SYNOPSIS

Name of the Sponsor/Company: Krka, tovarna zdravil, d.d., Novo mesto.

Names of Finished Products:

Trade names of finished products vary depending on the country and strength of the product.

Perindopril/amlodipine/indapamide single-pill combination, tested in this study, appears in following trade names, in the countries where this study was conducted: Co-Amlessa, Co-Dalneva, Co-Dalnessa and Ко-Дальнева and Amlewel. Throughout this document, it is refered to as Co-Amlessa. Perindopril/amlodipine single-pill combination, tested in this study, appears in following trade names, in the countries where this study was conducted: Amlessa, Dalneva, Dalnessa and Дальнева. Throughout this document, it is refered to as Amlessa.

Names of Active Ingredients: perindopril (tert-butylamine perindoprilate), amlodipine (amlodipine besylate), indapamide

Title of Study: Fixed-Dose Combination of Perindopril/Amlodipine (Amlessa®) and Fixed-Dose Combination of Perindopril/Indapamide/Amlodipine (Co-Amlessa®) - Contribution to Management in newly diagnosed and uncontrolled hypertensive patients (PRECIOUS study)

Protocol no.: KCT 06/2017

Investigators and study centres:

Clinical study was conducted in seven countries: Armenia, Croatia, Hungary, Poland, Russian Federation, Serbia and Slovenia. Study coordinating investigator was Assist. Prof. Jana Brguljan Hitij, MD, PhD, Division of Hypertension, Department of Internal Medicine, University Medical Centre Ljubljana, Vodnikova cesta 62, 1000 Ljubljana, Slovenia. Thirty-nine study sites have been initiated to participate in this study.

Country	Number of study sites	Names of principal investigators
Croatia	8	Prof. Bojan Jelaković, MD, PhD; Assoc. Prof. Ivan Bubić, MD, PhD; Zoran Miovski, MD; Ljiljana Fodor, MD, PhD; Tonko Gulin, MD, PhD; Prof. Mislav Vrsalović, MD, PhD; Damir Raljević, MD; Assoc. Prof. Goran Krstačić, MD, PhD; Stjepan Kranjčević, MD, MSc
Hungary	3	Péter Vajer MD, PhD, Ferenc Tamás MD, Péter Torzsa MD, PhD
Poland	8	Prof. Zbigniew Gaciong, MD, PhD; Włodzimierz Frasunkiewicz, MD; Assoc. Prof. Marek Rajzer, MD, PhD; Łukasz Wiśniowski, MD, PhD; Piotr Abramczyk, MD PhD; Jakub Sochacki, MD; Piotr Gryglas, MD PhD; Krzysztof Kincel, MD
Slovenia	9	Prim. Assist. Robert Marčun, MD, PhD; Tomaž Šavli, MD, Assist.; Mateja Verdinek, MD; Prim. Tatjana Golob Gulič, MD, Assist.; Gordana Dreisiebner, MD; Prim Dorjan Marušič, MD, MSc; Renata Verboten Kopriva, MD; Nataša Gorkič, MD; Zorica Ćuković, MD
Armenia	2	Prof. Parounak Zelveain, MD, PhD; Samvel Hayrumyan, MD
Serbia	4	Prof. Dragan Simić, MD, PhD; Assist. Prof. Maja Stefanović, MD PhD; Assist. Prof. Tomislav Kostić, MD, PhD; Slavica Radovanović, MD, PhD
Russian Federation	5	Blinova Natalia Vladimirovna, MD, PhD; Sviryaev Uriy Vladimirovich, MD, PhD; Nedogoda Sergey Vladimirovich, MD, PhD; Prof. Kislyak Oksana Andreevna, MD, PhD; Prof. Barbarash Olga Leonidovna, MD, PhD

Studies period (years): 1.7 years **Date of first enrolment:** 12 February 2018 **Date of last completed:** 27 September 2019	**Phase of development:** Phase III/IV

Objectives:

The objectives of this trial were to evaluate the effect of therapy with Amlessa and Co-Amlessa on the blood pressure reduction and to evaluate the safety of the therapy in patients with essential AH who were antihypertensive treatment naïve and in patients with uncontrolled hypertension with previous mono, dual or triple antihypertensive treatment.

Methodology:

This study was an interventional, open-label, prospective, international, multi-centre, phase IIIb/IV clinical study. Study started with an initial screening visit (visit -1), to assess patient eligibility. One day later patients underwent study baseline visit (visit 1), during which baseline assessments were performed and/or completed. Eligible patients were assigned to treatment with one of the two study medication (Amlessa and Co-Amlessa arm), based on their previous antihypertensive therapy:

- antihypertensive medication naïve patients and patients on previous antihypertensive monotherapy were assigned to Amlessa arm,
- patients on previous dual antihypertensive therapy (including perindopril/amlodipine) and patients on previous triple antihypertensive therapy (other than perindopril/indapamid/amlodipine) were assigned to Co-Amlessa arm,
- patients on previous dual antihypertensive therapy (other than perindopril/amlodipine) were allocated to either Amlessa or Co-Amlessa arm at the investigators discretion, targeting the allocation ratio of 1:1.

Patients started taking the allocated study medication on day of the visit 1. The total active treatment duration was 16 weeks, divided into four treatment periods. The main four follow-up visits were performed at:

- visit 2/week 4 (following completion of first treatment period),
- visit 3/week 8 (following completion of second treatment period),
- visit 4/week 12 (following completion of third treatment period) and
- visit 5/week 16; final study visit (following completion of fourth treatment period).

At each of the three follow-up visits: week 4, week 8 and week 12, patient office blood pressure (BP) was measured and if normal office blood pressure (NBP) was achieved, the treatment with the study medication prescribed for the previous treatment period was continued. If NBP was not achieved at a particular follow-up visit (either visit 2, visit 3 or visit 4), study medication dosage was increased at that visit, in the following manner:

Amlessa Arm: Amlessa 4mg/5mg (initial therapy) → Amlessa 8mg/5mg → Amlessa 8mg/10mg → Co-Amlessa 8mg/10mg/2.5mg

Co-Amlessa Arm: Co-Amlessa 4mg/5mg/1.25mg (initial therapy) → Co-Amlessa 8mg/5mg/2.5mg → Co-Amlessa 8mg/10mg/2.5mg → end of study no further escalation of study medication dosage

NBP was defined as SBP < 140 mmHg and DBP < 90 mmHg; patients with type 2 diabetes mellitus: SBP < 140 mmHg and DBP < 85 mmHg. Assessments in this study included office BP and heart rate (HR) measurements, electrocardiogram (ECG), clinical laboratory tests (including hematology, lipids, biochemistry and liver function tests) as well as ambulatory blood pressure monitoring (ABPM). Completion of all the procedures at visit 5 determined the end of the patient's involvement in this clinical study.

Number of patients (planned and analysed):

It was planned that a total of 510 patients would conclude the efficacy assessments and a per-protocol population of 450 patients was planned. To allow for the estimated drop-out rate, up to 570 patients were expected to be screened.

Of the 572 subjects who were screened, 471 were assigned to study treatment. 461 patients were analysed for main safety endpoints. A total of 440 patients provided sufficient efficacy data for inclusion to Full Analyses Set (FAS).

A total of 276 patients were included in Per Protocol Set (PPS). FAS population was used as the main population for the assessment of study efficacy endpoints.

Diagnosis and main criteria for inclusion:

Men and women aged ≥ 18 years, able to adhere to study protocol, who have provided written informed consent were eligible for this study. Patients with essential arterial hypertension with entry office blood pressures as defined below were eligible:

- antihypertensive treatment naïve patients with entry SBP ≥150 mmHg AND/OR DBP ≥ 95 mmHg (SBP ≥ 150 AND/OR DBP ≥ 90 mmHg for patients with type 2 diabetes mellitus)
- uncontrolled patients on antihypertensive monotherapy, dual or triple antihypertensive therapy with entry SBP ≥140 mmHg AND/OR DBP ≥ 90 mmHg (SBP ≥ 140 AND/OR DBP ≥ 85 mmHg for patients with type 2 diabetes mellitus)

Test product, dose and mode of administration, batch number:

- **Amlessa 4 mg/5 mg** tablets. Each tablet contains 4 mg perindopril tert-butylamine and 5 mg amlodipine (as amlodipine besilate). Oral use. *Batch numbers: D62511, D60766, D62335, D69274, D62389, D66122, D67749, D62334, 86351017.*
- **Amlessa 8 mg/5 mg** tablets. Each tablet contains 8 mg perindopril tert-butylamine and 5 mg amlodipine (as amlodipine besilate). Oral use. *Batch numbers: NE5751, NE3187, NE6003, NF5899, NE6043, NF1430, NF1435, NE6138, 86071017.*
- **Amlessa 8 mg/10 mg** tablets. Each tablet contains 8 mg perindopril tert-butylamine and 10 mg amlodipine (as amlodipine besilate). Oral use. *Batch numbers: NE5836, NE3648, NE6758, NF5079, NE3526, NF1479, NF3368, NE6659, 86041017.*
- **Co-Amlessa 4 mg/5 mg/1.25 mg** tablets. Each tablet contains 4 mg perindopril tert-butylamine, 5 mg amlodipine (as amlodipine besylate) and 1.25 mg indapamide. Oral use. *Batch numbers: NE6118, NE3414, NE6187, NF7475, NE6120, NE6119, NF7705, NE6055, 84720917.*
- **Co-Amlessa 8 mg/5 mg/2.5 mg** tablets. Each tablet contains 8 mg perindopril tert-butylamine, 5 mg amlodipine (as amlodipine besylate) and 2.5 mg indapamide. Oral use. *Batch numbers: NE7087, NE3593, NE6164, NF7754, NE6123, NE6168, NF1890, NE6021, 86891017.*

  Co-Amlessa 8 mg/10 mg/2.5 mg tablets. Each tablet contains 8 mg perindopril tert-butylamine, 10 mg amlodipine (as amlodipine besylate) and 2.5 mg indapamide. Oral use. *Batch numbers: NE5905, NE3101, NE5708, NF8009, NE5662, NE6833, NF2118, NE5704, 84580917*.

Duration of treatment:

The total active treatment duration was 16 weeks, with maximal allowed prolongation of three additional days per each active treatment period (in total up to 12 days) due to possible unpredicted causes for the delay in the follow-up visits.

Reference therapy, dose and mode of administration, batch number:

Not applicable. This study was open-label, non-comparative and un-controlled.

Criteria for evaluation:

Efficacy:

The following parameters were used to evaluate efficacy: office BP were performed at each study visit (representing primary and key secondary efficacy endpoint data; patient`s mean seated office measured SBP and DBP over the three consecutive BP measurements). ABPM was performed at baseline and visit 5 (representing secondary efficacy endpoint data, including: average 24h SBP and DBP, average awake-time SBP and DBP, average sleep-time SBP and DBP, average 24h central systolic pressure, average 24h pulse wave velocity [PWV]). Other ABPM efficacy parameters collected average 24h aortic augmentation index.

Safety:

The following parameters were used to evaluate safety: adverse events (AEs) were recorded and evaluated throughout the study and up to visit 5. Clinical laboratory tests were performed: hematology at visit 1 and 5, biochemistry and liver function tests at all study visits, except visit 4. Vital signs (HR, standing office BP) were performed at each study visits, while ECG was performed at screening only. Standard physical examinations were performed at screening and visit 5.

Statistical methods:

The efficacy analysis was performed on FAS and PPS, with the FAS as the primary analysis set. FAS was defined as the set of all screened patients who have received at least one dose of the study medication and have both baseline value and at least one post-baseline value of both SBP and DBP. PPS was defined as all subjects in the FAS who received any amount of study medication and have no important protocol deviations, have received the study-directed treatment, and have all assessments for all efficacy endpoints during the study.

The inferential part of statistical analysis was based on two-sided confidence intervals. Two-sided "equal-tails" Clopper-Pearson exact 95%-confidence intervals were calculated to estimate the population proportion of patients meeting a particular target BP or target BP/PWV decrease endpoints. To evaluate endpoints related to mean absolute and relative baseline to visits differences in office BP and ABPM BPs, the standard asymptotic 95%-confidence interval based on the normal (»z«-) distribution was employed throughout. Symmetrically, to test the null-hypothesis of zero mean absolute or mean relative difference, the standard two-tailed z-test with the corresponding asymptotic p-value was employed.

Summary statistics consisted of number of patients/observations, frequencies and corresponding percentages for categorical variables. The primary method of imputation of missing data was Last Observation Carried Forward (LOCF) approach, while worst-case (non-responder [NR]) imputation approach was the primary imputation method for individual efficacy endpoints where no post-baseline assessment, except visit 5, was performed (efficacy endpoints related to ABPM). NR data imputation method implies substitution of missing data with the value that represents the worst possible outcome; in terms of this study NR imputation meant that patient was not counted towards the number of patients achieving the target BP or target BP/PWV decrease.

Subject Disposition and Demography:

The number of patients treated, completed, discontinued from the study and analyzed, are summarized for each treatment arm in the table below.

	Amlessa Arm (no. patients)	**Co-Amlessa Arm (no. patients)**	**All patients (no. patients)**
Assigned to treatment (overall)	270	201	471
Assigned to treatment (FAS)	251	189	440
Completed (FAS)	230	180	410
Discontinued (FAS)	21	9	30
Reason: AE (FAS)	10	4	14
Other reasons (FAS)	11	5	16
Analyzed for efficacy			
FAS	251	189	440
PPS	160	116	276
Analyzed for AEs	265	196	461

In FAS, mean age was 53.7 ± 12.3 years and mean BMI was 30.6 ± 4.9 kg/m2. Notably more male (63.4%) than female (36.6%) patients were recruited to this study and included in FAS. At baseline, majority of patients in FAS had hypertension classified as grade 2 (45.5%) and grade 1 (43.2%). Baseline mean office seated SBP in FAS was

157.0 ± 11.7 mmHg and baseline DBP was 98.1 ± 8.7, with no major difference in mean baseline office seated SBP and DBP between Amlessa and Co-Amlessa arm. In Amlessa arm, 52.2% of patients were antihypertensive treatment-naïve whereas in Co-Amlessa arm, patients have been switched to study medication from either previous dual (78.3%) or triple (21.7%) antihypertensive therapy.

Efficacy Results:

Office NBP (blood pressure target) was defined as office SBP < 140 mmHg and office DBP < 90 mmHg; patients with type 2 diabetes mellitus: office SBP < 140 mmHg and office DBP < 85 mmHg.

Primary efficacy endpoint

Proportion of patients reaching normal blood pressure (NBP) at visit 5 by Treatment Arm and Overall in FAS (LOCF imputation) [95% CI for population proportion, lower and upper CI]

Patients reaching NBP at Visit 5	**Amlessa (n=251)**	**Co-Amlessa (n=189)**	**FAS patients (n=440)**
Proportion	77.7%	82.5%	79.8%
95% CI	[72.0%,82.7%]	[76.4%,87.7%]	[75.7%,83.4%]

Secondary efficacy endpoints:

1. Proportion of patients reaching NBP at visit 2, visit 3 and visit 4 by Treatment Arm and Overall in FAS (LOCF imputation) [95% CI for population proportion, lower and upper CI]

Patients reaching NBP at given visit		**Amlessa (n=251)**	**Co-Amlessa (n=189)**	**FAS patients (n=440)**
Proportion; 95% CI	Visit 2	49.4%; [43.1%,55.8%]	36.0%; [29.1%,43.3%]	43.6%; [38.9%,48.4%]
	Visit 3	64.5%; [58.3%,70.5%]	63.0%; [55.7%,69.9%]	63.9%; [59.2%,68.4%]
	Visit 4	75.3%; [69.5%,80.5%]	81.5%; [75.2%,86.7%]	78.0%; [73.8%,81.7%]

2. Mean absolute (mmHg) and relative (%) change from baseline in office SBP and DBP after 4, 8, 12 and 16 weeks by Treatment and Overall in FAS (LOCF imputation) [95% CI for population means, lower and upper CI]

Amlessa Arm (n=251)		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
SBP	Mean abs. change from baseline	-17.4	-21.3	-23.8	-27.1
	95% CI	[-19.1,-15.6]	[-23,-19.6]	[-25.4,-22.2]	[-28.6,-25.5]
	Mean rel. change from baseline	-10.8%	-13.4%	-14.9%	-17%
	95% CI	[-11.9%,-9.8%]	[-14.4%,-12.3%]	[-15.9%,-14%]	[-18%,-16.1%]
DBP	Mean abs. change from baseline	-11	-13.4	-15.2	-16.7
	95% CI	[-12.2,-9.8]	[-14.5,-12.2]	[-16.3,-14.1]	[-17.7,-15.6]
	Mean rel. change from baseline	-10.9%	-13.2%	-15.1%	-16.6%
	95% CI	[-12.1%,-9.7%]	[-14.3%,-12.1%]	[-16.1%,-14%]	[-17.6%,-15.6%]

Co-Amlessa Arm (n=189)		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
SBP	Mean abs. change from baseline	-14.5	-21.2	-25.8	-29
	95% CI	[-16.7,-12.3]	[-23.5,-18.9]	[-27.9,-23.8]	[-31.2,-26.7]
	Mean rel. change from baseline	-8.8%	-13.1%	-16%	-18%
	95% CI	[-10.1%,-7.5%]	[-14.4%,-11.8%]	[-17.1%,-14.8%]	[-19.3%,-16.7%]
DBP	Mean abs. change from baseline	-8.9	-13.3	-15.1	-16.7
	95% CI	[-10.4,-7.3]	[-14.8,-11.7]	[-16.5,-13.7]	[-18.2,-15.1]
	Mean rel. change from baseline	-8.6%	-13.1%	-14.9%	-16.6%
	95% CI	[-10.1%,-7.1%]	[-14.5%,-11.6%]	[-16.2%,-13.6%]	[-18%,-15.2%]

FAS patients (n=440)		Visit 2	Visit 3	Visit 4	Visit 5
SBP	Mean abs. change from baseline	-16.1	-21.3	-24.7	-27.9
	95% CI	[-17.5,-14.8]	[-22.6,-19.9]	[-25.9,-23.4]	[-29.2,-26.5]
	Mean rel. change from baseline	-10%	-13.2%	-15.4%	-17.4%
	95% CI	[-10.8%,-9.2%]	[-14.1%,-12.4%]	[-16.1%,-14.6%]	[-18.2%,-16.7%]
DBP	Mean abs. change from baseline	-10.1	-13.3	-15.1	-16.7
	95% CI	[-11.1,-9.1]	[-14.2,-12.4]	[-16,-14.3]	[-17.6,-15.8]
	Mean rel. change from baseline	-9.9%	-13.1%	-15%	-16.6%
	95% CI	[-10.8%,-8.9%]	[-14%,-12.3%]	[-15.8%,-14.2%]	[-17.4%,-15.8%]

3. Mean absolute (mmHg) and relative (%) changes from baseline to 16 weeks in average 24-hour SBP and DBP, average awake time SBP and DBP, and average sleep time SBP and DBP by Treatment and Overall in FAS (LOCF imputation) [95% CI for population means, lower and upper CI]

		Amlessa Arm	Co-Amlessa Arm	FAS patients
Average 24h SBP (mmHg)	**Change from baseline to Visit 5**	**(n=251)**	**(n=189)**	**(n=440)**
	Mean absolute change	-16.3	-21.7	-18.6
	95% CI	[-17.7,-14.8]	[-23.7,-19.7]	[-19.8,-17.4]
	Mean relative change	-11.2%	-14.4%	-12.6%
	95% CI	[-12.1%,-10.2%]	[-15.6%,-13.2%]	[-13.3%,-11.8%]
Average 24h DBP (mmHg)	**Change from baseline to Visit 5**	**(n=251)**	**(n=189)**	**(n=440)**
	Mean absolute change	-10.9	-13.9	-12.2
	95% CI	[-12,-9.8]	[-15.1,-12.6]	[-13,-11.4]
	Mean relative change	-11.4%	-14.5%	-12.8%
	95% CI	[-12.5%,-10.3%]	[-15.7%,-13.3%]	[-13.6%,-11.9%]
Average awake time SBP (mmHg)	**Change from baseline to Visit 5**	**(n=251)**	**(n=189)**	**(n=440)**
	Mean absolute change	-16.8	-22.8	-19.4
	95% CI	[-18.4,-15.3]	[-24.9,-20.7]	[-20.7,-18.1]
	Mean relative change	-11.3%	-14.8%	-12.8%
	95% CI	[-12.3%,-10.3%]	[-16.1%,-13.5%]	[-13.6%,-12%]
Average awake time DBP (mmHg)	**Change from baseline to Visit 5**	**(n=251)**	**(n=189)**	**(n=440)**
	Mean absolute change	-11	-14.5	-12.5
	95% CI	[-12.1,-9.8]	[-15.8,-13.2]	[-13.4,-11.6]
	Mean relative change	-11.1%	-14.8%	-12.7%
	95% CI	[-12.2%,-10%]	[-16%,-13.5%]	[-13.5%,-11.8%]
Average sleep time SBP (mmHg)	**Change from baseline to Visit 5**	**(n=251)**	**(n=189)**	**(n=440)**
	Mean absolute change	-14.5	-18.6	-16.3
	95% CI	[-16.3,-12.7]	[-20.8,-16.5]	[-17.6,-14.9]
	Mean relative change	-10.4%	-13%	-11.5%
	95% CI	[-11.6%,-9.1%]	[-14.4%,-11.5%]	[-12.4%,-10.5%]
Average sleep time DBP (mmHg)	**Change from baseline to Visit 5**	**(n=251)**	**(n=189)**	**(n=440)**
	Mean absolute change	-10.3	-11.8	-11
	95% CI	[-11.6,-9.1]	[-13.3,-10.4]	[-11.9,-10]
	Mean relative change	-11.5%	-13.2%	-12.2%
	95% CI	[-12.9%,-10.2%]	[-14.8%,-11.6%]	[-13.3%,-11.2%]

4. Proportion of patients reaching normal average 24h ABPM SBP and DBP, normal average awake time SBP and DBP and normal average sleep time SBP and DBP at 16 weeks by Treatment and Overall in FAS [95% CI for population proportion, lower and upper CI]

Normal average 24h ABPM was defined as average 24h SBP <130 mmHg and average 24h DBP < 80 mmHg, Normal average awake time was defined as average awake time SBP <135 mmHg and average awake time DBP < 85 mmHg. Normal average sleep time was defined as average sleep time SBP <120 mmHg and average sleep time DBP < 70 mmHg.

Note: NR imputation of missing data was used in this endpoint evaluation.

Patients reaching normal average BP at Visit 5		Amlessa	Co-Amlessa	FAS patients
Average 24h SBP and DBP	**n**	**251**	**189**	**440**
	Proportion 95% CI	32.3% [26.5%,38.4%]	42.9% [35.7%,50.2%]	36.8% [32.3%,41.5%]
Average awake time SBP and DBP	**n**	**251**	**189**	**440**
	Proportion 95% CI	44.2% [38.0%,50.6%]	55.0% [47.6%,62.3%]	48.9% [44.1%,53.6%]
Average sleep time SBP and DBP	**n**	**251**	**189**	**440**
	Proportion 95% CI	25.1% [19.9%,30.9%]	26.5% [20.3%,33.3%]	25.7% [21.7%,30.0%]

5. Proportion of patients reaching a reduction of office SBP by at least 20 mmHg or DBP by at least 10 mmHg at 16 weeks as compared to baseline measurements by treatment and overall in FAS (LOCF imputation) [95% CI for population proportion, lower and upper CI]

Patients reaching a reduction of office SBP by at least 20 mmHg or office DBP by at least 10 mmHg from baseline to Visit 5	Amlessa (n=251)	Co-Amlessa (n=189)	FAS patients (n=440)
Proportion 95% CI	90.4% [86.1%,93.8%]	87.8% [82.3%,92.1%]	89.3% [86.0%,92.0%]

6. Proportion of patients reaching a reduction of central (systolic) blood pressure below 120 mmHg at 16 weeks in FAS [95% CI for population proportion, lower and upper CI]

Note: NR imputation of missing data was used in this endpoint evaluation.

Patients with central (systolic) BP < 120mmHg at Visit 5		Amlessa	Co-Amlessa	FAS patients
	n	**251**	**189**	**440**
	Proportion 95% CI	62.5% [56.2%,68.6%]	67.7% [60.6%,74.3%]	64.8% [60.1%,69.2%]

7. Proportion of patients reaching a reduction of pulse wave velocity for at least 0.5 m/s at 16 weeks as compared to baseline measurements by treatment and overall in FAS [95% CI for population proportion, lower and upper CI]

Note: NR imputation of missing data was used in this endpoint evaluation.

Patients reaching a reduction of PWV for at least 0.5m/s from baseline to Visit 5		Amlessa	Co-Amlessa	FAS patients
	n	**251**	**189**	**440**
	Proportion 95% CI	53.0% [46.6%,59.3%]	64.0% [56.7%,70.9%]	57.7% [53.0%,62.4%]

Exploratory efficacy analysis:

Proportion of patients reaching normal average 24h ABPM SBP and separately DBP, normal average awake time SBP and separately DBP and normal average sleep time SBP and separately DBP at week 16 by Treatment and Overall in FAS [95% CI for population proportion, lower and upper CI]

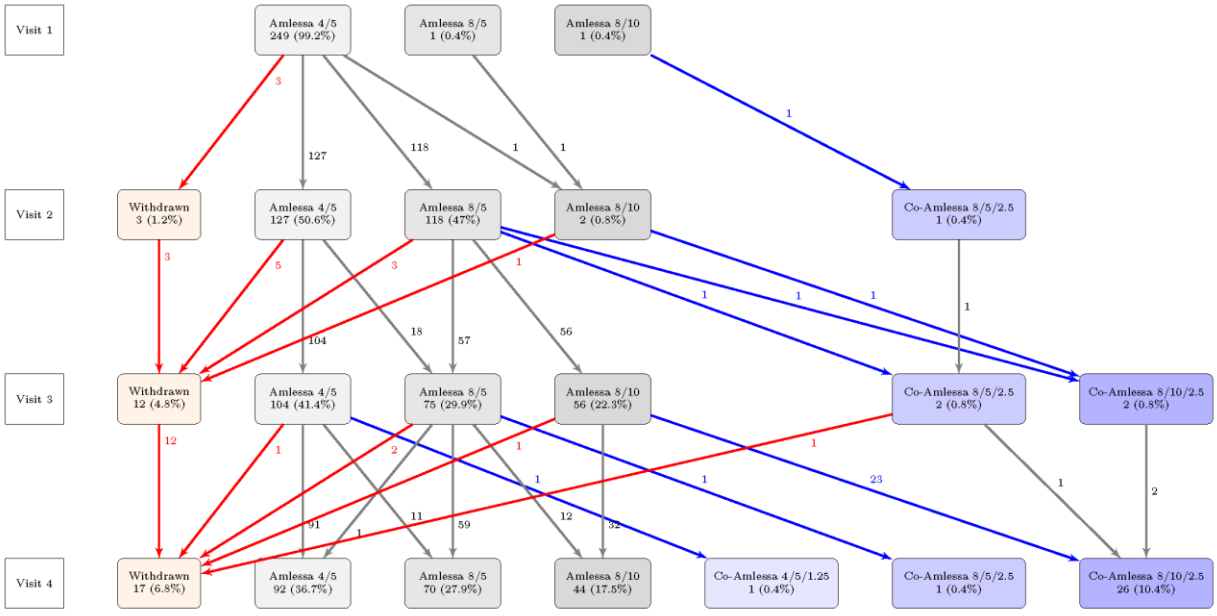
Note: NR imputation of missing data was used in this endpoint evaluation.

Patients reaching normal average BP at Visit 5		Amlessa	Co-Amlessa	FAS patients
Average 24h SBP < 130	**n**	**251**	**189**	**440**

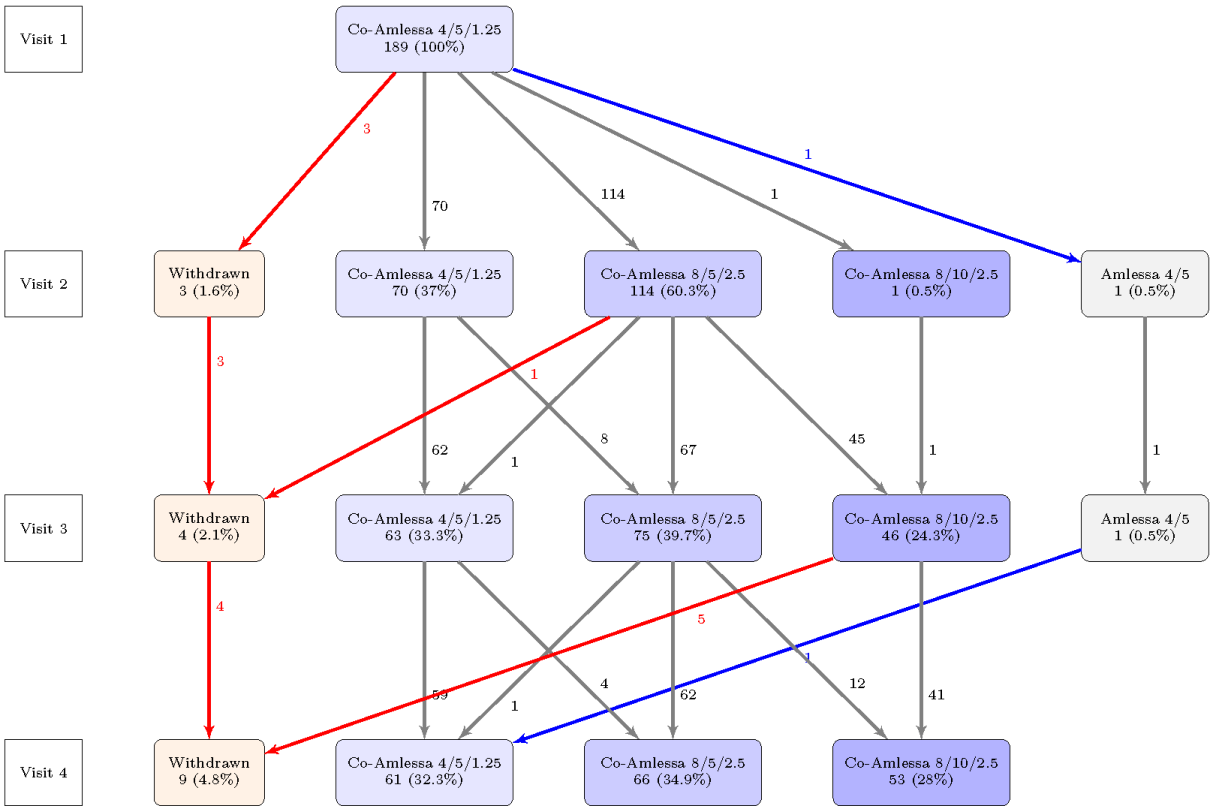
	Proportion 95% CI	64.9% [58.7%,70.8%]	67.7% [60.6%,74.3%]	66.1% [61.5%,70.6%]
Average 24h DBP < 80	**n**	**251**	**189**	**440**
	Proportion 95% CI	37.5% [31.4%,43.8%]	49.2% [41.9%,56.6%]	42.5% [37.8%,47.3%]
Average awake time SBP < 135	**n**	**251**	**189**	**440**
	Proportion 95% CI	67.7% [61.6%,73.5%]	74.6% [67.8%,80.6%]	70.7% [66.2%,74.9%]
Average awake time DBP < 80	**n**	**251**	**189**	**440**
	Proportion 95% CI	49.4% [43.1%,55.8%]	63.0% [55.7%,69.9%]	55.2% [50.4%,59.9%]
Average sleep time SBP < 120	**n**	**251**	**189**	**440**
	Proportion 95% CI	55.0% [48.6%,61.2%]	54.5% [47.1%,61.7%]	54.8% [50.0%,59.5%]
Average sleep time DBP < 70	**n**	**251**	**189**	**440**
	Proportion 95% CI	29.1% [23.5%,35.1%]	31.2% [24.7%,38.3%]	30.0% [25.8%,34.5%]

Treatment Pathways

In FAS analysis set 249 patients received Amlessa 4/5 mg at visit 1. Two patients have been misallocated to treatment at Visit 1 (one received Amlessa 8/5 mg, the other received Amlessa 8/10 mg). In Amlessa arm the two major up-titrations steps were at Visit 2 and (to a lesser extent) Visit 3, whereas at last possible up-titration step in this study (Visit 4) 182 of 251 (72.5%) Amlessa arm patients have maintained their previously dispensed medication dosage.



In FAS analysis set 189 patients received Co-Amlessa 4/5/1.25 mg at visit 1. In Co-Amlessa arm the two major up-titrations steps were at Visit 2 and (to a lesser extent) Visit 3, whereas at last possible up-titration step in this study (Visit 4) 162 of 189 (85.7%) Co-Amlessa arm patients have maintained their previously dispensed medication dosage.



Safety Results:

Out of 461 patients in SAS, 15.0% of patients reported AE. Proportion of patients with any reported AE in Amlessa arm was 17.0% and proportion in Co-Amlessa arm was 12.2%. Proportion of patients with any report of ADR was lower: 10.6% in complete SAS, 12.5% in Amlessa arm and 8.2% in Co-Amlessa arm.

The most prevalent treatment emergent non-serious AE in Amlessa arm (n=265) were Cough (3.0% total related, 0.4% total unrelated), Blood potassium increased (1.9% total related), Oedema peripheral (1.5% total related) and Gamma-glutamyltransferase increased (1.1% total related, 0.4% total unrelated). The most prevalent treatment emergent non-serious AE in Co-Amlessa arm (n=196) were Cough (1.5% total related), Hypotension (1.5% total related), Gamma-glutamyltransferase increased (1.0% total related, 1.5% total unrelated), Alanine aminotransferase increased (1.0% total related, 1.5% total unrelated) and Blood potassium decreased (1.0% total related).

There were no reports of deaths in this study. Two patients with treatment emergent SAE were recorded: breast cancer in one Co-Amlessa arm patient and back pain (leading to surgical intervention) in one Amlessa arm patient. Both events were assessed as not related to treatment by the investigators. A total of 12 (4.5%) patients in Amlessa arm have withdrawn or have been discontinued from the study due to AE or due to the need for major surgical intervention. The most prevalent Treatment Emergent Adverse Events (TEAEs) leading to study discontinuation in Amlessa arm (n=265) were Cough (four patients) and Oedema peripheral (two patients), while all other related events were recorded for a single patient. These included: Urticaria, Sciatica, Nervousness, Vomiting and Headache (one patient), Rash and Lip oedema (one patient), back pain [serious not-related AE] and Abdominal pain in addition to Cough (one patient). Four AEs leading to study discontinuation were recorded in Co-Amlessa arm (n=196): Rash erythematous, Urticaria, Blood potassium increased and Breast cancer [serious not-related AE]. Each of these events was recorded in a single patient.

The mean absolute changes in safety laboratory assessments (ALT, AST, GGT, creatinine, potassium, eGFR as well as hematological laboratory parameters) from baseline to follow-up visits, observed in this study, were small. The mean absolute changes between seated and standing office SBP and DBP, measured at each study visit, were small.

1. Summaries of Safety Laboratory Assessment Measurements at visits 1, 2, 3 and 5 for in Amlessa Arm and Co-Amlessa Arm in SAS:

		Amlessa Arm		Co-Amlessa Arm	
		n	**Mean ± SD**	**n**	**Mean ± SD**
ALT (µkat/L)	Visit 1	262	0.6 ± 0.3	195	0.5 ± 0.3
	Visit 2	249	0.5 ± 0.3	188	0.5 ± 0.3
	Visit 3	244	0.6 ± 0.6	187	0.6 ± 0.5
	Visit 5	230	0.5 ± 0.3	182	0.5 ± 0.3
AST (µkat/L)	Visit 1	262	0.5 ± 0.2	195	0.4 ± 0.2
	Visit 2	249	0.4 ± 0.2	188	0.4 ± 0.2
	Visit 3	241	0.4 ± 0.1	187	0.4 ± 0.3
	Visit 5	230	0.4 ± 0.2	182	0.4 ± 0.2
GGT (µkat/L)	Visit 1	261	0.7 ± 0.5	194	0.7 ± 0.5
	Visit 2	249	0.7 ± 0.5	187	0.7 ± 0.8
	Visit 3	243	0.7 ± 0.8	186	0.7 ± 1.0
	Visit 5	230	0.6 ± 0.5	182	0.7 ± 0.9
Creatinine (µmol/L)	Visit 1	262	76.7 ± 15.2	195	76.3 ± 15.1
	Visit 2	249	76.0 ± 15.0	188	78.2 ± 15.2
	Visit 3	244	76.3 ± 13.7	186	79.1 ± 14.8
	Visit 5	230	77.6 ± 14.3	182	79.1 ± 15.9
Potassium (mmol/L)	Visit 1	262	4.4 ± 0.3	195	4.4 ± 0.4
	Visit 2	249	4.5 ± 0.4	188	4.3 ± 0.4
	Visit 3	242	4.4 ± 0.4	187	4.2 ± 0.4
	Visit 5	229	4.4 ± 0.4	181	4.2 ± 0.4
eGFR (ml/min/1.73m^2)	Visit 1	262	91.8 ± 15.8	195	89.4 ± 15.1
	Visit 5	230	91.1 ± 15.4	182	87.1 ± 16.0

2. Summaries of Heamatology Laboratory Assessments at visit 1 and visit 5 in Amlessa Arm and Co-Amlessa Arm in FAS:

		Amlessa Arm		Co-Amlessa Arm	
		n	**Mean ± SD**	**n**	**Mean ± SD**
WBC (10^9/L)	Visit 1	248	7.4 ± 1.9	188	7.3 ± 1.7
	Visit 5	228	7.2 ± 1.9	180	7.5 ± 1.8
RBC (10^{12}/L)	Visit 1	248	5.0 ± 0.4	188	5.0 ± 0.5
	Visit 5	228	4.9 ± 0.4	180	4.8 ± 0.4
Hemoglobin (g/L)	Visit 1	248	149.5 ± 12.6	188	147.8 ± 14.9
	Visit 5	228	145.7 ± 11.5	180	143.9 ± 13.7
Hematocrit (L/L)	Visit 1	248	0.44 ± 0.04	188	0.44 ± 0.04
	Visit 5	228	0.43 ± 0.03	180	0.42 ± 0.04
MCV (fL)	Visit 1	248	88.9 ± 4.6	188	88.4 ± 5.4
	Visit 5	228	88.5 ± 4.5	180	88.2 ± 5.0
Platelets (10^9/L)	Visit 1	248	245.9 ± 56.7	188	245.6 ± 58.2
	Visit 5	228	249.2 ± 57.1	180	251.6 ± 63.3

Conclusions:

The results of the PRECIOUS study demonstrate that the treatment strategies with Amlessa and Co-Amlessa, tested in this study, result in effective reduction of office BP and lead to high rates of office BP target achievement after four months of treatment. Favourable results in office BP target achievement and reductions are further supported by clinically significant decrease in 24h BP and 24h cSBP observed in this study. Office BP decreased significantly within one month in both treatment arms and meaningful proportions of patients have achieved BP control after 1 month of treatment. The pattern of safety information in this study largely matched the established safety profile of the tested SPCs and the individual active substances, indicating good tolerability of the tested medications.

Results of clinical trial PRECIOUS provide additional support to the strategy of starting the antihypertensive treatment with a SPC in newly diagnosed patients and the strategy of intensifying the therapy in case of uncontrolled hypertension. Taking into consideration the findings of this study, it can be concluded that Amlessa and Co-Amlessa treatment strategies represent a useful tool for improving BP control in wide populations of patients, not only in significantly decreasing the office BP, but also the 24-hour BP and the central BP parameters; thus widening the possibility of a comprehensive hypertension management.

Date of Report:

15 February 2022