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CLINICAL TRIAL DESIGN

Rationale and protocol of the Study Of diabetic Nephropathy with AtRasentan (SONAR) trial: A clinical trial design novel to diabetic nephropathy

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Aims: Individuals with diabetes and chronic kidney disease (CKD) are at high risk for renal events. Recent trials of novel treatments have been negative, possibly because of variability in response to treatment of the target risk factor. Atrasentan is a selective endothelin A receptor antagonist that reduces urinary albumin-to-creatinine ratio (UACR), with a large variability between patients. We are assessing its effect on renal outcomes in the Study Of diabetic Nephropathy with AtRasentan (SONAR; NCT01858532) with an enrichment design (>30% lowering of albuminuria) to select patients most likely to benefit.

Materials and Methods: SONAR is a randomized, double-blind, placebo-controlled trial with approximately 3500 participants who have stage 2–4 CKD and macroalbuminuria and are receiving a maximum tolerated dose of a renin-angiotensin system inhibitor.

Results: After 6 weeks of exposure to atrasentan 0.75 mg once daily (enrichment period), participants with ≥30% UACR decrease and no tolerability issues (responders) were randomly assigned to placebo or atrasentan 0.75 mg/day. The responder group will be used for primary efficacy and safety analyses. Approximately 1000 participants with <30% UACR reduction (non-

responders) were also randomized to placebo or atrasentan. The primary endpoint is a composite of a sustained doubling of serum creatinine or end-stage renal disease. The original power calculation indicated that a total of 425 primary renal events in the responder group provides 90% power to detect a 27% reduction in relative risk (alpha level of .05).

Conclusion: SONAR aims to determine whether atrasentan added to guideline-recommended therapies safely reduces the risk of CKD progression and delays the onset of end-stage renal disease in patients with type 2 diabetes and nephropathy. SONAR also aims to establish whether the enrichment of patients based on their initial "surrogate" response to atrasentan will deliver a trial design in accord with personalized treatment of diabetic kidney disease.

KEYWORDS

atrasentan, diabetic kidney disease, endothelin receptor antagonist, personalized medicine, randomized controlled clinical trial

1 | INTRODUCTION

Endothelin receptor antagonists (ERAs) represent a new approach to reducing renal, and possibly cardiovascular (CV), risk in patients with type 2 diabetes and kidney disease. ERAs are proven to be effective in experimental models of progressive renal disease.[1-3] Recent clinical studies have shown that the ERA atrasentan markedly lowered urine albumin-to-creatinine ratio (UACR) in patients with type 2 diabetes and kidney disease when added to a maximum tolerated dose of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).[4] These initial results supported the conduct of a Phase 3 clinical outcome trial to determine whether atrasentan can delay or prevent progression to end-stage renal disease (ESRD).

Many Phase 3 trials conducted over the past decade with other new therapeutic agents for preventing loss of renal function failed to demonstrate treatment benefit, despite each having shown promising results in Phase 2 trials.[5-10] In retrospect, some of these failures may have been the result of deficiencies in trial design, including choice of dose, patient selection, and a frequency of adverse effects that was too high, reflecting known toxicity or "off-target" actions of the drugs tested.[11] To improve the likelihood of detecting a treatment effect, the trial design should maximize the potentially beneficial effects of therapy, while minimizing known adverse effects. In the case of an ERA, this equates to maximizing UACR reduction while minimizing sodium retention. Ideally, optimally balancing these pharmacologic actions prior to randomization would mean enrolling only those individuals at high risk of progressing to ESRD. This allows for selection of individuals at high risk of disease (prognostic enrichment) who also demonstrate a good response to study treatment (predictive enrichment).

With the above considerations in mind, the Study Of diabetic Nephropathy with AtRasentan (SONAR) was designed to test the possible renoprotective effects of the ERA atrasentan in a prospective, randomized, double-blind placebo-controlled clinical outcome trial in patients at high risk of progressing to ESRD. The challenge was to optimize the trial design, as outlined above, to identify the optimal patient population, thereby maximizing the benefit: risk ratio of this treatment. This paper describes such a strategy.

2 | MATERIALS AND METHODS

2.1 | Study objective

The primary objective of SONAR (NCT01858532; www.clinicaltrials.gov) is to assess the efficacy and safety of atrasentan compared with placebo in delaying the time to doubling of serum creatinine or the onset of ESRD in participants with type 2 diabetes and chronic kidney disease who are being treated with a maximum tolerated labeled daily dose (MTLDD) of an ACE inhibitor or ARB. In addition, the study is designed to assess the effects of atrasentan compared with placebo on CV morbidity and mortality, changes in estimated glomerular filtration rate (eGFR) and UACR, as well as on quality of life.

2.2 | Overall study design

SONAR is a multinational, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial assessing the effects of atrasentan on renal outcomes in individuals with type 2 diabetes and nephropathy. A total of 3668 participants have been randomized at 795 sites in 41 countries (Figure 1). The overall study design is presented in Figure 2.

2.3 | Study population

The study population includes patients with type 2 diabetes mellitus with an eGFR of 25–75 mL/min/1.73 m^2, a UACR ≥300 mg/g creatinine and <5000 mg/g, and brain natriuretic peptide (BNP) ≤200 pg/mL. Additional inclusion and exclusion criteria are reported in Table 1.

2.4 | Study periods

2.4.1 | Screening, run-in and enrichment

Study participants who meet all inclusion and no exclusion criteria proceed directly to the run-in period to optimize ACE inhibitor/ARB and/or diuretic doses. Subsequently, eligible participants enter the enrichment period and receive atrasentan 0.75 mg once daily. The rationale of using this atrasentan dose has been described in previous publications.[4,12] The 6-week enrichment period, a unique feature of the SONAR study design, was used to select participants who have a significant response to
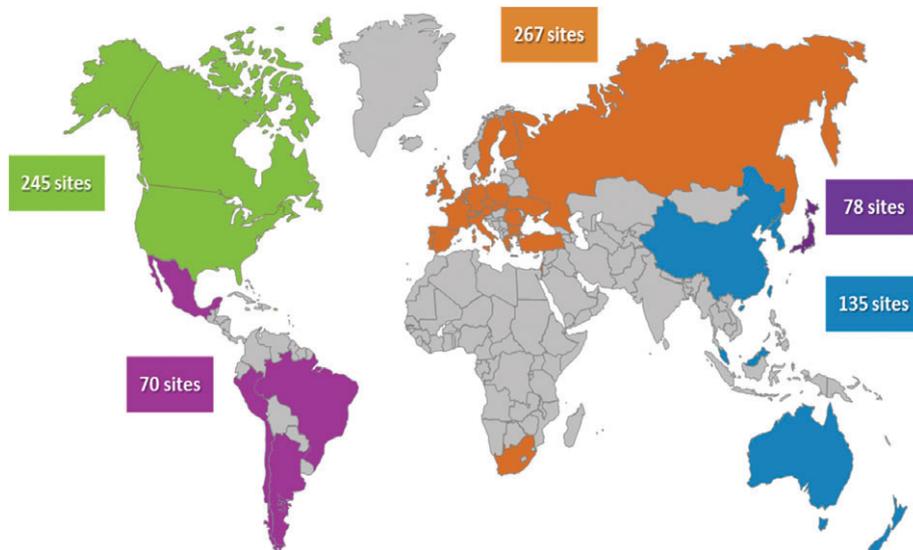
FIGURE 1 Countries participating in SONAR. Study Of diabetic Nephropathy with AtRasentan

atrasentan (≥30% reduction in UACR) without adverse effects, such as significant sodium and fluid retention (eg, weight gain >3 kg and BNP ≥300 pg/mL). The enrichment phase of the SONAR trial does not include a placebo arm. Thus, placebo-controlled inferences about the effect of atrasentan during this stage cannot be made.

2.4.2 | Randomization

Approximately 2500 "responders" (UACR reduction ≥30% from baseline) will be randomized 1:1 to atrasentan 0.75 mg/day or matching placebo. These participants will comprise the primary intention-to-treat (ITT) population for assessing the safety and efficacy of atrasentan. In addition, a selection of approximately 1000 "non-responders" (UACR reduction <30% from baseline) will be randomized to double-blind treatment in a parallel study stratum. Enrollment of 1000 non-responders will be distributed chronologically to provide an experience similar to that of responders (ie, comparable exposures, balancing enrollment across geographic regions). The rationale for the randomized non-responder cohort is to undertake an additional analysis to determine whether longer-term exposure to atrasentan can also delay progression of renal disease in participants with a modest UACR reduction on initial exposure to study drug. Randomization was performed centrally through an interactive voice response system on the basis of a computer-generated randomization schedule prepared by the study sponsor. A stratified randomization scheme ensures balance in treatment allocation within geographic regions, baseline UACR levels (≤ or >1000 mg/g), and categories of UACR reduction achieved

during the enrichment period (30% – <45%, 45% – <60% and ≥60%, respectively). Participants and all study personnel (with the exception of the Independent Data Monitoring Committee) are kept masked to treatment allocation and study drug; atrasentan and placebo are packaged identically, with uniform capsule appearance, labeling, appearance and odor, as well as administration schedule.

2.4.3 | Double-blind treatment, follow-up and management of participants

After randomization, telephone contacts are scheduled at 1- and 2-week time intervals, followed by in-person visits at 1 and 3 months and at 3-month intervals thereafter. Each follow-up visit includes assessment for primary outcomes, adverse events, concomitant therapies, study drug adherence and accountability, and provision of further study medication. In addition, vital signs are recorded, participants are examined for peripheral edema, and blood and urine are collected for laboratory measurements. Participants receive the study drug until they reach renal replacement therapy (dialysis or renal transplantation), discontinue the study drug or prematurely withdraw from the study. Upon study drug discontinuation, participants are to have a follow-up visit 45 days after the last dose of study drug to assess the effects of discontinuing the study drug. Participants who prematurely discontinue the study drug but do not terminate the study are to continue follow-up visits as scheduled; if this is not possible, they are asked to allow follow-up via phone, family or treating doctors.

FIGURE 2 SONAR study diagram. MTLD, maximum tolerated labeled dose; QD, once daily; RAS, renin-angiotensin system; SONAR, Study Of diabetic Nephropathy with AtRasentan; UACR, urinary albumin-to-creatinine ratio
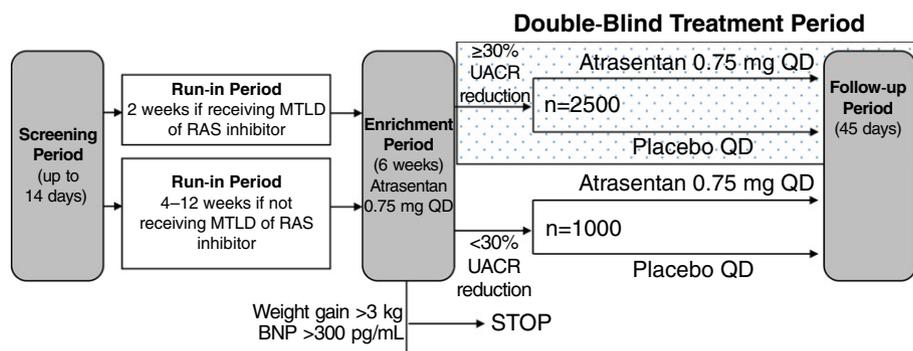
TABLE 1 Main inclusion and exclusion criteria of SONAR

Inclusion criteria
Criteria for entry into the study
18–85 years of age
History of type 2 diabetes and receiving at least 1 anti-diabetic medication
Criteria for entry into the run-in period
Estimated GFR 25–75 mL/min/1.73 m^2
UACR ≥300 and <5000 mg/g (≥34 mg/mmol and <565 mg/mmol)
BNP ≤ 200 pg/mL (200 ng/L)
Systolic blood pressure ≤ 180 mm Hg and ≥110 mm Hg
Criteria for entry into the enrichment period (open-label atrasentan treatment)
Stable treatment with an ACE inhibitor and/or ARB for at least 4 weeks prior to and during screening
Criteria for entry into the double-blind treatment:
≥30% reduction in UACR from the beginning of the enrichment visit to the end (atrasentan responders)
<30% reduction in UACR from the beginning of the enrichment visit to the end (atrasentan non-responders)
No more than 3-kg weight gain during enrichment *and* absolute serum BNP not ≥300 pg/mL (300 ng/L) at the last enrichment visit
No more than 0.5-mg/dL increase in serum creatinine (48 μmol/L) and no more than 20% increase from the beginning of enrichment to the end
RAS inhibitor at the MTLDD during enrichment with no dose adjustments
Participant has taken a diuretic at any dose unless medically contraindicated
Exclusion criteria
Type 1 diabetes mellitus
History of severe peripheral edema or facial edema requiring diuretics unrelated to trauma or a history of myxedema
History of pulmonary hypertension, pulmonary fibrosis or any lung disease requiring oxygen therapy
Documented diagnosis of heart failure, previous hospitalization for heart failure, or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea) indicative of heart failure
Known non-diabetic kidney disease
Elevated liver enzymes (serum ALT and/or serum AST) > 3 times the upper limit of normal
Hemoglobin <9 g/dL
Sensitivity to loop diuretics
Clinically significant CVD or CAD within 3 months of the screening S1 visit, defined as 1 of the following: • Hospitalization for MI or unstable angina; or • New onset angina with positive functional study or coronary angiogram revealing stenosis; or • Coronary revascularization procedure; or • TIA or stroke
Significant comorbidities (malignancies, liver disease) with life expectancy <1 year
Female participants who are premenopausal, defined as any female participant with a menses in the past 2 years

Abbreviations: ACE, angiotensin converting enzyme; ALT, alanine amino-transaminase; ARB, angiotensin receptor blocker; AST, aspartate amino-transaminase; BNP, brain natriuretic peptide; CAD, coronary artery disease; CVD, cerebrovascular disease; GFR, glomerular filtration rate; MI, myocardial infarction; MTLDD, maximum tolerated labeled daily dose; RAS, renin-angiotensin system; SONAR, Study Of diabetic Nephropathy with AtRasentan; TIA, transient ischemic attack; UACR, urinary albumin-to-creatinine ratio.

TABLE 2 Primary, secondary and exploratory endpoints of SONAR

1	Primary composite endpoint: 1. Time to doubling of serum creatinine from baseline (confirmed by 30-day serum creatinine) 2. Time to ESRD defined as eGFR <15 mL/min/1.73 m^2, need for chronic dialysis (both confirmed after 90 days), renal transplantation or renal death
2	Secondary endpoint: 1. Time to a 50% eGFR reduction 2. Time to cardio-renal composite endpoint: doubling of serum creatinine, ESRD, CV death, non-fatal MI, non-fatal stroke 3. Time to first occurrence of a component of composite renal endpoint: doubling of serum creatinine or the onset of ESRD for all randomized participants (responders and non-responders) 4. Time to the CV composite endpoint: CV death, non-fatal MI, and non-fatal stroke
3	Additional endpoints include (but not limited to): 1. Time to 40% reduction in eGFR (from values at randomization and 3 months post randomization) 2. Change in eGFR slope (from values at randomization and 3 months post randomization) 3. Change in eGFR (from values at randomization and 3 months post randomization) to 45 days after end of treatment 4. Change from baseline (from values at randomization) to 24 months post-randomization visit on UACR 5. Time to major vascular event: CV death, non-fatal MI, non-fatal stroke, hospitalized unstable angina 6. Time to congestive heart failure (hospitalized and non-hospitalized)

Abbreviations: CV, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MI, myocardial infarction; SONAR, Study Of diabetic Nephropathy with AtRasentan; UACR, urinary albumin-to-creatinine ratio.

2.5 | Outcome definitions and event adjudication

Primary efficacy analysis will be conducted in the responder group (Figure 2). The primary outcome for evaluation of the effect of atrasentan on delaying progression of renal disease is the time to first occurrence of any of the following components of the composite renal endpoint: doubling of serum creatinine (confirmed by a second serum creatinine measurement at least 30 days later), onset of ESRD or renal death (Table 2). Renal death is defined as death attributable to kidney failure (ie, necessity of dialysis/renal transplantation, without dialysis or transplantation available or implemented). A blinded and independent event adjudication committee (EAC), consisting of experts in nephrology, cardiology and neurology, will adjudicate primary and secondary endpoints. For the purpose of event adjudication, ESRD is defined as the necessity of maintenance dialysis (peritoneal or hemodialysis) > 90 days, renal transplantation or sustained eGFR <15 mL/min/1.73m^2 for >90 days. The 90-day criterion is included in the definition of the ESRD endpoint to avoid misclassification of ESRD caused by acute kidney injury or volume overload requiring renal replacement therapy (RRT). If ESRD is reached <90 days before study closure, or if the participant dies within 90 days of dialysis initiation, the EAC will adjudicate whether the endpoint meets ESRD criteria, using the detailed definitions and criteria defined in the EAC charter. Secondary and exploratory efficacy endpoints are described in Table 2.

2.6 | Background medication

All efforts are to be undertaken to maintain participants' stable doses of ACE inhibitors/ARBs and diuretics during the double-blind

treatment period throughout the study. If at any time during the study there is an interruption of or decrease in ACE inhibitor/ARB dose, resumption of the previous dose is attempted within 1 month, in line with the investigator's medical judgment. ERAs may induce sodium retention in some patients.[13,14] The investigator may increase the diuretic dose as needed in the presence of signs and symptoms of fluid overload (eg, peripherial edema, dyspnea or orthopnea). Management of glucose, blood pressure or lipid-lowering medications, and of other therapies is at the discretion of the investigator, according to local and/or international clinical practice guidelines.

2.7 | Statistical considerations

2.7.1 | Estimating risk reduction

Sample size for the double-blind treatment period is based on the expected rate of the primary efficacy endpoint and the anticipated size of the effect of treatment with atrasentan. In the Phase 2 RADAR trial, 51% of participants receiving atrasentan 0.75 mg/day achieved a ≥30% reduction in UACR. In this population, the mean UACR reduction was 54%, which is expected to reduce the risk of ESRD by up to 50%, based on the association between drug-induced reductions in UACR and risk changes in ESRD.[15] However, because the confidence intervals are large for this level of UACR reduction, a conservative effect size of 27% risk reduction in ESRD was chosen, using the lower boundary of the confidence interval. A modeling and simulation analysis, taking into account all other effects of atrasentan on renal and CV risk markers, confirmed that a 27% reduction in renal risk is highly plausible.[12] A total of 425 events are required to detect a 27% reduction in risk (hazard ratio, 0.73), with 90% power at a two-sided alpha level of .05. The size of the non-responder population is based on logistical and feasibility grounds.

During the course of the study, and after all patients had completed the enrichment period and were randomized into the study, it became apparent that the observed renal event rate in the atrasentan responder population was lower than originally expected. The very lengthy follow-up that would be required to collect the original 425 planned primary events led to the sponsor's decision not to continue with ongoing follow-up. Clinical trial sites were notified accordingly in late 2017. At the time the trial was discontinued, more than 121 renal events were projected to be accumulated, resulting in more than 90% power to detect a hazard ratio of 0.55, and more than 80% power to detect a hazard ratio of 0.60.

2.7.2 | Efficacy assessment, primary analysis

The primary efficacy analysis will be based on the ITT population, defined as all randomized participants in the responder group. The primary analysis will employ Cox proportional hazards regression to estimate the hazard ratio (and 95% confidence interval) of atrasentan to placebo; this will be adjusted based on relevant covariates (ie, UACR, eGFR, age and serum albumin). For determination of doubling of serum creatinine, values obtained prior to the enrichment period will be used as reference baseline values. Statistical tests for treatment comparisons will be performed using a stratified log-rank test, adjusting for the stratification factors used at randomization.

2.7.3 | Secondary efficacy assessment according to urine albumin-to-creatinine ratio response stratification

As it remains unknown whether the enrichment by albuminuria response is actually delivering better renal protection, which is the hypothesis tested in the SONAR trial, we are also enrolling 1000 non-responder participants, in whom the effect of atrasentan on renal outcome will be assessed. A weighted, pooled analysis of the responders and non-responders will provide an assessment of the treatment effect in the combined patient population as a secondary objective of the study. At the randomization visit, participants are randomized in different UACR response strata: <0%, 0% – <15% and 15% – <30% in non-responders; 30% – <45%, 45% – <60% and ≥60% in the responder population. This stratification by UACR response levels should enable identification of a minimum UACR response threshold that is associated with a beneficial effect of atrasentan on the primary renal endpoint.

2.7.4 | Safety assessment

The frequency and intensity of, and the relationship with, treatment-emergent adverse events and serious adverse events will be determined in all participants exposed to study medication during the enrichment and double-blind treatment periods. As ERAs may cause sodium retention, adverse events related to fluid retention, including edema and congestive heart failure, are carefully monitored. In addition, weight measurements are performed at each visit during the study, preferably under the same circumstances. Results are compared with those of previous visits. If there is an increase in body weight ≥2 kg, measurements error should be ruled out, presence of edema should be evaluated, and the dose of the diuretic should be re-evaluated and adjusted if necessary. Other adverse events of special interest include vasodilatation (eg, hypotension, headache, nasal congestion, hot flushes), CV toxicity and liver toxicity. Acute kidney injury will be monitored, diagnosed and treated as suggested in the KDIGO Clinical Practice Guideline for Acute Kidney Injury.[16] Other safety assessments include physical examination, vital sign measurements, 12-lead electrocardiograms and centrally analysed laboratory measurements.

2.7.5 | Patient-reported outcomes

Health-related quality-of-life outcomes, using the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) index score, Assessment of Quality of Life (AQOL)-4D (Australia only) and Kidney Disease Quality of Life questionnaires, are assessed at baseline and every 3 months during the first year of the trial, and at yearly intervals thereafter.

2.8 | Role of funding source

The study is overseen by a steering committee, including non-voting members from the sponsor. The steering committee designed the study, and it oversees the conduct of the trial and the analysis of all data. The sponsor is responsible for collection and analysis of data, in conjunction with the steering committee. All authors will have access to study results.

3 | DISCUSSION

Endothelin-1 (ET-1) is recognized as an important drug target in diabetic kidney disease. Elevated renal ET-1 levels in diabetic kidney disease are thought to contribute to renal vasoconstriction, glomerular cell dysfunction and proteinuria through activation of renal type A endothelin (ETA) receptors.[17] ETA receptor blockade attenuates progression of nephropathy in experimental models of diabetic kidney disease by improving glomerular function[17,18] and by attenuating inflammatory pathways.[2]

A previous trial with a different ERA showed that avosentan at doses of 25 and 50 mg/day markedly reduced UACR but increased the risk of heart failure and mortality, leading to early termination of a large outcome trial.[5,19] That study highlighted the importance of careful dose selection, to focus not only on the protective effect of the study drug, but also on drug-related adverse outcomes (eg, sodium retention). Our previous dose-finding study with the ERA atrasentan, which is highly selective for ETA, showed that a low dose (0.75 mg/day) of atrasentan had a significant UACR-lowering effect and led to minimal signs of sodium retention.[4] This study also showed that the extent of UACR lowering with atrasentan did not correlate with the degree of fluid retention. This allowed us to select a potentially optimal atrasentan dose and to identify a responder population with a substantial UACR reduction but with minimum sodium retention.[12]

SONAR, like other renal outcome trials in diabetic kidney disease, will examine the effect of the study drug on the "standard" composite renal endpoint in a population at high renal and CV risk. However, in contrast to other trials, it employs a response enrichment design. The rationale for introducing this enrichment strategy is to enhance the selection of patients who would benefit most and exclude those unlikely to benefit from the drug. Indeed, analyses from past trials in diabetic kidney disease confirmed a large patient heterogeneity in drug response, both in effects that lead to organ protection and in effects that lead to organ failure, highlighting the need to exclude the specific subgroup of patients in which the drug is not effective, and possibly even harmful.[20–23] The inclusion of patients who are more likely to show benefit (enrichment) maximizes the chance of identifying and registering a new beneficial drug for a complex disease such as diabetic kidney disease. As many drugs have failed in late-stage drug development,[24] this enrichment design is a potential way to make the drug development trajectory more successful and efficient. It also represents a step in the direction of personalized medicine.

The results from a predictive enrichment trial may apply only to the selected "responder" patient subgroup and may not be extrapolated to the broader population. While this may complicate general statements on drug efficacy and safety, it should not be interpreted as a limitation of the enrichment design. Clinical outcome trials that are conducted for the purpose of registering a new drug for use in clinical practice should represent the way the drug is used in daily practice. In clinical practice, drug treatment will commonly be discontinued if patients do not show a good response, and especially if patients develop side effects. The enrichment design of SONAR thus mimics clinical practice and may more reliably represent how the drug is used in practice, and it is in accord with the concept of personalized medicine for the treatment of diabetic kidney disease.

The enrichment design may have disadvantages. The impact on the intended study population of enrichment of the population based on a biomarker response is unknown. For example, by selecting patients based on their albuminuria response, the selected population may be at a lower renal risk, which could explain the low renal event rate observed in the SONAR trial. Alternatively, the low renal event rate could also be explained by the larger than anticipated treatment effect. The enrichment results, which are described in the accompanying SONAR article, actually show that atrasentan lowers UACR by nearly 50% in the responder population, raising the possibility of a very large renoprotective effect.[25]

Validated surrogate outcomes can facilitate the conduct of clinical trials in diabetic kidney disease and, ultimately, targeted patient care. There is an ongoing debate as to whether UACR is a valid surrogate of renal outcomes, because of the paucity of prospective clinical trials showing that short-term treatment effects on albuminuria predict long-term reduction in renal outcomes. Some claim that the failure of past trials is explained by the fact that albuminuria reduction is a poor surrogate for clinical renal outcomes. The alternative view is that multiple clinical trials have shown, albeit in post hoc analyses, that drug-induced reductions in albuminuria precede and predict long-term renoprotection, independently of the drug or population studied, and that lack of prediction in some trials is based on other drug effects offsetting the potential benefit of albuminuria reduction.[26] As randomization into the SONAR trial is stratified based on the UACR-lowering response, SONAR is designed to allow assessment, in a scientifically robust, prospective, blinded, placebo-controlled manner, of whether a drug-induced reduction in UACR is an independent predictor of long-term renoprotection. Thus, SONAR is expected to help in establishing UACR as a valid surrogate marker in future diabetic kidney disease trials.

In conclusion, an important lesson learned from all clinical trials conducted in the past decade in diabetic kidney disease is that ignoring individual drug response results in suboptimal patient selection and the failure of drug development programmes. SONAR, with its enrichment design, may establish a new precedent for clinical trials in diabetic kidney disease, and will define the effect of atrasentan on renal outcomes that are considered to be of clinical and regulatory importance in a population at high risk of progressive renal dysfunction and CV events.

3.1 | Members of the SONAR Steering Committee

Dick de Zeeuw (Chair), Hans-Henrik Parving (co-chair), George Bakris, Ricardo Correa-Rotter, Hiddo J. L. Heerspink, Fan Fan Hou, Donald Kohan, Dalane Kitzman, Hirofumi Makino, John McMurray, Vlado Perkovic, Sheldon W. Tobe, Dennis Andress, John J. Brennan (until November 2016), Blai Coll, Mark Houser (AstraZeneca, former employee of AbbVie), Melissa Wigderson, Joel Melnick (AbbVie, starting November 2016).

3.2 | Members of the SONAR Independent Data Monitoring Committee

Peter McCullough (Chair), John Lachin, Johannes Mann, Charles Herzog, Rudolph Bilous, David Webb, Mitchell Rosner.

3.3 | Members of the SONAR Event Adjudication Committee

Rajiv Agarwal (Chair until December 2015), Dalane Kitzman (Chair from January 2016), Michael Rocco, Chirag Parikh, Daniel Kolansky, Scott Kasner, Brett Kissela, Kausik Ray, Mihai Gheorghiade, Stephen Seliger, Philip Gorelick, James Januzzi (from July 2017).

3.4 | National coordinators

Argentina, Laura Maffei and Walter Douthat; *Australia*, Carol Pollock, Simon Roger and Muh Geot Wong; *Austria*, Gert Mayer; *Belgium*, Luc Van Gaal (until January 2015); *Brazil*, Maria Tereza Zanella and Emmanuel Burdmann; *Canada*, Sheldon Tobe; *Chile*, Fernando Gonzalez; *China*, Fan Fan Hou; *Czech Republic*, Vladimir Tesar; *Denmark*, Peter Rossing; *Finland*, Kaj Metsarinne; *France,* Philippe Zaoui; *Germany*, Christoph Wanner; *Greece*, Dimitrios Goumenos and K Siamopoulos; *Hong Kong*, Sidney Tang; *Ireland*, Joe Eustace; *Israel*, Julio Wainstein and Itamar Raz (until August 2014); *Italy*, Luca de Nicola; *Japan*, Hirofumi Makino; *Korea*, Lee Moon-Kyu; *Malaysia*, Mohammed Mafauzy; *Mexico*, Ricardo Correa-Rotter; *Netherlands*, Goos Laverman and Marc Vervloet (until January 2017); *New Zealand*, Hellen Pilmore; *Peru*, Luis Humberto Zapata; *Poland*, Michal Nowicki; *Portugal*, Anibal Ferreira; *Romania*, Covic Andrian (until December 2014); *Russia*, Marina Shestokova and Natalia Tomilina (until May 2015); *Singapore*, Adrian Liew; *Slovakia*, Adrian Oksa; *South Africa*, Larry Distiller; *Sweden*, Peter Rossing; *Spain*, Julio Pascual; *Taiwan*, Wayne Sheu; *Ukraine*, Mykola Kolesnyk; *UK*, Luigi Gnudi and Bruce Hendry; *USA*, Pablo Pergola, Alan Perlman, Srinivasan Beddhu (until July 2015), Luis Juncos (until July 2015), Aamir Jamal (until July 2015) and Gregory Todd Greenwood (until July 2015).

Conflict of interest

H. J. L. H. is a consultant for and received honoraria (to employer) from AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Janssen and Merck. G. B. is a consultant for Bayer, Merck, KBP, Relypsa, Janssen and AbbVie, is principal investigator of the FIDELIO trial (Bayer), and serves on Steering Committees for the CREDENCE (Janssen) and SONAR trials (AbbVie). R. C.-R. is a member of the Steering Committee of SONAR and has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim, and has lectured for Amgen, Takeda, AstraZeneca and Roche. F. F. H. is a consultant for and has received honoraria from AbbVie and AstraZeneca. D. W. K. is a consultant for AbbVie, Relypsa, Corvia Medical and Bayer, has received research grant funding from Novartis, Bayer and St. Luke's Hospital of Kansas City, and has stock ownership in Gilead Sciences.

D. K. consults for AbbVie and has received grant support from the US National Institutes of Health (NIH). H. M. is a consultant for AbbVie and Teijin, and receives speaker honoraria from AbbVie, Teijin, Astellas, Boehringer Ingelheim, MSD and Tanabe Mitsubishi.

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Author contributions

D. deZ., D. A., B. C. (Amgen, former employee of AbbVie), H. J. L. H. and H.-H. P. designed the protocol with the Steering Committee, the Chair of the Event Adjudication Committee (Rajiv Agarwal until December 2015; Dalane Kitzman from January 2016), the Chair of the Independent Data Monitoring Committee (Peter McCullough) and the statistical department at AbbVie. H. J. L. H. and D. deZ. wrote the draft of this report, and all authors contributed to its revision. D. deZ. takes full responsibility for this report.

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