

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205003Orig1s000**

**MEDICAL REVIEW(S)**



## DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

### *Divisional Memo*

**NDA:** 205003 Perindopril arginine-amlodipine (PRESTALIA) for hypertension.

**Sponsor:** Symplmed Pharmaceuticals

**Review date:** 12 January 2015

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

**Distribution:** NDA 205003

This memo conveys the Division's decision to approve this application.

This application has been the subject of reviews of CMC (Jewel; 14 November 2014, 23 December 2014), biopharmaceutics (Suarez-Sharp; 20 November 2014), microbiology (Riley; 16 May 2014), pharmacology and toxicology (Yang; 4 August 2014), clinical pharmacology (Hinderling; 8 December 2014 and Hariharan; 8 December 2014), clinical effectiveness and safety (Hicks; 26 November 2014), and biometrics (Zhang; 6 November 2014 and 8 January 2015).

There is also a CDTL memo (Thompson; 8 January 2014), with which I am in complete agreement. I comment here on a few aspects.

All manufacturing site inspections are satisfactory. There is an 18-month expiration date for the 3.5/2.5-mg tablets, 24 months for 7/5- and 14/10-mg strengths. There are no outstanding CMC or biopharmaceutics issues.

The sponsor conducted a 13-week toxicology study in rats, using both perindopril erbumine and perindopril arginine. There were no findings of concern.

There is no direct comparison of bioavailability between the to-be-marketed combination and ACEON, and the cross-study comparison gives reason to think they may not be bioequivalent. The review team and I agree that there are adequate safety data in the sponsor's studies to support approval, but not to cover special populations, so we will approve restricted labeling and a PMR to obtain data to support bridging.

Two studies supported effectiveness. One compared doses<sup>1</sup> of 3.5/2.5, 3.5/0, 5/0, 0/2.5, 0/5, and placebo. Not establishing an effect of the combination compared with high doses of the monotherapy, the sponsor conducted a second study comparing 14/10 with perindopril erbumine 16 mg and amlodipine besylate 10 mg—no placebo. The latter study demonstrated (systolic/diastolic; double differences from baseline and comparator) effects of -10.1/-6.3 mmHg compared with perindopril and -3.9/-2.5 mmHg compared with amlodipine, all difference highly statistically significant, but, of course, you cannot tell what the absolute effects were absent a placebo group.

The sponsor proposes to market doses of 3.5/2.5 mg (which had placebo-subtracted effects of -7.2/-4.1 mmHg), 14/10 mg, and 7/5 mg, the latter of which has no empirical data, but all reviewers believe its effects will lie somewhere between effects of 3.5/2.5 and 14/10 (i.e., one is not on a plateau by 7/5 mg), for blood pressure and edema rates. Dr. Hinderling is concerned enough over the uncertainty and the likelihood that the blood pressure step may not be very big compared with a dose of 3.5/2.5 mg or the

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<sup>1</sup> Expressed as mg of perindopril arginine / mg of amlodipine base.

reduction in edema very big compared with a dose of 14/10 mg, so he proposes we not approve 7/5 mg, but the rest of the review team and I believe that we know enough to recommend 7/5 be available for patients whose edema is intolerable at the higher dose.

I also wish to acknowledge concern raised about the process used to allocate subjects to treatment arms in the second study. While it was not random, the risk for unblinding was small, and all parties agree that the study was interpretable.

The safety database revealed no concerns not predictable from known effects of the two monotherapies.

Agreement on final labeling is the only barrier to approval.

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/s/  
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NORMAN L STOCKBRIDGE  
01/12/2015

## CLINICAL REVIEW

Application Type 505(b)(2)  
Application Number(s) NDA 205003  
SDN 1, Sequence No. 0000  
Priority or Standard Standard

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Reviewer Name(s) Karen A. Hicks, M.D.  
Review Completion Date November 26, 2014

Established Name Perindopril Arginine/  
Amlodipine Besylate  
(Proposed) Trade Name PRESTALIA<sup>®</sup>  
Therapeutic Class Antihypertensive  
Applicant Symplmed<sup>®</sup>

Formulation(s) Tablet  
Dosing Regimen 3.5/2.5 mg, 7/5 mg, 14/10 mg  
Indication(s) Treatment of Hypertension  
Intended Population(s) Adults

Template Version: March 6, 2009

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>8</b>
1.1	Recommendation on Regulatory Action .....	8
1.1.1.	Approval of the 7 mg/5 mg Dose.....	8
1.2	Risk Benefit Assessment.....	9
1.2.1.	Pivotal Trial Results .....	9
1.2.2.	Prescribing Information .....	12
1.2.3.	Safety Considerations .....	13
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	13
1.4	Recommendations for Postmarket Requirements and Commitments .....	13
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>14</b>
2.1	Product Information .....	14
2.2	Tables of Currently Available Treatments for Proposed Indications .....	15
2.3	Availability of Proposed Active Ingredient in the United States .....	18
2.4	Important Safety Issues With Consideration to Related Drugs.....	18
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	18
2.6	Other Relevant Background Information .....	19
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>20</b>
3.1	Submission Quality and Integrity .....	20
3.2	Compliance with Good Clinical Practices .....	20
3.2.1	Study X985400.....	20
3.2.1	Study CL2-05985-005 .....	20
3.3	Financial Disclosures.....	21
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>23</b>
4.1	Chemistry Manufacturing and Controls .....	23
4.2	Clinical Microbiology.....	24
4.3	Preclinical Pharmacology/Toxicology .....	24
4.4	Clinical Pharmacology.....	25
4.4.1	Mechanism of Action.....	27
4.4.2	Pharmacodynamics.....	28
4.4.3	Pharmacokinetics.....	29
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>29</b>
5.1	Tables of Studies/Clinical Trials .....	32
5.2	Review Strategy .....	37
5.3	Discussion of Individual Studies/Clinical Trials.....	37
5.3.1	Study X985400 (PATH).....	37
5.3.2	Study CL2-05985-005 and ABPM Substudy .....	45

<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>53</b>
	Efficacy Summary.....	53
6.1	Indication.....	53
6.1.1	Methods .....	53
6.1.2	Demographics.....	54
6.1.3	Subject Disposition .....	59
6.1.4	Analysis of Primary Endpoint(s) .....	61
6.1.6	Other Endpoints .....	70
6.1.7	Subpopulations .....	71
	Source: Jialu Zhang, Ph.D. (Office of Biometrics 1).....	72
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations ....	72
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	73
6.1.10	Additional Efficacy Issues/Analyses.....	73
<b>7</b>	<b>REVIEW OF SAFETY.....</b>	<b>74</b>
	Safety Summary .....	74
7.1	Methods.....	75
7.1.1	Studies/Clinical Trials Used to Evaluate Safety .....	75
7.1.2	Categorization of Adverse Events.....	75
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	76
7.2	Adequacy of Safety Assessments .....	76
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	76
7.2.2	Explorations for Dose Response.....	77
7.2.3	Special Animal and/or In Vitro Testing .....	78
7.2.4	Routine Clinical Testing .....	78
7.2.5	Metabolic, Clearance, and Interaction Workup .....	78
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	78
7.3	Major Safety Results .....	78
7.3.1	Deaths.....	78
7.3.2	Nonfatal Serious Adverse Events .....	78
7.3.3	Dropouts and/or Discontinuations .....	81
7.3.4	Significant Adverse Events .....	83
7.3.5	Submission Specific Primary Safety Concerns .....	83
7.4	Supportive Safety Results .....	84
7.4.1	Common Adverse Events .....	84
7.4.2	Laboratory Findings .....	87
7.4.3	Vital Signs .....	87
7.4.4	Electrocardiograms (ECGs) .....	87
7.4.5	Special Safety Studies/Clinical Trials.....	87
7.4.6	Immunogenicity.....	87
7.5	Other Safety Explorations.....	87
7.5.1	Dose Dependency for Adverse Events .....	87

7.5.2	Time Dependency for Adverse Events.....	88
7.5.3	Drug-Demographic Interactions .....	88
7.5.4	Drug-Disease Interactions.....	91
7.5.5	Drug-Drug Interactions.....	91
7.6	Additional Safety Evaluations .....	92
7.6.1	Human Carcinogenicity .....	92
7.6.2	Human Reproduction and Pregnancy Data.....	93
7.6.3	Pediatrics and Assessment of Effects on Growth .....	93
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	94
7.7	Additional Submissions / Safety Issues .....	94
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>94</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>95</b>
9.1	Literature Review/References .....	95
9.2	Labeling Recommendations .....	95
9.3	Advisory Committee Meeting.....	95
9.4	Pediatric Waiver.....	96

## Table of Tables

Table 1. Examples of Approved Drugs for Chronic Treatment of Hypertension .....	16
Table 2. Examples of Approved Antihypertensive Combinations .....	17
Table 3. Financial Disclosures: Studies X985400 (PATH), CL2-05985-005, X985401, PKH-05985-001, and PKH-05985-009.....	21
Table 4. Perindopril (Cross-Study Comparison).....	26
Table 5. Perindoprilat (Cross-Study Comparison).....	26
Table 6. Amlodipine (Cross-Study Comparisons) .....	27
Table 7. Type of FDC and Monocomponent Tablets used in the 5 Clinical Trials .....	32
Table 8. Clinical Studies.....	33
Table 9. Schedule of Procedures (S985400) (PATH).....	44
Table 10. Schedule of Procedures (Study CL2-05985-005, Main Study) .....	51
Table 11. Schedule of Procedures (Study CL2-05985-005, ABPM Study).....	52
Table 12. Analysis Sets (Study CL2-05985-005) .....	54
Table 13. Demographic and Baseline Characteristics (All Randomized Subjects) (Study X985400) .....	55
Table 14. Demographic and Baseline Characteristics (Study CL2-05985-005) (Randomized Set).....	57
Table 15. Disposition (All Randomized Subjects) (Study X985400).....	59
Table 16. Disposition (Study CL2-05985-005) .....	60
Table 17. Primary Endpoint (Study X985400): Seated Diastolic Blood Pressure at 6 Weeks (ITT with LOCF) .....	61
Table 18. Change from Baseline to Week 8 in Supine DBP (Superiority Comparison) (Full Analysis Set) (Study CL2-05985-005).....	63
Table 19. ABPM Substudy: Mean 24 Hour DBP (Change from Baseline to Last Post-Baseline Value/Week 8 Value) (Study CL2-05985-005) .....	64
Table 20. Secondary Endpoint (Study X985400): Seated Systolic Blood Pressure at 6 Weeks (LOCF).....	66
Table 21. Change from Baseline to Week 8 in Supine SBP (Superiority Comparison) (Full Analysis Set) (Study CL2-05985-005).....	67
Table 22. ABPM Substudy: Mean 24 Hour SBP (Change from Baseline to Last Post-Baseline Value/Week 8 Value) (Study CL2-05985-005) .....	68
Table 23. Applicant's Responder Analysis (LOCF) .....	70
Table 24. Responder's Analysis (Study CL2-05985-005).....	71
Table 25. Estimating Treatment Effects in Phase 3 Study .....	73
Table 26. Study X985400 (PATH): Treatment Exposure (Safety Population) .....	76
Table 27. Study CL2-05985-005: Treatment Exposure (Safety Set) .....	76
Table 28. Study CL2-05985-005 (ABPM): Treatment Exposure (Safety Set).....	77
Table 29. Incidence of Dose-Dependent Adverse Reactions with NORVASC <sup>®</sup> .....	77
Table 30. Adverse Reactions with NORVASC <sup>®</sup> by Sex.....	77
Table 31. Nonfatal Serious Treatment Emergent Adverse Events (Safety Population) (Study X985400) .....	79

Table 32. Nonfatal Serious Emergent Adverse Events (Study CL2-05985-005) (Safety Set) .....	80
Table 33. Subjects with Treatment Emergent Adverse Events who Discontinued Prematurely from the Trial (Study X985400).....	81
Table 34. Listing of Subjects who Discontinued Prematurely due to Treatment Emergent Adverse Events (Study X985400) (Safety Population) .....	82
Table 35. Common Treatment Emergent Adverse Events (Study X985400) .....	85
Table 36. Common Emergent Adverse Events (Study CL2-05985-005) .....	86
Table 37. Onset of Peripheral Edema (Days)(Study X985400).....	88
Table 38. Peripheral Edema by Sex (Study X985400) .....	88
Table 39. Peripheral Edema by Sex (Study CL2-05985-005) .....	89

## Table of Figures

Figure 1. Study Design (X985400) .....	38
Figure 2. Study Design (Study CL2-05985-005) .....	46
Figure 3. ABPM DBP Results (Study CL2-05985-005) .....	65
Figure 4. Study CL2-05985-005 ABPM SBP Results .....	69
Figure 5. Subgroup Analyses (Study X985400) .....	72

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend approval of PRESTALIA<sup>®</sup> (3.5/2.5 mg, 7/5 mg, 14/10 mg) for the treatment of hypertension as

- Add-on therapy in patients whose blood pressure is not adequately controlled on monotherapy
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (pending review and acceptability of the graphs and associated diagnostic plots submitted by the applicant with respect to the probability of achieving SBP < 140 mm Hg, SBP < 130 mm Hg, DBP < 90 mm Hg, and DBP < 80 mm Hg)

A bioequivalence (BE) study should be conducted as a postmarketing requirement because the applicant's cross-study comparison in this 505(b)(s) application failed to demonstrate bioequivalence for the dose-normalized AUC and C<sub>max</sub> for perindopril or perindoprilat between the to-be-marketed FDC PRESTALIA<sup>®</sup> tablet (perindopril arginine/amlodipine besylate 14/10 mg) and 2 tablets of ACEON (perindopril erbumine 8 mg). The plasma exposures to perindopril are ~2-fold higher with the to-be-marketed FDC PRESTALIA<sup>®</sup> than ACEON<sup>®</sup> by this cross-study pharmacokinetic (PK) comparison. The applicant's phase 2 and phase 3 trials provide data to support the safety and effectiveness of PRESTALIA<sup>®</sup> in the populations that were enrolled. However, the PK bridge is needed to provide dosing recommendations in patients with renal impairment (e.g., creatinine clearance < 60 mL/min), elderly patients, and patients with heart failure or hepatic insufficiency.

Once the applicant establishes the relationship between exposures to perindopril and perindoprilat in the to-be-marketed FDC PRESTALIA<sup>®</sup> tablet and ACEON<sup>®</sup>, the applicant could also receive (b) (4) if these products are found to be bioequivalent.

#### 1.1.1. Approval of the 7 mg/5 mg Dose

This application relied on data from two pivotal trials. Study X985400 (PATH) was a phase 3, multicenter, randomized, double-blind, parallel group trial in 837 subjects with moderate to severe hypertension, and Study CL2-05985-002 was a phase 2, multicenter, randomized, double-blind placebo-controlled study with a factorial design in 1581 subjects with mild to moderate hypertension.

Which doses to approve has been the subject of much discussion amongst members of the Review Team. First, PRESTALIA<sup>®</sup> (7/5 mg) was not studied in either Study X985400 or Study CL2-05985-005 and there are no data that directly address the effectiveness or safety of this dose as compared with the low and high dose FDC. Second, it is insufficient to know that this dose must be effective because it lies between two effective doses (3.5/2.5 mg and 14/10 mg); there should be some rationale in the titration to a target blood pressure. Third, the lack of a placebo arm (or 24-hour ambulatory blood pressure data which do not appear to be susceptible to a placebo effect) in Study X985400 (PATH) did not allow us to compare the effect size of the lower dose combination (perindopril arginine/amlodipine besylate 3.5/2.5) tested in Study CL2-05985-005 with the higher dose combination (perindopril arginine/amlodipine besylate 14/10 mg) tested in Study X985400. Treatment effects estimated by Dr. Peter Hinderling (Clinical Pharmacology) suggest that the diastolic blood pressure difference between the 3.5/2.5 and 7/5 mg strengths (and between the 7/5 mg and 14/10 mg strengths) may be too small to be detectable in clinical use (i.e. approximately 2-4 mm Hg). Having both doses could lead to a delay in getting a hypertensive patient to goal. From a safety perspective, however, since there is the potential for dose-dependent peripheral edema with amlodipine besylate, having an intermediate dose may help to mitigate this adverse reaction. For these reasons, I recommend approval of the intermediate dose.

## 1.2 Risk Benefit Assessment

The benefit of reducing blood pressure with PRESTALIA<sup>®</sup> outweighs the potential risks.

This complicated 505(b)(2) application relied on data from a phase 3 trial (Study X985400 (PATH)), a phase 2 trial (Study CL2-05985-005) with an ambulatory blood pressure monitoring (ABPM) substudy, and three pharmacokinetic studies. The three pharmacokinetic studies included a food effect study (Study X985401), a Bioequivalence (BE) Study (Study PKH-05985-001), and a Drug-Drug Interaction (DDI) Study PKH-05985-009.

The applicant also submitted a cross-study comparison to establish a PK bridge to ACEON<sup>®</sup> (NDA 20184) and NORVASC<sup>®</sup> (NDAs 22401 and 21540).

### 1.2.1. Pivotal Trial Results

#### 1.2.1.1. Study X985400 (PATH)

Study X985400 (PATH) was a phase 3, multicenter, randomized, double-blind, parallel group trial in 837 subjects with moderate to severe hypertension, defined as a mean seated DBP  $\geq 95$  mm Hg and  $\leq 115$  mm Hg. This study compared the highest strength of the combination product (PRESTALIA<sup>®</sup> 14/10 mg) with the highest approved strength

of the monotherapies (perindopril erbumine 16 mg (2 x 8 mg) and amlodipine besylate 10 mg). Subjects were randomized by current type 2 diabetes status, race (black/non-black), and baseline DBP (< 100 mm Hg vs.  $\geq$  100 mm Hg). Study duration was 6 weeks. Approximately 34% of subjects were Black, 48% of subjects were women, 21% had type 2 diabetes, and 7% of subjects were ages 65-75 years.

The primary endpoint was the change from baseline (Visit 2 [Day 0]) to Visit 4 (Day 42) in mean seated DBP (seDBP) at trough. The primary analysis was based on the intent-to-treat (ITT) Population, defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline DBP value. PRESTALIA<sup>®</sup> 14/10 mg significantly reduced the mean seDBP from baseline to Week 6 compared to perindopril erbumine (PERe) 16 mg (LS mean difference (SE): -6.3 (0.72) mm Hg,  $p < 0.0001$ ) and amlodipine besylate (AMLb) 10 mg (LS mean difference (SE): -2.5 (0.72) mm Hg,  $p = 0.0005$ ).

The secondary endpoint was the change from baseline (Visit 2 [Day 0]) to Visit 4 (Day 42) in mean seated SBP (seSBP) at trough and was also analyzed in the ITT Population. PRESTALIA<sup>®</sup> 14/10 mg significantly reduced mean seSBP from baseline to Week 6 compared to PERe 16 mg (LS mean difference (SE): -10.1 (1.25) mm Hg,  $p < 0.0001$ ) and AMLb 10 mg (LS mean difference (SE): -3.9 (1.25) mm Hg,  $p = 0.0017$ ).

In Study X985400 (PATH), a responder was defined as a subject who achieved a target blood pressure goal of < 140/90 mm Hg or a subject with diabetes who achieved a target blood pressure goal of < 130/80 mm Hg. The PRESTALIA<sup>®</sup> 14/10 mg treatment group had a higher percentage of subjects achieving 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 Days 21 and 42 (40.4% versus 13.9% and 24.8%, respectively) compared to the PERe 16 mg and AMLb 10 mg treatment groups.

#### **1.2.1.2. Study CL2-05985-005**

Study CL2-05985-005 was a phase 2, multicenter, randomized, double-blind, placebo-controlled study with a factorial design in 1581 subjects with mild to moderate hypertension, defined as  $95 \leq$  DBP < 110 mm Hg and  $150 \leq$  SBP < 180 mm Hg. An ABPM substudy was conducted in 1297 subjects. Study CL2-05985-005 compared the lowest strength of the Servier combination product (PERa/AMLb 3.5/2.5 mg) with the Servier monotherapies (PERa 3.5 mg, PERa 5 mg, AMLb 2.5 mg, AMLb 5 mg), and placebo. Randomized treatment was stratified by center. Study duration was 8 weeks. Approximately 98% of subjects were Caucasian, 52% of subjects were women, and 13% of subjects were  $\geq$  65 years of age.

The protocol and statistical analysis plan (SAP) for this study were not submitted to the FDA for review prior to study conduct. The primary endpoint was the change from

baseline (Week 0) to Week 8 (or last on-treatment post-baseline value) in mean supine DBP (suDBP) at trough or in mean 24 hour DBP (ABPM substudy). The primary analyses included three superiority comparisons and two non-inferiority comparisons as follows:

- **Superiority Comparisons**

- PERa 3.5/AMLb 2.5 mg versus placebo
- PERa 3.5/AMLb 2.5 mg versus PERa 3.5 mg
- PERa 3.5/AMLb 2.5 mg versus AMLb 2.5 mg

- **Non-Inferiority Comparisons**

- PERa 3.5/AMLb 2.5 mg versus PERa 5 mg
- PERa 3.5/AMLb 2.5 mg versus AMLb 5 mg

The non-inferiority tests used the same model as the superiority tests. The noninferiority margin was 2 mm Hg, but it was unclear how this margin was determined and whether the margin was clinically acceptable. For this review, FDA focused on the results from the superiority comparisons.

PRESTALIA<sup>®</sup> significantly reduced suDBP from baseline to Week 8 when compared with placebo (E(SE): -4.12 (0.77) mm Hg;  $p < 0.001$ ), PERa 3.5 mg (E(SE): -3.64 (0.76) mm Hg;  $p < 0.001$ ), and AMLb 2.5 mg (E(SE): -2.97 (0.75) mm Hg;  $p < 0.001$ ).

The secondary endpoint was the change from baseline (Week 0) to Week 8 in supine SBP (suSBP) at trough or in mean 24 hour SBP (ABPM substudy). PRESTALIA<sup>®</sup> significantly reduced suSBP from baseline to Week 8 when compared with placebo (E(SE): -7.22 (1.21) mm Hg;  $p < 0.001$ ), PERa 3.5 mg (E (SE): -5.01 (1.19);  $p < 0.001$ ); or AMLb 2.5 mg (E(SE): -5.20 (1.19);  $p < 0.001$ ).

The ABPM substudy demonstrated that PRESTALIA<sup>®</sup> significantly reduced mean 24 hour DBP and SBP compared to placebo, PERa 3.5 mg, and AMLb 2.5 mg.

Response to treatment was defined as

- Normalization of BP (SBP < 140 mm hg and DBP < 90 mm Hg)
- And/or a decrease from baseline in SBP  $\geq$  20 mm Hg
- And/or a decrease from baseline in DBP  $\geq$  10 mm Hg

At 8 weeks (or last post-baseline value), PRESTALIA<sup>®</sup> had a higher percentage of responders than the placebo and monocomponent treatment groups (PRESTALIA<sup>®</sup> 76.8% versus Placebo 52.8% versus PERa 3.5 mg 58.2% versus AMLb 2.5 mg 58.5%).

In summary, Study CL2-05985-005 demonstrated that PRESTALIA<sup>®</sup> significantly reduced supine DBP and SBP from baseline to Week 8, compared to PERa 3.5 mg and AMLb 2.5 mg.

### **1.2.2. Prescribing Information**

The following language should be included in prescribing information under “Indications and Usage”:

“Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including the class(es) to which this drug principally belongs. There are no controlled trials demonstrating risk reduction with PRESTALIA<sup>®</sup>.

“Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program’s Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

“Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

“Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mm Hg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

“Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.”

### 1.2.3. Safety Considerations

The pivotal trials did not identify any new safety issues. ACEON<sup>®</sup> (NDA 20184) and NORVASC<sup>®</sup> (NDA 19787) were approved by the FDA on December 30, 1993 and July 31, 1992, respectively, so the Agency has an extensive postmarketing safety database for these drug products.

The Safety Information Amendment for PRESTALIA<sup>®</sup> (IND 108,233) identified the following new postmarketing safety issues with the combination product: <sup>(b) (4)</sup>

[REDACTED]

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

### 1.4 Recommendations for Postmarket Requirements and Commitments

See Section 1.1. Clinical Pharmacology is currently recommending that the applicant conduct a BE study between the proposed FDC product (PERa/AMLb) and ACEON<sup>®</sup> (PERe) as a postmarketing requirement. Perindopril and perindoprilat should be measured with validated, sensitive assays allowing determination of AUC. Clinical Pharmacology also recommends including NORVASC<sup>®</sup> in this study to establish a PK bridge for amlodipine besylate. I agree with these recommendations.

## 2 Introduction and Regulatory Background

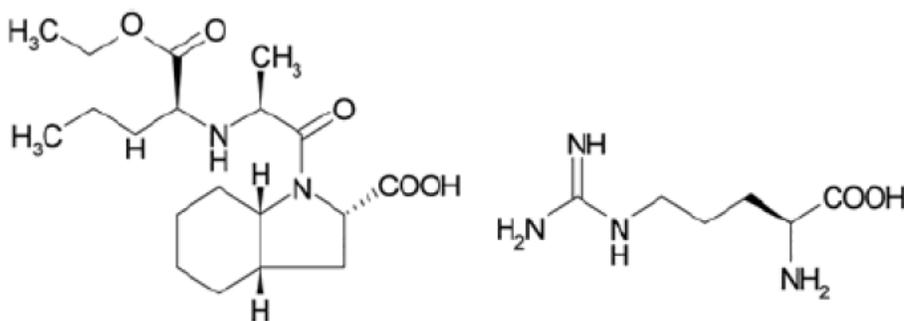
### 2.1 Product Information

**PRESTALIA<sup>®</sup>** is a fixed-dose combination (FDC) tablet of perindopril arginine (angiotensin converting enzyme inhibitor (ACE-I)) and amlodipine besylate (dihydropyridine calcium channel blocker) for the treatment of hypertension. The applicant proposes approval of three strengths (3.5/2.5 mg, 7/5 mg, and 14/10 mg).

PRESTALIA<sup>®</sup> tablets are uncoated, white, immediate-release tablets administered as a solid oral dosage form. Each tablet contains perindopril arginine and amlodipine besylate as active ingredients. Inactive ingredients include lactose (b) (4) magnesium stearate, microcrystalline cellulose, and colloidal silicon dioxide. Each tablet is debossed with the tablet strength.

The proposed prescribing information recommends initiating PRESTALIA<sup>®</sup> in patients who have not achieved adequate blood pressure control with their current therapeutic regimen. The recommended initial dose is 3.5/2.5 mg once daily. Dosage should be adjusted according to blood pressure goals and titration should occur every 7 to 14 days. If clinically warranted, PRESTALIA<sup>®</sup> can be titrated more rapidly, provided the patient is assessed frequently.

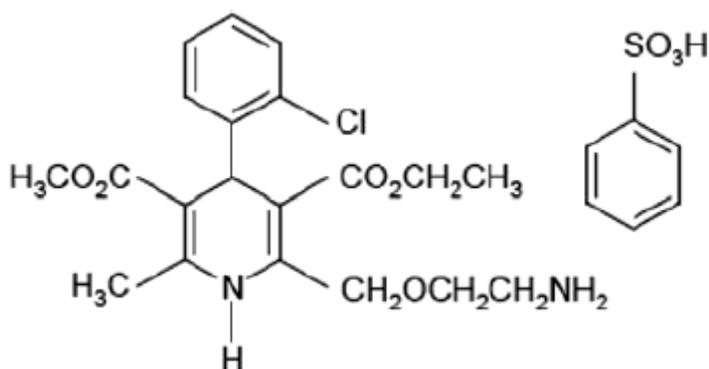
**Perindopril arginine** is the L-arginine salt of perindopril, the ethyl ester of a non-sulfhydryl ACE-I. Perindopril arginine is described chemically as L-arginine (2S,3aS,7aS)-1-[(2S)-2-[[1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate. Its empirical formula is C<sub>19</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>·C<sub>6</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub> and its structural formula is:



Perindopril arginine is a white, crystalline powder with a molecular weight of 368.5 (free acid) or 542.7 (salt form).

Perindopril is the free-acid form of perindopril arginine, and is synthesized stereoselectively as the *S*-enantiomer. A pro-drug, perindopril is metabolized *in vivo* by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite.

**Amlodipine besylate** is the besylate salt of amlodipine, a long-acting dihydropyridine calcium channel blocker (CCB). Amlodipine besylate is described chemically as 3-ethyl-5-methyl ( $\pm$ )-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulphonate. Its empirical formula is  $C_{20}H_{25}N_2O_5 \cdot C_6H_6O_3S$  and its structural formula is



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and minimally soluble in ethanol.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are numerous monotherapies and combination drug products that are approved for the treatment of hypertension; some of these are shown in Table 1 and Table 2. Other antihypertensives include fenoldopam (corlopam), a dopamine D<sub>1</sub>-like receptor agonist and rapid-acting vasodilator, and nitroprusside, an agent that dilates vascular smooth muscle as well as peripheral arteries and veins.

Currently, there are three combination ACE-inhibitors/calcium channel blockers that are approved for the treatment of hypertension: Lexxel (enalapril maleate/felodipine); Lotrel (amlodipine besylate/benazepril hydrochloride), and Tarka (trandolapril/verapamil hydrochloride).

**Table 1. Examples of Approved Drugs for Chronic Treatment of Hypertension**

<b>Pharmacologic Class</b>	<b>Approved Drugs</b>
Aldosterone antagonists	eplerenone, <b>spironolactone</b>
Alpha-Adrenergic Blockers	<b>doxazosin</b> , phenoxybenzamine, phentolamine, <b>prazosin</b> , terazosin
Angiotensin Converting Enzyme Inhibitors	benazepril, <b>captopril</b> , <b>enalapril</b> , fosinopril, <b>lisinopril</b> , moexipril, perindopril, quinapril, <b>ramipril</b> , trandolapril
Angiotensin II Receptor Blockers	<b>candesartan</b> , eprosartan, <b>irbesartan</b> , <b>losartan</b> , olmesartan, telmisartan, valsartan
Arteriolar Vasodilators	<b>hydralazine</b> , <b>minoxidil</b>
Autonomic Ganglionic Vasodilators	mecamylamine
Beta-adrenergic blockers	<b>acebutolol</b> , <b>atenolol</b> , betaxolol, bisoprolol, <b>carvedilol</b> , carteolol, esmolol, labetalol, <b>metoprolol</b> , nadolol, penbuterol, <b>pindolol</b> , <b>propranolol</b> , timolol
Catecholamine-Depleting Sympatholytics	deserpidine, <b>reserpine</b>
Central Alpha-2-Adrenergic Agonists	clonidine, guanabenz, guanfacine, methyl dopa
Non-Dihydropyridine Calcium Channel Blockers	<b>diltiazem</b> , <b>verapamil</b>
Dihydropyridine Calcium Channel Blockers	<b>amlodipine</b> , <b>felodipine</b> , <b>isradipine</b> , <b>nicardipine</b> , <b>nifedipine</b> , <b>nisoldipine</b>
Loop Diuretics	bumetanide, ethacrynic acid, <b>furosemide</b> , torsemide
Renin Inhibitors	aliskiren
Thiazide Diuretics	chlorothiazide, <b>hydrochlorothiazide</b> , hydroflumethiazide, methyclothiazide, polythiazide
Thiazide-like Diuretics	<b>chlorthalidone</b> , indapamide, metolazone
<b>Guidance for Industry. Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims. March 2011. The drugs shown in bold type have specific outcome data in either placebo-controlled or active-controlled trials as either primary or secondary treatment.</b>	

**Table 2. Examples of Approved Antihypertensive Combinations**

<b>Combination</b>	<b>Approved Drugs</b>
ACE Inhibitor/Diuretic	Accuretic (quinapril + HCTZ), Capozide (captopril + HCTZ) (captopril + HCTZ), Inhibace Plus (cilazapril + HCTZ), Lotensin HCT (benazepril + HCTZ), Monopril HCT (fosinopril + HCTZ), Prinzide (lisinopril + HCTZ), Uniretic (moexipril + HCTZ), Vaseretic (enalapril + HCTZ), Zestoretic (lisinopril + HCTZ)
ACE Inhibitor/Calcium Channel Blocker	Lexxel (enalapril + felopidine), Lotrel (amlodipine + benazepril), Tarka (trandolapril + verapamil)
Angiotensin Receptor Blocker/Diuretic	Atacand HCT (candesartan + HCTZ), Avalide (irbesartan + HCTZ), Benicar HCT (olmesartan + HCTZ), Diovan HCT (valsartan + HCTZ), Edarbyclor (azilsartan + chlorthalidone), Hyzaar (losartan + HCTZ), Micardis HCT (telmisartan + HCTZ), Teveten HCT (eprosartan + HCTZ)
Angiotensin Receptor Blocker/Calcium Channel Blocker	Azor (amlodipine + olmesartan), Exforge (amlodipine + valsartan), Twynsta (amlodipine + telmisartan)
Angiotensin Receptor Blocker/Calcium Channel Blocker/Diuretic	Exforge HCT (amlodipine + valsartan+ HCTZ), Tribenzor (amlodipine + olmesartan + HCTZ)
Beta-blocker/Diuretic	Corzide (nadolol + bendroflumethiazide), Dutoprol (metoprolol succinate + HCTZ), Inderide (propranolol + HCTZ), Lopressor HCT (metoprolol + HCTZ), Tenoretic (atenolol + chlorthalidone), Ziac (bisoprolol + HCTZ)
Calcium Channel Blocker/Statin	Caduet (amlodipine + atorvastatin)
Direct Renin Inhibitor/Calcium Channel Blocker	Tekamlo (aliskiren + amlodipine)
Direct Renin Inhibitor/Calcium Channel Blocker/Diuretic	Amturnide (aliskiren + amlodipine + HCTZ)
Direct Renin Inhibitor/Diuretic	Tekturna HCT (aliskiren + HCTZ)
Diuretic Combinations	Aldactazide (spironolactone + HCTZ), Dyazide (triamterene + HCTZ), Maxzide (triamterene + HCTZ), Moduretic (amiloride + HCTZ)
Diuretic/Miscellaneous Antihypertensive	Aldoril (methyldopa + HCTZ), Apresazide (hydralazine + HCTZ), Clorpres (clonidine + chlorthalidone), Minizide (prazosin + polythiazide)
<b>ACE = angiotensin converting enzyme; HCTZ = hydrochlorothiazide          2014 Tarascon Pocket Pharmacopoeia, pages 60-61.</b>	

### **2.3 Availability of Proposed Active Ingredient in the United States**

NORVASC<sup>®</sup> is available in the US and the active ingredient, perindopril, is also available as ACEON<sup>®</sup>.

PRESTALIA<sup>®</sup> will be manufactured by Patheon Pharmaceuticals, Inc. in Cincinnati, Ohio.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Important safety issues with ACE-Is include fetal toxicity and anaphylactoid and possibly related reactions, including head and neck angioedema; intestinal angioedema; increased risk of angioedema in patients with a history of angioedema unrelated to ACE-I therapy; anaphylactoid reactions during desensitization; and anaphylactoid reactions during membrane exposure. Safety issues with ACE-Is also include hypotension (especially in volume- or salt-depleted patients), impaired renal function, hyperkalemia, cough, and presumably "rare" hepatic failure and neutropenia/agranulocytosis.

Important safety issues with dihydropyridine CCBs include symptomatic hypotension, especially in patients with severe aortic stenosis; worsening angina and acute myocardial infarction (especially after starting or increasing the dose of NORVASC<sup>®</sup>); somnolence; and dose-dependent edema, dizziness, flushing, and palpitations. Other important safety issues include arrhythmias (e.g., ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, tachycardia, vasculitis, fatigue, nausea, abdominal pain, and sexual dysfunction. Since NORVASC<sup>®</sup> is extensively metabolized in the liver and the  $t_{1/2}$  is 56 hours in patients with impaired hepatic function, the dose must be titrated slowly, especially in patients with severe hepatic impairment.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

On September 21, 2010, XOMA (US) LLC opened IND 108,233 for perindopril arginine and amlodipine besylate.

On October 20, 2010, XOMA (US) LLC met with the Division of Cardiovascular and Renal Products to discuss submitting a new drug application (NDA) using the 505(b)(2) pathway. At the meeting, the Division indicated that for the combination to be approved, the applicant would need to conduct a study demonstrating that the highest dose of the combination (PERa/AMLb) was statistically and clinically superior to the highest doses of each monotherapy (PERa, AMLb). The sponsor stated that a 14-mg monotherapy of PERa was not available commercially and proposed a three-arm study evaluating PERe 16 mg versus AMLb 10 mg versus PERa 14 mg/AMLb 10 mg. The Division

agreed. XOMA also proposed perindopril/amlodipine as initial therapy in patients with hypertension. The meeting minutes document the following discussion:

“Assessment of the benefit and risk of combination therapy as initial treatment for hypertension would necessitate a full factorial dataset throughout the entire dose range to determine the hypertension envelope where combination therapy would be justified as initial therapy. . . . Given that the sponsor proposes only a 3-arm trial testing the highest dose combination product versus the highest doses of each monotherapy (or its equivalent), the sponsor [was asked to confirm] that the company is no longer seeking an indication for initial therapy in patients with hypertension, and is no longer seeking an indication for patients with mild hypertension. It was pointed out to the sponsor that a complete factorial study design would be needed to construct the response surface model from which the appropriateness of initial combination therapy in various patient subsets could be determined. None of the sponsor’s prior non-IND studies provide this information, nor does the study design being proposed here for testing only the highest dose combination against the highest dose monotherapies. The sponsor

(b) (4)



Preliminary Comments for a Type C Meeting were also sent to Symplmed Pharmaceuticals LLC on October 28, 2013 and included extensive advice with respect to submission of the biowaiver requests and the 505(b)(2) pathway for NDA submission.

Lastly, an advice letter about the NDA submission was sent to Symplmed Pharmaceuticals LLC on November 15, 2013.

## 2.6 Other Relevant Background Information

ACEON<sup>®</sup> (perindopril erbumine) was approved by the U.S. Food and Drug Administration on December 30, 1993 (NDA 20184). ACEON<sup>®</sup> is manufactured by Patheon Pharmaceuticals in Ohio and is marketed by XOMA LLC in the United States.

NORVASC<sup>®</sup> was approved by the U.S. Food and Drug Administration on July 31, 1992 (NDA 19787) and is distributed by Pfizer.

Perindopril arginine is not approved in the United States. Perindopril arginine “monocomponent” as well as perindopril arginine/amlodipine besylate FDC are approved outside of the United States only.

The sponsorship of Investigational New Drug Application (IND) 108,233 (perindopril arginine/amlodipine besylate) was transferred from XOMA (US) LLC to Symplmed on

August 20, 2013. The sponsorship of NDA 20184 (ACEON<sup>®</sup> (perindopril erbumine)) was transferred from XOMA (US) LLC to Symplmed on July 22, 2014.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The submission quality and integrity were acceptable. I did not identify any issues that would affect the overall study findings.

#### 3.2 Compliance with Good Clinical Practices

##### 3.2.1 Study X985400

Study X985400 was conducted in accordance with Good Clinical Practice requirements described in the current revision of the International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use Guidelines and all applicable regulations, including the current United States Code of Federal Regulation, Title 21, parts 11, 50, 54, 56, and 312 and Title 45, Part 164. The study was also compliant with the ethical principles described in the current revision of the Declaration of Helsinki and local legal requirements. The phase 3 protocol and informed consent were approved by a central Institutional Review Board (IRB).

**Treatment Compliance.** Mean compliance was similar across all treatment groups in the Safety Population. Most subjects were 80-120% compliant with their treatment regimen (271 (97.1%) of subjects in the PERa/AMLb 14/10 mg group, 269 (98.6%) subjects in the PERe 16 mg group, and 271 (96.8%) subjects in the AMLb 10 mg group).

**Protocol Deviations.** There were a total of 448 major protocol deviations in the Safety Population, including 157 in PERa/AMLb 14/10 mg (114 (40.9%) subjects) group, 136 in the PERe 16 mg (103 (37.1%) subjects) group, and 155 in AMLb 10 mg (109 (38.9%) subjects) group. These deviations were not thought to affect the overall results of the study.

##### 3.2.1 Study CL2-05985-005

Study CL2-05985-005 was conducted in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Tokyo, 2004. The phase 2 protocol and its two Amendments were reviewed by independent Ethics Committees. The study was initiated after the approval of the Ethics Committees in accordance with local regulations in each of the countries.

**Treatment Compliance.** During treatment, 98.6% of the Safety Set had an overall compliance with study drug between 70% and 130% in the main study. In the ABPM substudy, 99.5% of the Full Analysis Set had an overall compliance between 70% and 130%. Compliance was similar between treatment groups.

**Protocol Deviations.** In Study CL2-05985-005 (main study), a total of 365 subjects (23.1%) had at least one protocol deviation after inclusion (i.e. during the double-blind active treatment period), including 66 subjects (26.6%) in the PERa/AMLb 3.5/2.5 mg group, 49 subjects (19.6%) in the placebo group, 56 subjects (20.5%) in the PERa 3.5 mg group, 64 subjects (23.4%) in the AMLb 2.5 mg group, 64 subjects (23.5%) in the PERa 5 mg group, and 66 subjects (25.0%) in the AMLb 5 mg group. A total of 589 protocol deviations were detected after inclusion (103 protocol deviations with respect to the efficacy assessment, 205 protocol deviations with respect to the safety deviations, and 281 protocol deviations with respect to study management).

In the ABPM substudy, a total of 109 subjects (8.4%) had at least one protocol deviation after inclusion, including 19 subjects (9.3%) in the PERa/AMLb 3.5/2.5 mg group, 14 subjects (7.0%) in the placebo group, 18 subjects (8.0%) in the PERa 3.5 mg group, 19 subjects (8.4%) in the AMLb 2.5 mg group, 18 subjects (7.9%) in the PER 5 mg group, and 21 subjects (9.8%) in the AMLb 5 mg group. A total of 119 protocol deviations were detected after inclusion (76 protocol deviations with respect to the efficacy measurement and 43 protocol deviations with respect to study management).

Despite the large number of protocol deviations, these deviations were not thought to affect the overall results of the main study and the ABPM substudy.

### 3.3 Financial Disclosures

Information on financial disclosures is summarized in Table 3:

**Table 3. Financial Disclosures: Studies X985400 (PATH), CL2-05985-005, X985401, PKH-05985-001, and PKH-05985-009**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>776</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not applicable.  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____  Significant payments of other sorts: _____  Proprietary interest in the product tested held by investigator: _____  Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)  Not applicable <input checked="" type="checkbox"/>
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)  Not applicable <input checked="" type="checkbox"/>
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>30</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

**Comments:** The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the February 2013 Guidance for Clinical Investigators, Industry, and FDA Staff entitled “Financial Disclosure by Clinical Investigators.” Despite due diligence, the sponsor was unable to obtain financial disclosure information for 30 of the 339 investigators/subinvestigators involved in Study CL2-05985-005.

In the NDA submission, Symplmed provided a signed FDA Form 3454 certifying that it could not obtain the required information for these Investigators despite due diligence. The reasons financial disclosure was not obtained are summarized as follows:  
 1) Sponsor was unable to contact the Investigator (21); 2) Investigator refused to sign Financial Disclosure Form (2); 3) Financial Disclosure Form was never received from Investigator (2); 4) Investigator was not located (2); 5) Investigator was deceased (1); 6) Investigator had no patients in the trials (1); 7) Investigator did not take part in the study (1). Symplmed also provided a copy of the letter that was sent to each investigator to

obtain the financial disclosure information as well as a detailed account of the collection procedure.

This lack of disclosure does not raise questions about the integrity of the data because the study was randomized and blinded, had objective endpoints (ambulatory blood pressure substudy results), and was conducted at 164 centers in 6 countries. These clinical investigators contributed minimal data to the overall results, and there was no single site that drove the efficacy findings. In my opinion, the disclosed financial interests/arrangements and lack of disclosure despite due diligence do not affect the approvability of the application.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Dr. Charles Jewell's Chemistry Review dated November 14, 2014 recommends approval. At the time this review was completed, (b) (4) (amlodipine besylate) and the Patheon manufacturing site (drug product) had an approval recommendation from the Office of Compliance. (b) (4) (perindopril arginine) was still awaiting the final inspection report and decision. Dr. Jewell recommends an 18-month expiry for the 3.5 mg/2.5 mg strength of perindopril arginine/amlodipine besylate and 24-month expiry for the 7 mg/5 mg and 14 mg/10 mg strengths.

Dr. Sandra Suarez' Biopharmaceutical Review dated November 20, 2014 also recommends approval of PRESTALIA<sup>®</sup> (3.5/2.5 mg, 7/5 mg, and 14/10 mg). On July 3, 2014, the applicant agreed to the following dissolution method and acceptance criterion for both components and the three strengths of the proposed drug product:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 rpm	1000 mL	37°C	0.01N HCL pH 2	Q= (b) (4)% in 15 min

(Source: Sandra Suarez-Sharp, Ph.D., Biopharmaceutical Review, page 2)

The biowaiver requests for an in vivo dosage strength proportionality study and for a bioequivalence study to bridge the clinical studies conducted by Servier outside the US and the clinical studies conducted by XOMA in the US (different manufacturers) are

acceptable. The in vitro dissolution and manufacturing data support the following two claims:

- The tablets manufactured at XOMA and Servier are bioequivalent
- There is dose strength proportionality among the PRESTALIA<sup>®</sup> tablets

## 4.2 Clinical Microbiology

Per his review dated May 13, 2014, Dr. Bryan S. Riley found the microbial limits specification for PRESTALIA<sup>®</sup> to be acceptable and recommended approval from a Product Quality Microbiology perspective.

## 4.3 Preclinical Pharmacology/Toxicology

No new pharmacology or toxicology studies were submitted to support this 505(b)(2) application.

Dr. Baichun Yang's nonclinical review dated September 26, 2011 discussed the similarity between the arginine and erbumine salts of perindopril with respect to PK and safety profile.

In a 28-day repeat dose study in dogs, oral PERa resulted in decreases in red blood cell count and hemoglobin by approximately 20% in 1 of 3 females at 4.17 mg/kg and 1 of 3 females at 20.87 mg/kg. This finding was not observed in males. Renal medullary and papillary mineralization was observed at all dose levels, but there was no evidence of dose-dependence.

These findings were not observed in the 28-day study with PERa 0, 0.8, 8, or 33 or PERe 8 or 33 mg/kg/day in Wistar rats or in the 13-week study with PERa/AML (combination) at 0/0, 3.75/2, 7.5/4, 15/8, 15/0, or 0/8 mg/kg/day in Wistar rats.

Five impurities were identified [REDACTED] (b) (4) but there were no structural alerts.

Reproductive toxicity studies have not been conducted with perindopril arginine/amlodipine besylate combination. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.

## 4.4 Clinical Pharmacology

### *Clinical Pharmacology Summary:*

#### **Pharmacokinetic Studies:**

The applicant conducted three pharmacokinetic studies as follows:

- 1) Food Effect Study (Study X985401)
  - Studied PRESTALIA<sup>®</sup> FDC (PERa/AMLb 14/10 mg) fed versus fasted
  - **Conclusion:** There was no food interaction with PRESTALIA<sup>®</sup>
- 2) Bioequivalence Study (Study PKH-05985-001)
  - Studied Servier FDC tablet (PERa/AMLb 10/10 mg) versus Servier PERe 8 mg, AMLb 10 mg
  - **Conclusion:** Servier FDC and Servier mono-component tablets were bioequivalent
- 3) Drug-Drug Interaction Study (Study PKH-05985-009)
  - Studied Servier FDC (PERa/AMLb 14/10 mg) versus Servier PERa 14 mg, AMLb 10 mg
  - **Conclusion:** There was no PK-based drug-drug interaction between perindopril/perindoprilat and amlodipine

#### **Biowaiver Request:**

The sponsor also requested a biowaiver for a biocomparability study between PRESTALIA<sup>®</sup> FDC (PERa/AMLb 14/10 mg) and FDA approved ACEON<sup>®</sup> and NORVASC<sup>®</sup> (i.e., PK bridge supporting a 505(b)(2) NDA).

- Supporting data: Cross-study PK comparisons
- Perindopril: Food effect study versus relative bioavailability study from NDA 20184 (ACEON<sup>®</sup>)
- Amlodipine: Food effect study vs. published DDI study (drug interaction study of amlodipine and grapefruit juice) (Vincent, 2000)

**Conclusions:**

- 1) **Bridge to ACEON<sup>®</sup>:** Since Symplmed owns NDA 20184, Symplmed may rely on perindopril/perindoprilat information from the ACEON<sup>®</sup> NDA 20184 in their cross-study comparison with PRESTALIA<sup>®</sup>.

The applicant's cross-study comparison failed to demonstrate bioequivalence for the dose-normalized AUC and C<sub>max</sub> for perindopril or perindoprilat between the to-be-marketed FDC PRESTALIA<sup>®</sup> tablet (perindopril arginine/amlodipine besylate 14/10 mg) and 2 tablets of ACEON<sup>®</sup> (perindopril erbumine 8 mg), as shown in Tables 4 and 5. The plasma exposures to perindopril are ~2-fold higher with the to-be-marketed FDC PRESTALIA<sup>®</sup> than ACEON<sup>®</sup> by this cross-study PK comparison.

**Table 4. Perindopril (Cross-Study Comparison)**

Studies Compared	GM Ratio of AUC <sub>0-t</sub> <sup>a</sup>	GM Ratio of AUC <sup>a,b</sup>	GM Ratio of C <sub>max</sub> <sup>a</sup>
X985401 vs. MS 193 <sup>a</sup>	2.12 (1.86-2.40)	2.06 (1.82-2.33)	1.53 (1.34-1.76)
<sup>a</sup> dose normalized geometric mean ratios; <sup>b</sup> AUC=truncated AUC + Clast/k Source: Peter Hinderling, M.D.			

**Table 5. Perindoprilat (Cross-Study Comparison)**

Studies Compared	GM Ratio of AUC <sub>0-t</sub> <sup>a</sup>	GM Ratio of AUC <sup>a,b</sup>	GM Ratio of C <sub>max</sub> <sup>a</sup>
X985401 vs. MS 193 <sup>a</sup>	1.23 (1.03-1.46)	1.16 (1.00-1.34)	0.83 (0.69-1.00)
<sup>a</sup> dose normalized geometric mean ratios; <sup>b</sup> AUC=truncated AUC + Clast/k Source: Peter Hinderling, M.D.			

- 2) **Bridge to NORVASC<sup>®</sup>:** The applicant used information contained in the Summary Basis of Approvals (SBAs) for NORVASC<sup>®</sup> (NDAs 22401 and 21540) in their cross-study comparison; however, the Division did not need to rely on these data to establish a bridge and instead used data from the published literature submitted by the applicant (Vincent et al, 2000).

The applicant's cross-study comparison using data from the SBAs for NORVASC<sup>®</sup> (NDAs 22401 and 21540) as reference showed bioequivalence for amlodipine besylate between the PRESTALIA<sup>®</sup> FDC tablet (perindopril arginine/amlodipine besylate 14/10 mg) and NORVASC<sup>®</sup> (amlodipine besylate 10 mg). Dr. Hinderling's analysis using data on NORVASC<sup>®</sup> from the published literature (Vincent et al, 2000) also showed similar exposures for amlodipine besylate between the PRESTALIA<sup>®</sup> FDC and NORVASC<sup>®</sup>. These results are summarized in Table 6.

**Table 6. Amlodipine (Cross-Study Comparisons)**

<b>Studies Compared</b>	<b>Arithmetic Mean Ratio of AUC</b>	<b>Arithmetic mean Ratio of Cmax</b>
X985401 vs. Vincent <sup>a</sup>	1.01	0.95
X985401 vs. A0531029 <sup>a</sup>	1.05	0.97
X985401 vs. 1235.4 <sup>b</sup>	0.97	0.91
<b><sup>a</sup>PRESTALIA<sup>®</sup> FDC tablet (PERa/AMLb 14/10 mg) versus NORVASC<sup>®</sup> tablet (AMLb 10 mg)</b>		
<b>Source: Peter Hinderling, M.D.</b>		

- 3) This 505(b)(2) application was unable to establish an unequivocal pharmacokinetic (PK) bridge between the exposure to perindopril in the applicant's proposed FDC and ACEON<sup>®</sup>. At worst, exposures to perindopril could be about twice as high with the FDC than with ACEON<sup>®</sup>. From a labeling perspective, a clear understanding of the relative bioavailability of PRESTALIA<sup>®</sup> is essential to rely upon certain sections of the ACEON<sup>®</sup> product insert, and specifically to rely upon information related to use in elderly patients, patients with renal or hepatic impairment, and patients with heart failure who require dose adjustment because of increased exposure.

In an Information Request letter dated October 22, 2014, the Division recommended that the applicant conduct a bioequivalence study between their proposed FDC product (perindopril arginine/amlodipine) and ACEON<sup>®</sup> (perindopril erbumine). The primary analysis should be the comparative bioavailability in the exposure to perindopril with the comparison of perindoprilat serving as supportive evidence. Clinical Pharmacology has also recommended that the applicant include NORVASC<sup>®</sup> in this study and also establish a PK bridge for amlodipine besylate.

At this time, Clinical Pharmacology is recommending that the applicant conduct a BE as a postmarketing requirement. Initial approval and prescribing information should exclude elderly patients, patients with renal impairment (e.g., creatinine clearance < 60 mL/min), and those with heart failure or hepatic insufficiency.

#### **4.4.1 Mechanism of Action**

**PRESTALIA<sup>®</sup> FDC** contains perindopril arginine and amlodipine besylate.

**PERINDOPRIL.** Perindopril is a pro-drug for perindoprilat, which inhibits ACE in human subjects and animals. The mechanism through which perindoprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes conversion of the inactive decapeptide, angiotensin I, to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor, which stimulates aldosterone secretion by the adrenal cortex, and provides negative

feedback on renin secretion. Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and may be associated with a small increase of serum potassium.

ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ACEON remains to be elucidated.

Although the principal mechanism of perindopril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE-Is have some effect even in apparent low-renin hypertension. Perindopril has been studied in relatively few black patients, usually a low-renin population, and the average response of diastolic blood pressure to perindopril was about half the response seen in nonblack patients, a finding consistent with previous experience of other ACE inhibitors.

**AMLODIPINE.** Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

#### 4.4.2 Pharmacodynamics

See Section 6, Review of Efficacy, for further details on the pharmacodynamic effects observed with PRESTALIA<sup>®</sup>.

#### 4.4.3 Pharmacokinetics

Dosing and pharmacokinetic characteristics for ACEON<sup>®</sup> and NORVASC<sup>®</sup> are summarized below.

ACEON<sup>®</sup> is available in 2, 4, and 8 mg tablets. The usual dose is 4-8 mg QD or BID, and the maximum daily dose is 16 mg. ACEON<sup>®</sup> is probably biopharmaceutics classification system (BCS) 2 (high solubility/low permeability). ACEON<sup>®</sup> demonstrates dose proportional PK. The absolute oral bioavailability is approximately 75%. ACEON<sup>®</sup> is mainly metabolized, and 30% is hydrolyzed to perindoprilat, the active metabolite. The clearance of perindoprilat and its metabolites is almost exclusively renal. The T<sub>max</sub> and T<sub>1/2</sub> of perindopril is 1 hour and 1-2 hours, respectively. The T<sub>max</sub> and T<sub>1/2</sub> of perindoprilat is 3-7 hours and 30-120 hours, respectively.

NORVASC<sup>®</sup> is available in 2.5, 5, and 10 mg tablets. The maximum daily dose is 10 mg. The recommended starting dose in adults is 5 mg daily and in small, fragile, or elderly patients or patients with hepatic insufficiency is 2.5 mg daily. The recommended starting dose in pediatric patients is 2.5 to 5 mg daily. NORVASC<sup>®</sup> is probably BCS 2 and demonstrates dose proportional PK. NORVASC<sup>®</sup> is mainly metabolized via CYP3A. The absolute oral bioavailability is 64-90%. The T<sub>max</sub> and T<sub>1/2</sub> of NORVASC<sup>®</sup> is 6-12 hours and 30-50 hours, respectively.

## 5 Sources of Clinical Data

The applicant submitted an electronic NDA. Electronic submissions and SAS datasets can be found at the following links:

<\\CDSESUB1\EVSPROD\NDA0205003\0000> (SDN 1, 3/21/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0001> (SDN 2, 4/4/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0002> (SDN 3, 4/8/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0003> (SDN 4, 4/25/2014)

Responses to Information requests can be found at the following links:

<\\CDSESUB1\EVSPROD\NDA0205003\0004> (SDN 5, 5/5/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0005> (SDN 6, 5/6/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0006> (SDN 7, 5/15/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0008> (SDN 9, 6/27/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0009> (SDN 10, 7/3/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0010> (SDN 11, 7/8/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0011> (SDN 12, 7/25/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0013> (SDN 14, 8/6/2014)  
<\\CDSESUB1\EVSPROD\NDA0205003\0014> (SDN 15, 8/14/2014)

[\\CDSESUB1\EVSPROD\NDA0205003\0015](#) (SDN 16, 8/18/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0016](#) (SDN 17, 8/25/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0017](#) (SDN 18, 9/3/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0018](#) (SDN 19, 9/12/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0019](#) (SDN 20, 9/17/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0020](#) (SDN 21, 9/18/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0021](#) (SDN 22, 9/23/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0022](#) (SDN 23, 10/9/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0023](#) (SDN 24, 10/14/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0024](#) (SDN 25, 10/16/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0025](#) (SDN 26, 10/31/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0026](#) (SDN 27, 11/20/2014)  
[\\CDSESUB1\EVSPROD\NDA0205003\0027](#) (SDN 28, 11/21/2014)

This 505 (b)(2) application relied on data from a phase 3 trial (Study X985400 (PATH)), a phase 2 trial with ABPM substudy (Study CL2-05985-005), and three pharmacokinetic studies as summarized below and in Table 8.

- Phase 3 Trial, Study X985400 (PATH) (“Perindopril Amlodipine for the Treatment of Hypertension (PATH): A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Efficacy and Safety of a Fixed-Dose Combination of Perindopril Arginine Plus Amlodipine Besylate versus Perindopril Erbumine and Amlodipine Besylate in Subjects with Essential Hypertension”)

Study X985400 (PATH) compared the highest strength of PRESTALIA<sup>®</sup> (14/10 mg) with the highest approved strength of the monotherapies (PERe 16 mg and AMLb 10 mg) and was conducted by XOMA (US) LLC in the US.

- Phase 2 Trial, Study CL2-05985-005, with an ABPM Substudy (“Efficacy and Safety of the Fixed Oral Low-Dose Perindopril Arginine 3.5 mg/Amlodipine 2.5 mg Combination Compared with Each Component (Perindopril Arginine 3.5 mg and Amlodipine 2.5 mg) and with Perindopril Arginine 5 mg and Amlodipine 5 mg. Randomized, Double-Blind, Placebo-Controlled Study over 8 Weeks in Hypertensive Patients”)

Study CL2-05985-005 compared the lowest strength of PRESTALIA<sup>®</sup> (3.5/2.5 mg) with the Servier monotherapies (PERa 3.5 mg, PERa 5 mg, AMLb 2.5 mg, AMLb 5 mg) and placebo. This study was conducted by Servier outside of the US.

- Three Pharmacokinetic Studies
  - Food Effect Study (Study X985401) (“A Phase 1, Single-Dose, Open-Label, Randomized, Two-Way Cross-Over Study of Food Effect on the Pharmacokinetics of XOMA 985 (Perindopril Arginine/Amlodipine Besylate) in Healthy Subjects”)
  - Bioequivalence (BE) Study (PKH-05985-001) (“Bioequivalence Study of One Tablet of the Fixed Combination of Perindopril Arginine 10 mg/Amlodipine 10 mg versus One Tablet of Perindopril Tert-Butylamine 8 mg plus one tablet of Amlodipine 10 mg, after Single Oral Dose, in Healthy Volunteers”)
  - Drug-Drug Interaction (DDI) Study (PKH-05985-009) (“Investigation of Potential Pharmacokinetic Interaction between Perindopril Arginine 14 mg and Amlodipine 10 mg, after Single Oral Dose, in Healthy Volunteers”)

The applicant also submitted a cross-study comparison to establish a PK bridge to ACEON<sup>®</sup> (NDA 20184) and NORVASC<sup>®</sup> (NDAs 22401 and 21540). Since Symplmed owns NDA 20184, Symplmed could rely on information from the ACEON<sup>®</sup> NDA with respect to perindopril/perindoprilat. The applicant also used information contained in the SBA for NORVASC (NDAs 22401 and 21540) for their cross-study comparison (not acceptable since the applicant does not own these NDAs). However, the Division did not need to rely on these data to establish a bridge and instead used data from the published literature submitted by the applicant (Vincent et al, 2000).

The applicant requested 3 biowaivers as follows:

1. A biowaiver for a comparative bioavailability study between PRESTALIA<sup>®</sup> (14/10 mg) and US approved ACEON<sup>®</sup> and NORVASC<sup>®</sup>
2. A biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier outside the US and the clinical studies conducted by XOMA (Patheon) in the US due to different manufacturers
3. A biowaiver for a dosage strength equivalence study

## 5.1 Tables of Studies/Clinical Trials

Table 7 summarizes the drug products used in the studies. Table 8 summarizes the studies included in the application.

**Table 7. Type of FDC and Monocomponent Tablets used in the 5 Clinical Trials**

Study	FDC Tablet	Mono-Component Tablets
Phase 3	PERa/AMLb 14/10 mg	PERe 16 mg (2 x 8 mg), AMLb 10 mg
Phase 2	PERa/AMLb 3.5/2.5 mg	PERa 3.5 mg, PERa 5.0 mg, AMLb 2.5 mg, AMLb 5 mg, Placebo
Food	PERa/AMLb 14/10 mg fed	PERa/AMLb 14/10 mg fasted
BE	PERa/AMLb 10/10 mg	PERe 8 mg + AMLb 10 mg
DDI	PERa/AMLb 14/10 mg	PERa 14 mg, AMLb 10 mg
PERa: perindopril arginine; PERe: perindopril erbumine; AMLb: amlodipine besylate. Yellow: PRESTALIA <sup>®</sup> ; White: Servier FDC and monocomponent tablets; Green: PERe 16 mg (AUROBINDO) and Generic NORVASC <sup>®</sup> tablets		

**Table 8. Clinical Studies**

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
Phase 3 Complete Final Clinical Study Report: 2013	X985400 (PATH)	To evaluate the efficacy of the fixed dose combination of PERa/AML 14/10 mg QD compared to PERe 16 mg QD and AML 10 mg QD in controlling sitting DBP in subjects with essential hypertension	Randomized, Double-blind, Parallel-group	Study Drug: PERa/AML 14/10 mg  Reference Products: PERe 16 mg AML 10 mg  1 capsule study drug or reference product daily for 6 weeks  Oral  2-3 week washout period, followed by 6 weeks double-blind active treatment period	837 male or female subjects $\geq 18$ and $\leq 75$ years of age, with hypertension defined as DBP $\geq 95$ mm Hg and $\leq 115$ mm Hg at Visit 2 (Day 0)
Phase 2 Complete Final Clinical Study Report 2012	CL2-05985-005 Main	To demonstrate a statistically significant and clinically relevant greater blood pressure-lowering effect with the PERa/AML 3.5/2.5 mg combination than with placebo; to demonstrate a statistically greater blood pressure-lowering effect with PERa/AML 3.5/2.5 mg combination	Randomized, Double-blind, Placebo-controlled	Study Drug: PERa/AML 3.5/2.5 mg  Reference Products: PERa 3.5 mg AML 2.5 mg	1581 male or female subjects $\geq 18$ to $< 80$ years of age, with mild to moderate uncomplicated hypertension (DBP $\geq 95$ to $< 110$ mm Hg and SBP $\geq 150$ to $< 180$ mm Hg, measured in the supine position) and requiring antihypertensive treatment

Clinical Review  
 Karen A. Hicks, M.D.  
 NDA 205003  
 PRESTALIA<sup>®</sup> (perindopril arginine/amlodipine besylate)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
		than with each monotherapy component (i.e., PERa 3.5 mg and AML 2.5 mg given separately); and to demonstrate that the blood pressure-lowering effect of the PERa/AML 3.5/2.5 mg fixed low-dose combination was not inferior to those of PERa 5 mg		PERa 5 mg AML 5 mg Placebo  1 capsule study drug or reference product daily for 8 weeks  Oral  8 weeks double-blind active treatment period	institution or a change due to lack of efficacy or poor tolerability
	CL2-05985-005 ABPM	To demonstrate a statistically greater ambulatory blood pressure-lowering effect with the PERa/AML 3.5/2.5 mg combination than with placebo		Same as main study	1297 subjects from Main Study
Phase 1 Complete Final Clinical Study Report 2013	X985401 (Food Effects)	To determine the effect of food on the rate and extent of absorption of PERa/AML 14/10 mg following a single oral dose in healthy subjects when administered in the fasted and fed state	2-day, Open-Label, Randomized, Crossover	PERa/AML 14/10 mg  Single dose of test product with either fasted or fed treatment  Oral  Single dose	18 healthy male or female subjects ≥ 18 to ≤ 55 years of age

Clinical Review  
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 NDA 205003  
 PRESTALIA<sup>®</sup> (perindopril arginine/amlodipine besylate)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
Phase 1 Complete Final Pharmacokinetic Study Report 2006	PKH-05985-001	To demonstrate the bioequivalence between 1 tablet of the fixed combination of PERa/AML 10/10 mg versus 1 tablet of PERe 8 mg plus 1 tablet of AML 10 mg, after single oral dose, in healthy volunteers	2-period, Open-label, Randomized, Crossover	Study Drug: PERa/AML 10/10 mg  Reference Products: PERe 8 mg AML 10 mg  Treatment 1: PERa/AML fixed combination Treatment 2: PERe 8 mg + AML 10 mg  Oral  2 single dose with a 3-week period between treatments	36 healthy male or female subjects $\geq 18$ to $\leq 40$ years of age
Phase 1 Complete Final Pharmacokinetic Study Report: 2010	PKH-05985-009	To determine the pharmacokinetic interaction between PERa 14 mg and AML 10 mg in healthy subjects	3-period, Open-label, Randomized, Crossover	Study Drug: PERa/AML 14/10 mg  Reference Products: PERa 14 mg AML 10 mg	24 healthy male or female subjects $\geq 18$ to $\leq 40$ years of age

Clinical Review  
 Karen A. Hicks, M.D.  
 NDA 205003  
 PRESTALIA<sup>®</sup> (perindopril arginine/amlodipine besylate)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration Duration of Treatment	No. and Type of Subjects
				Treatment 1: fixed combination of PERa/AML 14/10 mg  Treatment 2: PERa 14 mg  Treatment 3: AML 10 mg  Oral  3 single doses with 3-week period between treatments	
<p><b>PERa = perindopril arginine; PERe = perindopril erbumine; AML = amlodipine besylate; DBP = diastolic blood pressure; SBP = systolic blood pressure; QD = once daily; ABPM = ambulatory blood pressure monitoring.</b>  <b>Sources: X985400 Clinical Study Report , CL2-05985-005 Clinical Study Report, CL2-05985-005 ABPM Clinical Study Report, X985401 Clinical Study Report, PKH-05985-001 Clinical Study Report, and PKH-05985-009 Clinical Study Report.</b></p>					

## 5.2 Review Strategy

The focus of this review is on the pivotal phase 3 trial (Study X985400 (PATH)) and on the phase 2 trial (CL2-05985-005) with the ABPM substudy.

## 5.3 Discussion of Individual Studies/Clinical Trials

The phase 3 trial (Study X985400 (PATH)) was conducted by XOMA (US) LLC at 59 centers in the United States. The phase 2 trial (Study CL2-05985-005) was conducted by Servier at 164 centers in France (115 centers, 431 patients), Russian Federation (20 centers, 562 patients), Ukraine (9 centers, 169 patients), Lithuania (8 centers, 142 patients), Hungary (6 centers, 125 patients), and Latvia (6 centers, 152 patients). The ABPM substudy was conducted at 158 centers (same sites as for the main study except for only 110 centers in France).

The design of these two trials is discussed in Sections 5.3.1 and 5.3.2.

### 5.3.1 Study X985400 (PATH)

#### 5.3.1.1 Trial Dates

Study X985400 (PATH) was conducted at 59 US sites from February 17, 2012 through October 9, 2012. The first patient was randomized on February 24, 2012, and the last patient was randomized on August 22, 2012. The date of final patient contact was October 9, 2012. Database lock occurred on November 9, 2012.

#### 5.3.1.2 Study Design and Objectives

Study X985400 (PATH) was a phase 3, multicenter, randomized, double-blind, parallel-group trial in subjects with moderate to severe hypertension, defined as a mean seDBP  $\geq 95$  mm Hg and  $\leq 115$  mm Hg at Visit 2 (Day 0). The primary objective was to evaluate the effectiveness of PERa/AMLb 14/10 mg compared to PERe 16 mg and AMLb 10 mg taken once daily for 6 weeks in controlling seDBP.<sup>1</sup> At the time the study was designed, the applicant reported that PERe 16 mg was bioequivalent to PERa 20 mg.

This study consisted of a screening visit, a 2 to 3-week washout period, and a 6-week double-blind treatment period. Eligible subjects meeting entry criteria were randomized in a 1:1:1 fashion to PERa/AMLb 14/10 mg, AMLb 10 mg, or PERe 16 mg once daily at Visit 2 (Day 0), as shown in Figure 1. Randomization was stratified by the following

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<sup>1</sup>PERe 16 mg is bioequivalent to PERa 20 mg.

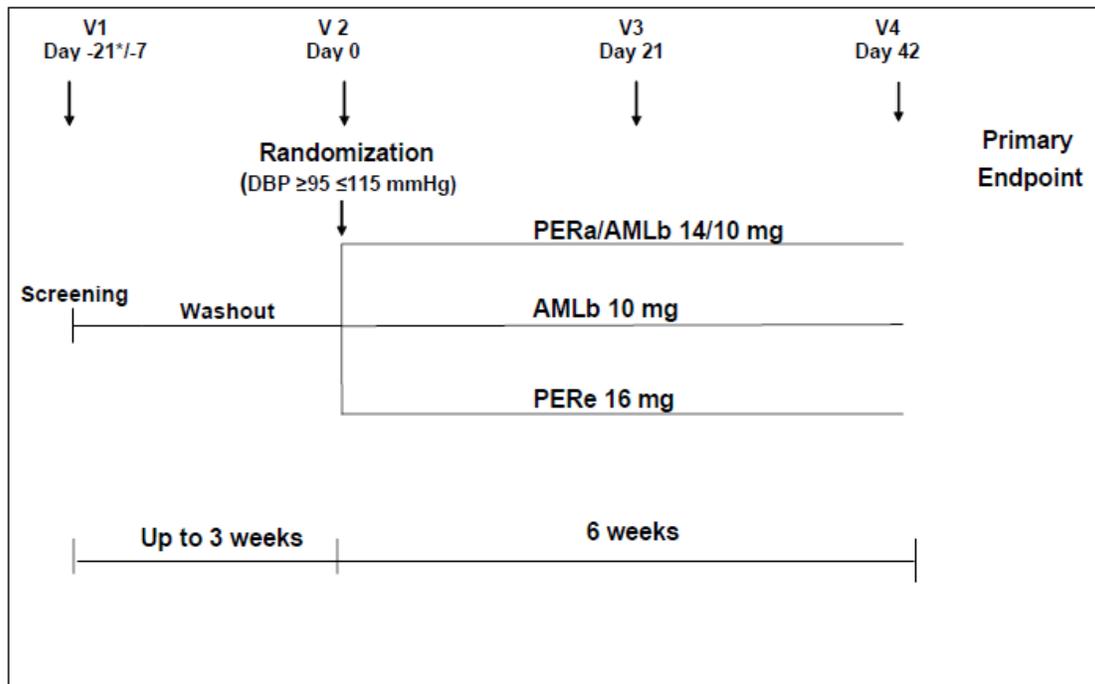
variables: current type 2 diabetes status (yes versus no), race (black versus non-black), baseline DBP (< 100 mm Hg versus ≥ 100 mm Hg), and per SAP Appendix, site.

At each visit, BP was measured using an OMRON automatic BP monitor model HEM-705CP. The clinic BP reference value for each subject was the average of 3 serial measurements taken at 2-minute intervals after the subject had rested for at least 5 minutes in a sitting position. A mean diastolic and systolic BP for each visit was calculated and was based on nonmissing measurements. Baseline mean seated BP (seBP) was established using the average of three measurements taken at Visit 2 (Day 0).

Subjects were to return for study visits on Days 21 (± 3 days) and 42 days (± 3 days). All study visits were to occur in the morning after a 10 hour fast and before study drug intake.

Eligible subjects who were receiving antihypertensive medications at Visit 1 (Screening) were to discontinue all antihypertensive drugs to begin a 2-3-week washout period. Eligible treatment naïve subjects could be randomized within 7 days (± 3 days) of Visit 1 (Screening).

**Figure 1. Study Design (X985400)**



\*Day -21 if subject requires washout of antihypertensive medication. Day -7 if subject is treatment-naïve and no washout is required.

(Original Protocol, page 81)

Subjects could be discontinued from the trial for reasons to include but not be limited to the occurrence of hyperkalemia (potassium  $\geq 5.5$  mEq/L), if the subject required the addition of another antihypertensive agent during double-blind treatment, or if the mean seSBP exceeded 180 mm Hg or seDBP exceeded 115 mm Hg (measured at the clinical site).

### **5.3.1.3 Blood Pressure Monitoring**

At all study visits, seSBP/seDBP and heart rate were measured using an OMRON automatic BP monitor, model HEM-705CP. SeBPs were taken with the subject sitting upright, with both feet touching the floor, and with the subject's arm supported at the level of the heart. Three separate, consecutive blood pressure and heart rate measurements were recorded at 2-minute intervals after the subject had been sitting quietly for at least 5 minutes. The three measurements were averaged to establish the mean blood pressure for that visit. Baseline mean seated BP (seBP) was established using the average of three measurements taken at Visit 2 (Day 0). At post-randomization visits, these measurements were taken approximately 24 hours after the last dose of study drug (trough). If these measurements were taken more than 36 hours after the last dose of study drug, the measurements were considered non-valid and excluded from efficacy analyses.

At Visit 1 (Screening), BP was measured in each arm. The arm that had the higher of the two mean DBPs was used for measuring BP throughout the study. For the purposes of determining eligibility (SBP at Visit 1 [Screening]) and Visit 2 [Day 0]) or subject withdrawal, the mean BP was used.

A large cuff provided with the machine could be used for a maximum arm size of 42 cm. If a subject's arm size exceeded the maximum limit of 42 cm, the subject was excluded from the study.

### **5.3.1.4 Inclusion and Exclusion Criteria**

Key inclusion criteria were

1. Essential hypertension defined as a mean seDBP  $\geq 95$  mm Hg and  $\leq 115$  mm Hg at Visit 2 (Day 0)
2.  $\geq 18$  and  $\leq 75$  years of age
3. For female subjects, a negative serum pregnancy test
4. For male and female subjects with reproductive potential, a willingness to have used contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the trial.

5. For subjects who previously received antihypertensive medication, the ability to have stopped antihypertensive therapy for the duration of the trial (21-day washout and 42-day treatment period) without unacceptable risk to the subject (Investigator's discretion)
6. Written informed consent

Key exclusion criteria were

1. Known or suspected secondary hypertension (e.g., renal artery stenosis, pheochromocytoma)
2. Mean seated SBP  $\geq$  180 mm Hg at Visit 1 (Screening) and Visit 2 (Day 0)
3. Renal dysfunction with a known creatinine clearance  $<$  60 mL/min using the Cockcroft-Gault calculation or clinical markers of severe renal impairment
4. Bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, subjects with only 1 kidney, or post-renal transplant subjects
5. Clinically significant hypokalemia or hyperkalemia (defined as potassium  $<$  3.0 or  $>$  5.1 mEq/L).
6. Uncorrected sodium or volume depletion
7. History of malignancy within 5 years prior to Visit 1 (Screening) other than carcinoma in situ of the cervix or adequately treated, non-metastatic carcinoma of the skin
8. Primary aldosteronism
9. Laboratory values (Visit 1 [Screening])
  - Alanine transaminase/serum glutamyl pyruvic transaminase [ALT/SGPT] or aspartate transaminase/serum oxaloacetic transaminase ([AST/SGOT])  $>$  3 x upper limit of normal (ULN)
  - Total bilirubin  $>$  2 x ULN
  - Potassium  $>$  5.1 mEq /L
10. Heart failure (New York Heart Association functional class 3-4), hypertrophic obstructive cardiomyopathy, or hemodynamically relevant stenosis of the aortic or mitral valve
11. Myocardial infarction, stroke, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or unstable angina within 6 months prior to Visit 1 (Screening)
12. Ventricular tachycardia, atrial fibrillation, atrial flutter, or other clinically significant cardiac arrhythmias, as determined by the Investigator
13. Subjects with a history of angioedema during treatment with ACE inhibitors or angiotensin-II receptor antagonists
14. Concomitant medications known to have affected blood pressure, except medications specifically allowed by the protocol

### 5.3.1.5 Prohibited Concomitant Medications

From Visit 1 (Screening) through the end of the trial (Visit 4 [Day 42/EOT]), the following medications were prohibited:

- Antihypertensive medication including thiazide diuretics, loop diuretics, potassium-sparing diuretics, anti-adrenergic, alpha- and beta-blockers, CCBs other than study drug, ACE inhibitors other than study drug, angiotensin II antagonists, and vasodilators
- Vasoactive agents (stable doses of nitrates were permitted)
- Antithyroid agents (stable dosage of thyroid replacement therapy, if stable for at least 3 months prior to Visit 1 [Screening])
- Amphetamines, amphetamine derivative agents, and weight loss medications (prescription or over-the-counter)
- Aspirin therapy > 325 mg/day or other non-steroidal anti-inflammatory drugs (NSAIDs) for more than 5 consecutive days (stable doses from Visit 1 [Screening] through the end of the trial and intermittent use for up to 5 consecutive days permitted)
- Potassium supplements, lithium, gold (sodium aurothiomalate), and gentamicin
- Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir)

### 5.3.1.6 Primary Endpoint

The primary endpoint was the change from baseline (Visit 2 [Day 0]) to Visit 4 (Day 42/EOT) in mean seDBP at trough.

### 5.3.1.7 Secondary Endpoints

Secondary endpoints included

1. change from baseline (Visit 2 [Day 0]) to Visit 4 (Day 42/EOT) in mean seSBP at trough
2. the number of subjects considered to be responders after treatment. A responder was defined as a subject who, after treatment, achieved a target blood pressure goal of < 140/90 mm Hg (or a target blood pressure goal of < 130/80 mm Hg if the subject had diabetes)

**Reviewer's Comments:** *The responder analysis was not prespecified as a secondary endpoint in the original protocol, Protocol Amendment 1, or Statistical Analysis Plan (SAP). This parameter was listed as a secondary endpoint in the Clinical Study Report only.*

### 5.3.1.8 Statistical Analysis Plan and Amendments

This review was based on the Statistical Analysis Plan dated August 30, 2012. See Section 6.1.10 for a detailed description of the Minimization Algorithm used in this trial.

The primary efficacy analysis was intent-to-treat which included all randomized subjects who took at least one dose of study drug and provided at least one valid post-randomization blood pressure assessment value for DBP. If no valid DBP measurements were obtained at Visit 4 (Day 42/EOT), the last valid post-randomization assessments was used per the last observation carried forward (LOCF) algorithm.

The applicant used an analysis of covariance model (ANCOVA) with treatment as a main effect and baseline DBP, current type 2 diabetes status (yes versus no), and race (black versus non-black) as covariates.

The secondary efficacy analysis was similar to that conducted for the primary analysis.

No interim analysis was formally planned for this trial but would be re-evaluated in a blinded fashion when 75% of the subjects had been randomized and their baseline DBP was available.

#### 5.3.1.10 Protocols and Amendments

The review of Study X985400 was based on the original protocol dated July 19, 2011 and a Protocol Amendment dated January 27, 2012.

##### The Protocol Amendment

- modified the list of medications that were prohibited from Visit 1 through the end of the study. Alpha- and beta-blockers, which had been permitted at a stable dose if used for pathology other than hypertension, were prohibited without exception. Potassium-sparing diuretics were removed from the list of prohibited medications. Potassium supplements, lithium, gold, and gentamicine, which had been prohibited only for subjects randomized to receive PERe 16 mg, were prohibited for all subjects. Strong CYP3A4 inhibitors, which had been prohibited only for subjects randomized to receive AMLb 10 mg, were prohibited for all subjects
- modified the 3-week washout period to a 2-3 week washout period at the discretion of the Investigator
- clarified that randomization could take place 7 days after Visit 1 (Screening)  $\pm$  3 days
- clarified the inclusion criterion regarding contraception in subjects as well as 3 exclusion criteria with respect to hypo- or hyperkalemia, removal of exclusion of subjects with severe obstructive coronary artery disease, and prior treatment in a study with an investigational drug or device

- clarified that BP was to be measured 24 hours after dosing (i.e. trough). If BP measurements were taken more than 36 hours after the last dose of study drug, the measurements were considered non-valid and were excluded from efficacy analyses
- instructed subjects on how to monitor blood pressure at home. Subjects were to obtain three separate, consecutive BP measurements at 2-minute intervals after sitting quietly for at least 5 minutes. BP was also to be monitored every other day.
- advised subjects to check BP if they were symptomatic. Subjects were instructed to contact the clinic if mean seSBP > 180 mm Hg or mean seDBP > 115 mm Hg or if the mean seSBP < 90 mm Hg or , mean seDBP < 60 mm Hg. Amendment 1 also clarified that for a subject to be discontinued from the trial, the mean seSBP and seDBP exceeding 180 mm Hg and 115 mm Hg, respectively, would have to be measured at the clinical site.
- instructed subjects to take BP at least 30 minutes after waking. Prior to measuring BP, subjects were instructed to fast for at least 10 hours and not take any medications (including study drug).
- no longer allowed the use of antihypertensives for other pathologies even if the dose was stable during the trial (prohibited concomitant medications)

#### **5.3.1.11 Schedule of Procedures**

The schedule of procedures for Study X985400 is displayed in Table 9. Safety assessments included physical examinations, vital signs, 12-lead electrocardiograms, laboratory testing, and adverse event reporting.

**Table 9. Schedule of Procedures (S985400) (PATH)**

ASSESSMENTS PERFORMED	STUDY PERIOD			
	Screening/Washout	6-Week, Double-Blind Treatment Period		
		Randomization		
Visit Number	1	2	3	4/EOT
Day	-21/-7 <sup>d</sup>	0	21	42
Visit Window	± 3 d	± 3 d	± 3 d	± 3 d
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Medical history and demographics <sup>a</sup>	X			
Physical examination	X			X
Height	X			
Weight	X			X
Confirm subject has not taken study drug dose			X	X
Blood pressure and heart rate	X	X	X	X
12-lead ECG	X			X
Blood chemistry	X		X	X
Hematology	X			X
Urinalysis (dipstick)	X			X
Serum pregnancy test <sup>b</sup>	X			X
Concomitant medications	X	X	X	X
Adverse events		X	X	X
Collect study drug bottle and assess compliance			X	X
Dispense study drug bottle <sup>c</sup>		X	X	
Study drug administration		X	X	

<sup>a</sup> Medical history includes information on prior and concomitant medications; prior and current diagnoses, conditions, and surgeries that are considered significant; and tobacco, alcohol, and drug use.

<sup>b</sup> Serum pregnancy test will be administered to all female subjects, regardless of childbearing potential.

<sup>c</sup> Subject will be instructed to return all unused study drug at Visits 3 and 4.

<sup>d</sup> For subjects not needing withdrawal from exclusionary medications, randomization may take place 7 days from Visit 1 (Screening) (± 3 days). Subjects currently receiving antihypertensive medication who have met all of the eligibility criteria at Visit 1 (Screening) will discontinue all antihypertensive drugs to begin a 2- to 3-week washout period at the discretion of the Investigator.

(Protocol Addendum 1, Appendix A, page 49)

### **5.3.2 Study CL2-05985-005 and ABPM Substudy**

#### **5.3.2.1 Trial Dates**

Study CL2-05985-005 (main study) was conducted from May 19, 2007 to December 30, 2008. The first patient was randomized on June 1, 2007, and the last patient was randomized on October 31, 2008. The date of the final patient contact was December 30, 2008. Database lock occurred on May 29, 2009.

Study CL2-05985-005 (ABPM substudy) was conducted from May 19, 2007 to December 30, 2008. The first patient was randomized on June 8, 2007, and the last patient was randomized on October 31, 2008. The date of the final patient contact was December 30, 2008. Database lock occurred on May 29, 2009.

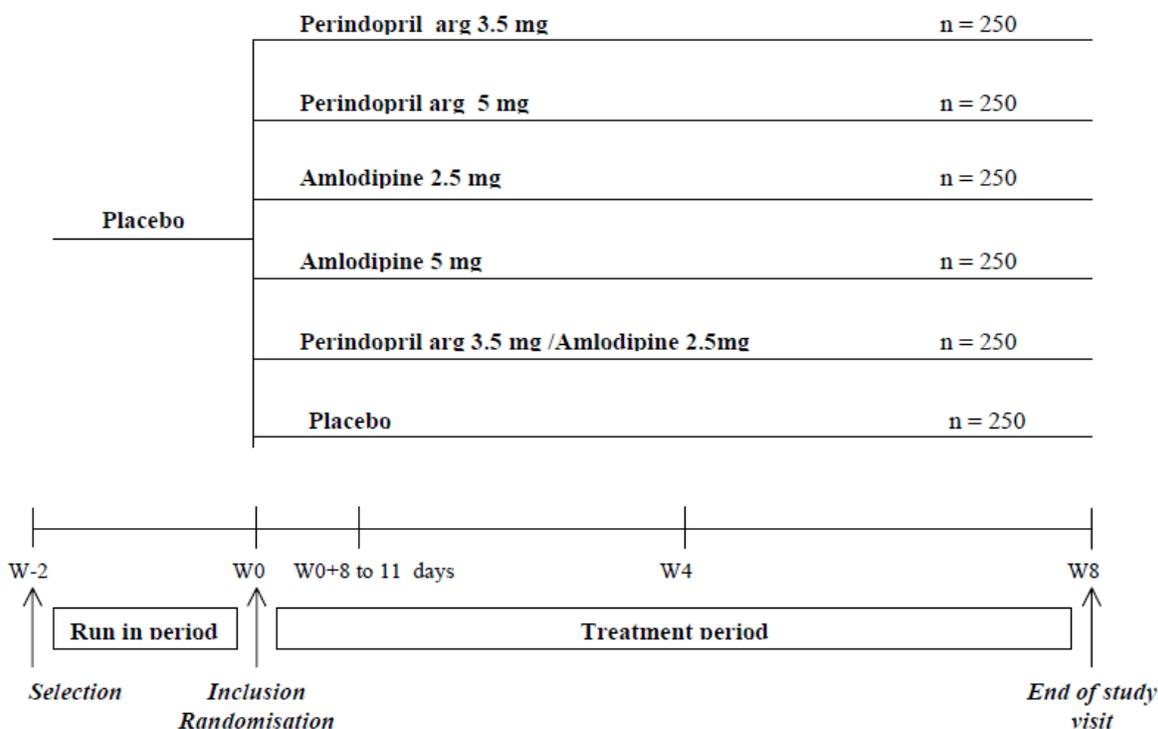
#### **5.3.2.2 Study Design and Objectives**

Study CL2-05985-005 was a phase 2, multicenter, randomized, double-blind, placebo-controlled study with a factorial design in 1581 subjects with mild to moderate hypertension, defined as  $95 \leq \text{DBP} < 110$  mm Hg and  $150 \leq \text{SBP} < 180$  mm Hg. An ABPM substudy was conducted in 1297 subjects. Study CL2-05985-005 compared the lowest strength of the Servier combination product (PERa/AMLb 3.5/2.5 mg) with the Servier monotherapies (PERa 3.5 mg, PERa 5 mg, AMLb 2.5 mg, AMLb 5 mg), and placebo. Randomized treatment was stratified by center. Study duration was 8 weeks. Approximately 98% of subjects were Caucasian, 52% of subjects were women, and 13% of subjects were  $\geq 65$  years of age.

Hypertensive patients were to have 2 – 3 weeks of placebo run-in (Selection [SEL] to Week 0) followed by an 8-week double-blind, randomized, active treatment period (Week 0 to Week 8).

Patients were provided with an automatic arm blood pressure device at the SEL visit and were instructed to measure BP twice a week (3 consecutive measurements in the morning) and to report the SBP and DBP values in a patient diary. Patients were to contact the investigator if  $\text{DBP} \geq 100$  mm Hg and/or  $\text{SBP} \geq 160$  mm Hg at the 3 consecutive measurements.

**Figure 2. Study Design (Study CL2-05985-005)**



(SAP, Main Study, Figure 1, page 3105)

### 5.3.2.3 Blood Pressure Monitoring

In the main study, BP was measured with a Microlife BP3AC1-1 automatic arm blood pressure device. Blood pressure was measured at Selection and at Weeks 0, 2, 4, and 8 in the supine position after at least 10 minutes of rest. The mean of 3 measurements at 1 minute intervals was determined. At all visits except at Selection, BP was also measured 1 and 3 minutes after standing up to assess the patient for orthostatic hypotension.

For the ABPM substudy, a validated ABPM device (Spacelabs 90207) was used. Patients were to take placebo for at least 10 days prior to the Week 0 visit. The ABPM device was applied 1-2 days prior to the Week 0 visit and was removed after at least 25 hours (i.e., 1 day before Week 0 or at Week 0). Pre-validation of the ABPM data was performed on site. Once the ABPM data were prevalidated, the investigator performed the Week 0 visit and transmitted the data to Medifacts for dataset entry. A copy of the ABPM report was sent to the investigator and the ABPM Corelab accessed the electronic ABPM report for definitive validation. If ABPM data were not prevalidated,

ABPM procedures could be repeated once within 1 to 2 days of assessment. If the second attempt was unsuccessful, the patient could continue in the main study but would be excluded from the ABPM substudy.

At Week 8, ABPM was performed on those patients who had a valid ABPM at Week 0 (i.e., pre-validation using site-specific software (Medicom) and definitive validation by the Corelab). The ABPM device was applied 1-2 days before Week 8 (later changed to up to 7 days prior to Week 8). The ABPM was removed after at least 25 hours (i.e., 1 day before Week 8 or at Week 8) and the data were pre-validated in a similar manner as previously described. If the ABPM data were pre-validated, the investigator would perform the Week 8 Visit.

#### **5.3.2.4 Inclusion and Exclusion Criteria**

Key inclusion criteria were

1. Men or women, 18 to 80 excluded years old with written informed consent
2. Outpatients with essential mild to moderate uncomplicated hypertension, defined as  $95 \leq \text{DBP} < 110$  mm Hg and  $150 \leq \text{SBP} < 180$  mm Hg measured with a validated automatic device in the supine position after initiation or intensification of appropriate healthy lifestyle modification, without antihypertensive treatment or not controlled under antihypertensive treatment and requiring a change due to lack of efficacy or poor tolerability in the investigator's opinion at the selection visit
3. Patients without known associated clinical conditions according to 2003 ESH guideline (i.e. not at very high cardiovascular risk patients), without type I and II diabetes and without known target organ damage such as left ventricular hypertrophy and microalbuminuria, in order to be able to go untreated during the study if in placebo arm

Key exclusion criteria were

1. Obesity, defined as a body mass index  $> 30 \text{ kg/m}^2$
2. Hypertension treated with more than 1 antihypertensive drug
3. Secondary hypertension (including known renal parenchymal hypertension, renovascular hypertension, pheochromocytoma, primary aldosteronism, Cushing's syndrome, coarctation of the aorta, drug-induced hypertension, liquorice-induced hypertension)
4. History of cerebrovascular disease: ischemic stroke, cerebral hemorrhage, transient ischemic attack
5. History of heart disease: myocardial infarction, angina, coronary revascularization, heart failure
6. History of renal disease: known renal impairment (serum creatinine  $> 133 \mu\text{mol/l}$  in men and  $> 124 \mu\text{mol/l}$  in women)
7. Known peripheral vascular disease
8. Known advanced retinopathy: hemorrhage or exudates, papilledema

9. Known left ventricular hypertrophy
10. Known microalbuminuria (30-300 mg/24 hour; albumin-creatinine ratio of  $\geq 22$  mg/g in men and  $\geq 31$  mg/g in women or  $\geq 2.5$  mg/mmol in men and  $\geq 3.5$  mg/mmol in women)
11. Type I and II diabetes mellitus (non diabetic patients with metabolic syndrome can be selected)
12. Known severe aortic or mitral valve stenosis or hypertrophic obstructive cardiomyopathy
13. Any history of significant hepatic, endocrine, and gastrointestinal disorders or other known severe disease, including infection and neoplasm
14. History of significant hepatic, endocrine, and gastrointestinal disorders
15. Known symptomatic hypotension
16. History of neutropenia ( $< 1500/\text{mm}^3$ ) or known hyperkalemia

#### 5.3.2.5 Prohibited/Allowed Concomitant Medications

Prohibited medications included

- Tricyclic antidepressants, antipsychotics, lithium
- Non-steroidal anti-inflammatory drugs, salicylates including aspirin
- Anesthetic medicinal products
- Potassium supplements or potassium-containing salt substitutes
- Immunosuppressants
- Allopurinol, procainamide, heparin
- Diuretics, including potassium sparing
- Glucocorticoids and mineralocorticoids
- Baclofen, dantrolene, itraconazole, ketoconazole, rifampin, digoxin
- Nitrates, molsidomine, hydralazine, beta-blocking agents including beta-blocker eye-drops, vasodilators, alpha 1-blockers, other antihypertensive drugs
- Oral hypoglycemics
- Insulin
- Non-antiarrhythmic drugs producing torsades de pointe: astemizole, bepridil, erythromycin IV, halofantrine, pentamidine, sultopride, terfenadine, vincamine
- Anti-arrhythmic drugs producing torsades de pointe: sotalol, amiodarone, bretylium, and group Ia antiarrhythmic drugs (quinidine, hydroquinidine, disopyramide)

The following medications were permitted under certain conditions:

- Aspirin at antiaggregant doses  $\leq 350$  mg/day
- Oral non-steroidal anti-inflammatory drugs or corticosteroids for periods  $\leq 10$  days provided they are not taken in the 5 days preceding a visit
- Topical non-steroidal anti-inflammatory drugs and topical corticosteroids

### 5.3.2.6 Primary Endpoint

The primary endpoint was the change from baseline (Week 0) to Week 8 (or last on-treatment post-baseline value) in mean suDBP at trough or in mean 24 hour DBP (ABPM substudy).

### 5.3.2.7 Secondary Endpoints

The secondary endpoints were :

- change from baseline (Week 0) to Week 8 (or last on-treatment post-baseline value) in mean suSBP at trough or in mean 24 hour SBP (ABPM substudy)
- Response to treatment defined as 1) SBP < 140 mm Hg and DBP < 90 mm Hg; and/or 2) decrease in SBP  $\geq$  20 mm Hg from baseline; and 3) and/or decrease in DBP  $\geq$  10 mm Hg from baseline
- Normalization of blood pressure, defined as SBP < 140 mm Hg and DBP < 90 mm Hg
- Pulse pressure (PP = SBP – DBP) and mean blood pressure (MBP =  $2/3 + 1/3$  SBP) assessed using validated automatic device
- Mean blood pressure

The secondary endpoints for the ABPM substudy were:

- Mean SBP over 24 hours (mean 24h SBP)
- Mean SBP and DBP over standard diurnal period (between 9 a.m. and 9 p.m.)
- Mean SBP and DBP over standard nocturnal period (between 1 a.m. and 6 a.m.)
- Mean SBP and DBP over real diurnal period (based on the diary information)
- Mean SBP and DBP over real nocturnal period (based on the diary information)
- Mean DBP and SBP over the last 6 hours of measurement before treatment intake
- Hourly means for SBP and DBP
- Pulse pressure (PP=SBP – DBP) over 24-hour, diurnal and nocturnal periods
- Individual smoothness index (SI =  $\Delta H/SD\Delta H$ ) for SBP and DBP.  $\Delta H$  is the mean treatment induced BP reduction for each hour during the 24-hour period and  $SD\Delta H$  is the standard deviation of that mean
- Trough-to-peak ratio (TPR). TPR will be calculated using individual trough (T) and Peak (P) changes from baseline. T and P changes will be calculated by considering the 2-hour BP means of respectively minimal drug efficacy and maximal drug effect
- Nocturnal fall (calculated as  $[(\text{mean diurnal BP} - \text{mean nocturnal BP}/\text{mean diurnal BP}) * 100]$  for SBP and DBP
- Mean DBP and SBP over the morning period, i.e. over the first 2 hours after wake-up time (morning BP)
- Morning blood pressure rise (morning BP – lowest BP) for SBP and DBP. The lowest BP is defined as the hourly mean centered on the lowest night-time reading.

- 24 hours blood pressure standard deviation (24-h BP SD) for SBP and DBP
- Percentage of dippers (> 10% and < 20% nocturnal SBP and DBP decrease), non-dippers (> 0% and < 10% nocturnal SBP and DBP decrease), extreme dippers (> 20% nocturnal SBP and DBP decrease) and reverse-dippers (< 0% nocturnal SBP and DBP decrease). The nocturnal BP decrease will be calculated as  $100(1 - \text{mean nocturnal BP}/\text{mean diurnal BP})$
- Ambulatory arterial stiffness index (AASI = 1 – regression slope of diastolic on systolic BP)
- Mean HR over 24-hour, diurnal period and nocturnal periods

### 5.3.2.8 Statistical Analysis Plan and Amendments

For the main study and the ABPM substudy, the review of Study CL2-05985-005 was based on the original SAP and one addendum, both dated May 29, 2009.

See Section 6.1.4.2 for further details with respect to the primary analyses including three superiority comparisons and two non-inferiority comparisons.

### 5.3.2.9 Protocol and Amendments

The review of Study CL2-05985-005 was based on the original protocol dated December 11, 2006, and two Protocol Amendments dated January 9, 2008 and February 23, 2009.

#### Amendment 1

- Extended the study to December 2008 in order to reach the targeted number of patients
- Added atrial fibrillation and atrial flutter to the exclusion criteria
- Clarified lifestyle recommendations and efficacy secondary endpoints (pulse pressure and mean blood pressure)
- Specified SBP and DBP instead of BP in the calculation of Trough-to-Peak ratio (TPR) among the secondary endpoints

#### Amendment 2

- Added a composite endpoint for the analysis of edema
- Included the ankle circumference measurement to the Case Report Form for the assessment of leg edema

### 5.3.2.10 Schedule of Procedures

The schedule of procedures for Study CL2-05985-005 (Main Study) is displayed in Table 10. Safety assessments included physical examinations, vital signs, ambulatory blood pressure monitoring (substudy), 12-lead electrocardiograms, laboratory testing, leg edema assessment, and adverse event reporting. The schedule of procedures for the ABPM substudy is shown in Table 11.

**Table 10. Schedule of Procedures (Study CL2-05985-005, Main Study)**

	Selection SEL*	Inclusion W0	Treatment period		
			W2 ± 2 days	W4 ± 3 days	W8 ± 5 days
Informed consent	X				
Selection / inclusion criteria	X	X			
Medical and surgical history	X				
Physical examination	X	X	X	X	X
Waist circumference, height	X				
β HCG test results (for non menauposal women)		X			
Compliance**		X		X	X
<b>Efficacy measurements</b>					
Blood pressure (automatic device at the office)	X	X	X	X	X
<b>Safety measurements</b>					
Heart rate, weight	X	X	X	X	X
Blood pressure supine	X	X	X	X	X
Blood pressure standing (orthostatic hypotension)		X	X	X	X
Adverse events		X	X	X	X
Leg edema assessment		X	X	X	X
Concomitant treatments	X	X	X	X	X
Complete laboratory tests ***		X			X
Simplified laboratory tests ****			X		
ECG results		X			X
<b>Allocation of treatments</b>	P0	P1		P2	

\*: at least 2 weeks and no more 3 weeks before W0

\*\* : calculated by the investigator at W0 (based on tablet count), but only tablet count at W4 and W8

\*\*\*: sampling after overnight fasting, including haematology (haemoglobin, haematocrit, red blood cell, white blood cell and platelets counts), biochemistry (sodium, potassium, creatinin, total protein, ASAT, ALAT, gammaglutamyl-transferase, total cholesterol, HDL cholesterol, Friedwald's formula LDL cholesterol, triglycerides, glycaemia) prescribed at SEL and W4.

\*\*\*\* : sampling after overnight fasting, simplified laboratory tests (creatinine, potassium) prescribed at W0 visit, performed 3 to 5 days prior W2 visit in order to have results available at W2 visit.

(SAP, Figure 2, page 3106)

**Table 11. Schedule of Procedures (Study CL2-05985-005, ABPM Study)**

	Selection (SEL)*	Inclusion (W0)	Treatment period		
			(W2) ± 2 days	(W4) ± 3 days	(W8) ± 5 days
Informed consent for participation in the ABPM ancillary study	X				
Selection/inclusion criteria	X	X			
<b>ABPM measurements **</b>		X			X
Treatment start		X			

\* SEL: at least 2 weeks and no more than 3 weeks before W0

\*\* ABPM applied 1 day (and no more than 2 days) before visits and removed the following day. One retest is allowed.

(Protocol, Figure 8.2.2, page 19/35 and Volume 2, page 26/3564)

### 5.3.2.11 Withdrawal Criteria

Study treatment was to be withdrawn prematurely for the following reasons:

- Onset of adverse event which presented a risk to the patient
- Renal function impairment with creatinine clearance decrease  $\geq 30\%$ , assessed with the Cockcroft-Gault formula
- Increased potassium level above the upper limit of normal, confirmed with a second blood sample in the following week
- Pregnancy
- Worsening of hypertension defined as supine DBP (mean of 3 measurements)  $\geq 110$  mm Hg and/or supine SBP (mean of 3 measurements)  $\geq 180$  mm Hg, and/or acute hypertensive events (acute retinopathy, acute eye hemorrhage, CNS alterations, chest pain)
- Patient decision

## 6 Review of Efficacy

### **Efficacy Summary**

See Section 1.2.1.

### **6.1 Indication**

The proposed indication is for “the treatment of hypertension.”

#### **6.1.1 Methods**

The pivotal trials were examined separately. Study X985400 was conducted by XOMA (US) LLC at 59 US sites and was a phase 3, 6-week, multicenter, randomized, double-blind, parallel group trial in 837 subjects with moderate to severe hypertension. Study CL1-05985-005 was conducted by Servier at 164 sites in France, the Russian Federation, the Ukraine, Lithuania, Hungary, and Latvia, and was a phase 2, 8-week, multicenter, randomized, double-blind, placebo-controlled study with a factorial design in 1581 subjects with mild to moderate hypertension. A total of 1297 of these subjects were enrolled in the ABPM substudy.

##### **6.1.1.1 Study X985400 Analysis Populations**

The “ITT population” was defined as all randomized subjects who had taken at least one dose of study drug and had at least one post-baseline blood pressure assessment value for DBP. The “ITT population” included a total of 820 subjects (271 subjects in the PERa/AMLb 14/10 mg group, 274 subjects in the PERe 16 mg group, and 275 subjects in the AMLb 10 mg group). There were eight patients in the combination arm, 4 patients in the PERe arm, and 5 patients in the AMLb arm that were excluded from the primary analysis because they did not have post-baseline blood pressure assessments.

##### **6.1.1.2 Study CL2-05985-005 Analysis Populations**

The randomized set was defined as all included patients to whom a therapeutic unit was randomly assigned using the interactive voice response system (IVRS). The full analysis set was defined as all randomized patients who had taken at least one dose of study treatment and who had at least one baseline value and one post-baseline value of DBP. The safety set included all patients who took at least one dose of study treatment. The analysis sets are summarized in Table 12.

**Table 12. Analysis Sets (Study CL2-05985-005)**

<b>Analysis Sets</b>		<b>PERa/AMLb 3.5/2.5 mg</b>	<b>Placebo</b>	<b>PERa 3.5 mg</b>	<b>AMLb 2.5 mg</b>	<b>PERa 5 mg</b>	<b>AMLb 5 mg</b>	<b>All</b>
<b>Randomized Set</b>	n (%)	248 (15.7)	250 (15.8)	273 (17.3)	274 (17.3)	272 (17.2)	264 (16.7)	<b>1581</b>
<b>Efficacy Sets</b>	n (%)							
<b>Full Analysis Set (FAS)</b>	n (%)	246 (15.7)	248 (15.9)	268 (17.1)	270 (17.3)	270 (17.3)	261 (16.7)	<b>1563</b>
<b>Per Protocol Set (PPS)</b>	n (%)	236 (16.0)	235 (16.0)	248 (16.8)	252 (17.1)	257 (17.4)	245 (16.6)	<b>1473</b>
<b>Safety Set</b>	n (%)	249 (15.7)	251 (15.9)	273 (17.2)	274 (17.3)	272 (17.2)	264 (16.7)	<b>1583</b>
<p>This table is based on actual treatment.            AMLb = amlodipine besylate; PERa = perindopril arginine.            Source: Clinical Study Report, Table 10.3, page 74.</p>								

## 6.1.2 Demographics

### 6.1.2.1 Study X985400

Demographic and baseline characteristics for Study X985400 are summarized in Table 13. The mean age of the randomized subjects was 51.4 years. Approximately 64.5% of the population was Caucasian and 34.3% of the subjects were Black. Approximately 48.6% of the study population was female and 20.4% of the subjects had diabetes type 2. Only 7% of subjects were  $\geq 65$  years of age. The population was relatively obese with a mean body mass index of 33.1 kg/m<sup>2</sup>. Approximately 67.7% of subjects required washout from prior antihypertensive medication.

Key demographic characteristics were generally well-balanced between treatment groups. The PERe treatment group had a lower percentage of subjects < 65 years of age and a higher percentage of women than the other treatment groups.

**Table 13. Demographic and Baseline Characteristics (All Randomized Subjects)  
 (Study X985400)**

<b>Characteristic Statistic</b>	<b>PERa/AMLb 14/10 mg QD (N = 279)</b>	<b>PERe 16 mg QD (N = 278)</b>	<b>AMLb 10 mg QD (N = 280)</b>	<b>TOTAL (N = 837)</b>
<b>Age at baseline (years)</b>				
n	279	278	280	837
Mean (SD)	51.2 (9.74)	51.4 (9.75)	51.6 (9.78)	51.4 (9.74)
<b>Age group (n, %)</b>				
< 65	261 (93.5)	254 (91.4)	262 (93.6)	777 (92.8)
65 – 75	17 (6.1)	24 (8.6)	18 (6.4)	59 (7.0)
>75	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
<b>Sex (n, %)</b>				
Male	145 (52.0)	135 (48.6)	150 (53.6)	430 (51.4)
Female	134 (48.0)	143 (51.4)	130 (46.4)	407 (48.6)
<b>Ethnicity (n, %)</b>				
Hispanic or Latino	47 (16.8)	52 (18.7)	43 (15.4)	142 (17.0)
Not Hispanic or Latino	232 (83.2)	226 (81.3)	237 (84.6)	695 (83.0)
<b>Race (n, %)</b>				
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	2 (0.7)	1 (0.4)	1 (0.4)	3 (0.4)
Black or African American	95 (34.1)	96 (34.5)	96 (34.3)	287 (34.3)
Native Hawaiian or Other Pacific Islander	3 (1.1)	1 (0.4)	0 (0.0)	4 (0.5)
White	179 (64.2)	180 (64.7)	181 (64.6)	540 (64.5)
Other	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.2)
<b>Grouped Race (n, %)</b>				
Black	95 (34.1)	96 (34.5)	96 (34.3)	287 (34.3)
Non-black	184 (65.9)	182 (65.5)	184 (65.7)	550 (65.7)
<b>Type 2 diabetes status (n, %)</b>				
Yes	59 (21.1)	56 (20.1)	56 (20.0)	171 (20.4)
No	220 (78.9)	222 (79.9)	224 (80.0)	666 (79.6)
<b>Prior antihypertensive medication usage (n, %)</b>				
Treatment-naïve	95 (34.1)	82 (29.5)	93 (33.2)	270 (32.2)
Subjects requiring washout	184 (65.9)	196 (70.5)	187 (66.8)	567 (67.7)
<b>Duration of hypertension (years)</b>				
n	279	278	280	837
Mean	7.9 (6.93)	8.8 (8.52)	9.2 (8.94)	8.6 (8.19)

Characteristic Statistic	PERa/AMLb 14/10 mg QD (N = 279)	PERe 16 mg QD (N = 278)	AMLb 10 mg QD (N = 280)	TOTAL (N = 837)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>				
n	279	278	280	837
Mean (SD)	33.1 (6.92)	33.2 (6.42)	33.0 (6.02)	33.1 (6.46)
<b>Baseline Blood Pressure</b>				
Diastolic (mm Hg)				
n	279	278	280	837
Mean (SD)	100.7 (4.64)	100.8 (4.85)	100.4 (4.77)	100.6 (4.75)
843449 Systolic (mm Hg)				
n	279	278	280	837
Mean (SD)	157.5 (12.02)	157 (11.48)	157.9 (11.75)	157.6 (11.74)
<b>N = number of subjects randomized.</b>				
<b>AMLb = amlodipine besylate; PERa = perindopril arginine; PERe = perindopril erbumine; QD = once daily; SD = standard deviation.</b>				
<b>Sources: Reviewer and CSR, Table 4 (pages 59-60) and Table 5 (page 61).</b>				

#### 6.1.2.2. Study CL2-05985-005

Demographic and baseline characteristics for Study CL2-05985-005 are summarized in Table 14. The mean age of the randomized subjects was 51.7 years. Only 13.3% of subjects were ≥ 65 years of age. Most subjects were Caucasian. Approximately 53.3% of the study population was female. The population had a mean body mass index of 26.8 kg/m<sup>2</sup>.

Key demographic characteristics were generally well-balanced between treatment groups, except for sex. There were a higher percentage of women than men in all treatment groups.

**Table 14. Demographic and Baseline Characteristics (Study CL2-05985-005) (Randomized Set)**

		<b>PERa/AMLb 3.5/2.5 mg (N = 248)</b>	<b>Placebo (N = 250)</b>	<b>PERa 3.5 mg (N = 273)</b>	<b>AMLb 2.5 mg (N = 274)</b>	<b>PERa 5 mg (N = 272)</b>	<b>AMLb 5 mg (N = 264)</b>	<b>TOTAL (N = 1581)</b>
<b>Age (years)</b>	<b>n</b>	248	250	273	274	272	264	1581
	<b>Mean ± SD</b>	51.6 ± 11.8	51.8 ± 11.7	52.2 ± 11.1	51.8 ± 11.2	51.1 ± 11.6	51.8 ± 11.0	51.7 ± 11.4
	<b>Min; Max</b>	23; 79	19; 79	24; 79	19; 78	19; 79	20; 77	19; 79
<b>&lt; 65 years</b>	<b>n (%)</b>	210 (84.7)	215 (86.0)	235 (86.1)	242 (88.3)	241 (88.6)	228 (86.4)	1371 (86.7)
<b>≥ 65 years</b>	<b>n (%)</b>	38 (15.3)	35 (14.0)	38 (13.9)	32 (11.7)	31 (11.4)	36 (13.6)	210 (13.3)
<b>Sex</b>								
<b>Men</b>	<b>n (%)</b>	116 (46.8)	116 (46.4)	128 (46.9)	128 (46.7)	129 (47.4)	122 (46.2)	739 (46.7)
<b>Women</b>	<b>n (%)</b>	132 (53.2)	134 (53.6)	145 (53.1)	146 (53.3)	143 (52.6)	142 (53.8)	842 (53.3)
<b>Race</b>		248	250	273	274	272	264	1581
<b>Caucasian</b>	<b>n (%)</b>	246 (99.2)	247 (98.8)	269 (98.5)	271 (98.8)	266 (97.8)	260 (98.5)	1559 (98.6)
<b>Black</b>	<b>n (%)</b>	2 (0.8)	3 (1.2)	2 (0.7)	3 (1.1)	5 (1.8)	3 (1.1)	18 (1.1)
<b>Asian</b>	<b>n (%)</b>	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)	3 (0.2)
<b>Other</b>	<b>n (%)</b>	0	0	1 (0.4)	0	0	0	1 (0.1)
<b>BMI (kg/m<sup>2</sup>)</b>	<b>n</b>	248	250	273	274	272	264	1581
	<b>Mean ± SD</b>	26.8 ± 2.8	26.7 ± 2.5	27.0 ± 2.4	26.9 ± 2.5	26.8 ± 2.8	26.7 ± 2.5	26.8 ± 2.6
	<b>Min; Max</b>	19; 37	19; 31	19; 31	17; 31	13; 31	18; 30	13; 37
<b>Duration of Hypertension (months)</b>	<b>n</b>	248	250	272	274	272	264	1580
	<b>Mean ± SD</b>	63.4 ± 72.3	59.6 ± 82.1	54.3 ± 63.6	52.3 ± 64.6	52.1 ± 64.8	55.2 ± 73.9	56.0 ± 70.3
	<b>Min; Max</b>	0; 388	0; 449	0; 374	0; 316	0; 398	0; 444	0; 449

		<b>PERa/AMLb 3.5/2.5 mg (N = 248)</b>	<b>Placebo (N = 250)</b>	<b>PERa 3.5 mg (N = 273)</b>	<b>AMLb 2.5 mg (N = 274)</b>	<b>PERa 5 mg (N = 272)</b>	<b>AMLb 5 mg (N = 264)</b>	<b>TOTAL (N = 1581)</b>
<b>Previous Treatment for Hypertension</b>								
<b>No</b>	<b>n (%)</b>	97 (39.1)	93 (37.2)	106 (38.8)	100 (36.5)	117 (43.0)	103 (39.0)	616 (39.0)
<b>Yes</b>	<b>n (%)</b>	151 (60.9)	157 (62.8)	167 (61.2)	174 (63.5)	155 (57.0)	161 (61.0)	965 (61.0)
<b>Supine DBP (mm Hg)</b>	<b>n</b>	248	250	273	274	272	264	1581
	<b>Mean ± SD</b>	100.7 ± 4.0	100.5 ± 3.9	100.7 ± 4.0	100.6 ± 4.0	100.1 ± 4.1	100.6 ± 4.0	100.5 ± 4.0
	<b>Min; Max</b>	93; 110	88; 109	94; 110	94; 111	90; 110	94; 110	88; 111
<b>Supine SBP (mm Hg)</b>	<b>n</b>	248	250	273	274	272	264	1581
	<b>Mean ± SD</b>	161.8 ± 7.5	160.9 ± 7.3	161.5 ± 7.8	161.0 ± 7.6	160.7 ± 7.3	162.3 ± 7.5	161.4 ± 7.5
	<b>Min; Max</b>	150; 178	150; 179	150; 180	150; 180	150; 180	150; 179	150; 180
<b>Supine Mean BP</b>	<b>n</b>	248	250	273	274	272	264	1581
	<b>Mean ± SD</b>	121.1 ± 3.9	120.7 ± 3.8	120.9 ± 3.8	120.7 ± 4.0	120.3 ± 3.7	121.2 ± 3.8	120.8 ± 3.9
	<b>Min; Max</b>	113.3; 131.0	114.0; 130.0	113.3; 130.7	113.3; 132.3	113.3; 132.0	113.7; 131.7	113.3; 132.3

AMLb = amlodipine besylate; BP = blood pressure; DBP = diastolic blood pressure; PERa = perindopril arginine; SBP = systolic blood pressure.

Source: CSR, Table 10.4.1, page 79/3939 and Form1-04, page 233/3939.

### 6.1.3 Subject Disposition

#### 6.1.3.1 Study X985400

Disposition for Study X985400 is summarized in Table 15. A total of 837 subjects were randomized and a total of 751 (90%) subjects completed the study. A total of 86 (10.2%) subjects discontinued from the study.

**Table 15. Disposition (All Randomized Subjects) (Study X985400)**

Characteristics	PERa/AMLb 14/10 mg QD n (%)	PERe 16 mg QD n (%)	AMLb 10 mg QD n (%)	TOTAL n (%)
Randomized	279	278	280	837
Dosed	279 (100.0)	278 (100.0)	280 (100.0)	837 (100.0)
Completed	253 (90.7)	246 (88.5)	252 (90.0)	751 (89.7)
Discontinued	26 (9.3)	32 (11.5)	28 (10.0)	86 (10.3)
Adverse Event	10 (3.6)	12 (4.3)	12 (4.3)	34 (4.1)
Subject Withdrew Consent	7 (2.5)	8 (2.9)	6 (2.1)	21 (2.5)
Lost to follow-up	6 (2.2)	4 (1.4)	6 (2.1)	16 (1.9)
Physician Decision	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Other	2 (0.7)	7 (2.5)	3 (1.1)	12 (1.4%)
<b>AMLb = amlodipine besylate; PERa = perindopril arginine; PERe = perindopril erbumine; QD = once daily. Source: Reviewer.</b>				

#### 6.1.3.2 Study CL2-05985-005

Disposition for Study CL2-05985-005 is summarized in Table 16. A total of 2053 subjects were screened, 1581 subjects were randomized, and 1497 (94.7%) subjects completed the trial.

**Table 16. Disposition (Study CL2-05985-005)**

<b>Status</b>	<b>PERa/AMLb 3.5/2.5 mg</b>	<b>Placebo</b>	<b>PERa 3.5 mg</b>	<b>AMLb 2.5 mg</b>	<b>PERa 5 mg</b>	<b>AMLb 5 mg</b>	<b>All</b>
<b>Included (randomized)</b>	<b>248</b>	<b>250</b>	<b>273</b>	<b>274</b>	<b>272</b>	<b>264</b>	<b>1581</b>
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
<b>Withdrawn due to</b>	<b>9</b>	<b>11</b>	<b>16</b>	<b>19</b>	<b>15</b>	<b>14</b>	<b>84</b>
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
<b>Completed</b>	<b>239</b>	<b>239</b>	<b>257</b>	<b>255</b>	<b>257</b>	<b>250</b>	<b>1497</b>
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
<b>AMLb = amlodipine besylate; PERa = perindopril arginine.</b>							
<b>Sources: Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table 10.1.1, page 67/3939.</b>							

## 6.1.4 Analysis of Primary Endpoint(s)

### 6.1.4.1 Study X985400

The primary endpoint was the change from baseline (Visit 2 [Day 0]) to Visit 4 (Day 42) in mean seDBP at trough. The primary analysis was based on the intent-to-treat (ITT) Population, defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline DBP value. PRESTALIA<sup>®</sup> 14/10 mg significantly reduced mean seDBP from baseline to Week 6 compared to PERe 16 mg (LS mean difference (SE): -6.3 (0.72) mm Hg,  $p < 0.0001$ ) and AMLb 10 mg (LS mean difference (SE): -2.5 (0.72) mm Hg,  $p = 0.0005$ ), as shown in Table 17.

**Table 17. Primary Endpoint (Study X985400): Seated Diastolic Blood Pressure at 6 Weeks (ITT with LOCF)**

Seated Diastolic Blood Pressure at 6 Weeks Statistic	PERa/AMLb 14/10 mg QD (N = 271)	PERe 16 mg QD (N = 274)	AMLb 10 mg QD (N = 275)
Baseline Mean (SD)	100.6 (4.59)	100.8 (4.86)	100.5 (4.79)
Day 42 Mean (SD)	85.0 (8.61)	91.4 (9.73)	97.2 (8.38)
Change from Baseline			
Mean (SD)	<b>-15.7 (8.38)</b>	<b>-9.5 (8.77)</b>	<b>-13.2 (8.33)</b>
LS Mean (SE)	-15.4 (0.56)	-9.1 (0.56)	-12.9 (0.56)
Comparisons	<b>Between Treatment Comparisons</b>		
	LS Mean Difference (SE)		P-value
PERa/AMLb 14/10 mg vs. PERe 16 mg	<b>-6.3 (0.72)</b>		<b>&lt;0.0001</b>
PERa/AMLb 14/10 mg vs. AMLb 10 mg	<b>-2.5 (0.72)</b>		<b>0.0005</b>
AMLb = amlodipine besylate; LOCF = last observation carried forward; LS = least squares; PERa = perindopril arginine; PERe = perindopril erbumine; SD = standard deviation; SE = standard error. Sources: Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table 7, page 64.			

#### 6.1.4.2. Study CL2-05985-005

The protocol and SAP for this study were not submitted to the FDA for review prior to study conduct. The primary endpoint was the change from baseline (Week 0) to Week 8 (or last on-treatment post-baseline value) in suDBP or mean 24 hour DBP(ABPM substudy). The primary analyses included three superiority comparisons and two non-inferiority comparisons as follows:

- **Superiority Comparisons**

- PERa 3.5/AMLb 2.5 mg versus placebo
- PERa 3.5/AMLb 2.5 mg versus PERa 3.5 mg
- PERa 3.5/AMLb 2.5 mg versus AMLb 2.5 mg

- **Non-Inferiority Comparisons**

- PERa 3.5/AMLb 2.5 mg versus PERa 5 mg
- PERa 3.5/AMLb 2.5 mg versus AMLb 5 mg

The non-inferiority tests used the same model as the superiority tests. The noninferiority margin was 2 mm Hg, but it was unclear how this margin was determined and whether the margin was clinically acceptable. For this review, FDA focused on the results from the superiority comparisons.

PRESTALIA<sup>®</sup> significantly reduced suDBP from baseline to Week 8 when compared with placebo (Estimate (E)(SE): -4.12 (0.77) mm Hg;  $p < 0.001$ ), PERa 3.5 mg (E(SE): -3.64 (0.76) mm Hg;  $p < 0.001$ ), and AMLb 2.5 mg (E(SE): -2.97 (0.75) mm Hg;  $p < 0.001$ ), as shown in Table 18.

**Table 18. Change from Baseline to Week 8 in Supine DBP (Superiority Comparison) (Full Analysis Set) (Study CL2-05985-005)**

Supine DBP at 8 Weeks (mm Hg)		PERa/AMLb 3.5/2.5 mg	Placebo	PERa 3.5 mg	AMLb 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; 115
END-Baseline	Mean ± SD	<b>-13.6 ± 9.2</b>	<b>-9.3 ± 9.2</b>	<b>-9.7 ± 9.9</b>	<b>-10.3 ± 9.7</b>
	Min; Max	-45; 13	-39; 15	-34; 31	-41; 18
<b>Main Statistical Analysis</b>					
	Estimate (SE)		<b>-4.12 (0.77)</b>	<b>-3.64 (0.76)</b>	<b>-2.97 (0.75)</b>
	95% CI		<b>[-5.63; -2.61]</b>	<b>[-5.12; -2.16]</b>	<b>[-4.45; -1.49]</b>
	p-value		<b>p &lt; 0.001</b>	<b>p &lt; 0.001</b>	<b>p &lt; 0.001</b>
Sources: Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table (11.1.1.1) 1, page 91/3939.					

The noninferiority comparisons can be found in Dr. Zhang's review.

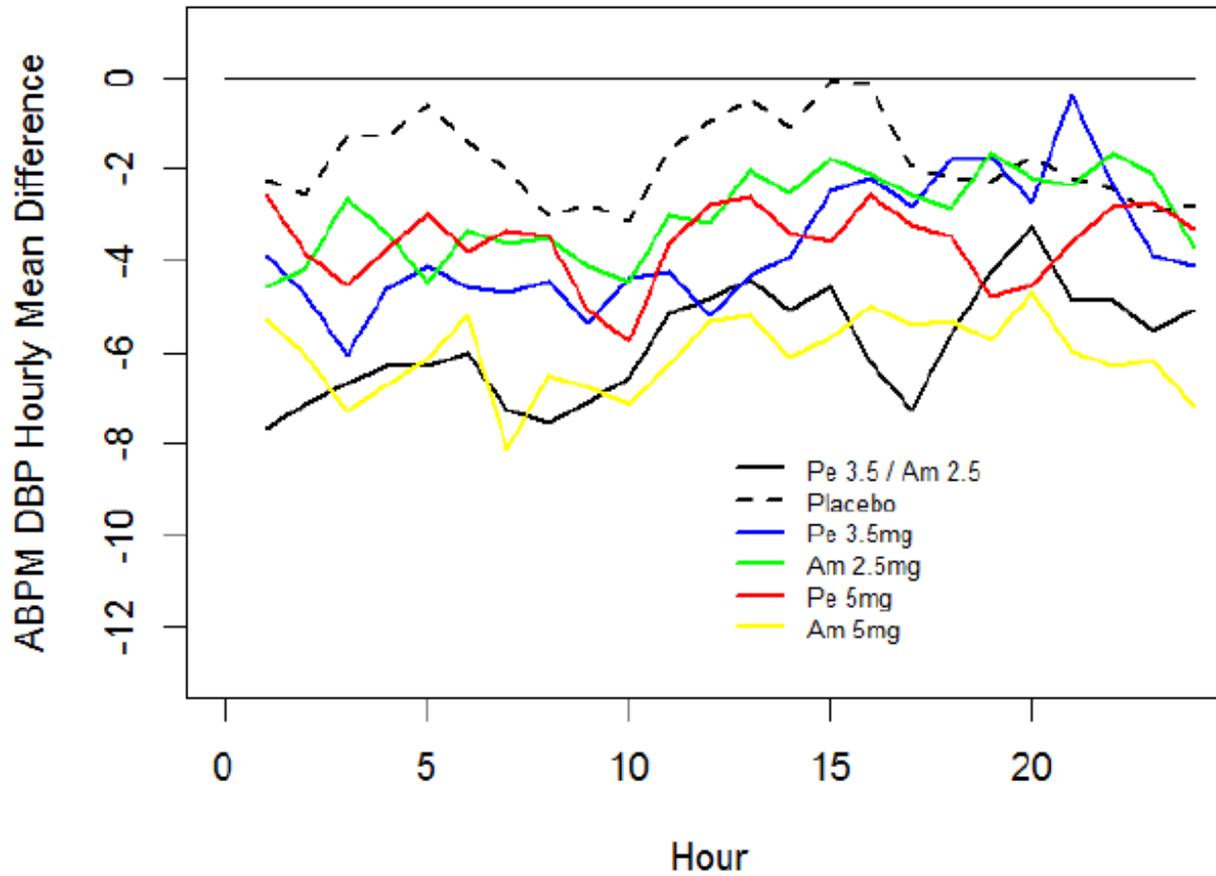
The ABPM substudy demonstrated that PERa/AMLb 3.5/2.5 mg significantly decreased mean 24 hour DBP from baseline to Week 8, compared to placebo, PERa 3.5 mg, and AMLb 2.5 mg, as shown in Table 19.

A graphical display of the ABPM DBP results is shown in Figure 3. The graph demonstrates that the greatest hourly mean differences in DBP were seen in the PERa/AMLb 3.5/2.5 mg and AMLb 5 mg treatment groups.

**Table 19. ABPM Substudy: Mean 24 Hour DBP (Change from Baseline to Last Post-Baseline Value/Week 8 Value) (Study CL2-05985-005)**

Mean 24-Hour DBP (mm Hg) (ABPM) at 8 Weeks		PERa/AMLb 2.5 mg	Placebo	PERa 3.5 mg	AMLb 2.5 mg	PERa 5 mg	AMLb 5 mg
Baseline	N	174	167	189	183	187	173
	Mean ± SD	82.93 ± 8.63	83.15 ± 9.68	83.52 ± 10.66	84.58 ± 9.03	83.66 ± 9.51	84.06 ± 8.81
	Min; Max	65.8; 108.0	63.6; 111.1	56.4; 123.7	64.5; 107.2	57.7; 109.1	63.9; 111.6
END	Mean ± SD	77.13 ± 8.47	81.26 ± 9.52	79.82 ± 10.06	81.59 ± 8.44	80.05 ± 9.06	78.11 ± 7.79
	Min; Max	48.2; 98.8	54.1; 104.2	50.1; 112.1	59.8; 109.8	58.6; 113.7	48.5; 94.7
END-Baseline	Mean ± SD	<b>-5.80 ± 8.31</b>	<b>-1.89 ± 8.74</b>	<b>-3.70 ± 9.16</b>	<b>-3.00 ± 7.09</b>	<b>-3.61 ± 7.76</b>	<b>-5.94 ± 7.78</b>
	Min; Max	-42.4; 13.5	-37.0; 23.5	-35.8; 33.4	-29.7; 20.8	-25.2; 30.1	-31.7; 20.1
<b>Main Statistical Analysis</b>							
	Estimate	<b>-3.99 (0.75)</b>					
	95% CI	<b>[-5.46; -2.51]</b>					
	p-value	<b>p &lt; 0.001</b>					
<b>Secondary Statistical Analysis</b>							
	Estimate			-2.17 (0.73)	-3.39 (0.74)	-2.40 (0.73)	-0.26 (0.75)
	95% CI			[-3.60; -0.73]	[-4.84; -1.94]	[-3.84; -0.97]	[-1.73; 1.21]
Sources: Jialu Zhang, Ph.D., (Division of Biometrics 1) and CSR, Table 11.1.2, page 57/531.							

**Figure 3. ABPM DBP Results (Study CL2-05985-005)**



Source: Jialu Zhang, Ph.D. (Division of Biometrics 1)

## 6.1.5 Analysis of Secondary Endpoints(s)

### 6.1.5.1 Study X985400

The secondary endpoint was the change from baseline (Visit 2 [Day 0]) to Visit 4 (Day 42) in mean seSBP at trough and was also analyzed in the ITT Population. PRESTALIA<sup>®</sup> 14/10 mg significantly reduced mean seSBP from baseline to Week 6 compared to PERe 16 mg (LS mean difference (SE): -10.1 (1.25) mm Hg,  $p < 0.0001$ ) and AMLb 10 mg (LS mean difference (SE): -3.9 (1.25) mm Hg,  $p = 0.0017$ ), as shown in Table 20.

**Table 20. Secondary Endpoint (Study X985400): Seated Systolic Blood Pressure at 6 Weeks (LOCF)**

Seated Systolic Blood Pressure at 6 Weeks Statistic	PERa/AMLb 14/10 mg QD (N = 271)	PERe 16 mg QD (N = 274)	AMLb 10 mg QD (N = 275)
Baseline Mean (SD)	157.5 (11.91)	157.5 (11.44)	158.0 (11.81)
Day 42 Mean (SD)	134.1 (13.48)	144.1 (15.72)	138.4 (13.40)
Change from Baseline			
Mean (SD)	<b>-23.4 (13.86)</b>	<b>-13.4 (14.66)</b>	<b>-19.6 (15.62)</b>
LS Mean (SE)	<b>-22.8 (0.98)</b>	<b>-12.7 (0.98)</b>	<b>-18.8 (0.98)</b>
Comparisons	<b>Between Treatment Comparisons</b>		
	LS Mean Difference (SE)		P-value
PERa/AMLb 14/10 mg vs. PERe 16 mg	<b>-10.1 (1.25)</b>		<b>&lt; 0.0001</b>
PERa/AMLb 14/10 mg vs. AMLb 10 mg	<b>-3.9 (1.25)</b>		<b>0.0017</b>
AMLb = amlodipine besylate; LOCF = last observation carried forward; LS = least squares; PERa = perindopril arginine; PERe = perindopril erbumine; SD = standard deviation; SE = standard error. Sources: Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table 8, page 65.			

### 6.1.5.2 Study CL2-05985-005

The secondary endpoint was the change from baseline (Week 0) to Week 8 in suSBP at trough or mean 24 hour SBP (ABPM substudy). PRESTALIA<sup>®</sup> significantly reduced suSBP from baseline to Week 8 when compared with placebo (E(SE): -7.22 (1.21) mm Hg; p < 0.001), PERa 3.5 mg (-5.01 (1.19) mm Hg; p < 0.001); or AMLb 2.5 mg (E(SE): -5.20 (1.19) mm Hg; p < 0.001), as shown in Table 21.

**Table 21. Change from Baseline to Week 8 in Supine SBP (Superiority Comparison) (Full Analysis Set) (Study CL2-05985-005)**

Supine SBP at 8 Weeks		PERa/AMLb 3.5/2.5 mg	Placebo	PERa 3.5 mg	AMLb 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	<b>-22.0 ± 14.0</b>	<b>-14.2 ± 16.1</b>	<b>-16.3 ± 17.0</b>	<b>-16.0 ± 15.3</b>
	Min; Max	-54; 16	-62; 34	-59; 34	-61; 25
Main Statistical Analysis					
	Estimate (SE)		<b>-7.22 (1.21)</b>	<b>-5.01 (1.19)</b>	<b>-5.20 (1.19)</b>
	95% CI		<b>[-9.60; -4.84]</b>	<b>[-7.35; -2.67]</b>	<b>[-7.53; -2.87]</b>
	p-value		<b>p &lt; 0.001</b>	<b>p &lt; 0.001</b>	<b>p &lt; 0.001</b>
Sources: Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table (11.2.1.1.1) 1, page 98/3939.					

The noninferiority comparisons can be found in Dr. Zhang's review.

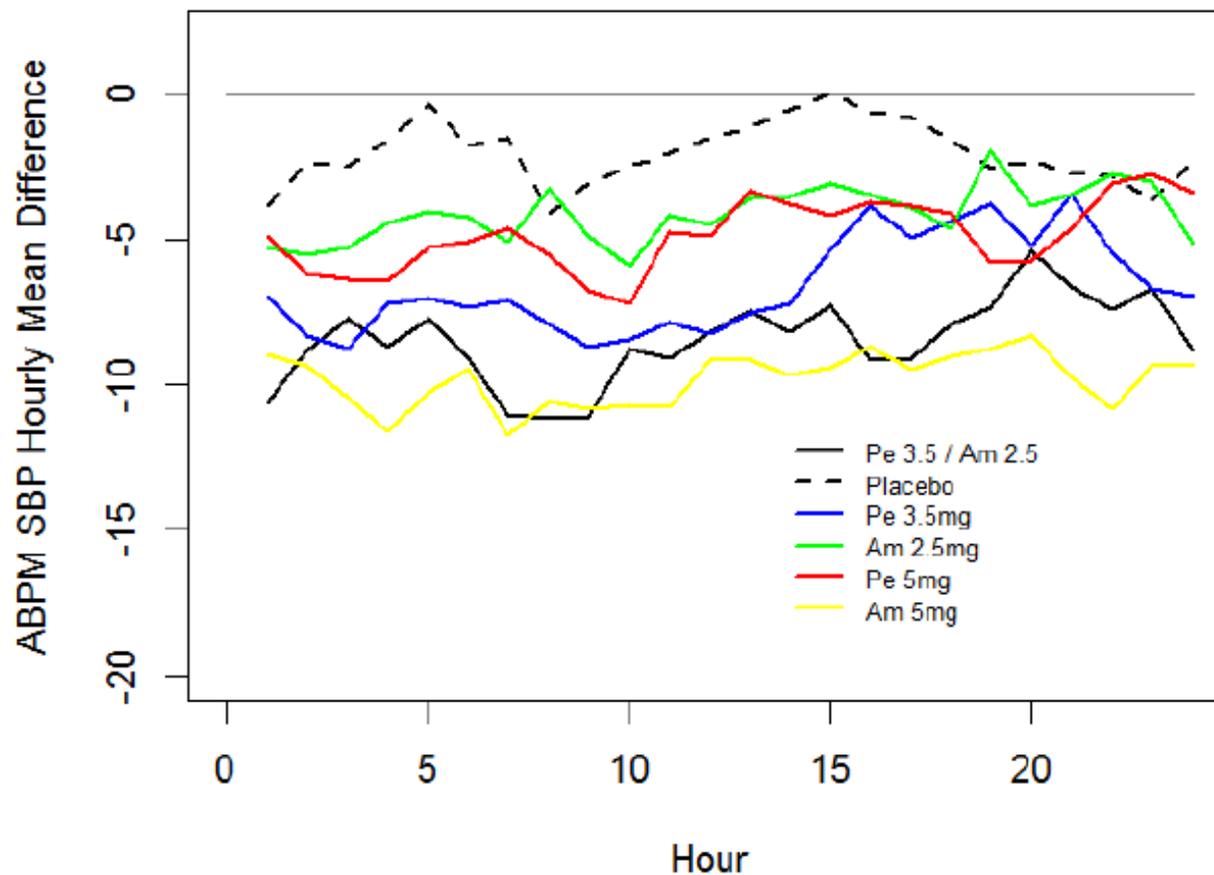
The ABPM substudy demonstrated that PERa/AMLb 3.5/2.5 mg significantly decreased mean 24 hour SBP from baseline to Week 8, compared to placebo, PERa 3.5 mg, and AMLb 2.5 mg, as shown in Table 22.

A graphical display of the ABPM SBP results is shown in Figure 4. The graph demonstrates that the greatest hourly mean differences in SBP were seen in the PERa/AMLb 3.5/2.5 mg and AMLb 5 mg treatment groups.

**Table 22. ABPM Substudy: Mean 24 Hour SBP (Change from Baseline to Last Post-Baseline Value/Week 8 Value) (Study CL2-05985-005)**

Mean 24-Hour SBP (mm Hg) (ABPM) at 8 Weeks		PERa/AMLb 3.5/2.5 mg	Placebo	PERa 3.5 mg	AMLb 2.5 mg	PERa 5 mg	AMLb 5 mg
Baseline	N	174	167	189	183	187	173
	Mean ± SD	133.10 ± 11.22	133.06 ± 12.13	134.61 ± 14.07	134.53 ± 11.57	133.84 ± 12.41	135.48 ± 14.00
	Min; Max	107.2; 168.8	104.9; 178.3	102.7; 192.3	102.6; 163.4	105.2; 196.1	106.5; 193.9
END	Mean ± SD	134.60 ± 10.53	130.86 ± 12.36	128.08 ± 13.05	130.41 ± 11.54	128.94 ± 11.33	125.82 ± 10.93
	Min; Max	100.6; 154.1	96.3; 160.3	93.8; 171.4	99.9; 165.4	96.3; 162.5	97.1; 160.3
END-Baseline	Mean ± SD	<b>-8.50 ± 11.78</b>	<b>-2.20 ± 13.21</b>	<b>-6.53 ± 11.59</b>	<b>-4.12 ± 10.50</b>	<b>-4.89 ± 12.22</b>	<b>-9.66 ± 12.99</b>
	Min; Max	-63.4; 25.1	-57.6; 45.4	-40.9; 27.2	-32.6; 34.6	-73.2; 45.3	-71.4; 27.6
Main Statistical Analysis							
	Estimate	<b>-6.25 (1.06)</b>					
	95% CI	<b>[-8.34; -4.16]</b>					
	p-value	<b>P &lt; 0.001</b>					
Secondary Statistical Analysis							
	Estimate			-2.49 (1.03)	-4.93 (1.04)	-3.82 (1.03)	-0.03 (1.06)
	95% CI			[-4.52; -0.47]	[-6.97; -2.89]	[-5.84; -1.79]	[-2.10; 2.04]
Analysis by Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table 11.2.1.2) 1, page 60/531.							

**Figure 4. Study CL2-05985-005 ABPM SBP Results**



Source: Jialu Zhang, Ph.D. (Division of Biometrics 1)

## 6.1.6 Other Endpoints

### 6.1.6.1 Study X985400

In Study X985400 (PATH), a responder was defined as a subject who achieved a target blood pressure goal of < 140/90 mm Hg or a subject with diabetes who achieved a target blood pressure goal of < 130/80 mm Hg. The PRESTALIA<sup>®</sup> 14/10 mg treatment group had a higher percentage of subjects achieving 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 Days 21 and 42 (40.4% versus 13.9% and 24.8%, respectively) compared to the PERe 16 mg and AMLb 10 mg treatment groups, as shown in Table 23.

**Reviewer's Comments:** *The responder analysis was not prespecified as a secondary endpoint in the original protocol, Protocol Amendment 1, or Statistical Analysis Plan (SAP). This parameter was listed as a secondary endpoint in the Clinical Study Report only.*

**Table 23. Applicant's Responder Analysis (LOCF)**

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

1. A responder or target achievement was a subject who achieved blood pressure of < 140/90 mm Hg or a subject with diabetes who achieved < 130/80 mm Hg.
  2. Reported p-values were based on a Chi-square test
- Sources: Jialu Zhang, Ph.D. (Division of Biometrics 1) and CSR, Table 11, page 69.

#### 6.1.6.2 Study CL2-05985-005

In Study CL2-05985-005, response to treatment was defined as:

- A normalization of BP (SBP < 140 mm Hg and DBP < 90 mm Hg) and/or
- A decrease from baseline in SBP ≥ 20 mm Hg and/or
- A decrease from baseline in DBP ≥ 10 mm Hg

Results of the responder's analysis are displayed in Table 24. There was a higher percentage of responders in the PERa/AMLb 14/10 mg treatment group, compared to placebo, PERa 3.5 mg, and AMLb 2.5 mg.

**Table 24. Responder's Analysis (Study CL2-05985-005)**

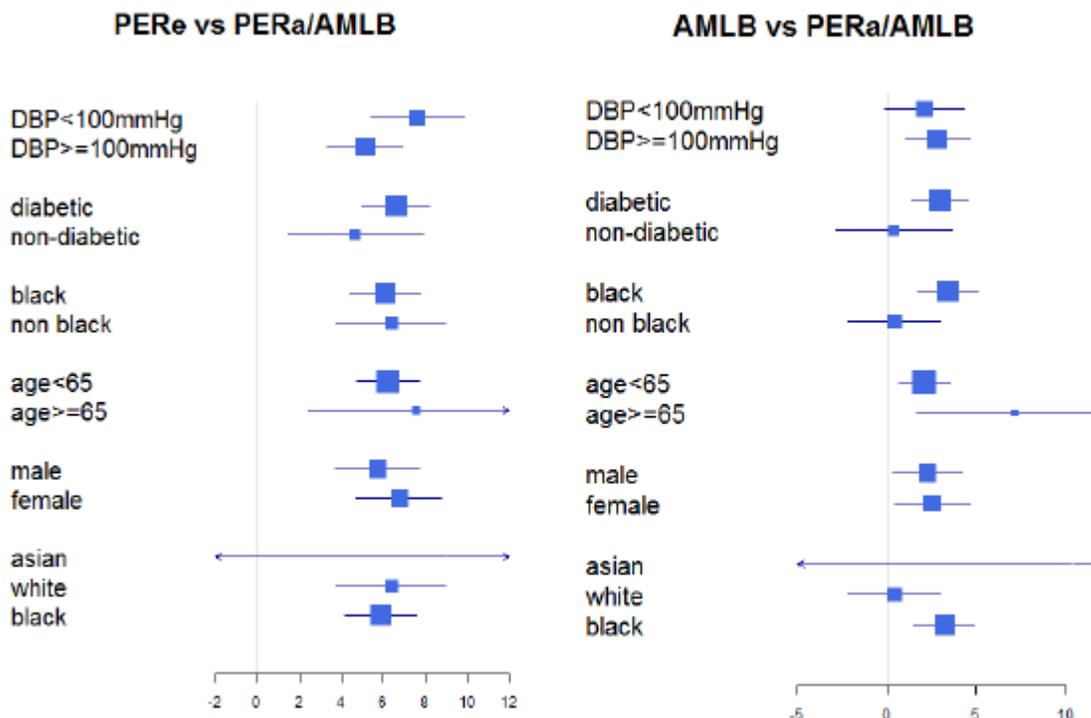
	PERa/AMLb 3.5/2.5 mg	Placebo	PERa 3.5 mg	AMLb 2.5 mg
Responders				
n (%)	189 (76.8)	131 (52.8)	156 (58.2)	158 (58.5)
Non-Responders				
n (%)	57 (23.2)	117 (47.2)	112 (41.8)	112 (41.5)

**Source: Jialu Zhang, Ph.D. (Office of Biometrics 1).**

#### 6.1.7 Subpopulations

Subgroup analyses for Study X985400 are shown in Figure 5. In non-black and non-diabetic subjects, the addition of PERa to AMLb did not appear to result in further reduction in DBP. What to make of this finding is unclear, given the small sample size in these subgroups.

**Figure 5. Subgroup Analyses (Study X985400)**



Source: Jialu Zhang, Ph.D. (Office of Biometrics 1)

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dr. Hinderling attempted to estimate treatment effects in Study X985400, since there was no placebo control and the PRESTALIA<sup>®</sup> 7/5 mg dose was not studied in either of the pivotal trials. Assuming various placebo effects, he constructed a table estimating the possible treatment effect of the 7/5 mg dose on placebo-subtracted diastolic blood pressure. He estimated a treatment effect ranging from 2.1 to 8.8 mm Hg between the PRESTALIA<sup>®</sup> 3.5/2.5 mg and 14/10 mg doses, as shown in Table 25.

Given the dose-dependent peripheral edema observed with NORVASC<sup>®</sup>, which is known to be worse in women, I think an intermediate dose may provide a meaningful benefit to some hypertensive patients. Therefore, I recommend approval of the intermediate dose. See Section 7.5.3 for further analyses conducted with respect to peripheral edema.

**Table 25. Estimating Treatment Effects in Phase 3 Study**

	Assumed Placebo Effect, mm Hg				
	9.3	8.2	6.2	4.2	2.6
<b>Treatment, mg</b>	<b>ΔΔ DBP, mm Hg<sup>a</sup></b>				
<b>PERa/AMLb 3.5/2.5</b>	4.3	4.3	4.3	4.3	4.3
<b>PERa/AMLb 14/10</b>	6.4	7.5	9.5	11.5	13.1
<b>PERe 16<sup>b</sup></b>	0.2	1.3	3.3	5.3	6.9
<b>AMLb 10</b>	3.9	5.0	7.0	9.0	10.6
<b>ΣPERe 16 + AMLb 10</b>	4.1	6.3	10.3	14.3	17.5
<b>ΔPERa/AMLb 14/10 – 3.5/2.5</b>	2.1	3.2	5.2	7.2	8.8
<b>Supra-/infra-additive effect</b>	2.3	1.2	-0.8	-2.8	-4.4

<sup>a</sup>baseline and placebo-corrected effect; <sup>b</sup>corresponds to 19.6 mg PERa. Yellow represents unlikely low or high DBP values for baseline and placebo-corrected treatment effects for PERe 16 mg and AMLb 10 mg, considering the reductions in DBP of 5-6 mm Hg for ACEON (8 and 16 mg PERe) and 7 mm Hg for NORVASC (5 and 10 mg AMLb)  
 AMLb = amlodipine besylate; PERa = perindopril arginine; PERe = perindopril erbumine  
 Source: Peter Hinderling, M.D.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

PRESTALIA<sup>®</sup> demonstrated persistence of treatment effect through Week 6 in Study X985400 and through Week 8 in Study CL2-05985-005. The effect of treatment withdrawal was not studied with PRESTALIA<sup>®</sup>.

### 6.1.10 Additional Efficacy Issues/Analyses

In her review dated November 6, 2014, Dr. Zhang (Biometrics I) expressed concerns about the minimization algorithm used for randomization in Study X985400 and discussed inconsistencies between the clinical study report (CSR), the statistical analysis plan (SAP), and its appendix. The CSR and SAP stated that randomization was stratified by type 2 diabetes status, race (black or non-black) and baseline DBP (< 100 mm Hg versus ≥ 100 mm Hg). Randomization was not stratified by site since Study X985400 was conducted exclusively in the US. In contrast, the SAP appendix described a minimization algorithm for treatment group assignments. The covariates for this algorithm included type 2 diabetes status, race (black or non-black), baseline DBP (< 100 mm hg versus ≥ 100 mm Hg), and site.

Dr. Zhang stated that the assignment of treatment groups was deterministic and could have potentially unblinded the treatment assignments. However, her analyses of baseline mean SBP and DBP versus the order of a patient's entry into the study

suggested a random walk pattern and not selection bias. She also examined the mean treatment effect and found no obvious trend. Although potential selection bias cannot be completely excluded, it seems unlikely that selection bias played any role in Study X985400 given the complexity in calculating scores based on previous treatment assignments and the fact that this study was conducted at 59 different centers. Dr. Zhang also stated that the standard tests may not be applicable under this minimization algorithm because the underlying assumption for statistical inference is that treatment is randomly assigned. She conducted a bootstrap t-test while applying the same minimization algorithm to assign treatment and found a  $p < 0.001$  for both comparisons between the combination therapy and its monocomponents. However, this test assumed that blood pressure measurements in this trial were identically distributed.

In summary, although the minimization algorithm could have unblinded treatment assignments, it does not appear to have affected the validity of the results for Study X985400 (PATH) for the reasons discussed above. Prestalia<sup>®</sup> 14/10 mg significantly reduced both mean seated DBP and SBP from baseline to 6 Weeks, compared to perindopril erbumine 16 mg and amlodipine besylate 10 mg.

## 7 Review of Safety

### **Safety Summary**

The safety database for Studies X985400 and CL2-05985-005 includes 2,420 subjects. A total of 528 subjects received PERa/AMLb, including 249 subjects who received the 3.5/2.5 mg dose and 279 subjects who received the 14/10 mg dose. In addition, 278 subjects received PERe 16 mg, 280 subjects received AMLb 10 mg, 273 subjects received PERa 3.5 mg, 274 subjects received AMLb 2.5 mg, 272 subjects received PERa 5 mg, 264 subjects received AMLb 5 mg, and 251 subjects received placebo.

ACEON<sup>®</sup> (NDA 20184) and NORVASC<sup>®</sup> (NDA 19787) were approved by the FDA on December 30, 1993 and July 31, 1992, respectively, so the Agency has a significant safety experience with the active ingredients of these monocomponents.

No new safety issues have been identified with respect to the monocomponents. In general, common adverse events observed with PERa/AMLb were reflective of common adverse events seen with the monocomponents.

The most common adverse events with PRESTALIA<sup>®</sup> included peripheral edema, headache, cough, and dizziness. The data suggest that PRESTALIA<sup>®</sup> may attenuate the peripheral edema usually seen with NORVASC<sup>®</sup> when administered as a monocomponent. See Section 7.4.1 for further details.

## 7.1 Methods

I focused my safety review on Study X985400 because this study compared the highest dose of the combination to the highest approved doses of the monocomponents.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed in Section 5.3, safety analyses focused on the phase 3 trial (Study X985400 (PATH)) and the phase 2 trial (Study CL2-05985-005) conducted in patients with hypertension.

In Study X985400, the Safety Population was defined as all randomized subjects who received any amount of study drug. The number of randomized subjects was equal to the number of subjects in the Safety Population (837 subjects).

In Study CL2-05985-005, the Safety Set was defined as all patients who had taken at least one dose of study treatment. A total of 1581 patients were randomized, and there were 1583 patients in the Safety Population. Two patients received at least one dose of study treatment (Patient 005348700000912 received PERa 3.5/AMLb 2.5 mg and Patient 005348700000917 received placebo of the treatment period instead of placebo of the run-in period) following an error in dispensation. These additional two patients were included in the Safety Set but were excluded from the Randomized Set.

### 7.1.2 Categorization of Adverse Events

In Study X985400, all adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0. A treatment emergent adverse event (TEAE) was defined as an adverse event that newly appeared, increased in frequency, or worsened in severity from pre-treatment following the initiation of treatment. Treatment-emergent adverse events were adverse events with an onset date on or after the first dose date up to the last dose date + 14 days. If the onset date of an adverse event was missing, the adverse event was considered treatment-emergent. Only treatment-emergent adverse events occurring and reported during the study period were included in the adverse event summaries.

In Study CL2-05985-005, all adverse events were coded using MedDRA, version 10. An emergent adverse event (EAE) was defined as adverse events which

- occurred between the first treatment administration date and the last treatment administration date + 7 days (included); or

- occurred before the first treatment administration date and which worsened between the first treatment administration date and the last treatment administration date + 7 days (included); or
- occurred before the first treatment administration date and which became serious between the first treatment administration date and the last treatment administration date + 7 days (included).

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

Given differences in study design and dosages studied in the pivotal trials, data were not pooled across studies.

## 7.2 Adequacy of Safety Assessments

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

Exposure for the pivotal trials is summarized in Tables 26 through 28. Duration of exposure was similar between treatment groups. The total number of patients and the duration of exposure seemed adequate to evaluate the safety of this product.

**Table 26. Study X985400 (PATH): Treatment Exposure (Safety Population)**

Treatment Duration (Days)*	PERa/AMLb 14/10 mg QD (N = 279)	PERe 16 mg QD (N = 280)	AMLb 10 mg QD (N = 280)
n	279	278	280
Mean (SD)	40.8 (5.73)	40.3 (8.15)	40.7 (7.38)
*Treatment duration = last dose date – first dose date + 1			

**Table 27. Study CL2-05985-005: Treatment Exposure (Safety Set)**

Treatment Duration (Days)	PERa/AMLb 3.5/2.5 mg (N = 249)	Placebo (N = 251)	PERa 3.5 mg (N = 273)	AMLb 2.5 mg (N = 274)	PERa 5 mg (N = 272)	AMLb 5 mg (N = 264)
n	247	250	273	271	270	264
Mean (SD)	57.3 (7.7)	56.7 (9.0)	56.4 (11.1)	56.2 (10.2)	56.8 (8.6)	56.3 (9.4)
<b>AMLb = amlodipine besylate; PERa = perindopril arginine</b>						

**Table 28. Study CL2-05985-005 (ABPM): Treatment Exposure (Safety Set)**

Treatment Duration (Days)	PERa/AMLb 3.5/2.5 mg (N = 174)	Placebo (N = 167)	PERa 3.5 mg (N = 189)	AMLb 2.5 mg (N = 183)	PERa 5 mg (N = 187)	AMLb 5 mg (N = 173)
n	174	167	189	182	187	173
Mean (SD)	58.3 (5.2)	57.5 (5.6)	58.0 (5.6)	58.3 (5.9)	58.2 (5.6)	57.2 (7.0)

**AMLb = amlodipine besylate; PERa = perindopril arginine**

### 7.2.2 Explorations for Dose Response

See Section 7.5.1 for further details. Prescribing information for NORVASC<sup>®</sup> reports the incidence of dose-dependent adverse reactions shown in Table 29 below. Edema, in particular, is highly dose-dependent and as shown in Table 30, occurs at a higher incidence in women than men.

**Table 29. Incidence of Dose-Dependent Adverse Reactions with NORVASC<sup>®</sup>**

	NORVASC <sup>®</sup>			Placebo N = 520
	2.5 mg (N = 275)	5 mg (N = 296)	10 mg (N = 268)	
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.1	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

**Prescribing Information, January 7, 2013.**

Adverse reactions with NORVASC<sup>®</sup> that appear to be drug and dose-related are summarized in Table 21.

**Table 30. Adverse Reactions with NORVASC<sup>®</sup> by Sex**

	NORVASC <sup>®</sup>		Placebo	
	Male = % (N = 1218)	Female = % (N = 512)	Male = % (N = 914)	Female = % (N = 336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

**Prescribing Information, January 7, 2013.**

### **7.2.3 Special Animal and/or In Vitro Testing**

No special animal or in vitro testing was conducted.

### **7.2.4 Routine Clinical Testing**

Clinical testing in studies was adequate and included adverse event data collection, laboratory parameter assessments, 12-lead electrocardiograms (ECGs), vital signs, and physical examinations. In Study CL2-05985-005, ambulatory blood pressure monitoring was also conducted.

A thorough QT study was not conducted. Both perindopril erbumine and NORVASC<sup>®</sup> are approved products and are not known to cause QT prolongation.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

See Section 4.4, Clinical Pharmacology, for further details.

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

Based on the safety profiles of ACE-Is and dihydropyridine CCBs, the evaluation for potential adverse events was adequate.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

There were no deaths in Study X985400. In Study CL2-05985-005, there was one death. Patient No. 005 643 5007 02337, a 47 year old Caucasian man, drowned (b) (6) days after initiating PERa 5 mg QD.

### **7.3.2 Nonfatal Serious Adverse Events**

In Study X985400, 5 patients (1 in the PERa/AMLb 14/10 mg arm, 2 in the PERe 16 mg arm, and 2 in the AMLb 10 mg arm) experienced serious, nonfatal treatment emergent adverse events, as summarized in Table 31. All 5 patients discontinued prematurely from the trial and permanently discontinued study drug. Four patients were hospitalized for the event. All adverse reactions resolved without sequelae.

The pulmonary embolism in the PERa/AMLb 14/10 mg treatment group was not likely drug-related, but the lip swelling in the PERe 16 mg group was likely drug-related. The event of hypotension/acute renal failure may have been related to PERe 16 mg, but the patient was also taking ibuprofen which could have contributed to the event.

**Table 31. Nonfatal Serious Treatment Emergent Adverse Events (Safety Population) (Study X985400)**

#	USUBJID Age/ Sex/ Race	Serious Adverse Reaction/ Severity/ Onset (days)/ Treatment	Treatment
1	4006311007 50/Male/Black	Gastrointestinal Hemorrhage/Mild/Day (b) (6) Hospitalized	AMLb 10 mg
2	4006741002 51/Female/Black	Lip swelling/Mild/Day 3/ Treated with medication	PERe 16 mg
3	4006831022 74/Female/Caucasian	Pulmonary Embolism/ Severe/Day (b) (6) Hospitalized	PERa/AMLb 14/10 mg
4	4006831044 67/Male/Caucasian	Acute myocardial infarction/Life-Threatening/ Day (b) (6) Hospitalized and underwent complicated left anterior descending coronary artery percutaneous coronary intervention and drug eluting stent placement; underwent cardiopulmonary resuscitation; also underwent percutaneous transluminal angioplasty of the first diagonal artery	AMLb 10 mg
5	4006831046 59/Male/Caucasian	1) Hypotension 2) Acute Renal Failure Moderate/Day (b) (6) Hospitalized	PERe 16 mg
<b>AMLb = amlodipine besylate; PERa/AMLb = perindopril arginine/amlodipine besylate; PERe = perindopril erbumine. Source: Reviewer.</b>			

In Study CL2-05985-005, there were 9 non-fatal serious adverse events (SAEs) (0 in the PERa/AMLb 14/10 mg arm, 1 in the PERa 3.5 mg arm, 3 in the PERa 5 mg arm, 1 in the AMLb 2.5 mg arm, 3 in the AMLb 5 mg arm, and 1 in the placebo arm), as summarized in Table 32.

**Table 32. Nonfatal Serious Emergent Adverse Events (Study CL2-05985-005) (Safety Set)**

#	USUBJID Age/ Sex/ Race	Serious Adverse Reaction/ Severity/ Onset (days)/ Treatment/Outcome	Treatment
1	005 440 3003 00542 49/Female/Caucasian	Appendicitis/ Severe <sup>(b) (6)</sup> Hospitalized for Appendectomy/Drug not withdrawn/Recovered	Placebo
2	005 250 1305 01237 52/Male/Caucasian	Acute coronary syndrome/ Severe <sup>(b) (6)</sup> Hospitalized for percutaneous coronary intervention/Drug withdrawn/Recovered	PERa 3.5 mg
3	005 250 0508 01203 43/Female/Black	Sciatica/ Severe <sup>(b) (6)</sup> Hospitalized/Drug not withdrawn/ Recovered	AMLb 2.5 mg
4	005 643 5005 01476 56/Male/Caucasian	Unstable angina/ Severe <sup>(b) (6)</sup> Hospitalized/Drug withdrawn/ Recovering	PERa 5 mg
5	005 804 6006 00646 70/Female/Caucasian	Abdominal strangulated hernia/ Moderate <sup>(b) (6)</sup> Hospitalized for Surgery/Drug not withdrawn/Recovered	PERa 5 mg
6	005 250 0101 01363 57/Female/Caucasian	Breast cancer (left)/Severe <sup>(b) (6)</sup> Biopsy/Drug not withdrawn/Recovered	PERa 5 mg
7	005 250 0700 00345 55/Male/Caucasian	Cerebrovascular accident (stroke) (thought due to lack of efficacy/ Severe <sup>(b) (6)</sup> Hospitalized/Drug withdrawn/Recovered	AMLb 5 mg
8	005 250 0714 01459 60/Male/Caucasian	Metastatic renal cancer/Severe <sup>(b) (6)</sup> Hospitalized/Drug withdrawn/Not recovered	AMLb 5 mg
9	005 440 3003 01269 50/Female/Caucasian	Renal colic (left urolithiasis)/Moderate <sup>(b) (6)</sup> /Hospitalized for ureteral stent insertion/Drug not withdrawn/Recovered	AMLb 5 mg
<b>AMLb = amlodipine besylate; PERa/AMLb = perindopril arginine/amlodipine besylate; PERa = perindopril arginine. Source: Reviewer.</b>			

### 7.3.3 Dropouts and/or Discontinuations

In Study X985400, there were a total of 35 (4.2%) subjects who discontinued study drug permanently due to an adverse event, including 10 (3.6%) subjects in the PERa/AMLb 14/10 mg group, 12 (4.3%) subjects in the PERe 16 mg group, and 13 (4.6%) subjects in the AMLb 10 mg group. With respect to treatment emergent adverse events (TEAEs), there were a total of 34 (4.1%) subjects who discontinued study drug permanently, including 10 (3.6%) subjects in the PERa/AMLb 14/10 mg treatment group, 11 (4.0%) subjects in the PERe 16 mg group, and 13 (4.6%) subjects in the AMLb 10 mg group. The number of subjects with TEAEs leading to premature discontinuation from the trial is summarized in Table 33. Some subjects experienced multiple TEAEs. Edema (peripheral, gravitational, pitting) was the leading cause of premature discontinuation from the trial.

**Table 33. Subjects with Treatment Emergent Adverse Events who Discontinued Prematurely from the Trial (Study X985400)**

#	Treatment Emergent Adverse Event	PERa/AMLb 14/10 mg QD (N = 279)	PERe 16 mg QD (N = 278)	AMLb 10 mg QD (N = 280)
	<b>TOTAL n (%)</b>	<b>10 (3.6%)</b>	<b>12 (4.3%)</b>	<b>12 (4.3%)</b>
1	Oedema peripheral, gravitational edema, pitting edema	5 (1.8%)	1 (0.4%)	8 (2.6%)
2	Cough	1 (0.4%)	2 (0.7%)	0
3	Blood potassium increased	0	2 (0.7%)	0
4	Dizziness	1 (0.4%)	1 (0.4%)	0
5	Headache	0	1 (0.4%)	1 (0.4%)
6	Acute myocardial infarction	0	0	1
7	Angioedema, lip swelling, epiglottitis	0	3 (1.1%)	0
8	Bradycardia	0	1 (0.4%)	0
9	Fatigue	1 (0.4%)	0	0
10	Gastrointestinal haemorrhage	0	0	1 (0.4%)
11	Irritability	1 (0.4%)	0	0
12	Photophobia	0	0	1 (0.4%)
13	Pulmonary embolism	1 (0.4%)	0	0
14	Renal failure acute	0	1 (0.4%)	0

**Source: Reviewer.**

A listing of subjects who prematurely discontinued from the trial because of TEAEs is included Table 34.

**Table 34. Listing of Subjects who Discontinued Prematurely due to Treatment Emergent Adverse Events (Study X985400) (Safety Population)**

Randomized Treatment Group Subject Number	Adverse Event Preferred Term	Serious
<b>PERa/AMLb 14/10 mg QD</b>		
578-1015	Edema Peripheral Fatigue	No No
615-1001	Gastroesophageal Reflux Disease Fatigue Sexual Dysfunction	No No No
644-1002	Edema Peripheral	No
660-1004	Cough	No
661-1028	Edema Peripheral Erythema	No No
662-1017	Irritability Rash Pruritic	No No
674-1017	Edema Peripheral	No
683-1022	Pulmonary Embolism	Yes
683-1041	Edema Peripheral	No
689-1004	Palpitations Dizziness	No No
<b>PERe 16 mg QD</b>		
580-1026	Headache	No
657-1013	Dizziness	No
661-1003	Bradycardia	No
662-1005	Epiglottitis	No
662-1012	Flatulence Nausea Cough	No No No
662-1013	Cough	No
663-1005	Blood Potassium Increased	No
667-1006	Angioedema	No
674-1002	Lip Swelling	Yes
678-1013	Blood Potassium Increased	No
683-1046	Renal Failure Acute Hypotension	Yes Yes
689-1002	Edema Peripheral	No

Randomized Treatment Group Subject Number	Adverse Event Preferred Term	Serious
<b>AMLb 10 mg QD</b>		
571-1007	Edema Peripheral	No
618-1028	Headache	No
631-1007	Gastrointestinal Hemorrhage	Yes
644-1019	Edema Peripheral	
656-1017	Edema Peripheral	No
665-1006	Pitting Edema	No
665-1015	Gravitational Edema	No
666-1003	Edema Peripheral	No
672-1011	Edema Peripheral	No
680-1013	Photophobia	No
683-1033	Edema Peripheral	No
683-1044	Acute Myocardial Infarction	Yes
690-1001	Edema Peripheral	No

### 7.3.4 Significant Adverse Events

See Sections 7.3.2 and 7.3.3 for details. One patient in the PERa/AMLb 14/10 mg group had a deep vein thrombosis and bilateral pulmonary emboli (Subject 683-1022).

### 7.3.5 Submission Specific Primary Safety Concerns

See Section 7.4.1. for details. Peripheral edema, angioedema, cough, hyperkalemia, hypokalemia, increases in transaminases, hypotension, orthostatic hypotension, and reduction of estimated glomerular filtration rate were the primary safety concerns for this drug product given the known safety profiles of the monocomponents.

Peripheral edema was the most commonly reported adverse event in Study X985400 and in Study CL2-05985-005. In general, the incidence of the events in the FDC arm was similar to the incidence in the monocomponent arms, with the exceptions of peripheral edema, cough, and angioedema. The incidence of peripheral edema was lower in the PERa/AMLb arm than in the AMLb 10 mg arm but was lowest in the PERe 16 mg treatment arm. The incidence of cough was highest in the PERa/AMLb 14/10 mg treatment group followed by the PERe 16 mg and AMLb 10 mg treatment groups. The incidence of angioedema was highest in the PERe 16 mg treatment arm.

The data suggest that PRESTALIA<sup>®</sup> may attenuate the peripheral edema usually seen with NORVASC<sup>®</sup> when administered as a monocomponent.

### **Study X985400**

In Study X985400, 1 patient each in the PERe 16 mg group reported treatment emergent “angioedema,” “face oedema,” “lip swelling,” and “epiglottitis.” Nine patients in the PERa/AMLb 14/10 mg combination group reported cough, compared to 8 patients in the PERe 16 mg group and 2 patients in the AMLb 10 mg group.

Three patients in the PERe 16 mg group reported blood potassium increased and one patient reported hyperkalemia. One patient each in the AMLb 10 mg and PERe 16 mg treatment groups, respectively, reported hypokalemia.

Four patients in the PERe 16 mg group reported alanine aminotransferase increased, and three patients in the PERe 16 mg group and one patient in the PERa/AMLb 14/10 mg group reported aspartate aminotransferase increased. Gamma-glutamyl transferase (GGT) was increased in one patient in the AMLb 10 mg group and one patient in the PERe 16 mg group. Two subjects in the AMLb 10 mg group reported “liver function test abnormal.” One subject in the PERe 16 mg group reported “hepatic enzyme increased.”

No reductions in estimated glomerular filtration rate were reported as adverse events. However there were 2 events of “creatinine renal clearance decreased,” including 1 event in the PERe 16 mg group and 1 event in the AMLb 10 mg group.

Two patients in the PERa/AMLb 14/10 mg group reported “hypotension”, compared to 1 patient in the PERe 16 mg group. One subject in the PERa/AMLb 14/10 mg group reported “diastolic hypotension,” one patient each in the PERe 16 mg group reported “dizziness postural” and “orthostatic hypotension.”

In the PERa/AMLb 14/10 mg group, four patients reported either “erythema” or “generalized erythema” compared to 1 patient in the PERe 16 mg group. One patient each in the PERa/AMLb 14/10 mg group also reported “rash pruritic” or “rash pustular.”

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

Common TEAEs are summarized in Table 35 for Study X985400. A total of 271 (32.4%) subjects experienced at least one TEAE, including 86 (30.8%) subjects in the PERa/AMLb 14/10 mg group, 77 (27.7%) subjects in the PERe 16 mg group, and 108 (38.6%) subjects in the AMLb 10 mg group.

**Table 35. Common Treatment Emergent Adverse Events (Study X985400)**

#	Adverse Event	PERa/AMLb 14/10 mg QD (N = 279)	PERe 16 mg QD (N = 278)	AMLb 10 mg QD (N = 280)
1	Oedema peripheral, gravitational edema, pitting edema	20 (7.2%)	1 (0.4%)	37 (13.2%)
2	Headache	7 (2.5%)	8 (2.9%)	8 (2.9%)
3	Cough	9 (3.2%)	8 (2.9%)	2 (0.7%)
4	Dizziness	7 (2.5%)	4 (1.4%)	3 (1.1%)
5	Fatigue	5 (1.8%)	4 (1.4%)	2 (0.7%)
6	Diarrhea	3 (1.1%)	5 (1.8%)	1 (0.4%)
7	Nausea	2 (0.7%)	4 (1.4%)	2 (0.7%)
8	Arthralgia	2 (0.7%)	3 (1.1%)	2 (0.7%)
9	Back Pain	3 (1.1%)	1 (0.4%)	2 (0.7%)
10	Hematuria	2 (0.7%)	1 (0.4%)	3 (1.1%)
11	Anemia	0	0	5 (1.8%)
12	Musculoskeletal Pain	2 (0.7%)	3 (1.1%)	0
13	Palpitations	1 (0.4%)	2 (0.7%)	2 (0.7%)
14	Pollakiuria	1 (0.4%)	0	4 (1.4%)
15	Tooth infection	2 (0.7%)	2 (0.7%)	1 (0.4%)
16	Upper Respiratory Tract Infection	2 (0.7%)	1 (0.4%)	2 (0.7%)
17	Vomiting	2 (0.7%)	2 (0.7%)	1 (0.4%)
<b>18</b>	<b>Hepatic - total</b>	<b>1 (0.4%)</b>	<b>9 (3.2%)</b>	<b>4 (1.4%)</b>
	Alanine aminotransferase increased	0	4	0
	Aspartate aminotransferase increased	1	3	0
	Liver function test abnormal	0	0	2
	Hepatic enzyme increased	0	1	1
	Gamma-glutamyl transferase increased	0	1	1
<b>19</b>	<b>Hypotension/orthostatic hypotension/diastolic hypotension/postural dizziness - total</b>	<b>2 (0.7%)</b>	<b>4 (1.4%)</b>	<b>0</b>
	Hypotension	2	1	0
	Orthostatic hypotension	0	1	0
	Diastolic hypotension	0	1	0
	Dizziness postural	0	1	0
20	Angioedema, lip swelling, epiglottitis, facial edema	1 (0.4%)	3 (1.1%)	0

**Source: Reviewer.**

In Study CL2-05985-005, a total of 290 subjects reported 348 EAEs including

- 47/249 subjects (18.9%) reporting 54 EAEs in the PERa/AMLb 3.5/2.5 mg group
- 40/251 subjects (15.9%) reporting 46 EAEs in the placebo group
- 51/273 subjects (18.7%) reporting 58 EAEs in the PERa 3.5 mg group
- 51/274 subjects (18.6%) reporting 66 EAEs in the AMLb 2.5 mg group
- 44/272 subjects (16.2%) reporting 56 EAEs in the PERa 5 mg group; and
- 57/264 subjects (21.6%) reporting 68 EAEs in the AMLb 5 mg group

Common EAEs are summarized in Table 36 for Study CL2-05985-005. Some subjects experienced multiple EAEs. Peripheral edema was the most commonly reported adverse event and was lower in the combination group (4 subjects, 1.6%) than in the AMLb 5mg group (13 subjects, 4.9%).

**Table 36. Common Emergent Adverse Events (Study CL2-05985-005)**

#	Adverse Event	PERa/AMLb 3.5/2.5 mg (N = 249)	Placebo (N = 251)	PERa 3.5 mg (N = 273)	AMLb 2.5 mg (N = 274)	PERa 5 mg (N = 272)	AMLb 5 mg (N = 264)
1	Oedema peripheral	4 (1.6%)	3 (1.2%)	8 (2.9%)	2 (0.7%)	4 (1.5%)	13 (4.9%)
2	Headache	3 (1.2%)	4 (1.6%)	5 (1.8%)	4 (1.5%)	3 (1.1%)	1 (0.4%)
3	<b>Hyperkalemia/blood potassium increased</b>	<b>7 (2.8%)</b>	<b>1 (0.4%)</b>	<b>1 (0.4%)</b>	<b>7 (2.6%)</b>	<b>3 (1.1%)</b>	<b>1 (0.4%)</b>
	Hyperkalemia	6 (2.4%)	0	0	6 (2.2%)	2 (0.7%)	1 (0.4%)
	Blood potassium increased	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0
4	Nasopharyngitis	3 (1.2%)	1 (0.4%)	2 (0.7%)	3 (1.1%)	2 (0.7%)	3 (1.1%)
5	Bronchitis	2 (0.8%)	4 (1.6%)	2 (0.7%)	3 (1.1%)	1 (0.4%)	0
6	Cough	2 (0.8%)	1 (0.4%)	3 (1.1%)	2 (0.7%)	3 (1.1%)	1 (0.4%)
7	Back pain	1 (0.4%)	1 (0.4%)	0	2 (0.7%)	2 (0.7%)	5 (1.9%)
8	Dyslipidemia	1 (0.4%)	2 (0.8%)	1 (0.4%)	4 (1.5%)	1 (0.4%)	2 (0.8%)
9	Creatinine renal clearance decreased	3 (1.2%)	1 (0.4%)	0	2 (0.7%)	2 (0.7%)	1 (0.4%)
10	Influenza	1 (0.4%)	1 (0.4%)	3 (1.1%)	0	1 (0.4%)	2 (0.8%)
11	Sinus tachycardia	1 (0.4%)	2 (0.8%)	0	3 (1.1%)	2 (0.7%)	0
12	Hypertension	1 (0.4%)	1 (0.4%)	0	2 (0.7%)	2 (0.7%)	1 (0.4%)
13	Hypertensive Crisis	0	0	0	0	0	1 (0.4%)
14	Blood glucose increased	1 (0.4%)	0	1 (0.4%)	0	3 (1.1%)	0
15	Glucose tolerance impaired	0	0	1 (0.4%)	1 (0.4%)	0	0
16	<b>Hot flush/flushing</b>	<b>1 (0.4%)</b>	<b>0</b>	<b>2 (0.7%)</b>	<b>0</b>	<b>0</b>	<b>5 (1.9%)</b>
	Hot flush	1 (0.4%)	0	2 (0.7%)	0	0	2 (0.8%)
	Flushing	0	0	0	0	0	3 (1.1%)

**Source: Reviewer.**

## **7.4.2 Laboratory Findings**

There were no clinically meaningful changes in laboratory parameters with PRESTALIA<sup>®</sup>, and changes in laboratory parameters were consistent with prior experience with the monocomponents. ACEON<sup>®</sup> prescribing information reports that elevations in ALT (1.6% ACEON<sup>®</sup> versus 0.9% placebo) and AST (0.5% ACEON<sup>®</sup> versus 0.4% placebo) have been observed in placebo-controlled clinical trials. Hepatic failure, jaundice (hepatocellular or cholestatic) have been observed postmarketing with ACEON<sup>®</sup>. See Section 7.3.5 for further details.

## **7.4.3 Vital Signs**

There were no clinically meaningful changes in body weight and heart rate.

## **7.4.4 Electrocardiograms (ECGs)**

There were no clinically meaningful changes in electrocardiographic parameters.

## **7.4.5 Special Safety Studies/Clinical Trials**

No special safety studies/clinical trials were conducted.

## **7.4.6 Immunogenicity**

Perindopril arginine has been marketed extensively in Europe and amlodipine besylate has been marketed globally. Both drug products are small molecules and are not known to have immunogenic potential.

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

See Section 7.4.1.

### 7.5.2 Time Dependency for Adverse Events

There was a wide variation between treatment groups and sexes with respect to the onset of peripheral edema. In general, the standard deviation was wide.

**Table 37. Onset of Peripheral Edema (Days)(Study X985400)**

Onset of Peripheral Edema (Days) (Study X985400)	PERa/AMLb 14/10 mg Median (SD)	PERe 16 mg Median (SD)	AMLb 10 mg Median (SD)
Men (Mean, SD)	6 (7.8)	2 (0)	16.5 (12.4)
Women (Mean, SD)	17 (10.5)	0	8 (11.6)
<b>AMLb = amlodipine besylate; PERa/AMLb = perindopril arginine/amlodipine besylate; PERa = perindopril arginine. Source: Reviewer.</b>			

### 7.5.3 Drug-Demographic Interactions

There were no meaningful differences in the overall incidence of adverse events by sex, race, and age.

- **Sex**

Peripheral edema by sex is summarized in Table 38 for Study X985400. The incidence of peripheral edema was highest in women and was almost two-fold the incidence of peripheral edema observed in men for both the PERa/AMLb 14/10 mg and AMLb 10 mg treatment groups. In both men and women, the incidence of peripheral edema appeared to be lower on FDC than on AMLb 10 mg.

**Table 38. Peripheral Edema by Sex (Study X985400)**

Peripheral Edema (Study X985400)	PERa/AMLb 14/10 mg	PERe 16 mg	AMLb 10 mg
<b>TOTAL (N = 837)</b>	20/279 (7.2%)	1/278 (0.4%)	35/280 (12.5%)
<b>Men</b>	7/145 (4.8%)	1/135 (0.7%)	14/150 (9.3%)
<b>Women</b>	13/134 (9.7%)	0/143 (0%)	21/130 (16.2%)
<b>AMLb = amlodipine besylate; PERa/AMLb = perindopril arginine/amlodipine besylate; PERa = perindopril arginine. Source: Reviewer.</b>			

Peripheral edema by sex is summarized in Table 39 for Study CL2-05985-005. The incidence of peripheral edema was low with AMLb 2.5 mg and PERa/AMLb 3.5/2.5 mg. A dose-dependent increase in the incidence of edema was observed in men and women with AMLb. In women only, the incidence of peripheral edema was lower in the PERa/AMLb 3.5/2.5 mg group than in the AMLb 5 mg group.

**Table 39. Peripheral Edema by Sex (Study CL2-05985-005)**

Peripheral Edema	PERa/AMLb 3.5/2.5 mg	Placebo	PERa 3.5 mg	AMLb 2.5 mg	PERa 5 mg	AMLb 5 mg
<b>TOTAL</b>	<b>4/249 (1.6%)</b>	<b>3/250 (1.2%)</b>	<b>8/272 (2.9%)</b>	<b>2/276 (0.7%)</b>	<b>4/272 (1.5%)</b>	<b>13/263 (4.9%)</b>
<b>Men, N</b>	<b>117</b>	<b>116</b>	<b>127</b>	<b>130</b>	<b>129</b>	<b>121</b>
<b>Men, n (%)</b>	<b>2 (1.7%)</b>	<b>1 (0.9%)</b>	<b>1 (0.8%)</b>	<b>1 (0.8%)</b>	<b>0 (0%)</b>	<b>2 (1.7%)</b>
<b>Placebo-subtracted</b>	<b>0.8%</b>		<b>-0.1%</b>	<b>-0.1%</b>	<b>-0.9%</b>	<b>0.8%</b>
<b>Women, N</b>	<b>132</b>	<b>134</b>	<b>145</b>	<b>146</b>	<b>143</b>	<b>142</b>
<b>Women, n (%)</b>	<b>2 (1.5%)</b>	<b>2 (1.5%)</b>	<b>7 (4.8%)</b>	<b>1 (0.7%)</b>	<b>4 (2.8%)</b>	<b>11 (7.7%)</b>
<b>Placebo-subtracted</b>	<b>0%</b>		<b>3.3%</b>	<b>0.8%</b>	<b>1.3%</b>	<b>6.2%</b>

**Source: Reviewer.**

Given that the patient populations studied in the two pivotal trials were substantially different (i.e., obese patients were studied in Study X985400), cross-study comparisons with respect to peripheral edema could be difficult to interpret.

- **Race**

With respect to race, 98% of subjects enrolled in Study CL2-05985-005 were Caucasian. In Study X985400, approximately 64% of subjects were Caucasian and 34% of subjects were Black, so comments on drug-race interactions will focus on the results of Study X985400.

- **Peripheral Edema**

In Black subjects, the incidence of treatment emergent peripheral edema was similar in the PERa/AMLb 14/10 mg (3 [3.2%] subjects) and AMLb 10 mg (3 [3.1%]) treatment groups. No Black subject in the PERe 16 mg treatment group reported peripheral edema.

In non-Black subjects, the incidence of peripheral edema was higher in the AMLb 10 mg group (33 [17.9%] subjects) than in the PERa/AMLb 14/10 mg (16 [8.7%] subjects) and PERe 16 mg (1 [0.5%] subject) treatment groups.

- **Cough**

In Black subjects, the incidence of cough was slightly higher in the PERe 16 mg group (4 [4.2%] subjects), compared to the PERa/AMLb 14/10 mg (2 [2.1%] subjects) and AMLb 10 mg (1 [1.0%] subject) treatment groups though the numbers are small.

In non-Black subjects, the incidence of cough was higher in PERa/AMLb 14/10 mg group (7 [3.8%] subjects) compared to the PERe 16 mg (4 [2.2%] subjects) and AMLb 10 mg group (1 [0.5%] subject) treatment groups though again the numbers are small.

- **Headache**

In Black subjects, the incidence of headache was highest in the PERa/AMLb 14/10 mg group (5 [5.3%] subjects), compared to the AMLb 10 mg (4 [4.2%] subjects) and PERe 16 mg (2 [2.1%]) treatment groups.

In non-Black subjects, the incidence of headache was highest in the PERe 16 mg group (6 [3.3%] subjects), compared to the AMLb 10 mg (5 [2.7%] subjects) and PERa/AMLb 14/10 mg (3 [1.6%] subjects).

- **Dizziness and Hypotension**

In Black subjects, the incidence of dizziness was 3 [3.1%] subjects in both the PERe 16 mg and AMLb 10 mg treatment groups. No subjects in the PERa/AMLb 14/10 mg group had a treatment emergent adverse event of dizziness.

In non-Black subjects, the incidence of dizziness was highest in the PERa/AMLb 14/10 mg group (7 [3.8%]), compared to the PERe 16 mg (3 [1.6%] subjects) and AMLb 10 mg (1 [0.5%] subject) treatment groups.

No treatment emergent adverse events of hypotension were reported in Black subjects. In non-Black subjects, 3 (1.6%) of subjects in the PERa/AMLb 14/10 mg, 2 (1.1%) subjects in the PERe 16 mg group, and no subjects in the AMLb 10 mg treatment groups had an incidence of hypotension.

- **Age**

Few elderly subjects were enrolled in the pivotal trials. With respect to Study X985400, there did not appear to be any meaningful differences in the overall incidence of adverse events comparing subjects < 65 years to ≥ 65 years of age.

#### 7.5.4 Drug-Disease Interactions

There were no meaningful differences in the overall incidence of adverse events by diabetes status.

Among subjects with type 2 diabetes, 47 (27.5%) subjects had a TEAE. No subjects had a SAE. Three subjects (1.8%) discontinued study drug due to an adverse event.

Among subjects without type 2 diabetes, 224 (33.6%) subjects had a TEAE and 5 (0.8%) of subjects had a SAE. Thirty-one (4.7%) subjects discontinued study drug due to an adverse event.

Among subjects with diabetes, the most common TEAEs were peripheral edema and headache. With respect to peripheral edema, 1 (1.7%) subject in the PERa/AMLb 14/10 mg group and 6 (10.7%) subjects in the AMLb 10 mg reported peripheral edema. No patients in the PERe 16 mg treatment group reported peripheral edema. With respect to headache, 1 (1.7%) subject in the PERa/AMLB 14/10 mg group, 2 (3.6%) subjects in the PERe 16 mg group, and 3 (5.4%) subjects in the AMLb 10 mg group reported headache.

Among subjects without diabetes, the most common TEAEs were peripheral edema, headache, and cough. Nineteen (8.6%), 1 (0.5%), and 29 (12.9%) subjects reported peripheral edema in the PERa/AMLb 14/10 mg, PERe 16 mg, and AMLb 10 mg treatment groups, respectively. Six (2.7%), 6 (2.7%), and 5 (2.2%) of subjects reported headache in the PERa/AMLb 14/10 mg, PERe 16 mg, and AMLb 10 mg treatment groups. Cough was reported in 8 (3.6%) subjects in the PERa/AMLb 14/10 mg group, 7 (3.2%) subjects in the PERe 16 mg group, and 2 (0.9%) of subjects in the AMLb 10 mg group.843449

#### 7.5.5 Drug-Drug Interactions

There were no apparent drug-drug interactions with PRESTALIA<sup>®</sup>. See Section 4.4, Clinical Pharmacology, for further details.

ACEON<sup>®</sup> has the potential for DDI with the following drug products:

- Diuretics: Following the initiation of ACEON<sup>®</sup> therapy, there may be an excessive reduction of blood pressure
- Potassium supplements and potassium-sparing diuretics: ACEON<sup>®</sup> or any ACE-I may increase serum potassium because of its potential to decrease aldosterone production
- Lithium: ACEON<sup>®</sup> may increase serum lithium and symptoms of lithium toxicity

- Gold: Patients on therapy with injectable gold and concomitant ACE-I therapy may experience nitritoid reactions, with symptoms including facial flushing, nausea, vomiting, and hypotension
- Digoxin: An effect of digoxin on the plasma concentration of perindopril/perindoprilat has not been excluded
- Gentamicin: Nonclinical data suggest the possibility of interaction between perindopril and gentamicin
- Non-steroidal anti-inflammatory agents including selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDS, including selective COX-2 inhibitors, with ACE-Is may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.)
- Dual blockade of the renin-angiotensin system (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE-Is, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

NORVASC<sup>®</sup> has known drug interactions with simvastatin, CYP3A4 inhibitors, and cyclosporine.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No cancer-related adverse reaction was reported in Study X985400. In Study CL2-05985-005, Subject 005 250 0101 01363 reported an adverse event of left breast cancer (PERa 5 mg) and Subject 005 250 0714 01459 reported an adverse event of metastatic renal cancer (AMLb 5 mg).

There was no evidence of carcinogenic effect observed in studies in rats and mice when perindopril was administered at dosages up to 20 times (mg/kg) or 2 to 4 times (mg/m<sup>2</sup>) the maximum proposed clinical doses (16 mg/day) for 104 weeks.

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day amlodipine, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m<sup>2</sup> basis, similar to the maximum recommended human

dose of 10 mg amlodipine/day (based on patient weight of 50 kg). For the rat, the highest dose was, on a mg/m<sup>2</sup> basis, about twice the maximum recommended human dose (based on patient weight of 50 kg).

### 7.6.2 Human Reproduction and Pregnancy Data

- There are no adequate or well-controlled studies of perindopril arginine/amlodipine besylate FDC in pregnant or lactating women and no reproductive toxicology studies have been conducted with the combination to date.
- Nonclinical studies found that ACEON<sup>®</sup>, perindopril, perindoprilat and other metabolites had no genotoxic potential in various in vitro and in vivo investigations, including the Ames test, the *Saccharomyces cerevisiae* D4 test, cultured human lymphocytes, TK ± mouse lymphoma assay, mouse and rat micronucleus tests and Chinese hamster bone marrow assay.

In the rat given up to 30 times (mg/kg) or 6 times (mg/m<sup>2</sup>) the proposed maximum clinical dosage of ACEON<sup>®</sup> during the period of spermatogenesis in males or oogenesis and gestation in females, there was no meaningful effect on reproductive performance or fertility.

- Mutagenicity studies with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose (based on patient weight of 50 kg) of 10 mg/day of a mg/m<sup>2</sup> basis.

- In Study CL2-05985-005, pregnancy was detected in 2 patients during the run-in period (No. 005 804 6007 02486, 35 years, and No. 005 348 7006 02557, 42 years) and these patients were not included in the study. One patient had a therapeutic abortion and one patient had an elective abortion.

ACE-Is have a box warning for fetal toxicity. When pregnancy is detected, the ACE-I should be discontinued as soon as possible because drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. PRESTALIA<sup>®</sup> should be labeled in the same manner.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant did not conduct pediatric studies. Safety and effectiveness have been established for amlodipine besylate but not for perindopril erbumine in the pediatric population.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

**Drug abuse potential.** There were no adverse reactions reported in the pivotal trials that were indicative of abuse or dependence potential. The risk of abuse or dependence with PRESTALIA is thought to be low.

**Withdrawal and Rebound:** Rapid withdrawal of any antihypertensive drug could lead to an increase in blood pressure and cardiovascular events. Randomized withdrawal studies with NORVASC<sup>®</sup> or ACEON<sup>®</sup> are not described in prescribing information.

#### 7.7 Additional Submissions / Safety Issues

There were no additional submissions. See Section 8 for additional safety issues.

### 8 Postmarket Experience

ACEON<sup>®</sup> (NDA 020184) and NORVASC<sup>®</sup> were approved by the FDA on December 30, 1993 and July 31, 1992, respectively, so the Agency has an extensive postmarketing safety database for these drug products. Prescribing information for these drug products includes all known safety risks and was last updated on January 7, 2013 (NORVASC<sup>®</sup>) and on February 26, 2013 (ACEON<sup>®</sup>).

The Safety Information Amendment for PRESTALIA was submitted to IND 108,233 on September 18, 2014 and included spontaneous serious and unexpected adverse events from March 28, 2013 to September 9, 2014 that were reported by Symplmed's development partner, Servier, in Europe. The Safety Information Amendment identified the following new safety issues with the combination product:

- Immune thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP)
- Status epilepticus/convulsions
- Allergic skin reactions
- Lymphohistiocytic inflammatory infiltrate

The ITP (PERa/AMLb 5/5 mg), TTP (PERa/AMLb 5/5 mg), and convulsion (PERa/AMLb dose unknown) adverse reactions were discussed with Mary Ross Southworth, PharmD., Deputy Director of Safety for the Division of Cardiovascular and Renal Products. The convulsions occurred in a 70 year old woman (France) with a history of multiple ischemic strokes, Alzheimer's disease, ischemic cardiomyopathy, diabetes, and depression. This patient had a positive rechallenge, suggesting that the convulsions were drug-related.

The ITP event occurred in a 61 year old woman (France) with a history of autoimmune thyroid goiter. Concomitant treatment, if any, was not provided.

The TTP event occurred in a 48 year old woman (Croatia) with an unspecified medical history. Concomitant treatment, if any, was not provided.

Causality for the ITP and TTP cases is difficult to determine, given the lack of details. Continued safety vigilance was recommended, and the above adverse reactions will be included in prescribing information for PRESTALIA<sup>®</sup>.

## **9 Appendices**

### **9.1 Literature Review/References**

James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith, Jr., SC, Svetkey LP, Taler SJ, Townsend RR, Wright, Jr. JT, Narva AS, Ortiz E. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311(5):507-520.

Go AS, Bauman MA, Coleman King SM, Fonarow GC, Lawrence W, Williams KA, Sanchez E. An Effective Approach to High Blood Pressure Control. *J Am Coll Cardiol* 2014;63:1230-8.

Krakoff LR, Gillespie RL, Ferdinand KC, Fergus IV, Akinboboye O, Williams KA, Walsh MN, Merz NB, Pepine CJ. 2014 Hypertension Recommendations From the Eighth Joint National Committee Panel Members Raise Concerns for Elderly Black and Female Populations. *J Am Coll Cardiol* 2014;64:394-402.

Gibbons GH, Shurin SB, Mensah GA, Lauer MS. Refocusing the Agenda on Cardiovascular Guidelines: An Announcement From the National Heart, Lung, and Blood Institute. *Circulation* 2013;128:1713-1715.

### **9.2 Labeling Recommendations**

Proposed labeling changes will be uploaded into SharePoint.

### **9.3 Advisory Committee Meeting**

No Advisory Committee Meeting is planned.

#### **9.4 Pediatric Waiver**

The applicant is requesting a waiver for all pediatric studies because PRESTALIA<sup>®</sup> FDC does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

The Division agrees with the request for the waiver because PRESTALIA<sup>®</sup> is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, Pediatrics 2004;114:555-578).

The PeRC will discuss the applicant's request for a pediatric waiver on December 3, 2014.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN A HICKS  
11/26/2014

ALIZA M THOMPSON  
11/26/2014

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 20,5003**

**Applicant: Symplmed  
Pharmaceuticals, LLC**

**Stamp Date: March 21, 2014**

**Drug Name: Prestalia  
(Perindopril arginine/Amlodipine  
besylate fixed dose  
combination/TABLET)  
(Strengths: 3.5 mg/2.5 mg;  
7 mg/5 mg; 14 mg/10 mg)**

**NDA/BLA Type: 505(b)(2)**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5.6 (Clinical Overview; Benefits and Risks Summary)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(2)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?	X			The reference drugs are perindopril erbumine (PERe) and amlodipine besylate (AML)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			Defer to Biopharmaceutics

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

15.	Describe the scientific bridge (e.g., BA/BE studies)	X		<p>In this NDA submission, the sponsor requested the following three biowaivers:</p> <ul style="list-style-type: none"> <li>• A biowaiver for a comparative bioavailability study for a 505(b)(2) NDA</li> <li>• A biowaiver for a bioequivalence study to bridge the clinical studies conducted by Servier outside the United States and the clinical studies conducted by XOMA in the US due to different manufacturers; and</li> <li>• A biowaiver for a dosage form equivalence study</li> </ul> <p>For the scientific bridge, the sponsor provided a cross-study comparison (Comparative Bioavailability Report) using information from a food effect PK study (X985401) of XOMA 985 fixed-dose combination (PERa/AML 14/10 mg) and publicly available PK data for ACEON<sup>®</sup> (perindopril erbumine [PERe]) and NORVASC<sup>®</sup> (amlodipine besylate).</p>
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	Indication: Hypertension				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			The trials appear to be adequate and well-controlled, but the submitted data may not be sufficient to support the proposed claim.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

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

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

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<b>OTHER STUDIES</b>				
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X
<b>PEDIATRIC USE</b>				
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X		
<b>ABUSE LIABILITY</b>				
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X
<b>FOREIGN STUDIES</b>				
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X		
<b>DATASETS</b>				
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X		
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X		
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X		
37.	Are all datasets to support the critical safety analyses available and complete?	X		
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X		
<b>CASE REPORT FORMS</b>				
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X		
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X		
<b>FINANCIAL DISCLOSURE</b>				
41.	Has the applicant submitted the required Financial Disclosure information?	X		
<b>GOOD CLINICAL PRACTICE</b>				
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X		

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IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes.

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

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

1. At the face-to-face meeting with the Division on October 20, 2010, XOMA (US) LLC confirmed that for any dose of the combination product (perindopril arginine/amlodipine besylate), (b) (4)



The proposed prescribing information in the NDA submission states that “PRESTALIA is indicated for the treatment of hypertension.”

It is not clear at this time whether the submitted data support such a broad claim.

2. The submission seeks approval of Prestalia® in three strengths: 3.5/2.5 mg, 7/5 mg, and 14/10 mg. Prestalia® (7/5 mg) was not evaluated in either the Phase 3 (Study X985400 (PATH)) or Phase 2 (Study CL2-05985-005) clinical trials. Hence, there are no data that directly address the effectiveness or safety of this dose as compared with the low and high dose combinations. Therefore, it is unclear how prescribing information for Prestalia® can provide adequate instructions for use of the 7/5 mg dose.
3. The lack of a placebo arm (or 24-hour ambulatory blood pressure data which do not appear to be susceptible to a placebo effect) does not allow us to compare the effect size of the lower dose combination with the higher dose combination (perindopril arginine/amlodipine besylate 3.5/2.5 mg versus 14/10 mg).
4. For Studies X985400 (PATH) and CL2-05985-005, please submit the following graphs by study and treatment group:
  - Probability of Achieving SBP < 140 mm Hg
  - Probability of Achieving SBP < 130 mm Hg
  - Probability of Achieving DBP < 90 mm Hg
  - Probability of Achieving DBP < 80 mm Hg

Karen A. Hicks, M.D.	5/16/2014
Reviewing Medical Officer	Date

Aliza Thompson, M.D.	5/16/2014
Clinical Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KAREN A HICKS  
05/16/2014

ALIZA M THOMPSON  
05/16/2014