DP13 – A Phase 2 Study in Patients with Primary Aldosteronism to Evaluate the Efficacy, Safety and Tolerability of the Aldosterone Synthase Inhibitor, DP13, over an 8-week Treatment Period

Status:	Version 6.0 (amended protocol)
Date:	18 May 2022
Study Drug:	DP13
Drug Class:	Aldosterone Synthase Inhibitor
Sponsor:	DAMIAN Pharma AG
EudraCT Number:	2019-000919-85
Sponsor Reference:	DP13C201

AMENDMENT 5
The primary purpose of this amendment is to include measurement of parathyroid hormone (PTH) from patient biological samples. No additional blood will be obtained from the patient. The PTH analysis will be performed by the Central Laboratory along with the already approved measurement of ACTH. The PTH measurement has been added to the following sections:

- Section 7.2. —Blood Sampling
- Section 7.4. —Central Blood Analyses
- Section 18. —Study Plan

AMENDMENT 4
The primary purpose of this amendment is to unify the protocol with the recommendations of the Committee on Research Involving Human Subjects for the Arnhem-Nijmegen Region of the Netherlands and Swissethics of the Canton of Bern in Switzerland and will include the following additional changes:

- Section 6.8– Patient Re-screening and Re-enrolment – has been added to address the occurrence of non-controllable events such as hospital closures due to the COVID-19 emergency or other similar extraordinary circumstances.
- Section 7.2– Blood Sampling – has been further specified for consistency with urine analysis to include DP13 metabolites.
- Section 7.4.– Central Blood Analyses – has been further specified for consistency with urine analysis to include DP13 metabolites.

Furthermore, in order to alleviate the burden on patients related to the number of site visits and/or to implement EMA- or other local authority-mandated actions limiting patient access to sites to reduce COVID-19 related risks, some of the visits may now be performed at the patient's home or workplace by medically qualified personnel. Some of the assessments planned for these visits have been removed or rescheduled to ease the workload of the visiting medical personnel. The changes are summarized as follows:

- Sections 4.1., 7.1., 7.3., and 18. now state that the Day -1, 14, 42 and 55 visits may be performed at the patient's home or workplace by medically qualified personnel.
- Sections 4.1., 5.1., 7.2., 7.3. and 18. now state that on Day 1 and Day 28, two jars of IMP capsules are to be dispensed to ensure supply for one month in the event of a home/workplace visit.
- Section 7.2. and 18. indicate that on Days 14 and 42, blood samples are collected by medically qualified personnel at the patient's home or workplace (if appropriate facilities are available) and that blood sampling for central analysis is limited to the evaluation of aldosterone/PRC, electrolytes and steroids.
- Section 7.1. has been added to describe home/workplace visits.
- Changes to (i) any other scheduled visit or (ii) scheduled assessment or (iii) assignment of the visit to the patient's home or place of work due to unanticipated emergent local COVID-19 restrictions must be made by the local PI and under his/her responsibility and will be documented as per standard procedures.

Additionally, the choice of calcium channel blockers for the hypertension control therapy is expanded to include diltiazem to reduce unnecessary within-class drug switching.

- Synopsis and Sections 4.1., 4.3., 4.6., 5.5., 5.6., 6.3., 6.4., 7.2., and 18. now include the use of diltiazem (slow-release 90 - 360 mg daily)

Finally, in order to allow BMI eligible patients with a greater height to participate in the study, the weight criterion has been expanded from 100 kg to 110 kg in Section 6.3. Inclusion Criteria.

AMENDMENT 3
The purpose of this amendment is to align the protocol with the recommendations of the Committee on Research Involving Human Subjects for the Arnhem-Nijmegen Region of the Netherlands. The main changes to the protocol are as follows:

- Section 5.6. – Concomitant Medication – has been extended.
- Section 6.4. – Exclusion Criteria – has been further specified.

AMENDMENT 2
The purpose of this amendment is to correct the wording in Section 4.5. – Patient withdrawal criteria. The section now states that in case of withdrawal of consent, all personal data and biological samples will continue to be used in a coded form (and not anonymous form); no further data or samples will be collected. The same wording change has been applied to Section 11.4.

AMENDMENT 1
The purpose of this amendment is to align the protocol with the recommendations of the Ethics Commission of the Canton of Bern Switzerland. The main changes to the protocol and corresponding sections of the synopsis are as follows:

- Section 3.2. – Secondary outcomes – has been corrected.
- Section 4.3. – Justification of study design – has been updated with additional information.
- Section 4.5. – Patient withdrawal criteria – now specifies that in case of withdrawal of consent, all personal data and biological samples will continue to be anonymized and that no further data or samples will be collected.
- Section 6.2. – Determination of sample size – has been revised providing additional information.
- Sexual abstinence as a means of contraception has been eliminated (see Section 6.4. and Section 6.6).
- Section 8.1. has been added describing the requirements for serious adverse event reporting at Swiss Centres.
- Section 10.1. First primary objective – has been modified to correct the effect size calculation for the first primary variable.
- Section 11.1. – Data quality assurance – now specifies the database compliant with the Human Research Act.
- Section 11.4. – Data storage and archiving – has been revised to clarify that biological samples may be retained exclusively for analyses stated in the protocol and until completion of the clinical study report, after which all samples will be destroyed.
- Section 14.2. – Informed consent filing procedures have been corrected for clarity.

Changes to the protocol are shown in the track changes version using strike through font for deletions and underlined font for insertions.

Title of Study:	DP13 – A Phase 2 Study in Patients with Primary Aldosteronism to Evaluate the Efficacy, Safety and Tolerability of the Aldosterone Synthase Inhibitor DP13 over an 8-week Treatment Period
Objectives:	**Primary Objectives** • To determine the efficacy of daily oral DP13 treatment to decrease the plasma aldosterone-to-renin ratio (ARR) from baseline in patients with primary aldosteronism (PA) • To determine the efficacy of daily oral DP13 treatment to reduce 24-hour ambulatory systolic blood pressure (aSBP) from baseline in patients with PA **Secondary Objectives** • To determine the safety and tolerability of DP13 treatment in patients with PA • To determine the efficacy of daily oral DP13 (all dose arms combined) to reduce office systolic blood pressure (oSBP) from baseline in patients with PA • To determine the efficacy to decrease the plasma ARR from baseline in each individual dose arm • To determine the efficacy of daily oral DP13 to reduce oSPB and 24-hour aSBP from baseline in each individual dose arm • To determine the DP13 dose-dependent efficacy to decrease the plasma ARR from baseline in patients with PA • To determine the DP13 dose-dependent efficacy to reduce oSBP and 24-hour aSBP from baseline in patients with PA **Exploratory Objectives:** • To determine the recovery of the plasma ARR after discontinuation of DP13 treatment in patients with PA • To determine the recovery of oSBP after discontinuation of DP13 treatment in patients with PA • To determine the DP13 dose-dependent treatment effects on mean diurnal (day and night) ambulatory systolic and diastolic blood pressure (aSBP/aDBP) in patients with PA • To determine the DP13 dose-dependent efficacy to decrease urinary aldosterone excretion from baseline in patients with PA • To determine the dose-dependent efficacy of daily oral DP13 treatments to raise blood potassium levels from baseline in patients with PA • To determine the steady-state pharmacokinetics of once daily DP13 administration in patients with PA
Methodology / Study Design:	A phase 2, multi-centre, randomized, parallel group, baseline-and withdrawal-controlled study in 36 patients with PA to determine the dose-dependent efficacy, safety and tolerability of once daily oral DP13 after a 2-week single-blind placebo run-in period followed by a randomized 8-week double-blind treatment period. After an additional single-blind, 2-week DP13 placebo withdrawal period, patients are switched to standard of care. Guideline-diagnosed patients with PA on fixed dose background hypertension control therapy are enrolled upon central eligibility verification. Baseline characteristics are determined by 24-hour ambulatory blood pressure monitoring and urine sampling starting on Day -1, by office blood pressure measurement and blood sample collections for central ARR and electrolyte determinations on Day 1. Patients are subsequently randomized into three parallel DP13 active treatment groups of 12 patients each and followed through biweekly visits. The end of treatment characteristics is determined by 24-hour ambulatory blood pressure monitoring and urine sampling starting on Day 55 and by office blood pressure measurement and blood sample collections for central ARR and electrolyte determinations on Day 56. Persistence of treatment effect and return of effects to baseline characteristics are determined on Day 70. The Day -1, 14, 42 and 55 visits may be performed at the patient's home or workplace (if appropriate facilities are available) by medically qualified personnel.
Number of Patients:	36 patients with PA are randomized into three treatment groups of 12 patients each.
Diagnosis and Main Criteria for Inclusion:	Patients with a recent (<1 year) diagnosis of PA irrespective of any subtype determination (aldosterone-producing adenoma or bilateral adrenal hyperplasia). The diagnosis includes case detection and confirmation following the Endocrine Society Clinical Practice Guidelines 2016 and locally approved protocols. Specifically, patients are female or male and 18 to 65 years of age with: • ARR of ≥40 with plasma aldosterone concentration (PAC) ≥15 ng/dL and plasma renin activity (PRA) <1.0 ng/mL/h. A pre-screening ARR of ≥3.7 results by using plasma renin concentration (PRC) <15 mU/L instead of PRA as denominator. • A IV saline loading test (2 litres of 0.9% saline infused over 4 hours) with resulting PAC >7.0 ng/dL after infusion. For patients at risk for volume expansion, a captopril test (50 mg captopril peroral) can be used instead with resulting ARR >30 and PAC >11 ng/dL (respectively ARR >2.4 using PRC in mU/L instead of PRA as denominator). • Systolic blood pressure >145 mmHg by automatic office blood pressure measurement and in presence of hypertension control therapy (doxazosin 1 - 8 mg QD and, only if necessary, verapamil slow release 40 - 120 mg BID or diltiazem slow-release 90 - 360 mg daily or amlodipine 2.5 - 10 mg QD). • Estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 using the MDRD-4 GFR equation Formal eligibility verification after implementation of a dose-adjusted blood pressure control therapy with a documented case review process led by the Central Review Board is mandatory prior to final enrolment.
Test Product, Dose and Mode of Administration:	Formulated white opaque capsules (VCaps® Plus) size I containing: • 0 mg DP13 (placebo) • 4 mg DP13 • 8 mg DP13 • 12 mg DP13 One capsule is taken per day (QD) orally in the morning between 06:30 and 08:30 before breakfast.
Duration of Treatment:	Patients start the study with a 2-week placebo run-in period that is followed by a 8-week DP13 treatment period and complete the study with a 2-week placebo withdrawal period.
Date and version	5 May 2022, v.6.0

1. INTRODUCTION

1.1. DP13 – Mechanism of Action

DP13 represents a first-in-class orally available, small molecular weight aldosterone synthase inhibitor compound. Aldosterone synthase or CYP11B2 is the rate-limiting enzyme for aldosterone synthesis in the adrenal glands. The enzyme mediates the conversion of 11-deoxycorticosterone to aldosterone in the zona glomerulosa of the adrenal cortex. DP13, by inhibiting the enzymatic conversion, causes an increase in the substrate 11-deoxycorticosterone and concomitant decrease in the product aldosterone. Steroid-binding proteins in plasma neutralize changes in 11-deoxycorticosterone levels in contrast to aldosterone, which is only weakly protein bound.

The principal regulators of adrenal aldosterone biosynthesis are the renin-angiotensin system, extracellular potassium and adrenocorticotropic hormone (ACTH). Renin is synthesized and released by the juxtaglomerular cells in the afferent arteriole of the kidney in response to reduced intravascular volume and sodium concentration of the macula densa. Renin catalyses the hydrolysis of liver-produced angiotensinogen to angiotensin I, which is converted in the vascular endothelium to biologically active angiotensin II. Angiotensin II raises blood pressure by direct vasoconstriction, increased sympathetic nerve activity and by stimulating adrenal aldosterone production and enhancing renal salt and water retention. Acutely, angiotensin II stimulates aldosterone biosynthesis whereas chronically, it leads to zona glomerulosa hypertrophy and hyperplasia with increased CYP11B2 expression. The resulting increased aldosterone secretion promotes sodium and water retention, which in turn suppress renin release. Potassium regulates aldosterone production sensitively and acutely. Potassium stimulates CYP11B2 expression and aldosterone secretion synergistically with angiotensin II via membrane depolarization and calcium-mediated activation of gene transcription. Increased aldosterone secretion regulates potassium homeostasis by stimulating sodium reabsorption in the distal tubules and collecting duct of the kidneys in exchange for potassium. ACTH is the principal effector peptide of the hypothalamic / pituitary adrenal axis and is primarily involved in the regulation of glucocorticoids. However, it controls the diurnal rhythm of aldosterone production.

In an extensive clinical phase 1 study (DP13C101) in healthy volunteers, DP13 demonstrated upon once daily dosing not only good safety and tolerability but also dose-dependent suppression of aldosterone production over time (DP13 – Investigator Brochure 2019). Pharmacological suppression of aldosterone triggered the expected physiological responses. Increased urinary sodium excretion was reflected in lower plasma sodium concentrations whereas concomitant reabsorption of potassium led to slightly higher plasma potassium concentrations. In addition, reduced plasma aldosterone concentrations (PAC) and inherent sodium loss were reflected in increased plasma renin activity (PRA). Therefore, in order to mediate sustained aldosterone suppression over time, DP13 had to overcome reactively increased angiotensin II and potassium levels, the physiological stimuli for aldosterone production. Plasma cortisol and ACTH levels were unaffected, as was the diurnal rhythm of adrenal steroid production.

1.2. DP13 – Treatment of Primary Aldosteronism

Dysregulation of the mechanisms regulating aldosterone biosynthesis results in primary aldosteronism (PA); a disorder characterized by elevated plasma aldosterone concentrations (PAC) and low plasma renin activity (PRA) levels, hypertension, often hypokalaemia and vascular fibrosis. The two major causes of PA are unilateral aldosterone producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), accounting for approximately 95% of all PA cases. In both forms, aldosterone production is autonomous and not or hardly suppressible by physiologic stimuli. Potassium channel defects have been identified in APA leading to sustained calcium signalling and aldosterone production independent of angiotensin II or potassium regulation. Occurrence of aldosterone-producing cell clusters or micronodules and genetic defects are proposed to sustain CYP11B2 activity in bilateral adrenal hyperplasia.

The Endocrine Society Clinical Practice guidelines for diagnosis of PA recommend the determination of the aldosterone-to-renin ratio (ARR) as the most reliable test because the ratio is less affected by diurnal and postural variations (*Funder et al., J Clin Endocrinol Metab 2016*). The variability of the ARR as an initial detection system is reduced practically if guideline recommendations for patient preparation are followed and technically if common units for PAC (ng/dL) and PRA (ng/mL per h) and assay systems (specified immunoassay) are used. The ARR is hence very sensitive but not very specific for the diagnosis of PA without the subsequent demonstration of at least partly autonomous, i.e., angiotensin II-independent aldosterone production. Angiotensin II can be removed with the intravenous saline loading test that leads to volume expansion and renin suppression or with the captopril challenge test to inhibit acutely angiotensin-converting enzyme. Likewise, the variability of the confirmatory aldosterone suppression test is reduced with standardized preparatory and technical procedures.

Autonomous aldosterone production, independent of renin activity, characterizes patients with PA and their higher risk for cardiovascular morbidity and mortality compared to patients with essential hypertension. Mineralocorticoid receptor (MR) antagonists are the recommended medical therapy for patients with PA. A retrospective cohort study analysed whether MR antagonist treatment effectively reduces events (stroke, heart failure, myocardial infarction) for patients with PA (*Hundemer et al., Lancet Diabetes Endocrinol 2017*). The incidence of cardiovascular events and mortality were higher in patients with PA treated with MR antagonists compared to age- and blood pressure-matched essential hypertensives. However, the excess risk was limited to patients whose PRA remained suppressed (<1 ng/mL per h). Patients who tolerated higher MR antagonist doses had unsuppressed PRA (>1 ng/mL per h) and no significant excess risk for events. The authors advocated that PA patients be medically adjusted not only to blood pressure control but also to raised renin levels.

Once daily intake of DP13 capsules by healthy volunteers led to a dose-dependent decrease of PAC and concomitant increase of PRA, hence a reduction in the ARR compared to placebo treatment. In addition, DP13 selectively suppressed aldosterone production without affecting cortisol secretion upon ACTH-stimulation. Placebo-treated volunteers responded hereby with PAC levels that are typically seen in patients with PA (*DP13 – Investigator Brochure 2019*). Therefore, once daily administration of DP13 capsules to patients with PA is expected to lower the plasma ARR by both decreasing PAC and increasing PRA. In response, the lowering of the ARR is expected to translate into a lower ambulatory systolic blood pressure within an 8-week treatment period.

1.3. DP13 – Risk / Benefit Assessment

The anticipated risk/benefits of treating PA patients with DP13 are predominantly derived from its DP13C101 phase I study but also from the extensive clinical database of the DP13 parent compound assembled from various studies in female and male patients (*DP13 – Investigator Brochure 2019*). DP13C101 (EudraCT 2016-003648-36; clinicaltrials.gov NCT03046589) was a single centre, 2-part, randomized, double blind, placebo controlled, single and multiple ascending oral dose study in healthy male volunteers. Part A was an alternating-group, 3-period study with 16 subjects and part B was a sequential group study with 32 subjects investigating the safety, tolerability, pharmacokinetics, renal metabolism and pharmacodynamics of once daily DP13 doses of 4 mg, 8 mg and 16 mg administered over 8 days. Dose-dependent linear drug exposure over 24 hours in blood led to selective pharmacological inhibition of aldosterone synthase in the adrenal glands as demonstrated by suppressed aldosterone levels, increased renin activity, increased potassium and decreased sodium levels.

Therefore, the anticipated benefits of treating PA patients with DP13 may include:

- Targeted suppression of uncontrolled and excessive aldosterone secretion at the rate-limiting step in the adrenal glands addressing the principal etiologic basis of the disease
- Correction of aldosterone-mediated hemodynamic changes leading to hypertension, volume retention, hypokalaemia and suppressed renin
- Higher target selectivity and therefore better tolerability and improved compliance over the standard of care medical therapy, spironolactone
- Suitable for mild to moderately renal impaired patients due to limited renal elimination of compound and metabolites
- Dose-dependent linear pharmacokinetic and pharmacodynamic properties without indication for drug accumulation or drug tolerance over time
- Convenient once daily oral administration of neutral tasting capsules without known susceptibility for metabolic drug-drug interactions

Mean serum potassium levels increased in a dose-dependent manner to the final timepoint on day 8, 24 hours post-dose, with mean changes from baseline of -0.11 mmol/L for placebo, +0.22 mmol/L for 4 mg DP13, +0.46 mmol/L for 8 mg DP13 and +0.78 mmol/L for 16 mg DP13. The multiple dosing part with 32 enrolled subjects recorded 13 treatment-emergent adverse events (TEAEs) in 10 subjects considered either possibly related or related to DP13. Two TEAEs (headache and pollakiuria) were reported following placebo treatment, 5 TEAEs (2 events of dizziness, 2 of headache, 1 of abnormal gastrointestinal sound) were reported following 4 mg DP13 QD, 3 TEAEs (headache, change of bowel habit and diarrhoea) were reported following 8 mg DP13 QD and 3 TEAEs (headache, dizziness and postural dizziness) were reported following 16 mg DP13 QD. No trends in vital signs and 12-lead ECG parameters were noted over time.

Therefore, the potential risks for PA patients on DP13 treatment may include:

- Development of hyperkalaemia
- Incidence of headaches, dizziness, orthostasis, hypotension
- Abdominal discomforts

Overall, the clinical phase I profile of DP13 supported by the safety history of the previously developed racemic parent compound suggests that the anticipated therapeutic benefits provided by DP13 outweigh the potential safety risks.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To determine the efficacy of daily oral DP13 treatment (all dose arms combined) to decrease the plasma aldosterone-to-renin ratio (ARR) from baseline in patients with primary aldosteronism (PA)
- To determine the efficacy of daily oral DP13 treatment (all dose arms combined) to reduce 24-hour ambulatory systolic blood pressure (aSBP) from baseline in patients with PA

2.2. Secondary Objectives

- To determine the safety and tolerability of DP13 treatment in patients with PA
- To determine the efficacy of daily oral DP13 treatment (all dose arms combined) to reduce office systolic blood pressure (oSBP) from baseline in patients with PA
- To determine the efficacy of daily oral DP13 treatment to decrease the plasma ARR from baseline in each individual dose arm
- To determine the efficacy of daily oral DP13 treatment to reduce 24-hour aSBP from baseline in each individual dose arm
- To determine the efficacy of daily oral DP13 treatment to reduce oSBP from baseline in each individual dose arm
- To determine the dose-dependent efficacy of daily oral DP13 treatment to decrease the ARR from baseline in patients with PA
- To determine the dose-dependent efficacy of daily oral DP13 treatment to reduce 24-hour aSBP from baseline in patients with PA
- To determine the dose-dependent efficacy of daily oral DP13 treatment to reduce oSBP from baseline in patients with PA

2.3. Exploratory Objectives

- To determine the recovery of the plasma ARR after discontinuation of daily DP13 treatment in patients with PA in all dosage arms combined and in each individual dosage arm
- To determine the recovery of the oSBP after discontinuation of daily oral DP13 treatment in patients with PA in all dosage arms combined and in each individual dosage arm
- To determine the dose-dependent effects of daily oral DP13 treatment on mean diurnal (day and night) ambulatory systolic and diastolic ambulatory blood pressure (aSBP/aDBP) in patients with PA
- To determine the dose-dependent efficacy of daily oral DP13 treatment to decrease urinary aldosterone excretion from baseline values in patients with PA
- To determine the dose-dependent efficacy of daily oral DP13 treatment to raise blood potassium values from baseline in patients with PA
- To determine the steady-state pharmacokinetics of daily oral DP13 treatment in patients with PA

3. STUDY OUTCOMES

3.1. Primary Outcomes

- Change in the plasma ARR from baseline (Day 1) to the end of the 8-week daily oral DP13 treatment period (Day 56) for all dose arms combined
- Change in mean 24-hour aSBP from baseline (Day 1) to the end of the 8-week daily oral DP13 treatment period (Day 56) for all dose arms combined

3.2. Secondary Outcomes

- Occurrence of treatment-emergent adverse events (TEAE) and serious adverse events (SAE) over the entire study duration
- Change in oSBP from baseline (Day 1) to the end of the 8-week daily oral DP13 treatment period (Day 56) for all dose arms combined
- Change in the plasma ARR from baseline (Day 1) to biweekly visits (week 2, week 4, week 6) and to the end of the 8-week daily oral DP13 treatment period (Day 56) in each individual dose arm
- Change in 24-hour aSBP from baseline (Day 1) to the end of the 8-week daily oral DP13 treatment period (Day 56) in each individual dose arm
- Change in oSBP from baseline (Day 1) to biweekly visits (week 2, week 4, week 6) and to the end of the 8-week daily oral DP13 treatment period (Day 56) in each individual dose arm

3.3 Exploratory Outcomes

- Change in the plasma ARR from end of daily oral DP13 treatment (Day 56) to end of the 2-week withdrawal period (Day 70) in all dose arms combined and in each individual dose arm
- Change in oSBP from end of daily oral DP13 treatment (Day 56) to end of the 2-week withdrawal period (Day 70) in all dose arms combined and in each individual dose arm
- Change in mean diurnal (day and night) aSBP/aDBP from baseline (Day 1) to end of the 8-week daily oral DP13 treatment period (Day 56) in all dose arms combined and in each individual dose arm
- Change in 24-hour urinary tetrahydroaldosterone excretion from baseline (Day 1) to end of the 8-week daily oral DP13 treatment period (Day 56) in all dose arms combined and in each individual dose arm
- Change in plasma potassium concentrations from baseline (Day 1) to biweekly visits (week 2, week 4, week 6) to the end of the 8-week daily oral DP13 treatment period (Day 56) and the end of the 2-week withdrawal period (Day 70) in all dose arms combined and in each individual dose arm
- Change in predose plasma DP13 concentrations (C_{min}) during biweekly visits (week 2, week 4, week 6) to the end of the 8-week daily oral DP13 treatment period (Day 56) in each individual dose arm

4. INVESTIGATIONAL PLAN

DP13C201 is a multi-centre, randomised, double-blind, baseline- and withdrawal-controlled study with single-blind placebo run-in and withdrawal periods. The start of the study is defined as the date the study-specific informed consent form (ICF) is signed by the first eligible study participant. The end of the study is defined as the date the last patient completes the study procedures including any follow-up visits, i.e., last patient last visit.

4.1. Study Design and Study Doses

Study Design: DP13C201 is a dose range-finding study with three parallel groups of 12 patients each treated with DP13. The treatment effects are baseline- and withdrawal-controlled at the study start and study end, respectively.

Recruitment Strategies: Patients with PA may enrol in the DP13C201 study as either *de novo* diagnosed patients not yet on disease specific treatment or recently diagnosed patients on standard of care (SoC) treatment for PA. Diagnosis in presence of hypertension control therapy and treatment recommendations for patients with PA are outlined in the Endocrine Society Clinical Practice guidelines (*Funder et al., J Clin Endocrinol Metab 2016*). The medications for hypertension control therapy are protocol-specified and selected from the guidelines. Doxazosin is used as first-line medication and verapamil or diltiazem or amlodipine as second-line medications. The medications are prescribed at the Investigator's discretion (exceptionally, a calcium channel blocker can be used first-line if medically justified).
De novo and per guideline diagnosed (Dx) PA patients who meet the inclusion/exclusion (I/E) criteria in the presence of protocol-specified hypertension control medications may sign an informed consent form (ICF) to maintain control therapy at fixed doses. Patient characteristics are entered into the eCRF system and undergo eligibility verification (EV) by the Central Review Board. The pre-screening diagnostic data collected as per local guideline can be used to address the I/E criteria if available as source document and performed within 10 weeks before study enrolment and include the local guideline-recommended plasma ARR and suppression test (ST), blood pressure (BP) and potassium concentrations [K] as well as a safety ECG recording.

Patients with a recent diagnosis of PA need to washout their SoC or other diagnosis interfering medications following informed consent to determine the applicability of the I/E criteria in presence of protocol-specified hypertension control medications. The washout period may last up to 8 weeks, as in the case of patients being treated with spironolactone. The screening diagnostic procedures necessary to address the applicability of the I/E criteria are performed within 10 weeks before study enrolment and include the plasma ARR, blood pressure (BP) and potassium concentrations [K] as well as a safety ECG recording (a repeat of the original diagnostic suppression test is not necessary if available as source document and performed within 1 year of study enrolment unless the original diagnosis did not include a suppression test). Eligible patients maintain the control therapy at fixed doses and have their characteristics entered into the eCRF system for central EV.

The formal eCRF-based eligibility case review process led by the Central Review Board verifies the patient's fulfilment of pre-screening/screening I/E criteria for study consistency. Importantly, the systolic blood pressure inclusion criterion is validated in the context of a recommended 2-week stable hypertension control therapy. Upon central approval the patient enrols into the study.

Study Duration and Visits: Patients start the study with a single-blind placebo run-in period of 2 weeks to stabilize their baseline characteristics. On the last run-in day, Day -1, blood pressure is measured by a 24-hour ambulatory blood pressure monitoring (ABPM) device to define baseline values. A 24-hour urine sample is collected in parallel to the ABPM recording. On the Day 1 office visit and after recording of all baseline characteristics, patients are randomized into three parallel groups and treated for 8 weeks with DP13. During the double-blind DP13 treatment period, patients are consulted on week 2, week 4 and week 6 visits. At the end of the 8-week DP13 treatment period, blood pressure is re-measured by a 24-hour ABPM device starting on Day 55. A 24-hour urine sample is collected in parallel to the ABPM recording. After a single-blind, placebo withdrawal period of 2 weeks, patients return for an end of study (EoS) visit on Day 70 to assess the persistence of treatment effect and recovery to baseline values. Subsequently, patients are switched to standard of care. The Day -1, 14, 42 and 55 visits may be performed at the patient's home or workplace (if appropriate facilities are available) by medically-qualified personnel.

Dose Regimen: Upon enrolment in the study, patients will receive an anonymised jar with 14(+4) placebo capsules to complete the run-in period. The capsules are taken daily (QD) with a glass of water on an empty stomach (prior to breakfast) in the morning between 06:30 and 08:30. Upon randomization, patients receive at each office visit an anonymised jar (or, in the case of a home/workplace visit, patients receive 2 jars in order to ensure supply for 1 month) with 14(+4) DP13 capsules of the same strength to be taken daily (QD) in the morning with a glass of water on an empty stomach (prior to breakfast) to complete the active treatment period. The DP13 capsule strength for the respective three study arms is 4 mg, 8 mg and 12 mg. During the treatment period patient and Investigator are blinded to actual capsule strength. On the last treatment day, Day 56, patients will receive an anonymised jar with 14(+4) placebo capsules to complete the 2-week withdrawal period. Throughout the entire study, patients are blinded to jar content (placebo versus DP13 capsules).

Safety and Safety Review: Patients will maintain their hypertension control therapy throughout the study until the end of study visit. An internal safety review group consisting of a Sponsor representative, the Investigator of the Central Laboratory and the Central Review Board will receive blinded data for safety (safety laboratory, treatment-emergent adverse event recordings, blood pressure values) after each visit to determine any study adaptations.

4.2. Interim Analysis and Additional Patients

Following a blinded interim analysis for sample size adjustment after 24 patients have completed the protocol to verify the statistical standard deviations of baseline and change from baseline values, additional patients may be added to the study after a protocol amendment. Up to 6 patients per dose group or up to 18 patients for the three dose groups combined may be added. The recommendation for additional patients will be agreed with the Sponsor and Investigators, documented in the Trial Master File (TMF) and the respective ethics committee (EC) will be notified of the changes.

4.3. Justification for Study Design

The design of the DP13C201 phase II study in recently diagnosed patients with PA intends to compare DP13 efficacy and safety in parallel arms over an 8-week treatment period. The dose-range finding for a future phase III study is provided by comparing absolute efficacy to baseline and after treatment discontinuation, as well as relative efficacy between study arms at the end of the 8-week treatment period. Efficacy and safety will be evaluated in the presence of a blood pressure control therapy to protect patients. Control therapy with the drugs doxazosin and amlodipine or diltiazem or verapamil must therefore be administered compliantly and at fixed doses over the entire study period in order to provide solid conclusions. Because stable blood pressure adjustment may take several weeks, it is recommended that the control therapy be dose-fixed 2 weeks prior to enrollment. Stabilization of hypertension control therapy followed by a placebo run-in period of 2 weeks allows standardization of patient disposition for biochemical and hemodynamic baseline assessment prior to randomization. Patients are randomized into three active but dose-blinded treatment arms in order to offer all patients disease control with DP13 over the 8-week treatment period. The opportunity for active treatment will also increase patient interest to enrol in the study and assure patient compliance during the study. Based on reported interventional studies with aldosterone-targeted therapies in patients with PA or essential hypertension, an 8-week treatment period is considered a minimal but adequate duration for blood pressure to adapt to ARR suppression in a majority of patients (*Amar et al., Hypertension 2010*; *Parthasarathy et al., J Hypertens 2011; Calhoun et al., Circulation 2011*). This timeline is also substantiated by observed blood pressure changes after adrenalectomies (*Williams et al., Lancet Diabetes Endocrinol 2017*). For the same reason, a biweekly or monthly dose-titration regimen as used previously in open-label interventional studies is considered not informative. Biweekly visits assure safety, compliance and blood pressure control during the 8-week treatment period as well as the 2-week run-in and treatment withdrawal periods. A DP13 withdrawal period of 2 weeks after eight weeks of treatment provides an opportunity to assess the persistence and reversibility of the treatment effect and to ensure the safety of investigational drug discontinuation.

4.4. Justification for Study Doses

The DP13C101 phase 1 study in healthy volunteers (EudraCT N° 2016-003648-36) demonstrated compelling safety and tolerability, as well as a clear pharmacokinetic and pharmacodynamic efficacy response profile for DP13. DP13C101 supported a once daily (QD) in the morning oral administration of DP13 capsules. Furthermore, three suitable dose levels for the treatment of PA were derived.

- The 4 mg DP13 QD dose is considered a low dose potentially benefiting milder disease phenotypes.
- The 8 mg DP13 QD dose is considered a target dose for patients with PA.
- The 12 mg DP13 QD dose is considered a higher dose that could be necessary to treat florid disease types.

The 12 mg QD dose is lower than the 16 mg QD dose tested in the DP13C101 phase 1 study. There were no dose-dependent safety or tolerability trends observed in healthy volunteers. The dose levels are kept constant over the 8-week treatment period as aldosterone-dependent blood pressure effects are expected to occur with large individual time-response variance.

4.5. Patient Withdrawal Criteria

Patients will be withdrawn after a scheduled or unscheduled visit by the Investigator if any of the following criteria are met during the DP13 treatment period:

- Any verified clinically relevant signs or symptoms that, in the opinion of the Investigator after consultation with the Central Review Board warrant subject withdrawal.
- A subject's absolute QTc value >500 msec (confirmed by repeat testing). If this criterion is met, QTcB will be calculated; if QTcB readings meet the same criterion, the ECGs will then be manually over-read to confirm the QTc increase.
- Evidence of tachycardia (>150 beats/min) is seen in the resting sitting position (confirmed by 2 repeat measurements) on at least 2 occasions within a 1-hour interval.
- Evidence of uncontrolled hypertension (systolic blood pressure >190 mmHg and/or diastolic blood pressure >110 mmHg) is seen in the resting sitting position (confirmed by 2 repeat measurements) on at least 2 occasions within a 2-week interval, i.e., two visits.
- Evidence of moderate hypotension (systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg) is seen in the resting sitting position (confirmed by 2 repeat measurements) on at least 2 occasions within a 2-week interval, i.e., two visits.
- Evidence of unexplained clinically significant increases in liver function tests (AST, ALT, ALP, bilirubin and/or GGT), defined as >3 times the upper limit of the reference range (confirmed with repeat testing within 48 hours).
- Evidence of clinically significant increases in serum creatinine, defined as >2.0-fold above the upper limit of the reference range.
- Evidence of clinically significant hyperkalaemia (serum potassium >6 mmol/L) confirmed with repeat testing (that is not caused by technical or laboratory issues, e.g., haemolysis).
- Evidence of persistent hypokalaemia (serum potassium <2.5 mmol/L) in presence of oral potassium supplements on a least 2 occasions within a 2-week interval, i.e., two visits.
- Evidence of clinically significant hyponatraemia (serum sodium <130 mmol/L) confirmed with repeat testing.
- Non-compliance with the study procedures/restrictions, as considered applicable by the Investigator.

- Patient self-withdrawal.

In case of withdrawal of consent, all personal data and biological samples will continue to be used encoded; no further data or samples will be collected.

4.6. Management of Patient Safety

Patients remain on a personalized background hypertension control therapy throughout the study, if required, consisting of a fixed-dose regimen with the first-line alpha receptor blocker doxazosin, 1 – 8 mg QD and, if necessary, only one calcium channel blocker: verapamil slow release, maximum 40 – 120 mg BID or diltiazem slow-release 90 - 360 mg daily or amlodipine 2.5 – 10 mg QD according to the Investigator's judgement to assure office systolic and diastolic blood pressure (oSBP) do not exceed 190 mmHg and/or 110 mmHg, respectively during the study. Biweekly compliance checks during visits will not only focus on the proper IMP intake but also on the prescribed intake of the blood pressure control medications. Upon enrolment, each patient is given a card to carry at all times in case of an emergency outside the Investigator's supervision. The card gives details of the study number, start and end date of the patient's involvement in the study, patient details, name of the study Investigator, and the address and telephone number of the clinical site. Patients may destroy the card 4 weeks after they have completed the study.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Description, Identification and Storage

DP13 active pharmaceutical ingredient (API) along with the batch numbers and Certificates of Analysis (CoA) is supplied by the Sponsor's contract manufacturing organization. DP13 formulated capsules are supplied by the Sponsor's contract manufacturing organization. The DP13 capsules contain a filling and glidant excipient and either 4 mg, 8 mg or 12 mg drug substance. A Certificate of Release authorized by a Qualified Person (QP) in the European Union (EU) and Switzerland is issued for each IMP batch prior to administration to patients. Placebo capsules are only composed of filling and glidant excipients. The formulated placebo capsules are sourced and supplied by the Sponsor's contract manufacturing organization. A Certificate of Release authorized by a Qualified Person (QP) in the European Union (EU) and Switzerland will be issued for each batch of IMP prior to administration to patients. The VCaps® Plus capsules are of size (I) and white opaque in appearance. The IMP is stored at room temperature at the respective clinical site pharmacy, which is locked with restricted access. No special procedures are required for the safe handling of the IMP by the patient.

Labelling of IMP and Unit Jars: The CMO will prepare jars with 14(+4) capsules for a biweekly (or monthly in the case of a home/workplace visit) supply. Further information on the manufacture and assembly of unit doses will be maintained in the pharmacy documentation, which will be generated by the CMO and approved by the Sponsor prior to the first manufacture. The sequence of jars and capsules for study DP13C201 is provided as follows:

2-Week Run-in Period				8-Week Treatment Period				2-Week Withdrawal Period			
Study Cohort	DP13 Dose	Caps per Patient	Jar per Patient	Study Group	DP13 Dose	Caps per Patient	Jar per Patient	Study Cohort	DP13 Dose	Caps per Patient	Jars per Patient
N=36	0 mg	14	1	N=12	4 mg	56	4	N=36	0 mg	14	1
				N=12	8 mg	56	4				
				N=12	12 mg	56	4				

Actual numbers of jars dependent on interim analysis and any size adaptation. Bulk medication labels will be in the local language, will comply with the legal requirements of each country and will include use instructions and storage conditions. The labels will not contain any personal information on the patient.

Drug Accountability: Records will be maintained showing the receipt and disposition of the study supplies. The Sponsor will be permitted at intervals and upon request during the study to check the supplies storage and records. Enrolled patients will be asked to return the IMP containing jar and any unused capsule(s) at every office visit. The Investigator records the reconciled IMP intake over the visit period. The Investigator will witness directly the IMP intake on the day of study enrolment (Day -14) and randomization (Day 1) and on the days starting the 24-hour ambulatory blood pressure monitoring (Day -1 and Day 55). Upon satisfactory completion of all accountability procedures, each patient jar and any unused capsule(s) as well as any unused IMP jars from the block supply will be retained until completion of the study and returned to the Sponsor. The Sponsor will perform a final study drug reconciliation and issue a Certificate of Destruction.

5.2. Blinding

Staff at the CMO not involved in patient recruitment or other study activities will label and pack the IMP-containing jars according to a standard operating procedure (SOP) and based on the randomization list provided by the CRO. The following controls will be employed to maintain the double-blind status of the study:

- The placebo capsules will be identical in appearance to the DP13 capsules.
- The IMP supply jar covers biweekly (or monthly in the case of a home/workplace visit) visits irrespective of the study period.
- The Investigator and other members of staff involved in the study will remain blinded to the treatment randomisation code.
- Interim bioanalytical/hemodynamic data will be provided to the Central Laboratory in a blinded manner.

5.3. Unblinding

Emergency unblinding should only be undertaken when it is essential for patient care. If unblinding becomes necessary to manage patient safety (in the event of possibly treatment-related severe adverse events, SAEs), the decision to unblind resides solely with the Investigator. Whenever possible and provided it does not interfere with or delay any decision in the best interest of the patient, the Investigator will discuss the intended code-break with the Central Review Board and Sponsor. Emergency unblinding is performed using the web-based electronic data capture system. As a backup to the eCRF, individual sealed envelopes containing the treatment codes for each patient are kept at the CMO's clinical supply department and at the biopharmaceutical analyst at the Central Laboratory. These individual sealed envelopes should be used only in case it is not possible to use the eCRF for unblinding and can only be requested by the Investigator when knowledge of the actual dose received is deemed essential for the patient's care. If it becomes necessary to break the patient code during the study, the date, time, and reason will be recorded in the subject's source data and eCRF. Also, in case of Serious Adverse Event (SAE) considered to be a Suspected Unexpected Serious Adverse Reaction (SUSAR), the Pharmacovigilance Unit delegated in agreement with the Sponsor will be able to break the code to permit the notification of the case to the Regulatory Authorities in unblind version (see 8.1. section).

5.4. Randomization

Upon central patient eligibility verification and registration in the web-based electronic data capture system, the system will randomize enrolled patients in a 1:1:1 ratio to one of the three interventional dosage arms. An independent statistician using a computer-generated pseudo-random permutation procedure will produce the randomization code and allocation sequence. Randomization is stratified by center and gender. An interactive web response system (IWRS) will manage the randomization and the shipment of clinical supply kits to a clinic. Prior to the start of the study, a copy of the master randomization code will be supplied to the CMO clinical supply services and to the biopharmaceutical analyst at the Central Laboratory in sealed envelopes. The statistician responsible for the final analysis will have no access to the code until the primary analysis of the trial is completed.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance.

- The first placebo dose on enrolment day (Day -14) will be administered under supervision of a suitably qualified clinical staff after completion of the office procedures.
- The first DP13 dose of the treatment (Day 1) will be administered under the supervision of a suitably qualified clinical staff after completion of the recording of the patient's baseline characteristics.
- The IMP intake upon starting the 24-hour ambulatory blood pressure monitoring on Day -1 and on Day 55 is supervised by a suitable qualified clinical staff.

- Blood samples collected during the biweekly (or monthly in the case of a home/workplace visit) visits will be assessed for steady-state DP13 drug concentrations. In addition, blood samples for testing of the hypertension control therapy (doxazosin, verapamil or diltiazem or amlodipine) are collected and can be verified for proper medication intake. Patients will be reminded that drug concentration levels in the blood will be used as compliance checks.
- At each office visit, a clinical supply inventory will be performed on the returned IMP containers counting the unused capsules. The capsule counts are compared with the patient's diary records.

5.6. Concomitant Medication

After *de novo* diagnosis or confirmed diagnosis of PA, patients should not take diagnosis-interfering medications as listed in the Endocrine Society Clinical Practice guidelines for the duration of the study (*Funder et al., J Clin Endocrinol Metab 2016*). The guidelines list beta-adrenergic blockers, central alpha agonists, non-steroidal anti-inflammatory drugs (NSAIDs), potassium-wasting as well as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), renin inhibitors. In order to prevent uncontrolled hypertension during the study, a fixed-dose regimen of the alpha-receptor blocker doxazosin (1 - 8 mg QD) as first-line medication and, if necessary, the calcium channel blocker verapamil slow release (40 – 120 mg BID) or diltiazem (slow-release 90 - 360 mg daily) or amlodipine (2.5 – 10 mg QD) is implemented if clinically applicable 2 weeks prior to eligibility verification and the placebo run-in period. The medications are prescribed by the Investigator and supplied by local practice. The pharmacology of the two drugs has minimal effects on the renin-angiotensin-aldosterone system and drug-metabolizing enzymes and are therefore recommended for use during the diagnosis of PA. At the Investigator's discretion, the doses of doxazosin, verapamil or diltiazem or amlodipine are adjusted up to the run-in period should office systolic blood pressure exceed 190 mmHg or fall below 145 mmHg. The Investigator may adapt the background hypertension control therapy if in his opinion medication-related severe clinical sign or symptoms can be alleviated. If the medications are required and the doses adapted, the brand name, strength, frequency of dosing and reason for use is documented in the patient's source data. The dosage and regimen of the hypertension control therapy is fixed 2 weeks prior to study enrolment until study end. In men, approximately 5% of an oral DP13 dose is excreted into the urine in both unchanged form or as hydroxylated and glucuronidated metabolites. Therefore, no interaction with renally cleared co-medications is expected. *In vitro*, no metabolism-relevant cytochrome P450 (CYP) enzyme revealed to be significantly responsible for DP13 metabolism or was significantly inhibited by DP13. Therefore, no specific drug-drug interactions can be anticipated. Doxazosin is primarily metabolized in the liver by CYP3A4 and excreted into the faeces (SmPC). Verapamil is subject of a significant first pass effect in the liver involving CYP3A4, 1A2, 2C8, 2C9, 2C18 and primarily cleared by the kidneys (SmPC). Diltiazem is primarily metabolized in the liver by CYP3A4 and excreted into the urine (SmPC). Amlodipine is primarily metabolized in the liver by CYP3A4 and excreted into the urine (SmPC).
Patients will not take any new prescription or over-the-counter (OTC) medication, or have medication changes within 14 days prior to study start through completion of the post-study assessments (the duration of the study) without consent from the Central Review Board and Sponsor. Initiation of a new medication, OTC medication or medication change more than 14 days prior to starting the study should be already captured in the electronic database under concomitant medications and reviewed by the Central Review Board as per protocol prior to study enrolment. Paracetamol (up to 2 g/day for up to 5 days) is an acceptable concomitant medication to treat minor discomforts, illnesses, headaches or colds. Patients are allowed to continue other medications that are not excluded by the Endocrine Society Guidelines for the diagnosis of PA and by the Central Review Board if the patient is taking the medications consistently as prescribed for a specified condition. Generally, if any medication is required, the name, brand, strength, dosing frequency and reason for use is documented in the patient's source data. Patients will be asked to contact the Investigator should they desire any new concomitant medication.

Rescue Medication: At the Investigator's discretion, the following rescue treatments are proposed: Patients with serum/plasma potassium levels <2.5 mmoL/L should be given oral potassium supplements up to 3 grams per day. Patients with serum/plasma potassium levels ≥6.0 mmol/L during study treatment should undergo repeat blood sampling to verify the value in absence of any haemolysis. If the repeat sample indicates potassium levels ≥6.0 mmol/L, an ECG will be performed. In the absence of ECG changes, furosemide can be given to produce renal potassium excretion. In the presence of ECG changes, calcium gluconate can be given to decrease membrane excitability or insulin together with glucose can be given to shift potassium out of the blood system. Patients with an adverse event of symptomatic hypoadrenalism can be given substitutive therapy such as cortisol and if necessary, fludrocortisone to replace glucocorticoid and mineralocorticoid hormones. Patients with symptomatic hypotension should be put in the supine position and saline infusion can be given to restore blood pressure.

6. STUDY POPULATION

6.1. Identification and Numbering of Patients

Each patient is identified in the study by a unique number that is automatically assigned by the system when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout the study. Once assigned, the patient identifier must not be changed or reused for any other patient. A list identifying the patients by their number will be kept in the trial master file.

6.2. Determination of Sample Size

The sample size is set to N=36 patients with PA randomized into three treatment arms of approximately N=12 each. The sample size calculation was based on representative individual patient data derived from the PATO study (*Monticone et al., J Am Coll Cardiol 2017*) and on reported interventional studies with the aldosterone synthase inhibitor LCI699 (*Amar et al., Hypertension 2010*) and mineralocorticoid receptor antagonists in patients with PA (*Parthasarathy et al., J Hypertens 2011*). A potential dropout of up to 6 patients is considered in the sample calculation. The power calculation is based on both primary endpoints, i.e., the change in ARR and the change in blood pressure. The calculation yields a total of 30 patients for ARR and 26 patients for blood pressure. Therefore, a minimum of 30 patients are required to answer the two primary study questions. In order to consider possible dropouts, a total of 36 patients are to be enrolled. Since we are testing the two endpoints hierarchically in the primary analysis, the overall type I error is preserved at the 5% level. For the first primary study objective, a change in the ARR of 40% in the combined treatment groups is expected. This corresponds to an effect size of 0.69 on the log scale based on a standard deviation of 0.74 of log-transformed ARR as calculated from the data of the PATO study. Assuming a correlation of 0.5 between values at start and end of the 8-week treatment period, 30 patients are required to detect an ARR decrease of 40% with a power of 95% at two-sided alpha levels of 0.05 based on a paired means test. For the second primary study objective, a change in ambulatory systolic blood pressure (aSBP) of 6 mmHg in the combined treatment groups can be significantly detected in 26 patients at a two-sided alpha level of 0.05 with a power of 95% based on a standard deviation of 8 mmHg. Furthermore, a 60% ARR decrease and a 10-mmHg aSBP reduction can be significantly measured in 11 patients. Therefore, these assumptions may allow the detection of treatment effects in the individual dose arms and allow the assessment of a dose-response relationship.

6.3. Inclusion Criteria

Patients will be required to satisfy all of the following eligibility criteria:

1. Patients with a guideline-recommended diagnosis of PA consisting of:
   - 1.1. ARR ≥40 derived from a PAC ≥15 ng/dL and a PRA <1.0 ng/mL/h; an ARR ≥3.7 is derived with PRC <15 mU/L instead of PRA as denominator and
   - 1.2. PAC >7.0 ng/dL after a 4-hour infusion of 2 litres 0.9% saline (saline load suppression test) or instead if clinically justified for risk of volume expansion ARR>30 and PAC >11 ng/dL (respectively ARR>2.4 with PRC in mU/L instead of PRA as denominator) after 2 hours of an oral intake of 50 mg captopril and
   - 1.3. determined within <1 year of study enrolment
2. Patients with PA per above criteria and
   - 2.1. sitting office systolic blood pressure (oSBP) >145 mmHg and if applicable
   - 2.2. in presence of non-interfering hypertension control therapy consisting of doxazosin (1 – 8 mg QD) as first-line medication and, if necessary, only verapamil slow release (40 – 120 mg BID) or diltiazem (slow-release 90 - 360 mg daily) or amlodipine (2.5 – 10 mg QD) at adjusted and fixed doses
3. Patients with PA per above criteria will have a:
   - 3.1. estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 using the MDRD-4 GFR equation: GFR = 175 x [serum creatinine (mg/dL)]$^{-1.154}$ x (age)$^{-0.203}$ x f* (*f=1.000 for men; f=0.742 for women; the formula is further multiplied by factor 1.210 for black skinned patients)
   - 3.2. body mass index (BMI) between 18 and 34 kg/m^2, inclusive
   - 3.3. body weight between 40 and 110 kg, inclusive

4. Patients with PA per above criteria will be:
   4.1. female or male patients between 18 and 65 years of age, inclusive
   4.2. able to provide voluntary informed written consent to study enrolment

6.4. Exclusion Criteria

Patients will be excluded from the study if they satisfy any of the following criteria:

1. Patients with PA and:
   1.1. treated with spironolactone within 2 months of enrolment
   1.2. hyperkalaemia of >5.0 mmol/L
   1.3. prolonged QT intervals with QTc of >500 msec using Bazett's formula
2. Patients with PA and:
   2.1. Sitting office systolic office blood pressure (oSBP) >190 mmHg and/or
   2.2. sitting office diastolic office blood pressure (oDBP) >110 mmHg and if applicable
   2.3. in presence of non-interfering hypertension control therapy consisting of doxazosin (1 – 8 mg QD) as first-line medication and, if necessary, only verapamil slow release (40 – 120 mg BID) or diltiazem (slow-release 90 - 360 mg daily) or amlodipine (2.5 – 10 mg QD) at adjusted and fixed doses
3. Patients with PA who will not consent to special contraception measures during the entire study period, specifically
   3.1. female patients not withdrawing oral contraceptives >2 weeks prior to enrolment
   3.2. female patients not using intrauterine devices (IUD), diaphragm or sponge with spermicide
   3.3. male patients not using condoms and not refraining from sperm donation
4. Patients with PA and a medical history of:
   4.1. cerebro- and cardiovascular events (stroke, myocardial infarction, percutaneous transluminal coronary angioplasty, long QT syndrome, Brugada syndrome, acute heart failure) within 6 months of study enrolment
   4.2. gastrointestinal tract surgeries or malabsorption syndromes
   4.3. chronic use of oral or parenteral corticosteroids
   4.4. use of drugs prolonging the QT interval (e.g., digoxin, sotalol)
5. Patients with PA who:
   5.1. participated in any clinical study within 6 weeks
   5.2. suffered a significant blood loss within <2 months
   5.3. had a significant illness within <2 weeks
   5.4. are pregnant or breastfeeding
   5.5. are unable to follow all study procedures

6.5. Central Eligibility Verification

To assure the enrolment of a homogenous patient population without any selection bias, central and formal eligibility verification with a documented eCRF-based case review process led by the Central Review Board is mandatory prior to enrolment by Day - 14. The Investigator presents via eCRF the case and the Central Review Board leads the case review through a structured assessment of patient diagnosis, meeting the inclusion and exclusion criteria and any clinical precautions. Eligibility confirmation must be completed by study Day -14. The Central Review Board has the final decision on enrolment. The criteria for enrolment or rejection are documented in the patient's source data and eCRF.

6.6 Specific Restrictions / Requirements

Patient Diary: Patients are requested to record their daily drug intake in a provided diary. The diary will list the time of the intake of the investigational drug as well as the control blood pressure medications. In addition, on the days of ambulatory blood pressure monitoring (Day -1/1 and Day 55/56), patients will record their physical activities, meals and sleep hours.

Diet: Patients are not requested to follow any specific dietary restrictions such as a salt-controlled diet or alcohol restrictions before or during the study. Alcohol consumption is however limited to 25 grams of ethanol per day (e.g., 2 ordinary beers, 2 glasses of wine). Patients have blood sampling (Day -14, Day 1, Day 14, Day 28, Day 42, Day 56 and Day 70) in an overnight fasted state.

Exercise: Patients will be requested not to undertake physical exercise on the days of visits prior to 8:00 am and on the days of 24-hour ABPM (Day -1/1 and Day 55/56).

Blood Donation: Patients are requested not to donate blood 2 weeks prior to study start, during the study and 1 month after the final visit.

Contraception: Female patients and male patients with partners of childbearing potential must use one barrier method of contraception and another method of proven efficacy. Acceptable methods of contraception include:

- Male condoms
- Female condoms
- Intrauterine device (IUD)
- Male sterilization or vasectomy
- Female sterilization
- Diaphragm, cap, or sponge in conjunction with spermicide

Hormonal contraceptives are not permitted during the study as they interfere with the renin-angiotensin-aldosterone system. Patients are required to refrain from donation of sperm from enrolment until 3 months after the last dose of study drug. For patients who are exclusively in same sex relationships, contraceptive requirements do not apply.

6.7. Patient Withdrawals / Replacements

A patient is free to withdraw from the study at any time. In addition, the Investigator together with the Central Review Board may decide for justified reasons of medical prudence to discontinue a patient (see section 4.5 on Patient Withdrawal Criteria). The Sponsor will be notified and date and reason(s) for the withdrawal documented in the patient's source data and eCRF. Should the randomization code be broken for a patient, the date, time and reason will be recorded in the patient's source data. According to the intention-to-treat (ITT) principle, no replacement of randomized patients if they are withdrawn or choose to withdraw is foreseen. Investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a patient is withdrawn or chooses to withdraw, all relevant end-of-treatment procedures such as physical and clinical laboratory evaluations and office blood pressure measurements will be performed prior to discharge from the study. If the patient has been on DP13 treatment for >1 week, a 24-hour ambulatory blood pressure monitoring is performed prior to discharge from the study if possible. The Investigator may also request that the patient return for an additional follow-up visit.

6.8. Patient Re-screening and Re-enrolment

Re-screening: Patients are eligible for re-screening after a >3-month time lapse from initial screening if non-controllable events such as the COVID-19 pandemic and/or hospital closures for ambulatory procedures or other extraordinary circumstances prevent study enrolment according to protocol. Patients may also be re-screened after a >6-month time lapse if disease progression as assessed by the Investigator justifies the re-assessment of study eligibility.

Re-enrolment: Patients are eligible for re-enrolment after a >3-month time lapse from initial enrolment prior to randomization if non-controllable events such as the COVID-19 pandemic and/or hospital closures for ambulatory procedures or other extraordinary circumstances prevent study continuation according to protocol.

7.STUDY PROCEDURES

The schedule and timing of study procedures is outlined in the appended Study Plan (section 18). All protocol-defined procedures including repeat evaluations must be reported in the patient's source documentation. Any other procedures are entered in the "Unscheduled Visit" eCRF page. Every

effort will be made to schedule and perform office procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions and the other procedures to be performed at the same time. The order of priority for scheduling procedures around is (in descending order of priority):

1) Collection of 24-hour urine bottle and ABPM devices (Day 1 and Day 56 only)
2) Spot urine, body weight recording, AE recording and ECG monitoring after rest and in a sitting position
3) Blood pressure measurements (after a >15-minute rest)
4) Blood sampling
5) Verification of treatment compliance
6) IMP supply
7) Supervised IMP intake (Day -14, Day -1, Day 1 and Day 55 only)
8) Any other procedures

Patients will schedule biweekly visits with a flexibility of +/- 3 days except for the Day 55/56 visits, where +/- 2 days flexibility is acceptable (note, like Day -1 and Day 1 visits, Day 55 and 56 visits must occur on subsequent days to accommodate 24-hour recordings). Patients will report to the clinical research unit for their visits in the morning and undergo all procedures as summarized below by 10:00 am. The Day -1, 14, 42 and 55 visits may be performed at the patient's home or workplace (if appropriate facilities are available) by medically qualified personnel. The study starts with the Day -14 visit to record the run-in baseline characteristics and a supervised first IMP intake. For the assessment of the baseline (Day 1 visit) and end of DP13 treatment characteristics (Day 56 visit), patients will be provided with the ambulatory blood pressure monitoring devices and 24-hour urine sample bottles 24 hours ahead (Day -1 and Day 55 visits). On these days and on Day 1, clinically qualified staff properly supervises IMP intake and activates the ABPM device. The visits will last up to 1 hour. During the patient's sitting rest period of ≥15 minutes, the Investigator will monitor body weight, adverse events, ECG, available safety and tolerability data i.e., laboratory safety data, urine pregnancy tests (UPT) and vital signs to confirm the patient's wellbeing and subsequently proceed with blood pressure recordings and blood sampling procedures. In addition, the Investigator will check on the patient's treatment adherence and clinical supply inventory and remind him/her of the importance of study compliance. If necessary, the patient will remain in the clinic until any adverse events or safety assessments of concern have been resolved. Additional non-residential visits may be required based on ongoing review of study data.

7.1. Home or Workplace Visits

The Investigator, according to the patient's needs and clinical condition and/or to implement EMA- or other local authority-mandated actions limiting patient access to sites to reduce COVID-19 related risks, may consider having the Day-1, Day 14, Day 42 and Day 55 visits at the patient's home or workplace. Home/workplace visits must be performed by medically qualified personnel if appropriate facilities are available. The home/workplace visits will be managed by medically qualified personnel approved, properly trained and delegated by the local PI. The home/workplace visits will be conducted according to a home/workplace visit-specific manual approved by the Sponsor.

7.2. Visit Procedures

Spot Urine Sample: The Investigator will collect a spot urine sample for a safety analysis. The sample will be analyzed at the local laboratory for routine measures. The results are reviewed and interpreted by the Investigator.
A pregnancy test by means of urine dipstick is performed on women of childbearing potential.

Body Weight Recording: The Investigator will record the patient's body weight (in underclothes and without shoes) upon arrival to the scheduled office visits. Subsequently, the patient is seated for resting and for AE/ECG recordings.

Adverse Event Reporting: The condition of each patient will be monitored from the time of signing the ICF to final discharge from the study including the follow-up period. Any signs or symptoms will be observed and elicited by the Investigator or medically-qualified personnel during the visit by open questioning such as: "How have you been feeling since you were last asked?" Patients will also be encouraged to spontaneously report adverse events occurring at any other time during the study and to list them in their diary.
Any adverse events and remedial action required will be recorded in the patient's source data. The nature, time of onset, duration and severity will be documented, together with the Investigator's opinion of the relationship to study drug administration. Any clinically significant abnormalities identified during the course of the study will be followed up until they return to normal or can be clinically explained.
Adverse event definitions, assignment of severity and causalities and procedures for reporting SAEs are detailed in section 8.

Lead Electrocardiogram: A single 12-lead resting ECG with a 10-second rhythm strip will be recorded after the patient has been sitting for at least 5 minutes on Day -14, Day 1, Day 28, Day 56 and Day 70 visits according to Study Plan. The ECG recording will be repeated if the QTc is >500 msec. If repeated, the repeat values will be used for data analysis. Additional 12-lead ECGs will be performed at other times if judged to be clinically appropriate or if the ongoing review of data suggests a more detailed analysis. Clinical reference ranges will be applied to all ECG parameters throughout the study. The ECG machine will compute the PR and QT intervals, QTc, QRS duration and heart rate. The QT interval will be corrected for heart rate using Bazett's formula (QTcB).

Blood Pressure Measurements: Blood pressure and pulse rate will be measured at each visit after a >15-minute rest in sitting position as indicated in the Study Plan. Blood pressure and pulse rate will be measured using a locally calibrated and validated automated oscillometric device. An adapted wrap cuff is placed on the dominant arm. Three repeat measurements with a 10-minute interval are recorded; the average of the 2nd and 3rd measurements are study relevant. Each single patient will be assessed throughout the study with the same equipment and procedure.

Blood Sampling: Blood samples from overnight fasted patients are collected for clinical laboratory evaluations at the visits indicated in the study plan. On Day 14 and Day 42, blood samples may be collected by medically qualified personnel at the patient's home or workplace (if appropriate facilities are available). Because of the diurnal rhythm of the renin-angiotensin-aldosterone system, blood is drawn as early as possible in the morning hours of the visits, i.e., prior to 10:00 am. Additional and/or more detailed clinical laboratory evaluations are performed at other times if judged to be clinically necessary by the Investigator. The maximum volume of blood drawn from each patient during one visit is 60 mL and over the entire study will not exceed the limit of 400 mL. Any changes to the scheduled times will be agreed with the Sponsor and documented in the TMF. Safety laboratory samples are analysed locally. The results are reviewed and interpreted by the Investigator. Samples for pharmacokinetics, pharmacodynamics and therapeutic drug monitoring are locally processed, stored frozen and at the end of the study shipped for central analysis. Detailed procedures for collecting and processing blood samples will be detailed in a separate Laboratory Manual.

Treatment Compliance Verification: The Investigator will verify treatment compliance on visit days by checking the patient's adherence to the daily drug intake reported in the patient's drug intake diary, by asking specific questions such as "When and how have you taken the capsule in the last days?" and by performing a clinical supply inventory by counting the content of the previous supply jar. In addition, the Investigator verifies adherence to the blood pressure control therapy and any other concomitant medication. The patient will also be reminded that treatment adherence will be demonstrated by the analysis of the blood samples for DP13 content along with any therapeutic drug monitoring of the hypertension control medications. Reasons for non-compliance have to be identified and documented in the patient's source data.

IMP/Hypertension Control Medication Supply: After verification of treatment compliance, the Investigator will handout an IMP jar(s), each containing 14(+4) capsules for a bi-weekly or monthly visit supply to the patient. The handout of a new supply jar at occurs only upon collection and inventory assessment of a previously used and returned jar. The required blood pressure control medications are prescribed by the Investigator after patients have signed their ICF for study enrolment. The content of the supply is eCRF recorded to verify treatment compliance at subsequent office visits.

7.3. Home Procedures

IMP/Hypertension Control Medication Intake: Patients receive an IMP jar from the Investigator for a biweekly supply containing 14(+4) capsules. In the event of a home/workplace visit on Day 1 and Day 28, a monthly supply of capsules can be provided in order to ensure supply for 1 month. Patients are instructed to take one capsule with water in the morning between 06:30 and 08:30 prior to breakfast. The capsule should be swallowed whole and not chewed, dissolved or opened. Patients will record the daily capsule intake in their diary along with any time or intake deviation. A supervised capsule intake occurs only on Day -14, Day -1, Day 1 and Day 55 during the visit. The hypertension control medication is administered as prescribed by the Investigator. Patients will record the daily intake of the control medication in their diary.

24-Hour Ambulatory Blood Pressure Monitoring: Twenty-four hour ambulatory blood pressure monitoring (ABPM) will include mean daytime systolic and diastolic blood pressure values (measured every 20 minutes from 8 am to 10 pm) and night-time values (measured every 20 minutes from 10 pm till 8 am) along with heart rate measurements on Day -1 prior to administration of the first DP13 dose and on Day 55 after the administration of the second-to-last DP13 dose. A locally calibrated and validated device will be used; the device is fitted at the hospital outpatient department or at the patient's home or workplace by medically-qualified staff on Day -1 and Day 55 prior supervised IMP intake by the patient. The particular device used for a patient cannot be switched during treatment. The light digital monitor with convenient carry pouches takes the blood pressure reading at regular

intervals by inflating and subsequently deflating customized cuffs placed around the non-dominant upper arm for 24-hour recording of about 70 readings. The patient may follow his/her regular routine yet refrain from exercising or taking a bath or shower. In addition, to assure proper measurements, the patient should sit down prior to reading, keep the cuff at the same level as the heart and rest the arm steady. The patient will also be asked to keep a diary on activities, meals and sleep to document what he/she was doing just before the reading was taken. At the end of the 24-hour period, the patient may remove the monitor and cuff, shower or bathe and return the device to the Investigator at the clinic. The machine will have stored all readings as source data that are uploaded in the eCRF.

24-Hour Urine Sampling: Urine will be collected into standard weight polyethylene containers over 24 hours on Day -1 (prior to the first treatment dose) and on Day 55 (prior to the last treatment dose). The Investigator or qualified staff will hand out the containers during the outpatient visit or home/workplace visit. Procedures for collecting and processing of the urine samples will be detailed in a separate document. The patient will return the urine containers to the Investigator on the subsequent office visit (Day 1 and Day 56). After measuring the total 24-hour urine volume, volume-adjusted aliquots are generated following the Laboratory Manual procedures and shipped to the Central Laboratory.

7.4. Laboratory Procedures

Sample Processing and Shipment: Spot urine samples and blood samples for safety laboratory analyses are processed according to local routine practice. The other collected blood and 24-hour urine samples are processed according to the Laboratory Manual. Frozen plasma and urine aliquots for pharmacokinetic, pharmacodynamics and therapeutic drug monitoring will be shipped at the end of the study to the Central Laboratory. Procedures for shipping will be detailed in a separate document.

Local Blood Analyses: The safety laboratory sample is analysed at the local clinic laboratory for routine electrolyte, metabolic and lipid panels. The screening blood samples are analysed at the local clinical laboratory for verification of applicability of I/E criteria.

Central Blood Analyses: The pharmacokinetic and pharmacodynamic blood samples are processed locally to plasma samples and analysed at the Central Laboratory.

Local Urine Analyses: The spot safety urine sample is analyzed at the local clinic laboratory for routine measures. Women of childbearing potential provide a pregnancy test. Any unclear results are clarified with a blood-based pregnancy test.

Central Urine Analyses: The aliquots generated from quantitative 24-hour urine samples are analyzed at the Central Laboratory.

8.SAFETY

8.1. Adverse Event Reporting

Adverse Event: An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and/or unintended sign, symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not related to the pharmaceutical product. Abnormal laboratory values constitute adverse events only if they induce clinical sign or symptoms that are considered clinically significant or require intervention.

The causal relationship between an adverse event and the study drug is defined as follows:

Not Related	The adverse event is definitely caused by the patient's clinical state or the study procedure/conditions.
Unlikely Related	The temporal association between the adverse event and the drug is such that the drug is not likely to have any reasonable association with the adverse event.
Possibly Related	The adverse event follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
Related	The adverse event follows a reasonable temporal sequence from the time of drug administration, abates upon discontinuation of the drug, and reappears when the drug is reintroduced.

The severity of an adverse event will be recorded as one of the following:

Mild	Easily tolerated; does not interfere with normal daily activities; does not require intervention
Moderate	Causes some interference with daily activities; minimal, local, or non-invasive intervention indicated
Severe	Medically significant event; daily activities limited or completely halted; hospitalisation or prolongation of hospitalisation indicated

Every reasonable effort will be made to follow-up patients who have an adverse event at the post-study visit, if possible, until resolution.

Adverse Event Reactions: All noxious and unintended responses to an IMP (i.e., where a causal relationship between an IMP and an adverse event is at least a reasonable possibility) related to any dose should be considered adverse drug reactions. For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function is to be considered an adverse drug reaction. An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved IMP). As Reference Safety Information (RSI), the Investigator Brochure will be used in order to evaluate the expectedness of each event.

Serious Adverse Event: A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- is a congenital anomaly/birth defect

An important medical event that may not result in death, be life threatening or require hospitalisation may be considered a serious adverse drug experience when, based upon appropriate medical judgement, it may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalisation, or the development of drug dependency or drug abuse. Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

Definition of Life Threatening: An adverse event is life threatening if the patient was at immediate risk of death from the time of the event as it occurred; i.e., it does not refer to an event that might have caused death if it had occurred in a more serious form. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalisation: Adverse events requiring hospitalisation should be considered serious. In general, hospitalisation signifies that the patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at home. When in doubt as to whether hospitalisation occurred or was necessary, the adverse event should be considered serious. Hospitalisation for elective surgery or routine clinical procedures, which are not the result of an adverse event, need not be considered adverse events and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an adverse event and either 'serious' or 'non-serious' attributed according to the usual criteria.

Serious Adverse Event Reporting: Every Serious Adverse Event (SAE), regardless of suspected causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment must be reported to the Sponsor within 24 hours of site awareness. Any SAE experienced after this 30-day period should only be reported to the Sponsor if the Investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. The follow-up information of an SAE should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation. Information about all SAEs will be recorded using the safety tool integrated into the eCRF. In case of technical difficulties, SAE notification can be carried out by using a paper form contacting the Contract Research Organization (CRO) in charge of Pharmacovigilance. The event is nevertheless to be reported on the eCRF once technical difficulties have been resolved. If unblinding of an individual patient treatment code is deemed necessary, such as in case of patient emergencies or medically important adverse events (i.e., SUSAR), the code break will be performed using the tool integrated in eCRF by the Pharmacovigilance unit in charge, after agreement with the Sponsor. The documentation in an unblinded version will permit the notification of the case to the Regulatory Authorities. The treatment information will remain internally at the Pharmacovigilance Department and will be notified to the Sponsor only at the end of the study.

Serious adverse event reporting requirements for Swiss Centers: Serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) are to be reported in accordance with the Swiss Ordinance on Clinical Trials in Human Research as follows:

Art. 40 - Serious adverse events (SAE) in clinical trials of medicinal products

1. If, in the course of a clinical trial, serious adverse events occur in participants, the Investigator must document these in a standardised manner and notify the sponsor within 24 hours after they become known.
2. The Investigator shall notify the responsible ethics committee of a fatal serious adverse event occurring at a trial site in Switzerland within 7 days.
3. The coordinating Investigator shall also report events as specified in paragraph 2 to the responsible ethics committees concerned within the same period.

Art.41 -Suspected unexpected serious adverse reactions (SUSAR) in clinical trials of medicinal products

1. If, in the course of a clinical trial, a suspected unexpected serious adverse reaction occurs in participants, the Investigator must document this in a standardised manner and notify the sponsor within 24 hours after it becomes known.
2. The Investigator shall notify the responsible ethics committee of a fatal suspected unexpected serious adverse reaction occurring in Switzerland within 7 days, and of any other suspected unexpected serious adverse reaction within 15 days.
3. If a suspected unexpected serious adverse reaction occurs at one of the trial sites, the coordinating Investigator shall also notify the responsible ethics committees concerned in accordance with paragraph 2, within the same period.
4. The notifications specified in paragraph 2 shall also be made to the Agency. This obligation rests on the sponsor.

Special Situations: Safety events of special situation include: 1) Medication error 2) Abuse/Misuse/Overdose. All events of special situation, with or without associated adverse event, should be monitored and recorded in the eCRF, as described in 8.1. section.

8.2. Reporting of Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the treatment under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. If a female patient becomes pregnant during the course of the study, the treatment should be discontinued immediately. Also, paternal exposure should be reported. Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. The Investigator shall report all pregnancy exposure occurring in a female patient or in a male patient's partner within 24 hours to the Sponsor using the safety tool integrated into the eCRF. In case of technical difficulties, pregnancy notification can be carried out using a paper form by contacting the Contract Research Organization (CRO) in charge of Pharmacovigilance. The Investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

9. STUDY TERMINATION

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may terminate part of or the entire study after consultation with the Sponsor. In addition, the Sponsor may terminate part of or the entire study for safety or administrative reasons. A written statement fully documenting the reasons for study termination will be provided to the EC/IRB and national Health Authorities. Patients completing per protocol the entire study are switched at the end of the study to their Investigator-prescribed standard of care. Any subsequent information on patient disease subtyping i.e., diagnostic work-up to identify the presence of an underlying aldosterone-producing adenoma (APA), the lateralization of an APA or the detection of bilateral adrenal hyperplasia (BAH) are requested by the Central Review Board and Sponsor for potential additional retrospective analyses. This information will be obtained through contacts with the patients' treating physician.

10. STATISTICAL METHODS

10.1. Hypothesis Testing and Sample Size Calculation

To maintain the overall type I error rate at 5%, a sequential test procedure for the two primary objectives is adopted. The first test determines the effect on ARR, the first primary objective at the nominal two-sided alpha level of 5%. If the null hypothesis can be rejected, the second test determines the effect on ambulatory systolic blood pressure, the second primary objective at the nominal two-sided alpha level of 5%. To have enough power for both primary comparisons as well as for secondary comparisons within single groups, the power for the individual tests is set at 95%.

First Primary Objective

Hypothesis:	The working hypothesis is that there is a difference in ARR between baseline and week 8 in all three groups combined.
Null-hypothesis H_0:	$m_1 = m_2$
Alternative hypothesis H_1:	$m_1 \neq m_2$
Primary outcome:	Change in ARR from baseline to week 8
Test:	Paired means test
Power:	95%
Significance level:	5% (two-sided)
Standard deviation:	The standard deviation of ARR determined as PAC/PRA was derived from a representative sample of 27 patients with PA. Due to the skewed data distribution, ARR was first log-transformed. The standard deviation of log-transformed ARR was 0.74, the back-transformed geometric mean was 1117 ng/L/ng/mL/h. Neither the correlation of log-transformed ARR between two time points nor the standard deviation of the change are known.
Sample size:	The sample size was calculated based on log-transformed values. The expected percent (%) decrease in ARR was log-transformed and expressed as effect size.
Total sample size:	The total number of patients with PA varies depending on the expected ARR decrease and expected correlation between baseline and week 8 values.

Second Primary Objective

Hypothesis:	The working hypothesis is that there is a difference in ambulatory systolic blood pressure (aSBP) between baseline and week 8 in all three groups combined.
Null-hypothesis H_0:	$m_1 = m_2$
Alternative hypothesis H_1:	$m_1 \neq m_2$
Primary outcome:	Change in aSBP from baseline to week 8
Test:	Paired means test
Power:	95%
Significance level:	5% (two-sided)
Standard deviation:	The standard deviation of the change in aSBP was derived from two publications and data from the DP13C101 phase I study. Amar *et al.* reported that treatment with LCI699 over 4 weeks reduced the 24-hour ambulatory SBP by -4.1 mmHg (95% CI: -8.1 to -0.1), which yields a standard deviation of 7.4 mmHg for the difference. Parthasarathy *et al.* reported that reductions from baseline in office SBP at the final visit were -9.9 mmHg (SE 2.3) for eplerenone and -27.0 mmHg (SE 2.3) for spironolactone, which yields a standard deviation of 19.1. In the DP13 phase 1 study, standard deviations ranging from 6 to 10 mmHg were observed for changes in supine SBP from baseline to day 2 to 8 in the group receiving 8 mg DP13 QD.
Total sample size:	The total number of patients with PA varies depending on the expected difference and the expected standard deviation of the difference between baseline and week 8 values.

The final sample size was set at 36 patients in total with 12 patients in each dose arm (see section 6.2).

10.2. Statistical Analysis Methods

The detailed statistical analyses will be described in the statistical analysis plan (SAP) as a separate document.

Analysis Set: The full analysis set (FAS) is defined as all randomized patients who received at least one dose of study drug. Following the intention-to-treat (ITT) principle, patients in this population will be analysed according to the treatment dose they were randomized to. The per-protocol (PP) set is based on the FAS excluding patients with major protocol violations and patients who did not receive the randomized treatment. Major protocol violation will be defined as follows: 1) patients who did not receive the assigned treatment dose; 2) patients with significant protocol violation that affect efficacy evaluations. The safety population is defined as all randomized patients who received at least one dose of study drug. Patients will be analysed according to the actual dose they received.

Baseline Characteristics: Baseline characteristics will be presented using descriptive statistics based on the FAS. Continuous variables will be summarized as mean and standard deviation as well as median and interquartile range. Categorical variables will be summarized as frequency and percentage.

Primary Analysis: The primary analysis will be an ITT analysis, i.e., all patients will be analysed in the dose arms they were allocated to. The first primary outcome, change in ARR from baseline (Day 1) to end of the 8-week DP13 treatment period (Day 56), will be calculated from a linear model. Before analysis, ARR will be log-transformed due to its log-normal distribution. The log-transformed ARR value at Day 56 will be used as dependent variable, the log-transformed baseline value, dosage group, and the stratification factors used for randomization as independent variables in the model. The overall change from baseline, the change in individual dosage groups, and the dose-dependence will be assessed using contrasts. All effect measures will be back-transformed to the original scale (i.e., exponentiated) and accompanied by a 95%-confidence interval and associated p-value. The second primary outcome, change in aSBP, will be analysed likewise. Since SBP values are normally distributed, no transformation is needed.

Secondary Analysis: Changes in secondary and exploratory outcomes from baseline (Day 1) to end of the 8-week DP13 treatment period (Day 56) and end of the 2-week withdrawal period (Day 70) will be analysed as described above using linear models. If necessary, values will be transformed in an adequate way to obtain normally distributed model residuals. Office blood pressure will be repeatedly measured at baseline (Day 1) and at biweekly office visits (week 2, week 4, week 6, week 8 and week 10), and therefore be analysed in a mixed-effects repeated-measure model, with dosage group, time point, and stratification factors as fixed effects and a random intercept for the patients. Adverse and serious adverse events will be presented descriptively, showing the total number of events as well as the absolute and relative frequency of patients with events in each dosage group. In a per-protocol analysis, all primary, secondary, and exploratory outcomes are analysed using the PP analysis set. Further secondary analyses such as subgroup analyses will be specified in the SAP.

Missing Data: In main analyses according to the ITT principle, patients with missing outcome values will not be disregarded from the analysis. In a sensitivity analysis, multiple imputations will be applied. The procedure will be described in the SAP.

10.3. Interim Analysis

There are currently no reliable data on the correlation between baseline and follow-up ARR and SBP values or on the standard deviation of the change of these values from baseline. Therefore, the sample size will be reassessed during the study to assure sufficient power. One blinded interim analysis is therefore planned after completion of two thirds of the patients (N=24) to reassess the sample size assumptions. The reassessment of the sample size will only be based on the standard deviation of the baseline and follow-up values, the standard deviation of changes from baseline and correlations between baseline and follow-up values observed in the study data. Observed changes will not be displayed, nor will expected changes used for power analysis be modified. No formal testing of changes will take place; therefore, the alpha-level does not require adjustment.

11. QUALTITY ASSURANCE AND CONTROL

11.1. Data Quality Assurance

The CRO working on behalf of the Sponsor a proprietary study web portal and database that is GCP and FDA 21 CFR Part 11 compliant. The CRO will review the data entered in the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. The occurrence of any protocol deviations will also be checked. If clarifications are needed, the Data Manager will raise queries through the web application. Designated Investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses. Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents. Concomitant medications and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using MedDRA. The database will be locked after all the above actions have been completed and the database has been declared complete and accurate.

11.2. Case Report Forms

Designated Investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the Electronic Data Capture system until they are trained. Web-based software will be used, and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a ‘login mask’ requiring user ID and password and may read, modify, and update only the information entered at his or her site and according to their profile. Each page lists a site code and a subject code. On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the Sponsor. The Investigator will certify that the data entered in the eCRF are complete and accurate. After database lock, the Investigator will receive a CD-ROM of subject data for archiving at the investigational site.

11.3. Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information. All information on CRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient). Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific Monitoring Plan (MP). No information in source documents about the identity of the patients/subjects will be disclosed.

11.4. Data Storage and Archiving

All primary data generated in the clinical study or copies thereof (e.g., laboratory records, data sheets, correspondence, photographs, computer records), which are a result of the original observations and activities of the clinical study and are necessary for the reconstruction and evaluation of the study report, will be retained in the archive of the clinic for a period of 25 years in coded form after issue of the final clinical study report (CSR). At this time the Sponsor will be contacted to determine whether the data should be returned, retained, or destroyed on their behalf. Regardless, all data shall remain encoded. The Sponsor will be notified of the financial implications of each of these options at the time. It is the Sponsor’s responsibility to consider any regulatory implications of these options. No data will be destroyed without the agreement of the Sponsor. Biological samples may be retained exclusively for analyses stated in the protocol and until completion of the clinical study report, after which all samples will be destroyed. The samples will not be used for any other purposes. The Sponsor will be notified of the intent to destroy samples and any financial implications before specimens are destroyed on their behalf.

12. REPORTS AND PUBLICATIONS

12.1. Reports to the EC/IRB and HAs

Upon completion of the study, the Investigator will provide the Ethics Committee (EC) or Institutional Research Board (IRB) with a summary of the study outcome. The national Health Authority (HA) will be provided with a Declaration of the End of a Clinical Trial form and safety report (within 90 days of completion or within 15 days of a premature termination).

12.2. Data Analysis

The CRO will perform the data analysis. The study results will be reported in one clinical study report (CSR). A detailed statistical analysis plan (SAP) describing the methodology to be used will be issued by the CRO and finalized upon Sponsor approval prior to database lock.

12.3. Clinical Study Report

The CRO will prepare an integrated clinical efficacy and safety report that requires Sponsor approval. The report will be in structure and content accordance with the International Council for Harmonisation (ICH). The draft report may be submitted for quality assurance audit, the findings of which will be incorporated into the final version. An electronic copy of the final report will be provided to the Sponsor. The study report will be provided in PDF format unless otherwise agreed with the CRO.

12.4. Publications

The sponsor assures that all results of this study are published in a peer-reviewed journal in line with the Declaration of Helsinki (World Medical Association, 2008 #2). All results relate to all outcomes as defined in this protocol regardless of the direction or statistical significance. It will be assured that the manuscript follows the principle of the CONSORT guidelines or any other applicable reporting guideline (www.equator.org). Co-authorship on any of the publications will be based on contribution to the study and manuscript according to the criteria of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors, 2009; www.icmje.org). Before any data from the study are published on the initiative of the Central Review Board, a manuscript will be sent to the Sponsor for review and approval at least 30 days prior to submission to the publisher.

13. REGULATORY CONSIDERATIONS

13.1. Clinical Trial Authorization

This investigation will only be performed after the national Health Authorities have issued a Clinical Trial Authorisation for this study. Health Authority approval will be sought in parallel with EC approval. The Health Authorities must also give their written approval of any substantial amendments to the approved protocol or IMP Dossier likely to affect the safety of the subjects or the conduct of the study (except for emergency modifications required for subject safety). The body responsible for making the submission of the clinical trial application will maintain records of all correspondence with the Health Authorities.

13.2. Visits by Regulatory Authorities

Except for statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site by an outside authority before the Inspectors are permitted access to any of the study records or study areas.

14. ETHICAL CONSIDERATIONS

14.1. Ethics Committee Approval

An Ethics Committee (EC) or Institutional Review Board (IRB) will consider this study. The study will not start until the EC have given their written approval of the protocol and informed consent form. If there are any changes to the approved protocol (except for emergency modifications required for subject safety), a protocol amendment will be issued by the Sponsor. The EC must give their written approval of any substantial amendments likely to affect the safety of the subjects or the conduct of the study. The EC must be notified of all other changes. The CRO will maintain records of all correspondence with the EC.

14.2. Informed Consent

Prior to the commencement of the study, each patient will be provided with a study-specific informed consent form (ICF) giving details of the investigational medicinal product (IMP), procedures, and potential risks involved. Patients will be asked to provide consent for their study samples to be used for further analysis, which will be reported separately from this study. Patients will also be instructed that they are free to obtain further information from the Investigator and that they are free to withdraw their consent and to discontinue their participation in the study at any time. The approved Informed Consent Form must be filed in the study files (clinical Trial Master File [TMF] and Investigator File [IF]). All signed ICFs will be filed in the Investigator's file at site only. Patients will be identified in documentation and throughout evaluation by the number assigned to them during the study. Patients will be informed that all study findings will be stored electronically and handled in the strictest confidence. Following discussion of the study with the Investigator, patients will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent.

14.3. Declaration of Helsinki

This study will be conducted in accordance with consensus ethics principles derived from the Declaration of Helsinki on medical research involving human subjects.

15. REGULATIONS

15.1. Good Clinical and Manufacturing Practice

This study will be conducted in accordance with the following guidelines and directives:

- ICH E6 (R2): Good Clinical Practice (GCP): Consolidated guideline CPMP/ICH/135/95 (effective 14 June 2017), adopted in the EU by CPMP, the committee for proprietary medicinal products at the EMA
- European Commission Directive 2001/20/EC (April 2001)
- European Commission Directive 2003/94/EC (October 2003)
- European Commission Directive 2005/28/EC (April 2005)
- Manufacture of Investigational Medicinal Products: Volume 4, Annex 13 of the EU Guidelines to Good Manufacturing Practice (GMP) (February 2010)

15.2. Protocol Adherence

The clinical site will adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the Investigator. All such deviations will be documented in the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the clinical study report. The CRO Quality Assurance Unit may conduct an audit of the study procedures at the site. The findings will be reported to the Project Manager and site management.

16. FINANCES AND INDEMNITY

The finances and indemnity for this study will be subject of separate agreements between the Sponsor and the Investigator-affiliated institutions as well as the Sponsor and the CRO.

17. INSURANCE

The Sponsor will provide insurance for the clinical study. A copy of the certificate is filed in each Investigator site file and the trial master file.

18. Study Plan

	Pre-screening Screening	2-Week Run-in		8-Week DP13 Treatment Period				2-Week Withdrawal
	-12 Weeks to Day -15 ± 3	**Day -14 ±3**	**Day -1**	**Day 1**	**Day 14 ± 3 Day 28 ± 3 Day 42 ± 3**	**Day 55 ± 2**	**Day 56 ± 2**	**Day 70 ± 3**
Enrollment / Safety and Tolerability								
Obtain Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographic Data	X							
Medical History	X							
Physical Examination	X							X
Local Safety Laboratory Blood Sample	X	X		X	X		X	X
BP Control Medication Prescription	X	X	X	X	X	X	X	X
Pregnancy test	X	X			Day 14 ± 3 Day 42 ± 3			X
Pick-up/Installation: Urine Bottle / ABPM Device			X			X		
Return/Collection: Urine Bottle / ABPM Device				X			X	
Patient Diary dispensation	X	X	X	X	X	X	X	
Local Spot Urinalysis	X	X		X	X		X	X
Body Weight Recording	X	X		X	X		X	X
AE Recordings	X	X		X	X		X	X
Resting ECG	X	X		X	Day 28 ± 3		X	X
Concomitant Medication Recording	X	X		X	X		X	X
Study Drug Administration								
Randomization				X				
Home IMP Intake					X		X	X
Compliance verification		X	X	X	X	X	X	X
IMP Supply Jar Handout		X		X[6]	X		X	
Supervised IMP Intake		X	X	X		X		
Efficacy								
Blood Pressure, Heart Rate (automatic electronic device)	X	X		X	X		X	X
Blood Sampling (central analysis):		X		X	X		X	X
Urine Sample Aliquot (central analyses):				X			X	
Pharmacokinetics								
Blood Sampling (central analyses):		X		X	Day 28		X	X
Urine Sample Aliquot (central analyses):				X			X	