Common Drug Review
Clinical Review Report

October 2016

Drug	Perindopril arginine/amlodipine (as amlodipine besylate) (Viacoram) (fixed-dose combination)
Indication	Viacoram is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate. Viacoram 3.5 mg/2.5 mg is indicated for initial therapy in patients with mild to moderate essential hypertension. Viacoram is not indicated for switching therapy from the individual drugs currently on the market (perindopril as erbumine or arginine salt, amlodipine)
Listing request	As per indication.
Dosage form(s)	• 3.5 mg perindopril arginine/2.5 mg amlodipine (as amlodipine besylate) oral tablet • 7 mg perindopril arginine/5 mg amlodipine (as amlodipine besylate) oral tablet • 14 mg perindopril arginine/10 mg amlodipine (as amlodipine besylate) oral tablet
NOC date	January 28, 2016
Manufacturer	Servier Canada Inc.

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ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
AE	adverse event
ARB	angiotensin II receptor blocker
BMI	body mass index
BP	blood pressure
CCB	calcium channel blocker
CHEP	Canadian Hypertension Education Program
CI	confidence interval
CV	cardiovascular
DB	double-blind
DBP	diastolic blood pressure
EMA	European Medicines Agency
FAS	full analysis set
FDC	fixed-dose combination
HBPM	home blood pressure monitoring
HCTZ	hydrochlorothiazide
HRQoL	health-related quality of life
HSBP	home systolic blood pressure
ITT	intention-to-treat
IVRS	interactive voice response system
LOCF	last observation carried forward
PP	per-protocol
PPS	per-protocol set
SAE	serious adverse event
SBP	systolic blood pressure
SR	sustained release
SS	safety set
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Hypertension is defined as persistently elevated arterial blood pressure (BP), specifically systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg. More than 90% of individuals with high BP have primary (essential) hypertension, which does not have an identifiable cause; the remaining patients are affected by hypertension that is secondary to another medical condition. Hypertension Canada's 2016 Canadian Hypertension Education Program (CHEP) guidelines generally recommend initial therapy with thiazide or thiazide-like diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or long-acting calcium channel blockers (CCBs). A combination of first-line drugs may be used as initial therapy if SBP is ≥ 20 mm Hg or DBP is ≥ 10 mm Hg above target.

The fixed-dose combination (FDC) of perindopril arginine/amlodipine comprises perindopril (an ACE inhibitor) in its arginine salt, and amlodipine (a dihydropyridine CCB) as amlodipine besylate, both of which are individually approved for the treatment of mild-to-moderate essential hypertension in Canada. Specifically, perindopril erbumine is approved at 2 mg, 4 mg, and 8 mg doses; perindopril arginine at 2.5 mg, 5 mg, and 10 mg doses; and amlodipine (as amlodipine besylate) at 2.5 mg, 5 mg, and 10 mg doses. Perindopril arginine/amlodipine FDC is approved at three doses in Canada: 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg. The recommended starting dose of perindopril arginine/amlodipine FDC is 3.5 mg/2.5 mg once daily. After four weeks of treatment, the dose may be increased to 7 mg/5 mg once daily in adult patients whose BP is not at the appropriate target. If necessary, titration to 14 mg/10 mg once daily may be considered in adult patients who are insufficiently controlled after four weeks of treatment with 7 mg/5 mg.

The objective of this review was to evaluate the beneficial and harmful effects of perindopril arginine/amlodipine (as amlodipine besylate) at 3.5 mg/2.5 mg FDC once daily (titrated to 7 mg/5 mg after four weeks if BP is still uncontrolled and, if necessary, to 14 mg/10 mg if BP is uncontrolled after four weeks of treatment with 7 mg/5 mg) for the treatment of mild-to-moderate essential hypertension in patients for whom combination therapy is appropriate.

Results and Interpretation

Included Studies

The evidence for this review of perindopril arginine/amlodipine FDC for the treatment of mild-to-moderate essential hypertension in patients for whom combination therapy is appropriate was primarily drawn from three randomized controlled trials (RCTs). CL2-005 (N = 1,581) was a phase 2 trial in which participants from Europe were randomized to receive one of six treatments: perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC; perindopril arginine 3.5 mg; amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg; or placebo. PATH (N = 837) was a phase 3 trial in which US participants were randomized to receive one of three treatments: perindopril arginine 14 mg/amlodipine besylate 10 mg FDC; perindopril erbumine 16 mg; or amlodipine besylate 10 mg. CL3-018 (N = 1,774) was a phase 3 trial in which participants from 18 countries, including Canada, were randomized to receive treatment according to one of two antihypertensive strategies: one initiated with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC, or another initiated with valsartan 80 mg. The up-titration steps in the perindopril arginine/amlodipine FDC strategy were perindopril arginine 7 mg/amlodipine 5 mg FDC, perindopril arginine 14 mg/amlodipine 10 mg FDC, and perindopril arginine 14 mg/amlodipine 10 mg FDC plus indapamide 1.5 mg sustained release (SR). The up-titration steps in the comparator group were

valsartan 160 mg, valsartan 160 mg/amlodipine 5 mg FDC, and valsartan 160 mg/amlodipine 10 mg FDC. The primary outcome was change in DBP (supine in CL2-005, seated in PATH) or SBP (supine in CL3-018). A fourth study (CL3-006) was identified; however, participants in that trial did not receive perindopril arginine/amlodipine FDC according to the approved dosage and administration in Canada.

All three trials included participants aged ≥ 18 years with hypertension. Approximately 80% of participants in CL2-005 and CL3-018 had stage 2 hypertension, defined as SBP 160 mm Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg, which the consulting clinical expert indicated would broadly reflect patients with moderate hypertension. In PATH, [redacted] of participants had stage 1 hypertension (SBP 140 mm Hg to 159 mm Hg and DBP 90 mm Hg to 99 mm Hg), which the expert indicated broadly reflected patients with mild hypertension, while [redacted] had stage 3 hypertension (SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg), which the expert indicated would broadly reflect patients with severe hypertension. Each study excluded individuals with comorbidities such as cerebrovascular diseases, heart disease, liver disease, or renal impairment. CL2-005 and CL3-018 also excluded participants with a body mass index (BMI) of more than 30 kg/m^2, while CL2-005 additionally excluded participants with type 1 or 2 diabetes. Across the studies, there were wide variations in the distribution of race, body composition, and certain risk factors reported as medical history. Overall, the included participants broadly reflected patients with hypertension who would be seen in usual Canadian practice.

Efficacy

In CL2-005, at the last post-baseline assessment over the eight-week treatment period, the mean decreases in supine DBP (primary efficacy outcome) and SBP were statistically significantly greater in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group than in the placebo, perindopril arginine 3.5 mg, and amlodipine 2.5 mg groups (Table 1). The mean decreases in supine DBP and SBP were statistically non-inferior in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group versus the perindopril arginine 5 mg and amlodipine 5 mg groups. A statistically significantly greater percentage of participants achieved BP normalization (SBP < 140 mm Hg and DBP < 90 mm Hg) or were considered responders (SBP < 140 mm Hg and DBP < 90 mm Hg and/or SBP decrease of ≥ 20 mm Hg from baseline and/or DBP decrease of ≥ 10 mm Hg from baseline) in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group (in which 43.5% achieved normalization and [redacted] were responders) than in the placebo group (in which 26.6% achieved normalization [*P* < 0.001] and [redacted] were responders, [redacted]). A greater percentage of participants achieved BP normalization or were considered responders in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group than in the perindopril arginine 5 mg group (in which 33.3% achieved normalization and [redacted] were responders), or in the amlodipine 5 mg group (in which 37.9% achieved normalization and [redacted] were responders).

In PATH, at day 42, the mean decreases in seated DBP (primary efficacy outcome) and SBP were statistically significantly greater in the perindopril arginine 14 mg/amlodipine 10 mg FDC group than in the perindopril erbumine 16 mg and amlodipine 10 mg groups (Table 1) There was a statistically significantly greater percentage of responders (BP < 140/90 mm Hg, or < 130/80 mm Hg if a participant had diabetes) in the perindopril arginine 14 mg/amlodipine 10 mg FDC group (51.6%) than in the perindopril erbumine 16 mg (27.1%) or amlodipine 10 mg (37.5%) groups (P < 0.001 for both comparisons).

In CL3-018, at the last post-baseline assessment over the first three-month treatment period, the mean decreases in supine DBP and SBP (primary efficacy outcome) were statistically significantly greater in participants randomized to the perindopril arginine/amlodipine FDC strategy versus those assigned to the valsartan/amlodipine strategy (Table 2). The results were similar over the entire six-month

treatment period, as well as at each study visit. A statistically significantly greater percentage of participants achieved BP control (SBP < 140 mm Hg and DBP < 90 mm Hg) or were considered responders (BP control and/or reduction in SBP ≥ 20 mm Hg and/or reduction in DBP ≥ 10 mm Hg) in the perindopril arginine/amlodipine FDC group (in which 56.4% achieved control and [redacted] were responders) than in the valsartan/amlodipine group (in which 49.0% achieved control [*P* = 0.002] and [redacted] were responders, [redacted]). The results were similar over the entire six-month treatment period, as well as at each study visit.

None of the trials evaluated the effects of the study treatments on hypertension-related morbidity, health-related quality of life (HRQoL), or adherence as an efficacy outcome, although treatment compliance was reported in each study.

Harms

Across all three studies, at least 15% of study participants in each trial experienced a treatment-emergent adverse event (TEAE) (Table 3, Table 4). A greater percentage of participants in PATH (which had a six-week treatment period) experienced a TEAE than did those in CL2-005 (eight weeks) and CL3-018 (six months). The most common TEAE across CL2-005 and PATH was peripheral edema, which appeared to occur more frequently at the higher dose of the perindopril arginine/amlodipine FDC and, in general, more frequently with amlodipine alone (5 mg in CL2-005 and 10 mg in PATH) versus other treatments, including perindopril arginine/amlodipine FDC. Other common TEAEs in CL2-005 and PATH were headaches (which occurred at a similar rate across the treatment groups) and cough, which in PATH appeared to occur more frequently in the perindopril arginine 14 mg/amlodipine 10 mg FDC (3.2%) and perindopril erbumine 16 mg (2.9%) groups compared with the amlodipine 10 mg (0.7%) group. In CL2-005, participants receiving perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC appeared to experience hyperkalemia at a rate similar to those in the amlodipine 2.5 group (2.4% versus 2.2%), but more frequently than those in the remaining treatment groups. In CL3-018, at each step of the titration strategy, there were no apparent differences between the two treatment groups in the percentage of participants who experienced a TEAE, although a greater percentage of participants experienced a TEAE at steps three and four (approximately 25%) than at the first two steps (approximately 18%). Results from the open-label, long-term extension phase of CL3-018 indicated a higher rate of TEAEs over the entire 14-month study period than during the initial six-month double-blind phase. Across all three trials, there were very few reports of serious adverse events (SAEs) (fewer than 1% in CL2-005 and PATH; fewer than 1.5% in CL3-018 in each group at every step) and deaths (one in CL2-005; two in CL3-018).

Potential Place in Therapy[1]

The average prevalence of hypertension in adults in Canada has remained at approximately 20%; however, because its incidence increases with age, its overall prevalence is likely to increase as the proportion of elderly people rises.

Over the past 25 years, substantial gains have been made in the treatment of hypertension in Canada due to:

- new drug classes with better tolerability and persistence, such as ACE inhibitors, CCBs, and ARBs

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

- the definition of evidence-based target BPs for patients with hypertension in the presence or absence of various concomitant diagnoses, such as diabetes or kidney disease
- a clearer understanding of the confounding impact of how, when, and where BP is measured
- the development and implementation of evidence-based guidelines by CHEP, which have been updated annually.

These changes have contributed to a considerable increase in the proportion of Canadians with hypertension whose BP is controlled. However, despite this progress, 34% of Canadians with hypertension still have uncontrolled BP. Uncontrolled BP places people at increased risk of stroke, kidney disease, kidney failure requiring dialysis, heart attack, heart failure, and cardiovascular death.

The results of the SPRINT study (an RCT assessing intensive BP management) suggested that a target systolic BP of < 120 mm Hg may be beneficial for some non-diabetic patients with hypertension compared with an SBP goal of < 140 mm Hg. The SPRINT protocol involved patients having their BP measured in a clinic with an automated sphygmomanometer (which, although previously recommended by CHEP, is not yet used by all physicians in Canada). If the SPRINT protocol becomes the standard of care for patient management, the unmet need for BP management will widen substantially; in that case, all physicians would require the appropriate sphygmomanometers or, at the very least, clarification on what the target BP should be for the type of sphygmomanometer used in their clinic.

The type and dose of antihypertensive drug(s), including single- and multi-drug products, are selected based on individual patient characteristics and responses. The clinical expert indicated that in Canadian practice, treatment is typically initiated with an ACE inhibitor or an ARB and, if there is no improvement, a diuretic or CCB is added. If still uncontrolled, a third drug — a diuretic or CCB (whichever was not added at the second step) — is added. For patients who have a concomitant disorder, such as diabetes or kidney disease, the dose of antihypertensive drug is very important and the choice of antihypertensive class and/or specific drug from within a class may also be very important. Perindopril arginine/amlodipine is an FDC that includes an ACE inhibitor and a CCB. The ACE inhibitor class has benefits in the treatment of patients with cardiovascular disease, such as heart failure, coronary artery disease, or diabetes. On the other hand, the CCB class of drugs is not generally recommended for the treatment of patients with heart failure or kidney disease unless they are already on the maximum dose of an ACE inhibitor or ARB.

Despite the typical single-drug, stepwise approach to treatment, the clinical expert consulted for this review believed that initial therapy with a combination product might be appropriate. This belief is supported by evidence from the STITCH study, which demonstrated that initiating treatment with a single-pill combination product and following the STITCH protocol (both steps address the challenge of "clinical inertia") resulted in more patients reaching their target BPs sooner than did the patients treated by physicians who followed the CHEP guidelines as per their usual practice. A single-pill combination product may also be advantageous for patients with chronic conditions, as their adherence to medication continues to be a challenge. Of note, the 2016 CHEP guidelines do not refer to the STITCH trial, even though it was published in 2009. Further, the 2016 CHEP guidelines only mention initiating therapy with a combination of first-line drugs if individuals present with SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg above target. It is unclear whether the 2017 guidelines will be revised to reflect (or perhaps even address) the apparent benefits of initiating therapy with a low-dose FDC for all patients, as the STITCH study demonstrated.

Conclusions

Results from two RCTs (CL2-005 and PATH) demonstrated that, with respect to DBP and SBP reduction, perindopril arginine/amlodipine FDC was statistically superior to placebo, perindopril arginine 3.5 mg, amlodipine 2.5 mg, perindopril erbumine 16 mg, and amlodipine 10 mg, and statistically non-inferior to perindopril arginine 5 mg and amlodipine 5 mg. Further, results from another RCT (CL3-018) indicated that a treatment strategy of perindopril arginine/amlodipine FDC was statistically superior to a treatment strategy of valsartan/amlodipine FDC in reducing DBP and SBP. However, the clinical benefit of perindopril arginine/amlodipine FDC remains uncertain, given the lack of data assessing more clinically meaningful outcomes, such as hypertension-related morbidity and mortality. Across the three studies, when compared with active comparators in general, a statistically significantly greater percentage of participants receiving perindopril arginine/amlodipine FDC achieved SBP/DBP < 140/90 mm Hg, which is considered by CHEP guidelines to be the target BP for the general population; however, the lack of multiplicity adjustment for this and other secondary outcomes necessitates some caution when interpreting these results. Further, the limited comparative evidence for drugs available in Canada limits the utility of the results. Data from the studies did not suggest improved compliance with the use of perindopril arginine/amlodipine FDC; the effects on HRQoL were not evaluated. Across the three studies, treatment with perindopril arginine/amlodipine FDC did not appear to be associated with any unexpected, consistent, or substantial harm up to 14 months. Longer-term, comparative studies are needed to adequately assess the morbidity and mortality profile of perindopril arginine/amlodipine FDC.

TABLE 1: RESULTS OF KEY EFFICACY OUTCOMES IN NON-TITRATION STUDIES

Outcome	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/ AMLO 2.5 mg FDC	Placebo	PERa 3.5 mg (not approved in Canada)	AMLO 2.5 mg	PER[a] 5 mg	AMLO 5 mg	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
DBP (mm Hg)[b]									
Baseline, N	246	248	268	270	270	261	271	274	275
Baseline, mean (SD)	100.7 (4.0)	100.5 (3.9)	100.7 (4.0)	100.6 (4.0)	100.1 (4.1)	100.6 (4.0)	100.6 (4.6)	100.8 (4.9)	100.5 (4.8)
End, mean (SD) change from baseline [CL2-005]/day 42, LS mean (SE) change from baseline [PATH]	–13.6 (9.2)	–9.3 (9.2)	–9.7 (9.9)	–10.3 (9.7)	–10.5 (9.7)	–12.6 (8.9)	–15.4 (0.6)	–9.1 (0.6)	–12.9 (0.6)
End, estimate (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC, *P* value [CL2-005]/day 42, LS mean difference (95% CI) vs. PER[a] 14 mg/AMLO 10 mg FDC, *P* value [PATH]		**–4.1 (–5.6 to –2.6), *P* < 0.001**	**–3.6 (–5.1 to –2.2), *P* < 0.001**	**–3.0 (–4.5 to –1.5), *P* < 0.001**	**–2.6 (–4.1 to –1.1), *P* < 0.001[c]**	**–0.8 (–2.3 to 0.7), *P* < 0.001[c]**		**–6.3 (–7.7 to –4.9), *P* < 0.0001**	**–2.5 (–3.9 to –1.1), *P* = 0.0005**
SBP (mm Hg)[b]									
Baseline, N	246	248	268	270	270	261	271	274	275
Baseline, mean (SD)	161.8 (7.5)	161.0 (7.4)	161.4 (7.7)	161.2 (7.6)	160.7 (7.3)	162.3 (7.5)	157.5 (11.91)	157.5 (11.4)	158.0 (11.8)
End, mean (SD) change from baseline [CL2-005]/day 42, LS mean (SE) change from baseline [PATH]	–22.0 (14.0)	–14.2 (16.1)	–16.3 (17.0)	–16.0 (15.3)	–18.2 (14.8)	–21.8 (15.4)	–22.8 (0.98)	–12.7 (1.0)	–18.8 (1.0)

Outcome	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/ AMLO 2.5 mg FDC	Placebo	PERa 3.5 mg (not approved in Canada)	AMLO 2.5 mg	PER[a] 5 mg	AMLO 5 mg	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
End, estimate (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC, *P* value [CL2-005]/day 42, LS mean difference (95% CI) vs. PERa 14 mg/AMLO 10 mg FDC, *P* value [PATH]		**–7.2 (–9.6 to –4.8), *P* < 0.001**	**–5.0 (–7.4 to –2.7), *P* < 0.001**	**–5.2 (–7.5 to –2.9), *P* < 0.001**	**–2.8 (–5.1 to –0.5), *P* < 0.001[c]**	**–0.3 (–2.6 to 2.1), *P* = 0.003[c]**		**–10.1 (–12.6 to –7.6), *P* < 0.0001**	**–3.9 (–6.4 to –1.5), *P* = 0.0017**
Response to treatment[d]									
N	[redacted]	[redacted]	NR		[redacted]	[redacted]	258	251	259
End, responders, n (%) [CL2-005]/day 42, responders, n (%) [PATH]	[redacted]	[redacted]			[redacted]	[redacted]	133 (51.6)	68 (27.1)	97 (37.5)
End, difference in % (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC; *P* value [CL2-005]/day 42, difference in % (95% CI) vs. PERa 14 mg/AMLO 10 mg FDC, *P* value [PATH]		[redacted] ***P* < 0.001**			[redacted]	[redacted]		**NR (NR), *P* < 0.001**	**NR (NR), *P* < 0.001**

Outcome	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/ AMLO 2.5 mg FDC	Placebo	PERa 3.5 mg (not approved in Canada)	AMLO 2.5 mg	PER[a] 5 mg	AMLO 5 mg	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
Normalization of BP[e]									
N	246	248	NR		[redacted]	[redacted]	Not evaluated		
End, normalization, n (%)	107 (43.5)	66 (26.6)			[redacted] (33.3)	[redacted] (37.9)			
End, difference in % (95% CI) vs. PERa 3.5 mg/ AMLO 2.5 mg FDC; *P* value		**16.9 (8.6 to 25.2), *P* < 0.001**			[redacted]	[redacted]			

AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; ITT = intention-to-treat; LS = least squares; NR = not reported; PERa = perindopril arginine; PERe = perindopril erbumine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] FAS in CL2-005, ITT in PATH.

[b] Supine in CL2-005, seated in PATH.

[c] *P* value for non-inferiority testing.

[d] CL2-005: SBP < 140 mm Hg and DBP < 90 mm Hg and/or SBP decrease ≥ 20 mm Hg from baseline and/or DBP decrease ≥ 10 mm Hg from baseline; PATH: BP < 140/90 mm Hg, or < 130/80 mm Hg if a participant had diabetes.

[e] CL2-005: SBP < 140 mm Hg and DBP < 90 mm Hg.

[f] No statistical testing conducted.

Note: Statistically significant results are bolded.

Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report.[2]

TABLE 2: RESULTS OF KEY EFFICACY OUTCOMES IN TITRATION STUDY

Outcome	CL3-018[a] (Six-Month Treatment Period)	
	PERa/AMLO FDC strategy (N = 881)	VAL/AMLO strategy (N = 876)
SBP (mm Hg)[b]		
Baseline, mean (SD)	163.6 (7.9)	163.3 (8.0)
Month 3, mean (SD) change from baseline	–25.9 (13.3)	–23.6 (14.2)
Month 3, estimate (95% CI), *P* value	**–2.0 (–3.2 to –0.9), *P* < 0.001**	
DBP (mm Hg)[b]		
Baseline, mean (SD)	100.2 (3.7)	100.3 (3.8)
Month 3, mean (SD) change from baseline	–16.9 (8.7)	–15.5 (9.2)
Month 3, estimate (95% CI), *P* value	**–1.5 (–2.2 to –0.7), *P* < 0.001**	
BP control[c]		
Month 3, yes, n (%)	497 (56.4)	429 (49.0)
Month 3, difference in % (95% CI), *P* value	**7.4 (2.8 to 12.1), *P* = 0.002**	
Response to treatment[d]		
Month 3, yes, n (%)	[redacted]	[redacted]
Month 3, difference in % (95% CI), *P* value	[redacted]	

AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.

[a] FAS.

[b] Supine.

[c] SBP < 140 mm Hg and DBP < 90 mm Hg.

[d] BP control and/or reduction in SBP ≥ 20 mm Hg and/or reduction in DBP ≥ 10 mm Hg.

Note: Statistically significant results are bolded.

Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg.
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

TABLE 3: HARMS IN NON-TITRATION STUDIES

	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 249)	**Placebo (N = 251)**	**PERa 3.5 mg (N = 273) (not approved in Canada)**	**AMLO 2.5 mg (N = 272)**	**PERa 5 mg (N = 272)**	**AMLO 5 mg (N = 264)**	**PERa 14 mg/ AMLO 10 mg FDC (N = 279)**	**PERe 16 mg (N = 278)**	**AMLO 10 mg (N = 280)**
Participants with > 0 [redacted], n (%)	47 (18.9)	40 (15.9)	51 (18.7)	51 (18.6)	44 (16.2)	57 (21.6)	86 (30.8)	77 (27.7)	108 (38.6)
Participants with > 0 SAEs, n (%)	0	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.1)	1 (0.4)	2 (0.7)	2 (0.7)
Participants with AEs that led to withdrawal, n (%)	3 (1.2)	0	6 (2.2)	9 (3.3)	7 (2.6)	8 (3.0)	10 (3.6)	11 (4.0)	13 (4.6)
Number of deaths, n (%)	0	0	0	0	1 (0.4)	0	0	0	0

AE = adverse event; AMLO = amlodipine; FDC = fixed-dose combination; PERa = perindopril arginine; PERe = perindopril erbumine; SAE = serious adverse event; [redacted].

[a] Safety set.

Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report.[2]

TABLE 4: HARMS IN TITRATION STUDY

		CL3-018[a] (Six-Month Treatment Period)	
		PERa/AMLO FDC strategy	VAL/AMLO strategy
Step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
Step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
Step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/ AMLO 5 mg FDC (not approved in Canada)	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
Step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC (not approved in Canada)	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]

AE = adverse event; AMLO = amlodipine; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VAL = valsartan.

[a] Safety set.

Source: CL3-018 Clinical Study Report.[3]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hypertension is defined as persistently elevated arterial blood pressure (BP), specifically systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg.[4,5] If left untreated, hypertension can cause end (target) organ damage, and lead to a number of debilitating medical conditions, such as heart disease, stroke, retinopathy, and chronic kidney disease.[6] To this end, the Global Burden of Disease, Injuries, and Risk Factor Study found that, in 2013, high SBP was the leading individual risk factor for disability (208.1 million attributable disability-adjusted life years) and mortality (10.4 million attributable deaths) globally.[7] In 2014, 5.3 million Canadians (17.7%) aged ≥ 12 years reported being diagnosed with high BP, with a greater percentage of males affected than females (18.5% versus 17.0%, respectively). More than 90% of individuals with high BP have primary (essential) hypertension that does not have an identifiable cause; the remaining patients are affected by hypertension that is secondary to another medical condition.[4]

1.2 Standards of Therapy

Management of hypertension begins with lifestyle modifications that target physical exercise, weight reduction, alcohol consumption, dietary recommendations, smoking cessation, and stress management.[8] The 2016 Canadian Hypertension Education Program (CHEP) guidelines recommend antihypertensive therapy for individuals with average SBP/DBP ≥ 160 mm Hg/100 mm Hg who do not present with macrovascular target-organ damage or other cardiovascular risk factors.[8] Patients with hypertension are managed by being treated to target; i.e., to a BP level at or beyond which their risk of hypertension-related morbidity and mortality is reduced. CHEP recommends a target of SBP/DBP < 140/90 mm Hg in the general patient population, SBP/DBP < 130/80 mm Hg in patients with diabetes mellitus, and SBP ≤ 120 mm Hg in selected high-risk patients.[8]

For individuals with hypertension without compelling indications for specific drugs, CHEP recommends initial therapy with thiazide/thiazide-like diuretics, beta blockers (in individuals under 60 years of age), angiotensin-converting enzyme (ACE) inhibitors (in non-black individuals), angiotensin II receptor blockers (ARBs), or long-acting calcium channel blockers (CCBs).[8] For individuals who have SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg above target, CHEP suggests initiating therapy with a combination of first-line drugs.[8]

1.3 Drug

Perindopril arginine/amlodipine (Viacoram) is a fixed-dose combination (FDC) of perindopril (an ACE inhibitor) in its arginine salt, and amlodipine (a dihydropyridine CCB) as amlodipine besylate.[9] Perindopril lowers BP by primarily suppressing the renin-angiotensin-aldosterone system, while amlodipine acts directly on the vascular smooth muscle calcium channels to reduce peripheral vascular resistance and BP.[9] Both drugs are individually approved for the treatment of mild-to-moderate essential hypertension in Canada.[10] Perindopril is approved in its erbumine salt at three doses — 2 mg, 4 mg, and 8 mg — and marketed as Coversyl.[10] The arginine salt of perindopril is also approved at three doses — 2.5 mg, 5 mg, and 10 mg, each being equimolar to the corresponding doses of the erbumine salt — although it is not currently marketed.[10] Amlodipine (as amlodipine besylate) is marketed in Canada as Norvasc and generics at 2.5 mg, 5 mg, and 10 mg doses.[10]

Perindopril arginine/amlodipine FDC is available at three doses in Canada: 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg.[9] No FDC of an ACE inhibitor plus a CCB is available as initial therapy in Canada.[10] Perindopril arginine/amlodipine FDC is approved in the US at the same three doses, although it is

marketed as Prestalia.[11] It has also been approved at different doses (5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, and 10 mg/10 mg) as Coveram in other countries.[12,13]

The recommended starting dose of perindopril arginine/amlodipine FDC in Canada is 3.5 mg/2.5 mg once daily.[9] After four weeks of treatment, the dose may be increased to 7 mg/5 mg once daily in adult patients whose BP is not at the appropriate target. If necessary, titration to 14 mg/10 mg once daily may be considered in adult patients who are insufficiently controlled after four weeks of treatment with 7 mg/5 mg.

Table 5 summarizes the antihypertensive drugs (by drug class) available in Canada.

Indication under review
Viacoram is indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate. Viacoram 3.5 mg/2.5 mg is indicated for initial therapy in patients with mild to moderate essential hypertension. Viacoram is not indicated for switching therapy from the individual drugs currently on the market (perindopril as erbumine or arginine salt, amlodipine).
Listing criteria requested by sponsor
As per indication.

TABLE 5: KEY CHARACTERISTICS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS, ANGIOTENSIN II RECEPTOR BLOCKERS, BETA BLOCKERS, CALCIUM CHANNEL BLOCKERS, AND DIURETICS

	Angiotensin-Converting Enzyme Inhibitors	Angiotensin II Receptors Blockers	Beta Blockers	Calcium Channel Blockers	Diuretics
Drugs Available in Canada	Benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	Acebutolol, atenolol, bisoprolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol (controlled-release), timolol	*Dihydropyridine:* amlodipine, felodipine (extended-release), nifedipine (extended-release) *Nondihydropyridine:* diltiazem, verapamil	Hydrochlorothiazide, chlorthalidone, indapamide, metolazone
Route of Administration	Oral				
Usual Dose[a]	• benazepril: 20 mg/day • captopril: 75 mg/day • cilazapril: 2.5 mg to 5 mg/day • enalapril: 10 mg to 40 mg/day • fosinopril: 20 mg/day • lisinopril: 20 mg/day • perindopril: ≤ 8 mg/day • quinapril: ≤ 40 mg/day • ramipril: 10 mg/day • trandolapril: ≤ 4mg/day	• azilsartan: ≤ 80 mg/day • candesartan: 8 mg to 16 mg/day • eprosartan: ≤ 800 mg/day • irbesartan: 150 mg to 300 mg/day • losartan: 25 mg to • 100 mg/day • olmesartan: ≤ 40 mg/day • telmisartan: 80 mg/day • valsartan: 80 mg to • 320 mg/day	• acebutolol: 400 mg/day • atenolol: 50 mg/day • bisoprolol: 10 mg/day • labetalol: 200 mg/day b.i.d. • metoprolol: 100 mg to 200 mg/day • nadolol: 160 mg/day • nebivolol: 10 mg/day • pindolol: 15 mg/day b.i.d. • propanolol (controlled-release): 320 mg/day • timolol: 20mg/day b.i.d.	• amlodipine: ≤ 10 mg/day • diltiazem: 240 mg to 360 mg/day • felodipine (extended-release): 10 mg/day • nifedipine (extended-release): 60 mg/day • verapamil (sustained release): 180 mg to 480 mg/day	• hydrochlorothiazide: 25 mg/day • chlorthalidone: 25 mg/day • indapamide: 12.5 mg to 25 mg/day • metolazone: 2.5 mg to 5 mg/day
Notes/ Contraindications/Adverse Effects	Special notes: none Contraindication(s): pregnancy Adverse effect(s): dry cough, hyperkalemia, angioedema	Special notes: none Contraindication(s): pregnancy Adverse effect(s): hyperkalemia, renal failure (in those with	Special: should not be used as initial therapy in patients aged > 60 years unless specifically indicated; avoid in patients with asthma or peripheral artery disease	*Dihydropyridine* Notes: felodipine - grapefruit juice causes marked elevations in felodipine serum levels and adverse events; nifedipine — do not use	Notes: particularly effective in ISH, the elderly, and black patients Contraindication(s):

	Angiotensin-Converting Enzyme Inhibitors	Angiotensin II Receptors Blockers	Beta Blockers	Calcium Channel Blockers	Diuretics
	(unusual), renal failure (in those with renovascular disease, volume depletion, or those receiving NSAIDs)	bilateral renovascular disease or volume depletion, or with concurrent NSAID use)	Contraindication(s): second- or third-degree heart block in the absence of a pacemaker. Adverse effect(s): fatigue, bradycardia, decreased exercise capacity, headache, impotence, vivid dreams; less common: hyperglycemia, depression, heart failure, heart block	short-acting nifedipine formulations for treatment of essential hypertension. Contraindication(s): none Adverse effect(s): ankle edema, flushing, headache, and palpitations *Nondihydropyridine* Notes: caution in patients with heart failure, or second- or third-degree heart block without a functioning pacemaker Contraindication(s): none Adverse effect(s): headache, dizziness, bradycardia, heart block, new onset or worsening of heart failure, constipation (verapamil only)	none Adverse effect(s): hypotension, weakness, muscle cramps, impotence; hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, hyperlipidemia; rare: azotemia, blood dyscrasias, allergic reactions (potential cross-sensitivity with other sulfonamide derivatives), photosensitivity, fatigue

b.i.d. = twice a day; ISH = isolated systolic hypertension; NSAID = nonsteroidal anti-inflammatory.
[a] Dosage must be individualized.
Source: e-CPS.[14]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of perindopril arginine/amlodipine (as amlodipine besylate) at 3.5 mg/2.5 mg FDC once daily for the treatment of mild-to-moderate essential hypertension in patients for whom combination therapy is appropriate, titrated to 7 mg/5 mg after four weeks if BP is uncontrolled; and, if necessary, to 14 mg/10 mg if BP is uncontrolled after four weeks of treatment with 7 mg/5 mg.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the criteria in Table 6.

TABLE 6: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with mild-to-moderate essential hypertension for whom combination therapy is appropriate. **Subgroups** • Race • Presence of comorbidities (chronic kidney disease, coronary artery disease, diabetes mellitus)
Intervention	Perindopril arginine/amlodipine (as amlodipine besylate) FDC tablet once daily: • 3.5 mg perindopril arginine/2.5 mg amlodipine[a] • 7 mg perindopril arginine/5 mg amlodipine • 14 mg perindopril arginine/10 mg amlodipine
Comparators	• Placebo • ACE inhibitors[b] • ARBs[b] • Beta blockers[b] • Long-acting CCBs[b] • Thiazide/thiazide-like diuretics[b]

Outcomes	**Key efficacy outcomes**
	• Change in BP (SBP and DBP)
	• Hypertension-related morbidity, including:
	  ○ CV disease: MI, HF, left ventricular hypertrophy, angina
	  ○ Cerebrovascular disease: stroke, TIA
	  ○ Other target-organ damage: hypertensive retinopathy, chronic kidney disease
	• Change in HRQoL
	• Adherence
	
	Harms outcomes
	• Mortality
	• AEs
	• SAEs
	• WDAEs
	• Notable harms: hypotension, peripheral edema, cough, hyperkalemia, AKI

Study Design	Published and unpublished phase 3 RCTs

ACE = angiotensin-converting enzyme; AE = adverse event; AKI = acute kidney injury; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CV = cardiovascular; DBP = diastolic blood pressure; FDC = fixed-dose combination; HF = heart failure; HRQoL = health-related quality of life; MI = myocardial infarction; RCT = randomized controlled trial; SAE = serious adverse event; SBP = systolic blood pressure; TIA = transient ischemic attack; WDAE = withdrawal due to adverse event.

[a] This is the recommended starting dose. After four weeks of treatment, the dose may be increased to 7 mg/5 mg once daily in adult patients whose BP is not at appropriate target. If necessary, titration to 14 mg/10 mg once daily may be considered in adult patients insufficiently controlled after four weeks of treatment with 7 mg/5 mg.

[b] Used alone or in combination with other listed comparators (as multi-tablet regimens or FDCs) at approved doses in Canada.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were perindopril and amlodipine.

No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 28, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on September 21, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the drug manufacturer was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 7; excluded studies (with reasons) are presented in Appendix 3.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified for inclusion in the systematic review (Figure 1). Three of the four studies (CL2-005, PATH, and CL3-018) were considered pivotal by Health Canada, and are summarized in the main report. The fourth study (CL3-006) is summarized in Appendix 5, since participants in that trial did not receive perindopril arginine/amlodipine FDC per the approved titration strategy in Canada.[9] Specifically, participants in one of the two treatment groups in that trial were up-titrated to perindopril arginine/amlodipine 14 mg/5 mg FDC, a dose that is not approved in Canada. Further, participants were instructed to take that dose as well as the subsequent dose (that is approved in Canada) in the titration strategy (i.e., 14 mg/10 mg twice daily), even though the intended dosage is once a day.[9] A list of excluded studies is presented in Appendix 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

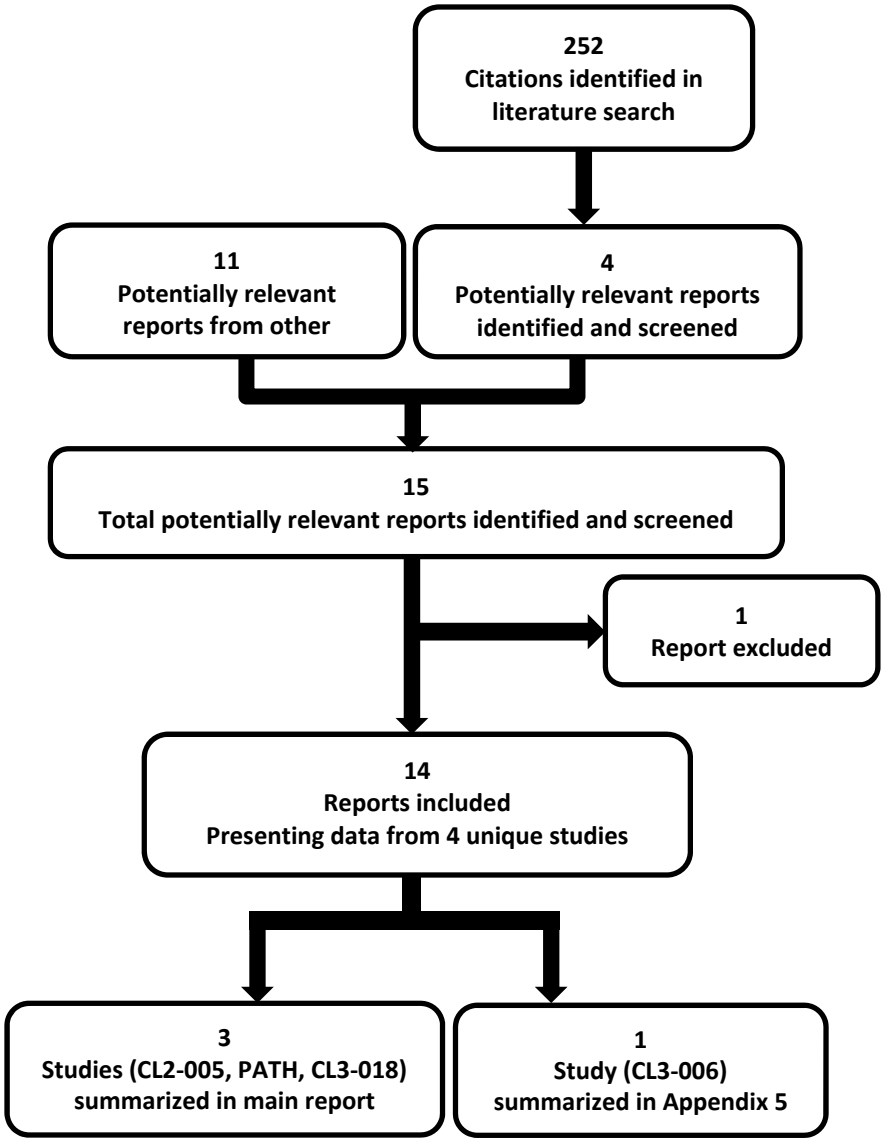

TABLE 7: DETAILS OF NON-TITRATION STUDIES

		CL2-005	PATH
DESIGNS & POPULATIONS	**Study design**	Multi-centre, DB, placebo- and active-controlled, parallel-group factorial phase 2 RCT	Multi-centre, DB, active-controlled, parallel-group phase 3 RCT
	Locations	France, Russia, Ukraine, Latvia, Lithuania, Hungary	US
	Randomized (N)	1,581	837
	Main inclusion criteria	Male or female aged 18 years to 80 years with essential mild-to-moderate uncomplicated hypertension (SBP ≥ 150 mm Hg and < 180 mm Hg; DBP ≥ 95 mm Hg and < 110 mm Hg) after initiation or intensification of appropriate healthy lifestyle modification, requiring antihypertensive treatment initiation or a change due to lack of efficacy or poor tolerability	Male or female aged 18 years to 75 years with essential hypertension (mean seated DBP ≥ 95 mm Hg and ≤ 115 mm Hg at baseline); participants who had previously received antihypertensive medication and had the ability to stop the therapy for the duration of the study without unacceptable risk could be included at the investigator's discretion
	Main exclusion criteria	BMI > 30 kg/m^2; history of cerebrovascular disease, heart disease, or renal disease; peripheral vascular disease; advanced retinopathy; LVH; microalbuminuria; type 1 or type 2 diabetes mellitus; liver disease; chronic pancreatitis; ventricular rhythm disorders; symptomatic orthostatic hypotension; hyperkaliemia; hypersensitivity, contraindication, or hypertension resistant to ACE inhibitors or dihydropyridine CCBs	Night shift worker; known or suspected secondary hypertension; baseline mean seated SBP ≥ 180 mm Hg; renal dysfunction; hypokalemia or hyperkalemia; HIV, hepatitis B, or hepatitis C; history of malignancy within five years; primary aldosteronism; HF; MI; stroke; ventricular tachycardia; concomitant medications known to affect BP; pregnancy; history of drug or alcohol dependency within six months; contraindication to study drugs
DRUGS	**Intervention**	Perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC once daily	Perindopril arginine 14 mg/amlodipine besylate 10 mg FDC once daily
	Comparators	Placebo; perindopril arginine 3.5 mg; amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg (all once daily)	Perindopril erbumine 16 mg; amlodipine besylate 10 mg (all once daily)
DURATION	**Phase**		
	Run-in/washout	Run-in: 2 weeks to 3 weeks	Washout: 2 weeks to 3 weeks
	Double-blind	8 weeks	6 weeks
	Follow-up	N/A	N/A
OUTCOMES	**Primary end point**	Supine DBP	Seated DBP
	Other end points	Supine SBP, response to treatment, normalization of BP, AEs, SAEs, WDAEs, notable harms	Seated SBP, response to treatment, AEs, SAEs, WDAEs, notable harms

		CL2-005	PATH
NOTES	**Publications**	Laurent et al., 2015[15]	Elliott et al., 2015[16]

ACE = angiotensin-converting enzyme; BP = blood pressure; AE = adverse event; BMI = body mass index; CCB = calcium channel blocker; DB = double-blind; DBP = diastolic blood pressure; FDC = fixed-dose combination; HF = heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction; N/A = not applicable; RCT = randomized controlled trial; SAE = serious adverse event; SBP = systolic blood pressure; WDAE = withdrawal due to adverse event.
Note: The following additional reports were included: Health Canada reviewer's report,[10] CDR submission binder.[17]
Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report.[2]

TABLE 8: DETAILS OF TITRATION STUDY

		CL3-018
DESIGNS & POPULATIONS	**Study design**	Multi-centre, DB, active-controlled, parallel-group phase 3 RCT
	Locations	Belgium, Brazil, Canada, Czech Republic, France, Germany, Italy, South Korea, Latvia, Lithuania, Mexico, The Netherlands, Portugal, Russia, Singapore, Spain, Taiwan, United Kingdom
	Randomized (N)	1,774
	Main inclusion criteria	Male or female aged ≥ 18 years with essential mild-to-moderate hypertension: for untreated participants, SBP ≥ 150 mm Hg and < 180 mm Hg, DBP ≥ 95 mm Hg and < 110 mm Hg; for treated participants (with no more than two antihypertensive drugs) who, in the investigator's opinion, require a change in medication because of lack of efficacy or poor tolerability, SBP < 160 mm Hg and DBP < 100 mm Hg
	Main exclusion criteria	BMI > 30 kg/m^2; secondary hypertension; history of an acute episode of cerebrovascular disease; MI; coronary revascularization; unstable angina pectoris; history of congestive HF (NYHA stage 3 or 4), severe uncorrected aortic or mitral valve stenosis; severe renal impairment (creatinine clearance < 30 mL/min; Cockcroft Gault formula); history of severe mental or psychiatric disorder; known liver disease; history of ventricular rhythm disorders; symptomatic orthostatic hypotension in the last 12 months; use of perindopril/amlodipine or valsartan/amlodipine free or fixed combinations at the highest available doses; and known contraindications or hypersensitivity to any of the study drugs
DRUGS	**Intervention**	Perindopril arginine/amlodipine strategy: • step 1 = perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC once daily • step 2 = perindopril arginine 7 mg/amlodipine 5 mg FDC once daily • step 3 = perindopril arginine 14 mg/amlodipine 10 mg FDC once daily • step 4 = perindopril arginine 14 mg/amlodipine 10 mg FDC once daily + indapamide 1.5 mg SR once daily. If BP was controlled at each monthly visit, participants remained on the same dosage as at previous visit; if BP was uncontrolled, treatments were up-titrated according to the schedule for the perindopril arginine/amlodipine strategy.
	Comparators	Valsartan/amlodipine strategy: • step 1 = valsartan 80 mg once daily • step 2 = valsartan 160 mg once daily • step 3 = valsartan 160 mg/amlodipine 5 mg FDC once daily • step 4 = valsartan 160 mg/amlodipine 10 mg FDC once daily. If BP was controlled at each monthly visit, participants remained on the same dosage as at previous visit; if BP was uncontrolled, treatments were up-titrated

		CL3-018
		according to the schedule for the valsartan/amlodipine strategy.
DURATION	**Phase**	
	Run-in/washout	Run-in: 2 weeks to 4 weeks
	Double-blind	6 months
	Follow-up	8 months
OUTCOMES	**Primary end point**	Office supine SBP
	Other end points	Office supine DBP, office BP control and response to treatment, ambulatory SBP and DBP, AEs, SAEs, WDAEs, notable harms
NOTES	**Publications**	Mancia et al., 2015[18]

AE = adverse event; BMI = body mass index; BP = blood pressure; CDR = CADTH Common Drug Review; DB = double-blind; DBP = diastolic blood pressure; FDC = fixed-dose combination; HF = heart failure; MI = myocardial infarction; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; SBP = systolic blood pressure; SR = sustained release; WDAE = withdrawal due to adverse event.
Note: The following additional reports were included: Health Canada reviewer's report;[10] CDR submission binder.[17]
Source: CL3-018 Clinical Study Report.[3]

3.2 Included Studies

3.2.1 Description of Studies

CL2-005 (N = 1,581) was a multi-centre, double-blind (DB), phase 3 randomized controlled trial (RCT) in which participants from Europe were randomized in an equal ratio to receive one of six treatments: perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC; perindopril arginine 3.5 mg; amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg; or placebo (Table 7). Randomization was conducted using an interactive voice response system (IVRS) and stratified according to centre. The trial comprised a run-in period with placebo that lasted between two and three weeks, followed by an eight-week treatment period. The manufacturer reported this study was designed as a "factorial trial" to comply with the requirements of the European Medicines Agency (EMA) at the time of the trial.[19] The manufacturer also conducted an ancillary study in which ambulatory blood pressure monitoring (ABPM) was evaluated in a subset of participants randomized to the main study, the results of which are summarized in Appendix 6.

PATH (N = 837) was a multi-centre, DB, phase 3 RCT in which participants from the US were randomized (1:1:1) to receive one of three treatments: perindopril arginine 14 mg/amlodipine besylate 10 mg FDC; perindopril erbumine 16 mg; or amlodipine besylate 10 mg (Table 7). Randomization was conducted using IVRS, and stratified according to current type 2 diabetes status, race, and baseline DBP. The study consisted of a washout period that lasted between two and three weeks, followed by a six-week treatment period. In this trial, eligible participants who were taking antihypertensive medications at screening discontinued all antihypertensive drugs to begin the washout period, after which they were randomized to one of the three aforementioned groups, while those who were treatment-naive were randomized seven days after screening. Per the manufacturer, this study was requested by the US Food and Drug Administration (FDA) for the registration of the high dose of Viacoram. The manufacturer noted that the FDA reviewed and approved the study design.[2] There were no associated ancillary studies.

CL3-018 (N = 1,774) was a multi-centre, DB, phase 3 RCT in which participants from 18 countries, including Canada, were randomized (1:1) to receive treatment according to one of two antihypertensive strategies: one initiated with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC, or another initiated with valsartan 80 mg (Table 8). Randomization was conducted using an interactive Web response system (IWRS) and stratified according to country. The study comprised a run-in period that lasted between two and four weeks, followed by a six-month treatment period. At the end of the treatment period, only participants with controlled BP entered an open-label follow-up period for eight months, the results of which are summarized in Appendix 8. In addition, several associated ancillary studies were conducted, including an ABPM substudy, as well as a home blood pressure monitoring (HBPM) substudy, the results of which are summarized in Appendix 6 and Appendix 7, respectively.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

All three trials included participants aged ≥ 18 years with essential hypertension, although the BP cut-offs for study entry varied: in particular, CL2-005 and CL3-018 included participants with SBP ≥ 150 and < 180 mm Hg and DBP ≥ 95 and < 110 mm Hg at baseline, while PATH included participants with DBP ≥ 95 mm Hg and ≤ 115 mm Hg (Table 7, Table 8). Each trial excluded participants with known associated clinical conditions. Specifically, all three trials excluded individuals with comorbidities (active or historical), such as cerebrovascular diseases, heart disease, liver disease, or renal impairment; CL2-005 and CL3-018 also excluded participants with BMI > 30 kg/m^2, while CL2-005 additionally excluded participants with type 1 or 2 diabetes. The manufacturer noted that CL2-005 recruited participants with uncomplicated hypertension due to the inclusion of a placebo group. Participants in all three trials could have been treatment-naive or received antihypertensive treatment in the past.

b) Baseline Characteristics

In each of the three included studies, the average age of participants was slightly greater than 50 years (Table 9, Table 10). The male to female ratio among participants varied across the trials: specifically, unlike PATH and CL3-018, CL2-005 included fewer females (less than 50%). More than half of all participants in each trial were white or Caucasian, although the percentage of such individuals ranged from approximately 64% in PATH to 99% in CL2-005. In addition, approximately 34% of the participants in PATH were Asian versus fewer than 1% in CL2-005 and approximately 5% in CL3-018. Further, the average participant in PATH would be considered obese (mean BMI of approximately 33 kg/m^2); while in the other studies, the average participant would be considered overweight, as indicated by a mean BMI of approximately 27 kg/m^2. Participants in CL2-005 appeared to have a shorter mean duration of hypertension than those in PATH and CL3-018; in PATH, however, the mean duration of hypertension appeared to be disproportionate across the treatment groups, and ranged from 7.9 years in the perindopril arginine 14 mg/amlodipine 10 mg group to 9.2 years in the amlodipine 10 mg group (Table 9).

Approximately 80% of participants in CL2-005 and CL3-018 had stage 2 hypertension, which was defined as SBP 160 mm Hg to 79 mm Hg, and DBP 100 mm Hg to 109 mm Hg (Table 9). In PATH, [redacted] of participants had stage 2 hypertension, which was defined as SBP 140 mm Hg to 159 mm Hg and DBP 90 mm Hg to 99 mm Hg, while [redacted] had stage 3 hypertension, which was defined as SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg (Table 10). At least 60% of participants in each trial had received previous treatment for hypertension — most commonly, drugs that acted on the renin-angiotensin system (ACE inhibitors or ARBs, either individually or in combination with other drugs) — although the percentage of treatment-experienced individuals was greater in CL3-018 (approximately 80%) than in the other studies (60% to 70%) (Table 9, Table 10).

A greater percentage of participants in PATH had certain risk factors for cardiovascular disease — including current smoking or tobacco consumption, current alcohol consumption, and a history of metabolism and nutrition diseases — than did those in CL2-005 and CL3-018. In CL2-005 specifically, a greater percentage of participants in the perindopril arginine 3.5 mg group appeared to currently smoke or consume tobacco compared with individuals in the remaining treatment groups. A patient history of metabolic and nutritional disorders commonly included dyslipidemia, which the expert expected. Further, a greater percentage of participants in CL3-018 had a history of cardiac disease ([redacted]) or vascular disease ([redacted]) compared with individuals in the other two studies; specifically, the percentage of participants in CL2-005 who had a history of cardiac disease ranged from [redacted] to [redacted] across the treatment groups, while the percentage of participants who had a history of vascular disease ranged from [redacted] to [redacted] across the groups, compared with a range of [redacted] to [redacted] and [redacted] to [redacted], respectively, in PATH. Overall, the clinical expert consulted for the review noted that any observed differences within and between trials were minor and unlikely to affect treatment response substantially.

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS OF PARTICIPANTS IN NON-TITRATION STUDIES

Characteristic	CL2-005[a]						PATH[a]		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 248)	Placebo (N = 250)	PERa 3.5 mg (N = 273) (not approved in Canada)	AMLO 2.5 mg (N = 274)	PERa 5 mg (N = 272)	AMLO 5 mg (N = 264)	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
Mean (SD) age (years)	51.6 (11.8)	51.8 (11.7)	52.2 (11.1)	51.8 (11.2)	51.1 (11.6)	51.8 (11.0)	51.2 (9.7)	51.4 (9.8)	51.6 (9.8)
Number of males (%)	116 (46.8)	116 (46.4)	128 (46.9)	128 (46.7)	129 (47.4)	122 (46.2)	145 (52.0)	135 (48.6)	150 (53.6)
Number of participants who were Caucasian or white (%)	246 (99.2)	247 (98.8)	269 (98.5)	271 (98.9)	266 (97.8)	260 (98.5)	179 (64.2)	180 (64.7)	181 (64.6)
Number of participants who were Asian (%)	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)	95 (34.1)	95 (34.2)	96 (34.3)
Number of participants who were black or African American (%)	2 (0.8)	3 (1.2)	2 (0.7)	3 (1.1)	5 (1.8)	3 (1.1)	2 (0.7)	1 (0.4)	1 (0.4)
Number of participants with type 2 diabetes	N/A (participants with diabetes were excluded from the trial)						59 (21.1)	56 (20.1)	56 (20.0)
Mean (SD) BMI (kg/m^2)	26.8 (2.8)	26.7 (2.5)	27.0 (2.4)	26.9 (2.5)	26.8 (2.8)	26.7 (2.5)	33.1 (6.92)	33.2 (6.42)	33.0 (6.02)
Mean (SD) duration of hypertension (months)	63.4 (72.3)	59.6 (82.1)	54.3 (63.6)	52.3 (64.6)	52.1 (64.8)	55.2 (73.9)	NR		
Mean (SD) duration of hypertension (years)	NR						7.9 (6.93)	8.8 (8.52)	9.2 (8.94)
Number of participants with stage 1 hypertension [SBP 140 mm Hg to 159 mm Hg and DBP 90 mm Hg to 99 mm Hg] (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of participants with stage 2 hypertension [SBP 160 mm Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg] (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	CL2-005[a]						PATH[a]		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 248)	Placebo (N = 250)	PERa 3.5 mg (N = 273) (not approved in Canada)	AMLO 2.5 mg (N = 274)	PERa 5 mg (N = 272)	AMLO 5 mg (N = 264)	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
Number of participants with stage 3 hypertension [SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg] (%)[b]	[redacted]						[redacted]	[redacted]	[redacted]
Number of participants who received previous treatment for hypertension (%)	151 (60.9)	157 (62.8)	167 (61.2)	174 (63.5)	155 (57.0)	161 (61.0)	184 (65.9)	196 (70.5)	187 (66.8)
Drugs acting on the renin–angiotensin system (ACE inhibitors or ARBs, individually or in combination with other drugs), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diuretics, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blockers, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Beta-blocking drugs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other antihypertensives,[c] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of participants who currently smoked or consumed tobacco (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	65 (23.3)	67 (24.1)	65 (23.2)
Number of participants who currently consumed alcohol (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	147 (52.7)	133 (47.8)	134 (47.9)
Number of participants with a history of metabolism and nutrition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	CL2-005[a]						PATH[a]		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 248)	Placebo (N = 250)	PERa 3.5 mg (N = 273) (not approved in Canada)	AMLO 2.5 mg (N = 274)	PERa 5 mg (N = 272)	AMLO 5 mg (N = 264)	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
disorders (%)									
Number of participants with a history of vascular disorders (other than hypertension) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of participants with a history of cardiac disorders (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) DBP (mm Hg)[d]	100.7 (4.0)	100.5 (3.9)	100.7 (4.0)	100.6 (4.0)	100.1 (4.1)	100.6 (4.0)	100.7 (4.6)	100.8 (4.9)	100.4 (4.8)
Mean (SD) SBP (mm Hg)[d]	161.8 (7.5)	160.9 (7.3)	161.5 (7.8)	161.0 (7.6)	160.7 (7.3)	162.3 (7.5)	157.5 (12.0)	157.3 (11.5)	157.9 (11.8)

ACE = angiotensin-converting enzyme; AMLO = amlodipine; ARB = angiotensin II receptor blocker; BMI = body mass index; DBP = diastolic blood pressure; FDC = fixed-dose combination; N/A = not applicable; NR = not reported; PERa = perindopril arginine; PERe = perindopril erbumine; SBP = systolic blood pressure; SD = standard deviation.
[a] Randomized set.
[b] Stages defined per European Society of Hypertension/European Society of Cardiology; number (%) of participants in safety set.
[c] Included drugs such as antiadrenergic drugs (centrally acting and peripherally acting).
[d] Supine for CL2-005, seated for PATH.
Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report,[2] HC reviewers report.[10]

TABLE 10: SUMMARY OF BASELINE CHARACTERISTICS OF PARTICIPANTS IN TITRATION STUDY

Characteristic	CL3-018[a]	
	Perindopril arginine/amlodipine FDC strategy (N = 888)	Valsartan/amlodipine strategy (N = 886)
Mean (SD) age (years)	55.7 (10.3)	55.2 (10.9)
Number of males (%)	479 (53.9)	469 (52.9)
Number of participants who were Caucasian or White (%)	[redacted]	[redacted]
Number of participants who were Asian (%)	[redacted]	[redacted]
Number of participants who were black or African American (%)	[redacted]	[redacted]

Characteristic	CL3-018[a]	
	Perindopril arginine/amlodipine FDC strategy (N = 888)	**Valsartan/amlodipine strategy (N = 886)**
Number of participants with type 2 diabetes	104 (13.5)	108 (14.1)
Mean (SD) BMI (kg/m^2)	27.1 (2.4)	27.1 (2.5)
Mean (SD) duration of hypertension (years)	8.3 (7.9)	7.8 (7.7)
Number of participants with stage 1 hypertension [SBP 160 mm Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg] (%)[b]	171 (19.3)	176 (19.9)
Number of participants with stage 2 hypertension [SBP 160 mm Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg] (%)[b]	717 (80.7)	710 (80.1)
Number of participants who received previous treatment for hypertension (%)	726 (81.8)	691 (78.0)
Drugs acting on the renin-angiotensin system (ACE inhibitors or ARBs, individually or in combination with other drugs), n (%)	[redacted]	[redacted]
Diuretics, n (%)	[redacted]	[redacted]
Calcium channel blockers, n (%)	[redacted]	[redacted]
Beta-blocking drugs, n (%)	[redacted]	[redacted]
Other antihypertensives[c], n (%)	[redacted]	[redacted]
Number of participants who currently smoked or consumed tobacco (%)	[redacted]	[redacted]
Number of participants who currently consumed alcohol (%)	[redacted]	[redacted]
Number of participants with a history of metabolism and nutrition disorders (%)	[redacted]	[redacted]
Number of participants with a history of vascular disorders (other than hypertension) (%)	[redacted]	[redacted]
Number of participants with a history of cardiac disorders (%)	[redacted]	[redacted]
Mean (SD) DBP (mm Hg)[d]	100.2 (3.7)	100.2 (3.8)
Mean (SD) SBP (mm Hg)[d]	163.6 (7.9)	163.4 (8.0)

ACE = angiotensin-converting enzyme; AMLO = amlodipine; ARB = angiotensin II receptor blocker; BMI = body mass index; DBP = diastolic blood pressure; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; PERe = perindopril erbumine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.

[a] Randomized set.

[b] Stages defined per European Society of Hypertension/European Society of Cardiology guidelines.

[c] Included drugs such as antiadrenergic drugs (centrally acting and peripherally acting).

[d] Supine blood pressure.

Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

3.2.3 Interventions

In CL2-005, participants received one of six treatments in a blinded fashion: perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC; perindopril arginine 3.5 mg; amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg; or placebo. Participants were instructed to take their assigned treatments orally once daily. Blinding was maintained by using identical capsules and packages. The manufacturer noted that the choice of interventions was guided by the EMA, which required that a first-line therapy (consisting of an FDC of two antihypertensive drugs at sub-therapeutic doses) be compared against placebo, with each component compared separately at the respective sub-therapeutic doses, and at the lowest approved dosage for each component.

In PATH, participants received one of three treatments: perindopril arginine 14 mg/amlodipine besylate 10 mg FDC; perindopril erbumine 16 mg; or amlodipine besylate 10 mg. Since no marketed perindopril arginine 14 mg tablet was available for use as a comparator, the manufacturer noted that, following consultation and agreement with the FDA, it was deemed appropriate to compare the FDC to the highest (and closest) monotherapy dose of perindopril erbumine 16 mg (two 8 mg tablets), which the manufacturer reported corresponded to perindopril arginine 20 mg.[2]

In CL3-018, participants were randomized to be treated with one of two antihypertensive strategies: one initiated with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC, or another initiated with valsartan 80 mg. At their one-, two-, and three-month study visits, participants with uncontrolled BP (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) were up-titrated to the next-highest dose. The up-titration steps in the perindopril arginine/amlodipine FDC strategy were:

- perindopril arginine 7 mg/amlodipine 5 mg FDC
- perindopril arginine 14 mg/amlodipine 10 mg FDC
- perindopril arginine 14 mg/amlodipine 10 mg FDC plus indapamide 1.5 mg sustained release (SR).

The up-titration steps in the comparator group were:

- valsartan 160 mg
- valsartan 160 mg/amlodipine 5 mg FDC
- valsartan 160 mg/amlodipine 10 mg FDC.

During the first three steps of each treatment strategy, participants received one capsule; at the last step of the titration schedule, they received one capsule and one tablet of either indapamide 1.5 mg SR or placebo, depending on the treatment strategy to which they had been randomized. The tablets of perindopril arginine/amlodipine FDC, valsartan, and valsartan/amlodipine FDC were disguised as orange hard-gelatin capsules of identical appearance. The manufacturer also noted the tablets for indapamide 1.5 mg SR and placebo were identical in appearance.

3.2.4 Outcomes

a) Efficacy

In CL2-005, the primary efficacy outcome was the change in supine DBP from baseline to the last post-baseline value over the six-week treatment period. BP was evaluated at the trough of drug activity (24 ± 3 hours after last drug administration) by the investigator at the office using an automatic arm device (Microlife BP3AC1-1) that the manufacturer noted was validated according to the International Protocol of the European Society of Hypertension.[1] BP was measured in the supine position after ≥ 10 minutes of rest, and the mean of three measurements at one-minute intervals was recorded. Secondary efficacy outcomes included: change in supine SBP from baseline to the last post-baseline

observation; response to treatment (SBP < 140 mm Hg and DBP < 90 mm Hg and/or SBP decrease ≥ 20 mm Hg from baseline and/or DBP decrease ≥ 10 mm Hg from baseline); and normalization of BP (SBP < 140 mm Hg and DBP < 90 mm Hg). The manufacturer also conducted an ancillary study in which ABPM was evaluated in a subset of participants randomized to the main study, the results of which are summarized in Appendix 6.

In PATH, the primary efficacy outcome was the change in seated trough (approximately 24 hours after the last dose) DBP from baseline at day 42 of the trial. BP was evaluated by the investigator at the office using an automatic arm device, the Omron Model HEM 705CP. BP was measured after at least five minutes of rest, and the mean of three measurements at two-minute intervals was recorded. At the first follow-up visit, BP was measured in each arm, and the arm that indicated the higher of the two mean DBPs was used for measuring BP for the remainder of the study. Secondary efficacy outcomes included: change in seated trough SBP from baseline at day 42, and response to treatment (BP < 140/90 mm Hg, or < 130/80 mm Hg if a participant had diabetes).

In CL3-018, the primary efficacy outcome was the change in supine SBP from baseline to the last post-baseline value at the third month. BP was evaluated at trough of drug activity (24 ± 3 hours after last drug administration) at the office using a validated (per the Association for the Advancement of Medical Instruction, the British Hypertension Society, or the International Protocol of the European Society of Hypertension) automatic device on the same arm (the one with the highest SBP value) and at the same time of the day for each visit. Three consecutive measures of supine SBP were performed, with the first one being performed after 10 minutes at rest. The mean of the two last measurements was selected as the BP value for the visit. If two consecutive BP measurements were different by ≥ 15 mm Hg, then all three measurements were repeated after an additional five minutes of rest. Secondary efficacy outcomes included: change in office supine DBP; office BP control (SBP < 140 mm Hg and DBP < 90 mm Hg); response to treatment (BP control and/or reduction in SBP ≥ 20 mm Hg and/or reduction in DBP ≥ 10 mm Hg); and ambulatory BP, which was evaluated in a substudy summarized in Appendix 6. The manufacturer also conducted an HBPM substudy, the results of which are summarized in Appendix 7.

None of the trials evaluated the effects of the study treatments on hypertension-related morbidity, health-related quality of life (HRQoL), or adherence as an efficacy outcome, although treatment compliance was reported in each study.

b) Harms

All trials collected safety data, including the occurrence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms.

3.2.5 Statistical Analysis

a) Analysis Populations

In CL2-005 and CL3-018, the randomized set was defined as all participants to whom a study treatment was randomly assigned. The safety set (SS) was defined as all participants who took at least one dose of study treatment. The full analysis set (FAS) was defined as all randomized participants who took at least one dose of study treatment and had at least one baseline value and one post-baseline value of BP (DBP in CL2-005, SBP in CL3-018). The per-protocol set (PPS) was a subset of participants within the FAS with several delimiters, such as overall drug compliance between 70% and 130%, and an overall treatment duration of ≥ 45 days.

In PATH, the intention-to-treat (ITT) set was defined as including all randomized participants who received at least one dose of study treatment and had at least one post-baseline value of DBP. The PPS included all participants in the ITT set who had overall drug compliance of between 80% and 120%, had DBP measurements through day 42, and did not have any major protocol violations. The SS included all randomized participants who received any amount of study drug.

b) Analysis Plan

In CL2-005, the primary efficacy analysis was the change from baseline value in supine DBP to last post-baseline value in the FAS. The analysis was conducted using a general linear model that included baseline DBP and centre (random factor) as covariates. The superiority of perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC was evaluated versus each of placebo, perindopril arginine 3.5 mg, and amlodipine 2.5 mg. At the same time, the non-inferiority of perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC was tested against each of perindopril arginine 5 mg and amlodipine 5 mg. The non-inferiority margin was 2 mm Hg, which was reported to be "in line with European guidelines."[15]

The sample size was calculated using a one-tailed Student's t-test for independent samples with the type-one error (alpha) set at 2.5%. The manufacturer used an intersection–union approach, which does not require a multiplicity adjustment. In brief, the intersection–union approach requires all pre-stated study objectives to be statistically significant to "declare the study successful."[20] A sample size of 224 participants per group was derived to ensure an overall power close to 80%, and was sufficient to provide a nominal power of 94% for the following:

- non-inferiority comparisons in case of a true difference of 1 mm Hg and standard deviation of 9 mm Hg between perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC and the other two treatments
- concluding superiority of perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC versus perindopril arginine 3.5 mg and amlodipine 2.5 mg in case of a true difference of 3 mm Hg between treatments
- concluding superiority of perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC versus placebo in case of a true difference of 5 mm Hg between treatments, and having a 95% confidence interval (CI) that did not include 2 mm Hg.

Based on an expected withdrawal rate of approximately 5%, about 250 participants per group were required.

No subgroup analyses relevant to this review were conducted in this trial. Sensitivity analyses were conducted using a general linear model with country instead of centre. Other analyses included conducting the main model in the randomized set as well as in the PPS, which evaluated the change from baseline to the week 8 values under treatment.

In CL2-005, for supine SBP, which was a secondary efficacy outcome in this study, the same analyses as for the primary efficacy outcome were conducted, although the non-inferiority margin for this outcome was 3 mm Hg, which was said to be "in line with European guidelines."[15] The rates of response to treatment and normalization were calculated using the FAS and PPS; formal statistical tests were conducted to compare perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC against each of placebo, perindopril arginine 5 mg, and amlodipine 5 mg. To evaluate the superiority of perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC versus placebo, the last post-baseline value was compared using a chi-squared test; for the comparison versus the two remaining treatment groups, the estimate of treatment differences and the corresponding 95% CIs were provided. Supine SBP comparisons were not adjusted for multiplicity.

In PATH, the primary efficacy analysis was the mean change from baseline to day 42 (or end of treatment) in mean sitting trough DBP in the ITT population. The analytical model was an analysis of covariance with treatment as the main effect and baseline DBP (< 100 mm Hg versus ≥ 100 mm Hg), current type 2 diabetes status (yes versus no), and race (black versus non-black) as covariates. The primary comparisons of interest were perindopril arginine 14 mg/amlodipine besylate 10 mg FDC versus each of perindopril erbumine 16 mg and amlodipine besylate 10 mg. If no valid DBP measurement was taken for day 42, then the last valid post-baseline assessment was used following the last observation carried forward (LOCF) method. DBP measurements taken after the use of hypertensive medications in a rescue fashion were excluded from the analyses. For each of the two comparisons of interest, a one-sided hypothesis of no difference in mean DBP values was tested with the type I error (alpha) set at 2.5%. The analysis plan reported the generation of the differences between least squares (LS) means as well as the associated one-sided 97.5% (CIs) and *P* values, although the actual results presented the 95% CIs corresponding to the LS mean differences.

The sample size was calculated based on an anticipated difference of ≥ 2.5 mm Hg between treatment group means in change in seated trough cuff DBP from baseline to day 42. Each of the two comparisons of interest was conducted at a two-sided alpha of 0.05 (or one-sided alpha of 0.025) and assumed a common standard deviation of 8.5 mm Hg. A sample size of ≥ 732 participants (244 per group) provided 90% power to detect a difference of at least 2.5 mm Hg. With an expected withdrawal rate of approximately 10%, 816 participants (272 per group) were required to be randomized to the three treatment groups.

Relevant subgroup analyses were by race (black versus non-black) and current type 2 diabetes status (yes or no). Similar analyses were conducted using data from participants in the PPS, as well as from those in the ITT set, without imputing missing evaluations using the LOCF method. Sensitivity analyses included a mixed-effects model with repeated measures; the primary analysis with covariates that included baseline characteristics that were significantly imbalanced between treatment groups; the primary analysis in which study site was an additional covariate; and a model (detail not specified) in which the impact of missing BP measurements was evaluated.

For seated trough SBP, which was a secondary efficacy outcome, analyses were conducted in a manner similar to the analyses for the primary efficacy outcome. Further, the proportions of responders across the treatment groups were compared using a chi-squared test. No adjustment for multiplicity was performed for the secondary efficacy outcomes.

In CL3-018, the primary efficacy analysis was the mean change from baseline to the last post-baseline value (over the first three-month period) in supine trough SBP using the FAS. The analysis was conducted using a general linear model that included treatment, as well as baseline and country as covariates. The estimate of the between-group difference in adjusted mean change in SBP along with the associated 95% CI and *P* value were calculated. A similar analysis was conducted using data from participants in the PPS. Further analyses included an examination of the change from baseline to the last post-baseline value over the entire six-month treatment period, as well change from baseline to the value at each study visit. These analyses used data from participants who received the highest possible step of dose, i.e., those not controlled with the previous step of dose.

The sample size was calculated based on a two-sided Student's t-test for independent samples with a type I error of 5%. Considering a standard deviation of 12 mm Hg, the manufacturer noted that 758 participants per group guaranteed a power of 90% to conclude superiority of the perindopril

arginine/amlodipine FDC strategy over the valsartan/amlodipine strategy, in case of a true difference of 2 mm Hg between the two groups. Based on an expected withdrawal rate of approximately 5%, approximately 800 participants per group were required.

A relevant subgroup analysis was conducted by diabetes mellitus status (i.e., yes versus no). Change in supine DBP was a secondary efficacy outcome that was analyzed in the same manner as the primary efficacy outcome. For BP control and response to treatment, the difference of the percentages (of responders and participants with controlled BP) at the last post-baseline over the first three-month period were compared using a chi-squared test, and the estimate of treatment differences and corresponding 95% CIs were calculated. The same analyses were performed from baseline at each visit and also at the last post-baseline value over the entire six-month treatment period. Sensitivity analyses were also conducted using the last post-baseline value on treatment. No adjustment for multiplicity for the secondary efficacy outcomes was performed.

3.3 Participant Disposition

Approximately twice as many participants discontinued from PATH and CL3-018 (10% in each trial) versus CL2-005 (5%) (Table 11, Table 12). In CL3-018, there were no apparent differences in discontinuation rates (overall or at each study visit) between treatment groups (Table 12). However, in CL2-005 and PATH, a smaller percentage of participants receiving the perindopril arginine/amlodipine FDC withdrew from study treatment compared with the other treatment groups (Table 11). Across all trials, the most common reason for discontinuation was due to an adverse event (AE). In CL2-005 and PATH, fewer participants in the perindopril arginine/amlodipine FDC group withdrew from study treatment due to AEs versus those in the other active treatment groups (i.e., those not receiving placebo). As expected by the consulting clinical expert, the rate of discontinuation due to an AE across the trials indicated that participants receiving higher doses of perindopril arginine/amlodipine FDC were more likely to withdraw than those receiving lower doses of the FDC.

TABLE 11: PARTICIPANT DISPOSITION IN NON-TITRATION STUDIES

	CL2-005						PATH		
	PERa 3.5 mg/AMLO 2.5 mg FDC	**Placebo**	**PERa 3.5 mg (not approved in Canada)**	**AMLO 2.5 mg**	**PERa 5 mg**	**AMLO 5 mg**	**PERa 14 mg/AMLO 10 mg FDC**	**PERe 16 mg**	**AMLO 10 mg**
Screened, N	2,053						1,617		
Randomized, N	248	250	273	274	272	264	279	278	280
Discontinued, n (%)	9 (3.6)	11 (4.4)	16 (5.9)	19 (6.9)	15 (5.5)	14 (5.3)	26 (9.3)	32 (11.5)	28 (10.0)
AE	3 (1.2)	0	6 (2.2)	9 (3.3)	7 (2.6)	8 (3.0)	10 (3.6)	12 (4.3)	12 (4.3)
Lack of efficacy	2 (0.8)	3 (1.2)	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)	0	0	0
Non-medical reason	2 (0.8)	5 (2)	3 (1.1)	5 (1.8)	3 (1.1)	3 (1.1)	0	0	0
Other	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.7)	7 (2.5)	3 (1.1)
Protocol deviation	1 (0.4)	2 (0.8)	3 (1.1)	2 (0.7)	1 (0.4)	0	0	0	0
Participant decision	0	0	0	0	0	0	7 (2.5)	8 (2.9)	6 (2.1)
Lost to follow-up	0	0	0	0	0	0	6 (2.2)	4 (1.4)	6 (2.1)
Physician decision	0	0	0	0	0	0	1 (0.4)	1 (0.4)	1 (0.4)
FAS, N	246	248	268	270	270	261	N/A		
ITT, N	N/A						271	274	275
PP, N	236	235	248	252	257	245	249	231	244
Safety, N	249[a]	251[a]	273	274	272	264	279	278	280

AE = adverse event; AMLO = amlodipine; FAS = full analysis set; ITT = intention-to-treat; N/A = not applicable; PERa = perindopril arginine; PERe = perindopril erbumine; PP = per-protocol.

Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report,[2] Elliott et al., 2015.[16]

[a] It was unclear why these numbers were reported to be larger than the number of participants randomized to the respective treatment groups.

TABLE 12: PARTICIPANT DISPOSITION IN TITRATION STUDY

		CL3-018	
		PERa/AMLO strategy FDC	**VAL/AMLO strategy**
Overall	Screened, N	2,740	
	Randomized, N	888	886
	Lost to follow-up, n (%)[a]	0	2 (0.2)
	Discontinued, n (%)[a]	88 (9.9)	87 (9.8)
	AE	55 (6.2)	45 (5.1)
	Non-medical reason	21 (2.4)	31 (3.5)
	Other protocol withdrawal criteria[b]	6 (0.7)	6 (0.7)
	Protocol deviation	6 (0.7)	5 (0.6)
	FAS, N	881	876
	PP, N	800	799
	Safety, N	887	884
Month 1 visit	Lost to follow-up, n (%)[a]	0	1 (0.1)
	Discontinued, n (%)[a]	19 (2.1)	23 (2.6)
	AE	9 (1.0)	9 (1.0)
	Non-medical reason	8 (0.9)	9 (1.0)
	Other protocol withdrawal criteria[b]	0	2 (0.2)
	Protocol deviation	2 (0.2)	3 (0.3)
	Ongoing, N	869	862
Month 2 visit	Lost to follow-up, n (%)[a]	0	0
	Discontinued, n (%)[a]	13 (1.5)	19 (2.1)
	AE	7 (0.8)	9 (1.0)
	Non-medical reason	1 (0.1)	7 (0.8)
	Other protocol withdrawal criteria[b]	2 (0.2)	2 (0.2)
	Protocol deviation	3 (0.3)	1 (0.1)
	Ongoing, N	856	843
Month 3 visit	Lost to follow-up, n (%)[a]	0	0
	Discontinued, n (%)[a]	22 (2.4)	15 (1.7)
	AE	17 (1.9)	7 (0.8)
	Non-medical reason	4 (0.5)	7 (0.8)
	Protocol deviation	1 (0.1)	1 (0.1)

		CL3-018	
		PERa/AMLO strategy FDC	**VAL/AMLO strategy**
	Ongoing, N	834	828
Month 6 visit	Lost to follow-up, n (%)[a]	0	1 (0.1)
	Discontinued, n (%)[a]	34 (3.8)	30 (3.4)
	AE	22 (2.4)	20 (2.3)
	Non-medical reason	8 (0.9)	8 (0.9)
	Other protocol withdrawal criteria[b]	4 (0.5)	2 (0.2)
	Completed, N	800	797

AE = adverse event; AMLO = amlodipine; FAS = full analysis set; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; PP = per-protocol; VAL = valsartan.
[a] Percentages based on number of participants randomized.
[b] Included the following: renal function impairment with creatinine clearance decrease ≥ 30%; increased potassium level above 5.5mmol/L; pregnancy.
Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

3.4 Exposure to Study Treatments

It was unclear how exposure to treatment was measured in PATH and CL3-018. In CL2-005, global exposure to treatment was calculated as the difference between the total treatment duration and the number of days of treatment interruptions. On average, CL3-018 participants were exposed to treatment for the longest time (approximately 170 days), followed by participants in CL2-005 (approximately 57 days) and PATH (approximately 40 days) (Table 13 and Table 14). This is in line with the treatment periods of the three studies. Across the trials, there were no apparent differences in overall mean treatment duration between treatment groups. However, in CL3-018, at steps 1, 2, and 3 of the titration strategy, the average participant in the perindopril arginine/amlodipine FDC group was exposed to treatment for longer than those in the valsartan/amlodipine group (Table 14).

Treatment compliance in all three trials was calculated as follows:

$$\left[\frac{Number\ of\ capsules\ taken}{Number\ of\ capsules\ to\ be\ taken}\right] \times\ 100$$

The number of capsules taken was the difference between the number of capsules dispensed and the number of capsules returned. The number of capsules to be taken was the product of the number of capsules prescribed per day and the theoretical treatment duration. Across all trials, the mean overall treatment compliance was at least [redacted] (Table 13 and Table 14); there were no apparent differences between treatment groups.

TABLE 13: TREATMENT EXPOSURE IN NON-TITRATION STUDIES

	CL2-005[a]						PATH[a]		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 247)	Placebo (N = 250)	PERa 3.5 mg (N = 273) (not approved in Canada)	AMLO 2.5 mg (N = 271)	PERa 5 mg (N = 270)	AMLO 5 mg (N = 264)	PERa 14 mg/ AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
Mean (SD) overall treatment duration (days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) overall treatment compliance (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AMLO = amlodipine; FDC = fixed-dose combination; PERa = perindopril arginine; PERe = perindopril erbumine; SD = standard deviation.
[a] Safety set.
Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report.[2]

TABLE 14: TREATMENT EXPOSURE IN TITRATION STUDY

		CL3-018	
		PERa/AMLO FDC strategy	VAL/AMLO strategy
Overall	N[a]	[redacted]	[redacted]
	Mean (SD) treatment duration (days)	[redacted]	[redacted]
Step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg	N[b]	[redacted]	[redacted]
	Mean (SD) treatment duration (days)	[redacted]	[redacted]
Step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg	N[b]	[redacted]	[redacted]
	Mean (SD) treatment duration (days)	[redacted]	[redacted]
Step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC (not approved in Canada)	N[b]	[redacted]	[redacted]
	Mean (SD) treatment duration (days)	[redacted]	[redacted]
Step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC (not approved in Canada)	N[b]	[redacted]	[redacted]
	Mean (SD) treatment duration (days)	[redacted]	[redacted]
Mean (SD) overall treatment compliance (%)*		[redacted]	[redacted]

AMLO = amlodipine; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; SD = standard deviation; VAL = valsartan.
[a] Safety set.
[b] Full analysis set.
Source: CL3-018 Clinical Study Report.[3]

In CL3-018, over the entire six-month treatment period, a [redacted] percentage of participants in the perindopril arginine/amlodipine FDC group ([redacted]) were up-titrated to the last step of the treatment strategy than in the valsartan/amlodipine group ([redacted]) (Table 15). Further, a [redacted] percentage of participants in the perindopril arginine/amlodipine FDC group ([redacted]) remained on the dose to which they were randomized than in the valsartan/amlodipine group ([redacted]) throughout the study.

TABLE 15: TITRATION PROFILES IN TITRATION STUDY

Baseline to Month 1	Month 1 to Month 2	Month 2 to Month 3	Month 3 to Month 6	CL3-018[a]	
				PERa/AMLO FDC strategy (N = 881)	VAL/AMLO strategy (N = 876)
Step 1	Step 2	Step 3	Step 4	[redacted]	[redacted]
Step 1	Step 2	Step 3	Step 3	[redacted]	[redacted]
Step 1	Step 2	Step 3		[redacted]	[redacted]
Step 1	Step 2	Step 2	Step 3	[redacted]	[redacted]
Step 1	Step 2	Step 2	Step 2	[redacted]	[redacted]
Step 1	Step 2	Step 2		[redacted]	[redacted]
Step 1	Step 2			[redacted]	[redacted]
Step 1	Step 1	Step 2	Step 3	[redacted]	[redacted]
Step 1	Step 1	Step 2	Step 2	[redacted]	[redacted]
Step 1	Step 1	Step 2		[redacted]	[redacted]
Step 1	Step 1	Step 1	Step 2	[redacted]	[redacted]
Step 1	Step 1	Step 1	Step 1	[redacted]	[redacted]
Step 1	Step 1	Step 1		[redacted]	[redacted]
Step 1	Step 1			[redacted]	[redacted]
Step 1				[redacted]	[redacted]

AMLO = amlodipine; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; VAL = valsartan.

[a] Full analysis set.

Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

3.5 Critical Appraisal

3.5.1 Internal Validity

All three studies were randomized, parallel-group trials with appropriate randomization and allocation concealment processes. Each trial was described as DB, although the steps taken to ensure that participants in PATH were unaware of their assigned treatments were unclear. Specifically, while it is noted that perindopril arginine/amlodipine besylate FDC was provided as an encapsulated white tablet, it was not specified how the other treatments (perindopril erbumine 16 mg as two 8 mg salmon-coloured tablets; amlodipine 10 mg as a single white tablet) were disguised to maintain blinding. However, it was noted that all participants in the trial were instructed to take one "capsule" each day. While the uncertainty around the blinding procedure would normally necessitate some caution in interpreting results, it is not a major concern in this trial because the primary efficacy outcome of change in BP is not a subjective measurement. However, it may have had an impact on the collection of subjective outcomes, especially AEs such as peripheral edema and cough. Further, investigators of CL3-018 used a double-dummy technique by providing participants in the valsartan/amlodipine group with a placebo tablet (at step 4) that was identical in appearance to the indapamide 1.5 mg SR tablet that participants in the other group received. Treatment compliance was reported in each trial, although the manner in which it was measured (i.e., based on capsule counts) may have introduced measurement error if participants failed to return their study drugs.

Baseline characteristics were generally similar across treatment groups in all trials, but some differences were noted. For example, in CL2-005, participants who were randomized to the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group appeared to have a longer duration of hypertension compared with individuals in the other groups; there were more participants with stage 2 versus stage 1 hypertension; and there were more participants with a history of vascular disorders other than hypertension. All of these differences might indicate that participants in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group had more severe hypertension. While it is plausible that treatment effects are artificially magnified among a more severe population — thus making the treatment appear to be better than reality in this trial — it may also be the case that more severely affected participants would have more treatment resistance, making them less likely to achieve BP targets. In PATH, compared with participants in the other treatment groups, individuals randomized to the perindopril arginine 14 mg/amlodipine 10 mg group tended to have a shorter duration of hypertension. In addition, a greater proportion of participants in the perindopril arginine 14 mg/amlodipine 10 mg group consumed alcohol and had a medical history of vascular disorders other than hypertension; a smaller proportion had a medical history of cardiac disorders. Overall, discussions with the consulting clinical expert highlighted that the between-group differences in both trials were minor and unlikely to affect treatment response substantially. Further, there did not appear to be any meaningful differences in baseline characteristics between treatment groups in CL3-018.

None of the trials used a true ITT population. Rather than including all randomized participants, the ITT analysis sets included only those participants who took at least one dose of the assigned study drug (i.e., a modified ITT population). Further, the manner in which the trials handled missing data was different. Specifically, in CL2-005 and CL3-018, the primary analyses were conducted on the FAS, which comprised all randomized participants who took at least one dose of study treatment, and who had at least one baseline and one post-baseline BP value. Thus, if participants did not have a post-baseline BP value, they did not contribute to the primary analyses. Nevertheless, an examination of the participant disposition in Table 11 reveals that fewer than 2% of participants in any treatment group across the two studies did not contribute to the FAS, thus minimizing concerns that the prognostic balance created by randomization was compromised. In PATH, if no valid DBP measurement was taken

on day 42, then the last valid post-baseline assessment was used following the LOCF method. However, carrying the last observation forward may artificially stabilize BP values among participants who dropped out; conversely, observed data could also be biased if the probability of withdrawal is related to increases in BP values.

Approximately twice as many participants discontinued from PATH and CL3-018 (10% in each trial) than from CL2-005 (5%). In CL3-018, there were no apparent differences in discontinuation rates (overall and at each study visit) between treatment groups. In CL2-005 and PATH, however, a smaller percentage of participants receiving the perindopril arginine/amlodipine FDC withdrew from study treatment versus those in the other treatment groups.

CL2-005 was designed to statistically evaluate five comparisons. Two of these involved testing the non-inferiority of perindopril arginine 3.5 mg/amlodipine 2.5 mg versus each of perindopril arginine 5 mg and amlodipine 5 mg. The non-inferiority margin was 2 mm Hg for change in supine DBP, which is in line with the European guidelines.[19] The non-inferiority margin for change in supine SBP was 3 mm Hg. Although it was said to be guided by the EMA, this fact could not be corroborated in the guidelines. The lack of rationale around the non-inferiority margin for the change in supine SBP necessitates some caution in interpreting the results, since it leaves the validity of the results uncertain. Nevertheless, the Health Canada review did not raise any concerns with the choice of margins.[10]

CL2-005 used an intersection–union approach, which requires all primary objectives to be statistically significant to "declare the study successful."[20] It is unclear whether, in addition to the primary objective(s), any secondary objectives were also taken into consideration before declaring success or failure. However, from the manner in which the manufacturer calculated the sample size for this trial, it appeared that the intersection–union approach was applied only to the primary efficacy outcome of change in supine DBP. Thus, the results of all outcomes other than change in supine DBP should be considered exploratory and interpreted with caution, since the trial was not powered to evaluate them, and they were not adjusted for multiplicity, which increases the risk for type I error.

In PATH, since there were two pairwise comparisons, the investigators set the one-sided alpha at 0.025. The manufacturer noted that no further adjustments for multiplicity were necessary because the primary objective of the study was to demonstrate superiority of the FDC in controlled DBP. Consequently, as with CL2-005, the results of all outcomes other than change in DBP should be considered exploratory and interpreted with caution. In PATH, a number of relevant subgroup analyses were conducted. However, rather than conducting formal tests of interactions to assess whether treatment effects significantly differed across the subgroups, the outcomes were analyzed within the sub-population separately, which leaves a greater possibility that any differences in treatment effects may be due to chance alone.[21]

In CL3-018, the primary objective was to demonstrate superiority of the perindopril arginine/amlodipine strategy versus the valsartan/amlodipine strategy for the change of supine SBP. There was no discussion of adjusting for multiplicity; thus, the results of all outcomes other than change in SBP should be considered exploratory and interpreted with caution. Further, the primary efficacy outcome was the change in supine SBP from the baseline value to the last post-baseline value over the first three-month treatment period. At this point, it is plausible that participants in both groups were receiving a variety of doses, as some would have had their BP controlled on the first (randomized) dose, while others would have been up-titrated once or multiple times. The resulting heterogeneous populations (in both groups) preclude a head-to-head comparison of the study groups. Further, some researchers have argued that

dissimilarities in the manner in which participants were treated in both treatment groups compromised the study results. Specifically, Kizilirmak and Ongen noted that, as a result of several differences, participants in the perindopril arginine/amlodipine FDC group "had been treated apparently more effectively" than those in the other group "at any single time point during the six months' treatment period with regards to classes, and numbers and doses of drugs administered."[22] The authors cite the following three differences between the groups:

1. During the first two months of the treatment period, participants randomized to the perindopril arginine/amlodipine FDC group essentially received two treatments, while participants in the other group received one.
2. During the first three months of the treatment period, participants randomized to the perindopril arginine/amlodipine FDC group received amlodipine at a higher dose than those in the comparator group.
3. During the last three months of the treatment period, participants randomized to the perindopril arginine/amlodipine FDC group essentially received three treatments, given the addition of indapamide, while participants in the other group received two.

In response to this criticism, Mancia and colleagues reiterated that their study was designed to evaluate two BP reduction strategies: one that was initiated with a monotherapy, and another that was initiated with a combination of two drugs.[23] Regardless, the manner in which the study was designed and conducted precludes a direct evaluation of each individual dose of perindopril arginine/amlodipine FDC under review; thus, limiting the utility of the data from this trial.

3.5.2 External Validity

Discussions with the consulting clinical expert for this review suggested that, across all three trials, the participants broadly reflected the characteristics of patients with hypertension who would be seen in usual Canadian practice. Of note, approximately 80% of participants in CL2-005 and CL3-018 had stage 2 hypertension — defined as SBP 160 mm Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg — which the consulting clinical expert indicated would broadly reflect patients with moderate hypertension. In PATH, [redacted] of participants had stage 1 hypertension (SBP 140 mm Hg to 159 mm Hg and DBP 90 mm Hg to 99 mm Hg), which the expert indicated broadly reflected patients with mild hypertension, while [redacted] had stage 3 hypertension (SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg), which the expert indicated would broadly reflect patients with severe hypertension who would fall outside the Health Canada–approved indication.

However, there were some issues of generalizability. First, more than half of all participants in each trial were white or Caucasian, although the percentage of such individuals ranged from approximately 64% in PATH to 99% in CL2-005. The clinical expert consulted by CDR for the purpose of this review suggested this range could be due to geographical differences, since CL2-005 recruited exclusively from Europe, while PATH recruited exclusively from the US. The expert indicated that the percentage of white or Caucasian patients seen in usual Canadian practice would likely fall within that 64% to 99% — perhaps near the midpoint, as was observed in CL3-018. Further, using traditional body mass index (BMI) cut-offs, the average participant in PATH would be classified as obese (mean BMI of approximately 33 kg/m^2) versus in the two other studies, where the average participant would be classified as overweight, as indicated by a mean BMI of approximately 27 kg/m^2. The expert suggested that the discrepancy might be attributable to geographical differences between the trials, as well as to the fact that CL2-005 and CL3-018 excluded participants with BMIs of more than 30 kg/m^2. The expert also noted that, when it comes to BMI, the US participants in PATH would be more reflective of Canadian patients versus those in the other trials. In addition, with respect to prognostic factors for hypertension, the expert indicated

the percentages of participants who currently smoked or consumed alcohol in all three trials were [redacted] than those seen in typical Canadian practice, where fewer than 10% to 15% of hypertension patients would be smokers and fewer than 25% would be consuming alcohol. Further, while average alcohol consumption across the trials was expressed as units per week, it was unclear what a unit entailed; thus, the corresponding context was uncertain. Last, discussions with the consulting clinical expert indicated that treatment compliance in a typical clinical setting would be substantially lower than what was observed across the trials.

There are issues related to the comparator groups in each of the three trials that further limit the generalizability of the results. First, perindopril arginine 3.5 mg, which was used in CL2-005, is not available in Canada. Similarly, with regards to CL3-018, the valsartan/amlodipine FDC that was used after two months of treatment in one of the treatment groups is not available in Canada. Further, the consulting clinical expert indicated that the monthly titration schedule prescribed in CL3-018 is unlikely to be followed by health care practitioners in Canada, as patients would be seen much less frequently in typical practice, i.e., about once every two months. In PATH, perindopril erbumine 16 mg was used as one of two active comparators. While this dose is not available in Canada, the treatment was administered as two 8 mg tablets, which are available in Canada. The product monograph for this treatment indicates that while the dose must be individualized, the usual maintenance dose is 4 mg to 8 mg daily.[9] It further states that "no additional [BP] lowering effects were achieved with doses greater than 8 mg daily," suggesting that 16 mg is not a dose of perindopril erbumine used in typical Canadian practice. The Health Canada review also noted the manufacturer's "willingness to replace currently approved products containing the perindopril erbumine salt with their equivalent products containing the perindopril arginine salt,"[10] which further reduces the likelihood of perindopril erbumine being used in Canada. Another limitation across the trials is the limited data comparing perindopril arginine/amlodipine FDC with many other treatments indicated for initial therapy for hypertension in Canada, as shown in Table 5. Further, the manner in which BP was measured across the trials was not consistent with the recommended technique in Canada; as noted by the consulting clinical expert, clinicians are advised to take three measurements of seated BP and record the mean of the last two values.

All three trials evaluated the efficacy and safety of the study treatments across a range of BP outcomes. However, the absence of a patient input submission for this review leaves the importance of the evaluated outcomes to patients uncertain. Nevertheless, discussions with the consulting clinical expert suggested that while BP reduction is important, it remains a surrogate marker; the ultimate goal of antihypertensive therapy is to prevent hypertension-related morbidity and mortality. To this end, none of the included trials evaluated the effects of perindopril arginine/amlodipine FDC on these outcomes. As well, the expert indicated that given that antihypertensive therapy is chronic in nature, the lengths of follow-up for each of the studies were insufficient to adequately evaluate the long-term efficacy and safety of perindopril arginine/amlodipine.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol have been reported (Section 2.2, Table 6). See Appendix 4 for detailed efficacy data.

3.6.1 Change in Diastolic and Systolic Blood Pressure

In CL2-005, at the last post-baseline assessment over the eight-week treatment period, the mean decreases in supine DBP (primary efficacy outcome) and SBP were statistically significantly greater in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group than in the placebo, perindopril arginine 3.5 mg, and amlodipine 2.5 mg groups (Figure 2, Table 18, Table 20). The mean decreases in supine DBP

and SBP were statistically non-inferior in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group versus the perindopril arginine 5 mg and amlodipine 5 mg groups.

In the ABPM substudy, participants receiving perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC experienced statistically significantly greater reductions in ambulatory 24-hour SBP and DBP at eight weeks when compared with individuals receiving placebo, perindopril 3.5 mg, amlodipine 2.5 mg, or perindopril 5 mg, but not when compared with those receiving amlodipine 5 mg (Appendix 6).

In the main study, a statistically significantly greater percentage of participants achieved BP normalization (SBP < 140 mm Hg and DBP < 90 mm Hg) or were considered responders (SBP < 140 mm Hg and DBP < 90 mm Hg, and/or SBP decrease of ≥ 20 mm Hg from baseline, and/or DBP decrease of ≥ 10 mm Hg from baseline) in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group (in which 43.5% achieved normalization and [redacted] were responders) than in the placebo group (in which 26.6% achieved normalization [$P < 0.001$] and [redacted] were responders [redacted]). (Table 18). A greater percentage of participants achieved BP normalization or were considered responders in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group than in the perindopril arginine 5 mg group (in which 33.3% achieved normalization and [redacted] were responders) and the amlodipine 5 mg group (in which 37.9% achieved normalization and [redacted] were responders) (Table 18).

No subgroup analyses relevant to this review were conducted in this trial. The results of the sensitivity analyses were consistent with those of the main analyses.

In PATH, at day 42, the mean decreases in seated DBP (primary efficacy outcome) and SBP were statistically significantly greater in the perindopril arginine 14 mg/amlodipine 10 mg FDC group than in the perindopril erbumine 16 mg and amlodipine 10 mg groups (Figure 3, Table 18).

There was a statistically significantly greater percentage of responders in the perindopril arginine 14 mg/amlodipine 10 mg FDC group (51.6%) than in the perindopril erbumine 16 mg (27.1%) or amlodipine 10 mg (37.5%) ($P < 0.001$ for both comparisons) group (Table 18).

Relevant subgroup analyses were those by race (black versus non-black) and current type 2 diabetes status (yes versus no). Among participants who were black or had type 2 diabetes, the mean decreases in seated DBP and SBP were statistically significantly greater in the perindopril arginine 14 mg/amlodipine 10 mg FDC group than in the perindopril erbumine 16 mg group, but not compared with the amlodipine 10 mg group (Table 23). Among participants who were not black or who did not have type 2 diabetes, the mean decreases in seated DBP and SBP were statistically significantly greater in the perindopril arginine 14 mg/amlodipine 10 mg FDC group than in the perindopril erbumine 16 mg and amlodipine 10 mg groups. The results of the sensitivity analyses were consistent with those of the main analyses.

There were no ancillary studies associated with PATH.

FIGURE 2: RESULTS OF KEY EFFICACY OUTCOMES IN CL2-005

FIGURE 3: RESULTS OF KEY EFFICACY OUTCOMES IN PATH

In CL3-018, at the last post-baseline assessment over the first three-month treatment period, the mean decreases in supine DBP and SBP (primary efficacy outcome) were statistically significantly greater in participants randomized to the perindopril arginine/amlodipine FDC strategy versus those assigned to the valsartan/amlodipine strategy (Figure 4, Table 19). The results were similar over the entire six-month treatment period, as well as at each study visit (Table 21)

In the ABPM substudy, participants in the perindopril arginine/amlodipine FDC group experienced statistically significantly greater reductions in ambulatory 24-hour SBP and DBP at three months when compared with individuals in the valsartan/amlodipine group (Appendix 6). Conversely, in the HBPM substudy, there were no statistically significant differences between the two treatment groups with respect to change in home SBP at three months; however, at six months, participants in the perindopril arginine/amlodipine FDC group experienced statistically significantly greater reductions in home SBP than those in the valsartan/amlodipine group (Appendix 7).

In the main study, there was a statistically significantly greater percentage of participants who achieved BP control or were considered responders in the perindopril arginine/amlodipine FDC group (in which 56.4% achieved control and [redacted] were responders) than in the valsartan/amlodipine group (in which 49.0% achieved control [*P* = 0.002] and [redacted] were responders, [redacted]) (Table 19). The results were similar over the entire six-month treatment period, as well as at each study visit (Table 21).

A relevant subgroup analysis was by type 2 diabetes status (yes versus no). Among participants who had type 2 diabetes, there was no statistically significant difference in mean decreases in supine DBP and SBP between participants randomized to the perindopril arginine/amlodipine FDC strategy versus the valsartan/amlodipine groups (Table 24). Among participants who did not have type 2 diabetes, the mean decreases in supine DBP and SBP were statistically significantly greater in participants randomized to the perindopril arginine/amlodipine FDC versus the valsartan/amlodipine groups. The results of the sensitivity analyses were consistent with those of the main analyses.

FIGURE 4: RESULTS OF KEY EFFICACY OUTCOMES IN CL3-018

3.6.2 Hypertension-Related Morbidity

None of the trials evaluated the effects of the study treatments on hypertension-related morbidity as an efficacy outcome.

3.6.3 Change in Health-Related Quality of Life

None of the trials evaluated the effects of the study treatments on HRQoL as an efficacy outcome.

3.6.4 Adherence

None of the trials evaluated adherence to study treatments as an efficacy outcome. Treatment compliance is discussed in section 3.4.

3.7 Harms

Only those harms identified in the review protocol are reported (2.2.1, Protocol).

3.7.1 Adverse Events

Overall, a greater percentage of participants in PATH (six-week treatment period) experienced a TEAE than did participants in either CL2-005 (eight weeks) or CL3-018 (six months) (Table 16, Table 17). In CL2-005, the overall rates of TEAEs appeared to be disproportional, with a greater percentage of participants who received amlodipine 5 mg (21.6%) experiencing a TEAE than did those in the remaining groups (ranging from 15.9% in the placebo group to 18.9% in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group) (Table 16). This trend was consistent with that observed in the PATH trial, in which a greater percentage of participants receiving amlodipine 10 mg (38.6%) experienced a TEAE than did those in the perindopril arginine 14 mg/amlodipine 10 mg FDC (30.8%) and perindopril erbumine 16 mg (27.7%) groups (Table 16). The most common TEAE across both CL2-005 and PATH was peripheral edema, which appeared to occur more frequently at the higher dose of the perindopril arginine/amlodipine FDC and, in general, more frequently with highest dose of amlodipine alone (5 mg in CL2-005 and 10 mg in PATH) than with other treatments, including perindopril arginine/amlodipine FDC (Table 16). Other common TEAEs in CL2-005 and PATH were headaches (which occurred at a similar rate across the treatment groups) and cough, which, in PATH, appeared to occur more frequently in the perindopril arginine 14 mg/amlodipine 10 mg FDC (3.2%) and perindopril erbumine 16 mg (2.9%) groups than in the

amlodipine 10 mg (0.7%) group. In CL2-005, participants receiving perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC appeared to experience hyperkalemia at a rate that was similar to those in the amlodipine 2.5 group (2.4% versus 2.2%), but more frequent than the rate experienced in the remaining treatment groups.

In CL3-018, at each step of the titration strategy, there were no apparent differences in the percentage of participants who experienced a TEAE between the two treatment groups, although a greater percentage of participants experienced a TEAE at steps three and four (approximately 25%) than at the first two steps (approximately 18%) (Table 17).

TABLE 16: HARMS IN NON-TITRATION STUDIES

	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 249)	**Placebo (N = 251)**	**PERa 3.5 mg (N = 273) (not approved in Canada)**	**AMLO 2.5 mg (N = 272)**	**PERa 5 mg (N = 272)**	**AMLO 5 mg (N = 264)**	**PERa 14 mg / AMLO 10 mg FDC (N = 279)**	**PERe 16 mg (N = 278)**	**AMLO 10 mg (N = 280)**
Participants with > 0 TEAEs, n (%)	47 (18.9)	40 (15.9)	51 (18.7)	51 (18.6)	44 (16.2)	57 (21.6)	86 (30.8)	77 (27.7)	108 (38.6)
Most common AEs[b], n (%)									
Hyperkalemia	6 (2.4)	0	0	6 (2.2)	2 (0.7)	1 (0.4)			
Peripheral edema	4 (1.6)	3 (1.2)	8 (2.9)	2 (0.7)	4 (1.5)	13 (4.9)	20 (7.2)	1 (0.4)	35 (12.5)
Headache	3 (1.2)	4 (1.6)	5 (1.8)	4 (1.5)	3 (1.1)	1 (0.4)	7 (2.5)	8 (2.9)	8 (2.9)
Nasopharyngitis	3 (1.2)	1 (0.4)	2 (0.7)	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)	0	1 (0.4)
Creatinine clearance decreased	3 (1.2)	1 (0.4)	0	2 (0.7)	2 (0.7)	1 (0.4)			
Bronchitis	2 (0.8)	4 (1.6)	2 (0.7)	3 (1.1)	1 (0.4)	0			
Cough	2 (0.8)	1 (0.4)	3 (1.1)	2 (0.7)	3 (1.1)	1 (0.4)	9 (3.2)	8 (2.9)	2 (0.7)
Back pain	1 (0.4)	1 (0.4)	0	2 (0.7)	2 (0.7)	5 (1.9)	3 (1.1)	1 (0.4)	2 (0.7)
Dyslipidemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Influenza	[redacted]	[redacted]	[redacted]	0	[redacted]	[redacted]			
Blood glucose increased	1 (0.4)	0	1 (0.4)	0	3 (1.1)	0			
Flushing	0	0	0	0	0	3 (1.1)			
Fatigue							5 (1.8)	4 (1.4)	2 (0.7)
Dizziness							7 (2.5)	4 (1.4)	3 (1.1)
Diarrhea							3 (1.1)	5 (1.8)	1 (0.4)
Nausea							2 (0.7)	4 (1.4)	2 (0.7)
Urinary tract infection							4 (1.4)	0	0
Arthralgia							2 (0.7)	3 (1.1)	2 (0.7)
Musculoskeletal pain							2 (0.7)	3 (1.1)	0
Alanine aminotransferase increased							0	4 (1.4)	0
Aspartate aminotransferase increased							1 (0.4)	3 (1.1)	0
Blood potassium increased							0	3 (1.1)	0
Erythema							3 (1.1)	1 (0.4)	0
Rash							1 (0.4)	0	3 (1.1)

	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 249)	Placebo (N = 251)	PERa 3.5 mg (N = 273) (not approved in Canada)	AMLO 2.5 mg (N = 272)	PERa 5 mg (N = 272)	AMLO 5 mg (N = 264)	PERa 14 mg / AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
Hematuria							2 (0.7)	1 (0.4)	3 (1.1)
Pollakiuria							1 (0.4)	0	4 (1.4)
Participants with > 0 SAEs, n (%)	0	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.1)	1 (0.4)	2 (0.7)	2 (0.7)
Participants with AEs that led to withdrawal, n (%)	3 (1.2)	0	6 (2.2)	9 (3.3)	7 (2.6)	8 (3.0)	10 (3.6)	11 (4.0)	13 (4.6)
Number of deaths, n (%)	0	0	0	0	1 (0.4)	0	0	0	0
Notable harms other than the most common AEs, n (%)									
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AKI	[redacted]								

AE = adverse event; AKI = acute kidney injury; AMLO = amlodipine; FDC = fixed-dose combination; PERa = perindopril arginine; PERe = perindopril erbumine; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Safety set.
[b] Occurring in ≥ 1% of participants in any treatment group.
Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report.[2]

TABLE 17: HARMS IN TITRATION STUDY

		CL3-018[a] (Six-Month Treatment Period)	
		PERa/AMLO FDC Strategy	VAL/AMLO Strategy
Step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Most common AEs[b], n (%)		
	Peripheral edema	[redacted]	[redacted]
	Cough	[redacted]	[redacted]
	Nasopharyngitis	[redacted]	[redacted]
	Headache	[redacted]	[redacted]
	Hypertriglyceridemia	[redacted]	
	Type 2 diabetes mellitus	[redacted]	[redacted]
	Hypercholesterolemia	[redacted]	[redacted]
	Dizziness	[redacted]	

		CL3-018[a] (Six-Month Treatment Period)	
		PERa/AMLO FDC Strategy	**VAL/AMLO Strategy**
	Asthenia	[redacted]	
	Back pain		[redacted]
	Gastroenteritis		[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
	Notable harms other than AEs reported above, n (%)		
	Orthostatic hypotension	[redacted]	[redacted]
	Hypotension	[redacted]	[redacted]
	AKI	[redacted]	
Step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Most common AEs[b], n (%)		
	Peripheral edema	[redacted](2.5)	[redacted]
	Cough	[redacted]	[redacted]
	Nasopharyngitis	[redacted]	[redacted]
	Headache	[redacted]	[redacted]
	Hypertriglyceridemia	[redacted]	[redacted]
	Type 2 diabetes mellitus	[redacted]	[redacted]
	Hypercholesterolemia	[redacted]	[redacted]
	Dizziness	[redacted]	
	Erectile dysfunction	[redacted]	
	Hyperuricemia	[redacted]	
	Back pain		[redacted]
	Gastroenteritis		[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
	Notable harms other than the most common AEs, n (%)		

		CL3-018[a] (Six-Month Treatment Period)	
		PERa/AMLO FDC Strategy	**VAL/AMLO Strategy**
	Orthostatic hypotension	[redacted]	[redacted]
	Hypotension	[redacted]	[redacted]
	AKI	[redacted]	
Step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC (not approved in Canada)	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Most common AEs[b], n (%)		
	Peripheral edema	[redacted](5.9)	[redacted](3.2)
	Cough	[redacted]	[redacted]
	Nasopharyngitis	[redacted]	[redacted]
	Headache	[redacted]	[redacted]
	Hypertriglyceridemia	[redacted]	[redacted]
	Type 2 diabetes mellitus	[redacted]	[redacted]
	Hypercholesterolemia	[redacted]	[redacted]
	Dizziness	[redacted]	
	Blood glucose increased	[redacted]	
	Erectile dysfunction	[redacted]	
	Back pain		[redacted]
	Gastroenteritis		[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
	Notable harms other than most common AEs reported above, n (%)		
	Orthostatic hypotension	[redacted]	[redacted]
	Hypotension	[redacted]	[redacted]
	AKI	[redacted]	
Step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC (not approved in Canada)	Participants with > 0 TEAEs, n (%)	[redacted]	[redacted]
	Most common AEs[b], n (%)		
	Peripheral edema	[redacted]	[redacted](5.9)
	Cough	[redacted]	[redacted]
	Nasopharyngitis	[redacted]	

		CL3-018[a] (Six-Month Treatment Period)	
		PERa/AMLO FDC Strategy	**VAL/AMLO Strategy**
	Headache		[redacted]
	Hypertriglyceridemia	[redacted]	[redacted]
	Type 2 diabetes mellitus	[redacted]	[redacted]
	Hypercholesterolemia	[redacted]	[redacted]
	Dizziness	[redacted]	
	Blood glucose increased	[redacted]	
	Erectile dysfunction	[redacted]	
	Hyperuricemia	[redacted]	
	Asthenia	[redacted]	
	Hypokalemia	[redacted]	
	Back pain		[redacted]
	Gastroenteritis		[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
	Participants with AEs that led to withdrawal, n (%)	[redacted]	[redacted]
	Number of deaths, n (%)	[redacted]	[redacted]
	Notable harms other than the most common AEs, n (%)		
	Orthostatic hypotension	[redacted]	[redacted]
	Hypotension	[redacted]	[redacted]
	AKI	[redacted]	

AE = adverse event; AKI = acute kidney injury; AMLO = amlodipine; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VAL = valsartan.

[a] Safety set.

[b] Occurring in ≥ 1% of participants in any treatment group.

Source: CL3-018 Clinical Study Report.[3]

3.7.2 Serious Adverse Events

Fewer than 1% of participants in CL2-005 and PATH experienced an SAE, with no apparent differences between treatment groups in each trial (Table 16). In CL3-018, over the six-month treatment period, fewer than 1.5% of participants in each group at every step experienced an SAE, with no apparent differences between the two treatment groups (Table 17). Further, in this trial, a greater percentage of participants experienced an SAE at steps 3 and 4 than at the first two steps.

3.7.3 Withdrawals Due to Adverse Events

In each of the three trials, fewer than 5% of participants in all treatment groups withdrew due to an AE (Table 16, Table 17). In particular, in CL2-005 and PATH, a smaller percentage of participants withdrew due to AEs in the perindopril arginine/amlodipine FDC group than in the other active treatment groups (Table 16). Overall, a greater percentage of participants withdrew due to AEs in PATH than in CL2-005. In CL3-018, at step 3 of the titration strategy, a greater percentage of participants withdrew due to an AE in the perindopril arginine/amlodipine FDC group than in the valsartan/amlodipine group (4.8% versus. 1.6%) (Table 17). There were no apparent differences between treatment groups at the other steps of the titration strategies.

3.7.4 Mortality

In CL2-005, one participant (0.4%) in the perindopril arginine 5 mg group died; the investigators did not consider this to be related to the study drug. No participant died in PATH (Table 16). In CL3-018, over the six-month treatment period, two participants died, both of whom were in the valsartan/amlodipine group: one died at step 3 of the titration strategy and the other at step 4 (Table 17). Both deaths were not considered by the investigators to be related to the study drug.

3.7.5 Notable Harms

a) Hypotension

In CL2-005, one participant (0.4%) experienced orthostatic hypotension and one participant (0.4%) experienced hypotension in the perindopril arginine 5 mg and amlodipine 2.5 mg groups, respectively (Table 16). In PATH, a greater percentage of participants in the perindopril arginine 14 mg/amlodipine 10 mg FDC group (1.1%) experienced hypotension compared with participants in the perindopril erbumine 16 mg (0.7%) and amlodipine 10 mg (0%) groups (Table 16). In CL3-018, 0.5% or fewer participants in each treatment group experienced orthostatic hypotension or hypotension, with no consistent trend of its occurrence across the four steps of the titration strategies (Table 17).

b) Peripheral Edema

In CL2-005, a greater percentage of participants in the amlodipine 5 mg group (4.9%) experienced peripheral edema compared with participants in the other treatment groups (range: from 0.7% in the amlodipine 2.5 mg group to 2.9% in the perindopril arginine 3.5 mg group) (Table 16,). In PATH, a greater percentage of participants in the amlodipine 10 mg group (12.5%) experienced peripheral edema compared with the perindopril arginine 14 mg/amlodipine 10 mg FDC (7.2%) and perindopril erbumine 16 mg (0.4%) groups (Table 16). In CL3-018, overall, with each subsequent step of the titration strategy in each treatment group, a greater percentage of participants experienced peripheral edema, with no consistent trend of the occurrence of this notable harm between the two treatment groups (Table 17).

c) Cough

In CL2-005, no more than 1.1% of participants in any treatment group experienced a cough, with no apparent differences between treatment groups (Table 16). In PATH, a greater percentage of participants in the perindopril arginine 14 mg/amlodipine 10 mg (3.2%) group and the perindopril erbumine 16 mg (2.9%) group experienced cough than in the amlodipine 10 mg (0.7%) group (Table 16). In CL3-018, at each step of the titration strategy, a greater percentage of participants in the perindopril arginine/amlodipine FDC group experienced cough than individuals in the valsartan/amlodipine group (Table 17).

d) Hyperkalemia

In CL2-005, the rate of hyperkalemia ranged from 0% in the placebo and perindopril arginine 3.5 mg groups to 2.4% in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group (Table 16). In PATH and CL3-018, fewer than 1% of participants in each treatment group experienced hyperkalemia (Table 17).

e) Acute Kidney Injury

[redacted] (Table 16, Table 17).

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review of perindopril arginine/amlodipine FDC for the treatment of mild-to-moderate essential hypertension in patients for whom combination therapy is appropriate was primarily drawn from three RCTs. First, CL2-005 (N = 1,581) was a phase 2 trial in which participants from Europe were randomized to receive one of six treatments: perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC; perindopril arginine 3.5 mg; amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg; or placebo. Second, PATH (N = 837) was a phase 3 trial in which participants from the US were randomized to receive one of three treatments: perindopril arginine 14 mg/amlodipine besylate 10 mg FDC; perindopril erbumine 16 mg; or amlodipine besylate 10 mg. Third, CL3-018 (N = 1,774) was a phase 3 trial in which participants from 18 countries, including Canada, were randomized to receive treatment according to one of two antihypertensive strategies: one initiated with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC, or another initiated with valsartan 80 mg. The up-titration steps in the perindopril arginine/amlodipine FDC strategy were perindopril arginine 7 mg/amlodipine 5 mg FDC, perindopril arginine 14 mg/amlodipine 10 mg FDC, and perindopril arginine 14 mg/amlodipine 10 mg FDC plus indapamide 1.5 mg SR. The up-titration steps in the other group were valsartan 160 mg, valsartan 160 mg/amlodipine 5 mg FDC, and valsartan 160 mg/amlodipine 10 mg FDC. A fourth study (CL3-006) was identified; however, participants in that trial did not receive perindopril arginine/amlodipine FDC according to the approved dosage and administration in Canada. Therefore, the utility of the results for this review is limited. The primary outcome was change in DBP (supine in CL2-005, seated in PATH) or SBP (supine in CL3-018).

All three trials included participants aged ≥ 18 years with hypertension. Approximately 80% of participants in CL2-005 and CL3-018 had stage 2 hypertension (defined as SBP 160 mm Hg to 179 mm Hg and DBP 100 mm Hg to 109 mm Hg), which the consulting clinical expert indicated would broadly reflect patients with moderate hypertension. In PATH, more than a third of participants had stage 1 hypertension (SBP 140 mm Hg to 159 mm Hg and DBP 90 mm Hg to 99 mm Hg), which the expert indicated broadly reflected patients with mild hypertension; more than 5% had stage 3 hypertension (SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg), which the expert indicated would broadly reflect patients with

severe hypertension. Each study excluded individuals with comorbidities such as cerebrovascular diseases, heart disease, liver disease, or renal impairment. CL2-005 and CL3-018 also excluded participants with a BMI of more than 30 kg/m^2, while CL2-005 additionally excluded participants with type 1 or 2 diabetes; therefore, the applicability of the results is limited. Across the trials, there was wide variation in the distribution of race, body composition, and certain risk factors for hypertension, although the participants broadly reflected patients with hypertension who would be seen in usual Canadian practice. Baseline characteristics were generally similar across groups in each trial, and the expert indicated that any observed differences were minor and unlikely to affect treatment response. The choice of comparators, as well as the manner in which BP was measured in each trial (which was inconsistent with the manner recommended by CHEP), limits the generalizability of the results. Also, there is limited evidence assessing the efficacy and safety of perindopril arginine/amlodipine FDC relative to treatments commonly used in Canada. Last, the design of CL3-018 precludes both a head-to-head comparison of the study drug as well as a direct evaluation of the three individual doses of perindopril arginine/amlodipine FDC under review.

4.2 Interpretation of Results

4.2.1 Efficacy

Across CL2-005, PATH, and CL3-018, participants receiving perindopril arginine/amlodipine FDC generally experienced statistically significantly greater reductions in DBP and SBP versus other treatments. However, two exceptions were noted in CL2-005, in which — at the last post-baseline assessment over the eight-week treatment period — the mean decreases in supine DBP and SBP were statistically non-inferior in the perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC group versus the perindopril arginine 5 mg and amlodipine 5 mg groups. Results from the ABPM substudies of CL2-005 and CL3-018 were consistent with those from the main trial; this provides greater assurance of the robustness of the primary findings. Conversely, the results from the HBPM substudy of CL3-018 were inconsistent with the other findings. While this may reduce certainty in the results from this trial, it is important to note that the 2016 CHEP guidelines indicate that ABPM is the recommended out-of-office BP measurement method.

In CL2-005, the clinical relevance limit for the comparison of perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC versus placebo was set (by the manufacturer) at 2 mm Hg for DBP and at 3 mm Hg for SBP. The threshold of 2 mm Hg for DBP appeared to be in line with the European guidelines,[19] but no recommendations for a clinically relevant change in SBP were made. Nevertheless, using these thresholds, compared with placebo, the relative reduction in DBP (–4.1 mm Hg) and SBP (–7.2 mm Hg) observed with perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC in this trial appeared to be clinically meaningful, despite the substantial placebo effect observed (26.6% achieved normalization and 52.8% were considered responders).

However, the degree to which the benefits of perindopril arginine/amlodipine FDC versus the active comparators across the trials were clinically meaningful remains uncertain. Discussions with the consulting clinical expert on this review suggested that while BP reduction is important, it remains a surrogate outcome; the ultimate goal of antihypertensive therapy is to prevent hypertension-related morbidity and mortality. To this end, none of the included trials evaluated the effects of perindopril arginine/amlodipine on these outcomes; thus, the clinical benefit of perindopril arginine/amlodipine FDC remains uncertain. Still, there is a well-established association between BP reduction and risk of future cardiovascular (CV) events, with evidence suggesting that a 10 mm Hg to 12 mm Hg reduction in SBP and a 5 mm Hg to 6 mm Hg reduction in DBP translate into clinical benefit.[24] Of note, in a recent meta-analysis of 123 studies (n = 613,815), Ettehad and colleagues found that every 10 mm Hg

reduction in SBP significantly reduced the risk of major CV disease events (relative risk 0.80; 95% CI, 0.77 to 0.83), coronary heart disease (relative risk 0.83; 95% CI, 0.78 to 0.88), stroke (relative risk 0.73; 95% CI, 0.68 to 0.77), heart failure (relative risk 0.72; 95% CI, 0.67 to 0.78), and all-cause mortality (relative risk 0.87; 95% CI, 0.84 to 0.91).[25] Nevertheless, health care professionals manage patients with hypertension by treating them to target, i.e., to a BP level at or beyond which the risk of future morbidity and mortality decreases. CHEP recommends a target of SBP/DBP < 140/90 mm Hg in the general patient population, SBP/DBP < 130/80 mm Hg in patients with diabetes mellitus, and SBP ≤ 120 mm Hg in selected high-risk patients. Data from CL2-005, PATH, and CL3-018 suggested that, except compared with amlodipine 5 mg in CL2-005, a statistically significantly greater percentage of participants receiving perindopril arginine/amlodipine FDC achieved SBP/DBP < 140/90 mm Hg (classified as "normalization of BP" in CL2-005, "response to treatment" in PATH, and "office BP control" in CL3-018) versus active comparators. Still, an important caveat is that the results of this outcome were not adjusted for multiplicity in any of the three trials, and should be interpreted with caution. The clinical expert involved in the review also indicated that antihypertensive therapy is chronic in nature, and that the lengths of follow-up for each of the studies were insufficient to adequately evaluate the long-term efficacy of perindopril arginine/amlodipine FDC.

The manufacturer also noted that as a "simpler" multi-drug regimen, perindopril arginine/amlodipine FDC would improve treatment adherence, which would help achieve and maintain treatment goals and ultimately lead to improved patient outcomes. None of the trials evaluated adherence to study treatments as an efficacy outcome. Nevertheless, treatment compliance was measured across all trials, and the data showed that the mean overall treatment compliance in each trial was at least 97%, with no apparent differences between treatment groups. This suggests no improved compliance with the use of perindopril arginine/amlodipine FDC. The expert also indicated that it would be unlikely to observe such high rates of adherence in typical Canadian practice. Further, there were no data in CL2-005, PATH, or CL3-018 related to the effect of perindopril arginine/amlodipine FDC on HRQoL.

4.2.2 Harms

Across all three studies, at least 15% of participants in each trial experienced a TEAE. The occurrence of AEs appeared to be dose-dependent for two reasons. First, a greater percentage of participants who received perindopril arginine/amlodipine FDC at the highest dose (14 mg/10 mg in PATH) experienced a TEAE compared with those who received the lowest dose (3.5 mg/2.5 mg in CL2-005). Second, in CL3-018, a greater percentage of participants at steps three and four of the perindopril arginine/amlodipine FDC titration strategy experienced an AE than did those at the first two steps. However, the Health Canada review attributed the increased rate of AEs to the observed (and expected) higher rate of dose-dependent amlodipine-induced peripheral edema, and noted that the safety profile of the highest dose of perindopril arginine/amlodipine FDC was "comparable" with that of the lower doses.[10]

In CL2-005, there did not appear to be any differences in the rate of overall AEs between participants receiving perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC and its components, i.e., perindopril 3.5 mg and amlodipine 2.5 mg, respectively. In PATH, overall, a greater percentage of participants receiving amlodipine 10 mg experienced an AE than did those in the perindopril arginine 14 mg/amlodipine 10 mg FDC and perindopril erbumine 16 mg groups. Nevertheless, it is challenging to compare the safety profile of perindopril arginine 14 mg/amlodipine 10 mg FDC with that of perindopril erbumine 16 mg due to dissimilarities between the two treatments in the perindopril salt as well as in the dosages. Of note, the manufacturer reported that perindopril erbumine 16 mg corresponds with perindopril arginine 20 mg. In CL3-018, at each titration step over the six-month treatment period, there did not appear to be any differences in the rate of AEs between participants in the perindopril

arginine/amlodipine FDC group versus the valsartan/amlodipine group. Results from the open-label long-term extension phase of CL3-018 indicated a higher rate of AEs over the entire 14-month study period than over the initial (six-month) DB phase, although the non-comparative and open-label nature of the extension phase necessitate caution in interpreting the results. Across all three trials, there were very few reports of SAEs, deaths, and notable harms. Overall, discussions with the expert suggested that the types of AEs observed with perindopril arginine/amlodipine FDC, particularly hyperkalemia, peripheral oedema, and headache, were consistent with the expected biological effects of the individual components. Nevertheless, as with the aforementioned efficacy results, the short durations of the three studies leave the long-term safety of perindopril arginine/amlodipine FDC uncertain.

4.3 Potential Place in Therapy[2]

The average prevalence of hypertension in adults in Canada has remained at approximately 20%; however, its incidence increases with age. Therefore, it is likely that the overall prevalence will increase along with the proportion of elderly people.[26]

Over the past 25 years, substantial gains have been made in the treatment of hypertension in Canada due to:

- new drug classes with better tolerability and persistence, such as ACE inhibitors, CCBs, and ARBs
- the definition of evidence-based target BPs for patients with hypertension in the presence or absence of various concomitant diagnoses, such as diabetes or kidney disease
- a clearer understanding of the confounding impact of how, when, and where the BP is measured
- the development and implementation of evidence-based guidelines by CHEP, which have been updated annually.

These changes have contributed to a considerable increase in the proportion of Canadians with hypertension whose BP is controlled.[26] However, despite this progress, 34% of Canadians with hypertension still have uncontrolled BP.[26] Uncontrolled BP places people at increased risk of stroke, kidney disease, kidney failure requiring dialysis, heart attack, heart failure, and CV death.

The results of the SPRINT study (an RCT assessing intensive BP management) suggested that a target systolic BP of < 120 mm Hg may be beneficial for some patients with hypertension in the absence of diabetes, compared with an SBP goal of < 140 mm Hg.[27] The SPRINT protocol involved patients having their BP measured in a clinic with an automated sphygmomanometer (which, although previously recommended by CHEP, is not yet used by all physicians in Canada). If the SPRINT protocol becomes the standard of care for patient management, the unmet need for BP management will widen substantially; in that case, all physicians would require the appropriate sphygmomanometers or, at the very least, clarification on what the target BP should be for the type of sphygmomanometer used in their clinic.

The type and dose of antihypertensive drug(s), including single-drug or multi-drug products, are selected based on individual patient characteristics and responses. The clinical expert indicated that in Canadian practice, treatment is typically initiated with an ACE inhibitor or an ARB and, if there is no improvement, a diuretic or CCB is added. If still uncontrolled, a third drug — a diuretic or CCB (whichever was not added at the second step) — is added. For patients who have a concomitant disorder, such as diabetes or kidney disease, the dose of antihypertensive drug is very important and the choice of antihypertensive

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

class and/or specific drug from within a class may also be very important. Perindopril arginine/amlodipine is an FDC that includes an ACE inhibitor and a CCB. The ACE inhibitor class has benefits in the treatment of patients with CV disease, such as heart failure or coronary artery disease, or diabetes. On the other hand, CCB drugs are not generally recommended for the treatment of patients with heart failure or kidney disease unless the patient is already on the maximum dose of an ACE inhibitor or ARB.

Despite the typical single-drug stepwise approach to treatment, the clinical expert believed that initial therapy with a combination product may be appropriate. This belief is supported by evidence from the STITCH study, which demonstrated that initiating treatment with a single-pill combination product and following the STITCH protocol (both steps address the challenge of "clinical inertia") resulted in more patients reaching their target BPs sooner than did patients who were treated by physicians following the CHEP guidelines as per their usual practice.[28] A single-pill combination product may also be advantageous for patients as adherence to medication for individuals with chronic conditions continues to be a challenge. Of note, the 2016 CHEP guidelines do not refer to the STITCH trial, even though it was published in 2009. Further, the 2016 CHEP guidelines only mention initiating therapy with a combination of first-line drugs if individuals present with SBP ≥ 20 mm Hg or DBP ≥ 10 mm Hg above target. It is unclear whether the 2017 guidelines will be revised to reflect (or perhaps even address) the apparent benefits of initiating therapy with a low-dose FDC for all patients, as the STITCH study demonstrated.

5. CONCLUSIONS

Results from two RCTs (CL2-005 and PATH) demonstrated that, with respect to DBP and SBP reduction, perindopril arginine/amlodipine FDC was statistically superior to placebo, perindopril arginine 3.5 mg, amlodipine 2.5 mg, perindopril erbumine 16 mg, and amlodipine 10 mg, and statistically non-inferior to perindopril arginine 5 mg and amlodipine 5 mg. Further, results from another RCT (CL3-018) indicated that a treatment strategy of perindopril arginine/amlodipine FDC was statistically superior to a treatment strategy of valsartan/amlodipine FDC in reducing DBP and SBP. However, the clinical benefit of perindopril arginine/amlodipine FDC remains uncertain, given the lack of data assessing more clinically meaningful outcomes, such as hypertension-related morbidity and mortality. Across the three studies, when compared with active comparators in general, a statistically significantly greater percentage of participants receiving perindopril arginine/amlodipine FDC achieved SBP/DBP < 140/90 mm Hg, which is considered by CHEP guidelines to be the target BP for the general population; nonetheless, the lack of multiplicity adjustment for this and other secondary outcomes necessitates some caution in the interpretation of these results. Further, the limited comparative evidence for drugs available in Canada limits the utility of the results. Data from the studies did not suggest improved compliance with the use of perindopril arginine/amlodipine FDC; the effects on HRQoL were not evaluated. Across the three studies, treatment with perindopril arginine/amlodipine FDC did not appear to be associated with any unexpected, consistent, or substantial harm up to 14 months. Longer-term comparative studies are needed to adequately assess the morbidity and mortality profile of perindopril arginine/amlodipine FDC.

APPENDIX 1: PATIENT INPUT SUMMARY

No patient input was received for this submission.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 28, 2016
Alerts:	Weekly search updates until (September 21, 2016 CDEC meeting)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(perindopril* and amlodipine*).ti,ab,ot,kw,kf,hw,rn,nm.
2	(Acerycal* or Amlecsa* or Amlessa* or Amtas-PRP* or Beatil* or Calversum* or Co-Prestarium* or Coveram* or Covercard* or Covercor* or Coverlam* or Coversam * or Coversyl-AM* or Dalnessa * or Dalneva* or Deflectum* or Dynoval* or Flamipax* or Mixanval* or Prestance* or Prestalia* or Reaptan* or Viacoram* or Vidonorm* or 1265624-53-0).ti,ab,ot,kw,kf,hw,rn,nm.
3	Perindopril/ and Amlodipine/
4	or/1-3
5	4 use pmez

MULTI-DATABASE STRATEGY	
6	amlodipine plus perindopril/
7	*perindopril/ and *amlodipine/
8	(Acerycal* or Amlecsa* or Amlessa* or Amtas-PRP* or Beatil* or Calversum* or Co-Prestarium* or Coveram* or Covercard* or Covercor* or Coverlam* or Coversam * or Coversyl-AM* or Dalnessa * or Dalneva* or Deflectum* or Dynoval* or Flamipax* or Mixanval* or Prestance* or Prestalia* or Reaptan* or Viacoram* or Vidonorm* or (perindopril* and amlodipine*)).ti,ab,kw.
9	or/6-8
10	9 use oemezd
11	5 or 10
12	11 not conference abstract.pt.
13	exp animals/
14	exp animal experimentation/ or exp animal experiment/
15	exp models animal/
16	nonhuman/
17	exp vertebrate/ or exp vertebrates/
18	or/13-17
19	exp humans/
20	exp human experimentation/ or exp human experiment/
21	or/19-20
22	18 not 21
23	12 not 22
24	remove duplicates from 23

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	May 2016
Keywords:	amlodipine, perindopril, hypertension
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Korneeva et al. 2015[29]	Unclear if appropriate dose

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 18: RESULTS OF KEY EFFICACY OUTCOMES IN NON-TITRATION STUDIES

Outcome	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/AMLO 2.5 mg FDC	Placebo	PERa 3.5 mg (not approved in Canada)	AMLO 2.5 mg	PERa 5 mg	AMLO 5 mg	PERa 14 mg/AMLO 10 mg FDC (N = 279)	PERe 16 mg (N = 278)	AMLO 10 mg (N = 280)
DBP (mm Hg)[b]									
Baseline, N	246	248	268	270	270	261	271	274	275
Baseline, mean (SD)	100.7 (4.0)	100.5 (3.9)	100.7 (4.0)	100.6 (4.0)	100.1 (4.1)	100.6 (4.0)	100.6 (4.6)	100.8 (4.9)	100.5 (4.8)
End, mean (SD) change from baseline [CL2-005]/day 42, LS mean (SE) change from baseline [PATH]	–13.6 (9.2)	–9.3 (9.2)	–9.7 (9.9)	–10.3 (9.7)	–10.5 (9.7)	–12.6 (8.9)	–15.4 (0.6)	–9.1 (0.6)	–12.9 (0.6)
End, estimate (95% CI) vs. PERa 3.5 mg/ AMLO 2.5 mg FDC, *P* value [CL2-005]/day 42, LS mean difference (95% CI) vs. PERa 14 mg/AMLO 10 mg FDC, *P* value [PATH]		**–4.1 (–5.6 to –2.6), *P* < 0.001**	**–3.6 (–5.1 to –2.2), *P* < 0.001**	**–3.0 (–4.5 to –1.5), *P* < 0.001**	**–2.6 (–4.1 to –1.1), *P* < 0.001[c]**	**–0.8 (–2.3 to 0.7), *P* < 0.001[c]**		**–6.3 (–7.7 to –4.9), *P* < 0.0001**	**–2.5 (–3.9 to –1.1), *P* = 0.0005**
SBP (mm Hg)[b]									
Baseline, N	246	248	268	270	270	261	271	274	275
Baseline, mean (SD)	161.8 (7.5)	161.0 (7.4)	161.4 (7.7)	161.2 (7.6)	160.7 (7.3)	162.3 (7.5)	157.5 (11.91)	157.5 (11.4)	158.0 (11.8)
End, mean (SD) change from baseline [CL2-005]/day 42, LS mean (SE) change from baseline [PATH]	–22.0 (14.0)	–14.2 (16.1)	–16.3 (17.0)	–16.0 (15.3)	–18.2 (14.8)	–21.8 (15.4)	–22.8 (0.98)	–12.7 (1.0)	–18.8 (1.0)
End, estimate (95% CI) vs. PERa 3.5 mg/ AMLO 2.5 mg FDC, *P* value [CL2-005]/day 42, LS mean difference (95% CI) vs. PERa 14 mg/AMLO 10 mg FDC, *P* value [PATH]		**–7.2 (–9.6 to –4.8), *P* < 0.001**	**–5.0 (–7.4 to –2.7), *P* < 0.001**	**–5.2 (–7.5 to –2.9), *P* < 0.001**	**–2.8 (–5.1 to –0.5), *P* < 0.001[c]**	**–0.3 (–2.6 to 2.1), *P* = 0.003[c]**		**–10.1 (–12.6 to –7.6), *P* < 0.0001**	**–3.9 (–6.4 to –1.5), *P* = 0.0017**
Response to treatment[d]									
N	[redacted]	[redacted]	NR		[redacted]	[redacted]	258	251	259
End, responders, n (%) [CL2-005]/day 42, responders, n (%) [PATH]	[redacted]	[redacted]			[redacted]	[redacted]	133 (51.6)	68 (27.1)	97 (37.5)

Outcome	CL2-005[a] (Six-Week Treatment Period)						PATH[a] (Eight-Week Treatment Period)		
	PERa 3.5 mg/AMLO 2.5 mg FDC	**Placebo**	**PERa 3.5 mg (not approved in Canada)**	**AMLO 2.5 mg**	**PERa 5 mg**	**AMLO 5 mg**	**PERa 14 mg/AMLO 10 mg FDC (N = 279)**	**PERe 16 mg (N = 278)**	**AMLO 10 mg (N = 280)**
End, difference in % (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC; *P* value [CL2-005]/day 42, difference in % (95% CI) vs. PERa 14 mg/AMLO 10 mg FDC, *P* value [PATH]		[redacted] ***P* < 0.001**			[redacted]	[redacted]		**NR (NR), *P* < 0.001**	**NR (NR), *P* < 0.001**
Normalization of BP[e]									
N	246	248	NR		270	261	Not evaluated		
End, normalization, n (%)	107 (43.5)	66 (26.6)			90 (33.3)	99 (37.9)			
End, difference in % (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC; *P* value		**16.9 (8.6 to 25.2), *P* < 0.001**			10.2 (1.8 to 18.5)[f]	5.6 (–3.0 to 14.1)[f]			

AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; ITT = intention-to-treat; LS = least squares; NR = not reported; PERa = perindopril arginine; PERe = perindopril erbumine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] FAS in CL2-005, ITT in PATH.

[b] Supine in CL2-005, seated in PATH.

[c] *P* value for non-inferiority testing.

[d] CL2-005: SBP < 140 mm Hg and DBP < 90 mm Hg or SBP decrease ≥ 20 mm Hg from baseline or DBP decrease ≥ 10 mm Hg from baseline; PATH: BP < 140/90 mm Hg, or < 130/80 mm Hg if a participant had diabetes.

[e] CL2-005: SBP < 140 mm Hg and DBP < 90 mm Hg.

[f] No statistical testing conducted.

Note: Statistically significant results are bolded.

Source: CL2-005 Clinical Study Report,[1] PATH Clinical Study Report.[2]

TABLE 19: RESULTS OF KEY EFFICACY OUTCOMES IN TITRATION STUDY

Outcome	CL3-018[a] (Six-Month Treatment Period)	
	PERa/AMLO FDC Strategy (N = 881)	VAL/AMLO Strategy (N = 876)
SBP (mm Hg)[b]		
Baseline, mean (SD)	163.6 (7.9)	163.3 (8.0)
Month 3, mean (SD) change from baseline	–25.9 (13.3)	–23.6 (14.2)
Month 3, estimate (95% CI), *P* value	**–2.0 (–3.2 to –0.9), *P* < 0.001**	
DBP (mm Hg)[b]		
Baseline, mean (SD)	100.2 (3.7)	100.3 (3.8)
Month 3, mean (SD) change from baseline	–16.9 (8.7)	–15.5 (9.2)
Month 3, estimate (95% CI), *P* value	**–1.5 (–2.2 to –0.7), *P* < 0.001**	
BP control[c]		
Month 3, yes, n (%)	497 (56.4)	429 (49.0)
Month 3, difference in % (95% CI), *P* value	**7.4 (2.8 to 12.1), *P* = 0.002**	
Response to treatment[d]		
Month 3, yes, n (%)	[redacted]	[redacted]
Month 3, difference in % (95% CI), *P* value	[redacted]	

AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.

[a] FAS.

[b] Supine.

[c] SBP < 140 mm Hg and DBP < 90 mm Hg.

[d] BP control and/or reduction in SBP ≥2 0 mm Hg and/or reduction in DBP ≥ 10 mm Hg.

Note: Statistically significant results are bolded.

Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

TABLE 20: RESULTS OF KEY EFFICACY OUTCOMES IN PER-PROTOCOL SET FOR NON-INFERIORITY COMPARISONS IN CL2-055

Outcome	CL2-005[a] (Six-Week Treatment Period)		
	PERa 3.5 mg/AMLO 2.5 mg FDC (N = 236)	PERa 5 mg (N = 257)	AMLO 5 mg (N = 245)
Supine DBP (mm Hg)			
Baseline, mean (SD)	100.7 (4.0)	100.2 (4.0)	100.7 (4.0)
End, mean (SD) change from baseline	–13.8 (9.2)	–10.8 (9.6)	–13.0 (8.6)
End, estimate (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC, *P* value		**–2.6 (–4.1 to –1.1), *P* < 0.001[a]**	**–0.7 (–2.2 to 0.8), *P* < 0.001[a]**
Supine SBP (mm Hg)			
Baseline, mean (SD)	161.9 (7.5)	160.6 (7.3)	162.3 (7.5)
End, mean (SD) change from baseline	–22.5 (13.7)	–18.5 (14.9)	–22.3 (15.1)
End, estimate (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC, *P* value		**–3.1 (–5.4 to –0.7), *P* < 0.001[a]**	**–0.4 (–2.8 to 2.0), *P* = 0.003[a]**
Response to treatment			
End, responders, n (%)	[redacted]	[redacted]	[redacted]
End, difference in % (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC, *P* value		[redacted]	[redacted]
Normalization of BP			
End, normalization, n (%)	105 (44.5)	86 (33.5)	95 (38.8)
End, difference in % (95% CI) vs. PERa 3.5 mg/AMLO 2.5 mg FDC, *P* value		**11.0 (2.5 to 19.6), NR**	5.7 (–3.1 to 14.5), NR

AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; NR = not reported; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; vs. = versus.

[a] *P* value for non-inferiority testing.

Note: Statistically significant results are bolded.

Source: CL2-005 Clinical Study Report.[1]

TABLE 21: RESULTS OF CHANGE IN SUPINE SBP AND DBP OVER EACH TITRATION PERIOD AND THE NUMBER (%) OF PARTICIPANTS WITH CONTROLLED BLOOD PRESSURE/RESPONSE TO TREATMENT IN CL3-018

Outcome	CL3-018[a] (Six-Month Treatment Period)	
	PERa/AMLO FDC Strategy	VAL/AMLO Strategy
SBP (mm Hg)[b]		
Baseline, N	881	876
Baseline, mean (SD)	163.6 (7.9)	163.3 (8.0)
Month 1, N	[redacted]	[redacted]
Month 1, mean (SD) change from baseline	[redacted]	[redacted]
Month 1, estimate (95% CI), *P* value	**–3.4 (–4.8 to –2.0), *P* < 0.001**	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 2, N	[redacted]	[redacted]
Month 2, mean (SD) change from baseline	[redacted]	[redacted]
Month 2, estimate (95% CI), *P* value	[redacted]	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 3, N	[redacted]	[redacted]
Month 3, mean (SD) change from baseline	[redacted]	[redacted]
Month 3, estimate (95% CI), *P* value	[redacted]	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 6, N	[redacted]	[redacted]
Month 6, mean (SD) change from baseline	[redacted]	[redacted]
Month 6, estimate (95% CI), *P* value	[redacted]	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
End of month 6, N	881	876

Outcome	CL3-018[a] (Six-Month Treatment Period)	
	PERa/AMLO FDC Strategy	**VAL/AMLO Strategy**
End of month 6, mean (SD) change from baseline	–30.9 (12.5)	–28.9 (13.5)
End of month 6, estimate (95% CI), *P* value	**–1.9 (–2.9 to –0.8), *P* < 0.001**	
DBP (mm Hg)[b]		
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 1, N	[redacted]	[redacted]
Month 1, mean (SD) change from baseline	[redacted]	[redacted]
Month 1, estimate (95% CI), *P* value	**–1.8 (–2.7 to –1.0), *P* < 0.001**	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 2, N	[redacted]	[redacted]
Month 2, mean (SD) change from baseline	[redacted]	[redacted]
Month 2, estimate (95% CI), *P* value	**–2.3 (–3.1 to –1.4), *P* < 0.001**	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 3, N	[redacted]	[redacted]
Month 3, mean (SD) change from baseline	[redacted]	[redacted]
Month 3, estimate (95% CI), *P* value	[redacted]	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
Month 6, N	[redacted]	[redacted]
Month 6, mean (SD) change from baseline	[redacted]	[redacted]
Month 6, estimate (95% CI), *P* value	[redacted]	
Baseline, N	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
End of month 6, N	881	876
End of month 6, mean (SD) change from baseline	–19.5 (7.8)	–18.5 (8.2)

Outcome	CL3-018[a] (Six-Month Treatment Period)	
	PERa/AMLO FDC Strategy	**VAL/AMLO Strategy**
End of month 6, estimate (95% CI), *P* value	**–1.1 (–1.8 to –0.4), *P* = 0.001**	
BP control[c]		
Month 1, N	881	876
Month 1, yes, n (%)	291 (33.0)	236 (26.9)
Month 1, difference in % (95% CI), *P* value	**6.1 (1.8 to 10.4), *P* = 0.005**	
Month 2, N	866	860
Month 2, yes, n (%)	375 (43.3)	296 (34.4)
Month 2, difference in % (95% CI), *P* value	**8.9 (4.3 to 13.5), *P* < 0.001**	
Month 3, N	852	836
Month 3, yes, n (%)	490 (57.5)	431 (51.6)
Month 3, difference in % (95% CI), *P* value	**6.0 (1.2 to 10.7), *P* = 0.014**	
Month 6, N	[redacted]	[redacted]
Month 6, yes, n (%)	[redacted]	[redacted]
Month 6, difference in % (95% CI), *P* value	[redacted]	
End of month 6, N	881	876
End of month 6, yes, n (%)	755 (85.7)	687 (78.4)
End of month 6, difference in % (95% CI), *P* value	**7.3 (3.7 to 10.9), *P* < 0.001**	
Response to treatment[d]		
Month 1, N	[redacted]	[redacted]
Month 1, yes, n (%)	[redacted]	[redacted]
Month 1, difference in % (95% CI), *P* value	[redacted]	
Month 2, N	[redacted]	[redacted]
Month 2, yes, n (%)	[redacted]	[redacted]
Month 2, difference in % (95% CI), *P* value	[redacted]	
Month 3, N	[redacted]	[redacted]
Month 3, yes, n (%)	[redacted]	[redacted]

Outcome	CL3-018[a] (Six-Month Treatment Period)	
	PERa/AMLO FDC Strategy	VAL/AMLO Strategy
Month 3, difference in % (95% CI), *P* value	[redacted]	
Month 6, N	[redacted]	[redacted]
Month 6, yes, n (%)	[redacted]	[redacted]
Month 6, difference in % (95% CI), *P* value	[redacted]	
End of month 6, N	[redacted]	[redacted]
End of month 6, yes, n (%)	[redacted]	[redacted]
End of month 6, difference in % (95% CI), *P* value	[redacted]	

AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.
[a] FAS.
[b] Supine.
[c] SBP < 140 mm Hg and DBP < 90 mm Hg.
[d] BP control and/or reduction in SBP ≥ 20 mm Hg and/or reduction in DBP ≥ 10 mm Hg.
Note: Statistically significant results are bolded.
Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

TABLE 22: CHANGE IN DIASTOLIC AND SYSTOLIC BLOOD PRESSURE BY RACE IN PATH

Outcome		PATH[a] (Eight-Week Treatment Period)		
		PERa 14 mg/AMLO 10 mg FDC	PERe 16 mg	AMLO 10 mg
DBP (mm Hg)[b]				
Black	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]

Outcome		PATH[a] (Eight-Week Treatment Period)		
		PERa 14 mg/AMLO 10 mg FDC	PERe 16 mg	AMLO 10 mg
Non-black	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]
SBP (mm Hg)[b]				
Black	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]
Non-black	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]

AMLO = amlodipine; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; ITT = intention-to-treat; LS = least squares; PERa = perindopril arginine; PERe = perindopril erbumine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.
[a] ITT population.
[b] Seated.
Note: Statistically significant results are bolded.
Source: PATH Clinical Study Report.[2]

TABLE 23: CHANGE IN DIASTOLIC BLOOD PRESSURE AND SYSTOLIC BLOOD PRESSURE BY DIABETES STATUS IN PATH

Outcome		PATH[a] (Eight-Week Treatment Period)		
		PERa 14 mg/AMLO 10 mg FDC	PERe 16 mg	AMLO 10 mg
DBP (mm Hg)[b]				
With type 2 diabetes	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]

Outcome		PATH[a] (Eight-Week Treatment Period)		
		PERa 14 mg/AMLO 10 mg FDC	PERe 16 mg	AMLO 10 mg
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]
Without type 2 diabetes	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]
SBP (mm Hg)[b]				
With type 2 diabetes	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]
Without type 2 diabetes	Baseline, N	[redacted]	[redacted]	[redacted]
	Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	Day 42, LS mean (SE) change from baseline	[redacted]	[redacted]	[redacted]
	Day 42, LS mean difference (95% CI), *P* value vs. PERa 14 mg/AMLO 10 mg FDC		[redacted]	[redacted]

AMLO = amlodipine; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; ITT = intention-to-treat; LS = least squares; PERa = perindopril arginine; PERe = perindopril erbumine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; vs. = versus.

[a] ITT population.

[b] Seated.

Note: Statistically significant results are bolded.

Source: PATH Clinical Study Report.[2]

TABLE 24: CHANGE IN DIASTOLIC BLOOD PRESSURE AND SYSTOLIC BLOOD PRESSURE BY DIABETES STATUS IN CL3-018

Outcome		CL3-018[a] (Six-Month Treatment Period)	
		PERa/AMLO FDC strategy	VAL/AMLO strategy
DBP (mm Hg)[b]			
With type 2 diabetes	Baseline, N	107	113
	Baseline, mean (SD)	[redacted]	[redacted]
	Month 3, mean (SD) change from baseline	[redacted]	[redacted]
	Month 3, estimate (95% CI), *P* value		[redacted] *P* = 0.06
Without type 2 diabetes	Baseline, N	774	763
	Baseline, mean (SD)	[redacted]	[redacted]
	Month 3, mean (SD) change from baseline	[redacted]	[redacted]
	Month 3, estimate (95% CI), *P* value		[redacted] ***P* = 0.002**
SBP (mm Hg)[b]			
With type 2 diabetes	Baseline, N	107	113
	Baseline, mean (SD)	[redacted]	[redacted]
	Month 3, mean (SD) change from baseline	[redacted]	[redacted]
	Month 3, estimate (95% CI), *P* value		[redacted] *P* = 0.13
Without type 2 diabetes	Baseline, N	774	763
	Baseline, mean (SD)	[redacted]	[redacted]
	Month 3, mean (SD) change from baseline	[redacted]	[redacted]
	Month 3, estimate (95% CI), *P* value		[redacted] ***P* = 0.003**

AMLO = amlodipine; CI = confidence interval; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.

[a] FAS.

[b] Supine.

Note: Statistically significant results are bolded.

Note: The titration strategy was as follows:

- step 1: PERa 3.5 mg/AMLO 2.5 mg FDC or VAL 80 mg
- step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg
- step 3: PERa 14 mg/AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC
- step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC.

Source: CL3-018 Clinical Study Report.[3]

APPENDIX 5: SUMMARY OF STUDY CL3-006

Objective

To summarize the results of the titration study CL3-006.

Findings

Study Design

CL3-006 (N = 3,270) was a multi-centre, double-blind (DB), phase 3 randomized controlled trial (RCT) in which participants were randomized (1:1) to receive treatment according to one of two antihypertensive strategies: one initiated with perindopril arginine 3.5 mg/amlodipine 2.5 mg fixed-dose combination (FDC), or another initiated with irbesartan 150 mg (Table 25). Since participants in that trial did not receive perindopril arginine/amlodipine FDC according to the approved dosage and administration in Canada, this study was not included in the main report. Randomization was balanced, fixed, centralized with an interactive voice response system (IVRS) or interactive Web response system (IWRS), and stratified by centre, age (≤ or > 65 years), and presence of known diabetes (yes/no). The study comprised a run-in period that lasted two weeks and a subsequent six-month treatment period in which up-titration was conducted treatment was locked for another three months (Table 25). Also, an ancillary study was conducted using ambulatory blood pressure monitoring (ABPM), the results of which are summarized in Appendix 6.

Statistical power calculations indicated the need to have 1,410 participants in each strategy in order to provide 80% power using the two-sided McNemar's test at 5% type I error. sample size of 1,500 participants in each group was needed to account for a 5% withdrawal rate.

TABLE 25: SUMMARY OF CL3-006 STUDY DESIGN

		CL3-006
DESIGNS & POPULATIONS	**Study design**	Multi-centre, DB, active-controlled, parallel-group, titrated dose, phase 3 RCT
	Locations	Ireland, The Netherlands, United Kingdom
	Randomized (N)	3,270
	Main inclusion criteria	Male or female aged ≥ 18 years with hypertension: for untreated participants, SBP ≥ 150 and < 180 mm Hg, DBP ≥ 95 and < 115 mm Hg; for treated participants (with no more than two antihypertensive drugs) who in the investigator's opinion require a change in medication because of lack of efficacy or poor tolerability, SBP < 165 mm Hg and DBP < 105 mm Hg
	Main exclusion criteria	Secondary hypertension; history of MI; history of stroke; history of transient ischemic attack; cerebrovascular surgery within the last 3 months; requiring an antihypertensive drug for any other concomitant illness or conditions than hypertension except beta blockers or alpha-blockers; second or third-degree atrioventricular block; aortic or mitral valve stenosis or hypertrophic obstructive myocardiopathy; uncontrolled arrhythmias, atrial fibrillation, atrial flutter, or presence of ventricular rhythm disorders; history of alcoholism, drug abuse, psychosis, or any emotional or intellectual problems that were likely to invalidate informed consent or limit the ability of the patient to comply with the protocol requirements; use of unauthorized medicine; presence of any contraindication to the study treatments

		CL3-006
DRUGS	**Intervention**	Perindopril arginine/amlodipine FDC strategy: • step 1: Perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC once daily • step 2: Perindopril arginine 7 mg/amlodipine 5 mg FDC once daily • step 3: Perindopril arginine 14 mg/amlodipine 5 mg FDC twice daily • step 4: Perindopril arginine 14 mg/amlodipine 10 mg FDC twice daily. If BP was controlled at each visit at months 1, 2, 3, and 6, participants remained on the same dosage as at previous visit; if BP was uncontrolled, treatments were up-titrated according to the perindopril arginine/amlodipine FDC strategy schedule.
	Comparators	Irbesartan/hydrochlorothiazide strategy: • step 1: Irbesartan 150 mg once daily • step 2: Irbesartan 150 mg + hydrochlorothiazide 12.5 mg once daily • step 3: Irbesartan 300 mg + hydrochlorothiazide 12.5 mg twice daily • step 4: Irbesartan 300 mg + hydrochlorothiazide 25 mg twice daily. If BP was controlled at each visit at months 1, 2, 3, and 6, participants remained on the same dosage as at previous visit; if BP was uncontrolled, treatments were up-titrated according to the irbesartan/hydrochlorothiazide strategy schedule.
DURATION	**Phase**	
	Run-in/washout	Run-in: 2 weeks
	Double-blind	9 months
	Follow-up	6 months
OUTCOMES	**Primary end point**	Proportion of patients in the perindopril arginine/amlodipine treatment group with blood pressure control, defined as supine SBP < 140 mm Hg and supine DBP < 90 mm Hg, or in the case of diabetic patients as supine SBP < 130 mm Hg and supine DBP < 80 mm Hg, at evaluation periods at months 1, 2, 3, and 6.
	Other end points	Proportion of patients with BP control at month 9, BP, DBP, pulse pressure, mean BP, response to treatment (reduction in SBP ≥ 20 mm Hg, and/or reduction in supine DBP ≥ 10 mm Hg), clinical events of special interest, safety
NOTES	**Publications**	Poulter et al., 2015[30]

BP = blood pressure; DB = double-blind; DBP = diastolic blood pressure; FDC = fixed-dose combination; MI = myocardial infarction; RCT = randomized controlled trial; SBP = systolic blood pressure.
Source: CL3-006 Clinical Study Report.[31]

The following analysis sets were defined:

- randomized set (RS): all included participants to whom a therapeutic unit was randomly assigned using the IVRS/IWRS
- safety set (SS): participants who had taken at least one dose of study treatment
- full analysis set (FAS): all randomized participants who had taken at least one dose of study treatment, had at least one value of both supine SBP and DBP available at baseline, and had at least one value of both supine SBP and DBP at the month 1, month 2, or month 3 visit
- per-protocol set (PPS): all participants in the FAS without a major deviation that could affect the evaluation of blood pressure (BP) control during the study until month 6.

The disposition of participants across the two titration strategies is summarized in Table 26. A large percentage of participants in both treatment strategies withdrew from the study, with a higher percentage in the perindopril arginine/amlodipine FDC group (31.3%) compared with the irbesartan/ hydrochlorothiazide (HCTZ) group (25.9%). Adverse events (AEs) were the most common reason for withdrawal.

TABLE 26: DISPOSITION OF PARTICIPANTS

Status	PERa/AMLO FDC Strategy	Irbesartan/HCTZ Strategy
Included and randomized (randomized set), N	1,617	1,653
Lost to follow-up, n (%)	-[a]	-[a]
Withdrawn due to, n (%)	506 (31.3)	428 (25.9)
AE	368 (22.8)	236 (14.3)
Non-medical reason	64 (4.0)	67 (4.1)
Lack of efficacy	49 (3.0)	96 (5.8)
Protocol deviation	25 (1.5)	29 (1.8)
Completed	1,111 (68.7)	1,225 (74.1)
Safety set, n	1617	1653
Full analysis set, n (%)	1,605 (99.3)	1,628 (98.5)
Per-protocol set, n (%)	1,227 (76.4)	1,318 (81.0)

AE = adverse event; AMLO = amlodipine; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine.
[a] Cells are unclear if they have a zero value or are not reported.
Source: CL3-006 Clinical Study Report.[31]

Results

The main demographics and baseline characters of CL3-006 were similar across both groups. These were summarized in Table 27.

TABLE 27: DEMOGRAPHICS AND MAIN BASELINE CHARACTERISTICS IN CL3-006 (RANDOMIZED SET)

Characteristic	CL3-006	
	PERa/AMLO FDC Strategy (N = 617)	Irbesartan/HCTZ Strategy (N = 1,653)
Mean (SD) age (years)	62.6 (9.8)	62.4 (9.8)
Number of males (%)	1,024 (63.33)	1,041 (62.98)
Mean (SD) BMI (kg/m^2)	29.34 (4.77)	29.68 (5.08)
Mean (SD) duration of hypertension (months)	90.5 (86.9)	90.3 (90.4)
Mean (SD) supine SBP (mm Hg)	163.69 (11.56)	163.45 (11.50)
Mean (SD) supine heart rate (BPM)	67.17 (11.23)	67.77 (11.42)
Number of participants with stage 1 hypertension (%) [mm Hg]	[redacted]	[redacted]
Number of participants with stage 2 hypertension (%) [mm Hg]	[redacted]	[redacted]
Number of participants with stage 3 hypertension (%) [mm Hg]	[redacted]	[redacted]
Number of participants with type 2 diabetes	[redacted]	[redacted]
Number of participants with a metabolic syndrome (%)	[redacted]	[redacted]

AMLO = amlodipine; BMI = body mass index; BPM = beats per minute; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation.
Source: CL3-006 Clinical Study Report.[31]

The primary outcome was the proportion of participants within the perindopril arginine/amlodipine FDC group achieving BP control after each titration step. Controlled BP was defined as supine systolic blood pressure (SBP) < 140 mm Hg and supine diastolic blood pressure (DBP) < 90 mm Hg, or in the case of participants stratified as diabetic, as supine SBP < 130 mm Hg and supine DBP < 80 mm Hg. In the main analysis, participants with a missing value at the end of the period were assumed to have uncontrolled BP. Results pertaining to the proportion of participants who achieved BP control in both treatment strategies are summarized in Table 28.

TABLE 28: PROPORTION OF PARTICIPANTS ACHIEVING CONTROLLED BLOOD PRESSURE AT EACH EVALUATION PERIOD, FULL ANALYSIS SET

Period			CL3-006	
			PERa/AMLO FDC Strategy[a]	Irbesartan/HCTZ Strategy
Month 0 to month 1	End, n (%)	All	[redacted]	[redacted]
		BP controlled	[redacted]	[redacted]
	Between-groups difference estimate (SE)[b]		[redacted]	
	Between-groups difference *P* value[b]		[redacted]	
Month 1 to month 2	Entry, n (%)	All	[redacted]	[redacted]
		BP controlled	[redacted]	[redacted]
	End, n (%)	BP controlled	[redacted]	[redacted]
	Within-group difference estimate (SE)[a]		[redacted]	[redacted]
	Within-group *P* value[a]		[redacted]	[redacted]
Month 2 to month 3	Entry, n (%)	All	[redacted]	[redacted]
		BP controlled	[redacted]	[redacted]
	End, n (%)	BP controlled	[redacted]	[redacted]
	Within-group difference estimate (SE)[a]		[redacted]	[redacted]
	Within-group *P* value[a]		[redacted]	[redacted]
Month 3 to month 6	Entry, n (%)	All	[redacted]	[redacted]
		BP controlled	[redacted]	[redacted]
	End, n (%)	BP controlled	[redacted]	[redacted]
	Within-group difference estimate (SE)[a]		[redacted]	[redacted]
	Within-group *P* value[a]		[redacted]	[redacted]
Last post-baseline assessment until month 6	BP controlled		[redacted]	[redacted]
	Between-groups difference estimate (SE)[b]		[redacted]	
	Between-groups *P* value[b]		[redacted]	

Period			CL3-006	
			PERa/AMLO FDC Strategy[a]	Irbesartan/HCTZ Strategy
Month 6 to month 9	Entry, n (%)	All	[redacted]	[redacted]
		BP controlled	[redacted]	[redacted]
	End, n (%)	BP controlled	[redacted]	[redacted]
	Within-group difference estimate (SE)[a]		[redacted]	[redacted]
	Within-group *P* value[a]		[redacted]	[redacted]

AMLO = amlodipine; BP = blood pressure; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; SE = standard error.
[a] Primary outcome (within-group difference).
[b] Secondary outcomes (between-group differences).
Source: CL3-006 Clinical Study Report.[31]

A summary of the results of the available secondary outcomes is presented in Table 29. In addition to these results, there were no statistically significant differences in SBP, pulse pressure, or mean BP changes between the perindopril arginine/amlodipine FDC strategy and the irbesartan/HCTZ strategy.

TABLE 29: SECONDARY OUTCOMES COMPARING THE TWO STRATEGIES, FULL ANALYSIS SET

Outcome		CL3-006	
		PERa/AMLO FDC strategy (N = 1,605)	Irbesartan/HCTZ strategy (N = 1,628)
Response to treatment	n (%)	[redacted]	[redacted]
	Estimate difference (SE)	[redacted]	
	P value	[redacted]	
SBP	Baseline, mean (SD)	[redacted]	[redacted]
	Last post-baseline assessment until month 6, mean (SD)	[redacted]	[redacted]
	Change from baseline, mean (SD)	[redacted]	[redacted]
	Estimate difference (SE)	[redacted]	
	P value	[redacted]	

AMLO = amlodipine; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error.
Source: CL3-006 Clinical Study Report.[31]

Safety outcomes are summarized in Table 30. There were five deaths in the study, two in the perindopril arginine/amlodipine FDC group and two in the irbesartan/HCTZ group; these deaths were determined not to have been related to the treatment. A higher rate of withdrawals due to AEs was seen in the perindopril arginine/amlodipine FDC group compared with the irbesartan/HCTZ group. A subanalysis showed that most withdrawals due to AEs occurred among patients taking the highest dose of perindopril arginine/amlodipine FDC (i.e., 14 mg/10mg). A higher proportion of participants in the perindopril arginine/amlodipine FDC group experienced peripheral edema and cough compared with the irbesartan/HCTZ group.

TABLE 30: SUMMARY OF SAFETY RESULTS, SAFETY SET

	PERa/AMLO FDC strategy (N = 1,617)	Irbesartan/HCTZ strategy (N = 1,653)
Participants with > 0 AEs, n (%)	1,392 (86.1)	1,382 (83.6)
Most common AEs, n (%)		
Peripheral edema	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Microalbuminuria	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
Participants with > 0 SAEs, n (%)	124 (7.7)	127 (7.7)
Participants with AEs or SAEs that led to withdrawal, n (%)	358 (22.1)	226 (13.7)
Number of deaths, n (%)	2 (0.1)	3 (0.2)
Notable harms other than most common AEs, n (%)		
Orthostatic hypotension	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]

AE = adverse event; AMLO = amlodipine; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; SAE = serious adverse event.
Source: CL3-006 Clinical Study Report.[31]

Summary

A total of 3,270 patients were randomized in this study. Overall, the study was well planned and well conducted in terms of size, randomization, allocation concealment, and statistical analysis, despite having a much higher number of participant withdrawals than anticipated. The study achieved the primary outcome by showing a statistically significant increase in the number of participants with controlled BP after each perindopril arginine/amlodipine FDC titration step. However, this outcome was non-comparative in nature (i.e., based on within-group changes in BP). When comparing the results from the perindopril arginine/amlodipine FDC group with the those from the irbesartan/HCTZ group, no statistically significant different was found throughout the main secondary outcomes, which also lacked clear adjustment for multiple outcomes. The overall number of AEs and serious AEs was similar across both groups. However, a higher proportion of participants in the perindopril arginine/amlodipine FDC group experienced peripheral edema and cough.

APPENDIX 6: SUMMARY OF THE AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDIES OF CL2-005, CL3-006, AND CL3-018

Objective

To summarize the results from the ambulatory blood pressure monitoring (ABPM) substudies of CL2-005, CL3-006, and CL3-018.

Findings

Study Design

Study design and characteristics are summarized in Table 31. A validated ABPM device was used in all three studies to provide 24 hours of blood pressure (BP) measurements throughout each patient's normal daily activities. The device consisted of a BP cuff worn around the arm, and a monitoring device placed on the participant's belt or trousers. One BP measurement was taken every 15 minutes.

TABLE 31: SUMMARY DESIGN AND CHARACTERS OF AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDIES

		ABPM-CL2-005	ABPM-CL3-006	ABPM-CL3-018
DESIGNS & POPULATIONS	**Original study design**	Multi-centre, DB, placebo- and active-controlled, parallel-group factorial phase 2 RCT	Multi-centre, DB, active-controlled, parallel-group, titrated dose, phase 3 RCT	Multi-centre, DB, active-controlled, parallel-group, titrated dose, phase 3 RCT
	Original number of participants randomized (N)	1,581	3,270	1,774
	Eligibility	All participants were eligible and offered participation	All participants were eligible and offered participation	All participants were eligible and offered participation
	Number of participants who agreed to enrol and included in ABPM substudy (N)	1,297	387	1,029
	Primary objective	To demonstrate a statistically greater ABPM BP lowering effect with perindopril 3.5 mg/amlodipine 2.5 mg FDC combination versus placebo	To determine the difference in treatment effect between perindopril/amlodipine FDC and irbesartan alone or with hydrochlorothiazide added, over a six-month period in approximately 500 hypertensive participants	To assess the efficacy of both combination strategies on the ABPM parameters at month 0 (baseline), after 3 months (month 3), and after 6 months (month 6) of treatment

		ABPM-CL2-005	ABPM-CL3-006	ABPM-CL3-018
DRUGS	**Intervention**	Perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC once daily	Step 1: Perindopril 3.5 mg/amlodipine 2.5 mg FDC once daily Step 2: Perindopril 7 mg/ amlodipine 5 mg FDC once daily Step 3: Perindopril 14 mg/ amlodipine 5 mg FDC twice daily Step 4: Perindopril 14 mg/ amlodipine 10 mg FDC twice daily	Step 1: Perindopril arginine 3.5 mg/amlodipine 2.5 mg FDC once daily Step 2: Perindopril arginine 7 mg/amlodipine 5 mg FDC once daily Step 3: Perindopril arginine 14 mg/amlodipine 10 mg FDC once daily Step 4: Perindopril arginine 14 mg/amlodipine 10 mg FDC once daily + indapamide 1.5 mg SR once daily
	Comparators	Placebo; perindopril arginine 3.5 mg; amlodipine 2.5 mg; perindopril arginine 5 mg; amlodipine 5 mg (all once daily)	Step 1: Irbesartan 150 mg once daily Step 2: Irbesartan 150 mg + hydrochlorothiazide 12.5 mg once daily Step 3: Irbesartan 300 mg + hydrochlorothiazide 12.5 mg twice daily Step 4: Irbesartan 300 mg + hydrochlorothiazide 25 mg twice daily	Step 1: Valsartan 80 mg once daily Step 2: Valsartan 160 mg once daily Step 3: Valsartan 160 mg/ amlodipine 5 mg FDC once daily Step 4: Valsartan 160 mg/ amlodipine 10 mg FDC once daily
DURATION	**Phase**			
	Run-in/washout	Run-in: 2 weeks to 3 weeks	Run-in: 2 weeks	Run-in: 2 weeks to 4 weeks
	Double-blind	8 weeks	9 months	6 months
	Follow-up	N/A	N/A	8 months
OUTCOMES	**Primary end point**	Mean DBP over 24 hours	Mean DBP over 24 hours	Mean SBP over 24 hours
	Other end points (review relevant outcomes)	Mean SBP over 24 hours	N/A	Mean DBP over 24 hours

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; DB = double-blind; DBP = diastolic blood pressure; FDC = fixed-dose combination; N/A = not applicable; RCT = randomized controlled trial; SBP = systolic blood pressure; SR = sustained release.
Source: CL2-005 ABPM,[32] CL3-006 ABPM,[33] CL3-018.[3]

Three analysis populations were defined in each of the substudies:

- randomized set ABPM (RS ABPM): randomized participants included in the substudy
- full analysis set ABPM (FAS ABPM): all RS ABPM participants who had taken at least one dose of study treatment and who had a valid baseline value and a valid post-baseline value of mean 24-hour BP
- per-protocol set ABPM (PPS ABPM): all participants of the FAS ABPM without relevant deviation(s) that could affect the evaluation of mean 24-hour BP.

The disposition of participants across the two titration substudies (ABPM-CL3-006 and ABPM-CL3-018) is summarized in Table 32. The disposition of participants in the non-titration ABPM substudy (ABPM-CL2-005) is summarized in Table 33.

TABLE 32: DISPOSITION OF PARTICIPANTS IN TITRATION AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDIES

	ABPM-CL3-006		ABPM-CL3-018	
	PERa/AMLO FDC Strategy	Irbesartan/HCTZ Strategy	PERa/AMLO FDC Strategy	VAL/AMLO Strategy
RS HBPM	193	194	514	515
Withdrawals n (%)	36 (18.7)	28 (14.4)	42 (8.2)	40 (7.8)
AE n (%)	26 (13.5)	11 (5.7)	27 (5.3)	23 (4.5)
Non-medical reason n (%)	3 (1.6)	5 (2.6)	11 (2.1)	11 (2.1)
Other protocol withdrawal criteria n (%)	0	0	1 (0.2)	3 (0.6)
Protocol deviation n (%)	3 (1.6)	2 (1.0)	3 (0.6)	3 (0.6)
Lack of efficacy n (%)	4 (1.9)	10 (5.2)	-	-
Completed n (%)	157 (81.3)	166 (85.6)	472 (91.8)	475 (92.2)
Full analysis set (FAS HBPM)	90	105	408	384
Per-protocol set (PPS ABPM)	85	100	393	378

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AMLO = amlodipine; FAS = full analysis set; FDC = fixed-dose combination; HBPM = home blood pressure monitoring; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; PPS = per-protocol set; RS = randomized set; VAL = valsartan.
Source: CL3-006 ABPM,[33] CL3-018.[3]

TABLE 33: DISPOSITION OF PARTICIPANTS IN THE NON-TITRATION AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDY

	PERa 3.5 mg/ AMLO 2.5 mg FDC	Placebo	PERa 3.5 mg	AMLO 2.5 mg	PERa 5 mg	AMLO 5 mg
RS HBPM	204	200	224	226	228	215
Withdrawn due to, total	6	9	12	14	14	11
AE	2	0	5	7	7	7
Non-medical reason	1	4	2	4	2	3
Lack of efficacy	2	2	3	2	3	1
Protocol deviation	0	2	2	1	1	0
Other	1	1	0	0	1	0
Completed	198	191	212	212	214	204
Full analysis set (FAS HBPM)	174	167	189	183	187	173
Per-protocol set (PPS ABPM)	154	151	176	167	171	153

ABPM = ambulatory blood pressure monitoring; AE = adverse event; AMLO = amlodipine; FAS = full analysis set; FDC = fixed-dose combination; HBPM = home blood pressure monitoring; PERa = perindopril arginine; PPS = per-protocol set; RS = randomized set.
Source: CL2-005 ABPM.[32]

Results

The main demographic and baseline characteristics of participants were similar across treatment groups within studies, but were variable across studies. Participant characteristics are summarized in Table 34 for the titration ABPM substudies (ABPM-CL3-006 and ABPM-CL3-018), and for the non-titration ABPM substudy (ABPM-CL2-005) in Table 35.

TABLE 34: DEMOGRAPHICS AND MAIN BASELINE CHARACTERISTICS IN THE TITRATION AMBULATORY BLOOD PRESSURE MONITORING SUBSTUDIES

	ABPM-CL3-006 (RS ABPM)		ABPM-CL3-018 (FAS ABPM)	
	PERa/AMLO FDC (N = 193)	Irbesartan/HCTZ (N = 194)	PERa/AMLO FDC strategy (N = 408)	VAL/AMLO strategy (N = 384)
Mean (SD) age (years)	60.6 (9.7)	60.6 (10.4)	55.9 (9.7)	55.3 (10.7)
Number of males (%)	137 (71.0)	135 (69.6)	237 (58.09)	213 (55.47)
Mean (SD) duration of hypertension	85.1 (79.1) months	88.7 (89.1) months	8.2 (8.1) years	7.7 (7.4) years
Mean (SD) BMI (kg/m^2)	29.61 (4.71)	29.47 (4.69)	27.09 (2.34)	27.04 (2.59)
Mean (SD) supine heart rate (bpm)	65.80 (10.28)	66.99 (10.69)	71.66 (12.00)	72.34 (11.05)
Mean (SD) SBP over 24 hours (mm Hg)	143.12 (12.04)	142.79 (11.97)	141.09 (12.37)	141.33 (12.19)
Mean (SD) DBP over 24 hours (mm Hg)	84.45 (9.58)	84.08 (9.06)	87.52 (8.67)	87.93 (8.51)
Mean (SD) office supine SBP (mm Hg)	162.3 (10.1)	161.9 (12.2)	NR	NR
Mean (SD) office supine DBP (mm Hg)	91.0 (8.4)	91.6 (8.4)	NR	NR

ABPM = ambulatory blood pressure monitoring; AMLO = amlodipine; BMI = body mass index; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; NR = not reported; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; RS = randomized set; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.
Source: CL3-006 ABPM,[33] CL3-018.[3]

TABLE 35: DEMOGRAPHICS AND MAIN BASELINE CHARACTERISTICS IN THE NON-TITRATION ABPM SUBSTUDY (RANDOMIZED SET ABPM)

	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 204)	Placebo (N = 200)	PERa 3.5 mg (N = 224)	AMLO 2.5 mg (N = 226)	PERa 5 mg (N = 228)	AMLO 5 mg (N = 215)
Mean (SD) age (years)	51.8 (11.3)	52.2 (11.6)	51.7 (11.0)	51.8 (10.8)	51.9 (11.3)	51.9 (11.1)
Number of males (%)	98 (48.0)	91 (45.5)	102 (45.5)	109 (48.2)	105 (46.1)	101 (47.0)
Mean (SD) duration of hypertension (months)	62.8 (73.6)	57.8 (80.5)	54.3 (64.0)	52.8 (67.4)	52.9 (67.9)	53.7 (72.7)
Mean (SD) BMI (kg/m^2)	26.6 (2.8)	26.7 (2.5)	27.0 (2.4)	26.8 (2.6)	26.9 (2.7)	26.8 (2.5)
Mean (SD) supine heart rate (bpm)	NR	NR	NR	NR	NR	NR

	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 204)	Placebo (N = 200)	PERa 3.5 mg (N = 224)	AMLO 2.5 mg (N = 226)	PERa 5 mg (N = 228)	AMLO 5 mg (N = 215)
Mean (SD) SBP over 24 hours (mm Hg)	132.7 (11.2)	132.9 (12.5)	134.3 (13.8)	134.4 (11.8)	133.9 (12.3)	135.2 (13.4)
Mean (SD) DBP over 24 hours (mm Hg)	82.5 (8.8)	83.1 (9.9)	83.6 (10.5)	84.6 (9.2)	83.6 (9.5)	83.9 (8.5)
Mean (SD) office supine SBP (mm Hg)	NR	NR	NR	NR	NR	NR
Mean (SD) office supine DBP (mm Hg)	NR	NR	NR	NR	NR	NR

ABPM = ambulatory blood pressure monitoring; AMLO = amlodipine; BMI = body mass index; DBP = diastolic blood pressure; FDC = fixed-dose combination; NR = not reported; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation.
Source: CL2-005 ABPM.[32]

A summary of the results of diastolic blood pressure (DBP) in the FAS ABPM population of titration studies is presented in Table 36, while the findings of the non-titration ABPM substudy results are presented in Table 37. Results of systolic blood pressure (SBP) in the FAS ABPM population are presented in Table 38, while results from the non-titration substudy are presented in Table 39.

TABLE 36: MEAN DBP OVER 24 HOURS (MM HG) FROM BASELINE TO LAST POST-BASELINE VALUE OF TITRATION ABPM SUBSTUDIES — FULL ANALYSIS SET ABPM

Ambulatory 24-hour DBP (mm Hg)	ABPM-CL3-006 (FAS ABPM)		ABPM-CL3-018 (FAS ABPM)	
	PERa/AMLO FDC strategy (N = 90)	Irbesartan/HCTZ strategy (N = 105)	PERa/AMLO FDC strategy (N = 386)	VAL/AMLO strategy (N = 356)
Mean (SD) baseline	85.59 (10.18)	84.79 (8.52)	87.20 (8.41)	87.97 (8.41)
Mean (SD) end	75.80 (8.34) at month 6	76.04 (7.32) at month 6	77.77 (6.88) at month 3	79.96 (7.77) at month 3
Mean (SD) change from baseline to end	–9.80 (6.84)	–8.75 (5.88)	–9.43 (7.44)	–8.01 (7.28)
Estimated between-groups difference in adjusted mean change from baseline to month 3 (SE)	–0.77 (0.76)		**–1.76 (0.44)**	
P value	NA, (95% CI [–2.26 to 0.72])		**< 0.001, (95% CI [–2.62 to –0.91])**	

ABPM = ambulatory blood pressure monitoring; AMLO = amlodipine; DBP = diastolic blood pressure; FAS = full analysis set; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.
Note: Statistically significant results are bolded.
Source: CL3-006 ABPM,[33] CL3-018.[3]

TABLE 37: MEAN DBP OVER 24 HOURS (MM HG) FROM BASELINE TO LAST POST-BASELINE VALUE OF NON-TITRATION ABPM SUBSTUDY – FULL ANALYSIS SET ABPM

Ambulatory 24-hour DBP (mm Hg)	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 174)	Placebo (N = 167)	PERa 3.5 mg (N = 189)	AMLO 2.5 mg (N = 183)	PERa 5 mg (N = 187)	AMLO 5 mg (N = 173)
Mean (SD) baseline	82.93 (8.63)	83.15 (9.68)	83.52 (10.66)	84.58 (9.03)	83.66 (9.51)	84.06 (8.81)
Mean (SD) end	77.13 (8.47)	81.26 (9.52)	79.82 (10.06)	81.59 (8.44)	80.05 (9.06)	78.11 (7.79)
Mean (SD) change from baseline to end (week 8)	–5.80 (8.31)	–1.89 (8.74)	–3.70 (9.16)	–3.00 (7.09)	–3.61 (7.76)	–5.94 (7.78)
Estimated between-groups difference in adjusted mean change from baseline to month 3 (SE)	Reference value	**–3.99 (0.75)**	**–2.17 (0.73)**	**–3.39 (0.74)**	**–2.40 (0.73)**	–0.26 (0.75)
P value	Reference value	***P* < 0.001**	NA	NA	NA	NA
95% CI	Reference value	**–5.81 to –2.68**	**–3.60 to –0.73**	**–4.84 to –1.94**	**–3.84 to –0.97**	–1.73 to 1.21

ABPM = ambulatory blood pressure monitoring; AMLO = amlodipine; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; PERa = perindopril arginine; SD = standard deviation; SE = standard error.
Note: Statistically significant results are bolded.
Source: CL2-005 ABPM.[32]

TABLE 38: MEAN SBP OVER 24 HOURS (MM HG) FROM BASELINE TO LAST POST-BASELINE VALUE OF TITRATION ABPM SUBSTUDIES — FULL ANALYSIS SET ABPM

Ambulatory 24-hour SBP (mm Hg)	ABPM-CL3-006 (FAS ABPM)		ABPM-CL3-018 (FAS ABPM)	
	PERa/AMLO FDC strategy (N = 90)	Irbesartan/HCTZ strategy (N = 105)	PERa/AMLO FDC strategy (N = 386)	VAL/AMLO strategy (N = 356)
Mean (SD) baseline	144.15 (11.81)	142.70 (10.71)	140.76 (12.19)	141.33 (12.28)
Mean (SD) end	127.65 (9.19) at month 6	127.60 (11.84) at month 6	125.27 (9.79) at month 3	128.64 (10.49) at month 3
Mean (SD) change from baseline to end	–16.50 (10.76)	–15.11 (9.71)	–15.49 (11.61)	–12.70 (11.74)
Estimated between-groups difference in adjusted mean change from baseline to month 3 (SE)	–0.86 (1.27)		**–3.02 (0.65)**	
P value	NA, (95% CI [–3.36 to 1.64])		**< 0.001, (95% CI [–4.30 to –1.73])**	

ABPM = ambulatory blood pressure monitoring; AMLO = amlodipine; FAS = full analysis set; FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; VAL = valsartan.
Note: Statistically significant results are bolded.
Source: CL3-006 ABPM,[33] CL3-018.[3]

TABLE 39: MEAN SBP OVER 24 HOURS (MM HG) FROM BASELINE TO LAST POST-BASELINE VALUE OF NON-TITRATION ABPM SUBSTUDY — FULL ANALYSIS SET ABPM

Ambulatory 24-hour SBP (mm Hg)	PERa 3.5 mg/ AMLO 2.5 mg FDC (N = 174)	Placebo (N = 167)	PERa 3.5 mg (N = 189)	AMLO 2.5 mg (N = 183)	PERa 5 mg (N = 187)	AMLO 5 mg (N = 173)
Mean (SD) baseline	133.10 (11.22)	133.06 (12.13)	134.61 (14.07)	134.53 (11.57)	133.84 (12.41)	135.48 (14.00)
Mean (SD) end	124.60 (10.53)	130.86 (12.36)	128.08 (13.05)	130.41 (11.54)	128.94 (11.33)	125.82 (10.93)
Mean (SD) change from baseline to end (week 8)	–8.50 (11.78)	–2.20 (13.21)	–6.53 (11.59)	–4.12 (10.50)	–4.89 (12.22)	–9.66 (12.99)
Estimated between-groups difference in adjusted mean change from baseline to month 3 (SE)	Reference value	**–6.25 (1.06)**	**–2.49 (1.03)**	**–4.93 (1.04)**	**–3.82 (1.03)**	–0.03 (1.06)
P value	Reference value	***P* < 0.001**	NA	NA	NA	NA
95% CI	Reference value	**–8.34 to – 4.16**	**–4.52 to – 0.47**	**–6.97 to – 2.89**	**–5.84 to – 1.79**	–2.10 to 2.04

ABPM = ambulatory blood pressure monitoring; AMLO = amlodipine; FAS = full analysis set; FDC = fixed-dose combination; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; SE = standard error.
Note: Statistically significant results are bolded.
Source: CL2-005 ABPM.[32]

Summary

In the non-titration ABPM substudy CL2-005, the perindopril arginine 3.5 mg/amlodipine 2.5 mg fixed-dose combination (FDC) showed a statistically significant greater reduction in SBP and DBP at eight weeks when compared with placebo, perindopril 3.5 mg, amlodipine 2.5 mg, and perindopril 5 mg, but not when compared with amlodipine 5 mg. In the titration substudy ABPM-CL3-006, participants in the perindopril arginine/amlodipine FDC group did not experience any statistically significant improvement in SBP or DBP at six months when compared with those in the irbesartan/HCTZ group. This is in contrast to the statistically significant improvement that participants in the perindopril arginine/amlodipine FDC group experienced at three months compared with those in the valsartan/amlodipine group in the titration substudy ABPM-CL3-018 for SBP and DBP.

APPENDIX 7: SUMMARY OF THE HOME BLOOD PRESSURE MONITORING SUBSTUDY CL3-018

Objective

To summarize the results from the home blood pressure monitoring (HBPM) substudy CL3-018.

Findings

Study Design

All participants included in the main study (CL3-018) were eligible for inclusion in the HBPM substudy. No additional inclusion/exclusion criteria were imposed. Participants who agreed to participate were provided with electronic blood pressure (BP) measuring devices (Omron model HEM-780E) for self-measurement. They were provided training, given a diary to record measurements, and instructed to take measurements on the same arm each time and at the same times every day. The Omron device automatically takes three BP measurements at one-minute intervals and stores them in its internal memory. Participants performed the home BP measurements in the sitting position in the morning between 6 a.m. and 10 a.m. (just before taking the study treatment), and in the evening between 6 p.m. and 10 p.m. (before the evening meal).

Data from the machine were uploaded at each visit by the investigator. The home systolic BP (HSBP) data were then transferred to a central database. A valid measurement constituted at least 12 measurements over the four days preceding or following the investigator visit. The substudy was conducted throughout the CL3-018 period, both during the double-blind (DB) phase and the open-label follow-up phase, for a total of 14 months. This summary will focus on the results obtained from the DB phase (month 0 to month 6).

All participants received the same treatment protocol regardless of their participation in the substudy.

Assessment

The primary objective of the substudy was to assess the efficacy of the perindopril arginine/amlodipine fixed-dose combination (FDC) strategy compared with the valsartan/amlodipine strategy on HBPM parameters at the end of the perindopril arginine/amlodipine FDC titration phase (month 3). This was primarily assessed through the mean HSBP over four days preceding the study visit.

Secondary objectives that were of relevance to this review were:

- to assess the efficacy of the perindopril arginine/amlodipine FDC strategy compared with the valsartan/amlodipine strategy in lowering home BP and derived parameters after the introduction of each higher dose as compared with the previous dose
- to assess the efficacy of the perindopril arginine/amlodipine FDC strategy as compared with the valsartan four-step strategy in lowering home BP at the end of the six-month DB period.

Statistical analysis for the study outcomes was performed over the following three population sets:

- randomized set HBPM (RS HBPM): participants randomized in the main study who participated in the HBPM, with at least one HBPM measurement performed at month 0 to serve as baseline
- full analysis set HBPM (FAS HBPM): participants randomized in the main study who were included in the HBPM substudy and received at least one dose of study treatment and had at least one valid HBPM at baseline, and one valid post-baseline HBPM of mean HSBP over the four days preceding the study visit during the first three months

- safety set 1 HBPM (SS1 HBPM): participants who received at least one dose of study treatment during the six-month DB period (month 0 to month 6) and performed at least one valid HBPM during the first six months.

Results

Of the 1,774 participants randomized in the main study, a total of 1,040 were enrolled in the substudy (RS HBPM population). Of those enrolled, 530 were in the perindopril arginine/amlodipine FDC group and 510 were in the valsartan/amlodipine group. The disposition of participants is presented in Table 40.

TABLE 40: PARTICIPANT DISPOSITION

	PERa/AMLO FDC Strategy	VAL/AMLO Strategy
Included set — randomized set HBPM	[redacted]	[redacted]
Lost to follow-up n (%)	[redacted]	[redacted]
Withdrawn due to, n (%)	[redacted]	[redacted]
AE n (%)	[redacted]	[redacted]
Non-medical reason n (%)	[redacted]	[redacted]
Other protocol withdrawal criteria n (%)	[redacted]	[redacted]
Protocol deviation n (%)	[redacted]	[redacted]
Completed until month 6 n (%)	[redacted]	[redacted]
Full analysis set (FAS HBPM)	[redacted]	[redacted]
Per-protocol set (PPS HBPM)	[redacted]	[redacted]
Safety set — HBPM	[redacted]	[redacted]

AE = adverse event; AMLO = amlodipine; FAS = full analysis set; FDC = fixed-dose combination; HBPM = home blood pressure monitoring; PERa = perindopril arginine; PPS = per-protocol set; VAL = valsartan.
Source: CL3-018-HBPM.[34]

The main demographic and baseline characteristics of the participants in the RS HBPM substudy population were similar across both groups, as summarized in Table 41.

TABLE 41: DEMOGRAPHICS OF THE RANDOMIZED SET HOME BLOOD PRESSURE MONITORING POPULATION

Characteristic	PERa/AMLO FDC Strategy Original Group (N = 530)	VAL/AMLO Strategy Original Group (N = 510)
Mean (SD) age (years)	[redacted]	[redacted]
Number of males (%)	[redacted]	[redacted]
Mean (SD) duration of hypertension in years	[redacted]	[redacted]
Number with stage 1 hypertension (%)	[redacted]	[redacted]
Number with stage 2 hypertension (%)	[redacted]	[redacted]
Mean (SD) BMI (kg/m^2)	[redacted]	[redacted]
Mean (SD) supine heart rate (BPM)	[redacted]	[redacted]
Mean (SD) office SBP (mm Hg)	[redacted]	[redacted]
Mean (SD) office DBP (mm Hg)	[redacted]	[redacted]

AMLO = amlodipine; BMI = body mass index; BPM = beats per minute; DBP = diastolic blood pressure; FDC = fixed-dose combination; PERa = perindopril arginine; SBP = systolic blood pressure; SD = standard deviation; VAL = valsartan.
Source: CL3-018-HBPM.[34]

A summary of the primary analysis of HSBP in the FAS from baseline to month 3 and month 6 is shown in Table 42.

TABLE 42: MEAN HSBP AND CHANGE FROM BASELINE TO MONTH 3 AND MONTH 6, FULL ANALYSIS SET

HSBP (mm Hg)	PERa/AMLO FDC Strategy Original Group (N = 431)	VAL/AMLO Strategy Original Group (N = 407)
Mean (SD) baseline	[redacted]	[redacted]
Mean (SD) end of month 3	[redacted]	[redacted]
Mean (SD) change from baseline to month 3	[redacted]	[redacted]
Estimated between-groups difference in adjusted mean change from baseline to month 3 (SE)	[redacted]	
P value	[redacted]	
Mean (SD) change from baseline to month 3	[redacted]	[redacted]
Estimated between-groups difference in adjusted mean change from baseline to month 6 (SE)	[redacted]	
P value	[redacted]	

AMLO = amlodipine; FDC = fixed-dose combination; HSBP = home systolic blood pressure; PERa = perindopril arginine; SD = standard deviation; SE = standard error; VAL = valsartan.
Source: CL3-018-HBPM.[34]

Table 43 shows a summary of the secondary analysis of changes of HSBP in the FAS with each titration step from baseline until month 6.

TABLE 43: EVALUATION OF STRATEGY EFFICIENCY AT EACH TITRATION STEP WITH MEAN HSBP IN THE FULL ANALYSIS SET HBPM POPULATION

Period	Strategy	Entry Mean (SD) mm Hg	End Mean (SD) mm Hg	Estimated Difference (SE) [95%CI] mm Hg	*P* Value
Baseline to month 1	PERa/AMLO FDC (n = 384)	[redacted]	[redacted]	[redacted]	[redacted]
	VAL/AMLO (n = 348)	[redacted]	[redacted]	[redacted]	[redacted]
Month 1 to month 2	PERa/AMLO FDC	[redacted]	[redacted]	[redacted]	[redacted]
	VAL/AMLO (n = 303)	[redacted]	[redacted]	[redacted]	[redacted]
Month 2 to month 3	PERa/AMLO FDC (n = 329)	[redacted]	[redacted]	[redacted]	[redacted]
	VAL/AMLO (n = 304)	[redacted]	[redacted]	[redacted]	[redacted]
Month 3 to month 6	PERa/AMLO FDC (n = 307)	[redacted]	[redacted]	[redacted]	[redacted]
	VAL/AMLO (n = 265)	[redacted]	[redacted]	[redacted]	[redacted]

AMLO = amlodipine; FDC = fixed-dose combination; HBPM = home blood pressure monitoring; HSBP = home systolic blood pressure; PERa = perindopril arginine; SD = standard deviation; SE = standard error; VAL = valsartan.
Source: CL3-018-HBPM.[34]

Summary

A total of 1,040 participants were enrolled in the HSBP substudy. There was no statistically significant difference in the efficacy outcome or change in HSBP between the perindopril arginine/amlodipine FDC strategy compared with the valsartan/amlodipine strategy at month three (the primary outcome); however, the perindopril arginine/amlodipine FDC strategy was statistically significantly superior to the valsartan/amlodipine strategy at month six (the secondary outcome). An analysis of the changes in HSBP at each titration step consistently showed statistically significant improvements at the end of the titration step in both strategies.

APPENDIX 8: SUMMARY OF EXTENSION PHASE OF STUDY CL3-018

Objective

To summarize the results of the long-term extension phase of study CL3-018.

Findings

Study Design

At month six of study CL3-018, participants entered an open-label follow-up period of eight months and began receiving only the perindopril arginine/amlodipine fixed-dose combination (FDC). Dosages were at the same titration step as the one reached at month six by participants originally treated in the perindopril arginine/amlodipine FDC group, or equivalent to the dosage given to participants originally treated in the valsartan/amlodipine group. As up-titration was not allowed in the extension phase, participants who did not achieve blood pressure (BP) control at the end of the original study's six-month period were not enrolled. Participants whose BP became uncontrolled at two consecutive visits during the extension phase were withdrawn from the study.

Assessment

The objective of the study was to describe the long-term safety of each dose of perindopril arginine/amlodipine FDC at the end of the open-label extension phase (month 14). Analysis was conducted using the safety set 2 (SS2) population. SS2 was defined as participants who received at least one dose of study treatment during any phase of the study (for participants stemming from the perindopril arginine/amlodipine FDC group in the double-blind [DB] period) or participants who received at least one dose of study treatment during the month six to month 14 open-label follow-up period (for participants stemming from the valsartan/amlodipine group).

The following criteria were used to assess safety in the open-label follow-up phase:

- treatment-emergent adverse events (TEAEs) occurring during the month 0 to month 14 period, according to the perindopril arginine/amlodipine FDC intake
- leg edema (as assessed by the investigators)
- clinically significant orthostatic hypotension evaluation, defined as a decline in systolic blood pressure (SBP) of ≥ 20 mm Hg and/or in diastolic blood pressure (DBP) of ≥ 10 mm Hg when moving from a supine to erect position
- clinically significant biochemical and hematological abnormalities, as assessed through a complete laboratory test and with abnormal measures reported for: sodium, potassium, calcium, creatinine, creatinine clearance, total protein, uric acid, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, fasting blood glucose, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, hemoglobin, hematocrit, and full blood cell counts
- vital signs and weight
- electrocardiogram (ECG) abnormalities.

Results

The SS2 population consisted of 1,554 participants. Among them, 1,239 (79.7%) remained in the study until month 14. Of those who completed the study, 653 were from the perindopril arginine/amlodipine FDC group (73.6% of participants were originally randomized to the perindopril arginine/amlodipine FDC group) and 586 were from the valsartan/amlodipine group (87.9% of participants were originally randomized into the valsartan/amlodipine group). The disposition of participants is presented in Table 44.

TABLE 44: PARTICIPANT DISPOSITION

	All Participants
Safety population 2, N	[redacted]
Withdrawn due to, n (%)	[redacted]
AE	[redacted]
Non-medical reason	[redacted]
Other protocol withdrawal criteria	[redacted]
Protocol deviation	[redacted]
Completed month 14, n (%)	[redacted]

AE = adverse event.
Source: CL3-018 M0-M14 Clinical Study Report.[35]

The main demographic and baseline characteristics of the SS2 population that entered the follow-up period were similar between groups, as shown in Table 45.

TABLE 45: DEMOGRAPHICS OF SAFETY SET 2 ANALYSIS POPULATION

Characteristic	PERa/AMLO FDC strategy (N = 887)	VAL/AMLO strategy (N = 667)
Mean (SD) age (years)	[redacted]	[redacted]
Number of males (%)	[redacted]	[redacted]
Mean (SD) duration of hypertension in years	[redacted]	[redacted]
Number with stage 1 hypertension (%)	[redacted]	[redacted]
Number with stage 2 hypertension (%)	[redacted]	[redacted]
Mean (SD) BMI (kg/m^2) at selection	[redacted]	[redacted]
Mean (SD) supine heart rate (BPM) at selection	[redacted]	[redacted]
Mean (SD) BMI (kg/m^2) at month 6	[redacted]	[redacted]
Mean (SD) supine heart rate (BPM) at month 6	[redacted]	[redacted]

AMLO = amlodipine; BMI = body mass index; BPM = beats per minute; FDC = fixed-dose combination; PERa = perindopril arginine; SD = standard deviation; VAL = valsartan.
Source: CL3-018 M0-M14 Clinical Study Report.[35]

Overall, from month 0 to month 14, participants had a mean exposure to perindopril arginine/amlodipine FDC of [redacted] days (standard deviation = [redacted]). Participants in the perindopril arginine/amlodipine FDC original group had a mean exposure of [redacted] days (standard deviation = [redacted]), while those who switched from the valsartan/amlodipine strategy had a mean exposure to perindopril arginine/amlodipine FDC of [redacted] days (standard deviation = [redacted]). Treatment compliance was calculated as the number of

capsules taken/to be taken multiplied by 100 from month 0 to month 14, and was a mean of [redacted] (standard deviation = [redacted]).

In the SS2 population, [redacted] participants ([redacted]) had [redacted] adverse events (AEs) during the overall study period. The results of the safety analysis are summarized in Table 46.

TABLE 46: SUMMARY OF SAFETY ANALYSIS RESULTS

		CL3-018 (14-Month Treatment Period)
Step 1: PERa 3.5 mg/ AMLO 2.5 mg FDC or VAL 80 mg (N = 994)	Participants with > 0 AEs, n (%)	[redacted]
	Most common AEs[a], n (%)	
	Peripheral edema	[redacted]
	Cough	[redacted]
	Nasopharyngitis	[redacted]
	Headache	[redacted]
	Hypertriglyceridemia	[redacted]
	Type 2 diabetes mellitus	[redacted]
	Hypercholesterolemia	[redacted]
	Dizziness	[redacted]
	Asthenia	[redacted]
	Back pain	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]
	Participants with AEs or SAEs that led to withdrawal, n (%)	[redacted]
	Number of deaths, n (%)	[redacted]
	Notable harms other than the most common AEs, n (%)	
	Orthostatic hypotension	[redacted]
	Hypotension	[redacted]
Step 2: PERa 7 mg/AMLO 5 mg FDC or VAL 160 mg (N = 1078)	Participants with > 0 AEs, n (%)	[redacted]
	Most common AEs n (%)	
	Peripheral edema	[redacted]
	Cough	[redacted]
	Nasopharyngitis	[redacted]
	Headache	[redacted]
	Hypertriglyceridemia	[redacted]
	Type 2 diabetes mellitus	[redacted]
	Hypercholesterolemia	[redacted]
	Dizziness	[redacted]
	Erectile dysfunction	[redacted]
	Hyperuricemia	[redacted]
	Back pain	[redacted]
	Gastroenteritis	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]
	Participants with AEs or SAEs that led to withdrawal,	[redacted]

		CL3-018 (14-Month Treatment Period)
	n (%)	
	Number of deaths, n (%)	[redacted]
	Notable harms other than the most common AEs, n (%)	
	Orthostatic hypotension	[redacted]
	Hypotension	[redacted]
Step 3: PERa 14 mg/ AMLO 10 mg FDC or VAL 160 mg/AMLO 5 mg FDC (not approved in Canada) (N = 695)	Participants with > 0 AEs, n (%)	[redacted]
	Most common AEs[a], n (%)	
	Peripheral edema	[redacted]
	Cough	[redacted]
	Nasopharyngitis	[redacted]
	Headache	[redacted]
	Hypertriglyceridemia	[redacted]
	Type 2 diabetes mellitus	[redacted]
	Hypercholesterolemia	[redacted]
	Dizziness	[redacted]
	Blood glucose increased	[redacted]
	Erectile dysfunction	[redacted]
	Back pain	[redacted]
	Gastroenteritis	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]
	Participants with AEs or SAEs that led to withdrawal, n (%)	[redacted]
	Number of deaths, n (%)	[redacted]
	Notable harms other than the most common AEs, n (%)	
	Orthostatic hypotension	[redacted]
	Hypotension	[redacted]
Step 4: PERa 14 mg/AMLO 10 mg FDC + IND 1.5 mg or VAL 160 mg/AMLO 10 mg FDC (not approved in Canada) (N = 202)	Participants with > 0 AEs, n (%)	[redacted]
	Most common AEs[a], n (%)	
	Peripheral edema	[redacted]
	Cough	[redacted]
	Nasopharyngitis	[redacted]
	Headache	[redacted]
	Hypertriglyceridemia	[redacted]
	Type 2 diabetes mellitus	[redacted]
	Hypercholesterolemia	[redacted]
	Dizziness	[redacted]
	Blood glucose increased	[redacted]
	Erectile dysfunction	[redacted]
	Hyperuricemia	[redacted]
	Asthenia	[redacted]
	Hypokalemia	[redacted]

		CL3-018 (14-Month Treatment Period)
	Back pain	[redacted]
	Participants with > 0 SAEs, n (%)	[redacted]
	Participants with AEs or SAEs that led to withdrawal, n (%)	[redacted]
	Number of deaths, n (%)	[redacted]
	Notable harms other than the most common AEs, n (%)	
	Orthostatic hypotension	[redacted]
	Hypotension	[redacted]

AE = adverse event; AMLO = amlodipine; FDC = fixed-dose combination; IND = indapamide; PERa = perindopril arginine; SAE = serious adverse event; VAL = valsartan.
Source: CL3-018 M0-M14 Clinical Study Report.[35]

Reported deaths were due to metastatic cancer in three cases, and suicide in one case. None were deemed to be related to treatment.

Summary

Efficacy outcomes were not measured in the open-label follow-up phase. Analysis of AEs and safety results over the 14-month study period were naturally higher than what was observed at the end of the initial DB phase. However, given the open-label, single-group study design, the interpretation of the results is limited to descriptive, non-comparative assessments. As such, the study design is unable to highlight the extent to which the treatment effects observed in the main study were maintained.

REFERENCES

1. Clinical study report: CL2-05985-005. 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 [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2012 Aug 2.
2. Clinical study report: X985400. 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 [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2013 Aug 30.
3. Clinical study report: CL3-05985-018 (M0-M6). Perindopril arginine/Amlodipine versus Valsartan/Amlodipine antihypertensive strategies: efficacy and safety in mild to moderate hypertensive patients. A randomised, double blind 6-month study followed by an 8-month open label long-term follow-up with Perindopril arginine/Amlodipine. [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2013 May 29.
4. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 9th ed. New York: McGraw-Hill Education Medical; 2014.
5. Hypertension [Internet]. Ottawa: Public Health Agency of Canada; 2013 Oct 7. [cited 2016 Jun 14]. Available from: http://www.phac-aspc.gc.ca/cd-mc/cvd-mcv/hypertension-eng.php
6. What is high blood pressure? [Internet]. Dallas (TX): American Heart Association; 2014. [cited 2016 Jun 14]. Available from: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/What-is-High-Blood-Pressure_UCM_301759_Article.jsp#.V2BG32f2b-c
7. GBD 2013 Risk Factors Collaborators, Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet [Internet]. 2015 Dec 5 [cited 2016 Jun 14];386(10010):2287-323. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4685753
8. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2016 May;32(5):569-88.
9. Viacoram[å] (perindopril arginine/amlodipine (as amlodipine besylate)) 3.5mg/2.5mg, 7mg/5mg, and 14mg/10mg tablets [product monograph]. Laval (QC): Servier Canada Inc.; 2016 Feb 17.
10. Health Canada reviewer's report: Viacoram (perindopril arginine and amlodipine) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2016 Jan 22.
11. NDA approval letter (NDA205003). In: Prestalia (perindopril arginine and amlodipine) 3.5/2.5 mg, 7/5 mg, and 14/10 mg tablets. Company: Symplmed Pharmaceuticals, LLC Application no.:205003. Approval date: 01/21/2015 [Internet]. Silver Spring (MD): Food and Drug Administration, Department of Health and Human Services; 2015 [cited 2016 Jun 24]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205003Orig1s000ltr.pdf

12. Transparency committee opinion: Coveram (perindopril arginine/amlodipine) 5mg-5mg, 5mg-10mg, 10mg-5mg and 10mg-10mg [Internet]. [Sainte-Denis]: Haute Autorité de santé; 2009 Jul 22. [cited 2016 Jun 23]. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-12/coveram_ct_6938.pdf

13. Perindopril arginine with amlodipine besylate, tablet, 5mg-5mg, 5mg-10mg, 10mg-5mg and 10mg-10mg, Coveram® [Internet]. [Canberra]: Pharmaceutical Benefits Scheme; 2010 Mar. [cited 2016 Jun 23]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2010-03/pbac-psd-perindopril-mar10

14. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2016 [cited 2016 Jun 14]. Available from: https://www.e-therapeutics.ca Subscription required.

15. Laurent S, Parati G, Chazova I, Sirenko Y, Erglis A, Laucevicius A, et al. Randomized evaluation of a novel, fixed-dose combination of perindopril 3.5 mg/amlodipine 2.5 mg as a first-step treatment in hypertension. J Hypertens. 2015 Mar;33(3):653-61.

16. Elliott WJ, Whitmore J, Feldstein JD, Bakris GL. Efficacy and safety of perindopril arginine + amlodipine in hypertension. J Am Soc Hypertens. 2015 Apr;9(4):266-74.

17. CDR submission: Viacoram® (perindopril arginine/amlodipine (as amlodipine besylate)) 3.5mg/2.5mg, 7mg/5mg, and 14mg/10mg tablets. Company: Servier Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Laval (QC): Servier Canada Inc.; 2016 Apr 29.

18. Mancia G, Asmar R, Amodeo C, Mourad JJ, Taddei S, Gamba MA, et al. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. J Hypertens. 2015 Feb;33(2):401-11.

19. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on clinical investigation of medicinal products in the treatment of hypertension [Internet]. London: European Agency for the Evaluation of Medicinal Products; 1998 Nov 19. [cited 2016 Jun 30]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173290.pdf

20. Dmitrienko A, Bretz F, Westfall PH, Troendle J, Wiens BL, Tamhane AC, et al. Multiple testing methodology. In: Dmitrienko A, Tamhane AC, Bretz F, editors. Multiple testing problems in pharmaceutical statistics [Internet]. New York: CRC Press; 2009 Dec [cited 2016 Jun 30]. Chapter 2. p. 35-98. (Chapman & Hall/CRC Biostatistics Series). Available from: https://web.njit.edu/~wguo/Math654_2012/DTB_Chapter2.pdf

21. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117.

22. Kizilirmak P, Ongen Z. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. J Hypertens. 2015 May;33(5):1114-5.

23. Mancia G. Comparison of single-pill strategies first line in hypertension: perindopril/amlodipine versus valsartan/amlodipine. J Hypertens. 2015 May;33(5):1115-6.

24. Kaplan NM. Cardiovascular risks of hypertension. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 [cited 2016 Jul 11]. Available from: www.uptodate.com Subscription required.

25. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016 Mar 5;387(10022):957-67.

26. Wilkins K, Campbell NR, Joffres MR, McAlister FA, Nichol M, Quach S, et al. Blood pressure in Canadian adults. Health Rep. 2010 Mar;21(1):37-46.

27. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med [Internet]. 2015 Nov 26 [cited 2016 Jun 30];373(22):2103-16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4689591

28. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension. 2009 Apr;53(4):646-53.

29. Korneeva O, Drapkina O. 2A.03: Diastolic function in obese hypertensive patients using different fixed combination with ACE inhibitor and antagonist calcium [abstract]. J Hypertens. 2015 Jun;33(Suppl 1):e19. (Presented at 11th APCH in conjunction with 9th InaSH Scientific Meeting; 2015 Jun 4 - 7; Bali, Indonesia).

30. Poulter NR, Whitehouse A, O'Brien E, Sever PS. PP.07.17 A randomized, double-blind study of the efficacy and safety of new first-line perindopril/amlodipine combinations [abstract]. J Hypertens [Internet]. 2015 [cited 2016 Aug 29];33(Suppl 1):e194. Available from: http://journals.lww.com/jhypertension/Abstract/2015/06001/PP_07_17___A_RANDOMIZED,_DOUBLE_BLIND_STUDY_OF_THE.580.aspx?trendmd-shared=0 (Presented at 25th European Meeting on Hypertension and Cardiovascular Protection; 2015 Jun 12-15; Milan, Italy).

31. Clinical study report: CL3-05985-006 [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2013 May 21.

32. Clinical study report: CL2-05985-005-ABPM. 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 [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2012 Jul 30.

33. Clinical study report: CL3-05985-006 ABPM [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2013 Apr 26.

34. Clinical study report: CL3-05985-018 (M0-M6) HBPM. Perindopril arginine/Amlodipine versus Valsartan/Amlodipine antihypertensive strategies: efficacy and safety in mild to moderate hypertensive patients. A randomised, double blind 6-month study followed by an 8-month open label long-term follow-up with Perindopril arginine/Amlodipine. [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2013 Apr 22.

35. Clinical study report: CL3-05985-018 (M0-M14) [**CONFIDENTIAL** internal manufacturer's report]. [Laval (QC)]: [Servier Canada Inc.]; 2013 Sep 10.