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Rationale, Design, and Baseline Characteristics of ARTS-DN: A Randomized Study to Assess the Safety and Efficacy of Finerenone in Patients with Type 2 Diabetes Mellitus and a Clinical Diagnosis of Diabetic Nephropathy

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Key Words
Antagonist · Diabetic nephropathy · Heart failure · Mineralocorticoid receptor · Type 2 diabetes mellitus

Abstract
Background/Aims: Finerenone decreases albuminuria in patients having heart failure with reduced ejection fraction and mild-to-moderate (stage 2–3) chronic kidney disease. The MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN; NCT01874431) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study. ARTS-DN investigated whether the mineralocorticoid receptor antagonist finerenone reduces albuminuria without causing major alterations in serum potassium levels in patients with type 2 diabetes mellitus and a clinical diagnosis of DN who were receiving a renin-angiotensin-system (RAS) inhibitor. ***Methods:*** Patients were randomized to oral finerenone 1.25–20 mg or placebo once daily. The primary objectives were to assess the ratio of the urinary albumin-to-creatinine ratio at day 90 to that at baseline in patients receiving finerenone, and to compare it with that in the placebo group. Additional exploratory analyses included evaluating changes from baseline in serum potassium levels, efficacy and safety biomarkers, and health-related quality of life. ***Results:*** Of 1,501 patients screened,

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821 (the sample population) received at least one dose of finerenone/placebo. Baseline characteristics included: male, 77.8%; white, 84.2%; very high albuminuria (formerly macroalbuminuria), 38.4%; high albuminuria (formerly microalbuminuria), 60.3%; median (range) estimated glomerular filtration rate, 66.3 (24.5–130.7) ml/min/1.73 m^2; and systolic blood pressure (mean ± standard deviation), 138.1 ± 14.4 mm Hg. There was a history of cardiovascular disease in 39.6%, diabetic neuropathy in 20.0%, and diabetic retinopathy in 19.9% of patients. ***Conclusion:*** ARTS-DN is the first phase 2b trial of finerenone in combination with a RAS inhibitor in patients with type 2 diabetes mellitus and a clinical diagnosis of DN.

Introduction

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) in the western world [1]. Among patients with type 2 diabetes mellitus, high (formerly known as micro-) albuminuria – a marker of cardiovascular risk [2] – has a global prevalence of approximately 40% [3, 4]. In post hoc analyses of large randomized trials in patients with diabetes, decreases in albuminuria are associated not only with a slower progression to ESRD in the long term but also with a reduction in the incidence of cardiovascular (CV) outcomes and mortality [5, 6]. Consequently, reduction of albuminuria is considered to be a marker of slowed nephropathy progression in the treatment of chronic kidney disease (CKD) [7].

For the medical management of patients with DKD, reduction of albuminuria has become a primary aim, in addition to optimizing control of hyperglycemia and blood pressure [8]. Guidelines currently recommend treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) for diabetic patients with hypertension and very high (formerly known as macro-) or high albuminuria [8]. Both ACEIs and ARBs act via inhibition of the renin-angiotensin-system (RAS) [9–11]. Despite initial down-regulation of plasma aldosterone levels, up to 50% of patients treated with a RAS blocker experience elevations of the hormone within a year of initiating treatment [12–14]. This 'aldosterone breakthrough/escape' is associated with increases in albuminuria and impairment of kidney function [13, 15, 16].

In patients with CKD, systematic reviews of small studies have suggested that, even when added to ACEIs and ARBs, mineralocorticoid receptor (MR) antagonists (MRAs) substantially reduce proteinuria [17, 18]. Thus, among adults with DKD, a potential role for the steroidal MRAs spironolactone and eplerenone as antiproteinuric agents has been identified in explorative clinical studies [19–22]. Furthermore, MRAs are well known for their ability to reduce mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF) [23–25]. As there is a high risk of CV-associated mortality and morbidity in patients with DKD, it is possible that MRAs may also have a part to play in preventing CV events in this population. However, long-term prospective studies confirming whether MRAs slow progression to ESRD in patients with DKD are lacking.

Finerenone (BAY 94-8862) is a next-generation oral MRA with a non-steroidal chemical structure [26]. In vitro, finerenone has shown higher selectivity for the MR over other steroid hormone receptors compared with spironolactone and improved affinity for the MR compared with eplerenone [26]. At equi-natriuretic doses in recent preclinical studies, finerenone reduced proteinuria and cardiac hypertrophy more efficiently than eplerenone [27]. In the phase 2a MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS), encouraging safety and efficacy profiles were observed in patients with HFrEF and mild-to-moderate CKD treated with finerenone [28]. Importantly, finerenone doses of 2.5–10 mg/day reduced albuminuria from baseline, particularly in patients with elevated albuminuria. In addition, finerenone was associated with a lower increase in serum potassium concentration and incidence of hyperkalemia than spironolactone. Thus, finerenone may be able to address the unmet medical need of safely managing albuminuria in patients with type 2 diabetes mellitus and a clinical diagnosis of DKD.

The ARTS-Diabetic Nephropathy (ARTS-DN; ClinicalTrials.gov identifier: NCT01874431), which is now completed, was designed to compare the short-term efficacy and safety of different once-daily oral doses of finerenone and placebo in patients with type 2 diabetes mellitus and DN who are receiving an ACEI or an ARB. Here we describe the ARTS-DN design and the baseline characteristics of the study population.

Patients and Methods

ARTS-DN is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study aiming to compare the effects of finerenone 1.25–20 mg once-daily with placebo on top of standard of care in adults with type 2 diabetes mellitus and DN.

Following a run-in and screening period of up to 12 weeks, eligible patients were randomized to once-daily finerenone 1.25–

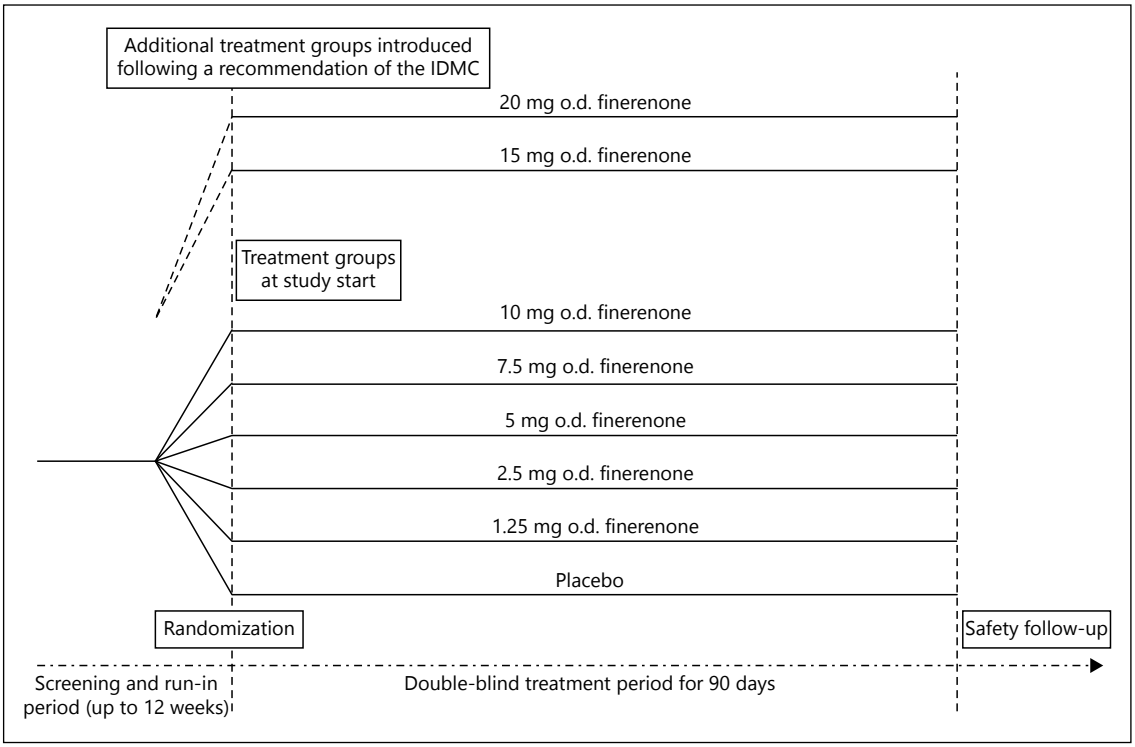

Fig. 1. Study flowchart. IDMC = Independent data monitoring committee; o.d. = once daily.

10 mg or placebo in combination with the current standard of care for 90 days (fig. 1). Treatment arms of finerenone 15 and 20 mg once-daily were added on the recommendation of an independent data monitoring committee (IDMC) after review of the safety data from the ongoing study.

Patients

After a run-in visit, patients who fulfilled the eligibility criteria (table 1) were enrolled in a run-in period of up to 12 weeks. To be included, patients had to have type 2 diabetes (i.e. medical history of a 2-hour plasma glucose level ≥11.1 mmol/l during an oral glucose tolerance test or of a fasting glucose level ≥7.0 mmol/l; or glycated hemoglobin [HbA_{1c}] levels of at least 6.5% in the medical history or at the run-in visit; or be receiving treatment with oral antidiabetics and/or insulin). Treatment with at least the minimum recommended dose of an ACEI and/or an ARB prior to the run-in period was also a requirement for inclusion in the study (following the run-in period, only an ACEI or an ARB, but not both, was allowed); antihypertensive therapy was optimized for renal and cardiovascular disease protection, according to local guidelines. As part of the run-in period, a screening visit to confirm eligibility for randomization took place within 14 days of the planned randomization. At this visit, it was assessed whether the patient still met the eligibility criteria (table 1) while receiving at least the minimum recommended dose of an ACEI or ARB. Adults meeting the above criteria for having type 2 diabetes mellitus who had a clinical diagnosis of DN (i.e. consistent urinary albumin-to-creatinine ratios [UACRs] in two of three first morning samples, with both being ≥300 mg/g [≥34 mg/mmol] or both being ≥30 to <300 mg/g [≥3.4 to <34 mg/mmol] plus an estimated glomerular filtration rate [eGFR] ≥30 to <90 ml/min/1.73 m^2) and a serum potassium level of 4.8 mmol/l or less at the run-in and screening visits were randomized to treatment (table 1). Patients with an eGFR of 30–45 ml/min/1.73 m^2 at the run-in visit had to start treatment with a non-potassium sparing-diuretic if not already receiving such treatment; this treatment must have been stable for at least 4 weeks before the screening visit (table 1).

Patients with a clinical diagnosis of HFrEF and persistent symptoms (New York Heart Association class II–IV) at the run-in visit, or HbA_{1c} levels of more than 12%, a UACR of more than 3,000 mg/g or hypertension at the run-in or screening visits were excluded from the study (table 1). Hypertension was defined at the run-in visit as mean sitting systolic blood pressure of at least 180 mm Hg or mean sitting diastolic blood pressure of at least 110 mm Hg, and at the screening visit as mean sitting systolic blood pressure of at least 160 mm Hg or mean sitting diastolic blood pressure of at least 100 mm Hg. If blood pressure was considered by the investigator to be uncontrolled during the double-blind study period, non-potassium-sparing diuretics were the first-line treatment if not already being used. Thereafter, antihypertensive medications could be added to the treatment regimen according to local guidelines. If the blood pressure was still not considered to be controlled by the investigator, the patient was withdrawn from the study.

Patients with non-diabetic renal disease, known bilateral clinically relevant renal artery stenosis or Addison's disease, or who experienced a stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening HF within 30 days before the run-in visit were not eligible for participation in the study.

Table 1. Main inclusion and exclusion criteria of ARTS-DN

Main inclusion criteria	Main exclusion criteria
Men or women ≥18 years (women with childbearing potential were required to have a negative pregnancy test and to have agreed to use adequate contraception)	Non-diabetic renal disease
Patients with type 2 diabetes mellitus fulfilling at least one of the following criteria:	Known bilateral clinically relevant renal artery stenosis (>75% reduction in artery diameter)
Receiving treatment with oral antidiabetics and/or insulin	HbA_{1c} >12% at the run-in or screening visit
Medical history of fasting glucose ≥7.0 mmol/l	UACR >3,000 mg/g (339 mg/mmol) in any of the first morning samples at the run-in or screening visit
Medical history of 2-hour plasma glucose ≥11.1 mmol/l during an oral glucose tolerance test	Hypertension with mean sitting SBP ≥180 mm Hg or mean sitting DBP ≥110 mm Hg at the run-in visit, or with mean sitting SBP ≥160 mm Hg or mean sitting DBP ≥100 mm Hg at the screening visit
HbA_{1c} ≥6.5% (NGSP/DCCT) in the medical history or at the run-in visit	Clinical diagnosis of HFrEF and persistent symptoms (NYHA class II–IV) at the run-in visit, or stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening HF within 30 days before the run-in visit
A clinical diagnosis of DN based on at least one of the following criteria at the run-in/screening visit:	Concomitant therapy with eplerenone, spironolactone or any renin inhibitor or potassium-sparing diuretic that cannot be discontinued for the run-in and the treatment period
Persistent very high albuminuria: UACR of ≥300 mg/g (≥34 mg/mmol) in two of three first morning samples and estimated eGFR (CKD-EPI) ≥30 to <90 ml/min/1.73 m^2	Concomitant therapy with high-dose (>500 mg/day) acetylsalicylic acid or daily treatment with other non-steroidal anti-inflammatory drugs for more than 5 consecutive days
Persistent high albuminuria: UACR of ≥30 to <300 mg/g (≥3.4 to <34 mg/mmol) in two of three first morning samples and eGFR (CKD-EPI) ≥30 to <90 ml/min/1.73 m^2	Use of potent CYP3A4 inhibitors/inducers or strong CYP2C8 inhibitors
In patients with an eGFR (CKD-EPI) of 30–45 ml/min/1.73 m^2, treatment with a non-potassium-sparing diuretic at the screening visit and without any adjustments for ≥4 weeks beforehand	
Treatment with at least the minimum recommended dose of an ACEI and/or ARB for at least 3 months without any adjustments to this therapy for at least 4 weeks prior to the screening visit	
Serum potassium ≤4.8 mmol/l at both the run-in and the screening visit	

ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; DBP = diastolic blood pressure; DCCT = Diabetes Control and Complications Trial; DN = diabetic nephropathy; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated hemoglobin; HF = heart failure; HFrEF = HF with reduced ejection fraction; NGSP = National Glycohemoglobin Standardization Program; NYHA = New York Heart Association; SBP = systolic blood pressure; UACR = urinary albumin-to-creatinine ratio.

Objectives

The primary efficacy variable was the ratio of the UACR at visit 5 (day 90 ± 2) to the UACR at baseline (visit 1; day 1). The main objective of ARTS-DN was to determine the effect of treatment with different doses of finerenone or placebo on this efficacy variable.

Further exploratory objectives were to assess:

- the ratio of UACR at visit 3 (day 30 ± 2) and visit 4 (day 60 ± 2) to UACR at baseline;
- the incidence of regression of albuminuria from baseline to visit 5, with regression of albuminuria defined as a change from either very high albuminuria (UACR ≥300 mg/g) to high albuminuria (UACR ≥30 to <300 mg/g)/normal albuminuria (UACR <30 mg/g) or from high albuminuria to normal albuminuria, in all cases accompanied by a change in UACR of more than 30%;
- changes in levels of efficacy biomarkers (aldosterone, B-type natriuretic peptide [BNP], N-terminal proBNP [NT-proBNP], galectin-3) from baseline to visits 3, 4 and 5;
- changes in health-related quality of life (HRQoL) from baseline to visit 3, visit 5, and the follow-up visit, using the Kidney Disease Quality of Life-36 and EuroQol 5-Dimension, 3-Level questionnaires.

A safety profile will be established using data from physical examinations, blood pressure and heart rate monitoring, electrocardiograms, adverse event monitoring, and blood sample analysis (hematology and clinical chemistry, including measurements of levels of liver enzymes, creatinine, potassium, HbA_{1c}, and safety biomarkers [troponin T and cystatin C]). The IDMC assessed safety and tolerability, with a particular focus on changes in serum potassium (number of patients with hyperkalemia [a confirmed value of serum potassium ≥5.6 mmol/l]) and eGFR (number of patients with an eGFR decrease of ≥30% from baseline).

Study Medication

Finerenone was administered as oral, immediate-release tablets. Eligible patients were randomized 1:1:1:1:1:1 in the 14 days following a screening visit to receive once-daily finerenone at doses of 1.25, 2.5, 5.0, 7.5, or 10 mg or matching placebo for 90 days. Two additional treatment arms, finerenone 15 and 20 mg once daily, were added on the recommendation of the IDMC in December 2013. When the additional treatment arms were added,

randomization was adapted to obtain equally balanced sample sizes across all treatment groups at the end of the study. Randomization was stratified by region (Europe, North America, Asia, others [Australia, Israel, South Africa]) and type of albuminuria (very high albuminuria or high albuminuria at screening).

Ideally, any medical therapy (e.g. antidiabetic, antihypertensive, or statin) would not be changed between the screening visit and the last dose of study drug; however, if this was necessary, the patient could continue to receive the study drug. Concomitant medications that were not allowed during the study included any marketed aldosterone antagonist or renin inhibitor; high-dose acetylsalicylic acid (>500 mg/day); daily treatment with non-steroidal anti-inflammatory agents; potent cytochrome P450 (CYP) isoenzyme 3A4 inhibitors or inducers; and strong CYP2C8 inhibitors such as gemfibrozil (table 1).

Serum/Plasma Potassium Monitoring

Patients had to maintain their normal diet throughout the study and were not given any specific advice on dietary sodium or potassium restrictions. With the exception of non-potassium-sparing diuretics, potassium-lowering agents (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate, insulin and glucose infusion) were not allowed to be started during treatment with study drug. In the case of hyperkalemia occurring with study treatment, the study treatment was discontinued prior to starting a potassium-lowering agent. Any potassium supplementation was stopped prior to randomization if potassium levels were within the normal range. If potassium levels were low at randomization or at any of the following visits, potassium supplementation was continued or re-started until potassium values were within the normal range again.

If a patient underwent a change in clinical status that was known to influence serum/plasma electrolyte levels or fluid balance (e.g. vomiting and/or diarrhea for >1 day), it was recommended that serum/plasma potassium concentration be reassessed as soon as possible after the acute event. Any reassessment of serum/plasma potassium concentration had to be analyzed locally and centrally. At each scheduled visit, blood samples were collected for the measurement of parameters including serum/plasma potassium concentration. Investigators were instructed to stop the study drug permanently in the event of a confirmed potassium concentration of 5.6 mmol/l or more or a locally measured potassium concentration of more than 6.0 mmol/l. Such a discontinuation had to be reported to the sponsor within 24 h as a serious adverse event.

Investigations

Patients were assessed at the run-in visit, the screening visit, visit 1 (day 1), visit 2 (day 7 ± 2), visit 3 (day 30 ± 2), visit 4 (day 60 ± 2) and visit 5 (day 90 ± 2); details of the assessments made at each visit are given in the online supplemental data (for all online suppl. material, see www.karger.com/doi/10.1159/000371497).

Follow-up visits were scheduled for 30 ± 5 days after the last intake of study medication. Patients who discontinued the study prematurely were also assessed as soon as possible after discontinuation.

Urine samples taken from the first void in the morning at the patient's home on three consecutive days were used to measure the levels of urinary creatinine, albumin, sodium, and potassium. At visits 1 and 5, urine samples were taken before the first and last intake of study drug, respectively. A local dipstick test was used to confirm sample validity for central analysis. Urine samples were frozen at –20°C, apart from the sample for assessment of albuminuria, which remained at ambient temperature.

Blood samples were used to determine levels of efficacy biomarkers (BNP, NT-proBNP, galectin-3, and aldosterone), safety biomarkers (ultrasensitive troponin T and cystatin C), and HbA_{1c}, and for hematology, clinical chemistry, pharmacokinetic analysis, and assessment of iohexol plasma clearance (for eGFR estimations in a subset of the study population), as indicated in supplementary table. Serum samples were frozen at –20°C, apart from the samples for troponin T and aldosterone, which remained at ambient temperature. Plasma was frozen at –20°C, with the exception of samples for pharmacokinetic analysis, which were frozen at –15°C. Whole blood samples remained at ambient temperature.

Statistics

The following sets will be used for statistical analysis: the safety analysis set (SAF; all randomized patients who have taken at least one dose of study drug and for whom there are post-treatment data); the full analysis set (FAS; all patients in the SAF who have baseline and at least one post-baseline UACR value); and the per-protocol analysis set (PPS; all patients in the FAS who have a valid UACR value at visit 5 and no major protocol deviations).

Analysis of the primary efficacy variable will be performed in the FAS (primary analysis) and PPS (supportive analysis). Dose-dependency will be assessed by fitting an analysis of covariance model (ANCOVA) to the log-transformed ratios of UACR at visit 5 to UACR at baseline, including the factors 'treatment group', 'region', and 'type of albuminuria' and the log-transformed baseline UACR as a covariate nested within 'type of albuminuria', and testing a pre-specified linear contrast (L_8' = [6.125, 5.125, 4.125, 2.125, 0.125, –1.875, –5.875, –9.875], one-sided; significance level, 5%). Subsequent hierarchical pairwise comparisons to placebo will also be performed in case the primary hypothesis could be rejected.

In the primary analysis, a last observation carried forward method will be applied, whereby the higher UACR value from the premature discontinuation measurement and the follow-up measurement will be used to impute missing UACR values at visit 5. Sensitivity analyses will also be conducted. In addition, descriptive statistics of the primary efficacy variable will be generated.

Further exploratory efficacy variables will be analyzed in the FAS and PPS. The ratios of UACRs at visits 3, 4, and 5 to those at baseline will be assessed by fitting a mixed-effect repeated measures model to the log-transformed ratios, with the same factors as for the primary analysis plus the factor time and the interaction between treatment and time. Changes in the type of albuminuria and categories of relative decreases of eGFR will be analyzed with frequency tables. Separate ANCOVAs, including factors of 'treatment group', 'region', and 'type of albuminuria', and with the baseline value as a covariate will be used to study changes in efficacy biomarkers and HRQoL scores from baseline to visits 3, 4, and 5 or visits 3 and 5, respectively.

Safety data will be assessed in the SAF. Adverse events and laboratory data will be analyzed by frequency tables and summary statistics, respectively. Changes in safety biomarkers, eGFR and levels of creatinine and serum potassium from baseline to visits 3, 4, and 5 will be analyzed by separate ANCOVAs as for the efficacy biomarkers. The incidence of patients with a potassium value of at least 5.6 mmol/l or of greater than 6 mmol/l, or in different catego-

ries of eGFR decreases or categories of creatinine increases, will be investigated with frequency tables. Percentages of patients in the above categories in the finerenone treatment groups will be compared with those in the placebo group by chi-squared tests with continuity correction.

The ratio of UACR at visit 5 to UACR at baseline of 0.91 or 0.95 is assumed for placebo, whereas UACR ratios are expected to decrease with an increasing dose of finerenone until a ratio of 0.64 to 0.46 for finerenone 15 mg in different scenarios. Sample size calculations were performed with nQuery Advisor® 7.0 (Statistical Solutions, Cork, Ireland). A sample size of 75 patients who were valid for the FAS in each treatment group would give power of at least 83% to demonstrate a dose-dependent effect on the primary variable for seven treatment groups (doses up to 15 mg) using the linear contrast L_7' = (4.714, 3.714, 2.714, 0.716, –1.286, –3.286, –7.286) at a significance level of 0.05 (one-sided), assuming a common standard deviation of 1.25 on the log scale and a true contrast of the log-transformed UACR ratios of at least 3.937. It is expected that the power will increase in the case of eight treatment groups (doses up to 20 mg). Taking into account that the 15 and 20 mg finerenone treatment arms were added, 600 patients were required in total. To achieve this, approximately 1,340 patients had to be enrolled into ARTS-DN (assuming a screening failure rate of up to 50%) and approximately 670 had to be randomized among treatment groups (assuming a drop-out rate of 10%). It was planned to increase the sample size when less than 35% of randomized patients were diagnosed with very high albuminuria. As a result, more than 670 patients were actually randomized.

Ethics

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that the sponsor and investigator abide by Good Clinical Practice guidelines and follow the guiding principles detailed in the Declaration of Helsinki.

The study was carried out in keeping with applicable local law(s) and regulation(s). Documented approval from appropriate independent ethics committee(s) or institutional review board(s) was obtained for all participating centers/countries before the start of the study. All individuals gave their informed consent for participation.

Results

Overall Cohort

The study started in June 2013 and was clinically completed in August 2014. Of 1,501 patients screened at 148 sites, 823 patients were randomized and reviewed by medical experts (Australia, n = 17; Austria, n = 27; Bulgaria, n = 84; Canada, n = 38; Czech Republic, n = 27; Denmark, n = 71; Finland, n = 52; France, n = 14; Germany, n = 14; Hong Kong, n = 7; Hungary, n = 25; Israel, n = 64; Italy, n = 82; Netherlands, n = 22; Norway, n = 7; Poland, n = 23; Portugal, n = 9; Republic of Korea, n = 12; South Africa, n = 51 Spain, n = 67; Sweden, n = 45; Taiwan, n = 22; USA, n = 43). Of these patients, two did not receive treatment: one owing to a protocol deviation and another because of withdrawal of informed consent. The baseline characteristics of the 821 patients who received at least one dose of finerenone/placebo (the sample population) are summarized in table 2.

Table 2. Demographics and baseline characteristics of all patients who were randomized to and recorded starting study treatment

Characteristic	Total (n = 821)
Men, n	639 (77.8)
Age, years	64.2±9.2
Ethnicity, n	
Not hispanic/latino	797 (97.1)
Hispanic/latino	18 (2.2)
Not reported	6 (0.7)
Race, n	
White	691 (84.2)
Black	28 (3.4)
Asian	84 (10.2)
Mixed	16 (1.9)
Not reported	2 (0.2)
BMI, kg/m^2	31.8±5.5
Blood pressure, mm Hg	
Systolic	138.1±14.4
Diastolic	77.1±9.7
Baseline laboratory variables	
UACR, mg/g	192.8 [6.3–4,948.0]
>300 mg/g, n	301 (36.7)
≥30 to <300 mg/g, n	498 (60.7)
<30 mg/g, n	22 (2.7)
Serum potassium, mmol/l	4.29±0.42
eGFR (CKD-EPI), ml/min/1.73 m^2	66.3 [24.5–130.7]
<30 ml/min/1.73 m^2, n	16 (1.9)
30–45 ml/min/1.73 m^2, n	138 (16.8)
>45–60 ml/min/1.73 m^2, n	175 (21.3)
>60 ml/min/1.73 m^2, n	492 (59.9)
Serum creatinine (range), mg/dl	1.1 [0.5–2.6]
BNP, pg/ml	43.0 [2.5–2,060.5]
NT-proBNP, pg/ml	116.1 [10.0–8,212.3]
Galectin-3, ng/ml	9.0 [1.9–160.0]
Troponin T, ng/ml	
<0.05, n	795 (96.8)
0.05–0.16, n	5 (0.6)
Not reported, n	21 (2.6)
Cystatin C, ng/ml	960.0 [100.0–2,720.0]
HbA_{1c}, %	7.4 [4.9–11.9]

Data are expressed as means ± SD, numbers with percentages in parentheses or medians with ranges in square brackets. BMI = Body mass index; BNP = B-type natriuretic peptide; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated hemoglobin; NT-proBNP = N-terminal proBNP; SD = standard deviation; UACR = urinary albumin-to-creatinine ratio. Data on BNP, NT-proBNP, galectin-3 and cystatin C were available for 804, 739, 807, and 812 patients, respectively.

Table 3. Medications of interest that were initiated before starting study treatment and diabetic disease and cardiovascular history of all patients who were randomized to and recorded starting study treatment

	Total (n = 821)
Medication[a]	
Drugs used in the treatment of diabetes	798 (97.2)[b]
Serum-lipid-lowering agents	616 (75.0)[b]
Diuretics	557 (67.8)[c]
Biguanides	531 (64.7)[b]
Antithrombotic agents	481 (58.6)[b]
ARBs	453 (55.2)[c]
Insulin/insulin analogues	453 (55.2)[b]
Calcium-channel blockers	409 (49.8)[b]
ACEIs	383 (46.7)[c]
β-blockers	378 (46.0)[c]
Sulfonylureas	219 (26.7)[b]
Dipeptidyl peptidase-4 inhibitors	162 (19.7)[b]
Potassium supplementation	31 (3.8)[b]
ESAs	1 (0.1)[b]
Intravenous iron	1 (0.1)[b]
Variable[d]	
Diabetic complications	
Neuropathy	164 (20.0)
Retinopathy	163 (19.9)
Diabetic foot	10 (1.2)
Any cardiovascular disorder	325 (39.6)
Myocardial ischemia	77 (9.4)
Atrial fibrillation	66 (8.0)
Coronary artery disease	65 (7.9)
Myocardial infarction	62 (7.6)
Coronary artery bypass	44 (5.4)
Peripheral arterial occlusive disease	37 (4.5)
Angina pectoris	36 (4.4)
Left ventricular hypertrophy	21 (2.6)
Heart failure[e]	20 (2.4)
Atrioventricular block (first degree)	16 (1.9)
Bundle branch block (right)	16 (1.9)
Coronary angioplasty	16 (1.9)
Coronary arterial stent insertion	13 (1.6)
Cardiac pacemaker insertion	13 (1.6)
Transient ischemic attack	12 (1.5)
Bundle branch block (left)	11 (1.3)
Hypertensive heart disease	9 (1.1)
Ischemic stroke	8 (1.0)
Percutaneous coronary intervention	5 (0.6)
Aortic valve replacement	4 (0.5)
Arrhythmia	4 (0.5)

Data are expressed as numbers with percentages in parentheses. ACEIs = Angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; ESAs = erythropoiesis-stimulating agents.

[a] Patients may be taking more than one type of medication.

[b] Based on World Health Organization Drug Dictionary classification.

[c] Based on Bayer Drug Grouping.

[d] Medical Dictionary for Regulatory Activities primary system organ class/preferred term; patients may have more than one comorbidity.

[e] Medical history of heart failure was based on heart failure diagnosis by the investigator before the start of the study; patients with heart failure with reduced ejection fraction (HFrEF) (New York Heart Association class II–IV) and those who were hospitalized for worsening HF within 30 days before the run-in visit were excluded from the study.

The majority of treated patients were men (77.8%), and most were white (84.2%); 69.1% were European. At screening, UACR data were available for 815 patients: 495 (60.3%) had high albuminuria; 315 (38.4%) had very high albuminuria and 5 (0.6%) had normal albuminuria.

At baseline, the median UACR was 192.8 mg/g. In total, 60.7% of patients had high albuminuria, 36.7% had very high albuminuria, and 2.7% had normal albuminuria. The median eGFR was 66.3 ml/min/1.73 m^2, and 18.8% of treated patients had an eGFR less than or equal to 45 ml/min/1.73 m^2.

Concomitant Medication and Medical History

Medications initiated before baseline (including those stopped before baseline) are listed in table 3. ARBs and ACEIs were initiated prior to baseline in 55.2 and 46.7% of the study population, respectively, and calcium-channel blockers in 49.8%. In addition, 97.2% of patients were using medication to manage their diabetes, 75.0% were using agents to reduce lipid levels, 67.8% of patients were receiving diuretics, and 45.8% were taking β-blockers.

Almost all patients (94%) had a medical history of hypertension. Neuropathy and retinopathy were the most common diabetic complications, with a prevalence of 20.0% and 19.9%, respectively (table 3). In terms of CV history, with ARTS-DN excluding patients with symptomatic HFrEF, the most common disorder was myocardial ischemia (9.4%; table 3).

Only 18.9% of patients were current smokers, whereas 41.8% were former smokers and 39.3% had never smoked. A large proportion of patients (49.9%) did not drink alcohol, 39.8% were light drinkers, 9.9% were moderate drinkers and 3.0% were heavy drinkers.

Discussion

Recent developments in DKD research, including the clinical evaluation of several new candidates for DKD therapy, such as bardoxolone, aliskiren and darbepoetin alfa, have failed to achieve the ultimate aim of limiting both progression to ESRD and CV morbidity/mortality in long-term studies in patients with DKD [29–31]. There is strong evidence that MRAs in combination with ACEIs or ARBs reduce mortality, morbidity, and rates of hospitalization in individuals with HFrEF [24, 25, 32]. As a result, the steroidal MRAs eplerenone and spironolactone are recommended in international guidelines for the treatment of patients with HFrEF who remain symptomatic with ACEIs and β-blockers [23, 33, 34]. These MRAs have also shown promise in early studies in patients with DKD or CKD [17, 19–22, 35]. However, MRAs as a drug class are often underused, especially in patients with diabetes and/or renal dysfunction, because steroidal MRAs are associated with an increased risk of hyperkalemia [17, 28, 36]. There is thus an urgent need to evaluate novel therapies that might safely improve CV and renal outcomes in patients with DKD.

Finerenone shows higher selectivity for the MR over other steroid hormone receptors compared with spironolactone and improved affinity for the MR compared with eplerenone in vitro [26]. In preclinical studies, finerenone was seen to distribute equally to the heart and kidneys in rats [27]. Finerenone might therefore confer end-organ protection with a reduced risk of electrolyte perturbation compared with the marketed MRAs eplerenone and spironolactone. In ARTS, a phase 2a study of finerenone in patients with HFrEF and mild-to-moderate CKD, finerenone decreased levels of albuminuria to at least the same degree as spironolactone. Furthermore, finerenone was associated with only infrequent and mostly mild adverse events and was associated with significantly smaller mean increases in serum potassium concentration and a lower incidence of both hyperkalemia and worsening renal function than spironolactone [28]. As hyperkalemia is a major limitation of present treatment strategies with MRAs, finerenone may significantly change the therapeutic possibilities in patients with CKD.

ARTS-DN is the first large clinical trial of finerenone in combination with a RAS inhibitor in patients with type 2 diabetes and a clinical diagnosis of DN. Owing to the inclusion criteria, UACRs and levels of HbA_{1c} were elevated above the normal range in the study population. Average systolic blood pressure was also slightly higher than normal, as expected in patients with type 2 diabetes mellitus and DKD [19, 21]; however, the average blood pressure reading was within the normal range. Despite the high prevalence of historical hypertension in the study population, and because of the exclusion of patients with severe hypertension from this study, patients generally had good blood pressure control at baseline. This may mean that only small changes in blood pressure can be expected under treatment with finerenone over 90 days in ARTS-DN.

Both type 2 diabetes mellitus and CKD are associated with an elevated risk of CV disease, and hence it is no surprise that a substantial proportion (39.6%) of patients in ARTS-DN have a history of CV disorders. The percentage of patients using lipid-lowering agents in this study is in line with that seen in other studies of patients with type 2 diabetes mellitus who are at CV-renal risk [37, 38]. Previously, in ARTS, finerenone (10 mg once daily/5 mg twice daily) in combination with the standard of care for HFrEF was shown to be at least as effective as spironolactone at decreasing levels of hemodynamic stress biomarkers (BNP and NT-proBNP) as well as at reducing albuminuria. Even though patients with symptomatic HFrEF were excluded from ARTS-DN because a placebo-group would have been unethical given the knowledge that MRAs are life-prolonging in such patients, it is still predicted that a large number of participants in ARTS-DN, especially those with CV disease, might experience a dual CV-renal benefit from finerenone treatment. The 2013 American College of Cardiology HF guidelines state that clinical evaluations of patients with HF are best informed by the use of multiple biomarkers, including natriuretic peptides and indicators of both myocardial fibrosis and injury [34]. In ARTS-DN, the levels of galectin-3 (a marker of myocardial fibrosis) and troponin T (a marker of myocardial injury) will be monitored along with the levels of the natriuretic peptides BNP and NT-proBNP, which are differentially affected by renal function. Assessments of the levels of soluble ST-2, another marker of myocardial fibrosis, will not be performed in this phase 2b study. Markers of renal function will, however, be followed and should provide further insight into cardiac health because renal injury is thought to be involved in the progression of HF [34].

Should finerenone satisfy the criteria of reducing albuminuria as well as being well tolerated and having a good safety profile in this phase 2b trial, there are plans to initiate a comprehensive phase 3 program of clinical trials in patients with DKD. After the failure of other potential therapies such as bardoxolone, aliskiren and darbepoetin

alfa to progress beyond the clinical trial stage of drug development, new medications in this field are keenly awaited. It is hoped that eventually finerenone will succeed in fulfilling the unmet clinical need of improving long-term cardiovascular and renal outcomes in patients with DKD.

Conclusion

ARTS-DN is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b study started in June 2013. The recruitment rate was faster than expected, and enrolment had to be stopped more than 6 months earlier than planned. The trial was clinically completed in August 2014. Based on the results of this trial, future long-term clinical studies examining the effects of finerenone on the progression of renal disease as well as on CV morbidity and mortality in patients with DKD would be warranted [39].

Conflicts of Interest

R.A. has participated in Steering Committees for Abbvie, Bayer HealthCare AG and Sandoz; has performed data safety monitoring for Amgen and Celgene; has been a consultant to AstraZeneca, Daiichi Sankyo, Genkyotex, Eli Lilly and Takeda Pharma; and has received grant and research funding from VA and NIH. G.L.B. has received an investigator-initiated grant/research support from Takeda (direct funding to University of Chicago); has been a principal investigator in national/international clinical trials sponsored by Bayer HealthCare AG, Medtronic and Relypsa (direct funding to University of Chicago); and has been an advisor/consultant for AbbVie, Bayer HealthCare AG, BMS, CVRx, Elcelyx, Eli Lilly/Boehringer-Ingelheim, Janssen, Medtronic, Novartis GSK, Takeda, Tengion and ZS Pharma. J.C.C. is a member of steering committees of international projects funded by AstraZeneca, Bayer HealthCare AG, Lilly, MSD, Pfizer and Sanofi; is a member of global/regional advisory boards of Boehringer-Ingelheim, Eli Lilly, MSD, Pfizer; and has received honorarium and travelling support from Amylin, AstraZeneca, Bayer HealthCare AG, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Impeto, Lilly, MSD, Novartis, Pfizer, Sanofi and Takeda, with the honorarium donated to the Chinese University of Hong Kong for diabetes research and education; her institution has also received research and educational grants from these companies. M.E.C. has received grants and lecture fees from Novo-Nordisk, AbbVie, Boehringer-Ingelheim, Eli Lilly, Bayer HealthCare AG, MSD and AstraZeneca. A.C.F., N.K.K. and C.N. are employees of Bayer HealthCare AG. R.T.G. has consultancy agreements with AbbVie, Bayer HealthCare AG, Ipsen, Novartis Pharma and Otsuka Pharmaceuticals – no personal remuneration is accepted (compensations are paid to his institution for research). H.H. and R.S. have received honoraria for presentations from Bayer HealthCare AG. A.P. provided clinical trial support funded by Bayer HealthCare AG. G.R. has consultancy agreements with Alexion Pharmaceuticals, Bayer HealthCare AG, Novartis Pharma, and REATA Pharmaceuticals – no personal remuneration is accepted (compensations are paid to his institution for research and educational activities). P.R. has consultancy agreements with AbbVie, AstraZeneca, Bayer HealthCare AG, BMS, Eli Lilly, Boehringer Ingelheim, Novartis Pharma, and Novo Nordisk: no personal remuneration is accepted (compensations are paid to his institution). L.M.R. has been a speaker and advisor for Bayer HealthCare AG.

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