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*APPLICATION NUMBER:*

**205003Orig1s000**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	January 8, 2015
<b>From</b>	Aliza Thompson
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 205003
<b>Supplement#</b>	
<b>Applicant</b>	Symplmed Pharmaceuticals, LLC
<b>Date of Submission</b>	March 21, 2014
<b>PDUFA Goal Date</b>	January 21, 2015
<b>Proprietary Name/ Established (USAN) names</b>	Prestalia / perindopril arginine and amlodipine
<b>Dosage forms / Strength</b>	Oral tablets of perindopril arginine and amlodipine in doses of 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg
<b>Proposed Indication(s)</b>	Treatment of hypertension
<b>Recommended:</b>	Approval of Prestalia (3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg tablets) for the treatment of hypertension, to lower blood pressure, in patients whose blood pressure is not adequately controlled on monotherapy and as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals

This secondary review is based on the following reviews:

Product Quality Microbiology Review (May 16, 2014)	Bryan Riley
Chemistry Review (November 14 and December 23, 2014)	Charles Jewell
Biopharmaceutics Review (November 20, 2014)	Sandra Suarez Sharp
Pharmacology Toxicology Review (August 4, 2014)	Baichun Yang
Clinical Pharmacology Reviews Primary Review (December 8, 2014) Secondary Review (December 8, 2014)	Peter Hinderling Sudharshan Hariharan
Clinical Review (November 26, 2014)	Karen Hicks
Statistical Reviews (November 6, 2014 and January 8, 2015)	Jialu Zhang
Division of Medication Error Prevention and Analysis Reviews (April 15, July 16 and December 23, 2014)	Janine Stewart
Office of Scientific Investigations Clinical Inspection Summary (September 22, 2014)	Sharon Gershon
Patient Labeling Review (December 12, 2014)	Karen Dowdy and Zarna Patel

## 1. Introduction

On March 21, 2014, Symplmed Pharmaceuticals, LLC submitted a 505 (b)(2) application for Prestalia, a fixed-dose combination of perindopril arginine and amlodipine in doses of 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg, for the treatment of hypertension. Amlodipine, a calcium channel antagonist, was first approved in the U.S. in 1987. Perindopril arginine, an angiotensin converting enzyme inhibitor, is not approved in the U.S.; however, perindopril erbumine, which shares the same active ingredient, is.

In support of the proposed indication for Prestalia, the applicant submitted, among other items, the results of:

- a phase 3 trial comparing the highest proposed dose of Prestalia with the highest approved doses of perindopril erbumine and amlodipine
- a phase 2 trial comparing the efficacy and safety of the lowest proposed dose of Prestalia with two doses of amlodipine (2.5 mg and 5.0 mg) and two doses of perindopril arginine (3.5 mg and 5.0 mg)
- pharmacokinetic studies including a cross-study comparison to demonstrate bioequivalence for perindopril, perindoprilat and amlodipine between Prestalia, Aceon (perindopril erbumine) and Norvasc (amlodipine besylate).

The submitted data indicate that the highest proposed dose of Prestalia (14 mg/10 mg) is more effective than the highest approved dose of perindopril erbumine and amlodipine in reducing systolic and diastolic blood pressure. The data also indicate that the low dose of Prestalia (3.5 mg/2.5 mg) is more effective in reducing blood pressure than its monocomponents at those doses. However, the applicant's cross study comparison failed to establish a pharmacokinetic bridge between exposure to perindopril and perindoprilat in Prestalia and Aceon (perindopril erbumine).

From a clinical pharmacology and clinical perspective, the main review issues have been:

- 1) the applicant's failure to establish a pharmacokinetic bridge between exposure to perindopril in Prestalia and Aceon (perindopril erbumine) and the implications of this failure
- 2) whether to approve the 7 mg/5 mg dose of Prestalia, which was not evaluated in either the phase 2 or phase 3 trial

Dr. Zhang, the statistical reviewer, has also voiced concern about the randomization algorithm used to balance treatment group assignments across strata in the applicant's phase 3 trial. According to Dr. Zhang's review and subsequent email correspondence, the algorithm that was used was deterministic and represents bad practice, but it is not a barrier to approval.

## 2. Background

*Hypertension and the regulatory basis for approval of products intended to treat hypertension*

Hypertension is common in the U.S. and can cause adverse outcomes including stroke, myocardial infarction, end-stage kidney disease and death. Lowering blood pressure using drugs from a variety of pharmacologic classes has been shown in randomized controlled trials to reduce the risk of adverse cardiovascular outcomes in adults with hypertension.

As noted in Dr. Hicks' review (see Tables 1 and 2), many agents, including fixed-dose combination products, have been approved to treat chronic hypertension in adults. In general, products are approved to treat hypertension based on their ability to lower blood pressure, a surrogate endpoint, and an acceptable safety profile. To date, development programs for fixed-dose combination products have also been required to demonstrate that the fixed-dose combination product provides a clinically meaningfully greater reduction in blood pressure than the highest approved dose of its corresponding monocomponents.

***Prestalia's regulatory history***

The fixed-dose combination of perindopril arginine and amlodipine was developed for the treatment of hypertension by XOMA (US) LLC under IND 108233. A preIND meeting was held with the Division in October 2010. At that time, a fixed-dose combination of perindopril arginine-amlodipine was approved and marketed in Europe at the following doses of perindopril arginine/amlodipine: 5 mg/5 mg; 10 mg/5 mg; 5 mg/10 mg; 10 mg/10 mg. The stated purpose of the meeting was to obtain the Division's feedback on the adequacy of the available information to support a marketing application in the U.S. for the following dosage strengths of the fixed-dose combination of perindopril arginine/amlodipine: 3.5 mg/2.5 mg; 7 mg/5 mg; 14 mg/10 mg.

In its preliminary responses to the sponsor's questions, the Division indicated that the data described in the briefing document were not sufficient to support a marketing application, and noted that none of the referenced studies delineated the superiority of the combination product to the highest doses of each of the monotherapies. The Division stated that for the combination therapy to be approved, the efficacy of the combination would need to be statistically and clinically superior to the highest approved doses of the corresponding monotherapies. During the meeting, the sponsor indicated that the highest approved dose of perindopril erbumine was 16 mg and stated that this dose was equivalent to approximately 20 mg of perindopril arginine. To supply the data needed to support approval, the sponsor proposed a three-arm study comparing perindopril erbumine 16 mg, amlodipine 10 mg and perindopril arginine 14 mg/amlodipine 10 mg; the Division agreed that the proposal was reasonable.

The sponsor also asked about an indication as initial therapy in patients with hypertension. The Division responded that "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." The Division also commented that "None of the sponsor's prior non-IND studies provide this information, nor does the study design being proposed here (b) (4)

[REDACTED]

Approximately 10 months after the preIND meeting, XOMA submitted a new IND for the fixed-dose combination product. The protocol for the aforementioned phase 3 trial was submitted as the IND opening study.

For further discussion of the regulatory history, see pages 18 and 19 of Dr. Hicks' review.

*Reviewer's comment: It is important that a development program identify a set of doses that provide reasonable dose titration steps, but I do not think a full factorial study is needed to do so. It is also not obvious to me that a full factorial dataset throughout the entire dose range is needed to support a claim as initial therapy for a two-drug combination antihypertensive.*

### 3. CMC/Biopharmaceutics

According to Drs. Jewell and Suarez, the application can be approved from a CMC and biopharmaceutics perspective. As per the CDER Office of Compliance (Reviewer: Vibhakar Shah), the manufacturing sites are also acceptable.

#### ***General description***

Prestalia is a combination of perindopril arginine and amlodipine besylate.

- Perindopril arginine is the L-arginine salt of perindopril, the ethyl ester of a non-sulphydryl angiotensin converting enzyme inhibitor. It is a white, crystalline powder, has a molecular weight of 542.7, and is readily soluble in purified water, slightly soluble in 95% ethanol, and practically insoluble in chloroform.

Perindopril is the free-acid form of perindopril arginine. Perindopril is a pro-drug and is metabolized in vivo by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite.

- Amlodipine besylate is the benzene sulphonic acid salt of amlodipine, a long-acting dihydropyridine calcium channel blocker. It is a white, crystalline powder, has a molecular weight of 567.1 and is slightly soluble in water and sparingly soluble in ethanol. The content of the tablets is expressed as amlodipine (free base) which has a molecular weight of 409.1.

Prestalia tablets are formulated in three different strengths of perindopril arginine/amlodipine: 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg. Inactive excipients include lactose, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.

#### ***Biopharmaceutics***

The application included data to support the dissolution method and acceptance criterion. The application also contained biowaiver requests for (1) an in vivo dosage strength proportionality study, and (2) a BE study to bridge the clinical studies conducted by Servier outside the U.S. and the clinical studies conducted by XOMA in the U.S. According to Dr. Suarez,

- The applicant submitted adequate information to support the discriminating ability of the dissolution method and agreement has been reached on the dissolution acceptance criterion ( $Q = \frac{(b)}{(4)}\%$  in 15 min).

- The biowaiver requests are acceptable. The in vitro dissolution and manufacturing data indicate that: (1) the tablets manufactured at the XOMA and Servier sites are bioequivalent; and (2) the three commercial strengths of Prestalia tablets are identical with regard to dosage form, mechanism of drug release, and the proportion of active and inactive ingredients.

#### ***Expiration dating period for Prestalia***

An expiration dating period of 18 months is assigned for the 3.5 mg/2.5 mg strength and 24 months for the 7 mg/5 mg and 14 mg/10 mg strengths in the described packaging configurations.

## **4. Nonclinical Pharmacology/Toxicology**

According to Dr. Yang's review, the application can be approved from a pharmacology and toxicology perspective. Because perindopril arginine has never been marketed in the U.S., preclinical studies were performed to compare the pharmacokinetic and safety profiles of perindopril arginine and perindopril erbumine. Bridging studies were also conducted to establish that the fixed-dose combination did not result in any unexpected toxicities or drug-drug interactions between the components.

Per Dr. Yang:

- The nonclinical studies demonstrated that the arginine and erbumine salts of perindopril have a similar PK profile and, in general, a similar safety profile. Her review notes that in the 28-day repeat dose study in dogs, decreases in red blood cell count (~20% vs. pre-test value) and hemoglobin (one out of three females in two dose groups) were observed in perindopril arginine but not perindopril erbumine treated dogs. Minimal to moderate medulla and/or papilla mineralization in the kidneys (one out of three dogs at all dose-levels) were also observed in perindopril arginine but not perindopril erbumine treated dogs. Based on these findings, she calculates a NOAEL of 0.83 mg/kg/day, ~2 times the recommended human maximal dose of perindopril arginine of 14 mg in the combination product for a 60-kg human on a body surface basis. Of note, these findings were not observed with perindopril arginine or perindopril erbumine in a 28-day study in Wistar rats or in a 13-week study with perindopril arginine/amlodipine in Wistar rats. Otherwise, safety findings were similar between perindopril arginine and erbumine in repeat-dose oral studies in rats and dogs. Her review also notes that perindopril arginine was not mutagenic in either in vitro or in vivo genotoxic assays.
- No new target organs or relevant additive effects were identified with the combination of perindopril arginine and amlodipine and there were no toxicokinetic drug-drug interactions between perindopril arginine and amlodipine.
- Studies of drug substance impurities and drug product impurities did not raise any safety concerns. According to Dr. Yang (primary review and email correspondence dated November 3, 2014), there were no structural alerts for genotoxicity for the five impurities and hence the impurities are considered qualified at the proposed specifications.

## 5. Clinical Pharmacology

### *Pharmacokinetic considerations*

As previously noted, the applicant performed:

- a drug interaction study to assess for a pharmacokinetic interaction between Prestalia's monocomponents;
- a food interaction study;
- a cross-study comparison to demonstrate bioequivalence for perindopril, perindoprilat and amlodipine between the XOMA FDC tablet (perindopril arginine/amlodipine besylate 14/10 mg), Aceon (perindopril erbumine 16 mg) and Norvasc (amlodipine besylate 10 mg).

*Reviewer's comment: The cross study comparison used exposure measures obtained for perindopril/perindoprilat and amlodipine from the applicant's food effect study (fasted state) and from studies reported in the NDAs for Aceon and Norvasc. While the applicant has right of reference to the Aceon NDA, the applicant does not have right of reference to any Norvasc NDAs. However, as discussed in Dr. Hinderling's review, the applicant also submitted a published study (Vincent et al, 2000) containing summary PK data for Norvasc that could be used to establish bioequivalence.*

Per Dr. Hinderling, the submitted data demonstrate the following:

- The exposure to perindopril, perindoprilat and amlodipine is not impacted when Prestalia is administered with food.
- The pharmacokinetics of perindopril and amlodipine are not altered when the drugs are co-administered.
- The arithmetic ratios for the exposure measures of amlodipine between Norvasc and Prestalia are within the bioequivalence limit.

In contrast, the applicant's cross-study comparison failed to demonstrate bioequivalence for the dose-normalized AUC and  $C_{max}$  for perindopril or perindoprilat between the two-be-marketed Prestalia tablet and Aceon. According to Dr. Hinderling, the mean plasma exposure to perindopril was ~2-fold higher with Prestalia than with Aceon by the cross-study PK comparison, and the bounds of the 90% confidence interval for the geometric mean ratio for the plasma exposure for perindoprilat were also outside the bioequivalence limits. The reason for this discrepancy in exposure to perindopril and perindoprilat remains unclear.

Because the applicant is unable to bridge pharmacokinetic information on perindopril and perindoprilat from Aceon to Prestalia, the Office of Clinical Pharmacology is recommending that approval be limited to the population in whom efficacy and safety was demonstrated in the applicant's phase 2 and phase 3 trials.

### ***PD considerations and the clinical utility of the intermediate dose strength (perindopril arginine/amlodipine 7 mg/5 mg)***

The proposed intermediate dose of Prestalia (7 mg/5 mg) was not tested in the phase 2 or phase 3 trial and there are differences of opinion among the members of the review team as to whether to approve the 7 mg/5 mg dose. Whereas Dr. Hinderling, does not support approval of

the 7 mg/5 mg dose, Dr. Hariharan (the secondary reviewer), Dr. Mehta (the Director of DCP-1) and Dr. Hicks support approval.

To assess the clinical utility of the intermediate dose, Dr. Hinderling estimated the likely effect of the intermediate dose on blood pressure and peripheral edema (a dose-limiting adverse effect of amlodipine) using data from the applicant's two pivotal trials. Assuming a linear-dose response relationship for efficacy and peripheral edema over the proposed dose-range, Dr. Hinderling projected:

- a mean reduction of 6.5 mmHg for the intermediate dosage strength, as compared to a reduction of 4 mmHg for the lower dosage strength and 9 mmHg for the higher dosage strength.
- a 4.5% increase in the incidence of peripheral edema (IPE) between the highest and lowest dosage strengths, an incidence of 2.3% with the intermediate dosage strength in a population with equal numbers of men and women and an incidence of 3.2% with use of the intermediate dosage strength in women.

Dr. Hinderling concludes that "It is difficult to justify the use of the intermediate strength tablet given that the projected decrease in DBP of 2.5 mm Hg may be accompanied by a projected increase in IPE of 3.1% in females."

In his secondary review, Dr. Hariharan agrees that using linear interpolation to derive the blood pressure lowering effect of the intermediate dosage strength is reasonable since the doses of perindopril and amlodipine lie in the linear range of the dose-blood pressure lowering effect relationship. However Dr. Hariharan questions Dr. Hinderling's assumption that the dose-response relationship for edema is linear over the proposed dose range. According to Dr. Hariharan's review, data from other development programs which evaluated amlodipine as monotherapy do not suggest a linear dose-response relationship for peripheral edema over the range of strengths of amlodipine included in Prestalia. Instead, the data suggest a more substantial increase in the incidence of peripheral edema when the dose of amlodipine is increased from 5 mg to 10 mg than from 2.5 mg to 5 mg. He further notes that data from trial CL3-05985-006, which the applicant submitted late in the review cycle, also suggest a more substantial increase in the incidence of edema with an increase in the dose of perindopril arginine/amlodipine from 7 mg/5 mg to 14 mg/10 mg than from 3.5/2.5 mg to 7 mg/5 mg. Dr. Hariharan's review also includes a discussion of data from the Prestalia development program and other development programs that indicate that utilizing amlodipine with an ACE inhibitor or ARB reduces the risk of peripheral edema when compared to utilizing amlodipine as monotherapy. Dr. Hariharan concludes his review as follows:

"In summary, when used as initial therapy the intermediate strength represents a clinically relevant titration step, as it lies in the linear range of the dose-response curve for the individual components with no meaningful increase in incidence of peripheral edema. The intermediate strength seems to be a viable option for patients who need modest reductions in blood pressure to reach their goal, but are sensitive to peripheral edema. As the standard dose of amlodipine in females and elderly is 5 mg, it would be clinically meaningful to have a comparable FDC strength containing amlodipine 5 mg. Finally, due to beneficial effects of combining RAS inhibitor with a CCB, the

intermediate strength may potentially alleviate peripheral edema concerns for patients who are not tolerable to amlodipine 5 mg.”

*Reviewer’s comment: The available data suggest that the intermediate dosage strength of Prestalia (7 mg/5 mg) has clinical utility and will allow prescribers to better individualize therapy from both an efficacy and tolerability perspective.*

## 6. Clinical Microbiology

This product is not an antimicrobial therapeutic. According to Dr. Riley, the microbial limits specification for Prestalia is acceptable from a Product Quality Microbiology perspective.

## 7. Clinical/Statistical- Efficacy

In support of the proposed indication, the applicant submitted the results of a phase 3 trial comparing the highest proposed dose of Prestalia with the highest approved doses of perindopril erbumine and amlodipine and a phase 2 trial comparing the efficacy and safety of the lowest proposed dose of Prestalia with two doses of amlodipine (2.5 mg and 5.0 mg) and two doses of perindopril arginine (3.5 mg and 5.0 mg). The phase 3 trial, known as the PATH study, was initiated in February 2012 and was conducted in the U.S. by XOMA under the U.S. IND. The phase 2 study, CL2-05985-005, was conducted outside the U.S. by Servier and was completed in December 2008 (final patient final contact), almost 2 years prior to XOMA’s preIND meeting with the Division.

### ***Overview of the PATH study (also known as Study X985400)***

PATH was a phase 3, randomized, double-blind, parallel group trial in 837 subjects with moderate to severe hypertension, as defined below. The trial evaluated the efficacy and safety of the fixed-dose combination of perindopril arginine/amlodipine 14 mg/10 mg relative to perindopril erbumine 16 mg and amlodipine 10 mg.

Key entry criteria are listed on pages 39-40 of Dr. Hicks’ review and included essential hypertension (defined as a mean seated DBP  $\geq 95$  mm Hg and  $\leq 115$  mm Hg) and age  $\geq 18$  and  $\leq 75$  years. Patients with a mean seated SBP  $\geq 180$  mm Hg, known or suspected secondary hypertension, renal dysfunction with a creatinine clearance  $< 60$  mL/min using the Cockcroft Gault equation, or heart failure (New York Heart Association functional class 3-4) were excluded.

The study included a screening visit, a 2 to 3-week washout period, and a 6-week double-blind treatment period. During the treatment phase, subjects were to return for study visits on Days 21 ( $\pm 3$  days) and 42 days ( $\pm 3$  days). At these visits, seated blood pressure measurements were taken as described on page 39 of Dr. Hicks’ review. All study visits were to occur in the morning after a 10 hour fast and before study drug intake.

The prespecified primary endpoint was the mean change from baseline to Day 42/EOT in mean seated trough DBP. The prespecified secondary efficacy endpoint was the mean change from baseline to Day 42/EOT in mean seated trough SBP.

The statistical analysis plan was initially submitted in April 2012. In response to Agency feedback, a revised version was submitted in August 2012.

- According to the statistical analysis plan, the primary endpoint analysis population was to include all randomized subjects who received at least 1 dose of study drug and had at least 1 post baseline blood pressure assessment value for DBP. If no valid DBP measurements were obtained at Day 42/EOT, the last valid post-randomization assessment was used (i.e., last observation carried forward). An analysis of covariance model with treatment as the main effect and baseline DBP ( $< 100$  mmHg versus  $\geq 100$  mg), current type 2 diabetes status (yes versus no) and race (black versus non-black) as covariates was to be used to compare the change from baseline in the fixed-dose combination group with the change from baseline in the monotherapy groups. The model and population for the secondary endpoint analysis mirrored the model and population used for the primary endpoint analysis.
- Per Dr. Zhang's review, the appendix to the statistical analysis plan also contained a description of the multiple-pass, minimization algorithm that was to be used to determine a subject's assignment. An overview of the factors considered at each pass is provided below.
  - 1st pass – Optimal assignment based on Current Type 2 Diabetes Status, Race, DBP Stratum, site balance
  - 2nd pass – If no optimal assignment from the first pass, the optimal assignment was based on Current Type 2 Diabetes Status, Race, DBP Stratum
  - 3rd pass – If no optimal assignment from the second pass, optimal assignment was based on just DBP Stratum and Current Type 2 Diabetes status
  - 4th pass—If no optimal assignment from the third pass, optimal assignment was based on just DBP Stratum status
  - 5th pass- If no optimal assignment from the fourth pass, optimal assignment was based on overall study balance
  - 6th pass – If no optimal assignment from the fifth pass, select at random using a pre-generated list of random numbers

For each treatment group, the system summed the total number of subjects who had been randomized within the strata/factors that the new subject fell into. The new subject was then assigned to the treatment group with the lowest score. If more than one treatment group had the lowest score, additional prespecified passes were taken to resolve the ties and define the treatment group with the lowest score. For additional details, see Dr. Zhang's review.

*Reviewer's comment: During the IND phase, the statistical reviewer questioned why a complex randomization procedure was needed given the number of subjects per treatment arm and suggested that the sponsor use a simple randomization procedure (Advice letter dated July 23, 2012). In their response submitted on August 8, 2012, the sponsor indicated that they would consider the Division's advice in future trials since enrollment in the trial*

*was almost complete. As discussed later in this review, Dr. Zhang also has concerns with the algorithm that was used.*

***Overview of Study CL2-05985-005***

CL2-05985-005 was a phase 2, randomized, double-blind, placebo-controlled, factorial study in ~1580 subjects with hypertension, as defined below. Study subjects were randomized into one of 6 treatment arms: perindopril arginine/amlodipine 3.5 mg/2.5 mg, perindopril arginine 2.5 mg, perindopril arginine 5 mg, amlodipine 2.5 mg, amlodipine 5.0 mg or placebo. A total of 1297 subjects were also enrolled in an ABPM sub-study.

Key entry criteria are listed on pages 47-48 of Dr. Hicks' review and included essential "mild to moderate" uncomplicated hypertension, defined as a DBP greater than or equal to 95 mmHg and less than 110 mmHg and SBP greater than or equal to 150 mmHg and less than 180 mmHg in the supine position, and age 18 to 80 years. Patients with hypertension treated with more than 1 antihypertensive drug, secondary hypertension, a history of renal disease or heart disease, known microalbuminuria or diabetes were excluded.

The main study included a screening visit, a 2 to 3-week run in period, and an 8-week double-blind treatment period. In the main study, blood pressure measurements were made at baseline (week 0) and weeks 2, 4 and 8. Subjects enrolled in the substudy were treated for 8-weeks in the main study and then, after taking placebo for at least 10 days, were treated for an additional 8 weeks in the sub-study. In the ABPM substudy, ABPM measurements were made at baseline (week 0) and week 8. For further information on how blood pressure was measured in the main study and in the ABPM substudy, see pages 46-47 of Dr. Hicks' review.

The primary efficacy endpoint was the change from baseline (Week 0) to Week 8 (or last on-treatment post-baseline value) in mean supine DBP at trough or in mean 24 hour DBP (ABPM substudy). The first secondary efficacy endpoint was the change from baseline (Week 0) to Week 8 (or last on-treatment post-baseline value) in mean supine SBP at trough or in mean 24 hour SBP (ABPM substudy); other secondary endpoints also assessed effects on blood pressure (see page 49 of Dr. Hicks' review).

The primary analyses included three superiority comparisons (perindopril arginine/amlodipine 3.5 mg/ 2.5 mg versus placebo, perindopril arginine 3.5, and amlodipine 2.5 mg) and two non-inferiority comparisons (perindopril arginine/amlodipine 3.5 mg/2.5 mg versus perindopril arginine 5 mg, and amlodipine 5 mg). According to Dr. Zhang's review, the superiority analyses were based on the change from baseline to the last on-treatment post-baseline value for supine DBP using a general linear model with baseline and center (random factor) as covariates. The basis for the margin that was used in the non-inferiority comparisons (2 mmHg) is not clear and the clinical and statistical reviews focused on the superiority comparisons.

***Patient disposition and demographic characteristics in PATH***

A total of 837 subjects were randomized into PATH and a total of 751 subjects (90%) completed the study. A similar percentage of subjects discontinued early in each of the treatment arms (9.3% of subjects on perindopril arginine/amlodipine, 10% on amlodipine and

11.5% on perindopril erbumine). The most common reason for discontinuation was an adverse event (3.6% of subjects on perindopril arginine/amlodipine, and 4.3% of subjects on amlodipine and perindopril erbumine).

The mean age of the study population was 51 years and approximately 93% of the study population was less than 65 years of age. Approximately 51% of patients were male, 34% were Black and 20% had type 2 diabetes. The majority of subjects (68%) required washout from a prior antihypertensive medication.

### ***Efficacy findings in PATH***

As shown in the tables below, treatment with the fixed-dose combination of perindopril arginine/amlodipine 14 mg/10 mg resulted in a greater reduction in diastolic and systolic blood pressure than treatment with perindopril erbumine 16 mg or with amlodipine 10 mg. The amlodipine component appeared to contribute to a greater extent to the blood pressure lowering effect than the perindopril component. Compared to the highest approved dose of perindopril erbumine, the fixed-dose combination product reduced diastolic blood pressure by an additional 6.3 mmHg and systolic blood pressure by an additional 10.1 mmHg. In contrast, compared to the highest approved dose of amlodipine, the fixed-dose combination product reduced diastolic blood pressure by an additional 2.5 mmHg and systolic blood pressure by an additional 3.9 mmHg.

**Table 1. Prespecified primary efficacy endpoint and analysis: Change in diastolic blood pressure from baseline to day 42 with last observation carried forward**

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

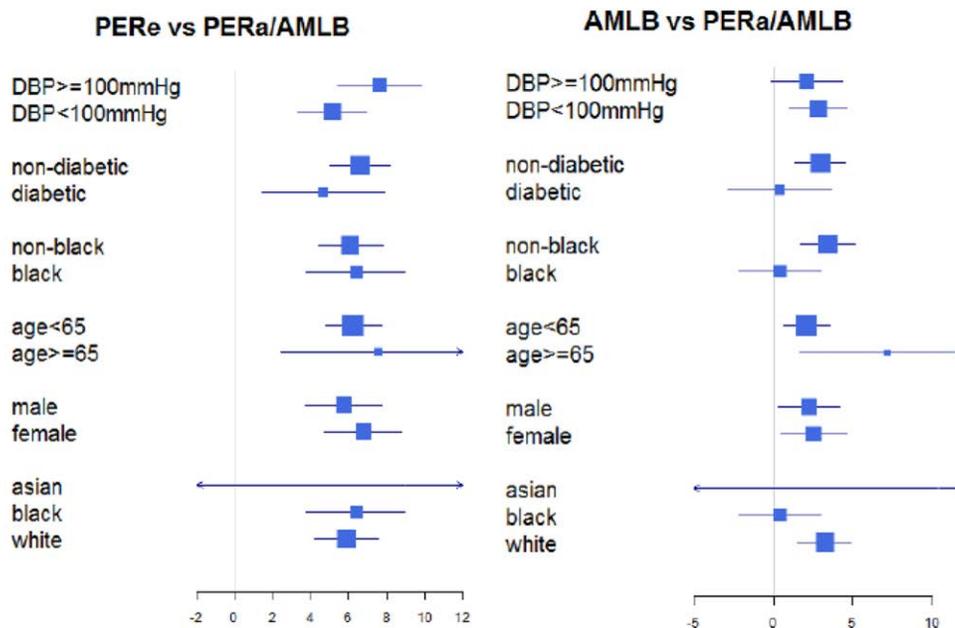
[Source: Table 7, Clinical Study Report for PATH; results confirmed by Dr. Zhang]

**Table 2. Prespecified secondary efficacy endpoint and analysis: change in systolic blood pressure from baseline to day 42 with last observation carried forward**

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

[Source: Table 8, Clinical Study Report for PATH; results confirmed by Dr. Zhang]

The results of subgroup analyses are shown in the figure below, taken from Dr. Zhang’s addendum dated January 8, 2015. In black patients and diabetics, adding perindopril to amlodipine did not result in greater blood pressure lowering than that seen with amlodipine alone. In black patients, the LS mean change from baseline in blood pressure (systolic/diastolic) was -20.9/13.3 mmHg on amlodipine 10 mg as compared to -20.1/13.8 mmHg on perindopril arginine/amlodipine 14 mg/10 mg (source: Tables 18 and 19, Clinical Study Report for the PATH study). In diabetic patients, the LS mean change from baseline in blood pressure (systolic/diastolic) was -17.8/13.7 mmHg on amlodipine 10 mg as compared to -19.9/13.7 mmHg on perindopril arginine/amlodipine 14 mg/10 mg (source: Tables 18 and 19, Clinical Study Report for the PATH study).



**Figure 1. Subgroup analyses in the PATH trial: change in diastolic blood pressure**

[Source: Figure 1, Dr. Zhang’s Statistical Review dated January 8, 2015]

*Reviewer's comment: Similar findings were reported in black patients treated with the fixed dose-combination of amlodipine and benazepril (an ACE inhibitor). According to that label, while both components contributed to the antihypertensive efficacy in non-blacks, "virtually all of the antihypertensive effect in blacks could be attributed to the amlodipine component."*

***Statistical concerns with the randomization algorithm used in PATH and potential implications for interpretation of the efficacy findings***

According to Dr. Zhang's review, the treatment algorithm used in the PATH trial was deterministic. When a patient entered the study, she was assigned to the treatment group with the lowest score; if more than one treatment group had the lowest score, additional prespecified passes were taken to resolve the ties and define the treatment group with the lowest score. Because a deterministic algorithm was used, one could, in theory, unblind all treatment assignments in PATH. If treatment assignments were unblinded, one could also, in theory, subvert the randomization process and preferentially assign subjects to a specific treatment arm.

While Dr. Zhang indicates that the use of such a deterministic algorithm is bad practice, she also acknowledges that it is unlikely than an individual investigator would have been able to derive the treatment assignment of the next patient entering PATH given both the number of centers involved in the study and also the complexity of the algorithm used to assign subjects. To explore whether selection bias may have occurred, Dr. Zhang examined (1) the mean baseline blood pressure by order of patient entry into the trial and (2) the efficacy findings (mean treatment difference between the fixed-dose combination arm and each monocomponent) by order of patient entry into the trial. These analyses (see Figures 2-5 of her review) show no obvious trend in baseline blood pressure or treatment effect by order of patient entry, and hence are not suggestive of selection bias.

Dr. Zhang also makes the point that it may not be possible to use standard tests to assess the treatment effect in PATH since random treatment assignment is an underlying assumption of statistical inference for most tests. To address this concern, Dr. Zhang used a bootstrap t-test to compare the treatment effect of the fixed-dose combination with its monocomponents. She notes that using this test, the results are still highly significant ( $p$ -values  $< 0.001$  for the comparisons of the combination product with each of the monocomponents), but also cautions that the validity of the test result relies on the assumption that the distribution of the blood pressure measurements in the trial is identical to the distribution in the patient population of interest.

*Reviewer's comment: Given both the number of centers involved in the study and also the complexity of the algorithm used to assign subjects, I think it would have been difficult to unblind the trial and preferentially assign subjects to a particular treatment arm. The results of the analyses conducted by Dr. Zhang are also reassuring. Hence, I do not think the algorithm that was used in PATH invalidates the trial's findings or presents a barrier to approval. In a follow-up discussion of the issues raised in her statistical review, Dr. Zhang indicated that, in general, the use of a deterministic algorithm does not reflect good practice.*

However, in this particular case, she does not think the algorithm that was used poses a barrier to interpreting the results of the trial.<sup>1</sup>

### **Patient disposition and demographic characteristics in CL2-05985-005**

A total of 1581 subjects were randomized into CL2-05985-005; a total of 1497 subjects (~95%) completed treatment. The mean age of the study population was 52 years and approximately 87% of the study population was less than 65 years of age. Approximately 47% of patients were male and 99% were Caucasian.

### **Efficacy findings in CL2-05985-005**

As shown in the tables below, treatment with the fixed-dose combination of perindopril arginine/amlodipine 3.5 mg/2.5 mg resulted in a 5.0/3.6 mmHg greater blood pressure reduction than treatment with perindopril arginine 3.5 mg, a 5.2/3.0 mmHg greater blood pressure reduction than treatment with amlodipine 2.5 mg and a 7.2/4.1 mmHg greater blood pressure reduction than placebo. Of note, the placebo-corrected mean change in blood pressure was small in the perindopril arginine 3.5 mg and amlodipine 2.5 mg arms.

*Reviewer's comment: According to the label for amlodipine, the usual initial antihypertensive dose of amlodipine is 5 mg once daily; "small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine besylate USP to other antihypertensive therapy."*

**Table 3. Change in supine diastolic blood pressure in Study CL2-05985-005**

<b>Supine Diastolic Blood Pressure Statistic</b>	<b>PERa/AMLb 3.5/2.5 mg (N=246)</b>	<b>Placebo (N=248)</b>	<b>PERa 3.5 mg (N=268)</b>	<b>AMLb 2.5 mg (N=270)</b>
Baseline Mean (SD)	100.7 ± 4.0	100.5 ± 3.9	100.7 ± 4.0	100.6 ± 4.0
END Mean (SD)	87.1 ± 9.0	91.2 ± 9.2	91.0 ± 10.1	90.3 ± 9.8
Mean change (SD): END-Baseline	-13.6 ± 9.2	-9.3 ± 9.2	-9.7 ± 9.9	-10.3 ± 9.7
<b>Main Statistical Analysis</b>				
Estimate (SE)		-4.12 (0.77)	-3.64 (0.76)	-2.97 (0.75)
95% CI		[-5.63; -2.61]	[-5.12; -2.16]	[-4.45; -1.49]
p-value		p < 0.001	p < 0.001	p < 0.001

[Source: Table 11.1.1.1, Clinical Study Report for CL2-05985-005; results confirmed by Dr. Zhang]

<sup>1</sup> Correspondence from Dr. Zhang to Drs. Stockbridge and Thompson dated December 31, 2014.

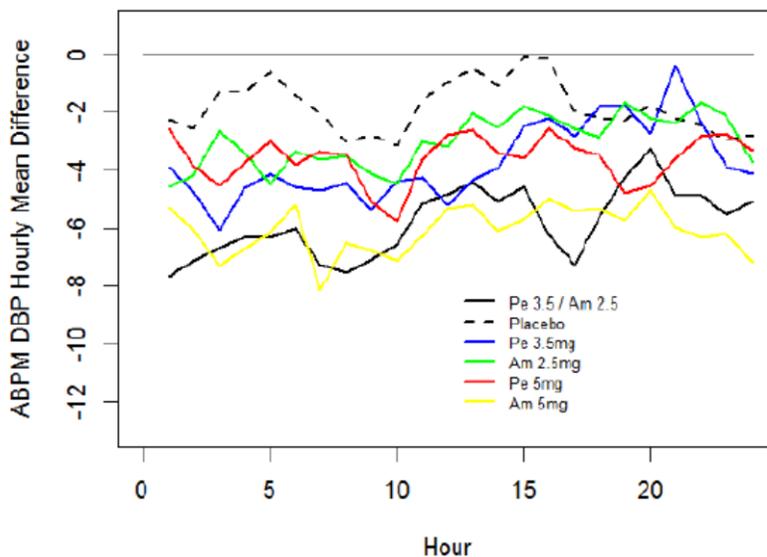
**Table 4. Change in supine systolic blood pressure in Study CL2-05985-005**

Supine Systolic Blood Pressure Statistic	PERa/AMLb 3.5/2.5 mg (N=246)	Placebo (N=248)	PERa 3.5 mg (N=268)	AMLb 2.5 mg (N=270)
Baseline Mean (SD)	161.8 ± 7.5	161.0 ± 7.4	161.4 ± 7.7	161.2 ± 7.6
END Mean (SD)	139.9 ± 13.8	146.7 ± 15.4	145.1 ± 16.5	145.1 ± 15.5
Mean change (SD): END-Baseline	-22.0 ± 14.0	-14.2 ± 16.1	-16.3 ± 17.0	-16.0 ± 15.3
<b>Main Statistical Analysis</b>				
Estimate (SE)		-7.22 (1.21)	-5.01 (1.19)	-5.20 (1.19)
95% CI		[-9.60; -4.84]	[-7.35; -2.67]	[-7.53; -2.87]
p-value		p < 0.001	p < 0.001	p < 0.001

[Source: Table 11.2.1.1.1, Clinical Study Report for CL2-05985-005; results confirmed by Dr. Zhang]

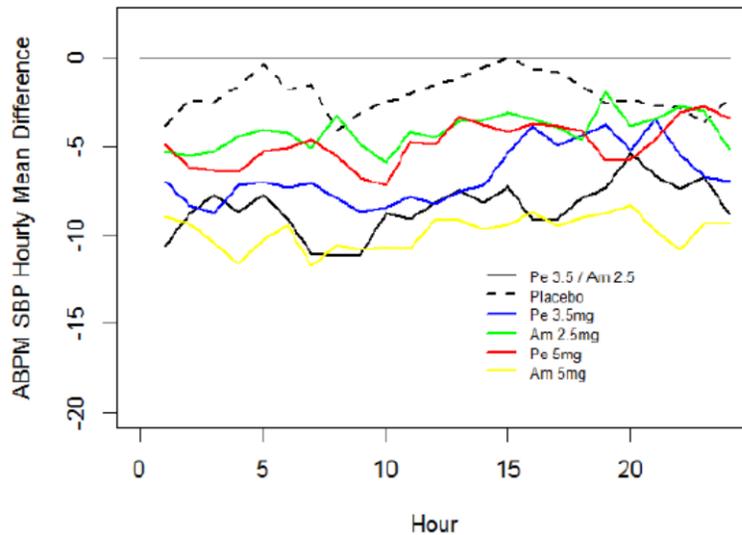
Tables 12 and 13 of Dr. Zhang’s review show the results for the comparison of the fixed-dose combination of perindopril arginine/amlodipine 3.5 mg/2.5 mg with perindopril arginine 5 mg and amlodipine 5 mg. The analyses suggest that the fixed-dose combination lowers systolic and diastolic blood pressure to a greater extent than perindopril arginine 5 mg. In contrast, the fixed-dose combination does not appear to be more effective in lowering blood pressure than amlodipine 5 mg (the “usual initial antihypertensive dose” per the amlodipine label).

For the most part, the findings in the ABPM substudy were consistent with the main study. In the ABPM substudy, perindopril arginine/amlodipine 3.5 mg/2.5 mg caused a greater reduction in mean 24-hour SBP and DBP from baseline to Week 8/last post-baseline value than placebo, perindopril arginine 3.5 mg and 5.0 mg and amlodipine 2.5 mg (see Tables 19 and 22 of Dr. Hicks’ review and the figures below). As in the main study, the fixed-dose combination was not more effective in lowering blood pressure than amlodipine 5 mg.



**Figure 2. Study CL2-05985-005 ABPM DBP Results**

[Source: Figure 3, Dr. Hicks’ Clinical Review; figure generated by Dr. Zhang]



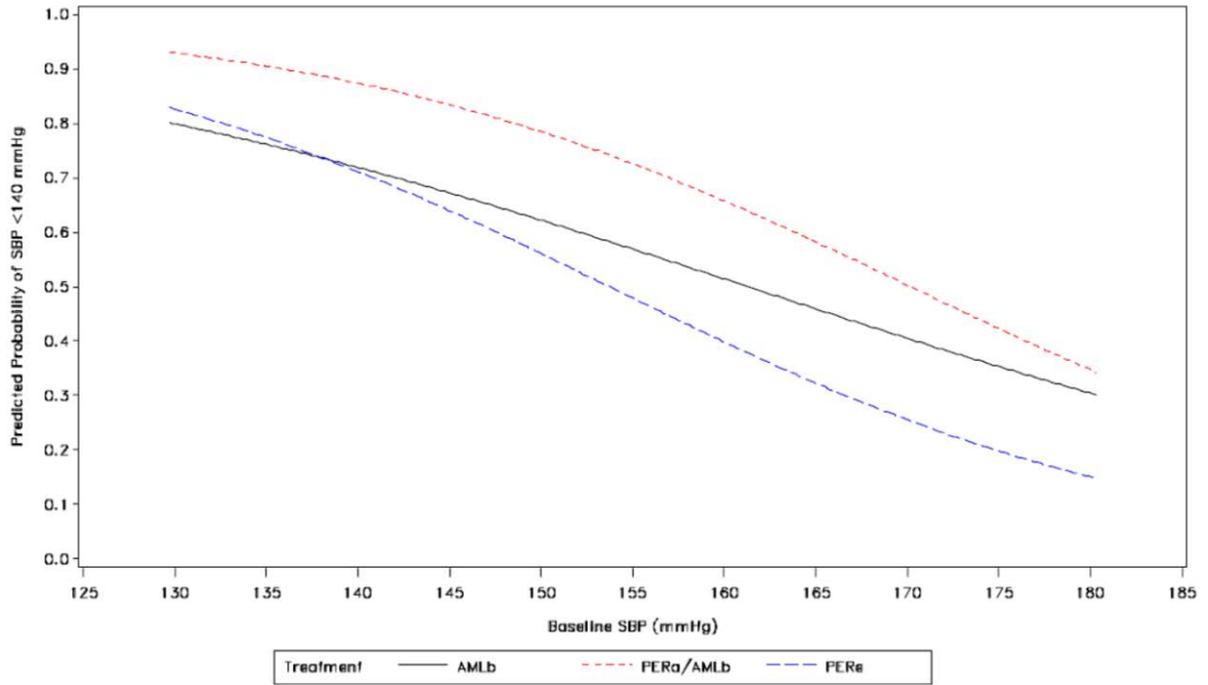
**Figure 3. Study CL2-05985-005 ABPM SBP Results**

[Source: Figure 4, Dr. Hicks' Clinical Review; figure generated by Dr. Zhang]

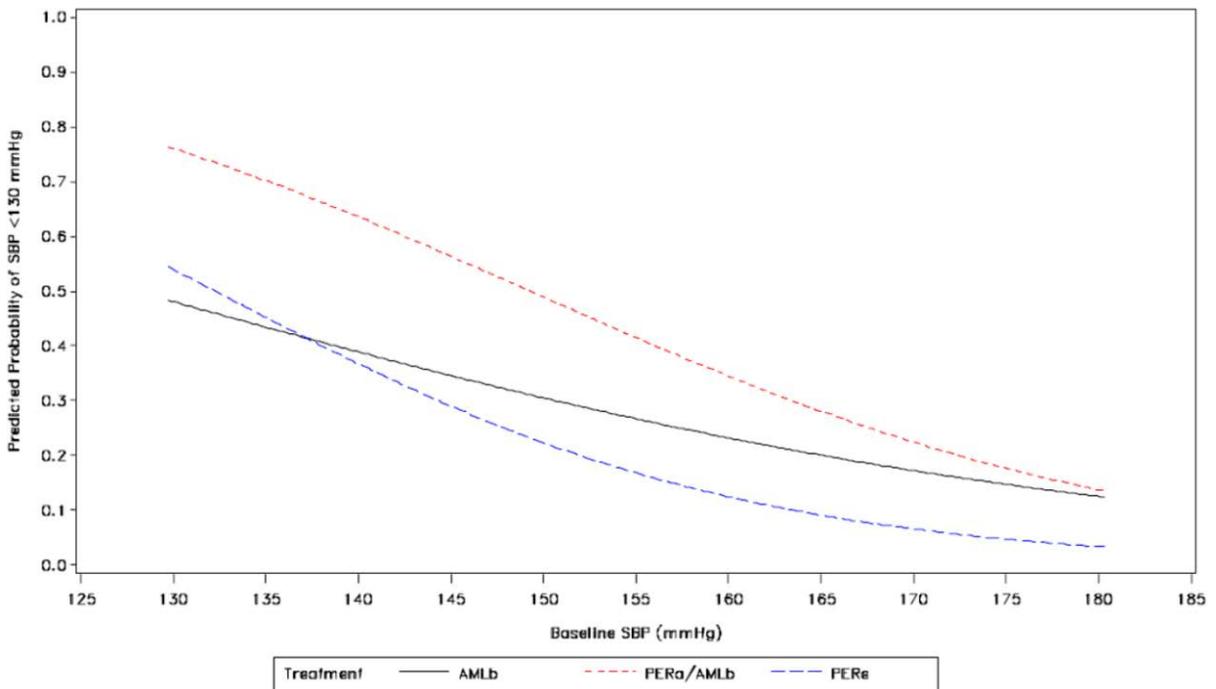
**Data supporting use as initial therapy**

To support a claim for use as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals, the applicant submitted logistic regression curves showing the likelihood of reaching certain blood pressure targets as a function of baseline blood pressure for each treatment. The logistic regression curves for the PATH trial using all data for each blood pressure goal are shown below.<sup>2</sup> The curves from the PATH trial suggest that the high dose of the combination product provides an advantage over the highest approved doses of perindopril erbumine and amlodipine in getting patients to blood pressure targets. The graphs also suggest that none of the products (the combination product, perindopril monotherapy, or amlodipine monotherapy) is particularly effective at getting patients with higher baseline blood pressures to these targets, especially if the target is a systolic blood pressure < 130 mmHg or a diastolic blood pressure < 80 mmHg.

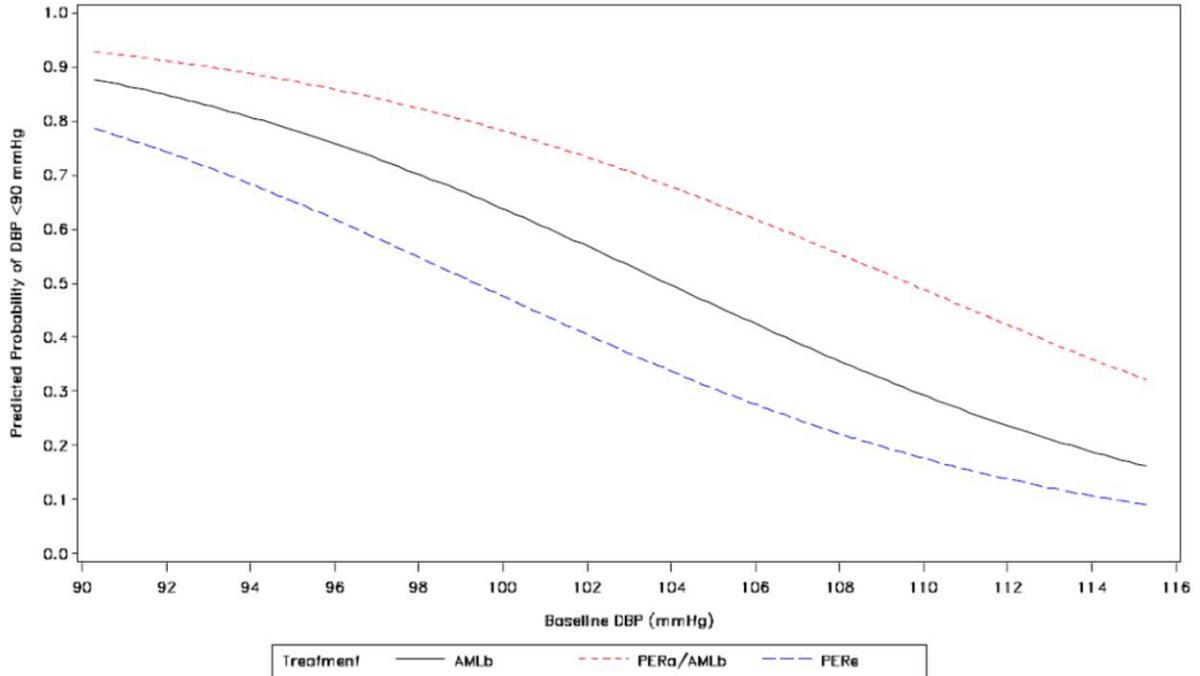
<sup>2</sup> According to Dr. Zhang's review, no lack of fit was detected and the trimmed samples did not provide significant improvement when compared with models that used all of the data; hence, all of the data in the PATH trial should be retained for the probability curves.



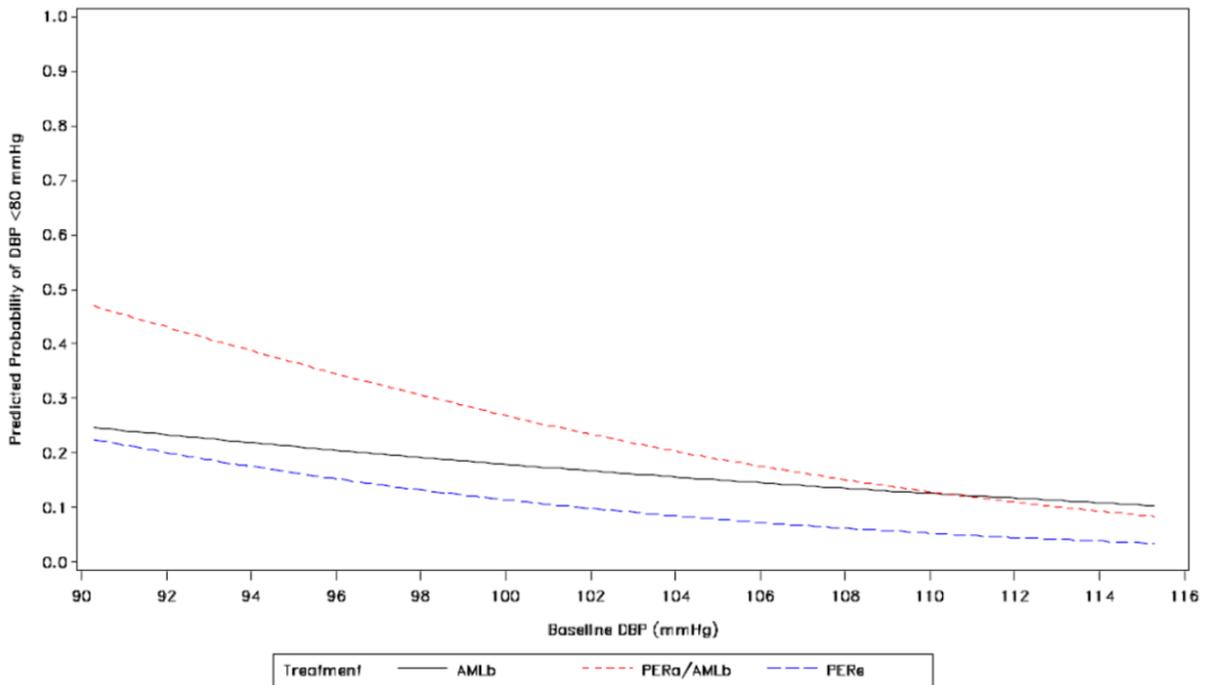
**Figure 4. Predicted probability of SBP < 140 mmHg by baseline SBP for each treatment arm in PATH**



**Figure 5. Predicted probability of SBP < 130 mmHg by baseline SBP for each treatment arm in PATH**



**Figure 6. Predicted probability of DBP < 90 mmHg by baseline DBP for each treatment arm in PATH**



**Figure 7. Predicted probability of DBP < 80 mmHg by baseline DBP for each treatment arm in PATH**

For all figures, the x-axis shows the baseline blood pressure and y-axis shows the predicted probability of reaching a particular target. Red line=perindopril arginine/amlodipine 14 mg/10 mg; Blue line=perindopril erbumine 16 mg; Black line= amlodipine 10 mg.

[Source: Figures 2-5, Dr. Zhang's Statistical Review dated January 8, 2015]

*Reviewer's comment: I think the analyses support a claim as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. Graphs showing the likelihood of reaching particular blood pressure targets as a function of baseline blood pressure should be included in labeling.*

## 8. Safety

The safety profiles of Prestalia's active ingredients are well characterized. According to the Norvasc (amlodipine besylate) label, amlodipine was evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. According to the Aceon label, perindopril erbumine was evaluated for safety in over 3,000 patients with hypertension in U.S. and foreign clinical trials; perindopril erbumine's safety was also evaluated in a clinical trial in over 12,000 patients with stable coronary artery disease (in that trial, over 6000 patients were treated with perindopril). Since both Norvasc and Aceon were initially approved over 20 years ago, there is also extensive postmarketing experience with these agents.

The safety of the maximum dose of Prestalia (14/10 mg) was evaluated in the applicant's phase 3 trial. In this study, a total of 279 subjects received one or more doses of Prestalia for up to 6 weeks; a similar number of subjects were treated with the maximum approved dose of perindopril erbumine (16 mg) and amlodipine (10 mg). As noted in Dr. Hicks' review:

- There were no deaths in the study. Of the five SAEs that were reported, one, a pulmonary embolism, was reported in the FDC arm. Based on what is known about the safety profiles of the monocomponents, this SAE was not likely drug related.
- The percentage of subjects discontinuing study medication because of an adverse event was relatively low and was similar across the treatments arms (3.6% in the FDC arm, and 4.3 % in the perindopril and amlodipine arms). Edema was the most common-treatment emergent event leading to study discontinuation in the FDC arm (5 subjects (1.8%) receiving the FDC; as compared to 1 (0.4%) subject on perindopril erbumine and 8 (2.6%) subjects on amlodipine).
- The most common adverse event in the FDC arm (incidence of 2% or greater) were edema, headache, cough and dizziness (see table below). Although edema was reported in ~7% of subjects in the FDC arm, the incidence of edema in the FDC arm was lower than that reported in the amlodipine arm (~13%).

*Reviewer's comment: According to the label for Lotrel (amlodipine besylate and benazepril hydrochloride) capsules, the incidence of edema was also substantially reduced when benazepril, also an ACE inhibitor, was added to a regimen of amlodipine. See also Dr. Hariharan's review for further discussion of data indicating that utilizing amlodipine with an ACE inhibitor or ARB reduces the risk of peripheral edema when compared to utilizing amlodipine as monotherapy.*

**Table 5. Common adverse events (incidence of 2% or greater in the Prestalia arm) in the PATH trial.**

<b>Adverse Event</b>	<b>PRESTALIA 14/10 mg (N = 279) n (%)</b>	<b>PERe 16 mg (N = 278) n (%)</b>	<b>AML 10 mg QD (N = 280) n (%)</b>
Edema peripheral	20 (7.2)	1 (0.4)	37 (13.2)
Cough	9 (3.2)	8 (2.9)	2 (0.7)
Headache	7 (2.5)	8 (2.9)	8 (2.9)
Dizziness	7 (2.5)	4 (1.4)	3 (1.1)

PERe = perindopril erbumine; AML = amlodipine besylate

[Source: Table 35, Dr. Hicks' Clinical Review]

- According to Dr. Hicks' review, there were no clinically meaningful changes in laboratory parameters with Prestalia.

With regard to drug-demographic interactions (see pages 88-90 of Dr. Hicks' review):

- In both the perindopril arginine/amlodipine 14 mg/10 mg and amlodipine 10 mg treatment arms, the incidence of peripheral edema was higher in women than in men. However, in both men and women, the incidence of peripheral edema appeared to be lower on perindopril/arginine 14 mg/10 mg than on amlodipine 10 mg. In women, the incidence of peripheral edema was also lower on perindopril/arginine 3.5 mg/2.5 mg than on amlodipine 5 mg. In men, the incidence of edema was low on both perindopril/arginine 3.5 mg/2.5 mg and amlodipine 5 mg.

**Table 6. Peripheral edema by sex in the PATH trial**

<b>Peripheral Edema (Study X985400)</b>	<b>PERa/AMLb 14/10 mg</b>	<b>PERe 16 mg</b>	<b>AMLb 10 mg</b>
<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%)

**AMLb = amlodipine besylate; PERa/AMLb = perindopril arginine/amlodipine besylate; PERa = perindopril arginine. Source: Reviewer.**

[Source: Table 38, Dr. Hicks' Clinical Review]

**Table 7. Peripheral edema by sex in 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>	4/249 (1.6%)	3/250 (1.2%)	8/272 (2.9%)	2/276 (0.7%)	4/272 (1.5%)	13/263 (4.9%)
<b>Men, N</b>	117	116	127	130	129	121
<b>Men, n (%)</b>	2 (1.7%)	1 (0.9%)	1 (0.8%)	1 (0.8%)	0 (0%)	2 (1.7%)
<b>Placebo- subtracted</b>	0.8%		-0.1%	-0.1%	-0.9%	0.8%
<b>Women, N</b>	132	134	145	146	143	142
<b>Women, n (%)</b>	2 (1.5%)	2 (1.5%)	7 (4.8%)	1 (0.7%)	4 (2.8%)	11 (7.7%)
<b>Placebo- subtracted</b>	0%		3.3%	0.8%	1.3%	6.2%

[Source: Table 39, Dr.Hicks' Clinical Review]

- Few black patients developed peripheral edema in the phase 3 trial and the incidence was similar in the perindopril/arginine 14 mg/10 mg and amlodipine 10 mg treatment groups (3 subjects in each, or ~3.0%).

*Reviewer's comment: It is difficult to know what to make of the edema findings in black patients given the size of this subgroup and the low event rate. According to the label for Lotrel (amlodipine besylate and benazepril hydrochloride) capsules, all patient groups benefited from the reduction in amlodipine-induced edema seen with Lotrel.*

- The number of elderly subjects was too small to permit subgroup analysis.

Based on her analyses, Dr. Hicks believes that there are no safety issues that would preclude approval. I agree with her assessment.

## 9. Advisory Committee Meeting

No Advisory Committee Meeting was held.

## 10. Pediatrics

The applicant proposed and the PeRC and Division agreed to a full waiver of pediatric studies. The product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients.

## 11. Other Relevant Regulatory Issues

Five domestic clinical investigator sites were inspected for the PATH study and one foreign investigator site was inspected for CL2-05985-005 and the ABPM sub-study. A sponsor site inspection was also conducted for the PATH study. No regulatory violations were found during the five domestic site inspections or during the sponsor site inspection; the foreign site (Site 3007 in Lithuania) was classified as VAI because of regulatory violations related to inadequate and inaccurate drug accountability records, failure to adhere to the investigational plan; and inadequate and inaccurate records during the study. Although these violations were found, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. OSI's Clinical Inspection Summary indicates that the data from the foreign site, as well as the data from the other sites, may be considered reliable.

The application has also been reviewed by the 505(b)(2) committee and has been cleared from a 505(b)(2) perspective (see 505(b)(2) assessment for further information).

## 12. Labeling

*Proprietary name:* DMEPA has completed its review of the proposed proprietary name, Prestalia, and determined that it is acceptable.

*Physician labeling:* As discussed in section 5, the applicant failed to establish a pharmacokinetic bridge between exposure to perindopril and perindoprilat in Prestalia and Aceon. Hence, the Office of Clinical Pharmacology is recommending that: (1) special populations, including the elderly, patients with renal impairment (creatinine clearance < 60 mL/min), and patients with hepatic impairment or congestive heart failure who were not enrolled in the pivotal phase 2 and 3 trial be excluded from the prescribing information; (2) only PK information on perindopril and perindoprilat obtained after administration of the fixed-dose combination tablet (perindopril arginine/amlodipine) be presented in the label. I agree with their recommendations.

The label should also describe:

- the favorable findings for edema when utilizing the combination product relative to utilizing amlodipine as monotherapy. Consideration should also be given to describing this finding in the Dosage and Administration Section of the label as was done in the Lotrel (amlodipine besylate and benazepril hydrochloride) label (i.e., indicating that this therapy should be considered in patients who are unable to achieve adequate antihypertensive effect with amlodipine therapy without developing edema).
- the finding that in black patients and diabetic patients adding perindopril to amlodipine did not result in greater blood pressure lowering than that seen with amlodipine alone.

*Carton and immediate container labels:* According to Dr. Stewart's review dated December 23, 2014, the revised container labels adequately address DMEPA's concerns from a medication error perspective.

*Patient labeling:* The applicant's patient labeling has been reviewed and edited by Karen Dowdy (Division of Medical Policy Programs), Zarna Patel (Office of Prescription Drug Promotion) and Mary Ross Southworth (DCaRP Deputy Director for Safety). I agree with their edits.

## 13. Recommendations/Risk Benefit Assessment

### ***Recommended Regulatory Action***

Approval of Prestalia (3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg tablets) for the treatment of hypertension, to lower blood pressure, in patients whose blood pressure is not adequately controlled on monotherapy and as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

### ***Risk Benefit Assessment***

The applicant's phase 3 trial demonstrated that treatment with the fixed-dose combination of perindopril arginine/amlodipine 14 mg/10 mg resulted in clinically and significantly greater reductions in diastolic and systolic blood pressure than treatment with the highest approved doses of perindopril erbumine (16 mg) and amlodipine (10 mg) in the study population. Compared to the highest approved dose of perindopril erbumine, perindopril arginine/amlodipine 14 mg/10 mg reduced systolic blood pressure by an additional 10.1 mmHg and diastolic blood pressure by an additional 6.3 mmHg. The benefit was smaller when perindopril was added to the highest approved dose of amlodipine, but still clinically meaningful (an additional reduction in systolic and diastolic blood pressure of 3.9 mmHg and 2.5 mmHg, respectively). The applicant's phase 2 trial also demonstrated that the low dose of the combination product (3.5 mg/2.5 mg) was more effective in reducing blood pressure than its components when administered at the same doses as monotherapy, thus satisfying the combination rule.

The safety profiles of Prestalia's active ingredients, amlodipine and perindopril are well characterized. As both Norvasc (amlodipine besylate) and Aceon were initially approved in the U.S. over 20 years ago, there is also extensive postmarketing experience with these agents. The safety of the high dose of Prestalia was evaluated in 279 patients in the applicant's phase 3 trial, while the safety of the low dose (3.5 mg/2.5 mg) was evaluated in a similar number of patients in the applicant's phase 2 trial. Review of these data did not reveal any additional or unexpected risks related to the use of Prestalia, as compared to amlodipine or perindopril. If anything, the trial data suggest that the use of perindopril in combination with amlodipine may lessen the risk of amlodipine-induced edema. Of note, a similar finding is reported in the label for Lotrel (amlodipine/benazepril), another fixed-dose combination of amlodipine and an ACE inhibitor.

### ***Findings in blacks***

While the study population in the applicant's phase 2 trial was almost exclusively Caucasian, 287 subjects in the phase 3 trial (approximately a third of the trial population) were reported to be Black or African American. In Caucasian patients, both components appeared to contribute

to the antihypertensive effect of the combination product and the incidence of edema was substantially lower in the treatment arm receiving perindopril arginine/amlodipine 14 mg/10 mg than in the treatment arm receiving amlodipine 10 mg. In contrast, adding perindopril to amlodipine did not result in greater blood pressure lowering than that seen with amlodipine alone in Black patients. Few Black patients developed peripheral edema in the phase 3 trial and the incidence of edema was no different in the perindopril/arginine 14 mg/10 mg and amlodipine 10 mg treatment arms (3 subjects in each, ~3.0%). A description of these findings should be included in labeling.

*Applicant's failure to establish a PK bridge*

As discussed in section 5, the applicant failed to establish a pharmacokinetic bridge between exposure to perindopril and perindoprilat in Prestalia and Aceon. Because the applicant is unable to bridge pharmacokinetic information on perindopril and perindoprilat from Aceon to Prestalia, the Office of Clinical Pharmacology is recommending that approval be limited to the population in whom efficacy and safety were demonstrated in the applicant's phase 2 and phase 3 trials. I agree with this approach, as does Dr. Hicks.

*Doses that should be approved*

As also discussed in section 5, there are differences of opinion among the members of the review team as to whether to approve the 7 mg/5 mg dose. The dose-response relationship for efficacy is thought to be linear over the proposed dose range and, based on Dr. Hinderling's analysis, increasing the dose of Prestalia from 3.5 mg/2.5 mg to 7 mg/5 mg would be expected to result in an additional 2.5 mmHg reduction in diastolic blood pressure. Per Dr. Hariharan's review, the dose-response relationship for edema with amlodipine is not linear and available data suggest a more substantial increase in the incidence of peripheral edema when the dose of amlodipine is increased from 5 mg to 10 mg than from 2.5 mg to 5 mg. Based on these data, I support approval of the intermediate dosage strength. I think having all three dosage strengths available (3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg) will allow prescribers to better tailor therapy to an individual's needs from both an efficacy and tolerability perspective.

***Recommendation for Postmarketing Risk Evaluation and Management Strategies***

None.

***Recommendation for other Postmarketing Requirements and Commitments***

The Office of Clinical Pharmacology is recommending a Postmarketing Requirement (PMR) to conduct a standard bioequivalence study to determine the biocomparability of perindopril and perindoprilat in the Prestalia 14 mg/10 mg tablet and the Aceon (perindopril erbumine) tablet (two 8 mg tablets) using validated specific and sensitive assays allowing a determination of AUC<sub>0-∞</sub> and C<sub>max</sub>. Per Dr. Hinderling's review, confirmation of the bioequivalence of amlodipine in the Prestalia 14 mg/10 mg tablet and the Norvasc (amlodipine besylate) 10 mg tablet is also highly desirable.

I believe there is precedent for making such a study a requirement as opposed to a commitment (i.e., PMRs for PK studies to support dosing recommendations in special populations, which is essentially the purpose of this PMR). I support the PMR, as does Dr. Hicks.

***Recommended Comments to Applicant***

Per Dr. Jewell's review, the following statement regarding the assignment of the expiration dating period for the drug product should be included in the approval letter:

The Agency has assigned an expiration dating period of 18 months for the 3.5 mg/2.5 mg strength of PRESTALIA and 24 months for the 7 mg/5 mg and 14 mg/10 mg strengths of PRESTALIA (perindopril arginine/amlodipine) fixed-dose combination tablets in the described packaging configurations.

I have no other comments for the applicant at this time.

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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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ALIZA M THOMPSON  
01/08/2015