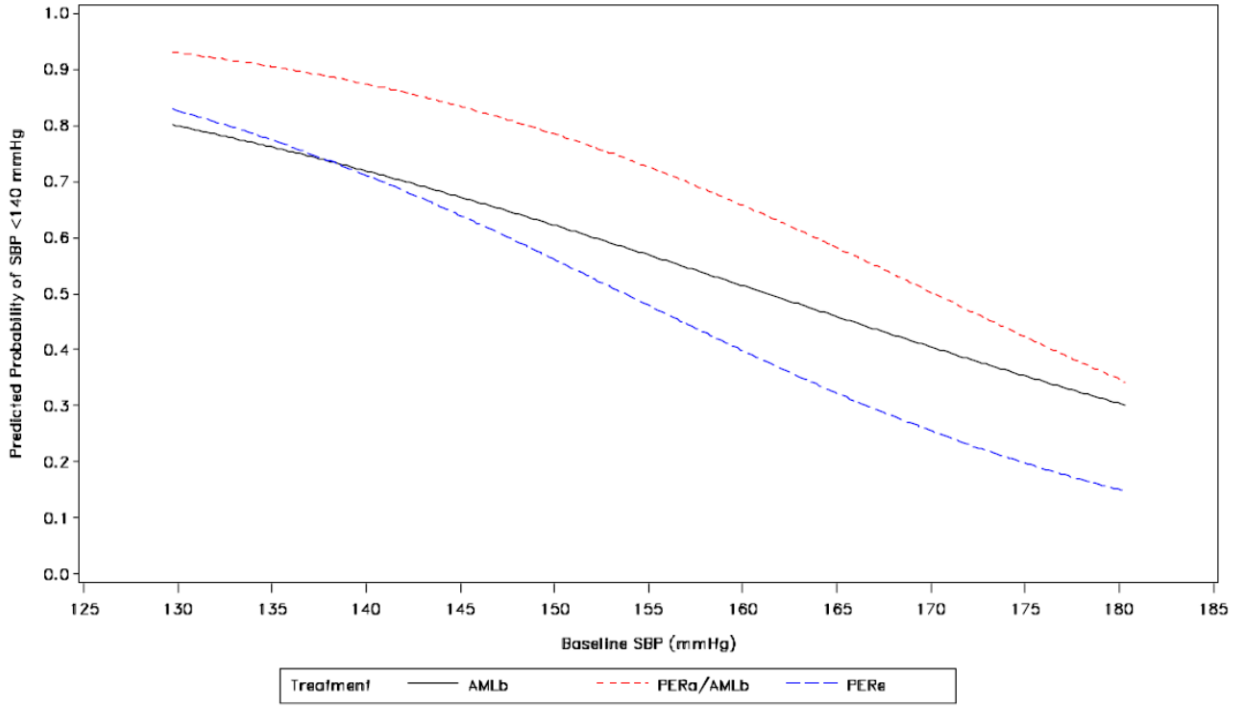


Figure 3: Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg in PATH trial

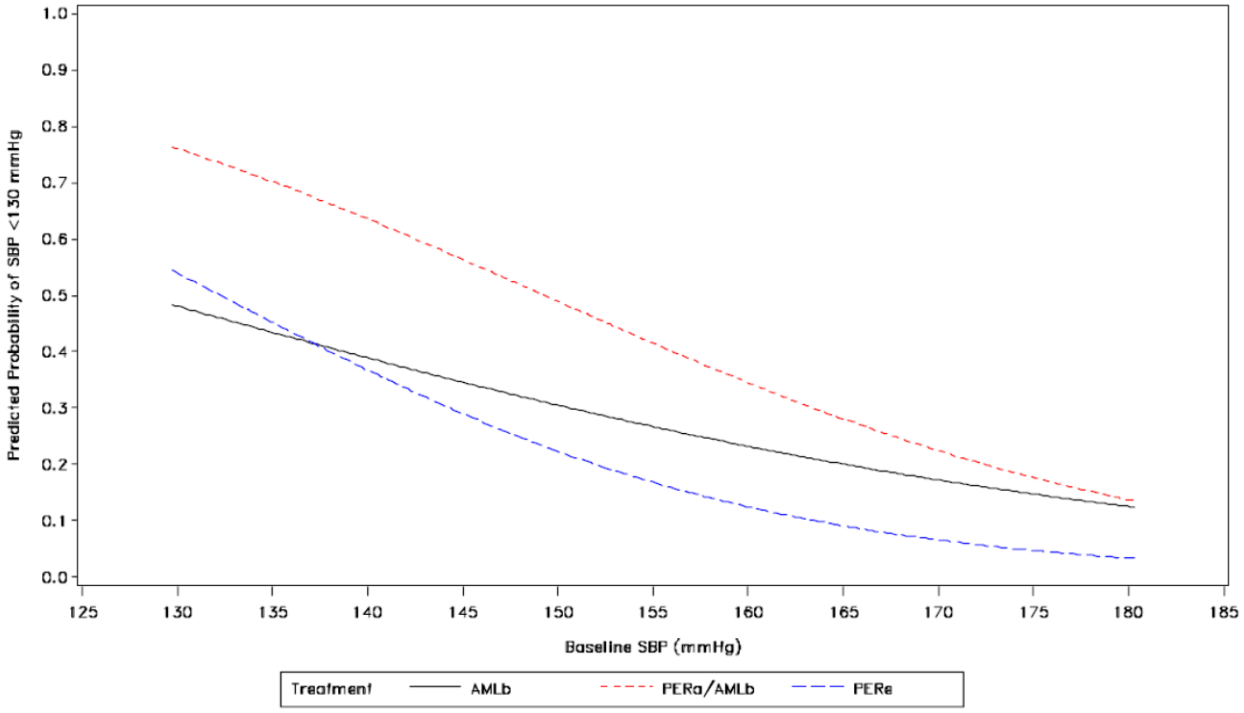


Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg in PATH trial

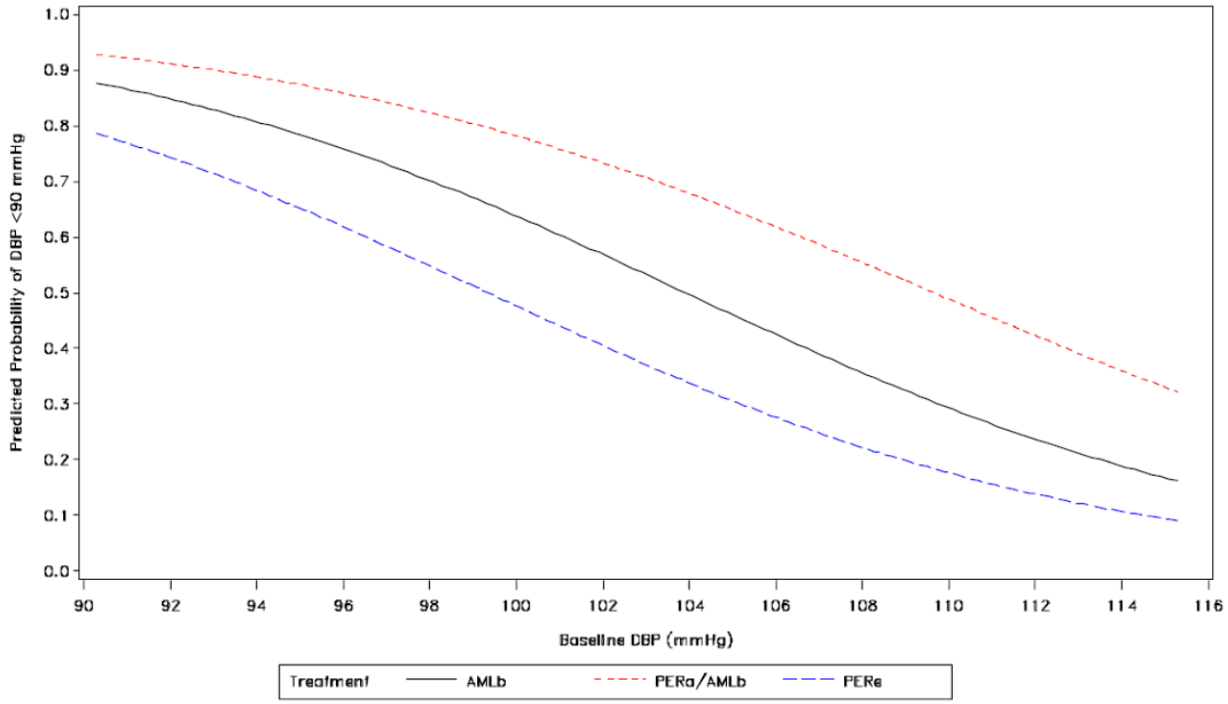
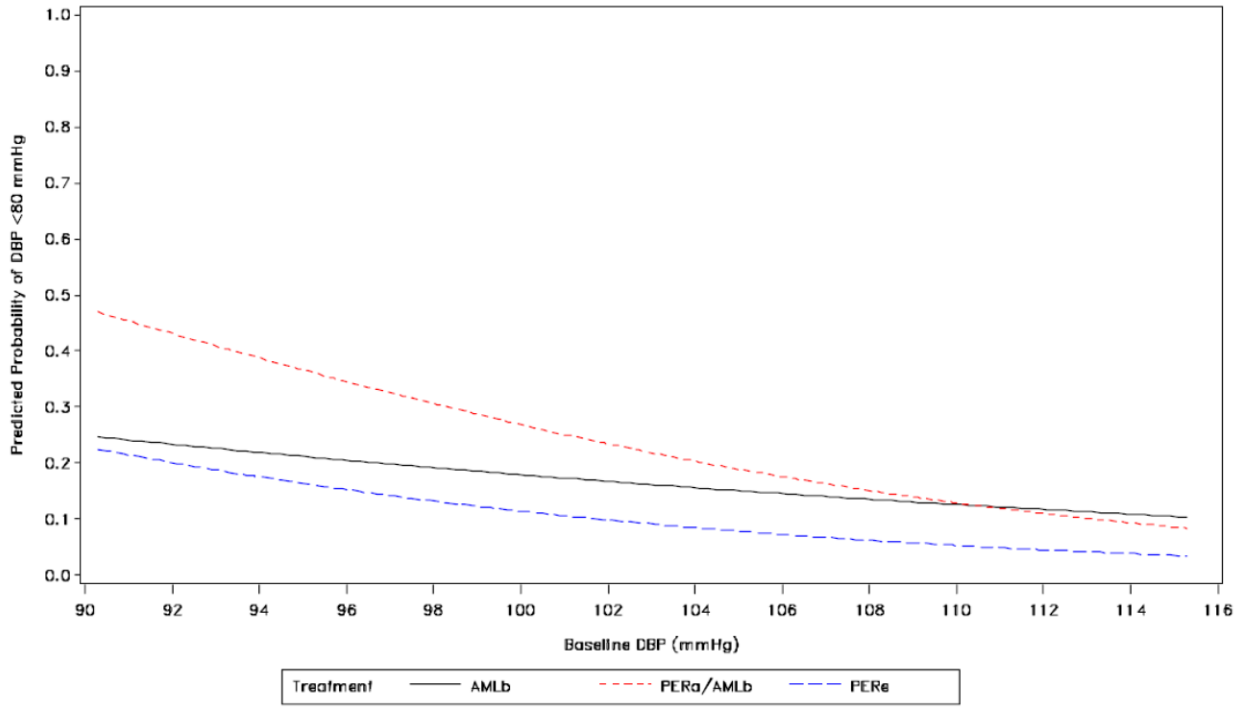


Figure 5: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg in PATH trial



Hosmer-Lemeshow test was applied for goodness-of-fit assessment to check whether the overall logistic regression model was fitted adequately. A large p-value suggests that the overall fit using a logistic regression model may be reasonable. Table 1 summarizes the test results.

Table 1: Hosmer-Lemeshow Test Results in PATH Trial

Graph	Treatment group	p-value of Hosmer-Lemeshow test	baseline range	# of outliers excluded
SBP<140 mmHg	PERe 16 mg	0.271	All data	0
	AMLb 10 mg	0.428	All data	0
	PERa/AMLb 14/10 mg	0.105	All data	0
SBP<130mmHg	PERe 16 mg	0.544	All data	0
	AMLb 10 mg	0.887	All data	0
	PERa/AMLb 14/10 mg	0.394	All data	0
DBP<90mmHg	PERe 16 mg	0.193	All data	0
	AMLb 10 mg	0.936	All data	0
	PERa/AMLb 14/10 mg	0.374	All data	0
DBP<80mmHg	PERe 16 mg	0.153	All data	0
	AMLb 10 mg	0.907	All data	0
	PERa/AMLb 14/10 mg	0.274	All data	0

None of the models in PATH trial using all data appeared to show a lack of fit according to the Hosmer-Lemeshow Test. The LOESS curves also compares reasonably well with each corresponding individual logistic regression curve using all data.

The sponsor further examined a number of trimmed samples.

For SBP, three trimmed samples were evaluated:
Trimmed sample A: Exclude 13 subjects with SBP<135 mmHg and 20 subjects with SBP>178 mmHg
Trimmed sample B: Exclude 13 subjects with SBP<135 mmHg and 10 subjects with SBP≥ 179 mmHg
Trimmed sample C: Exclude 8 subjects with SBP<133 mmHg and 7 subjects with SBP>179 mmHg

For DBP, three trimmed samples were evaluated:
Trimmed sample A: Exclude 1 subject with DBP<94 mmHg and 22 subjects with DBP≥ 112 mmHg
Trimmed sample B: Exclude 1 subject with DBP<94 mmHg and 14 subjects with DBP≥ 113 mmHg
Trimmed sample C: Exclude 1 subject with DBP<94 mmHg and 8 subjects with DBP≥ 114 mmHg

The trimmed samples did not provide significant improvement when compared with models that used all data. Therefore, all data in the PATH trial should be retained to present the probability curves.

Study CL2-05985-005

The logistic regression curves using all data for each blood pressure goal were displayed below.

Figure 6: Probability of Achieving Systolic Blood Pressure (SBP) <140 mmHg in Study CL2-05985-005

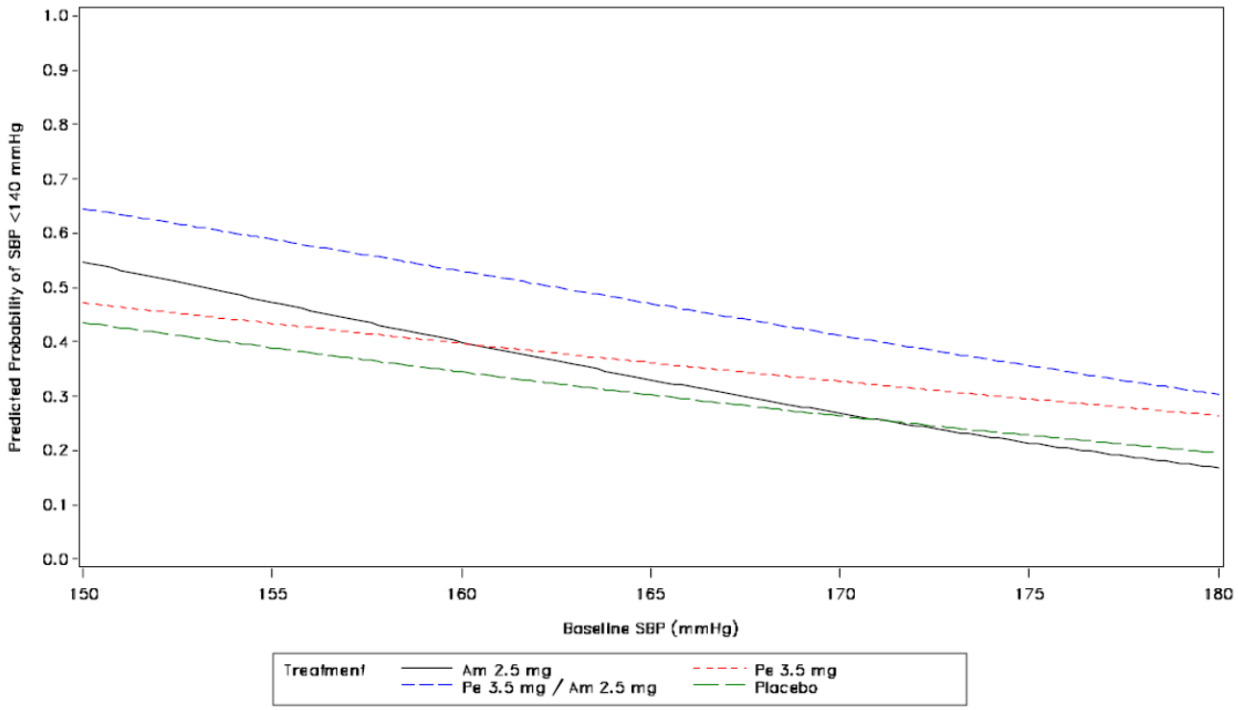


Figure 7: Probability of Achieving Systolic Blood Pressure (SBP) <130 mmHg in Study CL2-05985-005

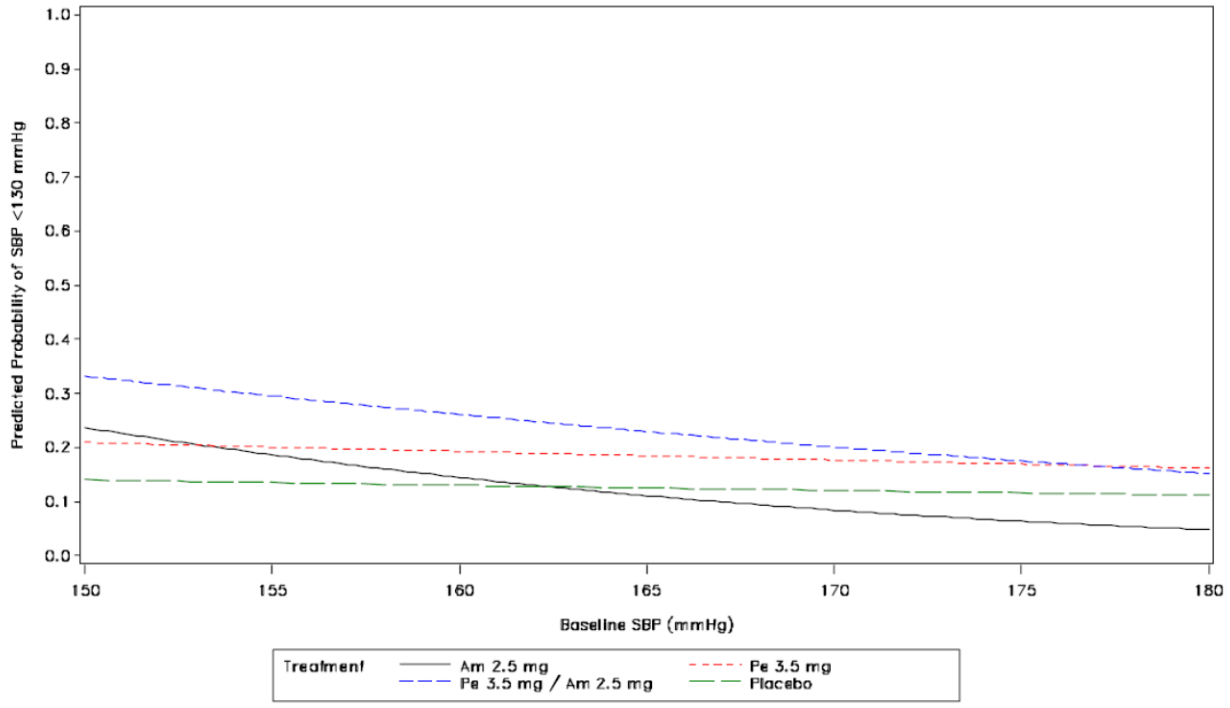


Figure 8: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mmHg in Study CL2-05985-005

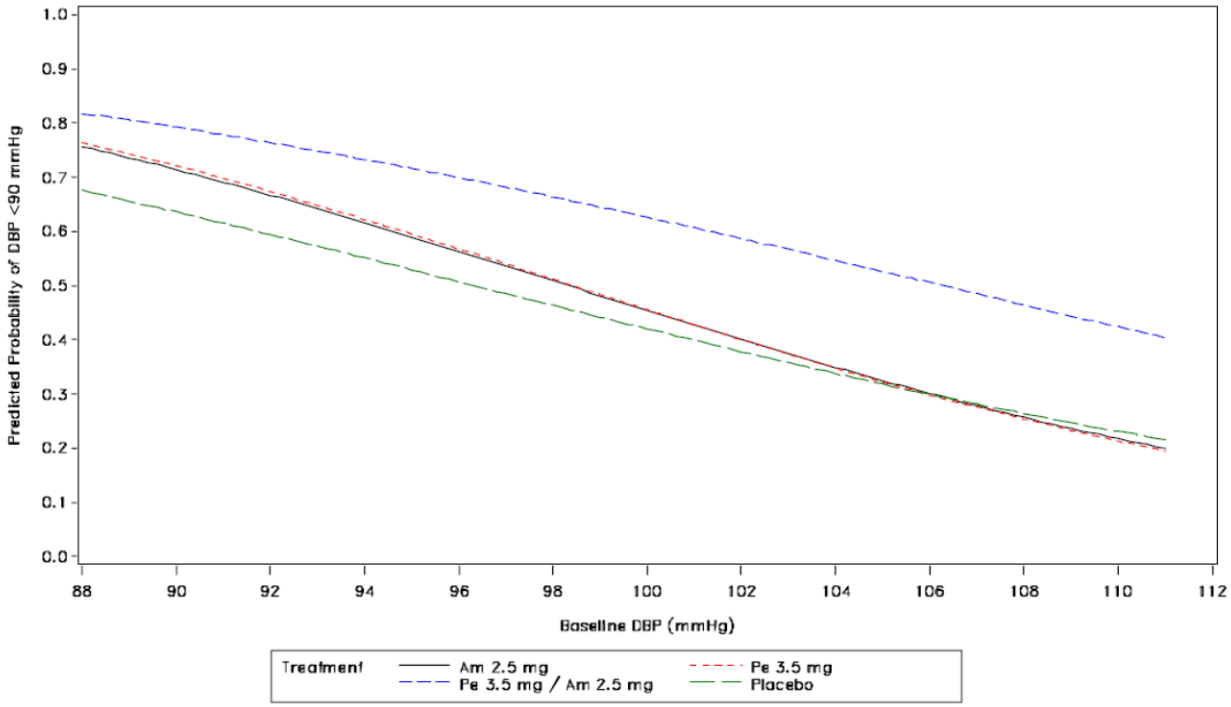
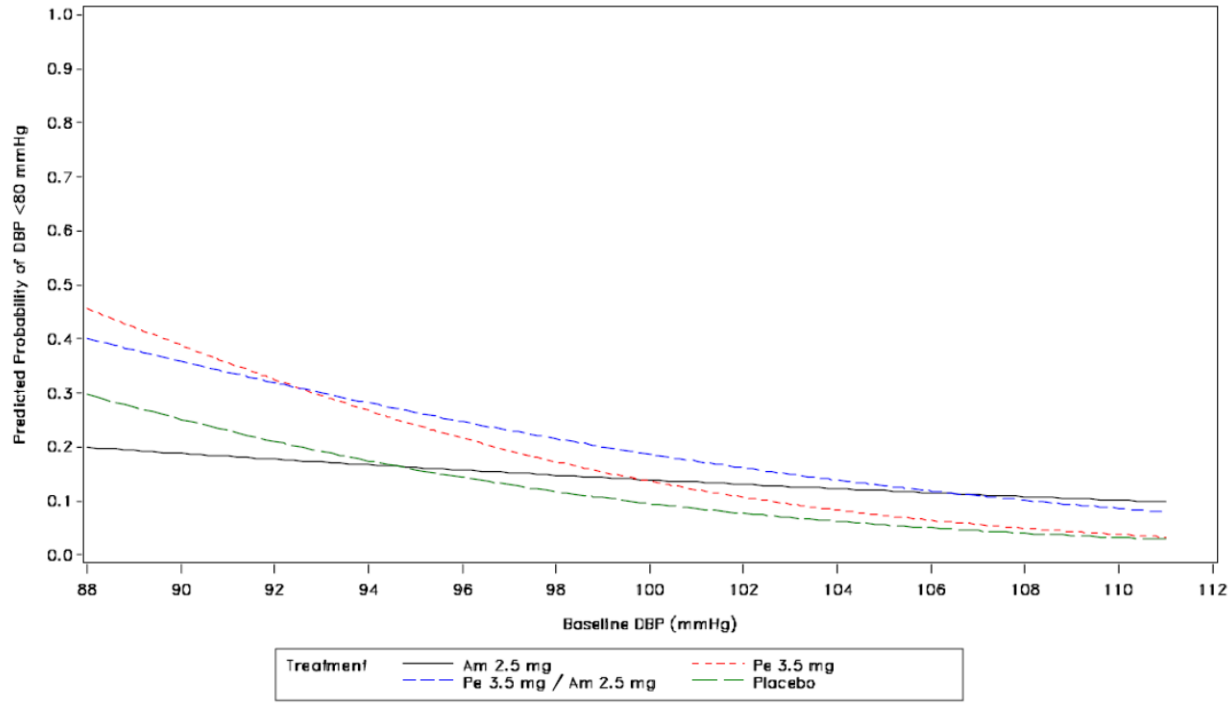


Figure 9: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mmHg in Study CL2-05985-005



Hosmer-Lemeshow test was applied to assess goodness-of-fit ofthe overall logistic regression model.

Table 2: Hosmer-Lemeshow Test Results in Study CL2-05985-005

Graph	Treatment group	p-value of Hosmer-Lemeshow test	baseline range	# of outliers excluded
SBP<140 mmHg	Placebo	0.083	All data	0
	PER 3.5 mg / AML 2.5 mg	0.312	All data	0
	PER 3.5 mg	0.074	All data	0
	AML 2.5 mg	0.817	All data	0
SBP<130mmHg	Placebo	0.872	All data	0
	PER 3.5 mg / AML 2.5 mg	0.471	All data	0
	PER 3.5 mg	0.973	All data	0
	AML 2.5 mg	0.032	All data	0
DBP<90mmHg	Placebo	0.797	All data	0
	PER 3.5 mg / AML 2.5 mg	0.020	All data	0
	PER 3.5 mg	0.586	All data	0
	AML 2.5 mg	0.353	All data	0
DBP<80mmHg	Placebo	0.754	All data	0
	PER 3.5 mg / AML 2.5 mg	0.425	All data	0
	PER 3.5 mg	0.828	All data	0
	AML 2.5 mg	0.079	All data	0

The models that appear to have a lack of fit based on Hosmer-Lemeshow test are highlighted. The SBP<130mmHg model in AML 2.5 mg arm and the DBP<90mmHg model in PER 3.5 mg / AML 2.5 mg combination therapy arm had a p-value less than 0.05 from Hosmer-Lemeshow test as shown in Table 2. The sponsor further examined the models using all data as well as data excluding some extreme baseline BP observations.

For SBP, four trimmed samples were evaluated:
Trimmed sample A: Exclude 31 subjects with SBP>176 mmHg
Trimmed sample B: Exclude 25 subjects with SBP>177 mmHg
Trimmed sample C: Exclude 9 subjects with SBP>178 mmHg
Trimmed sample D: Exclude 2 subjects with SBP>179 mmHg

For DBP, two trimmed samples were evaluated:
Trimmed sample A: Exclude 4 subjects with DBP<95 mmHg and 26 subjects with DBP>108 mmHg
Trimmed sample B: Exclude 4 subjects with DBP<95 mmHg and 2 subjects with DBP>109 mmHg

The SBP<130mmHg model in the AML 2.5 mg arm did not improve much even with a considerable number of subjects excluded. Based on Hosmer-Lemeshow test, the goodness-of-fit improved little in the AML 2.5 mg arm after excluding at least 25 subjects. The comparison of

LOESS curves and logistic regression curves also did not show much difference in trimmed samples versus all data in AML 2.5 mg arm (Figure 10 and Figure 11). Since excluding outliers did not improve much on the model fitting, all data would still be used.

Figure 10: Plot of LOESS and Model-Based Predicted SBP<130mmHg in AML 2.5 mg Arm (All Data)

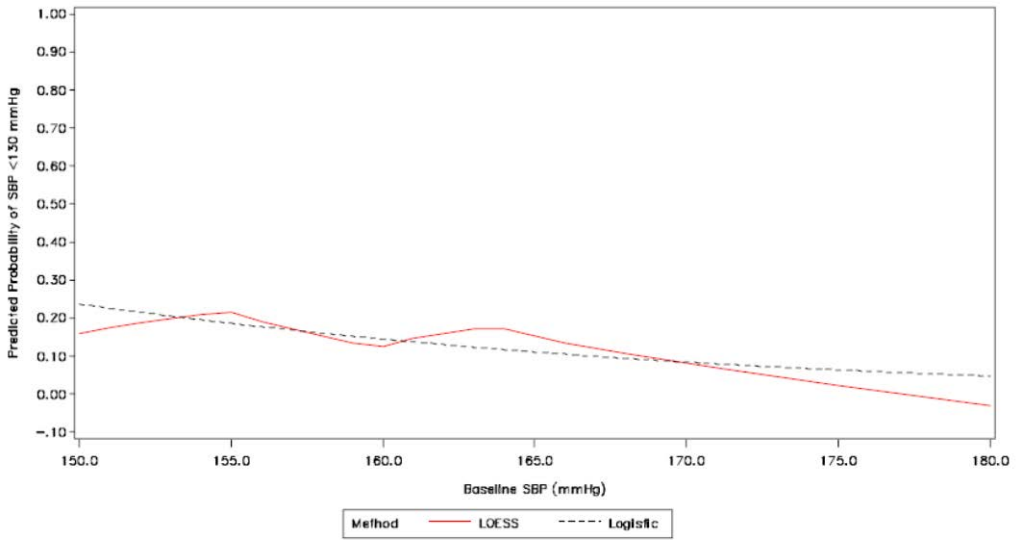
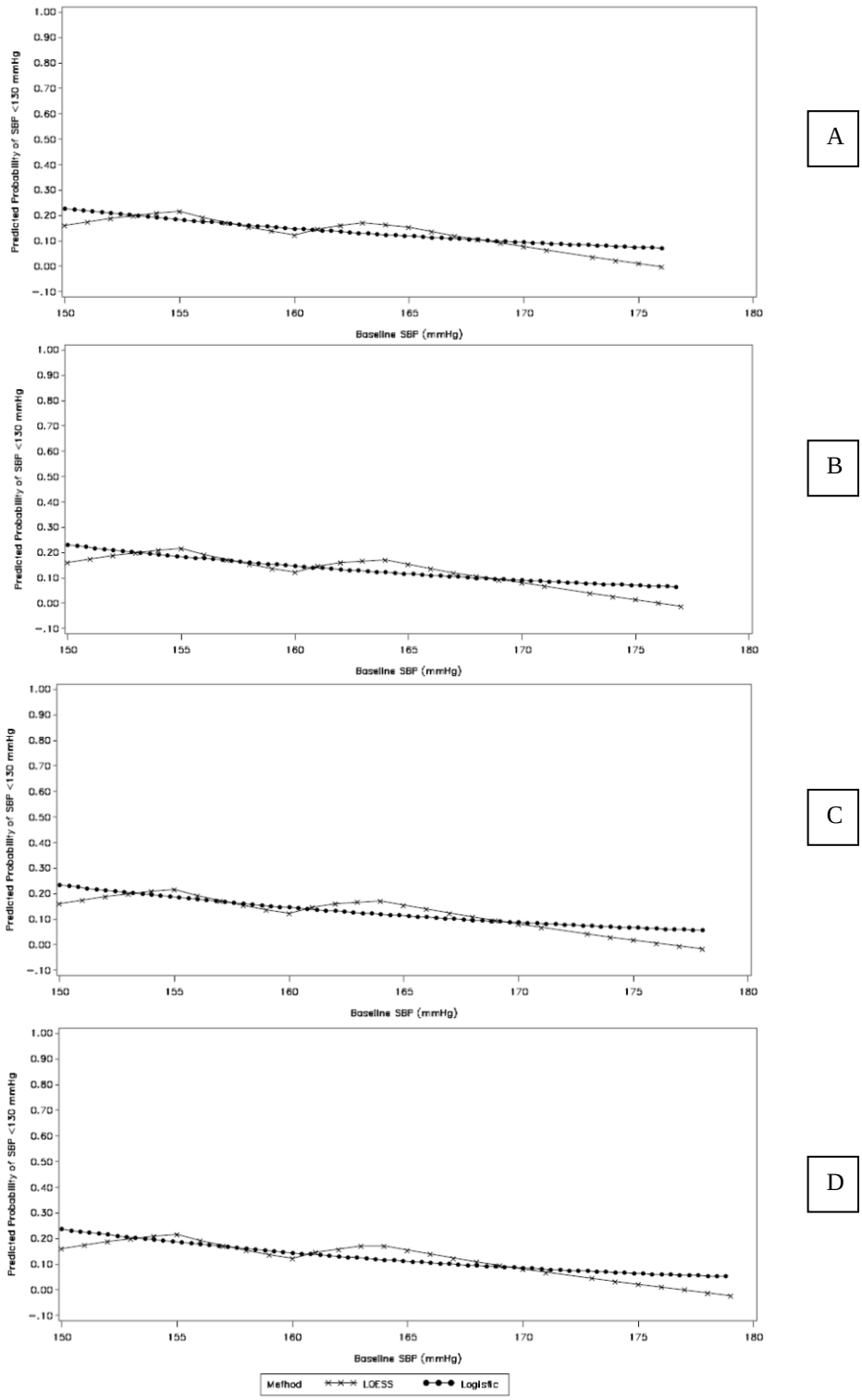


Figure 11: Plots of LOESS and Model-Based Predicted SBP<130mmHg in AML 2.5 mg Arm (Trimmed Samples)



Note: Plot A, B, C and D correspond to the trimmed SBP sample A, B, C, and D.

The DBP<90mmHg model in PER 3.5 mg / AML 2.5 mg combination therapy arm did not improve much either by trimming the baseline DBP outliers. The sponsor examined two trimmed samples, one excluding 6 subjects and the other excluding 30 subjects. The p-values of the Hosmer-Lemeshow test remained 0.02, suggesting a lack of fit. The comparison of LOESS curves and logistic regression curves showed some differences between trimmed samples and all data in AML 2.5 mg arm but this is mainly due to trimming of the x-axis (Figure 12 and Figure 13). Excluding outliers did not improve the model fitting much and hence all data should still be used.

Figure 12: Plot of LOESS and Model-Based Predicted DBP<90mmHg in PER 3.5 mg/AML 2.5 mg Arm (All Data)

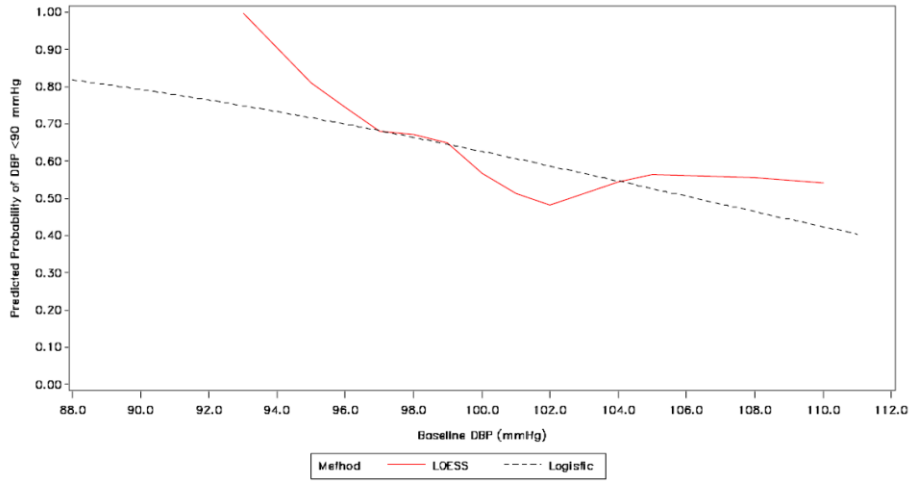
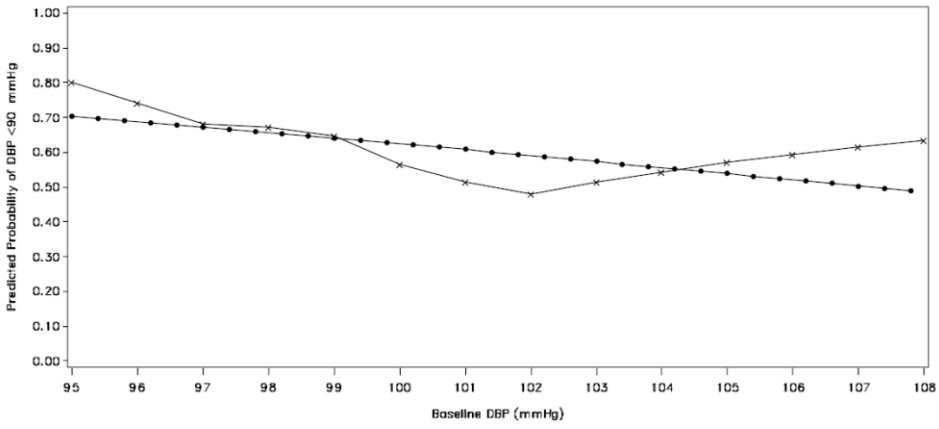
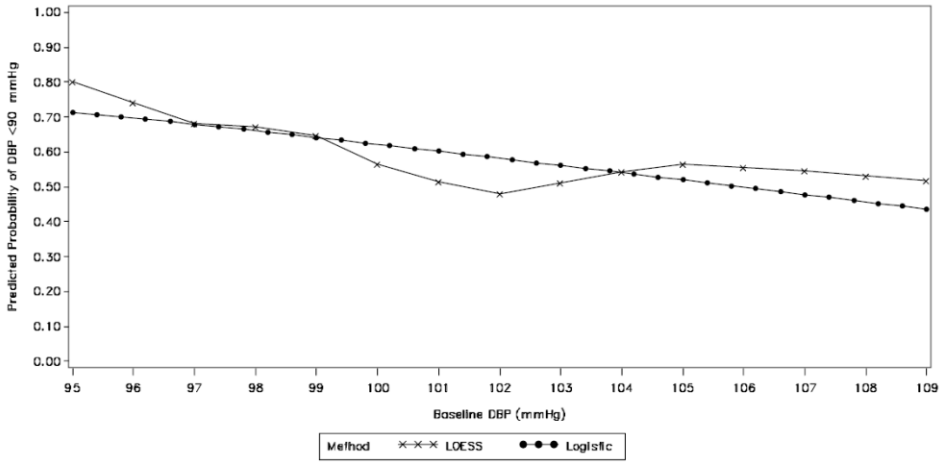


Figure 13: Plots of LOESS and Model-Based Predicted DBP<90mmHg in PER 3.5 mg/AML 2.5 mg Arm (Trimmed Samples)



A



B

Note: Plot A and B correspond to the trimmed DBP sample A and B.

In summary, all data in PATH trial should be retained to present the probability graphs in every model. No lack of fit was detected.

In Study CL2-05985-005, despite a lack of fit in the SBP<130mmHg model in AML 2.5 mg arm and the DBP<90mmHg model in PER 3.5 mg / AML 2.5 mg combination therapy arm, all data should still be used to generate the probability graphs since trimming the outliers showed little improvement and all other models fitted to all data did not show a lack of fit in the probability graphs.

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/s/

JIALU ZHANG
01/08/2015

HSIEN MING J HUNG
01/08/2015

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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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 205-003
Drug Name:	Prestalia (Perindopril arginine/amlodipine besylate)
Indication(s):	hypertension
Applicant:	Symplmed Pharmaceuticals
Date(s):	Date of Document: 03/21/2014
	PDUFA due date: 01/21/2015
Review Priority:	Standard
Biometrics Division:	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:	Karen Hicks, M.D.
Project Manager:	Wayne Amchin

Keywords:

Minimization algorithm, hypertension, factorial trial

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1. EXECUTIVE SUMMARY

Prestalia consists of fixed-dose combination tablets containing perindopril arginine (PERa) and amlodipine (AMLb). This NDA includes two controlled clinical studies (PATH trial and CL2-05985-005) to support the clinical efficacy and safety of Prestalia (XOMA 985) in treating hypertension.

PATH trial was a multicenter, randomized, double-blind, parallel-group study to compare the highest strength of the combination product (PERa/AMLb 14/10 mg) to the highest strength of the individual components available on the US market administered as monotherapies (perindopril erbumine 16 mg and amlodipine 10 mg). In total, 837 subjects were randomized. Over 90% patients were 65 years or younger and 34% patients were black. The primary efficacy analysis for this study was the mean change from baseline to Day 42/end of treatment (EOT) in mean sitting trough diastolic blood pressure (DBP). The overall results appeared positive in PATH trial. However, as discussed extensively in Section 3.2.1 (page 12-16), the deterministic minimization for treatment assignment used in the trial generates many difficulties to interpretation of the trial results.

A multiple-pass, minimization algorithm was used to balance treatment group assignments across strata in PATH trial. When a patient came in, he/she would be assigned to the treatment group with the lowest score according to the algorithm. This deterministic algorithm can potentially unblind all the treatment assignment. Selection bias is another concern for this deterministic minimization algorithm. Patient's baseline blood pressure or mean treatment effect by the order of entry was examined for any noticeable pattern. Involving multiple centers in the trial probably alleviated some concerns that the study can easily be unblinded and there can be serious selection bias as a result. However, some issues remained, such as, covariates other than the ones used in the adaptive algorithm, known or unknown, may not be balanced among treatment groups due to the deterministic nature of the assignment.

In addition, the standard tests may not apply under this minimization algorithm. The reviewer performed the bootstrap t-test proposed in Shao et al (2010, Biometrika). The p-values for both comparisons between the combination therapy and its monocomponents were <0.001. If the assumption of "identically distributed" holds (which is unknown since the patients are rarely a random sample of the interested patient population), this test provided some assurance that the combination therapy had a significantly larger treatment effect than the monocomponents.

Study CL2-05985-005 was a randomized, double-blind, placebo-controlled, parallel-arm, factorial study to compare the effects of the lowest strength of the combination product with those of the individual components administered as monotherapies. The study had 6 parallel treatment arms: PERa 3.5 mg, PERa 5 mg, AMLb 2.5 mg, AMLb 5 mg, PERa/AMLb 3.5/2.5 mg, and placebo. A total of 1581 patients were randomized to one of the 6 treatment groups. About 87% patients were 65 years or younger. Most patients (98.6%) were Caucasian. The primary efficacy measurement was the change from baseline to Week 8 in supine DBP.

The analyses on the primary endpoint included three superiority comparisons and two non-inferiority comparisons. No multiplicity adjustment was discussed and the statistical analysis plan for Study CL2-05985-005 was never reviewed by the Agency. The reviewer focused on the superiority comparisons between the combination therapy and the corresponding low dose monocomponents or placebo. The low dose combination therapy PERa/AMLb 3.5mg/2.5mg appeared to have a statistically significant treatment effect in reducing blood pressure when compared with the monocomponents (PERa 3.5 mg and AMLb 2.5mg) in Study CL2-05985-005.

2. INTRODUCTION

2.1 Overview

This NDA includes two controlled clinical studies (PATH trial and CL2-05985-005) to support the clinical efficacy and safety of Prestalia (XOMA 985) in treating hypertension. Prestalia consists of fixed-dose combination tablets containing perindopril arginine (PERa) and amlodipine (AMLb). The NDA is submitted as a 505(b)(2) application since approval needs to rely upon the Agency's previous finding of hypertension drugs NORVASC (amlodipine besylate) and ACEON (perindopril erbumine, also referred as PERe in this review). The proposed dosage strengths of the combination product are 3.5/2.5 mg, 7/5 mg and 14/10 mg.

PATH trial was a multicenter, randomized, double-blind, parallel-group study, which consisted of a screening visit, a 2- to 3-week washout period, and a 6-week double-blind treatment period. PATH trial compared the highest strength of the combination product (14/10 mg) to the highest strength of the individual components available on the US market administered as monotherapies (PERe 16 mg and AMLb 10 mg). Adult subjects $\leq$ 75 years of age with essential hypertension were randomized in a 1:1:1 ratio to receive PERa/AMLb 14/10 mg QD, PERe 16 mg QD, or AML 10 mg QD. In total, 837 subjects were randomized. Over 90% patients were 65 years or younger and 34% patients were black.

Study CL2-05985-005 was a randomized, double-blind, placebo-controlled, parallel-arm, factorial study in subjects $\geq$ 18 to <80 years of age with mild to moderate uncomplicated essential hypertension (95 mmHg $\leq$ DBP <110 mmHg and 150 mmHg $\leq$ SBP <180 mmHg). It compared the effects of the lowest strength of the combination product with those of the individual components administered as monotherapies. The study had 6 parallel treatment arms: PERa 3.5 mg, PERa 5 mg, AMLb 2.5 mg, AMLb 5 mg, PERa/AMLb 3.5/2.5 mg, and placebo. A total of 1581 patients were randomized into one of the 6 treatment groups. About 87% patients were 65 years or younger. Most patients (98.6%) were Caucasian.

Table 1: List of all efficacy studies included in the review

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
PATH (Study X985400)	*Phase 3*	2 to 3 week washout period, and a 6 week double blind treatment period.	272 subjects per arm	Adult subjects ≤ 75 years of age with essential hypertension
Study CL2-05985-005	*Phase 2*	2 to 3 weeks run in period with placebo followed by a 8-week double-blind active treatment period	250 in each treatment arm	Subjects with essential mild to moderate uncomplicated arterial hypertension (DBP < 110 mmHg and SBP < 180 mmHg measured with a validated automatic device in supine position)

2.2 Data Sources

The analysis datasets of PATH trial is located at \\CDSESUB1\evsprod\NDA205003\0000\m5\datasets\x985400\analysis\legacy\datasets.

The SDTM datasets of PATH trial is located at \\CDSESUB1\evsprod\NDA205003\0000\m5\datasets\x985400\tabulations\legacy.

The raw datasets of PATH trial is located at \\CDSESUB1\evsprod\NDA205003\0003\m5\datasets\x985400\tabulations\legacy.

The analysis datasets of Study CL2-05985-005 is located at \\CDSESUB1\evsprod\NDA205003\0000\m5\datasets\cl2-05985-005-main\analysis\legacy\datasets.

The raw datasets of Study CL2-05985-005 is located at \\CDSESUB1\evsprod\NDA205003\0000\m5\datasets\cl2-05985-005-main\tabulations\legacy.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer was able to reproduce the results of the primary analysis and secondary analyses. The applicant submitted the tabulation datasets used to derive the primary analysis dataset and the reviewer was able to trace how the primary analysis dataset was derived.

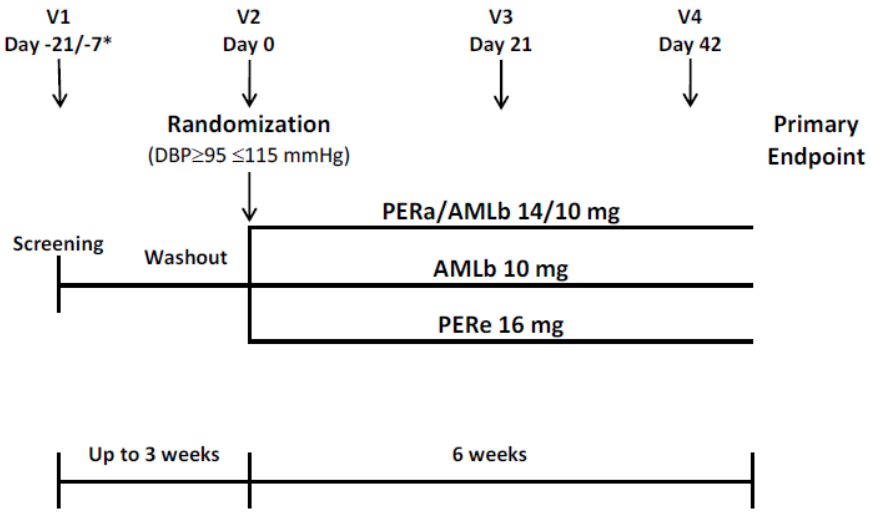
3.2 Evaluation of Efficacy

3.2.1 PATH Trial

Study Design and Endpoints

PATH trial is a phase 3, multicenter, randomized, double blind, parallel group study consisted of a screening visit, a 2 to 3 week washout period, and a 6 week double blind treatment period. Adult subjects ≤ 75 years of age with essential hypertension were enrolled in the study and randomized in a 1:1:1 ratio to receive PERa/AMLb 14/10 mg QD, PERe 16 mg QD, or AMLb 10 mg QD.

Figure 1: Study Design



[Source: Sponsor's clinical study report Figure 1]

Subjects taking antihypertensive medication who met all of the eligibility criteria at Visit 1 (screening) discontinued all antihypertensive drugs to begin a 2- to 3-week washout period. Treatment-naïve subjects who met all eligibility criteria were randomized 7 days from Visit 1.

The planned fixed dose combination to be marketed is PERa/AMLb 14/10 mg. Currently, no marketed PERa 14 mg tablet is available for use as a comparator. The closest monotherapy dose that is commercially available is PERe 16 mg (two 8-mg tablets), which is bioequivalent to PERa 20 mg. The sponsor had agreement with the Division that it is deemed appropriate to compare the fixed dose combination to PERe 16 mg as monotherapy.

The primary efficacy analysis for this study was the mean change from baseline to Day 42/EOT in mean sitting trough DBP. The comparisons of primary interest were the combination treatment PERa/AMLb 14/10 mg versus PERe 16 mg and PERa/AMLb 14/10 mg versus AMLb 10 mg.

Patient Disposition, Demographic and Baseline Characteristics

In total, 837 subjects were randomized: 278 subjects in the PERe 16 mg group, 280 subjects in the AMLb 10 mg group, and 279 subjects in the PERa/AMLb 14/10 mg group. 86 subjects discontinued from the study drug: 32 (11.5%) subjects in the PERe 16 mg group, 28 (10.0%) subjects in the AMLb 10 mg group, and 26 (9.3%) subjects in the PERa/AMLb 14/10 mg group. The most common reason for discontinuation was adverse event.

Table 2: Patient Disposition

Characteristics	PERe 16 mg QD n (%)	AMLb 10 mg QD n (%)	PERa/AMLb 14/10 mg QD n (%)
Randomized	278	280	279
Dosed	278 (100.0)	280 (100.0)	279 (100.0)
Completed the study	246 (88.5)	252 (90.0)	253 (90.7)
Discontinued early	32 (11.5)	28 (10.0)	26 (9.3)
Adverse event	12 (4.3)	12 (4.3)	10 (3.6)
Subject withdrew consent	8 (2.9)	6 (2.1)	7 (2.5)
Lost to follow-up	4 (1.4)	6 (2.1)	6 (2.2)
Physician decision	1 (0.4)	1 (0.4)	1 (0.4)
Other	7 (2.5)	3 (1.1)	2 (0.7)

AMLb = amlodipine besylate; PERa = perindopril arginine; PERe = perindopril erbumine; QD = once daily.

[Source: Table 3 in sponsor's clinical study report, confirmed by the reviewer]

The ITT population was defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline blood pressure assessment value for DBP. The ITT population included 274 subjects in the PERe 16 mg group, 275 subjects in the AMLb 10 mg group, and 271 subjects in the PERa/AMLb 14/10 mg group. There were 4 patients in the PERe arm, 5 patients in the AMLb arm and 8 patients in the combination arm who did not have post-baseline blood pressure assessment and therefore were excluded from the primary analysis. Exclusion of these patients from the primary efficacy analysis does not affect the efficacy results and conclusions.

The majority of subjects were <65 years of age and the mean age of the population was 51.4 years. About half of the subjects were male. Overall, 34.3% of the total population was black and

20.4% of the population had type 2 diabetes. The majority (67.7%) of the population required washout from prior antihypertensive medication.

Table 3: Demographics and Baseline Characteristics

		PERe 16mg QD	AMLb 10 mg QD	PERa/AMLb 14/10 mg QD
N		278	280	279
Age	Mean (SD)	51.4 (9.7)	51.6 (9.8)	51.2 (9.7)
	<65 (n, %)	255 (91.7)	262 (93.6)	261 (93.5)
	>=65 (n, %)	23 (8.3)	18 (6.4)	18 (6.5)
Gender	Male	135 (48.6)	150 (53.6)	145 (52.0)
	Female	143 (51.4)	130 (46.4)	134 (48.0)
Race	Asian	1 (0.4)	1 (0.4)	2 (0.7)
	Black	96 (34.5)	96 (34.3)	95 (34.1)
	White	180 (64.7)	181 (64.6)	179 (64.2)
	Other	1 (0.4)	2 (0.7)	3 (1.1)
Type 2 Diabetes	Yes	56 (20.1)	57 (20.4)	59 (21.1)
	No	222 (79.9)	223 (79.6)	220 (78.9)
Prior antihypertensive med usage	treatment-naïve	82 (29.5)	93 (33.2)	95 (34.1)
	requiring washout	196 (70.5)	187 (66.8)	184 (65.9)

[Source: reviewer's table]

Statistical Methodologies

The primary analysis was based on the ITT Population, which was defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 post baseline blood pressure assessment value for DBP. Change from baseline in DBP at Day 42 of PERa/AMLb 14/10 mg dose group was compared to the change from baseline in DBP in the PERe 16 mg group and in the AMLb 10 mg group at Day 42. If no valid DBP measurement was taken for Day 42, then the last valid post-baseline assessment was used following the last observation carried forward (LOCF). The statistical model to test the 2 hypotheses was an analysis of covariance model with treatment as the main effect and baseline DBP (<100 mmHg versus ≥ 100 mmHg), current type 2 diabetes status (yes versus no), and race (black versus non-black) as covariates.

The secondary efficacy analysis for this study was the mean change from baseline to Day 42/EOT in mean sitting trough SBP, analyzed in the ITT Population. Change from baseline to Visit 4 (Day 42/EOT) in mean seated trough SBP was analyzed in a similar way as the primary efficacy analysis.

The sponsor used an adaptive randomization to balance treatment group assignments across strata. According to the appendix in the SAP, a multiple-pass, minimization algorithm was used to determine a subject's assignment.

☐ 1st pass – Optimal assignment based on Current Type 2 Diabetes Status, Race, DBP Stratum, site balance
☐ 2nd pass – If no optimal assignment from the first pass, the optimal assignment was based on Current Type 2 Diabetes Status, Race, DBP Stratum
☐ 3rd pass – If no optimal assignment from the second pass, optimal assignment was based on just DBP Stratum and Current Type 2 Diabetes status
☐ 4th pass—If no optimal assignment from the third pass, optimal assignment was based on just DBP Stratum status
☐ 5th pass- If no optimal assignment from the fourth pass, optimal assignment was based on overall study balance
☐ 6th pass – If no optimal assignment from the fifth pass, select at random using a pre-generated list of random numbers

For each treatment group, the system summed the total number of subjects who have been randomized within the protocol strata/factors that the next subject being randomized fell in to. The stratification sums for each treatment group were then summed to produce a treatment groups overall "score." The subject was assigned to the treatment group with the minimum score.

If more than one treatment group had the lowest score after the first pass, the system summed the total number of subjects randomized from the "tied" groups within the protocol strata, but dropped the site factor and used only the two tied treatment groups. If more than one treatment group had the lowest score after the first two passes, the system summed the total number of subjects randomized from the "tied" groups within the protocol strata, but dropped the site and race factors and used only the two tied treatment groups. A fourth pass was performed if there were still tied groups from the third pass. Site, Race and Type 2 Diabetic Status were eliminated and only the two tied treatment groups were used. Fifth pass eliminated all the stratification factors and compared the total number of subjects in the "tied" treatment groups if there were still "ties" after 4th pass. If more than one treatment group had the lowest score after the fifth pass, the system assigned the group at random from the "tied" groups at the study level.

The Division raised concern on the randomization algorithm during the IND reviews. In a statistical review filed on July 16, 2012, the comment clearly stated that "with sample size of 272 per treatment group, it is unclear why the complex randomization procedure is needed. We suggest that you use simple randomization procedure." The sponsor responded to the comment in August 2012 that they "recognize the sample size is sufficiently large in this trial. …We appreciate the Agency's comment and we will consider it in future trials since enrollment in this trial is almost complete."

There was also inconsistency between the clinical study report, the SAP and its appendix. Both the clinical study report and the SAP stated that randomization was "stratified" by type 2 diabetes status, race (black or non-black), and baseline DBP (<100 mmHg versus >= 100 mmHg). Also "randomization will not be stratified by site since the study will be performed using only sites in the United States". On the other hand, the SAP appendix described a detailed minimization algorithm to

assign treatment groups. The covariates used in the minimization algorithm included type 2 diabetes status, race (black or non-black), and baseline DBP (<100 mmHg versus >= 100 mmHg) as well as site.

Results and Conclusions

The combination therapy PERa/AMLb 14/10 mg had a statistically significant reduction in mean change in DBP from baseline to Day 42 when compared to each monotherapy (Table 4).

Table 4: Change in Diastolic Blood Pressure from Baseline to Day 42 (LOCF)

Diastolic Blood Pressure Statistic	PERe 16 mg QD (N = 274)	AMLb 10 mg QD (N = 275)	PERa/AMLb 14/10 mg QD (N = 271)
n	274	275	271
Baseline Mean (SD)	100.8 (4.86)	100.5 (4.79)	100.6 (4.59)
Day 42 Mean (SD)	91.4 (9.73)	87.2 (8.38)	85.0 (8.61)
Change from Baseline			
Mean (SD)	-9.5 (8.77)	-13.2 (8.33)	-15.7 (8.38)
LS Mean (SE) [1]	-9.1 (0.56)	-12.9 (0.56)	-15.4 (0.56)
	Between treatment comparisons [1]		
Comparisons	LS Mean difference (SE)	p-value	
PERa/AMLb 14/10 mg vs. PERe 16 mg	-6.3 (0.72)	<0.0001	
PERa/AMLb 14/10 mg vs. AMLb 10 mg	-2.5 (0.72)	0.0005	

[Source: Table 7 in sponsor's clinical study report, confirmed by the reviewer]

The combination therapy PERa/AMLb 14/10 mg had a statistically significant reduction in mean change in SBP from baseline to Day 42 when compared to each monotherapy (Table 5).

Table 5: Change in Systolic Blood Pressure from Baseline to Day 42 (LOCF)

Systolic Blood Pressure Statistic	PERe 16 mg QD (N = 274)	AMLb 10 mg QD (N = 275)	PERa/AMLb 14/10 mg QD (N = 271)
n	274	275	271
Baseline Mean (SD)	157.5 (11.44)	158.0 (11.81)	157.5 (11.91)
Day 42 Mean (SD)	144.1 (15.72)	138.4 (13.40)	134.1 (13.48)
Change from Baseline			
Mean (SD)	-13.4 (14.66)	-19.6 (15.62)	-23.4 (13.86)
LS Mean (SE) [1]	-12.7 (0.98)	-18.8 (0.98)	-22.8 (0.98)
	Between treatment comparisons [1]		
Comparisons	LS Mean difference (SE)	p-value	
PERa/AMLb 14/10 mg vs. PERe 16 mg	-10.1 (1.25)	<0.0001	
PERa/AMLb 14/10 mg vs. AMLb 10 mg	-3.9 (1.25)	0.0017	

[Source: Table 8 in sponsor's clinical study report, confirmed by the reviewer]

In this study, a responder was defined as a subject who achieved a target blood pressure goal of <140/90 mmHg or a subject with diabetes who achieved a target blood pressure goal of <130/80 mmHg. The combination therapy PERa/AMLb 14/10 mg had a greater percentage of subjects reaching their target blood pressure goal at Day 21 (50.4% versus 20.9% and 35.4%, respectively), Day 42 (52.4% versus 25.9% and 37.1%, respectively), and at both Day 21 and

Day 42 (40.4% versus 13.9% and 24.8%, respectively) compared to the PERe 16 mg and AMLb 10 mg monotherapy.

Table 6: Responder Analysis (LOCF)

Endpoint Statistic	PERe 16 mg QD (N = 274) n (%)	AMLb 10 mg QD (N = 275) n (%)	PERa/AMLb 14/10 mg QD (N = 271) n (%)
Day 21			
n	273	274	270
Responder [1]	57 (20.9)	97 (35.4)	136 (50.4)
Non-responder	216 (79.1)	177 (64.6)	134 (49.6)
p-value [2]	<0.001	<0.001	
Day 42			
n	274	275	271
Responder [1]	71 (25.9)	102 (37.1)	142 (52.4)
Non-responder	203 (74.1)	173 (62.9)	129 (47.6)
p-value [2]	<0.001	<0.001	
Day 21 and Day 42			
n	273	274	270
Responder [1]	38 (13.9)	68 (24.8)	109 (40.4)
Non-responder	235 (86.1)	206 (75.2)	161 (59.6)
p-value [2]	<0.001	<0.001	

1. A responder or target achievement was a subject who achieved blood pressure of <140/90 mmHg or a subject with diabetes who achieved <130/80 mmHg.
2. Reported p-values were based on a Chi-square test.

[Source: Table 11 in sponsor's clinical study report, verified by the reviewer]

Overall the results appeared positive. However, the minimization algorithm used by the sponsor for randomization is quite concerning.

First of all, the assignment of treatment groups was deterministic. When a patient came in, he/she would be assigned to the treatment group with the lowest score according to the algorithm. The algorithm also went through six passes in order to eliminate the situation where more than one treatment group had the lowest score. A deterministic algorithm can unblind all the treatment assignment. This can be very serious when a trial is conducted in a single center, where the investigator can easily obtain the information on all previous assignments and therefore predict the treatment assignment of the incoming patients. It is less concerning in this trial since the study involved 59 centers. Given the total number of study centers and the degree of the complexity in calculating scores based on previous treatment assignments, it is probably unlikely that an investigator would be able to derive the treatment assignment of the next patient coming into the trial. However, this does not exclude the possibility that a person who had access to the central database may still be able to do so. ICH E9 Guidance specifically states that a random element must be incorporated into randomization. Selection bias is another concern for this deterministic minimization algorithm if treatment assignments were unblinded or partially unblinded. Also, other covariates other than the ones used in the algorithm, known or unknown, may not be balanced among treatment groups due to the deterministic nature of the assignment.

The reviewer examined the data by plotting the mean baseline SBP and DBP versus the order of patient's entry into the trial (Figure 2 and Figure 3). The mean baseline was computed for every 10 patients entered into the trial by treatment arm. Any obvious trend in the mean baseline blood pressure may be an indicator of selection bias. The baseline blood pressure appeared to follow a random walk pattern.

Figure 2: Mean Baseline DBP by the Order of Patient's Entry into PATH Trial

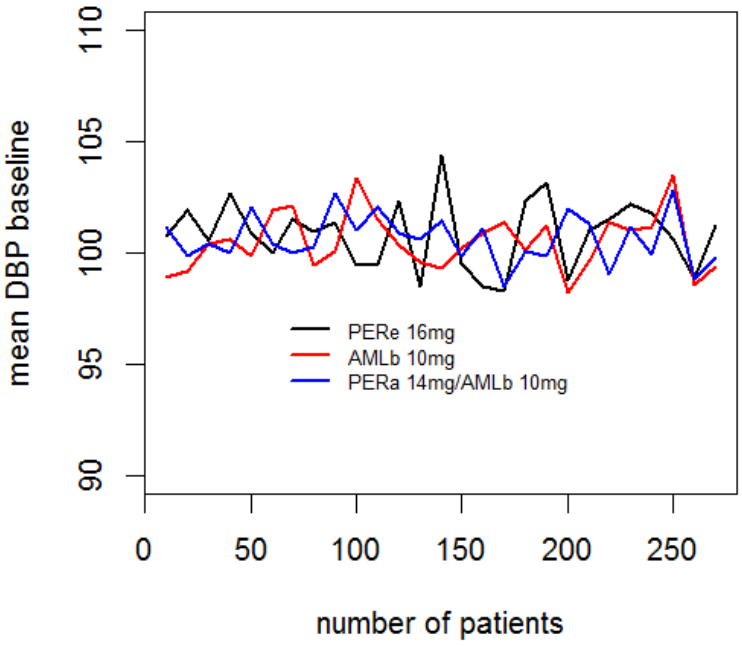
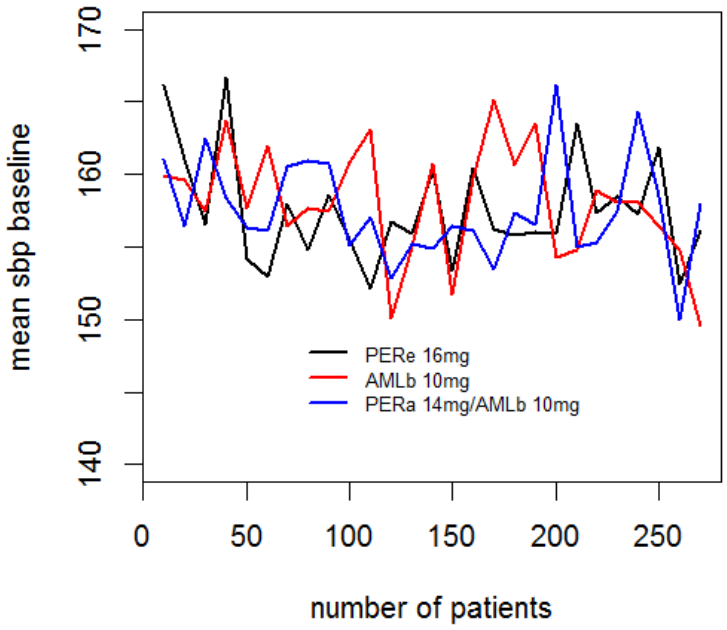


Figure 3: Mean Baseline SBP by the Order of Patient's Entry into PATH Trial



The mean treatment effect was also examined using graphs. The mean treatment difference between the combination therapy and each monocomponent in terms of change from baseline in SBP or DBP was calculated by every 50 patients in the order of patient's entry to the trial. The mean treatment effect was then plotted by the order of patient's entry (Figure 4 and Figure 5). No obvious trend in the mean treatment effect was observed.

Figure 4: Mean Treatment Effect in DBP by the Order of Patient's Entry (PATH trial)

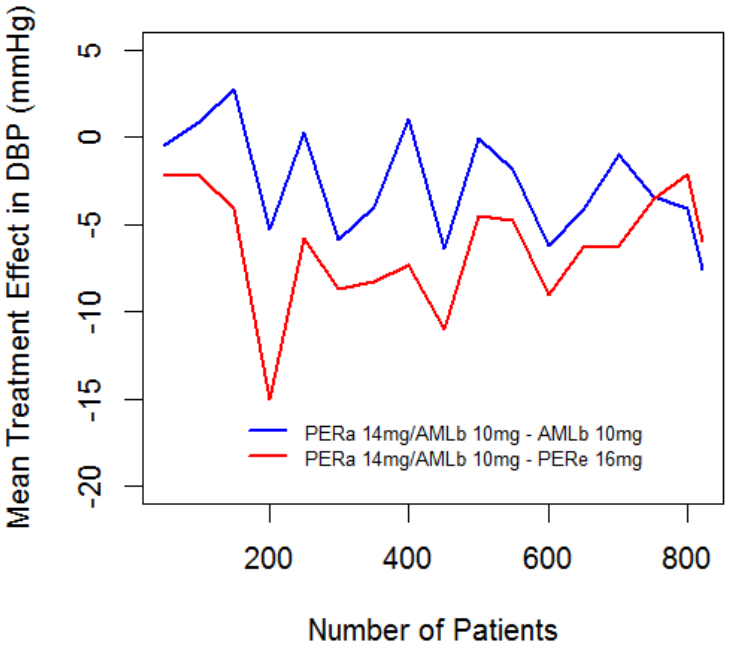
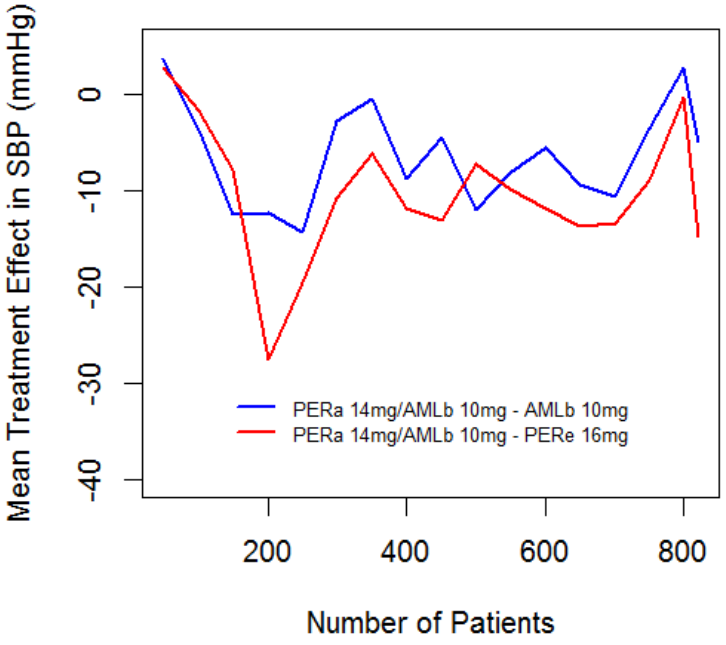


Figure 5: Mean Treatment Effect in SBP by the Order of Patient's Entry (PATH Trial)



These graphs provide some assurance although potential selection bias cannot be completely ruled out.

Secondly, the standard tests may not be applicable under this minimization algorithm. Random treatment assignment is the underlying assumption for the statistical inference used in standard tests. Shao et al (2010, Biometrika) provided some theoretical results for testing hypotheses after covariate-adaptive randomization and proposed a valid bootstrap t-test, assuming that the blood pressure measurements of the patients are identically distributed. The reviewer performed the bootstrap t-test according to the paper by generating bootstrap sample with replacement and applying the same minimization algorithm to assign treatment. The p-values for both comparisons between the combination therapy and its monocomponents were <0.001. This is not surprising since the results based on the standard test were also highly significant. The validity of this test relies on the assumption that the blood pressure measurements of the patients in the trial are identically distributed. If the assumption of "identically distributed" holds (which is unknown since the patients are rarely a random sample of the interested patient population), this test provided some assurance that the combination therapy had a significantly larger treatment effect than the monocomponents.

In essence, the deterministic randomization used in this study is a bad practice for clinical trials that generated unnecessary hurdles to interpretation of the study results; generally it should not be accepted in confirmatory trials. If the assumption that the blood pressures of the patients in this trial are identically distributed is reasonable, the highly significant results of the bootstrap t-test seem to provide some assurance that the combination therapy had a significantly larger treatment effect than both monocomponents. Involving many clinical centers in the trial probably alleviates some concerns that the study can easily be unblinded and there can be serious selection bias as a result. Although it is not able to exclude completely the possibility of selection bias, no obvious trend in the baseline blood pressure measurements as well as in treatment effects by the order of patient's entry also provides some assurance.

3.2.2 Study CL2-05985-005

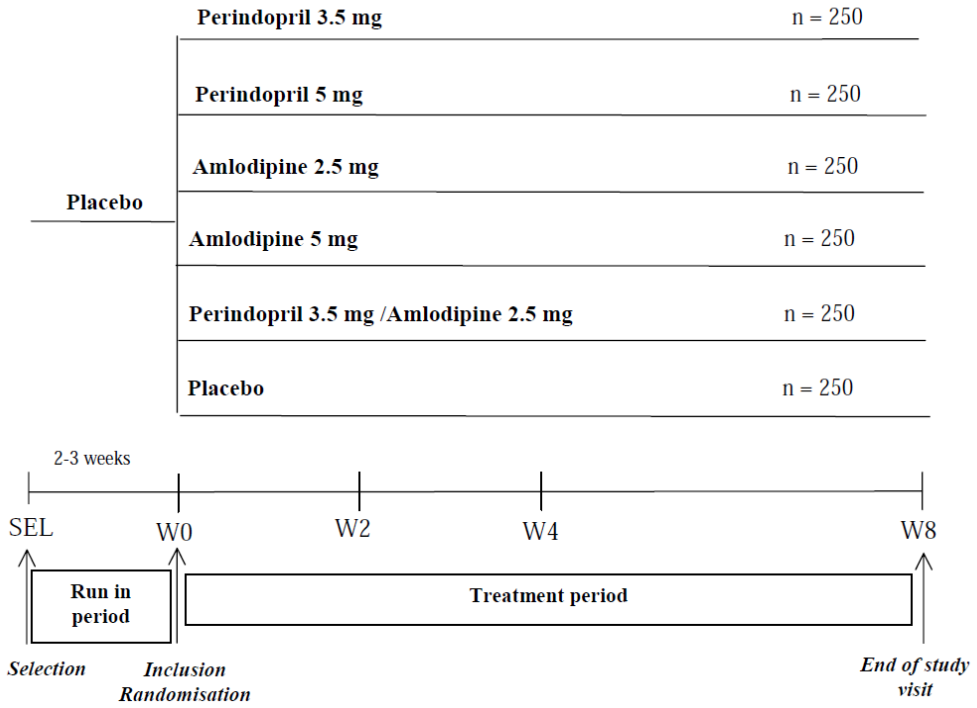
Study Design and Endpoints

This was a phase II, multicentre, international, randomized, double-blind, placebo-controlled study with a factorial design. Patients were randomized into 6 parallel arms: perindopril 3.5 mg/amlodipine 2.5 mg low-dose combination, perindopril 3.5 mg, amlodipine 2.5 mg, perindopril 5 mg, amlodipine 5 mg, and placebo. The randomization of treatments was stratified by center. Men or women suffering from essential mild to moderate uncomplicated hypertension (95 ≤ Diastolic Blood Pressure [DBP] < 110 mmHg and 150 ≤ Systolic Blood Pressure [SBP] < 180 mmHg measured in supine position) can be enrolled into the study.

The study included a run-in period with placebo which lasted at least 2 weeks and no more than 3 weeks and an 8-weeks double-blind active treatment period.

The selection visit was performed in the morning before midday. At W0, W2, W4 and W8, the measurements were performed before the study drugs were taken.

Figure 6: Study design



[Source: Figure (9.1)1 in sponsor's clinical study report]

The primary efficacy endpoint was the change in supine DBP (mmHg) from baseline to last post-baseline value.

Secondary efficacy endpoints included supine SBP, response to treatment, normalization of blood pressure, mean blood pressure, and pulse pressure.

Patient Disposition, Demographic and Baseline Characteristics

A total of 2053 patients were selected for the study in 188 centres and 1581 patients were randomly assigned to one of the six treatment arms and 1497 patients completed the study. A total of 84 patients (5.3%) were withdrawn from the study.

Table 7: Patient Disposition

Status	*Per 3.5/ Amlo 2.5*	*Placebo*	*Per 3.5 mg*	*Amlo 2.5 mg*	*Per 5 mg*	*Amlo 5 mg*	*All*
Included (randomised)	**248**	**250**	**273**	**274**	**272**	**264**	**1581**
In compliance with the protocol	196	212	223	219	223	213	1286
With a protocol deviation before or at inclusion	52	38	50	55	49	51	295
Withdrawn due to	**9**	**11**	**16**	**19**	**15**	**14**	**84**
Adverse event	3	-	6	9	7	8	33
Lack of efficacy	2	3	3	2	3	3	16
Non-medical reason	2	5	3	5	3	3	21
Other	1	1	1	1	1	-	5
Protocol deviation	1	2	3	2	1	-	9
Completed	**239**	**239**	**257**	**255**	**257**	**250**	**1497**
In compliance with the protocol	181	200	217	208	207	197	1210
With a protocol deviation after inclusion	58	39	40	47	50	53	287

[Source: Table (10.1.1) 1 in sponsor's clinical study report]

The Full Analysis Set was defined as all randomized patients who have taken at least one dose of study treatment and who have at least one baseline value and one post-baseline value of DBP.

Table 8: Analysis Sets

Analysis sets		*Per 3.5/ Amlo 2.5*	*Placebo*	*Per 3.5 mg*	*Amlo 2.5 mg*	*Per 5 mg*	*Amlo 5 mg*	**All**
Randomised Set	n (%)	248 (15.7)	250 (15.8)	273 (17.3)	274 (17.3)	272 (17.2)	264 (16.7)	**1581**
Efficacy Sets								
Full Analysis Set (FAS)	n (%)	246 (15.7)	248 (15.9)	268 (17.1)	270 (17.3)	270 (17.3)	261 (16.7)	**1563**
Per Protocol Set (PPS)	n (%)	236 (16.0)	235 (16.0)	248 (16.8)	252 (17.1)	257 (17.4)	245 (16.6)	**1473**
Safety Set	n (%)	249 (15.7)	251 (15.9)	273 (17.2)	274 (17.3)	272 (17.2)	264 (16.7)	**1583**

* the table is based on actual treatment

[Source: Table (10.3) 1 in sponsor's clinical study report, verified by the reviewer]

Majority of patients were under 65 years old and the mean age was 51.7 years. Most patients (98.6%) were Caucasian (Table 9).

Table 9: Baseline Characteristics in the Full Analysis Set

		Per 3.5/ Amlo 2.5 (N = 246)	*Placebo (N = 248)*	*Per 3.5 mg (N = 268)*	*Amlo 2.5 mg (N = 270)*	*Per 5 mg (N = 270)*	*Amlo 5 mg (N = 261)*	**All** *(N = 1563)*
Age (years)	n	246	248	268	270	270	261	1563
	Mean ± SD	51.6 ± 11.8	51.8 ± 11.7	52.2 ± 11.0	51.9 ± 11.2	51.1 ± 11.6	51.8 ± 10.9	51.7 ± 11.4
	Min ; Max	23 ; 79	19 ; 79	24 ; 79	19 ; 78	19 ; 79	20 ; 77	19 ; 79
< 65 years	n (%)	208 (84.6)	213 (85.9)	231 (86.2)	238 (88.2)	239 (88.5)	226 (86.6)	1355 (86.7)
≥ 65 years	n (%)	38 (15.5)	35 (14.1)	37 (13.8)	32 (11.9)	31 (11.5)	35 (13.4)	208 (13.3)
Sex Men	n (%)	116 (47.2)	114 (46.0)	126 (47.0)	126 (46.7)	128 (47.4)	120 (46.0)	730 (46.7)
Women	n (%)	130 (52.9)	134 (54.0)	142 (53.0)	144 (53.3)	142 (52.6)	141 (54.0)	833 (53.3)

[Source: Table (10.4.2) 1 in sponsor's clinical study report, verified by the reviewer]

Statistical Methodologies

The primary endpoint was supine DBP and the primary analyses included three superiority comparisons and two non-inferiority comparisons.

The superiority comparisons were:

- PERa 3.5/AMLb 2.5 *versus* placebo.
- PERa 3.5/AMLb 2.5 *versus* PERa 3.5.
- PERa 3.5/AMLb 2.5 *versus* AMLb 2.5.

The analyses were based on the change from baseline value to last on-treatment post-baseline value of supine DBP using a general linear model with baseline and center (random factor) as covariates.

The non-inferiority comparisons are:
PERa 3.5/AMLb 2.5 *versus* PERa 5.
PERa 3.5/AMLb 2.5 *versus* AMLb 5.

The non-inferiority tests were based on the same model as superiority tests. The non-inferiority margin was 2mmHg. The SAP was never reviewed by the FDA. It was unclear how the non-inferiority margin was determined. Furthermore, the margin is most likely a clinical margin and it is unclear whether the margin is clinically acceptable.

The secondary endpoints included supine SBP, response to treatment, normalization of blood pressure, mean blood pressure, and pulse pressure. For supine SBP, same analyses as the analyses for the primary endpoint were performed except that the non-inferiority margin was 3 mmHg. For response to treatment, the PERa 3.5/AMLb 2.5 combination was compared with placebo on the last post baseline value using a Chi square test. Summary statistics were computed for the pulse pressure and mean blood pressure.

There was no multiplicity adjustment mentioned by the sponsor. According to the sponsor's clinical study report, the comparisons between PERa 3.5 mg / AMLb 2.5 mg and the 5 other treatments were considered as 2 sets: the set of the 3 superiority comparisons and the set of the 2 non-inferiority comparisons. Multiple testing over both sets were based on an Intersection-Union approach, therefore no type one error adjustment was needed. However, the SAP was never reviewed by the FDA.

Results and Conclusions

A total of 365 patients (23.1%) presented at least one protocol deviation after inclusion *i.e.* during the double-blind active treatment period: 66 patients (26.6%) in the PERa 3.5/AMLb 2.5 group, 49 patients (19.6%) in the placebo group, 56 patients (20.5%) in the PERa 3.5 group, 64 patients (23.4%) in the AMLb 2.5 group, 64 patients (23.5%) in the PERa 5 group and 66 patients (25.0%) in the AMLb 5 group.

Due to the fact that the SAP was never reviewed by the Division and the comparison of the combination therapy (PERa/AMLb 3.5mg/2.5mg) versus higher dose monotherapies (PERa 5 mg and AMLb 5mg) was not essential in interpreting the treatment effect of the low dose combination therapy, the reviewer focused on the superiority comparisons between the combination therapy (PERa/AMLb 3.5mg/2.5mg) and the corresponding low dose monotherapies (PERa 3.5 mg and AMLb 2.5mg).

The low dose combination therapy had a statistically significant reduction in supine DBP from baseline when compared with placebo or each of the monocomponent (Table 10). The low dose combination therapy also had a statistically significant treatment effect in supine SBP when compared with placebo or the each of the monocomponent (Table 11).

Table 10: Superiority comparisons in supine DBP (Full Analysis Set)

		Per 3.5/ Amlo 2.5	*Placebo*	*Perindopril 3.5 mg*	*Amlodipine 2.5 mg*
	n	246	248	268	270
Baseline	Mean ± SD	100.7 ± 4.0	100.5 ± 3.9	100.7 ± 4.0	100.6 ± 4.0
	Min ; Max	93 ; 110	88 ; 109	94 ; 110	95 ;111
END	Mean ± SD	87.1 ± 9.0	91.2 ± 9.2	91.0 ± 10.1	90.3 ± 9.8
	Min - Max	60 - 115	68 - 114	65 - 126	61 - 116
END-Baseline	Mean ± SD	-13.6 ± 9.2	-9.3 ± 9.2	-9.7 ± 9.9	-10.3 ± 9.7
	Min ; Max	-45 ; 13	-39 ; 15	-34 ; 31	-41 ; 18
Main statistical analysis					
	E (SE)		-4.12 (0.77)	-3.64 (0.76)	-2.97 (0.75)
	95% CI		[-5.63 ; -2.61]	[-5.12 ; -2.16]	[-4.45 ; -1.49]
	p-value		p < 0.001	p < 0.001	p < 0.001

[Source: Table (11.1.1.1)1 in sponsor's clinical study report, verified by the reviewer]

Table 11: Superiority comparisons in supine SBP (Full Analysis Set)

	Per 3.5/Amlo 2.5	*Placebo*	*Perindopril 3.5 mg*	*Amlodipine 2.5 mg*
n	246	248	268	270
Baseline				
Mean ± SD	161.8 ± 7.5	161.0 ± 7.4	161.4 ± 7.7	161.2 ± 7.6
Min ; Max	150 ; 178	150 ; 179	150 ; 180	150 ; 180
END*				
Mean ± SD	139.9 ± 13.8	146.7 ± 15.4	145.1 ± 16.5	145.1 ± 15.5
Min ; Max	113 ; 189	108 ; 196	112 ; 192	104 ; 194
END - Baseline				
Mean ± SD	-22.0 ± 14.0	-14.2 ± 16.1	-16.3 ± 17.0	-16.0 ± 15.3
Min ; Max	-54 ; 16	-62 ; 34	-59 ; 34	-61 ; 25
Main statistical analysis				
Estimate (1.1)		-7.22 (1.21)	-5.01 (1.19)	-5.20 (1.19)
95% CI (2)		[-9.60 ; -4.84]	[-7.35 ; -2.67]	[-7.53 ; -2.87]
p-value (3.1)		p < 0.001	p < 0.001	p < 0.001

[Source: Sponsor's clinical study report Table (11.2.1.1.1)1, verified by the reviewer]

The comparisons between the low dose combination versus PERa 5mg or AMLb 5mg were shown in Table 12 and Table 13.

Table 12: Comparisons to PERa 5 mg and AMLb 5 mg in supine DBP (Full Analysis Set)

		Per 3.5/ Amlo 2.5	*Perindopril 5 mg*	*Amlodipine 5 mg*
	n	246	270	261
Baseline	Mean ± SD	100.7 ± 4.0	100.1 ± 4.1	100.6 ± 4.0
	Min ; Max	93 ; 110	90 ; 110	94 ; 110
END*	Mean ± SD	87.1 ± 9.0	89.6 ± 9.9	88.0 ± 8.7
	Min ; Max	60 ; 115	63 ; 117	61 ; 112
END-Baseline	Mean ± SD	-13.6 ± 9.2	-10.5 ± 9.7	-12.6 ± 8.9
	Min ; Max	-45 ; 13	-45 ; 15	-37 ; 14
Main statistical analysis				
	Estimate		-2.59 (0.75)	-0.76 (0.76)
	95% CI		[-4.07 ; -1.11]	[-2.25 ; 0.73]

[Source: Table (11.1.1.2) 1 in sponsor's clinical study report, verified by the reviewer]

Table 13: Comparisons to PERa 5 mg and AMLb 5 mg in supine SBP (Full Analysis Set)

		Per 3.5/Amlo 2.5	*Perindopril 5 mg*	*Amlodipine 5 mg*
	n	246	270	261
Baseline	Mean ± SD	161.8 ± 7.5	160.7 ± 7.3	162.3 ± 7.5
	Min ; Max	150 ; 178	150 ; 180	150 ; 179
END*	Mean ± SD	139.9 ± 13.8	142.5 ± 15.0	140.5 ± 14.3
	Min ; Max	113 ; 189	106 ; 193	108 ; 193
END-Baseline	Mean ± SD	-22.0 ± 14.0	-18.2 ± 14.8	-21.8 ± 15.4
	Min ; Max	-54 ; 16	-62 ; 18	-58 ; 33
Main statistical analysis				
	Estimate		-2.78 (1.19)	-0.29 (1.20)
	95% CI		[-5.11 ; -0.45]	[-2.64 ; 2.06]

[Source: Sponsor's clinical study report Table (11.2.1.1.2)1, verified by the reviewer]

Response to treatment was defined as:

- A normalization of BP (SBP < 140mmHg and DBP < 90mmHg).
- And/or a decrease from baseline in SBP ≥ 20mmHg.
- And/or a decrease from baseline in DBP ≥ 10mmHg.

The responder's analysis was shown in Table 14. The combination therapy had a higher percentage of responders than the placebo group as well as the monocomponent treatment arms (PERa 3.5 mg and AMLb 2.5 mg).

Table 14: Responder's Analysis (Full Analysis Set)

	PERa 3.5 mg / AMLb 2.5 mg	Placebo	PERa 3.5 mg	AMLb 2.5 mg
Responders n (%)	189 (76.8)	131 (52.8)	156 (58.2)	158 (58.5)
Non-responders n (%)	57 (23.2)	117 (47.2)	112 (41.8)	112 (41.5)

[source: reviewer's analysis]

The low dose combination therapy PERa/AMLb 3.5mg/2.5mg appeared to have a statistically significant treatment effect in reducing blood pressure when compared with the corresponding monocomponents (PERa 3.5 mg and AMLb 2.5mg).

3.3 Evaluation of Safety

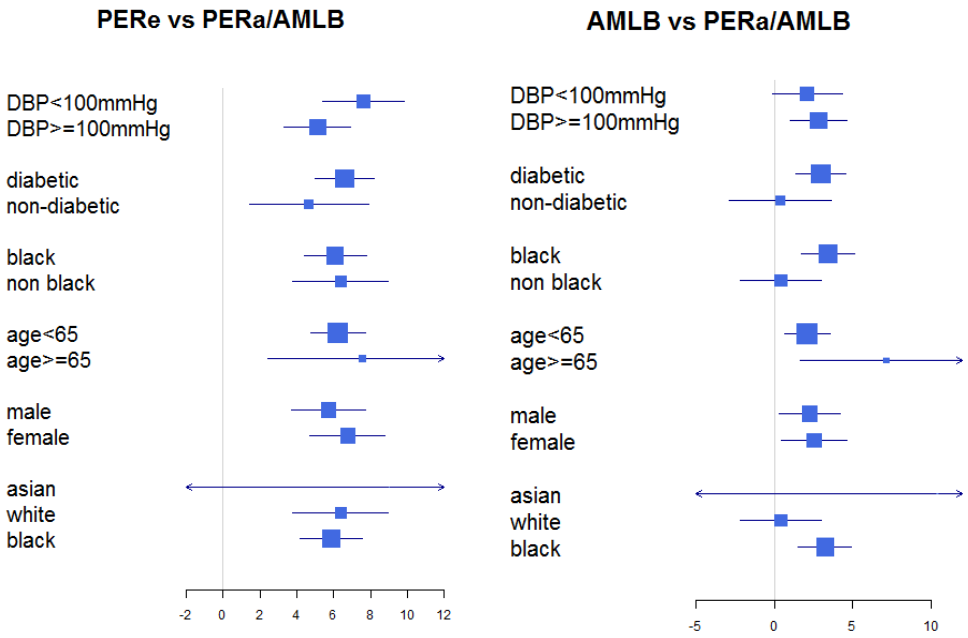
Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed in PATH trial to examine the consistency of study results among various subgroups. Figure 7 summarized the change from baseline in DBP at Day 42 after randomization by various subgroups, for example, gender, age, diabetic status and baseline DBP. Overall, the component perindopril arginine in the combination therapy seemed to contribute less to the overall treatment effect, especially in the non-black subpopulation as well as in the non-diabetic patients. But the small sample size in these subpopulations can limit interpretation and caution should be taken in interpreting the finding.

Figure 7: Subgroup analyses (PATH trial)



4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A multiple-pass, minimization algorithm was used to balance treatment group assignments across strata in PATH trial. This deterministic randomization used in the study is a bad practice that generated unnecessary hurdles to interpretation of the study results.

First of all, the assignment of treatment groups was deterministic. When a patient came in, he/she would be assigned to the treatment group with the lowest score according to the algorithm. A deterministic algorithm can unblind all the treatment assignment. This can be very serious when a trial is conducted in a single center. Selection bias is another concern for this deterministic minimization algorithm. Graphs of patients' baseline blood pressure or mean treatment effect by the order of patient's entry showed no obvious trend but potential selection bias cannot be completely ruled out. Involving multiple centers in the trial probably also alleviated some concerns that the study can easily be unblinded and there can be serious selection bias as a result. However, this does not exclude the possibility that a person who had access to the central database may still be able to do so. In addition, the issue remains that covariates other than the ones used in the adaptive algorithm, known or unknown, may not be balanced among treatment groups due to the deterministic nature of the assignment.

Secondly, the standard tests may not be applicable under such minimization. The reviewer performed the bootstrap t-test according to Shao et al (2010, Biometria) paper by generating bootstrap sample with replacement and applying the same minimization algorithm to assign treatment. The validity of this test relies on the assumption that the blood pressure measurements of the patients in the trial are identically distributed. The p-values for both comparisons between the combination therapy and its monocomponents were <0.001. If the assumption of "identically distributed" holds (which is unknown since the patients are rarely a random sample of the interested patient population), this test provided some assurance that the combination therapy had a significantly larger treatment effect than the monocomponents.

The statistical analysis plan for Study CL2-05985-005 was never reviewed by the Agency. The analyses on the primary endpoint (supine DBP) in the study involved three superiority comparisons and two non-inferiority comparisons. No multiplicity adjustment was discussed. Furthermore, it is not clear how the non-inferiority margin was determined. Since the non-inferiority comparison of the combination therapy versus higher dose monotherapies was not essential in interpreting the treatment effect of the low dose combination, the reviewer focused on the superiority comparisons between the combination therapy and the corresponding low dose monocomponents or placebo.

5.2 Conclusions and Recommendations

The low dose combination therapy PERa/AMLb 3.5mg/2.5mg appeared to have a statistically significant treatment effect in reducing blood pressure when compared with the corresponding low dose monocomponents (PERa 3.5 mg and AMLb 2.5mg) in Study CL2-05985-005.

The overall results appeared positive in PATH trial. However, as discussed extensively in Section 3.2.1 (pages 12-16), the deterministic minimization for treatment assignment used in the trial generates many difficulties to interpretation of the trial results. Though involving multiple centers in the trial probably can alleviate the concerns of biases and graphs of patients' baseline blood pressure or mean treatment effect by the order of patients' entry showed no obvious trend, these together with the statistical testing that needs to rely on an unverifiable assumption still did not address all the issues associated with the deterministic minimization.

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/s/

JIALU ZHANG
11/06/2014

HSIEN MING J HUNG
11/06/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205-003 **Applicant: XOMA LLC** **Stamp Date: 3/21/2014**

Drug Name: Prestalia **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	No interim analysis was performed
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

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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JIALU ZHANG
05/08/2014

HSIEN MING J HUNG
05/08/2014