Safety and efficacy of once-daily dexfadrostat phosphate in patients with primary aldosteronism: a randomised, parallel group, multicentre, phase 2 trial

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Summary

Background Primary aldosteronism (PA) is caused by autonomous aldosterone overproduction and characterised by uncontrolled hypertension. There are currently no treatments that target aldosterone synthesis. We evaluated the safety and efficacy of a novel aldosterone synthase inhibitor, dexfadrostat phosphate, in patients with PA.

Methods This multi-centre, randomised, phase 2 trial was conducted between November 2019 and May 2022 (NCT04007406; EudraCT code 2019-000919-85). Adults with PA and an office systolic blood pressure of 145–190 mmHg were included. After a 2-week single-blind placebo run-in period, participants were randomised 1:1:1 to receive oral dexfadrostat phosphate 4, 8, or 12 mg once daily for an 8-week double-blind treatment period, followed by a 2-week single-blind placebo withdrawal period. Randomisation was conducted centrally and stratified by centre and sex. At the beginning and end of the treatment period, 24 h ambulatory systolic blood pressure (aSBP) was recorded. Blood samples were taken every 2 weeks. Primary endpoints were the change in aldosterone-to-renin ratio (ARR) and mean 24 h aSBP from baseline to the end of the treatment period in the combined dose group of all participants receiving any dose of dexfadrostat phosphate. Safety endpoints were the occurrence of treatment-emergent adverse events (TEAEs) and serious adverse events over the entire study in all randomised participants who received at least one dose of dexfadrostat phosphate.

Findings In total, 35 participants received dexfadrostat phosphate and all participants completed the study. Twenty-six participants (74.3%) were male, the mean age was 51.9 years (SD 8.7), and most were White (n = 32, 91.4%). The median ARR and the mean 24 h aSBP significantly decreased from the beginning to the end of the treatment period in the combined dose group (ARR: 15.3 vs 0.6, least-squares mean [LSM] change in log-normal values −2.5, $p < 0.0001$; aSBP: 142.6 vs 131.9 mmHg, LSM change −10.7 mmHg, $p < 0.0001$). There were no safety concerns; all TEAEs were mild or moderate and there were no serious TEAEs.

Interpretation Dexfadrostat phosphate corrected the ARR and aSBP and was well tolerated in patients with PA, demonstrating the benefit of pharmacologically targeting the source of hyperaldosteronism.

Funding DAMIAN Pharma AG.

Keywords: Aldosterone; Renin; Aldosterone synthase inhibition; Primary aldosteronism; Hypertension

Introduction

Aldosterone, the production of which is catalysed by aldosterone synthase in the adrenal gland, promotes sodium retention and potassium excretion in the kidney to regulate blood pressure and electrolyte homeostasis as part of the renin–angiotensin–aldosterone system (RAAS) biofeedback loop.[1] Primary aldosteronism (PA), caused by excessive autonomous aldosterone production

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Research in context

Evidence before this study

We searched the PubMed database for clinical trials and randomised controlled trials published between January 1, 2008 and September 27, 2023, using the term 'aldosterone synthase inhibitor'. The search results were screened to include only publications that reported studies of aldosterone synthase inhibitors in healthy volunteers or in patients with hypertension or primary aldosteronism and reported relevant outcomes, including pharmacokinetics, pharmacodynamics, blood pressure, aldosterone levels, renin activity, cortisol secretions, and adverse events.

In our phase 1 trial of healthy volunteers, dexfadrostat phosphate demonstrated dose-dependent suppression of aldosterone production, decreased plasma sodium levels, and increased renin and potassium levels compared with placebo, with no evidence of drug-induced changes in the hypothalamic–pituitary–adrenal axis or abnormal adrenocorticotropic hormone-stimulated stress responses.

Aside from dexfadrostat phosphate, four other aldosterone synthase inhibitors have been investigated in clinical trials: two in patients with hypertension, one in healthy volunteers only, and one compound, osilodrostat, in patients with primary aldosteronism. However, following evidence of inhibition of cortisol secretion, osilodrostat is now approved for the treatment of Cushing's disease.

These clinical trials support the use of aldosterone synthase inhibitors to reduce aldosterone levels, increase plasma renin activity, and decrease blood pressure in patients with resistant hypertension. However, there is a lack of data supporting the efficacy and safety of aldosterone synthase inhibitors in patients with primary aldosteronism.

Added value of this study

This study is the first to report the efficacy and tolerability of an aldosterone synthase inhibitor to selectively correct the biochemical and clinical manifestations of primary aldosteronism, regardless of disease subtype, without dose up-titration. Our study adds to the body of evidence suggesting the importance of directly targeting the underlying cause of excess aldosterone production to reduce blood pressure and minimize the direct damage to target organs.

Implications of all the available evidence

Current treatment options for patients with primary aldosteronism are either removal of the diseased adrenal gland (adrenalectomy in patients with unilateral disease only) or treatment with mineralocorticoid receptor antagonists. Medical inhibition of aldosterone synthase may provide a targeted treatment for patients with hyperaldosteronism and its resulting clinical manifestations, particularly patients with uncontrolled hypertension, heart failure, kidney disease, and the many undiagnosed patients with primary aldosteronism.

relative to sodium, is characterised by hypertension, cardiovascular damage, sodium retention, and frequently by hypokalaemia.[2,3]

The pathophysiology of PA consists of two separate and distinct pathways. First, hypertension; second, elevated aldosterone levels that are associated with structural damage to blood vessels and kidneys, and tissue fibrosis.[4] Indeed, patients with PA have a higher risk of cardiovascular disease and cardiovascular mortality than patients with primary hypertension,[5,6] suggesting an increased morbidity and mortality in PA that is independent of blood pressure.

PA can present unilaterally or bilaterally. The Endocrine Society guidelines and European Society of Hypertension consensus recommend that the lateralisation subtype is confirmed by adrenal venous sampling.[2,4] For unilateral disease, surgery is recommended to remove the diseased adrenal gland, whereas in patients with bilateral disease or those who are ineligible for surgery, treatment with a mineralocorticoid receptor antagonist (MRA) is recommended.[2]

Although MRAs control hypertension, they do not correct but can, in fact, further elevate aldosterone levels.[7] Patients with PA treated with inadequate MRA doses remain at an increased risk of cardiovascular events compared with those with primary hypertension[8] or those who undergo an adrenalectomy.[9] However, diagnosing unilateral or bilateral disease by adrenal venous sampling can be costly, invasive for the patient, and requires a centre with the diagnostic expertise.[10] The diagnosis of unilateral PA is, therefore, not always feasible and surgery is not always preferred by patients. Furthermore, expanding the spectrum of PA to patients earlier in the disease course will increase the need for a specific, well-tolerated drug that addresses the underlying cause of disease: excess aldosterone production.

The development of inhibitors of aldosterone synthase has thus far proved challenging; few compounds have reached clinical trials in patients with PA or hypertension.[11–13] Osilodrostat was the first clinically investigated aldosterone synthase inhibitor,[14,15] which was subsequently approved for the treatment of Cushing's disease after demonstrating potent and predominant pharmacological inhibition of 11β-hydroxylase, an enzyme involved in the biosynthesis of adrenal corticosteriods.[11,16,17] Three other inhibitors of aldosterone synthase are in clinical development: baxdrostat and lorundrostat for the treatment of resistant and/or uncontrolled hypertension, and BI 690517 for the treatment of chronic kidney disease.[12,18–20] Another aldosterone

synthase inhibitor, LY3045697, has only been evaluated in healthy volunteers.[21]

Dexfadrostat phosphate is a novel aldosterone synthase inhibitor under development for the treatment of PA. A phase 1 trial of once-daily oral dexfadrostat phosphate in healthy volunteers revealed dose-dependent drug exposure and an elimination half-life of 9.5–11 h.[22] At all doses, plasma aldosterone was suppressed and renin activity increased, while blood cortisol was unchanged and no disruption of the hypothalamic–pituitary–gonadal axis was observed.[22]

Overall, dexfadrostat phosphate was well tolerated and there was no evidence of drug-induced adrenal insufficiency.[22] Therefore, we conducted a phase 2, dose-finding trial to determine the efficacy and safety of dexfadrostat phosphate for correcting the clinical and biochemical manifestations of hyperaldosteronism in patients with PA.

Methods

Study design

This randomised, phase 2 trial was conducted across 11 centres in Italy, Switzerland, and the Netherlands between November 2019 and May 2022. The trial consisted of a single-blind 2-week placebo run-in period, a double-blind 8-week treatment period, and a single-blind 2-week withdrawal period during which participants received placebo (Figure S1).

This trial is registered with ClinicalTrials.gov (NCT04007406) and the European Union Clinical Trials Register (EudraCT code: 2019-000919-85). The study protocol is available at www.damianpharma.com.

Participants

A central review board ensured that eligibility criteria were met and approved each patient for participation in the study. Adults aged 18–65 years with a diagnosis of PA within 1 year before study enrolment were included. Participants were enrolled as either *de novo* diagnosed not yet receiving disease-specific treatment, or recently diagnosed and receiving standard–of–care treatment. PA diagnosis was defined as an aldosterone-to-renin ratio (ARR) of at least 40 with a plasma aldosterone concentration (PAC) of at least 15 ng/dL and a plasma renin activity of less than 1.0 ng/mL/h; or a plasma renin concentration of less than 15 mU/L, and a PAC greater than 7.0 ng/dL after a 4 h saline load suppression test or, in patients at risk of volume expansion, a PAC greater than 11.0 ng/dL 2 h after oral intake of 50 mg captopril. Key inclusion criteria were a sitting office systolic blood pressure (oSBP) greater than 145 mmHg and an estimated glomerular filtration rate of at least 45 mL/min/1.73 m^2 (calculated with the Modified Diet in Renal Disease-4 equation). Key exclusion criteria were treatment with spironolactone in the 2 months before enrolment, hyperkalaemia (plasma potassium concentration of >5.0 mmol/L), a prolonged QT interval, a sitting oSBP greater than 190 mmHg, and/or a sitting office diastolic blood pressure (DBP) greater than 110 mmHg, or long-term corticosteroid use.

A fixed dose of concomitant medication to prevent uncontrolled hypertension, as prescribed by the study investigator, was permitted. Such treatments included specified doses of doxazosin, verapamil, diltiazem, and amlodipine. However, participants were not permitted to take any diagnosis-interfering medications, such as RAAS inhibitors or β-adrenoreceptor antagonists, as listed in the Endocrine Society clinical practice guidelines.[2]

Participants could be withdrawn from the study by the investigator if they showed any clinical signs or symptoms warranting withdrawal. These included an absolute QTc value of greater than 500 ms, tachycardia (>150 bpm), uncontrolled hypertension (SBP >190 mmHg and/or DBP >110 mmHg), hypotension (SBP <90 mmHg and/or DBP <50 mmHg), clinically significant changes in liver or renal function, or evidence of severe hypokalaemia or hyperkalaemia (serum potassium concentrations of <2.5 mmol/L or >6.0 mmol/L, respectively).

Randomisation and masking

For the treatment period, participants were randomised 1:1:1 to receive oral dexfadrostat phosphate 4, 8, or 12 mg once daily. Randomisation was conducted centrally by a computerised system and stratified by centre and sex. During the treatment period, investigators and patients were masked to dose allocation. To maintain blinding, placebo and dexfadrostat phosphate capsules were identical in appearance.

Procedures

All doses of placebo and dexfadrostat phosphate were taken in the morning as single oral capsules by participants in a fasted state. The dexfadrostat phosphate 4–12 mg dose range was selected based on the results of a phase 1 study in healthy volunteers.[22] Participants were not required to follow any specific dietary restrictions.

Study visits took place on days –14, –1, 1, 14, 28, 42, 55, 56, and 70 (Figure S1). Participants' office blood pressure and body weight were recorded, and urine and blood samples were collected on days –14, 1, 14, 28, 42, 56, and 70. Electrocardiography was performed on days –14, 1, 28, 56, and 70. Day –1, 14, 42, and 55 visits could be conducted at the participants' home or office by qualified medical personnel, if necessary, to reduce COVID-19 risk. All other visits were conducted at a study site. On day –1, before the first dexfadrostat phosphate administration, and on day 55, 24 h ambulatory blood pressure was recorded using a calibrated and validated device fitted by medically qualified staff

during a study visit. On days –1 and 55, 24 h urine sampling was conducted.

Blood samples were assessed for key markers such as plasma concentrations of aldosterone, renin, and electrolytes, including potassium. In addition, 24 h urine samples were assessed for levels of potassium and other electrolytes and steroid hormones including tetrahydroaldosterone, the major metabolite of aldosterone that serves as a biomarker of aldosterone production.[23] Pharmacodynamic analyses were conducted at a central laboratory (University Hospital Bern, Bern, Switzerland). Routine safety assessments were conducted locally.

Safety and tolerability were monitored from the time of signing an informed consent form to final discharge from the study.

Outcomes

The primary endpoints were the changes in plasma ARR and in the mean 24 h ambulatory systolic blood pressure (aSBP) from baseline to the end of the 8-week treatment period with dexfadrostat phosphate for all dose arms combined.

Secondary endpoints included: the change in oSBP from baseline to the end of the 8-week treatment period with dexfadrostat phosphate for all dose arms combined; the change in oSBP and plasma ARR from baseline to weeks 2, 4, 6, and to the end of the 8-week treatment period with dexfadrostat phosphate in each dose arm; and the change in 24 h aSBP from baseline to the end of the 8-week treatment period with dexfadrostat phosphate in each dose arm.

Exploratory endpoints included: the change in plasma ARR and oSBP from the end of the 8-week treatment period to the end of the 2-week withdrawal period in all dose arms combined and in each dose arm; the change in 24 h ambulatory DBP from baseline to the end of the 8-week treatment period with dexfadrostat phosphate in each dose arm; the change in 24 h urinary tetrahydroaldosterone excretion from baseline to the end of the 8-week treatment period in all dose arms combined and in each dose arm; and the change in plasma potassium levels from baseline to weeks 2, 4, 6, the end of the 8-week treatment period, and the end of the 2-week withdrawal period in all dose arms combined and in each dose arm.

The safety endpoints were the occurrence of treatment-emergent adverse events (TEAEs) and serious adverse events over the entire study. Adverse events (AEs) were classed as related or not related to the study drug; if its cause was unknown, an AE was considered to be treatment related. Causal relationships were assessed by the study investigator.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent. All participating sites obtained independent ethics committee or institutional review board approval (Comitato Etico Interaziendale A.O. Città della Salute e della Scienza di Torino [CS2/1360], Comitato Etico Unico Regionale Friuli [3064], Comitato Etico Regionale delle Marche [2019 343/6617], Comitato Etico Indipendente di Area Vasta Emilia Centro [676/219/Farm/AOUBo], Comitato Etico dell'IRCCS Istituto Auxologico Italiano di Milano [2021_03_23_14], Comitato Etico Area Vasta Centro c/o A.O.U. Careggi di Firenze [19069_spe], Comitato Etico Regione Toscana Area Vasta Nord Ovest [19069], Gesundheits und Fürsorgedirektion des Kanton Bern [2019-01174], Commission cantonale d'éthique de la recherche sur l'être humain [2019-01174], Radboud Universitair Medical Center Commissie Mensgebonden Onderzoek-348 [2019-5965], Radboud Universitair Medical Center Commissie Mensgebonden Onderzoek-348 [21-247/G-R].

Statistics

A minimum sample size of 30 participants was calculated based on both primary endpoints with an ability to detect a decrease in ARR of 40% and a change in aSBP of 6 mmHg, with a power of 95% and a two-sided significance level of 0.05. Using representative individual patient data derived from the PATO study[24] and from interventional studies of aldosterone synthase inhibitors and MRAs,[7,11] with an estimated dropout of six patients, the target enrolment was 36 participants.

The full analysis set and safety analysis set were defined as all randomised participants who received at least one dose of dexfadrostat phosphate. The per-protocol set was defined as all participants in the full analysis set, excluding those with major protocol deviations that would affect efficacy evaluation, those who did not receive the dose to which they had been randomised, or those who did not receive the study drug.

For efficacy endpoints, except those detailed below, changes from baseline were calculated from linear models accompanied by 95% CI, SD, and p values. Log-transformed values were used for changes in ARR. For the primary endpoints hierarchical testing was performed, with the first test assessing the effect on ARR and the second test assessing the effect on aSBP in the combined dose arms. For the analysis of the change in ARR, oSBP, or potassium concentration from baseline in individual dose arms, mixed-effects repeated-measure models with symmetric variance–covariance matrices were used. For this analysis, the changes in ARR (log-transformed), oSBP, or potassium concentration were the dependent variables; baseline ARR (log-transformed), baseline oSBP, or baseline potassium concentration were the independent variables; and dose group, time point, dose group–time point interaction, and sex were fixed effects, and were a random intercept for patients. The same mixed-effects repeated-measure

models were used for the analysis of change in ARR, oSBP, or potassium concentration from the end of the treatment period to the end of the withdrawal period. In this analysis, the changes in ARR (log-transformed), oSBP, or potassium concentration between day 56 and 70 were the dependent variables; ARR (log-transformed), oSBP, or potassium concentration on day 56 were the independent variables; and dose group, time point, dose group–time point interaction, and sex were the fixed effects, and a random intercept for patients.

A *post hoc* analysis was performed to determine the change in PAC in patients with unilateral disease vs patients with bilateral disease or undetermined lateralisation, based on investigator-reported computerised tomography scans or adrenal vein sampling procedures.

Data analyses were performed using SAS version 9.4 or later (SAS Institute, Inc., Cary, NC, USA).

Role of funding source

The sponsor was involved in the study design and data interpretation, and approval of the final study report. All authors approved the decision to submit the paper for publication.

Results

Between December 19, 2019, and January 25, 2022, 51 participants were screened, of whom 36 were enrolled in the study and entered the placebo run-in period. Overall, 35 participants were randomised for the treatment period (dexfadrostat phosphate 4 mg, n = 10; dexfadrostat phosphate 8 mg, n = 12; dexfadrostat phosphate 12 mg, n = 13). One participant discontinued the study before randomisation owing to COVID-19 restrictions. All randomised participants completed the study and were included in the full analysis set and safety analysis set (Fig. 1). No home study visits were required.

Most participants were male (n = 26, 74.3%) and White (n = 32, 91.4%), with a mean age of 51.9 years (SD 8.7) (Table 1). PA was newly diagnosed in 25 participants (71.4%) and recently diagnosed in 10 participants (28.6%). Mean oSBP and office DBP at baseline were 147.7 mmHg (SD 11.8) and 92.4 mmHg (SD 9.9), respectively, and 32 participants (91.4%) were receiving at least one fixed hypertension control medication. Mean plasma potassium concentration was 3.5 mmol/L (SD 0.4) at baseline.

The study met both primary endpoints. From the beginning to the end of the treatment period, the median ARR significantly decreased in the combined dose analysis from 15.3 (interquartile range [IQR] 5.3–25.9) to 0.6 (IQR 0.3–3.0). This corresponded to a 92.1% relative reduction and a least-squares mean (LSM) change in log-normal values of –2.5 (95% CI –2.9, –2.2; $p < 0.0001$) (Fig. 2A). The LSM 24 h aSBP significantly decreased by 10.7 mmHg (95% CI –13.6, –7.9; $p < 0.0001$) in the combined dose group from 142.6 mmHg (SD 14.2) to 131.9 mmHg (SD 13.4) between the beginning and end of the treatment period (Fig. 2B). This was accompanied by a decrease in mean 24 h ambulatory DBP from 87.7 mmHg (SD 7.7) to 82.1 mmHg (SD 7.3) (Fig. 2C); a LSM change from baseline of –5.7 mmHg (95% CI –7.8, –3.5; $p < 0.0001$).

The evaluation of individual dose arms indicated that dexfadrostat phosphate decreased the LSM aSBP at all doses between day 1 and day 56 ($p \leq 0.0005$ for all doses; Fig. 3A). The LSM change in aSBP was greatest in participants receiving dexfadrostat phosphate 8 mg and lowest in participants receiving the 4 mg dose (–7.5 mmHg vs –5.4 mmHg). The LSM ambulatory DBP also decreased in all dose groups between day 1 and day 56 ($p < 0.01$ for all doses; Fig. 3B).

Urinary tetrahydroaldosterone excretion, a marker for aldosterone production, significantly decreased between days 1 and 56 in all dose groups combined and in individual dose arms ($p < 0.0001$, all doses; Fig. 3C). Similar decreases in urinary tetrahydroaldosterone excretion were observed in participants in the 8 mg and 12 mg dose arms (LSM change –31.0 µg/24 h and –30.7 µg/24 h, respectively).

The onset and offset of aldosterone suppression were apparent within 2 weeks of dexfadrostat phosphate treatment and placebo withdrawal, respectively. By day 14 of the treatment period, the log-normal ARR had significantly decreased in all dose arms compared with day 1 ($p < 0.0001$, all doses; Fig. 4A). In all dose arms, the reduction in the log-normal ARR was maintained for the duration of the treatment period. After the 2-week placebo withdrawal period, log-normal ARR significantly increased compared with day 56 in all dose arms ($p < 0.0001$, all doses).

Across all doses, the mean oSBP decreased compared with day 1 for all time points throughout the treatment period (Fig. 4B). All reductions were statistically significant, except for day 14 and day 28 for the 12 mg dose group. In all dose arms, the mean oSBP significantly increased compared with day 56 after the 2-week placebo withdrawal period ($p < 0.005$, all doses).

In all dose arms, the mean plasma potassium concentration increased by day 14 of the treatment period compared with day 1 ($p < 0.0001$, all doses; Fig. 4C). The mean plasma potassium concentration remained within the normal range throughout the treatment period for all dose groups. After the 2-week placebo withdrawal period, the mean plasma potassium concentration significantly decreased compared with day 56 in the 4 mg and 8 mg dose groups (LSM change: 4 mg = –0.5, $p < 0.0001$; 8 mg = –0.3, $p = 0.002$) and numerically decreased in the 12 mg dose group (LSM change –0.2, $p = 0.05$). Of the 22 participants who began the study with hypokalaemia (serum potassium concentrations of <3.6 mmol/L), 20 (90.9%) had potassium levels in the normal range (>3.6 mmol/L and <5.0 mmol/L)[25] by day 56.

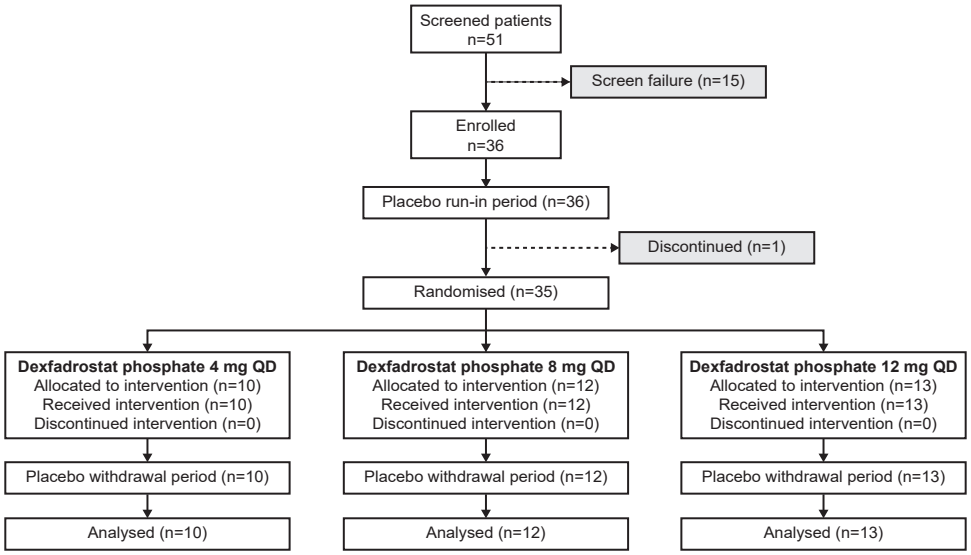

***Fig. 1:* CONSORT flow chart**. QD, once daily.

Demographic or characteristic	Full analysis set N = 35
Age, years, mean (SD)	51.9 (8.7)
Sex male, n (%)	26 (74.3)
Female, n (%)	9 (25.7)
BMI, kg/m^2, mean (SD)	28.1 (3.6)
Race, n (%)	
Asian	1 (2.9)
Black or African American	2 (5.7)
White	32 (91.4)
PA disease history[a], n (%)	
De novo diagnosed	25 (71.4)
Recently diagnosed	10 (28.6)
SBP, mmHg, mean (SD)	147.7 (11.8)
DBP, mmHg, mean (SD)	92.4 (9.9)
PAC, ng/dL, mean (SD)	
De novo diagnosed	37.6 (18.7)
Recently diagnosed	31.2 (10.6)
PRC, mU/L, mean (SD)	
De novo diagnosed	3.8 (3.8)
Recently diagnosed	5.6 (4.7)
Plasma ARR, PAC/PRC, median (IQR)	15.3 (20.6)
Plasma potassium, mmol/L, mean (SD)	3.5 (0.4)
Creatinine, µmol/L, mean (SD)	73.1 (13.3)
eGFR, mL/min/1.73 m^2, mean (SD)	95.3 (18.3)
Participants receiving at least one fixed hypertension control medication, n (%)	32 (91.4)
Amlodipine, n (%)	17 (48.6)
Diltiazem, n (%)	1 (2.9)
Doxazosin, n (%)	24 (68.6)
Verapamil, n (%)	5 (14.3)

ARR, aldosterone-to-renin ratio; BMI, body mass index; DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate; IQR, interquartile range; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRC, plasma renin concentration; SBP, systolic blood pressure. [a]Participants were either enrolled as *de novo* diagnosed patients not yet on disease-specific treatment, or recently diagnosed patients on standard-of-care treatment.

***Table 1:* Patient characteristics at baseline.**

In participants with unilateral disease, the change in PAC across the treatment period was similar to those with bilateral or undetermined disease (Figure S2).

Plasma concentrations of the aldosterone precursors deoxycorticosterone and corticosterone increased by day 14 of the treatment period, remained relatively stable, and then decreased during the withdrawal period (Table S1). Cortisol levels remained stable throughout the treatment and withdrawal periods (Table S1).

On day 14, 24 participants (68.6%) had an increase in their plasma renin concentration compared with day 1. Plasma aldosterone concentrations decreased in all participants between day 1 and day 14. In male participants, 26 (100.0%) had a decrease in ARR and 23 (88.5%) had a decrease in aSBP between day 1 and day 56. All 9 female participants (100.0%) had a decrease in both ARR and aSBP between day 1 and day 56.

There were no serious TEAEs, and no participants discontinued the study owing to a TEAE (Table S2). At least one TEAE was reported for 16 participants (45.7%); the most common TEAEs were gastrointestinal disorders (n = 6), headache (n = 4), and investigations (n = 3). Investigations included increases in amylase, blood lactate dehydrogenase, and blood pressure. Most TEAEs were mild or moderate; there were no severe TEAEs.

Discussion

This randomised, phase 2 trial demonstrated that dexfadrostat phosphate is effective in treating the clinical and biochemical manifestations of PA over a treatment duration of 8 weeks. At all doses, dexfadrostat phosphate reduced the plasma ARR from baseline to day 56 of treatment and this was accompanied by a proportional reduction in 24 h aSBP. Moreover,

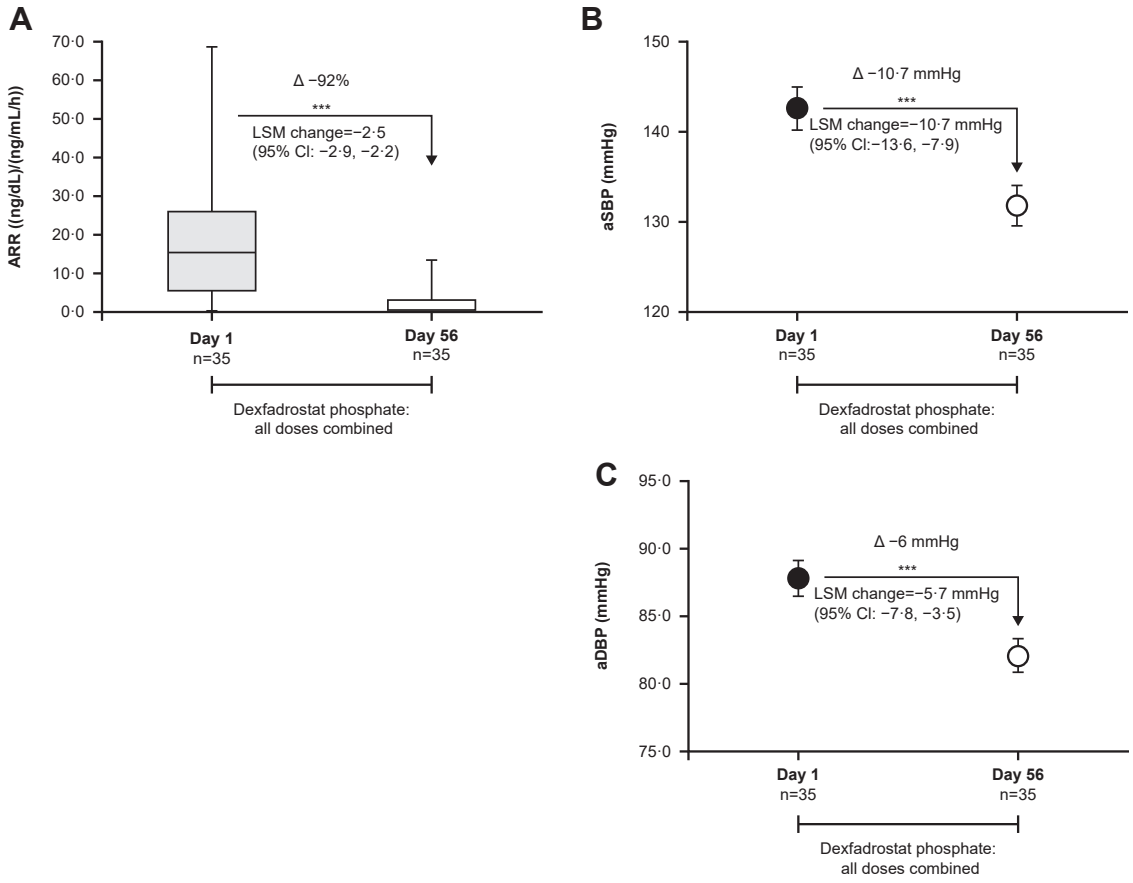

***Fig. 2:* Change in ARR and 24 h aSBP and aDBP between the beginning and end of the treatment period across all doses combined**. Data are presented as (A) the median (midline), IQR (box), and range (whiskers) change in ARR, (B) the mean (SEM) change in aSBP, and (C) the mean (SEM) change in aDBP. ***p < 0.0001. aDBP, ambulatory diastolic blood pressure; ARR, aldosterone-to-renin ratio; aSBP, ambulatory systolic blood pressure; IQR, interquartile range; LSM, least-squares mean.

treatment with dexfadrostat phosphate resulted in decreased aldosterone production, as assessed by 24 h urinary tetrahydroaldosterone excretion, and increased plasma concentrations of potassium over the treatment period.

The correction of ARR and aSBP was dose-dependent up to dexfadrostat phosphate 8 mg. However, dexfadrostat phosphate 12 mg did not confer any additional clinical benefit compared with the 8 mg dose. The 4 mg dose was effective in correcting ARR and aSBP and, therefore, may be considered as the starting dose going forward.

Across all doses of dexfadrostat phosphate, changes in the biochemical and clinical manifestations of hyperaldosteronism were observed by day 14 of dexfadrostat phosphate treatment. In patients who were hypokalaemic despite the use of oral potassium supplements, potassium levels were rapidly normalised. The onset of oSBP reduction, within 2 weeks of dexfadrostat phosphate 4 mg or 8 mg treatment, compares favourably with the MRAs eplerenone and spironolactone, for which reductions in blood pressure have been reported by week 4 of treatment.[7,26] This reduction in ARR and blood pressure and elevation in plasma potassium was maintained for the entire 8-week treatment period in all dose groups, which was indicative of sustained and effective aldosterone synthase inhibition without the need for dose adjustment. Upon withdrawal from dexfadrostat phosphate, ARR, blood pressure, and potassium concentration trended towards baseline levels, indicating reversal of the pharmacological suppression of aldosterone production. Moreover, concentrations of the aldosterone precursors deoxycorticosterone and corticosterone increased from baseline during the treatment period and trended towards baseline levels upon withdrawal, again indicating stable, selective, and reversible aldosterone synthase inhibition over 8 weeks.[27]

Dexfadrostat phosphate was well tolerated at all doses. There were no serious AEs and all TEAEs were mild or moderate. Notably, there was no evidence of

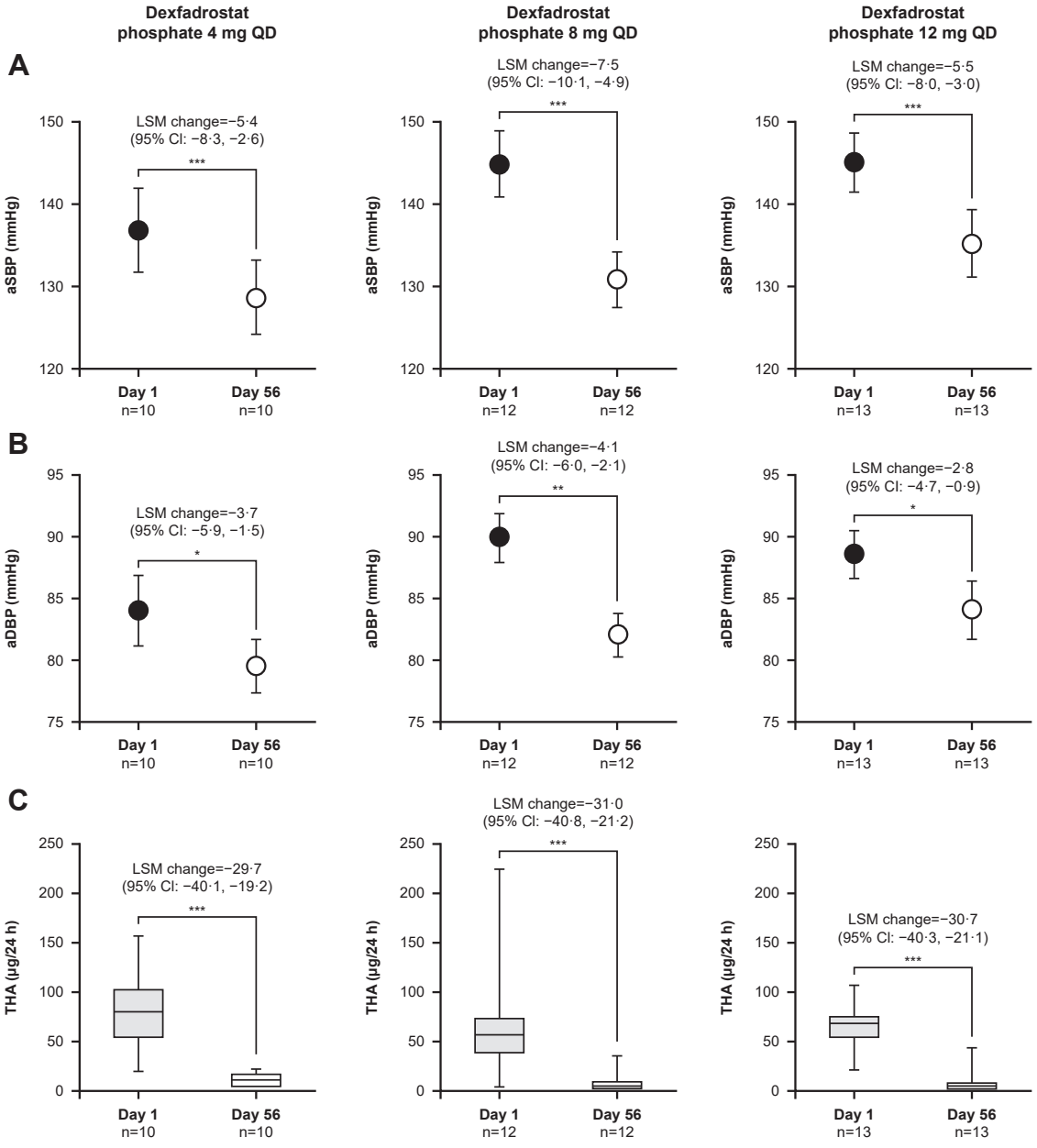

***Fig. 3:* Change in 24 h aSBP, aDBP, and urinary THA excretion by dose group**. Data are presented as (A) the mean (SEM) change in aSBP, (B) the mean (SEM) change in aDBP, and (C) the median (midline), IQR (box), and range (whiskers) change in THA. *p < 0.01, **p < 0.001, ***p < 0.0001. aDBP, ambulatory diastolic blood pressure; aSBP, ambulatory systolic blood pressure; IQR, interquartile range; LSM, least-squares mean; QD, once daily; THA, tetrahydroaldosterone.

hyperkalaemia during the 8-week treatment period; mean plasma potassium concentrations did not exceed the normal range or meet the criteria for hyperkalaemia[28] and there were no clinically significant cases of hyperkalaemia among individual participants. Cortisol levels remained stable throughout the study, indicating a lack of off-target cortisol suppression by dexfadrostat phosphate.

PA is characterised by excess aldosterone production, leading to hypertension, hypokalaemia, and an increased risk of cardiovascular events compared with healthy populations and patients with primary hypertension.[2,5,6] The currently available pharmacological treatments, MRAs, are limited by undesirable side effects at doses required to treat PA and a need for prolonged dose titration at treatment initiation.[2,4,29] Such

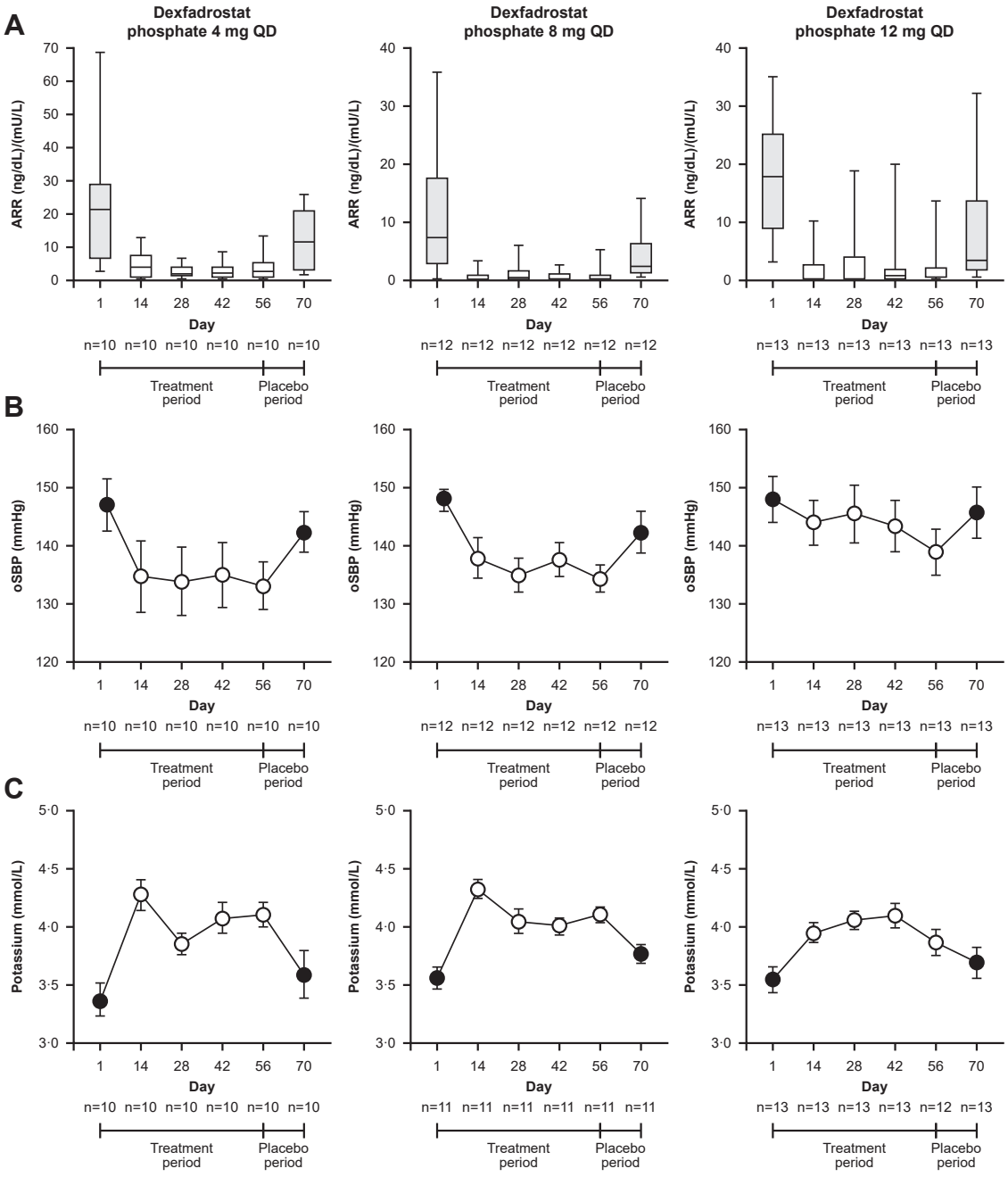

Fig. 4: **Onset and offset of changes in ARR, oSBP, and plasma potassium concentration**. Data are presented as (A) the median (midline), IQR (box), and range (whiskers) change in ARR, (B) the mean (SEM) change in oSBP and (C) the mean (SEM) plasma potassium concentration. ARR, aldosterone-to-renin ratio; IQR, interquartile range; oSBP, office systolic blood pressure; QD, once daily.

factors may lead to reduced treatment compliance. Furthermore, MRAs cannot block the mineralocorticoid receptor-independent effects of aldosterone, such as rapid intracellular signalling mediated by activation of G protein-coupled oestrogen receptors.[30] Such signalling events could instead be blocked by treatments that reduce aldosterone synthesis. Moreover, there is a lack of randomised placebo-controlled clinical trial data to investigate the optimal use of MRAs in PA. While an adrenalectomy may be more effective in reducing hypertension and cardiac markers, and hence cardiovascular risk, and has a more rapid onset than current

medical treatment, surgery is generally only performed for unilateral disease.[2] Surgical treatment is further limited by a need for expert centres, a proportion of patients who do not wish to undergo surgery, and a population for whom an adrenalectomy does not cure hypertension or hyperaldosteronism.[31–33] Therefore, there is a need for an effective and well-tolerated pharmacological treatment that targets the underlying cause of disease by reducing aldosterone production.

By targeting the pathophysiological cause of the disease, dexfadrostat phosphate has potential as a medical therapy for all patients with PA; dexfadrostat phosphate was equally effective in patients with unilateral disease and those with bilateral disease or an undetermined disease subtype. Treatment with dexfadrostat phosphate could, therefore, be initiated immediately when PA is confirmed if subtyping for surgical intervention is not feasible or desired. Dexfadrostat phosphate treatment could also bridge patients with PA from subtyping to surgery due to its rapid reversal of efficacy upon discontinuation. The favourable safety profile observed with dexfadrostat phosphate may facilitate better adherence rates than treatment with MRAs. Lastly, a targeted treatment option may support the diagnosis of PA and protect patients currently not receiving an aldosterone-targeted therapy.

Approximately 11–29% of patients with resistant hypertension may have underlying PA.[34] Indeed, the MRA spironolactone demonstrated efficacy as an add-on therapy in patients with resistant hypertension.[35] Hyperaldosteronism has also been shown to be present in patients with normal blood pressure and in all stages of hypertension.[36] Resistant hypertension is primarily driven by sodium retention, while cardiovascular events are associated with elevated aldosterone.[5,35] Therefore, an aldosterone synthase inhibitor that is effective in reducing both ARR and SBP, such as dexfadrostat phosphate, may benefit any patient with hypertension with underlying hyperaldosteronism, and not be limited only to patients diagnosed with PA.

Although this study produced robust evidence on the efficacy and tolerability of dexfadrostat phosphate in a patient population diagnosed with strict criteria for severe disease expression, several limitations should be considered. First, the study did not include a parallel placebo-control arm and comparisons were instead made among dose groups and to the placebo run-in and withdrawal periods. The decision not to include a placebo-control arm was intended to ensure that patients did not experience harmful increases in blood pressure during the study, given that this study represented the first-time use of dexfadrostat phosphate in patients with PA and hypertension. However, this may limit some interpretations of the study results. Although trial participants can experience placebo-related decreases in office blood pressure, the placebo effect on 24-h ambulatory blood pressure monitoring is considered to be low. Moreover, plasma biomarkers such as aldosterone and potassium are unaffected by placebo. Our study used hierarchical statistical testing such that changes in aSBP would only be evaluated if ARR changes were statistically significant, in addition mitigating the risk of a placebo effect on SBP readings confounding the results. Furthermore, the increases in ARR and SBP, and the decrease in plasma potassium levels upon treatment withdrawal, provide confidence that the changes seen during the treatment period are pharmacologically mediated and robust. Second, a relatively small number of patients were included in this study; however, the sample size calculation for patients with severe PA ensured the study was adequately powered to meet both primary endpoints. Third, most patients enrolled in the study were White, with a low representation of other races and ethnicities. There was also a lower proportion of women enrolled in the study than men, and the relatively small sample size of female participants prevented any statistical analysis of response rates by sex. However, all female participants had both a biochemical and clinical response to dexfadrostat phosphate. Fourth, as a first evaluation of dexfadrostat phosphate in patients, an 8-week treatment period was chosen to minimise the risk of lack of efficacy in patients with hypertension and to minimise safety concerns. Previous interventional studies of aldosterone synthase inhibitors in patients with PA or hypertension, and the observed blood pressure changes after adrenalectomy, report treatment responses over a similar time period.[11,14,31] Future trials will assess the long-term efficacy and safety of dexfadrostat phosphate and ensure that long-term compensatory mechanisms are evaluated. Fifth, only referral centres were selected for participation in the study, which may be considered a source of referral bias. Finally, although randomisation is expected to reduce the risk of confounding, there may be confounding variables that were not accounted for, such as age, duration of disease, body mass index, blood pressure, and aldosterone levels at baseline. Because these variables were restricted during patient enrolment and participants were randomised across treatment arms, we do not anticipate a significant effect of residual confounding on the results reported here.

In conclusion, these findings demonstrate that dexfadrostat phosphate is efficacious in reducing both the biochemical and the clinical manifestations of PA by addressing the underlying pathology of excess aldosterone production. Dexfadrostat phosphate may represent an effective and well-tolerated treatment option for patients with PA and other diseases of RAAS dysfunction.

Contributors

PM was involved in study conceptualization, data curation, investigation, methodology, writing–review and editing, and verified the data. GW was involved in data curation, investigation, methodology, and

writing–review and editing. MG was involved in project administration, data acquisition, data analyses, and writing–review and editing.

ES was involved in data curation, investigation, and writing–review and editing.

AD was involved in data curation, investigation, and writing–review and editing.

VF was involved in data curation, investigation, and writing–review and editing. BV was involved in study conceptualization, data analyses, investigation, methodology, and writing–review and editing.

HB was involved in study conceptualization, methodology, and writing—review and editing.

TG was involved in project administration, resourcing, and writing—review and editing.

RS was involved in study conceptualization, methodology, writing—review and editing, and verified the data.

CS was involved in study conceptualization, funding acquisition, methodology, resourcing, and writing—review and editing.

All authors read and approved the final version of the manuscript.

Data sharing statement

The individual patients and investigators have been provided with their own data. Data collected for the study overall will not be made publicly available for privacy reasons and it is not in line with the study informed consent and Ethics Committee agreements. The study protocol is available at www.damianpharma.com.

Declaration of interests

PM has received speaker fees from DIASORIN.

GW has received research grants from Aktiia and Bayer AG, consulting fees from AstraZeneca, Bayer, and Servier Laboratories, and speaker fees from Medtronic.

ES, AD, VF and BV declare no competing interests. MG, HB and TG are shareholders of DAMIAN Pharma AG. RS and CS are founders and shareholders of DAMIAN Pharma AG.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102576.

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