DP13 * A Phase II 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

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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54894

Source
ToetsingOnline

Brief title
DP13C201 study

Condition

- Other condition

Synonym
Primary Aldosteronism

Health condition

Hormonal diseases

Research involving
Human

Sponsors and support

Primary sponsor: DAMIAN Pharma AG
Source(s) of monetary or material Support: Industry (Damian Pharma)

Intervention

Keyword: Aldosterone Synthase Inhibitor DP13, Dose finding, phase 2, Primary Aldosteronism

Outcome measures

Primary outcome

* Change in the plasma aldosterone-to-renin ratio (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 ambulatory systolic blood pressure (aSBP) from

baseline (Day 1) to the end of the 8-week daily oral DP13 treatment period (Day

56) for all dose arms combined

Secondary outcome

* Occurrence of treatment-emergent adverse events (TEAE) and serious adverse

events (SAE) over the entire study duration

* Change in systolic blood pressure (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

Study description

Background summary

Please refer to the paragraph 1.2 of the protocol
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.

Study objective

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

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

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

Study design

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.

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.

Intervention

* DP13 and placebo capsule intake once daily in the morning
* Physical examination, including weight and blood pressure measurements
* Electrocardiograms (ECG) recordings
* Blood samplings
* Urine collections
* Spot tests on urine
* Urine pregnancy tests

Study burden and risks

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

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.

Contacts

Public
DAMIAN Pharma AG

Haltli 6
Walchwil 6318
CH
Scientific
DAMIAN Pharma AG

Haltli 6
Walchwil 6318
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 m2 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/m2, 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

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, 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 are unable to follow all study procedures

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-08-2020
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DP13
Generic name:	DP13

Ethics review

Approved WMO Date:	04-02-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-05-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2021
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-000919-85-NL
ClinicalTrials.gov	NCT04007406
CCMO	NL71652.091.19