27 February 2025
EMA/90836/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Filspari

International non-proprietary name: Sparsentan

Procedure No. EMEA/H/C/005783/0002

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	19 Aug 2024	19 Aug 2024	☐
☐	CHMP Rapporteur Assessment Report	17 Sep 2024	17 Sep 2024	☐
☐	PRAC Rapporteur Assessment Report	20 Sep 2024	19 Sep 2024	☐
☐	PRAC members comments	25 Sep 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	26 Sep 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	03 Oct 2024	03 Oct 2024	☐
☐	CHMP members comments	07 Oct 2024	07 Oct 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	10 Oct 2024	10 Oct 2024	☐
☐	Request for supplementary information	17 Oct 2024	17 Oct 2024	☐
☐	Re-start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	02 Jan 2025	02 Jan 2025	☐
☐	PRAC Rapporteur Assessment Report	06 Jan 2025	03 Jan 2025	☐
☐	PRAC members comments	08 Jan 2025	08 Jan 2025	☐
☐	Updated PRAC Rapporteur Assessment Report	09 Jan 2025	09 Jan 2025	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	16 Jan 2025	16 Jan 2025	☐
☐	CHMP members comments	20 Jan 2025	20 Jan 2025	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	22 Jan 2025	☐
☐	Request for supplementary information	30 Jan 2025	30 Jan 2025	☐
☐	Start of procedure	05 Feb 2025	05 Feb 2025	☐
☐	CHMP Rapporteur Assessment Report	12 Feb 2025	12 Feb 2025	☐
☐	PRAC Rapporteur Assessment Report	12 Feb 2025	13 Feb 2025	☐
☐	PRAC members comments	17 Feb 2025	n/a	☐
☐	CHMP members comments	17 Feb 2025	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	20 Feb 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Feb 2025	n/a	☐
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Procedure resources	
Rapporteur:	Vilma Petrikaite

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List Of Abbreviations

Abbreviation	Definition
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event(s)
AEOI	adverse event of interest
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Ang II	angiotensin II
AEOI	adverse event of interest
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
CMA	Conditional Marketing Authorisation
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019 that is caused by the SARS-Cov-2 virus;
CSR	clinical study report
DB	double-blind
eGFR	estimated glomerular filtration rate
GD	glomerular diseases
OLE	open-label extension.
IgA	immunoglobulin A
ISS	Integrated Summary of Safety
Max	maximum
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum;
NA	not applicable
NR	not reported
PT	preferred term
Q1	first quartile
Q3	third quartile
RCT	randomized controlled trial
RGD	rare glomerular disease
RSI	reference safety information
SAE	serious adverse event;
SAS	Safety Analysis Set
SCS	Summary of Clinical Safety
SD	standard deviation
SE	standard error

Abbreviation	Definition
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UP/C	urine protein/ creatinine ratio.
ULN	upper limit of normal.

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vifor France submitted to the European Medicines Agency on 26 June 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Update of sections 4.8 and 5.1 of the SmPC based on final results from study 021IGAN17001 (PROTECT) listed as a specific obligation in Annex II; this is a randomized, multicenter, double-blind parallel-group, active control study of the efficacy and safety of sparsentan for the treatment of immunoglobulin A nephropathy. The Package Leaflet is updated accordingly. The RMP version 1.0 has also been submitted. Accordingly, the MAH took the opportunity to update Annex II and, in addition, to bring the PI in line with the latest QRD template version 10.4. Consequently, the MAH proposes a switch from conditional marketing authorisation to standard marketing authorisation.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

At the time of initial marketing authorisation (MA) for Filspari (sparsentan), the MAH provided top line data of the PROTECT study which suggested a clinically meaningful reno-protective effect.

The following uncertainties and limitations regarding proteinuria and eGFR were detected by the CHMP:

- Analyses according to baseline proteinuria of > 1.75 g/day do not clearly demonstrate a relation between the baseline degree of proteinuria and effect size on eGFR based on both chronic slope and total slope in the full analysis set (FAS), as might have been anticipated.
- Proteinuria change may be acute and reversible (reflecting functional changes) *versus* chronic and persistent (reflecting structural changes). It is unclear whether the effect on proteinuria persists after the end of the treatment period.
- At baseline, both treatment groups were comparable regarding the haematuria (both groups 56%). At week 36, the proportion of patients reporting haematuria was slightly lower for sparsentan (60 (44%)) as compared to irbesartan (67 (51%)) (p = 0.14). The clinical relevance of haematuria is still unclear.

Filspari was therefore granted a conditional marketing authorisation (CMA) on 19 April 2024 with the following specific obligation (SOB): in order to further characterise the long-term efficacy and safety of Filspari in the treatment of adults with primary immunoglobulin A nephropathy, the MAH shall submit the final results (Clinical Study Report) of the PROTECT study, a randomised, double-blind, active-controlled, multicentre, global phase 3 trial in patients with primary immunoglobulin A nephropathy.

With this type-II variation, the MAH submitted the final clinical study report of the PROTECT (021IGAN17001) Study in order to fulfil the SOB of the Filspari CMA and convert the CMA to a standard MA for the currently approved indication and posology. In addition, the MAH proposes updates to the Filspari SmPC affecting Sections 4.8 and 5.1. No changes to the indication wording was requested.

Baseline degree of proteinuria and effect size on eGFR based on both chronic slope and total slope

Chronic slope analysis

The initial acute effect of randomized therapy was defined as the change from baseline in eGFR during the first 6 weeks of randomized treatment with PROTECT study drug; thus, the analysis of eGFR chronic slope in the confirmatory analysis at 2 years assesses the effect after the initial acute effect (from 6 weeks post randomization to 110 weeks post-randomization). Statistically significant difference versus irbesartan in positive sparsentan's effect on eGFR chronic slope was shown. A slower rate of change in eGFR was observed in sparsentan-treated subjects relative to irbesartan-treated subjects following the acute effect of randomized therapy.

A slower rate of decline in eGFR was observed in sparsentan-treated subjects with baseline proteinuria <1.75 g/day versus irbesartan-treated subjects. A similar trend was observed in subjects with baseline proteinuria >1.75 g/day: a slower rate of decline in eGFR was seen in sparsentan group versus irbesartan-treated subjects. The annualized difference in slopes between the sparsentan group and irbesartan group according to baseline proteinuria subgroups showed no significant differences between sparsentan and irbesartan on eGFR chronic slope.

Total slope analysis

The analysis of eGFR total slope at 2 years in the confirmatory analysis was performed to estimate the effect over the entire course of the treatment period (the rate of change in eGFR over 110 weeks following the initiation of randomized therapy). A slower rate of decline in eGFR was observed in sparsentan-treated subjects versus irbesartan-treated subjects. In the FAS, the annualized difference in slopes between the sparsentan and irbesartan groups was 1.0 (95% CI: -0.03, 1.94) mL/min/1.73 m^2 per year. However, statistical significance in the total slope has not been achieved (p = 0.0582).

A slower rate of decline in eGFR was observed in sparsentan-treated subjects with baseline proteinuria <1.75 g/day versus irbesartan-treated subjects. A similar trend was observed in subjects with baseline proteinuria >1.75 g/day: a slower rate of decline in eGFR was in sparsentan group versus irbesartan-treated subjects.

The annualized difference in slopes between the sparsentan group and irbesartan group according to baseline proteinuria subgroups showed no significant differences between sparsentan and irbesartan on the total slope.

Based on the chronic slope and the total slope analyses, it is concluded that sparsentan showed a long-term improvement over irbesartan with respect to eGFR slopes, with similar magnitudes of effect between chronic slope and total slope. Statistical significance was reached in the chronic slope but not in the total slope. Hence, a more pronounced effect was seen in chronic slope which is a relevant endpoint to inform on the long-term effect. In order to further inform on the longer-term maintenance of efficacy, the MAH has committed to submit the final results from the open-label part of the PROTECT study by October 2027 (not part of the original SOB imposed by CHMP at the time of initial opinion).

Persistence of the effect on proteinuria after the end of the treatment period.

eGFR remained stable in both treatment groups post cessation of randomized treatment with a LS mean change from week 106 to 114 of -0.1 mL/min/1.73 m^2 for the sparsentan group and -0.2 for the irbesartan group. The initial decline in eGFR following the initiation of sparsentan remains not fully understood, since no increase of eGFR following discontinuation and thus no reversibility is established, that would be in support of a haemodynamical mechanism. However, similar absence of increase of eGFR is seen following discontinuation of irbesartan, which may be related to the duration of the interval between initiation and discontinuation of irbesartan and sparsentan.

In addition, an increase in proteinuria and UP/C in both treatment groups after randomized treatment discontinuation was observed: in UP/C a geometric LS mean percent change of 64.65% for the sparsentan group and 34.30% for the irbesartan group. These findings show that the benefit of sparsentan treatment on UP/C after discontinuation is reversible. A pronounced effect of discontinuation of sparsentan on proteinuria may be a signal of haemodynamical or functional changes, as opposed to structural changes.

Overall, no conclusion can be made on the persistence of the effect after discontinuation.

Relevance of haematuria

At baseline and across visits, the proportion of subjects with haematuria was similar between the treatment groups (54.4% sparsentan subjects and 59.8% irbesartan subjects). There was an observed reduction in the proportion of subjects reporting haematuria postbaseline for both treatment groups.

Upon the CHMP's request, the MAH submitted analysis assessing change from baseline in eGFR and UP/C by presence or absence of haematuria at baseline. These analyses demonstrate the favourable treatment effect of sparsentan, regardless of the presence or absence of haematuria. The positive effect of sparsentan on eGFR slope was statistically significant for patients without haematuria and statistically insignificant for patients with haematuria. However, it is agreed that baseline haematuria is not a prognostic factor for successful treatment with sparsentan.

Overall, the provided data demonstrated that sparsentan significantly reduces proteinuria and demonstrates a significant effect on the chronic eGFR slope with a comparable numerical beneficial effect on the important endpoint of total eGFR slope. Such data are acceptable considering a comparable initial acute eGFR decline in both treatment arms (sparsentan *versus* irbesartan). These results further reassure that treatment with sparsentan will likely results in a long-term renal protection in the target indication. The SmPC Section 5.1 is updated to remove reference to the interim analysis of proteinuria and to update rounded values for the proportion of patient ≥ 65 years (7.4% instead of 8%) and mean reduction from baseline in UP/C for sparsentan (42.8% instead of 43%).

The confirmatory safety results from the PROTECT study were consistent with the interim data, with no change in the overall safety profile of sparsentan and no new safety concerns identified. The frequency of the adverse reaction hypotension is updated from common to very common in SmPC Section 4.8. The safety profile remains acceptable for sparsentan.

RMP version 1.0 is agreed, the main change introduced is to remove the PROTECT study from Part IV as a specific obligation.

The benefit-risk balance of Filspari remains positive.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

In order to fulfil the specific obligation and convert the CMA into a standard marketing authorisation, the MAH submitted the final results of the active-controlled phase of the PROTECT study in order to further characterise the long-term efficacy and safety of Filspari in the treatment of adults with primary immunoglobulin A nephropathy. Based on the comprehensive clinical data provided by the MAH, conversion of the CMA of Filspari to a standard marketing authorisation is acceptable.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Update of sections 4.8 and 5.1 of the SmPC based on final results from study 021IGAN17001 (PROTECT) listed as a specific obligation in Annex II; this is a randomized, multicenter, double-blind parallel-group, active control study of the efficacy and safety of sparsentan for the treatment of immunoglobulin A nephropathy. The Package Leaflet is updated accordingly.

As a result of this variation, the SmPC, Annex II and PL are also updated to reflect the completion of the specific obligation and the CHMP recommendation to grant a marketing authorisation no longer subject to specific obligation.

The RMP version 1.0 is agreed.

In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4 and to introduce editorial changes.

☒is recommended for approval.

The CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for Filspari (sparsentan).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB are recommended.

As a result of this variation, it is recommended that the following obligation is deleted from the Annex II:

Description	Due date
In order to further characterise the long-term efficacy and safety of Filspari in the treatment of adults with primary immunoglobulin A nephropathy, the MAH shall submit the final results (Clinical Study Report) of the PROTECT study, a randomised, double-blind, active-controlled, multicentre, global phase 3 trial in patients with primary immunoglobulin A nephropathy.	30 September 2024

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Filspari-H-C-II-002'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

At the time of initial marketing authorisation (MA) for Filspari (sparsentan), the MAH provided top line data of the PROTECT study which suggested a clinically meaningful reno-protective effect.

The following uncertainties and limitations regarding proteinuria and eGFR were detected by the CHMP at the time of MA of Filspari:

- Analyses according to baseline proteinuria of > 1.75 g/day do not clearly demonstrate a relation between the baseline degree of proteinuria and effect size on eGFR based on both chronic slope and total slope in the full analysis set (FAS), as might have been anticipated.
- Proteinuria change may be acute and reversible (reflecting functional changes) *versus* chronic and persistent (reflecting structural changes).

Filspari was granted a conditional marketing authorisation (CMA) on 19 April 2024 under the following specific obligation (SOB): in order to further characterise the long-term efficacy and safety of Filspari in the treatment of adults with primary immunoglobulin A nephropathy, the MAH shall submit the final results (Clinical Study Report) of the PROTECT study, a randomised, double-blind, active-controlled, multicentre, global phase 3 trial in patients with primary immunoglobulin A nephropathy.

With this type-II variation, the MAH submitted the final clinical study report of the PROTECT (021IGAN17001) Study in order to fulfil the SOB of the Filspari CMA and convert the CMA to a standard MA for the currently approved indication and posology. In addition, the MAH proposes updates to the Filspari SmPC affecting Sections 4.8 and 5.1.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Study design and description

Study 021IGAN17001 (PROTECT) is a randomized, Phase 3, multicenter, double-blind, parallel-group, active-control study with a double-blind period of 114 weeks (following the 110-week blinded treatment period, study medication was discontinued for 4 weeks), followed by an open-label extension (OLE) period of up to 156 weeks for a total duration of up to 270 weeks in subjects with IgAN. The study was designed to evaluate the efficacy and safety of sparsentan in subjects with IgAN with persistent overt proteinuria who therefore remained at high risk of disease progression despite being on a stable dose (or doses) of an ACEI and/or ARB at a maximum tolerated dose that is at least one-half of the maximum labeled dose (MLD).

Eligible patients were randomized in a 1:1 ratio to receive sparsentan or active control (irbesartan). Treatment was initiated with sparsentan at 200 mg QD) or irbesartan 150 mg QD. After 14 days, dose was titrated to the recommended dose of sparsentan 400 mg QD or irbesartan 300 mg QD as tolerated.

Study population

Main eligibility criteria included age (≥18 years of age), biopsy-proven IgAN, urine total protein ≥1.0 g/day, eGFR ≥30 mL/min/1.73 m^2, systolic blood pressure (BP) ≤150 mmHg, and diastolic BP ≤100 mmHg at screening, and subjects must have been on a maximized stable dose of ACEI and/or ARB therapy (that was at the subject's maximum tolerated dose that was at least one-half of the MLD according to approved labeling) for at least 12 weeks prior to screening.

Treatment

RCT phase

Treatment was initiated with sparsentan at 200 mg QD or irbesartan 150 mg QD. After 14 days, dose was titrated to the recommended dose of sparsentan 400 mg QD or irbesartan 300 mg QD as tolerated. Dose tolerance after 2 weeks of treatment is characterized as SBP >100 mm Hg and DBP >60 mm Hg, no AEs and no laboratory findings (e.g., serum potassium >5.5 mEq/L [5.5 mmol/L]). If the patient tolerated the drug but had asymptomatic hypotension with BP ≤100/60 mm Hg or orthostatic hypotension symptoms, the patient continued the initial dose of 200 mg once daily.

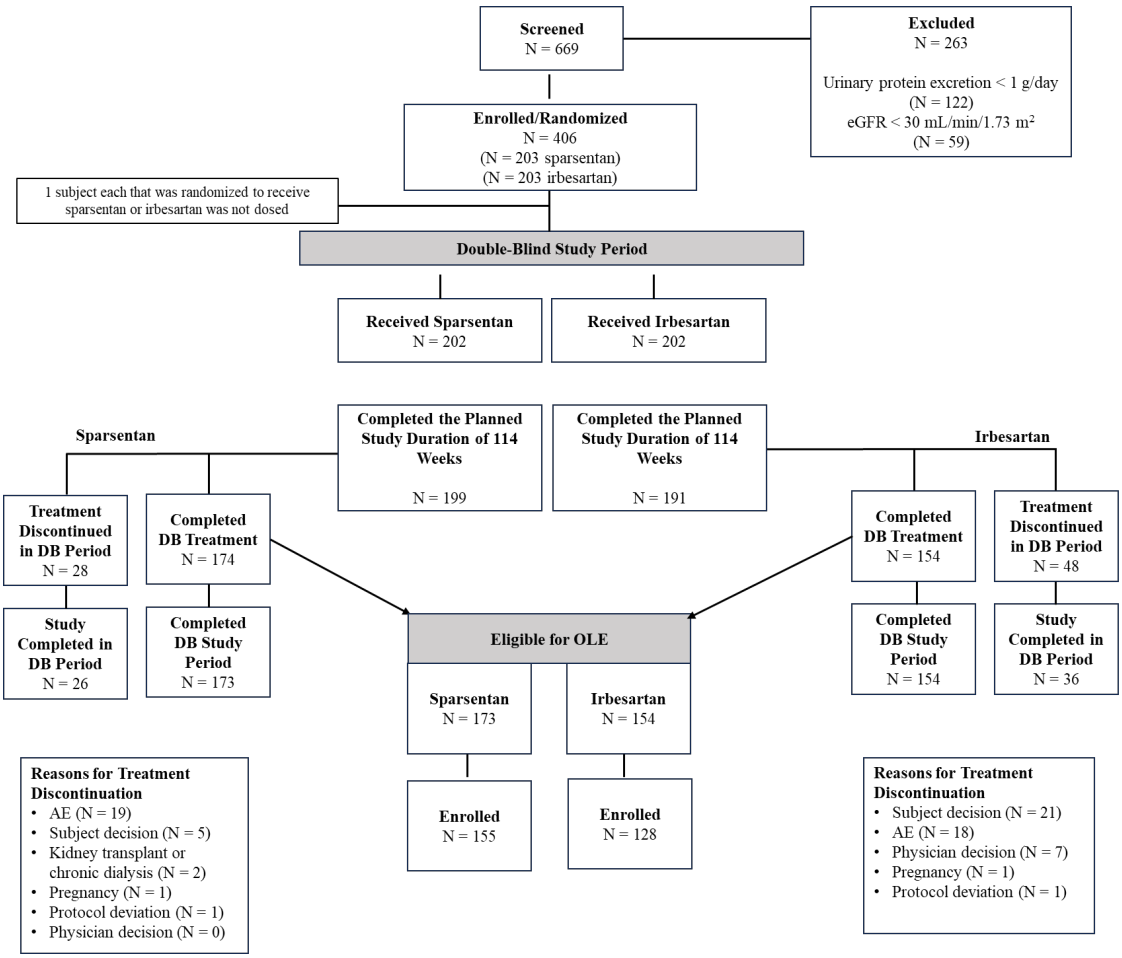
The study drug was taken for a 110-week period. After that, the treatment was discontinued for 4 weeks, and the patients came for the visit at week 114.

Sample size

Approximately 380 subjects were planned to be enrolled in the study. Final enrolment was 406 subjects: 203 subjects in each of the sparsentan and irbesartan groups.

The Full Analysis Set (FAS) and Safety Analysis Set (SAS) are the same and included 404 subjects each, with 202 subjects (50%) in each treatment group who were randomized and received at least one dose of study medication.

Figure 1 Patient Disposition During the 021IGAN17001 (PROTECT) Study



Abbreviations: AE = adverse event; DB = double-blind; eGFR = estimated glomerular filtration rate; N = number of subjects; OLE = open-label extension.

Randomisation

Patients were randomized in a 1:1 ratio using an interactive response technology system based on a permuted-block randomization method to receive either sparsentan or irbesartan. The study utilized a centralized stratified randomization based on the following variables: (1) eGFR value 30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2 and (2) urine protein excretion (≤1.75 g/day and >1.75 g/day)

Blinding (masking)

This is a double-blind, active-control study. The randomization code and corresponding treatment assignments were maintained by the interactive randomization technology (IRT).

Objectives

The efficacy objective of the double-blind period of the study is to determine the effect of sparsentan on proteinuria and preservation of renal function, as compared to an angiotensin receptor blocker (ARB), in subjects with immunoglobulin A nephropathy (IgAN).

The RCT phase assessed the effect of sparsentan on proteinuria, preservation of renal function, and safety and tolerability in subjects with IgAN, compared to an ARB. The OLE's objective was the assessment of the long-term efficacy, safety, and tolerability of sparsentan in patients with IgAN. Overall, the aim was to demonstrate the clinical superiority of sparsentan over irbesartan.

Endpoints

Primary Efficacy Endpoint

The change from baseline (Day 1) in the urine protein/creatinine ratio (UP/C), based on a 24-hour urine sample at Week 36.

Key Secondary Efficacy Endpoints

- The rate of change in estimated glomerular filtration rate (eGFR) over a 52-week (approximately 1 year) period following the initial acute effect of randomized therapy (the initial acute effect of randomized therapy is defined as the first 6 weeks of randomized treatment with study medication; thus, the analysis is from 6 weeks post randomization to 58 weeks post randomization; eGFR chronic slope at 1 year)

- The rate of change in eGFR over a 104-week (approximately 2 years) period following the initial acute effect of randomized therapy (the initial acute effect of randomized therapy is defined as the first 6 weeks of randomized treatment with study medication; thus, the analysis is from 6 weeks post randomization to 110 weeks post randomization; eGFR chronic slope at 2 years)

- The rate of change in eGFR over a 110-week (approximately 2 years) period following the initiation of randomized therapy (thus, the analysis is from Day 1 to 110 weeks post randomization; eGFR total slope at 2 years)

Other Secondary Efficacy Endpoints

- The mean change from baseline over time in eGFR and selected proteinuria variables based on a 24-hour urine sample (e.g., urine protein excretion, urine albumin excretion, urine albumin/creatinine ratio [UA/C] and UP/C) up to Week 110

- The proportion of subjects reaching a confirmed 40% reduction in eGFR, end-stage renal disease (ESRD), or death (ESRD is defined as initiation of renal replacement therapy or sustained eGFR value of <15 mL/min/1.73 m^2)

Exploratory Endpoints:

- The rate of change in eGFR over a 58 Week (approximately 1 year) period following the initiation of randomized therapy (thus, the analysis is from Day 1 to 58 weeks post randomization; eGFR total slope at 1 year); The change from baseline in eGFR at 6 weeks post-randomization (i.e., the acute effect of randomized therapy); The change from End of Treatment (EOT; i.e., Week 110) in eGFR 4 weeks following cessation of treatment (i.e., at Week 114); Change in eGFR from baseline to 4 weeks post cessation of randomized treatment (Week 114)

- Achievement of urinary protein excretion of <0.3 g/day up to Week 110; Achievement of urinary protein excretion of <1.0 g/day up to Week 110

- The proportion of subjects with haematuria at each visit

- Changes from baseline in blood pressure at each visit; Mean changes from baseline in quality of life (QoL), measured via patient-reported outcome (PRO) at each visit; Frequency and duration of hospitalizations (for any reason and reasons related to the kidney)

- The proportion of subjects requiring systemic immunosuppressive medication during the study; through plasma pharmacokinetic (PK) concentrations

Statistical methods

The primary analysis of proteinuria was conducted on the primary analysis set (PAS) after 36 weeks. As UP/C is a highly right-skewed variable, analyses were performed on log-transformed data. The statistical evaluation was performed using available data from all subjects at the cut-off date (01 August 2021) for the primary analysis, using a mixed model repeated measures (MMRM) analysis, at the significance level of $\alpha = 0.05$.

The confirmatory analyses (database lock 07 September 2023) were conducted once all subjects had completed the 114-week double-blind period. Efficacy analyses (including sensitivity analyses) were based on the FAS and safety analyses on the SAS.

eGFR slope was analysed using a random coefficients analysis with fixed effects of treatment group (sparsentan and irbesartan), baseline eGFR, time (i.e., study visit when the analysis was conducted in weeks), treatment group by time interaction, and randomization stratification variable. The treatment effect was the contrast between sparsentan and irbesartan marginal slope estimates. The slope estimates, differences in slopes, 95% confidence interval (CI), and two-sided p-values were extracted from the model; slopes and differences in slopes over approximately 2 years were annualized.

Change from baseline in eGFR, UP/C, urine albumin/creatinine ratio, urine protein excretion, and urine albumin excretion up to Week 110 and change from baseline in blood pressure were analysed via MMRM; missing data were not imputed. The treatment effect was the contrast between sparsentan and irbesartan least squares means. Change in eGFR from baseline to Week 6, baseline to Week 114, and end of treatment (ie, Week 110) to Week 114 was assessed with analysis of covariance (ANCOVA).

Relative risks and odds ratios for the composite kidney failure and proteinuria remission endpoints were assessed with a logistic regression model, while relative risks were estimated from a Poisson regression model with the same fixed effects as the logistic regression model.

Multiple hypothesis testing correction was performed using a combination of gatekeeping and fixed sequence procedure. As the primary endpoint analysis yielded a two-sided p-value of less than 0.05, formal hierarchical testing of key secondary endpoints was performed.

6.1. Results

Primary efficacy endpoint results

Urine Protein/Creatinine Ratio

PROTECT achieved its prespecified primary endpoint of change from baseline in UP/C at Week 36 at the interim analysis conducted in August 2021.

At Week 36, sparsentan demonstrated a -49.77% mean change from baseline in proteinuria (95% CI: -54.98, -43.95) compared to -15.05% (95% CI: -23.72, -5.39) for irbesartan.

This resulted in a statistically significant greater relative reduction from baseline UP/C in subjects on sparsentan than on irbesartan (geometric mean ratio [sparsentan/irbesartan] [95% CI]: 0.59 [0.51, 0.69]; p <0.0001), corresponding to a 41% relative reduction.

The robust reduction in proteinuria with sparsentan was maintained following more than 2 years of treatment; sparsentan demonstrated a 43% mean reduction from baseline in proteinuria compared to 4% for irbesartan at Week 110, with a rapid and durable effect on proteinuria.

Key secondary Efficacy endpoint results (Chronic eGFR slope and total eGFR slope)

eGFR

For the United States (US) region, testing of total slope at confirmatory analysis occurred first in the statistical hierarchy at a 0.05 alpha level; for non-US regions, testing of chronic slope occurred first at the confirmatory analysis in the statistical hierarchy at 2-sided 0.04 alpha level.

Results on eGFR chronic slope and total slope are provided in Table 1 eGFR chronic slope and total slope.

Table 1 eGFR chronic slope and total slope

eGFR Endpoint	**Sparsentan N = 202**	**Irbesartan N = 202**	**Difference (Sparsentan – Irbesartan) (95% CI)**
eGFR Chronic Slope (mL/min/1.73 m^2 per year) (95% CI)	–2.7 (-3.43, -2.05)	–3.8 (-4.60, -3.07)	1.1 (0.07, 2.12) p = 0.037
eGFR Total Slope (mL/min/1.73 m^2 per year) (95% CI)	–2.9 (-3.58, -2.24)	–3.9 (-4.59, -3.13)	1.0 (–0.03, 1.94) p = 0.058
Change from baseline at Week 110 (mL/min/1.73 m^2) (95% CI)	–5.8 (-7.38, -4.24)	–9.5 (-11.17, -7.89)	3.7 (1.45, 5.99) p = 0.0014
Change from baseline to 4 weeks post-cessation of randomized treatment (mL/min/1.73 m^2) (95% CI)	–6.1 (-7.74, -4.48)	–9.0 (-10.71, -7.21)	2.9 (0.45, 5.25) p = 0.0199

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate.

Kidney Composite Outcomes

Although the sparsentan group had an imbalance of more subjects with eGFR <30 mL/min/1.73 m^2 upon study entry, fewer subjects treated with sparsentan (n = 18) reached the composite endpoint of 40% reduction in eGFR, ESRD, or death compared to subjects treated with irbesartan (n = 26) (relative risk for rates of events [sparsentan/irbesartan] 0.68 [95% CI: 0.37, 1.24]). When the composite endpoint is

defined more conservatively with regard to kidney function (50% reduction in eGFR, ESRD, or death), there was an even larger difference favoring sparsentan compared to irbesartan (relative risk for rates of events [sparsentan/irbesartan] 0.55 [95% CI: 0.26, 1.16]).

Initiation of Immunosuppressive Rescue Therapy

A similar proportion of subjects in the sparsentan (33 [16.3%]) and irbesartan (38 [18.8%]) groups used any systemic IST while on treatment.

However, for IST use with a renal indication (mostly corticosteroids), more subjects in the irbesartan group (16 subjects, 7.9%) initiated IST therapy than subjects in the sparsentan group (6 subjects, 3.0%) and initiation occurred sooner in the irbesartan group. The mean number of days of IST with renal indication taken was greater for the irbesartan group (20.2 days) than for the sparsentan group (4.6 days).

When prespecified sensitivity analyses were performed that excluded data collected after IST rescue initiation, the CIs for both total and chronic eGFR slope differences excluded the null in favor of sparsentan.

Other

At baseline and across visits, the proportion of subjects with haematuria were similar between the treatment groups (54.4% sparsentan subjects and 59.8% irbesartan subjects). There was an observed reduction in the proportion of subjects reporting hematuria postbaseline for both treatment groups.

The duration and frequency of hospitalizations, both for any reason and for reasons related to the kidney, were similar between the irbesartan and sparsentan groups.

The mean baseline blood pressure (BP) was 128/82 mm Hg for the sparsentan treatment group and 130/83 mm Hg for the irbesartan treatment group. There was initial least squares (LS) mean decrease in both systolic and diastolic BP (-5.0 mm Hg and 4.5 mm Hg, respectively, at Week 6) for sparsentan-treated subjects, with subsequent stabilization starting at Week 12. For irbesartan treated subjects, there was an initial LS mean decrease in systolic and diastolic BP of -2.7 mm Hg and -0.1 mm Hg at Week 6, respectively), with subsequent stabilization starting at Week 12.

eGFR Chronic Slope Subgroup Analyses

eGFR Chronic Slope, Week 6 to Week 110 (Confirmatory Analysis)

In the FAS, the annualized difference in chronic slopes between the sparsentan group and irbesartan group (sparsentan-irbesartan) was 1.1 mL/min/1.73 m^2/year (95% CI: 0.07, 2.12; p = 0.0369).

Table 2 eGFR Chronic Slope at 2 Years – Rate of Change in eGFR over 104 Weeks (Week 6 to Week 110) Following Acute Effect of Randomized Therapy with Multiple Imputation (FAS)

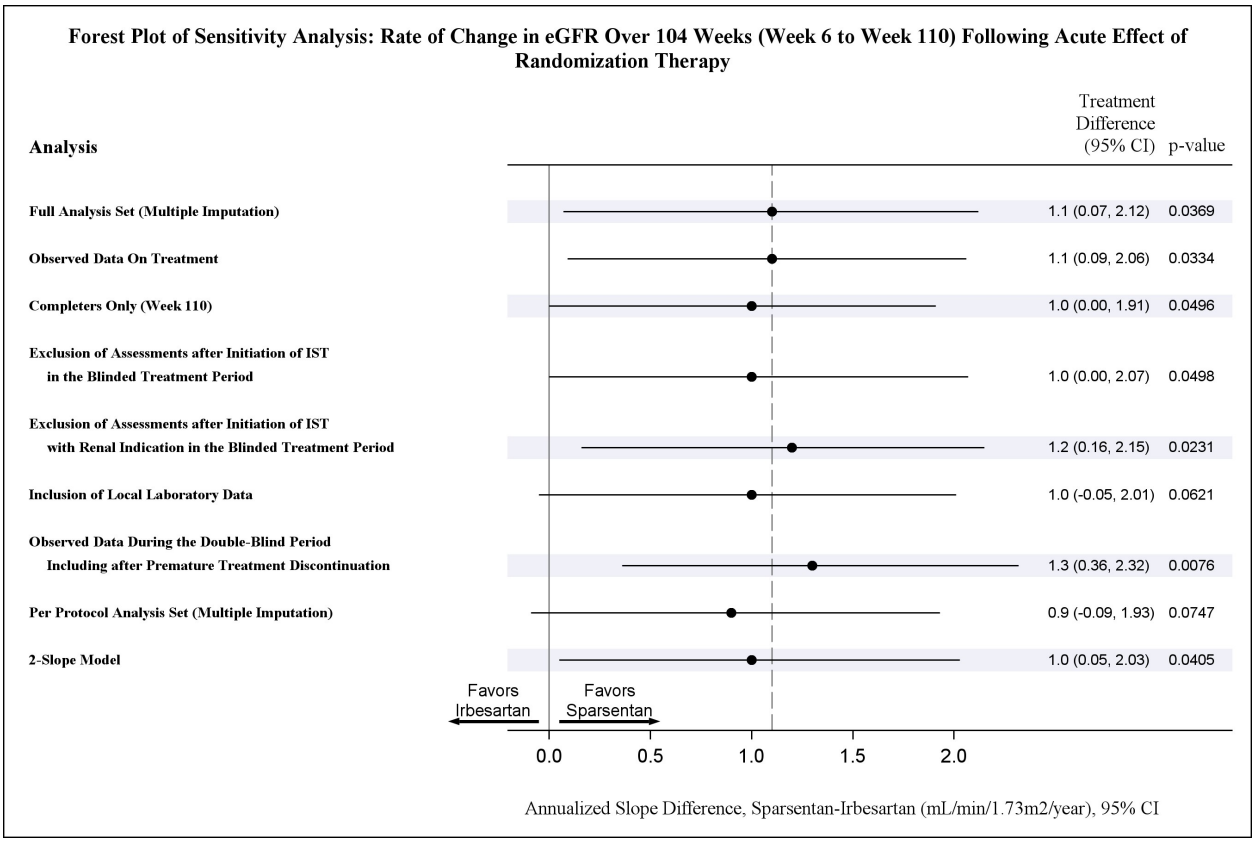
eGFR (mL/min/1.73 m^2)	Sparsentan (N = 202)	Irbesartan (N = 202)
Annualized Change from Week 6 to Week 110		
N	153	137
Mean (SD)	-2.1 (4.97)	-3.4 (5.18)
SE	0.40	0.44
Median	-2.5	-3.0
Q1, Q3	-4.5, 0.0	-6.0, -0.5
Mean (SD)	-14, 15	-29, 9
Annualized Slope[a]		
LS mean	-2.7	-3.8
95% CI	(-3.43, -2.05)	(-4.60, -3.07)
Slope difference, Week 6 to Week 110(sparsentan-irbesartan)		
Estimate		1.1
SE		0.52
95% CI		(0.07, 2.12)
p-value		0.0369

Abbreviations: CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology; CSR = clinical study report; DB = double blind; eGFR = estimated glomerular filtration rate; LS = least squares; MAR = missing at random; MI = multiple imputation; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SE = standard error.
Note: The eGFR is determined using the CKD-EPI equation. Only results through Week 110 are included.
[a] Thirty imputed datasets are created by MI procedure under the assumption of MAR. Within each imputed dataset, the estimates of the annualized slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomization stratification factors as fixed effects, random intercept and random slope per subject. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates for slopes, 95% CIs, and the p-value. An unstructured covariance structure is used in each model.

Sensitivity Analyses of Chronic eGFR Slope at 2 years

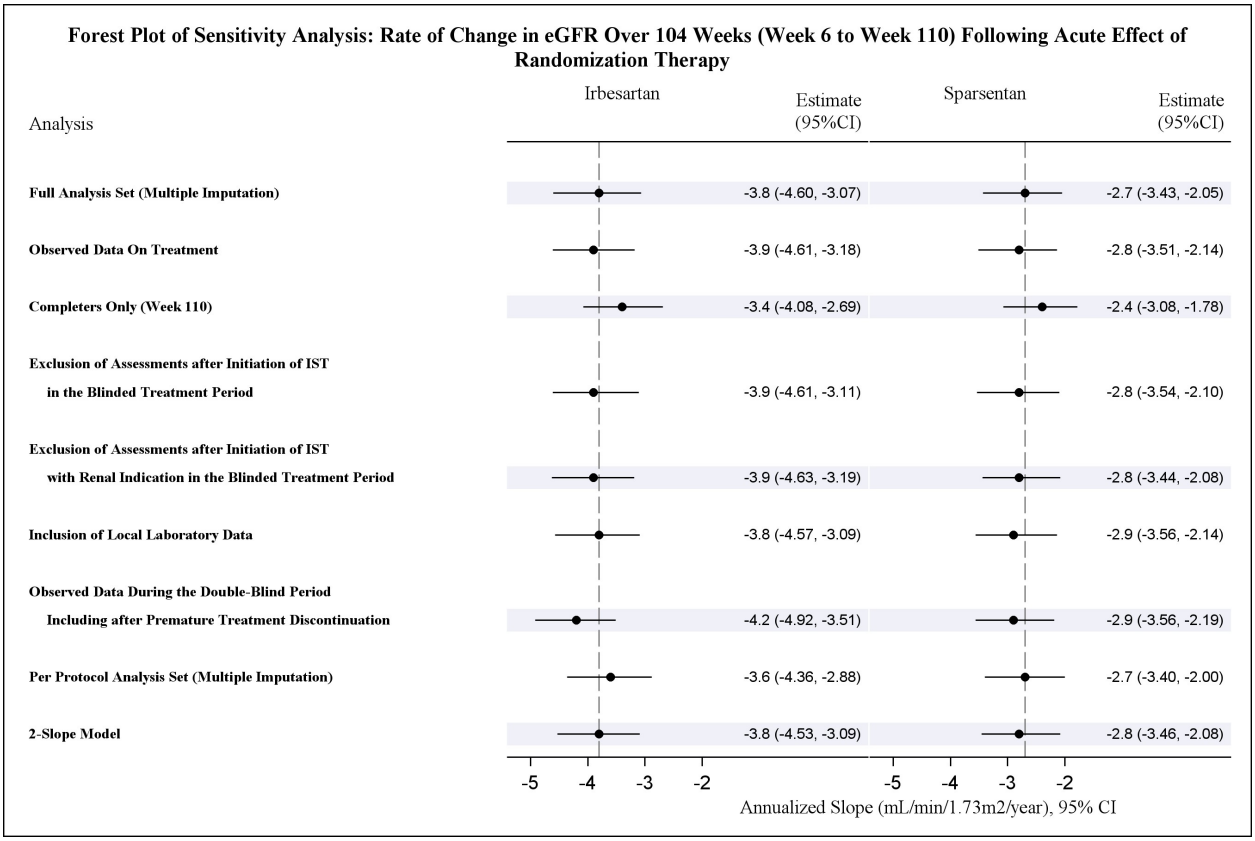
Sensitivity analyses are consistent with and supportive of the conclusions from the primary analyses for chronic eGFR slope, including all prespecified sensitivity analyses. There was an imbalance in intercurrent events, in particular differential rates and reasons for premature treatment discontinuation due to subject or physician decision (14% for irbesartan versus 2% for sparsentan) as well as initiation of immunosuppressive rescue therapy with a renal indication (7.9% for irbesartan versus 3.0% for sparsentan).

Figure 2 Chronic Slope Forest Plot of Sensitivity Analysis: Rate of Change in eGFR Over 104 Weeks Following Initiation of Randomization Therapy – Annualized Slope Difference (FAS)



Abbreviations: CI = confidence interval; CSR = clinical study report; DB = double blind; eGFR = estimated glomerular filtration rate; FAS = full analysis set; IST = immunosuppressive rescue therapy.
Notes: - Error bars represent 95% CIs.

Figure 3 Chronic Slope Forest Plot of Sensitivity Analysis: Rate of Change in eGFR Over 104 Weeks Following Initiation of Randomization Therapy – Annualized Slope (FAS)



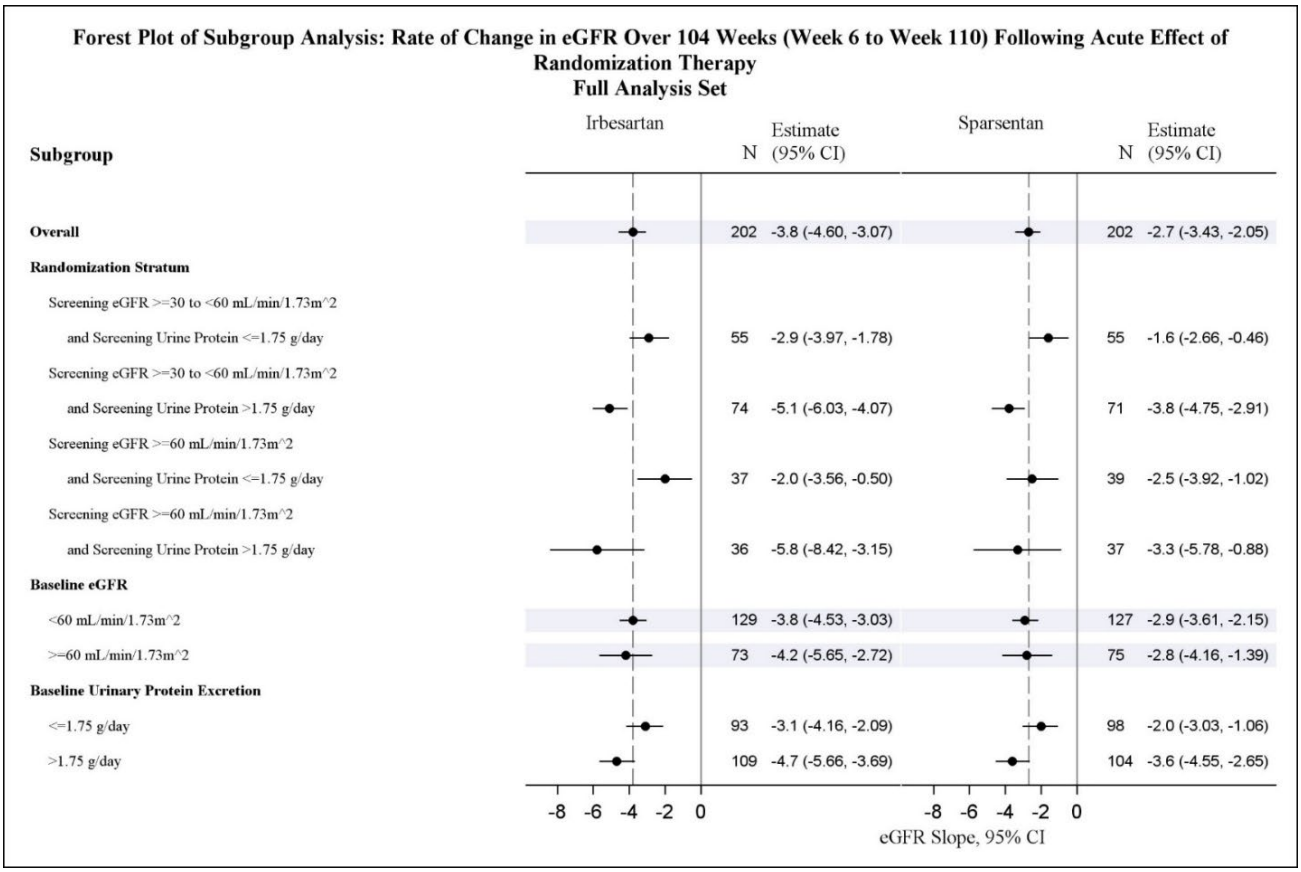
Abbreviations: CI = confidence interval; CSR = clinical study report; DB = double blind; eGFR = estimated glomerular filtration rate; FAS = full analysis set; IST = immunosuppressive rescue therapy.

eGFR Chronic Slope Subgroup Analyses

Subgroup analyses according to demographic and baseline characteristics demonstrate the consistency of the effect of sparsentan and irbesartan across different subgroups. While the response to sparsentan was consistent across subgroups, some groups (Asians, females) showed slower rates of decline on irbesartan, demonstrating a smaller treatment effect when comparing sparsentan to irbesartan.

Examination of chronic slope across 2 prespecified subgroup analyses, baseline eGFR <60 mL/min/1.73 m^2 and >60 mL/min/1.73 m^2, as well as baseline UPC <1.75 g/day and >1.75 g/day, demonstrates the consistency of sparsentan's effect across these groups.

Figure 4 eGFR Chronic Slope Forest Plot of Randomization Strata, Baseline eGFR, and Baseline Urinary Protein Excretion Subgroup Analysis: Rate of Change in eGFR Over 104 Weeks (Week 6 to Week 110) Following Acute Effect of Randomized Therapy (FAS)



Abbreviations: CI = confidence interval; CSR = clinical study report; DB = double-blind; eGFR = estimated glomerular filtration rate; FAS = full analysis set; N = number of subjects.

eGFR Total Slope, Day 1 to Week 110 (Confirmatory Analysis)

Table 3 eGFR Total Slope – Rate of Change in eGFR over 110 Weeks (Day 1 to Week 110) Following Initiation of Randomized Therapy with Multiple Imputation (FAS)

eGFR (mL/min/1.73 m^2)	Sparsentan (N = 202)	Irbesartan (N = 202)
Annualized Change from Day 1 to Week 110		
N	159	138
Mean (SD)	-2.3 (4.80)	-4.2 (5.00)
SE	0.38	0.43
Median	-2.4	-4.0
Q1, Q3	-5.2, 0.0	-6.6, -1.4
Min, max	-16, 21	-28, 7
Annualized Slope[a]		
LS mean	-2.9	-3.9

eGFR (mL/min/1.73 m^2)	Sparsentan (N = 202)	Irbesartan (N = 202)
95% CI	-3.58, -2.24	-4.59, -3.13
Slope difference, Day 1 to Week 110 (sparsentan-irbesartan)		
Estimate		1.0
SE		0.50
95% CI		-0.03, 1.94
p-value		0.0582

Abbreviations: CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology; CSR = clinical study report; DB = double-blind; eGFR = estimated glomerular filtration rate; LS = least squares; MAR = missing at random; max = maximum; MI = multiple imputation; min = minimum; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SE = standard error.
Note: The eGFR is determined using the CKD-EPI equation. Only results through Week 110 are included.
[a] Thirty imputed datasets are created by MI procedure under the assumption of MAR. Within each imputed dataset, the estimates of the annualized slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomization stratification factors as fixed effects, random intercept and random slope per subject. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates for slopes, 95% CIs, and the p-value. An unstructured covariance structure is used in each model.

Sensitivity Analyses of Total eGFR Slope at 2 Years

Sensitivity analyses are consistent with and supportive of the conclusions from the primary analyses for total eGFR slope, including all prespecified sensitivity analyses. There was an imbalance in intercurrent events between the treatment groups. In particular, treatment discontinuation due to subject or physician decision was more commonly reported in the irbesartan group (28 subjects, 14%) than in the sparsentan group (5 subjects, 2%). Initiation of immunosuppressive therapy (IST) with a renal indication was also more common in the irbesartan group (16 subjects, 8%) than the sparsentan group (6 subjects, 3%).

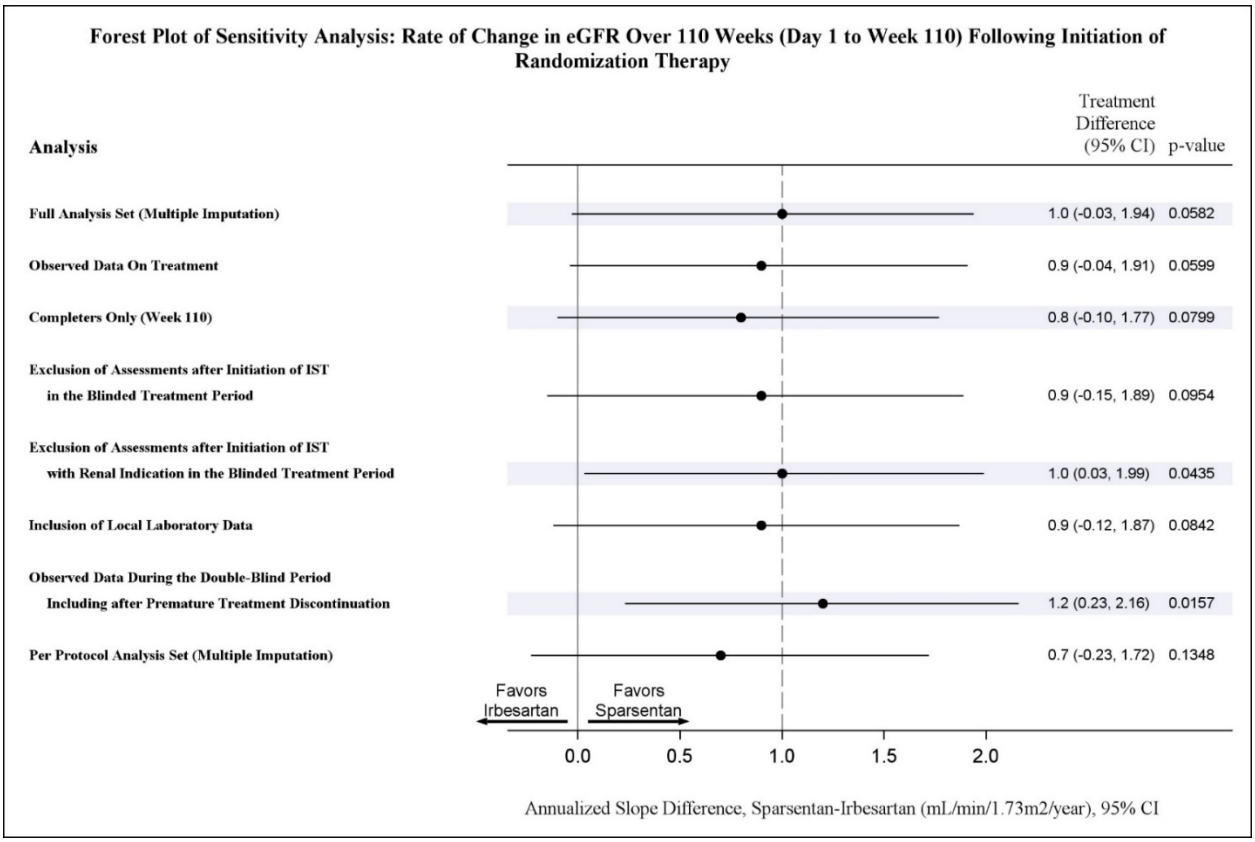
The imbalance in premature treatment discontinuation can be partially addressed by the sensitivity analysis including data collected from subjects remaining on-study following treatment discontinuation, showing a treatment difference of 1.2 (95% CI: 0.23, 2.16; nominal p = 0.016).

Sensitivity analyses excluding data collected after initiation of immunosuppressive rescue therapy (IST) were also conducted. The treatment difference excluding data collected after initiation of IST for a renal indication was 1.1 (95% CI: 0.11, 204; nominal p = 0.029).

Random coefficients models for 2-year total slope using both on-treatment and on-study data were robust to reasonable missing data configurations. Tipping point analyses of the random coefficients model for total slope using on-study data demonstrated that more than 130% adjustment to the missing at random assumption in the sparsentan group is required before the conclusions of the primary on-study analysis are reversed.

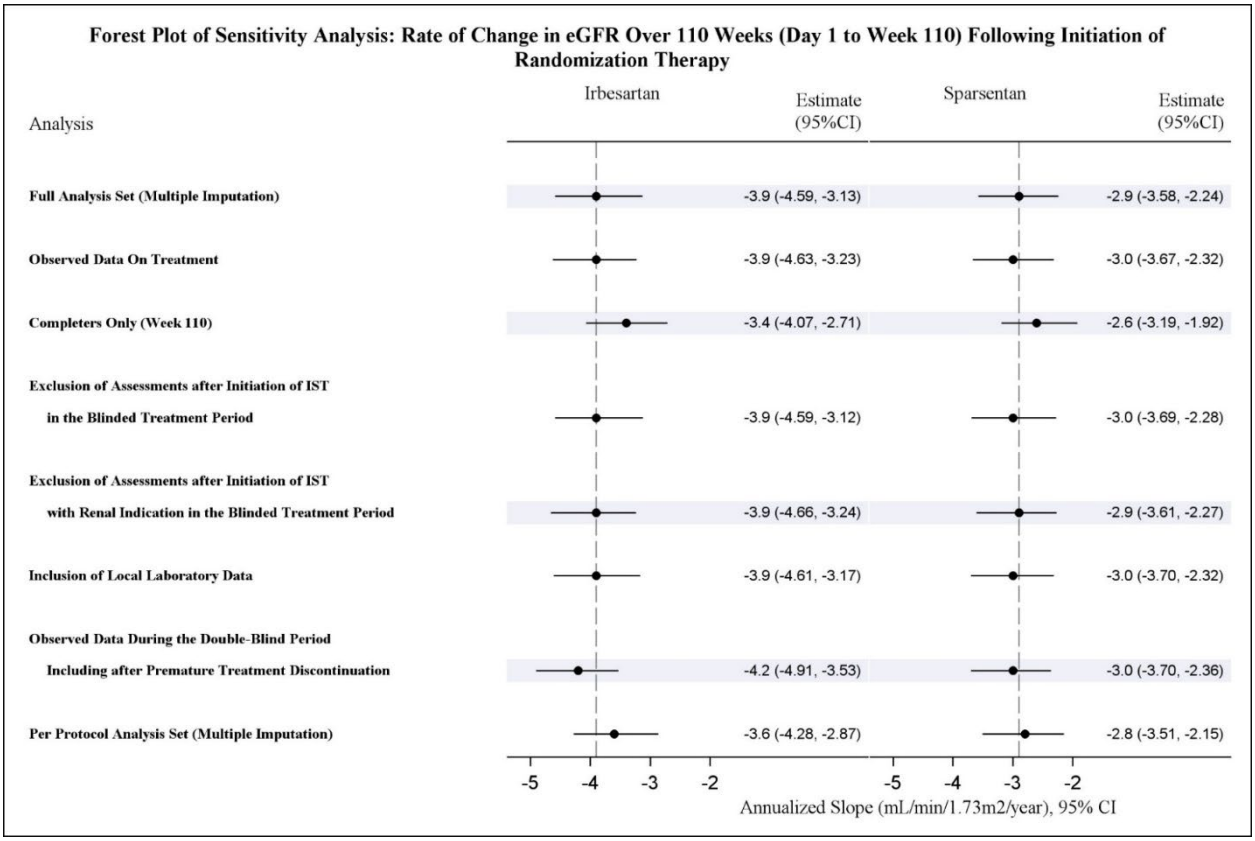
A post hoc analysis of eGFR total slope at 2 years assessing the effect over the entire course of the treatment period (from baseline to 110 weeks post randomization) that included baseline as a response variable was consistent with and supportive of the primary analysis for total eGFR slope prespecified in the SAP (which did not include baseline as a response variable). When baseline was included as a response variable, the treatment difference (1.0 [95% CI: 0.05, 1.97; p = 0.0392] mL/min/1.73 m^2 per year) was clinically meaningful in favour of sparsentan compared to irbesartan.

Figure 5 Total Slope Forest Plot of Sensitivity Analysis: Rate of Change in eGFR Over 110 Weeks Following Initiation of Randomization Therapy – Annualized Slope Difference



Abbreviations: CI = confidence interval; CSR = clinical study report; DB = double blind; eGFR = estimated glomerular filtration rate; IST = immunosuppressive rescue therapy.
Note: Error bars represent 95% CIs.

Figure 6 Total Slope Forest Plot of Sensitivity Analysis: Rate of Change in eGFR Over 110 Weeks Following Initiation of Randomization Therapy – Annualized Slope



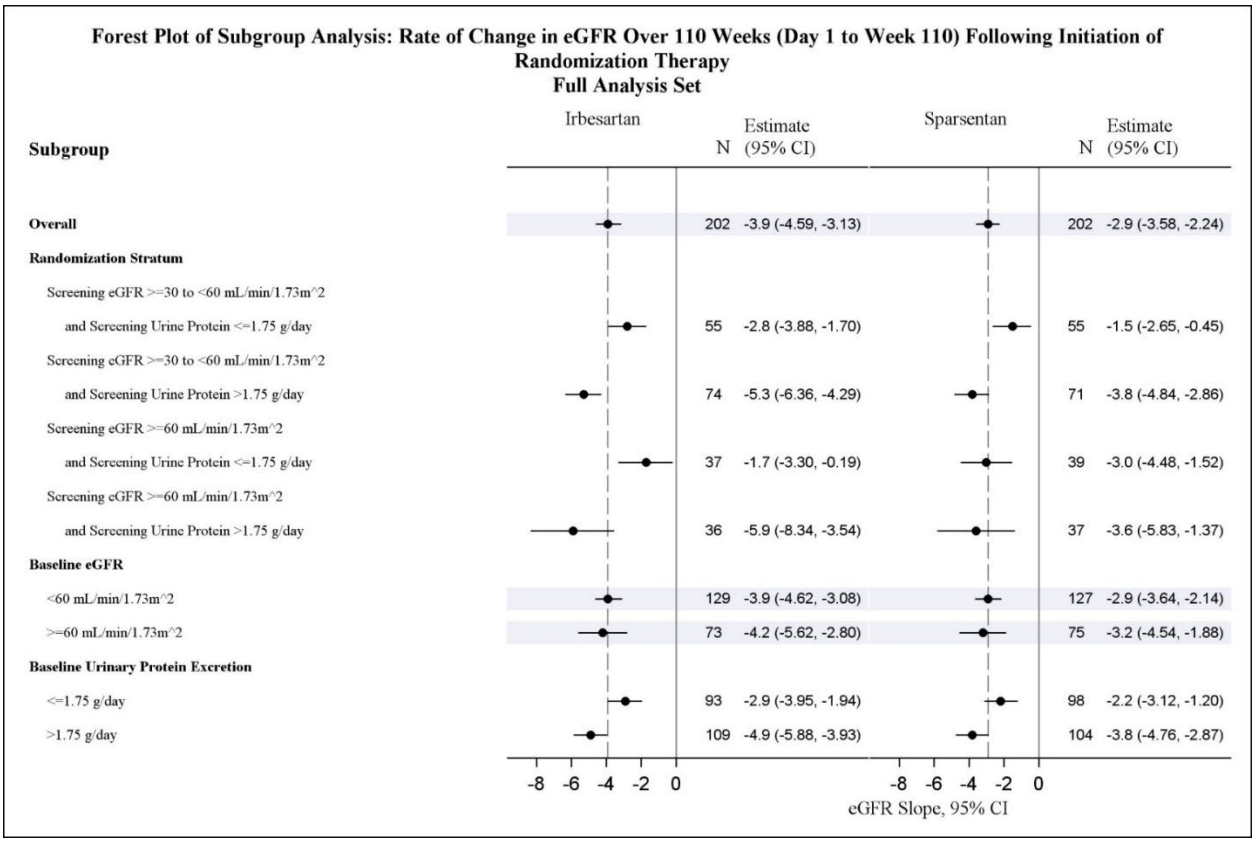
Abbreviations: CI = confidence interval; CSR = clinical study report; DB = double blind; eGFR = estimated glomerular filtration rate; IST = immunosuppressive rescue therapy.

eGFR Total Slope Subgroup Analyses

Subgroup analyses of demographic and baseline characteristics demonstrate the consistency of the effect of sparsentan and irbesartan across the different subgroups. While the response to sparsentan was consistent across subgroups, some groups (Asian, females) showed slower rates of decline on irbesartan, demonstrating a smaller treatment effect when comparing sparsentan to irbesartan.

Examination of total slope across 2 prespecified subgroup analyses, baseline eGFR <60 mL/min/1.73 m^2 per year and >60 mL/min/1.73 m^2 per year, as well as baseline UPC <1.75 g/day and >1.75 g/day demonstrates the consistency of sparsentan's effect across these groups (Figure 7).

Figure 7 eGFR Total Slope Forest Plot of Randomization Strata, Baseline eGFR, and Baseline Urinary Protein Excretion Subgroup Analysis: Rate of Change in eGFR Over 110 Weeks (Day 1 to Week 110) Following Initiation of Randomized Therapy (FAS)



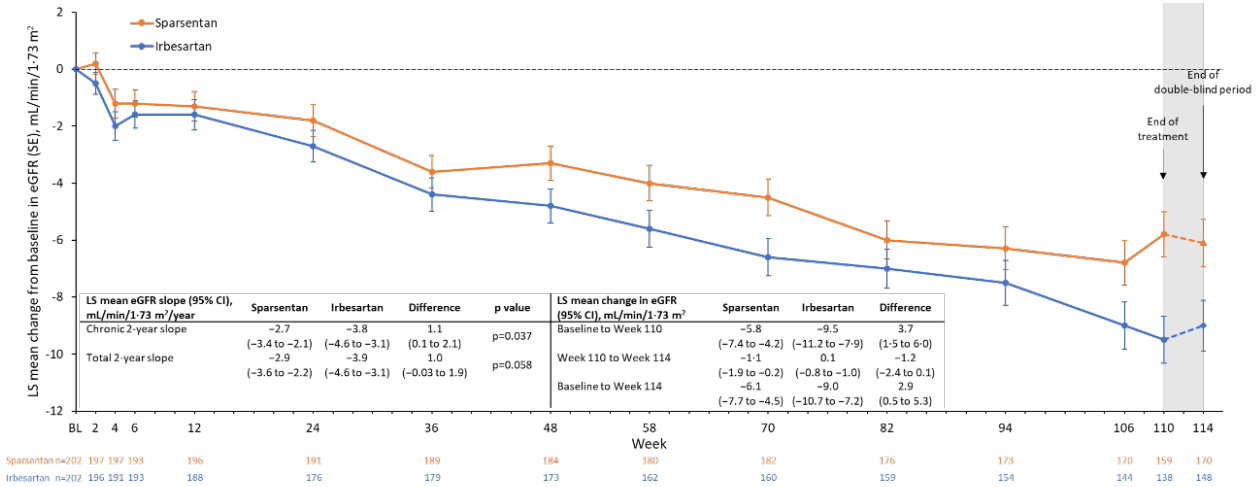
eGFR Values at Each Visit, Week 1 to Week 114 (Confirmatory Analysis)

The initial, acute effect of randomized therapy in eGFR reduction at Week 6 was comparable between the 2 treatment groups. At Week 6, the LS mean change from baseline (95% CI) was -1.2 (-2.17, -0.27) mL/min/1.73 m^2 for the sparsentan group and -1.6 (-2.56, -0.65) mL/min/1.73 m^2 for the irbesartan group. Analyses using Analysis of Covariance (ANCOVA) were consistent with the mixed model repeated measures analyses.

In the confirmatory analysis, after Week 6 and at each subsequent week up to Week 110 and post-treatment cessation (Week 114), the LS mean change in eGFR from baseline was lower in magnitude in the sparsentan group.

Variability was observed in the change in eGFR from baseline in the 4-week interval between Weeks 106 and 110, however the overall absolute trend for preservation of eGFR over 110 weeks favoured sparsentan, accrued over time, and was found to be durable 4 weeks post treatment cessation.

Figure 8 Change from Baseline in eGFR (mL/min/1.73 m2) by Visit (FAS)



Abbreviations: ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CSR = clinical study report; DB = double blind; eGFR = estimated glomerular filtration rate; FAS = full analysis set; LS = least squares; MMRM = mixed model for repeated measures; N = subjects with data at each visit; SE = standard error.
Notes: eGFR is determined using the CKD-EPI equation.
Baseline is defined as the last non-missing observation on or prior to the start of dosing.
Results through Week 110 are based on a mixed model repeated measures (MMRM) model on the change from baseline in eGFR with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit interaction, and randomization stratification factors as fixed effects, and subject as a random effect. An unstructured covariance structure is used in the model.
Results at Week 114 are based on an ANCOVA model on the change from baseline eGFR with treatment, baseline eGFR, and randomization stratification factors as fixed effects.

Table 4 eGFR Values by Visit (FAS)

	Sparsentan (N = 202)	**Irbesartan (N = 202)**	**Between-group Difference**
Observed eGFR Value (mL/min/1.73 m²)	**Mean (SD)**	**Mean (SD)**	
Baseline	56.8 (24.3)	57.1 (23.6)	NA
Week 6[a]	55.8 (23.6)	55.5 (23.0)	NA
Week 58[b]	53.8 (24.6)	52.7 (23.7)	NA
Week 110[c]	52.4 (25.1)	48.3 (24.7)	NA
Week 114[d]	51.2 (25.3)	49.7 (25.6)	NA
Change in eGFR from Baseline (mL/min/1.73 m²)	**LS Mean (95% CI)**	**LS Mean (95% CI)**	**Difference (95% CI)**
Week 6[a]	-1.2 (-2.2 to -0.3)	-1.6 (-2.6 to -0.7)	0.4 (-1.0 to 1.7)
Week 58[b]	-4.0 (-5.2 to -2.7)	-5.6 (-6.9 to -4.4)	1.7 (-0.1 to 3.5)
Week 110[c]	-5.8 (-7.4 to -4.2)	-9.5 (-11.2 to -7.9)	3.7 (1.5 to -6.0)

	Sparsentan (N = 202)	Irbesartan (N = 202)	Between-group Difference
Week 114[d]	-6.1 (-7.7 to -4·5)	-9.0 (-10.7 to -7.2)	2.9 (0.5 to -5.3)
Change in eGFR from End of Treatment (Week 110) to 4 Weeks After Cessation of Randomized Treatment (Week 114) (mL/min/1.73 m²)[d]	-1.1 (-1.9 to -0.2)	0.1 (-0.8 to 1.0)	-1.2 (-2.4 to 0.1)

Abbreviations: CI = confidence interval; CSR = clinical study report; DB = double-blind; eGFR = estimated glomerular filtration rate; FAS = full analysis set; LS = least squares; NA = not applicable; SD = standard deviation.
[a] Sparsentan, n=193; irbesartan, n=193.
[b] Sparsentan, n=180; irbesartan, n=162.
[c] Sparsentan, n=159; irbesartan, n=138.
[d] Sparsentan, n=170; irbesartan, n=148.
[e] These results are based on an MMRM model on the change from baseline in eGFR with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit interaction, and randomisation stratification factors as fixed effects and patient as a random effect. An unstructured covariance structure is used in the model.
[f] These results are based on an ANCOVA model on the change from end of treatment eGFR with treatment, end of treatment eGFR, and randomisation stratification as fixed effects.

Change in eGFR from Baseline to 4 Weeks Post-Cessation of Randomized Treatment (Week 114)

ANCOVA analysis of the change from baseline in eGFR at 4 weeks post-cessation of randomized treatment among subjects who completed double-blind treatment (ie, change from baseline in eGFR at Week 114) showed a difference in favour of sparsentan compared to irbesartan. The LS mean change from baseline (95% CI) was -6.1 (-7.74, -4.48) mL/min/1.73m^2 for the sparsentan group and -9.0 (-10.71, -7.21) mL/min/1.73 m^2 for the irbesartan group, indicating preservation of effect following discontinuation of study medication and initiation of standard of care treatment. These findings were consistent with the sensitivity analysis that included all subjects in the study.

Table 5 Change from Baseline in eGFR at Week 114 Using ANCOVA (FAS – Subjects who Completed Blinded Treatment)

eGFR (mL/min/1.73 m²)	Sparsentan (N = 174)	Irbesartan (N = 154)
Change from Baseline to Week 114[a]		
N	170	148
Mean (SD)	-6.2 (10.63)	-8.9 (11.30)
SE	0.82	0.93
Median	-5.0	-9.0
Q1, Q3	-12.0, 0.0	-15.0, -2.0
Min, max	-42, 39	-67, 18
ANCOVA Results at Week 114[b]		
LS mean change from baseline	-6.1	-9.0
95% CI for LS mean change	(-7.74, -4.48)	(-10.71, -7.21)
Difference (sparsentan-irbesartan)	2.9	
95% CI for difference	(0.45, 5.25)	

eGFR (mL/min/1.73 m²)	Sparsentan (N = 174)	Irbesartan (N = 154)
p-value	0.0199	

Abbreviations: ANCOVA = Analysis of Covariance; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology; CSR = clinical study report; DB = double-blind; eGFR = Estimated glomerular filtration rate; FAS = full analysis set; LS = least squares; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SE = standard error.
Notes: - The estimated glomerular filtration rate (eGFR) is determined using the CKD-EPI equation.
- Baseline is defined as the last nonmissing observation on or prior to the start of dosing.
[a] 4-Weeks Post-Cessation of Randomised Treatment is based on the analysis window of '>Last Dose-Date'.
[b] Results are based on an ANCOVA model on the change from baseline eGFR with treatment, baseline eGFR, and randomisation stratification factors as fixed effects.

Change in eGFR from End of Treatment (Week 110) to 4 Weeks Post-cessation of Randomised Treatment (Week 114)

eGFR decreased slightly in the sparsentan group but remained the same in the irbesartan group following cessation of randomised treatment and commencement of standard of care therapy among subjects who completed double-blind treatment.

Table 6 Absolute Change in eGFR from EOT (Week 110) to 4 Weeks Post-cessation of Randomised Treatment (Week 114) (FAS – Subjects who Completed Blinded Treatment)

eGFR (mL/min/1.73 m²)	Sparsentan (N = 174)	Irbesartan (N = 154)
Absolute Change from EOT to 4-Weeks Post-Cessation of Randomized Treatment[a]		
N	170	148
Mean (SD)	-1.1 (6.08)	0.1 (4.91)
SE	0.47	0.40
Median	-1.0	0.0
Q1, Q3	-4.0, 2.0	-3.0, 2.0
Min, max	-20, 17	-14, 16
ANCOVA Results at Week 114 [b]		
LS mean change from end of treatment	-1.1	0.1
95% CI for LS mean change	(-1.91, -0.22)	(-0.81, 1.00)
SE	0.43	0.46
Difference (sparsentan-irbesartan)	-1.2	
95% CI for difference	(-2.40, 0.08)	
p-value	0.0672	

Abbreviations: ANCOVA = Analysis of Covariance; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology; CSR = clinical study report; DB = double-blind; eGFR = Estimated glomerular filtration rate; EOT = end of treatment; FAS = full analysis set; LS = least squares; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SE = standard error.
Note: The estimated glomerular filtration rate (eGFR) is determined using the CKD-EPI equation.
[a] 4 Weeks Post-Cessation of Randomised Treatment is based on the analysis window of '>Last Dose-Date'.
[b] Results are based on an ANCOVA model on the change from end of treatment eGFR with treatment, end of treatment eGFR, and randomisation stratification factors as fixed effects.

Proportion of Subjects with Haematuria at Each Visit

At baseline and across visits, the proportion of subjects with hematuria was similar between the treatment groups. At baseline, 54.4% of subjects in the sparsentan group and 59.8% of subjects in the irbesartan group experienced hematuria. There was an observed reduction in the proportion of subjects reporting hematuria postbaseline for both treatment groups.

6.2. Discussion

With this Type II variation, the MAH submitted the final Clinical Study Report of Study 021IGAN17001 entitled PROTECT. Full analyses and data from the PROTECT study were expected to be provided by the MAH to fulfil the imposed condition in the frame of the conditional marketing authorisation for Filspari. The MAH proposes a switch from conditional marketing authorisation to standard marketing authorisation.

The following uncertainties and limitations about favourable effects were identified at the time of MA:

- Analyses according to baseline proteinuria of > 1.75 g/day do not clearly demonstrate a relation between the baseline degree of proteinuria and effect size on eGFR based on both chronic slope and total slope in the full analysis set (FAS).
- Proteinuria change may be acute and reversible (reflecting functional changes) *versus* chronic and persistent (reflecting structural changes). Persistence of the effect on proteinuria after the end of the treatment period.
- At baseline, both treatment groups were comparable regarding the haematuria (both groups 56%). At week 36, the proportion of patients reporting haematuria was slightly lower for sparsentan (60 (44%)) as compared to irbesartan (67 (51%)) (p = 0.14). The clinical relevance of haematuria is still unclear.

Baseline degree of proteinuria and effect size on eGFR based on both chronic slope and total slope

The MAH has performed extended post-hoc subgroup analyses by splitting baseline proteinuria in <1.75 g/day and >1.75 g/day subgroups. Chronic slope and total slope analysis have been performed in response to questions raised during the MA procedure.

Chronic slope analysis

The initial acute effect of randomized therapy was defined as the change from baseline in eGFR during the first 6 weeks of randomized treatment with PROTECT study drug; thus, the analysis of eGFR chronic slope in the confirmatory analysis at 2 years assesses the effect after the initial acute effect (from 6 weeks post randomization to 110 weeks post-randomization). Statistically significant (p = 0.0369) difference versus irbesartan in positive sparsentan's effect on eGFR chronic slope has been presented. A slower rate of change in eGFR was observed in sparsentan-treated subjects (-2.7 [95% CI: -3.43, -2.05] mL/min/1.73 m^2/year) relative to irbesartan-treated subjects (-3.8 [95% CI: -4.60, -3.07] mL/min/1.73 m^2/year) following the acute effect of randomized therapy.

A slower rate of decline in eGFR was observed in sparsentan-treated subjects that have baseline proteinuria <1.75 g/day (-2.0 [95% CI: -3.03, -1.06] mL/min/1.73 m^2) versus irbesartan-treated subjects (-3.1 [95% CI: -4.16, -2.09] mL/min/1.73 m^2).

A similar trend was observed in subjects that have baseline proteinuria >1.75 g/day: A slower rate of decline in eGFR was in sparsentan group (-3.6 [95% CI: -4.55, -2.65] mL/min/1.73 m^2) versus irbesartan-treated subjects (-4.7 [95% CI: -5.66, -3.69] mL/min/1.73 m^2). However, it should be noted that the annualized difference in slopes between the sparsentan group and irbesartan group according to

baseline proteinuria subgroups has not been calculated. The MAH is requested to provide missed data (**OC, first request for supplementary information**).

It should also be noted that a slower rate of decline in eGFR was observed in all subjects that have baseline proteinuria <1.75 g/day.

Total slope analysis

The analysis of eGFR total slope at 2 years in the confirmatory analysis has been performed to estimate the effect over the entire course of the treatment period (the rate of change in eGFR over 110 weeks following the initiation of randomized therapy).

A slower rate of decline in eGFR was observed in sparsentan-treated subjects (-2.9 [95% CI: -3.58, -2.24] mL/min/1.73 m^2/year) versus irbesartan-treated subjects (-3.9 [95% CI: -4.59, -3.13] mL/min/1.73 m^2/year). In the FAS, the annualized difference in slopes between the sparsentan group and irbesartan group was 1.0 (95% CI: -0.03, 1.94) mL/min/1.73 m^2 per year. However, statistical significance in the total slope was not achieved (p = 0.0582).

A slower rate of decline in eGFR was observed in sparsentan-treated subjects that have baseline proteinuria <1.75 g/day (-2.2 [95% CI: -3.12, -1.20] mL/min/1.73 m^2) versus irbesartan-treated subjects (-2.9 [95% CI: -3.95, -1.94] mL/min/1.73 m^2).

A similar trend was observed in subjects that have baseline proteinuria >1.75 g/day: A slower rate of decline in eGFR was in sparsentan group (-3.8 [95% CI: -4.76, -2.87] mL/min/1.73 m^2) versus irbesartan-treated subjects (-4.9 [95% CI: -5.88, -3.93] mL/min/1.73 m^2).

It can be concluded that based on the final analyses, there is no strong effect modification according to baseline proteinuria and thus no reason to limit the indication to patients with higher baseline proteinuria. However, it should be noted that the annualized difference in slopes between the sparsentan group and irbesartan group baseline proteinuria subgroups has not been calculated. The MAH is requested to provide missed data (**OC, first request for supplementary information**).

In conclusion, the detailed analysis regarding sparsentan effect on eGFR has been presented based on both the chronic slope and the total slope. Sparsentan demonstrated improvement over irbesartan with respect to eGFR slopes, with similar magnitudes of effect between chronic slope (1.1 mL/min/1.73 m^2 per year) and total slope (1.0 mL/min/1.73 m^2 per year). It should be noted that according to the p-value, statistical significance has been achieved only in the chronic slope (p = 0.037) but not in the total slope (p = 0.0582). It means that a more pronounced effect was in chronic slope. The uncertainties regarding sparsentan's long-term effect on the total slope have not been resolved. However, it could be agreed that chronic eGFR slope could also be considered a relevant endpoint in this scenario.

Persistence of the effect on proteinuria after the end of the treatment period

It is unclear whether the effect on proteinuria persists after the end of the treatment period (**OC, first request for supplementary information**).

Long-term efficacy data

The MAH indicated that there is currently no evidence of attenuation or degradation of efficacy with prolonged treatment with sparsentan based on the data from PROTECT and the pharmacology of sparsentan. Collectively, the available data suggest that the efficacy of sparsentan in treating subjects with IgAN would persist with continued treatment. Sparsentan therapy shows long-term benefit in reducing the rate of decline of renal function based on the 2 years of data presented here. However, the MAH did not provide new data to characterize sparsentan effect on the total slope.

Additional data from open-label extension (OLE) period of PROTECT study regarding the long-term

efficacy (proteinuria, eGFR) has not been submitted by the MAH. It is unclear whether the effect on eGFR slope maintain over time (**OC, first request for supplementary information**)

Relevance of haematuria

Information on the proportion of Subjects with Haematuria at Each Visit was included in the CSR but no discussion on the relevance of haematuria was provided. Further, an analysis of the trends over time and possible association with other clinical data has not been presented.

The MAH is requested to provide a detailed analysis of the changes in the proportion of subjects reporting haematuria from baseline over treatment time until week 110. The statistical analysis to investigate patients with haematuria in association with the amount of proteinuria, eGFR, and other kidney composite outcomes could be beneficial to find the clinical relevance of haematuria (**OC, first request for supplementary information**).

Conclusion. The MAH has submitted the final results from the randomised double blind active-controlled phase of PROTECT to fulfil the imposed specific obligation in the frame of the conditional marketing authorisation for Filspari. However, the MAH is expected to provide responses to a few issues raised (**first request for supplementary information**) before a conclusion can be made.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Sparsentan safety was evaluated through assessment of safety data from both solely PROTECT and pooled data from 3 studies – PROTECT, DUPLEX, and DUET, referred further as Rare Glomerular Disease (RGD) study pool. The data cut-off dates were 01 Aug 2023 for DUPLEX and DUET and 07 Sep 2023 for PROTECT.

The safety objective of the double-blind period of PROTECT is to assess the safety and tolerability of sparsentan by double-blind monitoring of safety endpoints. The safety endpoints are 1 - Changes from baseline in body weight, vital signs, physical examinations, peripheral oedema, and clinical laboratory parameters, and 2 - The incidence of treatment-emergent adverse events (TEAEs). Corresponding safety results from RGD study pool were also provided, where possible. The pooled analyses focus primarily on the comparison of 400/800 mg sparsentan group versus irbesartan group during double-blind treatment of PROTECT, DUPLEX, or DUET. Secondary focus is on subjects in the 'All Sparsentan' group. The "All Sparsentan" group includes sparsentan safety data for subjects who received at least 1 dose of sparsentan during any treatment period. It includes subjects who received 200 mg sparsentan in DUET and subjects who received irbesartan during the double-blind period and then received sparsentan during the open-label extension.

Safety objective was assessed by performing a descriptive analysis.

7.2. Results

Exposure

PROTECT

In the PROTECT study, 404 subjects received study drug, 202 patients in sparsentan group and 202 in the irbesartan group. In the SAS during DB treatment, the mean (SD) duration of treatment was 102.83

(22.279) weeks for the sparsentan group and 96.75 (29.302) weeks for the irbesartan treatment group, consistent with the higher rate of discontinuation observed in the irbesartan group.

Overall, 96% of subjects titrated to the target dose (95% in the sparsentan group and 97% in the irbesartan group), with a mean (SD) duration of treatment at the target dose of 84.55 (37.591) weeks in the sparsentan group and 87.65 (34.097) weeks in the irbesartan group.

The number of subjects who had dose reductions after achieving target dose was 34 (16.8%) in the sparsentan and 23 (11.4%) in the irbesartan treatment groups. A total of 49 subjects in the sparsentan group and 36 subjects in the irbesartan group had study medication interruptions with a mean (SD) duration of 29.8 (45.33) days and 25.9 (33.13) days, respectively.

RGD Study Pool

The overall median (range) duration of exposure in the DB period was similar in the 400/800 mg sparsentan group (756 [1 to 874 days] with 712.47 total subject-years) and irbesartan group (756 [1 to 826 days] with 700.55 total subject-years).

The median duration of exposure in the All Sparsentan group was 768.5 (1 to 3291 days) with 1731.59 total subject-years. The exposure in the All Sparsentan group is approximately twice the exposure in the irbesartan group, with a total of 243 (33%) subjects treated with sparsentan who had over 1008 exposure days. This difference in duration of exposure means that direct comparisons cannot be made between the All Sparsentan group and the irbesartan group.

Table 7 Overview of the RGD Study Pool (Safety Analysis Set)

	Double-Blind					
	400 mg Sparsentan n (%) (N = 228)	**800 mg Sparsentan n (%) (N = 218)**	**400/800 mg Sparsentan n (%) (N = 446)**	**Irbesartan n (%) (N = 425)**	**All Sparsentan n (%) (N = 736)**	**All Subjects n (%) (N = 884)**
RGD study pool	228 (100.0)	218 (100.0)	446 (100.0)	425 (100.0)	736 (100.0)	884 (100.0)
PROTECT	202 (88.6)	NA	202 (45.3)	202 (47.5)	330 (44.8)	404 (45.7)
DUPLEX	NA	184 (84.4)	184 (41.3)	187 (44.0)	298 (40.5)	371 (42.0)
DUET	26 (11.4)	34 (15.6)	60 (13.5)	36 (8.5)	108 (14.7)	109 (12.3)

n = number of subjects in sample; N = number of subjects; Note: The All Sparsentan column includes subjects who received at least 1 dose of sparsentan during any treatment period. Subjects are counted only once regardless of different sparsentan doses received. Note: The All Subjects column includes subjects who received at least 1 dose of study medication during any treatment period. Subjects are counted only once regardless of different treatments received.

Of the 884 subjects in the RGD study pool Safety Analysis Set (SAS) (All Subjects), 188 (21.3%) subjects discontinued DB study treatment, and 53 (6.0%) withdrew from DB study participation.

Adverse events

PROTECT

An overall summary of TEAEs during the double-blind study period is provided in the Table 8 below.

Table 8 Overall Summary of TEAEs During the Double-Blind Period of PROTECT (SAS)

	Sparsentan (N = 202) n (%) [event]	Irbesartan (N = 202) n (%) [event]	Total (N = 404) n (%) [event]
Any TEAEs	187 (93) [1373]	177 (88) [1299]	364 (90) [2672]
Any Related TEAEs	93 (46) [248]	70 (35) [170]	163 (40) [418]
Any Severe TEAEs	24 (12) [41]	29 (14) [40]	53 (13) [81]
Any SAEs	75 (37) [110]	71 (35) [107]	146 (36) [217]
Any AEOIs	5 (2) [10]	7 (3) [14]	12 (3) [24]
Any TEAEs Leading to Treatment Discontinuation	21 (10) [26]	18 (9) [20]	39 (10) [46]
Any TEAEs Leading to Death	0 (0) [0]	1 (<1) [2]	1 (<1) [2]

Notes: - Percentages are based on all subjects in the SAS within each group. - Adverse events with missing relationship or missing severity are counted under "Related" and "Severe."

TEAES by PT Occurring in ≥5% of Subjects in Any Group During the Double-Blind Period of PROTECT are presented in Table 8.

Most TEAEs during the double-blind study period in both treatment groups were mild or moderate in severity. Overall, 53 subjects (13%) had TEAEs considered severe, including 24 subjects (12%) who received sparsentan and 29 subjects (14%) who received irbesartan.

Table 9 TEAEs by PT Occurring in ≥5% of Subjects in Any Group During the Double-Blind Period of PROTECT (Safety Analysis Set)

Preferred Term	Sparsentan (N = 202) n (%)	Irbesartan (N = 202) n (%)
Subjects with Any TEAEs	187 (93)	177 (88)
COVID-19	53 (26)	46 (23)
Hyperkalaemia	32 (16)	26 (13)
Peripheral oedema	31 (15)	24 (12)
Headache	27 (13)	26 (13)
Hypertension	22 (11)	28 (14)
Dizziness	30 (15)	13 (6)
Upper respiratory tract infection	18 (9)	18 (9)
Hypotension	26 (13)	8 (4)
Muscle spasms	14 (7)	17 (8)
Nasopharyngitis	15 (7)	16 (8)
Diarrhea	10 (5)	19 (9)
Back pain	12 (6)	16 (8)
Fatigue	17 (8)	11 (5)
Proteinuria	13 (6)	15 (7)
Arthralgia	14 (7)	13 (6)

Preferred Term	Sparsentan (N = 202) n (%)	Irbesartan (N = 202) n (%)
Anaemia	16 (8)	9 (4)
Blood creatine phosphokinase increased	15 (7)	10 (5)
Blood creatinine increased	10 (5)	14 (7)
Cough	15 (7)	7 (3)
Gout	11 (5)	10 (5)
Lipase increased	12 (6)	9 (4)
Pruritus	11 (5)	8 (4)
Renal impairment	7 (3)	12 (6)
Urinary tract infection	7 (3)	12 (6)
Alanine aminotransferase increased	10 (5)	8 (4)
Hyperuricemia	7 (3)	11 (5)
Pain in extremity	6 (3)	12 (6)
Gastrooesophageal reflux disease	10 (5)	8 (4)
Acute kidney injury	12 (6)	5 (2)
Nausea	10 (5)	5 (2)
Myalgia	10 (5)	4 (2)

Note: Percentages are based on all subjects in the SAS within each group. Adverse events are coded with MedDRA Version 23.0. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.

Related TEAEs During the Double-Blind Period by SOC and PT Occurring in ≥5% of the Total Population in PROTECT are presented in Table 10.

Table 10 Related TEAEs During the Double-Blind Period by SOC and PT Occurring in ≥5% of the Total Population in PROTECT (SAS)

System Organ Class Preferred Term	Sparsentan (N = 202) n (%) [event]	Irbesartan (N = 202) n (%) [event]	Total (N = 404) n (%) [event]
Subjects With Any Related TEAEs	93 (46) [248]	70 (35) [170]	163 (40) [418]
Metabolism and Nutrition Disorders	25 (12) [34]	22 (11) [30]	47 (12) [64]
Hyperkalemia	20 (10) [29]	16 (8) [23]	36 (9) [52]
Nervous System Disorders	27 (13) [38]	17 (8) [24]	44 (11) [62]
Dizziness	19 (9) [23]	7 (3) [8]	26 (6) [31]
Vascular Disorders	25 (12) [37]	14 (7) [16]	39 (10) [53]
Hypotension	16 (8) [23]	6 (3) [8]	22 (5) [31]
Investigations	24 (12) [60]	14 (7) [34]	38 (9) [94]
General Disorders and Administration Site Conditions	18 (9) [24]	13 (6) [16]	31 (8) [40]
Peripheral edema	14 (7) [17]	4 (2) [4]	18 (4) [21]
Gastrointestinal Disorders	15 (7) [22]	11 (5) [12]	26 (6) [34]
Renal and Urinary Disorders	13 (6) [15]	9 (4) [9]	22 (5) [24]

Notes: Percentages are based on all subjects in the SAS within each group. Adverse events with missing relationship are considered as related and included in this summary. If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.

RGD Study Pool

Table 11 Overview of TEAEs (RGD Study Pool) (Safety Analysis Set)

	Double-Blind				
	400 mg Sparsentan n (%) (N = 228)	**800 mg Sparsentan n (%) (N = 218)**	**400/800 mg Sparsentan n (%) (N = 446)**	**Irbesartan n (%) (N = 425)**	**All Sparsentan n (%) (N = 736)**
Any TEAEs	205 (89.9)	199 (91.3)	404 (90.6)	376 (88.5)	634 (86.1)
Any Related TEAEs	102 (44.7)	101 (46.3)	203 (45.5)	169 (39.8)	328 (44.6)
Any Serious TEAEs	74 (32.5)	62 (28.4)	136 (30.5)	141 (33.2)	279 (37.9)
Any Severe TEAEs[b]	25 (11.0)	40 (18.3)	65 (14.6)	62 (14.6)	118 (16.0)
Any TEAEs Leading to Discontinuation of Study Medication	23 (10.1)	27 (12.4)	50 (11.2)	39 (9.2)	97 (13.2)
Any TEAEs Leading to Dose Interruption	35 (15.4)	32 (14.7)	67 (15.0)	61 (14.4)	128 (17.4)
Any TEAEs Leading to Dose Change	29 (12.7)	43 (19.7)	72 (16.1)	47 (11.1)	131 (17.8)
Any TEAEs Leading to Death	0 (0.0)	3 (1.4)	3 (0.7)	3 (0.7)	4 (0.5)

Abbreviations: n = number of subjects in sample; N = number of subjects. Note: Percentages are based on all subjects in the Safety Analysis Set within each group. Note: AE with missing relationship are counted under "Related."
[b] AE with missing severity are counted under "Severe."

The most frequent TEAEs by preferred term during the DB period in subjects in the 400/800 mg sparsentan group and irbesartan group were COVID-19 (400/800 mg sparsentan 20.4%, irbesartan 21.4%); oedema peripheral (400/800 mg sparsentan, 16.4%, irbesartan 14.4%); hypotension (400/800 mg sparsentan, 15.0%, irbesartan 7.3%); hyperkalaemia (400/800 mg sparsentan 13.9%, irbesartan 11.1%); dizziness (400/800 mg sparsentan 13.7%, irbesartan 8.9%); and headache (400/800 mg sparsentan 12.8%, irbesartan 13.2%).

The following additional TEAEs occurred in ≥5% of subjects in the 400/800 mg sparsentan group but occurred in <5% of subjects in the irbesartan group: anaemia (9.0% versus 4.0%), blood creatine phosphokinase increased (7.6% versus 4.5%), and vomiting (5.2% versus 2.8%).

In the All Sparsentan group, the most frequent TEAEs by preferred term were COVID-19 (26.0%), hyperkalaemia (16.4%), oedema peripheral (16.4%), hypotension (14.4%), headache (13.7%), dizziness (11.0%), and hypertension (10.2%).

Overall, in the RGD study pool, most TEAEs were mild or moderate in severity. During the DB period, 65 (14.6%) subjects in the 400/800 mg sparsentan group and 62 (14.6%) subjects in the irbesartan group experienced at least 1 severe TEAE.

The most common severe TEAEs in the 400/800 mg sparsentan group were acute kidney injury (AKI) and chronic kidney disease (CKD) (8 [1.8%] subjects each) followed by COVID-19 (6 [1.3%] subjects). The most common severe TEAEs in the irbesartan group were nephrotic syndrome (6 [1.4%] subjects) followed by COVID-19 and CKD (5 [1.2%] subjects each).

In the All Sparsentan group, 118 (16.0%) subjects experienced at least 1 severe TEAE with severe AKI (13 [1.8%] subjects), severe CKD and severe COVID-19 (9 [1.2%] subjects each) being the most common.

Table 12 Treatment-Related Adverse Events by Preferred Term Reported in ≥5% of Subjects in Any Group (RGD Study Pool) (Safety Analysis Set)

	Double-Blind				
Preferred Term	400 mg Sparsentan n (%) (N = 228)	800 mg Sparsentan n (%) (N = 218)	400/800 mg Sparsentan n (%) (N = 446)	Irbesartan n (%) (N = 425)	All Sparsentan n (%) (N = 736)
Any treatment-related TEAEs	102 (44.7)	101 (46.3)	203 (45.5)	169 (39.8)	328 (44.6)
Hyperkalaemia	20 (8.8)	23 (10.6)	43 (9.6)	33 (7.8)	81 (11.0)
Hypotension	18 (7.9)	30 (13.8)	48 (10.8)	27 (6.4)	79 (10.7)
Dizziness	22 (9.6)	13 (6.0)	35 (7.8)	21 (4.9)	47 (6.4)
Oedema peripheral	15 (6.6)	9 (4.1)	24 (5.4)	9 (2.1)	37 (5.0)
Headache	10 (4.4)	12 (5.5)	22 (4.9)	9 (2.1)	31 (4.2)

n = number of subjects in sample; N = number of subjects. Note: Percentages were based on all subjects in the Safety Analysis Set within each group. If a subject experienced more than 1 event in a given SOC, that subject was counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject was counted only once for that PT. AEs with missing relationship are counted under "related."

Serious Adverse Events

PROTECT

The most frequently reported serious TEAEs in both treatment groups was COVID-19 (21% sparsentan, 19% irbesartan). Per the study protocol, during the pandemic, any symptomatic case of COVID-19 was reported as a SAE. No other SAE occurred in ≥5% of subjects in either treatment group.

Thirteen sparsentan-treated subjects (6%) and 14 irbesartan-treated subjects (7%) had serious TEAEs in the SOC of renal and urinary disorders:

- Serious TEAEs of CKD were reported in 3% of subjects overall (6 sparsentan subjects and 6 irbesartan subjects). Study medication was discontinued in 2 sparsentan-treated subjects due to serious TEAE of CKD; it was not considered related to treatment by the investigator.
- Serious TEAEs of AKI were reported in 4 sparsentan-treated subjects (2%) and 1 irbesartan-treated subject (<1%). The serious TEAEs were considered possibly related to study medication in 3 of the 4 sparsentan-treated subjects. No serious TEAEs of AKI led to discontinuation of study medication. In the irbesartan-treated subject, the serious TEAE of AKI was assessed by the investigator as possibly related to the study medication and led to the discontinuation of the study medication. None of the subjects required acute dialysis for the treatment of AKI.

RGD Study Pool

The overall incidence of SAEs was comparable between the 400/800 mg sparsentan group (136 [30.5%] subjects) and irbesartan group (141 [33.2%] subjects) during DB treatment.

The most frequently reported serious TEAE in the sparsentan 400/800 mg and irbesartan groups was COVID-19 (400/800 mg sparsentan 61 [13.7%] subjects, irbesartan 73 [17.2%] subjects). During the pandemic, symptomatic COVID-19 infections were considered medically important/clinically significant events and reported as SAEs as mandated by study protocols.

Serious TEAEs in the SOC of renal and urinary disorders were reported in 28 (6.3%) subjects in the sparsentan 400/800 mg group and 27 (6.4%) subjects in the irbesartan group:

- Serious TEAEs of CKD were reported for 10 (2.2%) subjects in the 400/800 mg sparsentan group and 8 (1.9%) subjects in the irbesartan group.
- Serious TEAEs of AKI were reported for 6 (1.3%) subjects in the 400/800 mg sparsentan group and 8 (1.9%) subjects in the irbesartan group.

SAEs were reported for 279 (37.9%) subjects in the All Sparsentan group. The increased incidence of any SAEs in the All Sparsentan group is driven by the incidence of serious COVID-19 infections (140 [19.0%] subjects).

Deaths

PROTECT

In PROTECT, one subject in the irbesartan treatment group had 2 TEAEs that led to death during the double-blind period. On Study Day 549, the subject, a 61- to 70-year-old White male, had a severe TEAE of cardiac failure chronic which was considered possibly related to study medication by the investigator and a severe TEAE of cardio-respiratory arrest that was considered not related to the study medication by the investigator.

RGD Study Pool

In RGD Study Pool, eleven deaths have been reported: 2 subjects who received sparsentan 200 mg, 1 subject who received sparsentan 400 mg, 4 subjects who received sparsentan 800 mg, and 4 subjects who received irbesartan. Among the death SAEs, 2 were considered possibly related to study medication (neuroendocrine carcinoma in 1 subject treated with sparsentan 800 mg and cardiac failure chronic in 1 subject treated with irbesartan 300 mg). Among the 11 deaths in the SAS, 4 events (3 subjects who received sparsentan and 1 subject who received irbesartan) occurred more than 30 days after the last dose of study medication and, therefore, did not meet the criteria for TEAEs.

Discontinuations and/or Dose Modifications Due to Adverse Events

PROTECT

Table 13 Treatment-Emergent AEs Leading to Treatment Discontinuation During the Double-Blind Period Occurring in ≥2 Subjects by PTs (SAS)

Preferred Term	Sparsentan (N = 202) n (%) [event]	Irbesartan (N = 202) n (%) [event]	Total (N = 404) n (%) [event]
Subjects with Any TEAEs Leading to Treatment Discontinuation	21 (10) [26]	18 (9) [20]	39 (10) [46]
Chronic kidney disease	3 (1) [3]	3 (1) [3]	6 (1) [6]
Renal impairment	1 (<1) [1]	4 (2) [4]	5 (1) [5]
Acute kidney injury	3 (1) [3]	0 (0) [0]	3 (1) [3]
Alanine aminotransferase increased	3 (1) [3]	0 (0) [0]	3 (1) [3]
Lipase increased	2 (1) [2]	0 (0) [0]	2 (<1) [2]
Hypotension	2 (1) [2]	0 (0) [0]	2 (<1) [2]
Rash	1 (<1) [1]	1 (<1) [1]	2 (<1) [2]

Notes: Percentages are based on all subjects in the SAS within each group. If a subject experienced more than 1 event in a given SOC, that subject is counted once for the SOC. If a subject experienced more than 1 event with a given PT, that subject is counted only once for that PT.

RGD Study Pool

The overall incidence of TEAEs leading to permanent discontinuation of study medication was comparable in the 400/800 mg sparsentan group (50 [11.2%] subjects) and irbesartan group (39 [9.2%] subjects]) during DB treatment:

- Hypotension led to permanent discontinuation of study medication in 6 (1.3%) subjects in the 400/800 mg sparsentan group and 0 (0.0%) subjects in the irbesartan group.
- CKD led to permanent discontinuation of study medication in 5 (1.1%) subjects in the 400/800 mg sparsentan group and 6 (1.4%) subjects in the irbesartan group.

In the All Sparsentan group, 97 (13.2%) subjects reported any TEAEs leading to permanent discontinuation of study medication, with CKD (9 [1.2%] subjects) and hypotension (7 [1.0%] subjects) being the most common.

In the RGD Study pool, the incidence of TEAEs leading to dose interruptions was consistent across groups. Sixty-seven (15.0%) subjects in the 400/800 mg sparsentan group and 61 (14.4%) subjects in the irbesartan group reported at least 1 TEAE leading to dose interruption.

Adverse Events of Interest

AEs Associated with Abnormal Liver Function Tests and Hepatotoxicity

Hepatotoxicity and elevated serum aminotransferases are known side effects of some ERA therapeutics and were pre-defined in the PROTECT and DUPLEX study protocols as AEOIs.

In DUPLEX and PROTECT, abnormal liver function test results were considered AEOIs if they met one of the following criteria:

- The abnormality represents a new elevation in ALT or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN.
- The abnormality represents a 2-fold increase in ALT or AST above the baseline value for the double-blind period (ie, Day 1) in subjects who had elevated values prior to starting study medication, or a 2-fold increase in ALT or AST above the baseline value for the OLE period (ie, Week 114) in subjects who had elevated values prior to starting open-label sparsentan.

AEOI criteria were not defined in the DUET study protocol. AEs associated with abnormal liver function tests for DUET were identified by the AE preferred terms of ALT increased, AST increased, Hepatic enzyme increased.

Table 14 Overview of TEAEs Associated with Abnormal Liver Function Tests and TEAEs of Hepatotoxicity in PROTECT and RGD Study Pool Double-Blind Periods (SASs)

	PROTECT Double-Blind		RGD Pool Double-Blind		
	Sparsentan n (%) (N = 202)	Irbesartan n (%) (N = 202)	400/800 mg Sparsentan n (%) (N = 446)	Irbesartan n (%) (N = 425)	All Sparsentan n (%) (N = 736)
Subjects with Any TEAEs associated with Abnormal Liver Function Tests	5 (2)	7 (3)	13 (2.9)	12 (2.8)	27 (3.7)
Subjects with Any Hepatic Disorder TEAEs	18 (9)	12 (6)	34 (7.6)	24 (5.6)	57 (7.7)

[a] If a subject experienced more than one event in a given safety topic of interest, that subject is counted once for the topic. All events are counted under their respective categories.

AEs Associated with Abnormal Liver Function Tests

PROTECT

The incidence of AEOIs was low and comparable between treatment groups (2% sparsentan, 3% irbesartan). ALT increase was the most common AEOI overall (2% in each treatment group). All AEOIs in sparsentan-treated subjects occurred during the first 60 weeks of treatment. AEOIs were considered serious in 3 irbesartan-treated subjects; PTs included rhabdomyolysis, AST increased, and ALT increased. No sparsentan-treated subjects had AEOIs that were considered serious.

AEOIs led to treatment discontinuation in 3 sparsentan-treated subjects (PTs included ALT increased, AST increased, hypertransaminasemia) and 1 irbesartan-treated subject (PT of rhabdomyolysis, which was also considered serious).

No subjects experienced an incidence of AST or ALT elevation >3× ULN accompanied by concurrently elevated bilirubin, and no elevations met the criteria for Hy's law.

RGD Study Pool

Overall, 13 (2.9%) subjects in the 400/800 mg sparsentan group and 12 (2.8%) subjects in the irbesartan group experienced at least 1 liver function test-associated TEAE during the DB treatment period. The most common liver function test-associated TEAEs were ALT increased (9 [2.0%] subjects in the 400/800 mg sparsentan group and 6 [1.4%] subjects in the irbesartan group) and AST increased (7 [1.6%] subjects in both the 400/800 mg sparsentan group and the irbesartan group).

Treatment-related AEOIs were reported by 8 (1.8%) subjects in the 400/800 mg sparsentan group and 5 (1.2%) subjects in the irbesartan group.

No subject in the 400/800 mg sparsentan group reported a serious AEOI. Serious AEOIs were reported by 4 (0.9%) subjects in the irbesartan group. No AEOIs resulted in death.

AEOIs led to permanent discontinuation of study medication in 6 (1.3%) subjects in the 400/800 mg sparsentan group and 2 (0.5%) subjects in the irbesartan group.

In the All Sparsentan group, 27 (3.7%) subjects had at least 1 AEOI, with ALT increased (18 [2.4%] subjects) and AST increased (13 [1.8%] subjects) being the most common (Table 14). Fourteen (1.9%) subjects in the All Sparsentan group reported a total of 23 treatment-related AEOIs and 2 (0.3%) subjects reported a total of 3 serious AEOIs.

AEs Associated with Hepatic Disorders

PROTECT

Overall, 9% of sparsentan-treated subjects and 6% of irbesartan-treated subjects had at least 1 hepatic disorder TEAE during the DB period. ALT increased was the most common TEAE in both treatment groups (5% sparsentan, 4% irbesartan), followed by AST increased (2% sparsentan, 4% irbesartan) and gamma-glutamyltransferase (GGT) increased (3% sparsentan, 2% irbesartan).

Treatment-related hepatic disorder TEAEs occurred in 4% of sparsentan-treated subjects and 1% of irbesartan-treated subjects. Those reported in more than 1% of sparsentan-treated subjects included ALT increased (2% sparsentan, 1% irbesartan), GGT increased (2% sparsentan, <1% irbesartan), and AST increased (1% sparsentan, 1% irbesartan).

Two irbesartan-treated subjects had serious hepatic disorder TEAEs: ALT increased, and AST increased (1 subject each). No sparsentan-treated subjects had serious hepatic disorder TEAEs.

RGD Study Pool

Overall, 34 (7.6%) subjects in the 400/800 mg sparsentan group and 24 (5.6%) subjects in the irbesartan group experienced at least 1 hepatic disorder TEAE during the DB treatment period. The incidences of hepatic disorder TEAEs preferred terms were generally similar across treatment groups in the RGD study pool.

Treatment-related hepatic disorder TEAEs occurred in 13 (2.9%) subjects in the 400/800 mg sparsentan group and 7 (1.6%) subjects in the irbesartan group.

No subject in the 400/800 mg sparsentan group had a serious hepatic disorder TEAE. Five (1.2%) subjects in the irbesartan group reported a serious hepatic disorder TEAE.

Hepatic-disorder TEAEs led to permanent discontinuation of study medication for 7 (1.6%) subjects in the 400/800 mg sparsentan group and 2 (0.5%) subjects in the irbesartan group.

In the All Sparsentan group 57 (7.7%) subjects reported a total of 115 hepatic disorder TEAEs, with ALT increase being the most common (33 [4.5%] subjects). Twenty-two (3.0%) subjects in the All Sparsentan group reported a total of 49 treatment-related hepatic disorder TEAEs and 2 (0.3%) subjects reported serious hepatic disorder TEAEs. Hepatic disorder TEAEs led to permanent discontinuation of study medication for 10 (1.4%) subjects (16 events).

Safety Topics of Interest During the Double-Blind Period (SAS)

	Sparsentan (N = 202) n (%) [event]	Irbesartan (N = 202) n (%) [event]	Total (N = 404) n (%) [event]
Subjects with Any Cardiovascular-associated TEAEs	63 (31) [106]	60 (30) [99]	123 (30) [205]
Subjects with Any Cardiac Arrhythmia-associated TEAEs	12 (6) [16]	21 (10) [31]	33 (8) [47]
Subjects with Any Hypotension-associated TEAEs	33 (16) [46]	13 (6) [15]	46 (11) [61]
Subjects with Any Hepatic Disorder TEAEs	18 (9) [40]	12 (6) [23]	30 {7) [63]
Subjects with Acute Kidney Injury TEAEs	12 (6) [13]	5 (2) [5]	17 (4) [18]
Subjects with Any Pancreatic Enzyme-associated TEAEs	15 (7) [31]	14 (7) [21]	29 (7) [52]
Subjects with Any Fluid Retention-associated TEAEs	36 (18) [53]	31 (15) [38]	67 (17) [91]
Subjects with Any Anemia-associated TEAEs	21 (10) [23]	11 (5) [11]	32 (8) [34]
Subjects with Any Hyperkalemia-associated TEAEs	34 (17) [49]	27 (13) [43]	61 (15) [92]

Abbreviations: n = number of subjects in sample; N = number of subjects. Note: Percentages are based on all subjects in the Safety Analysis Set within each group. Note: If a subject experienced more than one event with a given preferred term, that subject is counted only once for that preferred term.

Cardiac-Arrhythmia-Associated Events

PROTECT

Overall, 33 subjects (8%) experienced at least 1 cardiac arrhythmia-associated TEAE, with a higher incidence in subjects receiving irbesartan (10%) than subjects receiving sparsentan (6%). The most common cardiac arrhythmia-associated TEAE was palpitations, reported by 5 sparsentan-treated subjects (2%) and 8 irbesartan-treated subjects (4%).

Overall, there were 3 serious cardiac arrhythmia-associated TEAEs: 2 sparsentan-treated subjects (preferred terms of cardiac arrest and syncope) and 1 irbesartan-treated subject (preferred term of cardio-respiratory arrest). There were no cases of ventricular tachycardia or torsades de pointes in either treatment group, and no evidence of associated symptoms.

RGD Study Pool

Overall, in the RGD study pool, 37 (8.3%) subjects in the 400/800 mg sparsentan group and 32 (7.5%) subjects in the irbesartan group experienced at least 1 cardiac-arrhythmia-associated TEAE during the DB treatment period.

The most common cardiac arrhythmia-associated TEAE in both the 400/800 mg sparsentan and irbesartan groups was palpitations (400/800 mg sparsentan 12 [2.7%] subjects, irbesartan 9 [2.1%] subjects). Others were Sinus bradycardia (400/800 mg sparsentan 6 [1.3%] subjects, irbesartan 1 (0.2%) subject), Syncope (5 subjects each in the 400/800 mg (1.1%) and irbesartan (1.2%) groups), Tachycardia (400/800 mg sparsentan 5 (1.1%) subjects, irbesartan 6 (1.4%) subjects).

In the All Sparsentan group 65 (8.8%) subjects had at least 1 cardiac arrhythmia-associated TEAE, with palpitations being the most common (22 [3.0%] subjects).

Hypotension Events

PROTECT

Hypotension-associated TEAEs were reported in 16% and 6% of sparsentan and irbesartan-treated subjects, respectively. The most common hypotension-associated TEAE PT in sparsentan and irbesartan-

treated subjects was hypotension (13% versus 4%, respectively), and orthostatic hypotension (4% versus 2%, respectively).

Treatment-related hypotension-associated TEAEs occurred in 10% of sparsentan-treated subjects and in 4% of irbesartan-treated subjects. One subject (<1%) who received sparsentan had a serious hypotension-associated TEAE (PT hypotension).

RGD Study Pool

Table 15 Symptomatic Hypotension-Associated TEAEs (RGD Study Pool) (Safety Analysis Set)

Preferred Term	Double-Blind				All Sparsentan n (%) (N = 736)
	400 mg Sparsentan n (%) (N = 228)	800 mg Sparsentan n (%) (N = 218)	400/800 mg Sparsentan n (%) (N = 446)	Irbesartan n (%) (N = 425)	
Subjects with any symptomatic hypotension-associated TEAEs	62 (27.2)	67 (30.7)	129 (28.9)	73 (17.2)	192 (26.1)
Hypotension	28 (12.3)	39 (17.9)	67 (15.0)	31 (7.3)	106 (14.4)
Dizziness	32 (14.0)	29 (13.3)	61 (13.7)	38 (8.9)	81 (11.0)
Orthostatic hypotension	9 (3.9)	9 (4.1)	18 (4.0)	10 (2.4)	31 (4.2)
Dizziness postural	3 (1.3)	3 (1.4)	6 (1.3)	2 (0.5)	10 (1.4)
Syncope	2 (0.9)	3 (1.4)	5 (1.1)	5 (1.2)	10 (1.4)
Blood pressure decreased	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)	2 (0.3)
Blood pressure diastolic decreased	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)	1 (0.1)
Blood pressure systolic decreased	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)

Treatment-related symptomatic hypotension-associated TEAEs were more frequent in the 400/800 mg sparsentan group (87 [19.5%] subjects) than in the irbesartan group (52 [12.2%]).

Seven (1.6%) subjects in the 400/800 mg sparsentan group and 5 (1.2%) subjects in the irbesartan group reported a serious symptomatic hypotension-associated TEAE. No symptomatic hypotension-associated TEAEs resulted in death.

Ten (2.2%) subjects in the 400/800 mg sparsentan treatment group and no subject in the irbesartan group permanently discontinued study treatment due to a hypotension-associated TEAE.

In the All Sparsentan group, Treatment-related symptomatic hypotension-associated TEAEs were reported by 136 (18.5%) subjects [218 events] and serious symptomatic hypotension-associated TEAEs occurred in 12 (1.6%) subjects [13 events]. Eleven (1.5%) subjects reported 11 symptomatic hypotension-associated TEAEs that lead to permanent discontinuation of study medication.

Acute Kidney Injury

PROTECT

Overall, 6% of sparsentan-treated subjects and 2% of irbesartan-treated subjects had TEAE of AKI. Treatment-related AKI events were reported in 2% of sparsentan-treated subjects and 1% of irbesartan-treated subjects.

Serious TEAEs of AKI were reported in 4 sparsentan-treated subjects (2%) and 1 irbesartan treated subject (<1%). The serious TEAEs were considered possibly related to study medication in 3 of the 4 sparsentan-treated subjects. None of the serious TEAEs of AKI led to the discontinuation of the study medication. Three (1%) sparsentan-treated subjects permanently discontinued medication due to non-serious TEAEs of AKI. In the irbesartan-treated subject, the serious TEAE of AKI was assessed by the investigator as possibly related to the study medication and led to the discontinuation of the study medication. None of the subjects required acute dialysis for the treatment of AKI.

RGD Study Pool

TEAEs of AKI were reported in 20 (4.5%) subjects in the 400/800 mg sparsentan group and 16 (3.8%) subjects in the irbesartan group during the DB treatment period AKI. Treatment-related TEAEs of AKI were reported in 10 subjects each in the 400/800 mg sparsentan group (2.2%) and irbesartan group (2.4%).

Serious TEAEs of AKI were reported in 6 (1.3%) subjects in the 400/800 mg sparsentan group and 8 (1.9%) subjects in the irbesartan group. No TEAEs of AKI resulted in death. TEAEs of AKI led to permanent discontinuation of study medication in 4 (0.9%) subjects treated with 400/800 mg sparsentan and 2 (0.5%) subjects treated with irbesartan.

In the All Sparsentan group 43 (5.8%) subjects reported a total of 52 TEAEs of AKI. Treatment-related AKI TEAEs were reported in 18 (2.4%) subjects and serious TEAEs of AKIs were reported by 21 (2.9%) subjects. Six (0.8%) subjects reported an AKI TEAE that led to permanent discontinuation of study medication.

Fluid Retention-Associated Events

PROTECT

Fluid retention-associated TEAEs were reported in 17% of subjects overall (18% sparsentan, 15% irbesartan). Peripheral oedema was the most common preferred term overall (15% sparsentan, 12% irbesartan). Peripheral swelling was the only other PT that occurred in more than 1% of subjects in either treatment group (2% sparsentan, 2% irbesartan).

Treatment-related fluid retention-associated TEAEs occurred in 8% of sparsentan-treated subjects and 2% of irbesartan-treated subjects. More subjects in the sparsentan group had related events of peripheral oedema compared with subjects in the irbesartan group (7% versus 2%).

Serious fluid retention-associated TEAEs occurred in 2 subjects overall. One sparsentan-treated subject had a serious TEAE of pleural effusion, and 1 irbesartan-treated subject had a serious TEAE of perinephric collection.

RGD Study Pool

Overall, 89 (20.0%) subjects in the 400/800 mg sparsentan group and 79 (18.6%) subjects in the irbesartan group experienced at least 1 fluid retention-associated TEAE during the DB treatment period. Oedema peripheral was the most common fluid retention-associated TEAE (73 [16.4%] subjects in the 400/800 mg sparsentan group and 61 [14.4%] subjects in the irbesartan group).

Peripheral swelling occurred in 9 (2.0%) subjects in the 400/800 mg sparsentan group versus 6 (1.4%) subjects in the irbesartan group. Treatment-related fluid retention-associated TEAEs were more frequent in the subjects in the 400/800 mg sparsentan group (30 [6.7%] subjects) than in the irbesartan group (11 [2.6%] subjects).

Serious fluid retention-associated TEAEs occurred in 5 (1.1%) subjects in the 400/800 mg sparsentan group and 10 (2.4%) subjects in the irbesartan group. No fluid retention-associated TEAEs led to death.

Five (1.1%) subjects in the 400/800 mg sparsentan group and 3 (0.7%) subjects in the irbesartan group permanently discontinued treatment due to a fluid retention-associated TEAE.

In the All Sparsentan group, 149 (20.2%) subjects reported a total of 238 fluid retention-associated TEAEs, with oedema peripheral being the most common (121 [16.4%] subjects). Treatment-related fluid retention-associated TEAEs were reported in 44 (6.0%) subjects and serious fluid retention-associated TEAEs were reported in 13 (1.8%) subjects.

Anaemia-Associated Events

PROTECT

Anaemia-associated TEAEs were reported in a higher proportion of sparsentan-treated subjects (10%) than in irbesartan-treated subjects (5%). Anaemia was the most common PT overall (8% sparsentan, 4% irbesartan). Treatment-related anaemia-associated TEAEs occurred in 1% of sparsentan-treated subjects and 2% of irbesartan-treated subjects.

One sparsentan-treated subject had a serious TEAE of anaemia. No irbesartan-treated subjects had anaemia-associated TEAEs that were considered serious. There were moderate decreases in hemoglobin and hematocrit levels reported in the sparsentan group from baseline to Week 6, which then stabilized through Week 110.

RGD Study Pool

In the RGD study pool, 51 (11.4%) subjects in the 400/800 mg sparsentan group and 23 (5.4%) subjects in the irbesartan group experienced at least 1 anaemia-associated TEAE during the DB treatment period. TEAEs that occurred in >1% of subjects in the 400/800 mg sparsentan group and >2 times as frequent when compared with the irbesartan group included the following:

- Anaemia: 40 (9.0%) subjects in the 400/800 mg sparsentan group and 17 (4.0%) subjects in the irbesartan group
- Iron deficiency anaemia: 5 (1.1%) subjects in the 400/800 mg sparsentan group and 2 (0.5%) subjects in the irbesartan group

Treatment-related anaemia-associated TEAEs occurred in 4 (0.9%) subjects in the 400/800 mg group and 6 (1.4%) subjects in the irbesartan group. Three (0.7%) subjects in the 400/800 mg sparsentan group reported a serious anaemia-associated TEAE. No subjects in the irbesartan group reported a serious anaemia-associated TEAE. No subject reported an anaemia-associated TEAE that resulted in permanent discontinuation of study medication or resulted in death.

In the All Sparsentan group 96 (13.0%) subjects reported a total of 117 anaemia-associated TEAE, with anaemia being the most common (73 [9.9%] subjects). Sixteen (2.2%) subjects reported treatment-related anaemia-associated TEAEs. Eight (1.1%) subjects reported serious anaemia-associated TEAEs. One (0.1%) subject in the All Sparsentan group permanently discontinued study medication due to an anaemia-associated TEAE.

Hyperkalaemia-Associated Events

Hyperkalaemia-associated TEAEs were reported in a higher proportion of sparsentan-treated subjects (17%) than in irbesartan-treated subjects (13%). Hyperkalaemia-associated TEAEs in sparsentan- and irbesartan-treated subjects included hyperkalaemia (16% versus 13%, respectively) and blood potassium increased (1% in each group).

Treatment-related hyperkalaemia-associated TEAEs occurred in 10% of sparsentan-treated subjects and in 8% of irbesartan-treated subjects. One subject (<1%) who received irbesartan reported a serious event of hyperkalaemia (none in the sparsentan group).

RGD Study Pool

Overall, 70 (15.7%) subjects in the 400/800 mg sparsentan group and 49 (11.5%) subjects in the irbesartan group experienced at least 1 hyperkalaemia-associated TEAE during the DB treatment period. Hyperkalaemia was reported by 62 (13.9%) subjects in the 400/800 mg sparsentan group and 47 (11.1%) subjects in the irbesartan group. Blood potassium increased was reported by 8 (1.8%) subjects in the 400/800 mg sparsentan group and 2 (0.5%) subjects in the irbesartan group.

Treatment-related hyperkalaemia-associated TEAEs occurred in 47 (10.5%) of 400/800 mg-treated subjects and 35 (8.2%) irbesartan-treated subjects.

One subject each in the 400/800 mg sparsentan group (0.2%) and irbesartan group (0.2%) reported a serious hyperkalaemia-associated TEAE.

No subject in the 400/800 mg sparsentan group permanently discontinued treatment due to a hyperkalaemia-associated TEAE compared to 1 (0.2%) in the irbesartan group.

In the All Sparsentan group 134 (18.2%) subjects reported 236 hyperkalaemia-associated TEAEs, with hyperkalaemia being the most common preferred term (121 [16.4%] subjects). Treatment-related hyperkalaemia-associated TEAEs were reported in 88 (12.0%) subjects, and serious hyperkalaemia-associated TEAEs occurred in 9 (1.2%) subjects. Two (0.3%) subjects in the All Sparsentan group permanently discontinued study medication due to a hyperkalaemia TEAE (2 events).

Clinical laboratory evaluations

Hematology

PROTECT

In the final analysis, there were no clinically relevant trends or changes over time in either PROTECT treatment group in any hematology parameters, except for hemoglobin levels and hematocrit with moderate (mean [SD] and median) decreases in the sparsentan group from baseline (hemoglobin: 137.5 [15.52] and 138.0 g/L; hematocrit: 0.416 [0.0445] and 0.420 v/v) to Week 6 (hemoglobin: 129.0 [15.06] and 128.0 g/L; hematocrit: 0.391 [0.0449] and 0.390 v/v), which remained stable through Week 110 and returned to near-baseline values by Week 114 after study medication was discontinued (hemoglobin: 133.9 [17.87] and 134.0 g/L; hematocrit: 0.411 [0.0495] and 0.410 v/v).

Serum Chemistry

Liver Function Tests

PROTECT

Overall, both treatment groups had a low number of subjects with elevations in ALT, AST, alkaline phosphatase (ALP), and total bilirubin. Two sparsentan-treated subjects had ALT elevations >8× ULN. Elevations in the remaining subjects were generally comparable between the treatment groups. Elevations were generally asymptomatic, and there was no other clinical evidence of hepatotoxicity. No cases of Hy's law were observed.

RGD Study Pool

No subjects treated with sparsentan experienced AST or ALT elevation >3x ULN accompanied by concurrently elevated bilirubin >1.5x ULN. No cases of Hy's law were observed.

Potassium

PROTECT

An early, small increase in potassium levels was observed in both treatment groups in the PROTECT study, which then stabilized with a mean increase of <0.1 mmol/L through Week 94 and a maximum mean increase of 0.11 mmol/L at Week 106. At Week 110, study medication was discontinued for 4 weeks, during which time values recovered to near or below baseline values by Week 114.

Urinalysis

In PROTECT, there were no clinically relevant trends or changes over time through Week 114 in either treatment group in any urinalysis parameters in the PROTECT study.

In RGD Study Pool, no pooled analysis of hematology parameters, potassium levels or urinalysis parameters was not performed.

Vital signs, physical findings, and other observations related to safety

Vital Signs

In PROTECT, there were no apparent differences in mean changes from baseline in respiratory rate, heart rate, body temperature, or body weight in either treatment group, and there were no meaningful differences between groups.

The mean baseline BPs were 128/82 mm Hg for the sparsentan treatment group and 130/83 mm Hg for the irbesartan treatment group. There was an initial least squares (LS) mean decrease in both systolic and diastolic BP (-5.0 mm Hg and -4.5 mm Hg, respectively, at Week 6) for sparsentan-treated subjects, with subsequent stabilization starting at Week 12. For irbesartan-treated subjects, there was an initial LS mean decrease in systolic and diastolic BP of -2.7 mm Hg and -0.1 mm Hg at Week 6, respectively), with subsequent stabilization starting at Week 12.

In RGD Study Pool, pooled analysis of vital signs parameters was not performed.

Assessment of Peripheral Oedema

Overall, in PROTECT, the incidence of shifts from baseline to Grade 3 or 4 was low across both treatment groups. In the sparsentan group, no subjects had a post-baseline shift from Grade 0 to Grade 4. In the irbesartan group, 2 subjects had post-baseline shifts from Grade 0 to Grade 4 and 2 subjects had post-baseline shifts from Grade 1 to Grade 4.

In the RGD Study Pool, pooled analysis of shift from baseline to Grade 3 or 4 peripheral oedema was not performed.

Age

PROTECT

In the age group of ≤45 years, 94% of patients in sparsentan group and 89% of patients in irbesartan group experienced any TEAE; 41% and 39%, respectively, any related TEAE; and 44% and 41%, respectively, any SAE.

In the age group of >45 years, 92% of patients in sparsentan group and 86% of patients in irbesartan group experienced any TEAE; 51% and 30%, respectively, any related TEAE; and 31% and 29%, respectively, any SAE.

RGD study pool

In the RGD study pool, in the All Sparsentan group, there were no meaningful differences in overall TEAE incidence between subjects <18 years (91.1%) and subjects aged ≥18 years (85.8%).

Among subjects <18 years, the most common TEAEs were COVID-19 (28.9%) and headache (28.9%). The most common TEAEs among subjects ≥18 years were COVID-19 (25.8%) and oedema peripheral (16.8%).

Sex

In CKD RCT Study Pool, the incidence of TEAEs was similar in males (86.3%) and females (85.9%) in the All Sparsentan group. There were no clinically meaningful differences in TEAE preferred terms between males and females.

Race, Ethnicity

TEAEs in the RGD study pool by race/ethnicity did not reveal notable differences between subgroups.

7.3. Discussion

Sparsentan safety was evaluated through the provision of safety data from both the PROTECT and Rare Glomerular Disease (RGD) study pool, which consists of pooled data from 3 studies – PROTECT, DUPLEX, and DUET. The safety of sparsentan was evaluated through an assessment of the incidence of treatment-emergent adverse events (TEAEs), changes from baseline in body weight, vital signs, physical examinations, peripheral oedema, and clinical laboratory parameters in PROTECT. Corresponding safety results from the RGD study pool were also provided, where possible. The pooled analyses focused primarily on comparing 400/800 mg sparsentan group versus irbesartan group during double-blind treatment of PROTECT, DUPLEX, or DUET.

In the PROTECT study, 404 subjects received study drug, 202 patients in sparsentan group and 202 in irbesartan group. In the Safety analysis set (SAS) during double-blind (DB) treatment, the mean (SD) duration of treatment was 102.83 (22.279) weeks for the sparsentan group and 96.75 (29.302) weeks for the irbesartan treatment group. The mean (SD) duration of treatment at the target dose was of 84.55 (37.591) weeks in the sparsentan group and 87.65 (34.097) weeks in the irbesartan group. The number of subjects who had dose reductions after achieving the target dose was 34 (16.8%) in the sparsentan and 23 (11.4%) in the irbesartan treatment groups. In RGD Study Pool, the overall median duration of exposure in the DB period was similar in the 400/800 mg sparsentan group (756 with 712.47 total subject-years) and irbesartan group (756 with 700.55 total subject-years).

In PROTECT, 93% of sparsentan subjects and 88% of irbesartan subjects had at least 1 TEAE during the double-blind period. Substantially higher numbers of related TEAEs in the sparsentan group compared to irbesartan were detected (46% versus 35%), mainly because of higher numbers of specific PTs – Dizziness (9% versus 3%), Hypotension (8% versus 3%), and Peripheral oedema (7% versus 2%). In RGD Study Pool, similarly to PROTECT, higher numbers of related TEAEs in the sparsentan 400/800 mg group compared to irbesartan were revealed, although the difference between groups was smaller (45.5% versus 39.8%). There were higher numbers in sparsentan 400/800 mg group of Any TEAEs Leading to Dose Change versus irbesartan group as well (16.1% versus 11.1%). The most common treatment-related TEAEs in RGD Study Pool were hypotension (400/800 mg sparsentan 10.8%, irbesartan 6.4%), hyperkalaemia (400/800 mg sparsentan 9.6%, irbesartan 7.8%), dizziness (400/800 mg sparsentan 7.8%, irbesartan 4.9%), and oedema peripheral (400/800 mg sparsentan 5.4 %, irbesartan 2.1 %). The most frequent related TEAEs in RGD Study Pool are, in general, similar to the ones in PROTECT. The most common related TEAEs are listed in the currently approved SmPC section 4.8.

In general, the frequency of serious TEAEs were similar in PROTECT and in RGD Study Pool between sparsentan and sparsentan 400/800 mg groups compared to irbesartan groups, except for AKI in PROTECT, which was reported in 4 sparsentan-treated subjects (2%) and considered possibly related in 3

of them, and 1 irbesartan-treated subject (<1%). The PT of AKI is listed in currently approved SmPC section 4.8. It is to be noted as well that in RGD Study Pool Anaemia was reported more frequently in sparsentan 400/800 mg group, compared with irbesartan (3 subjects (0.7%) versus 0 (0.0), respectively). PT Anaemia is listed in the currently approved SmPC section 4.8. There were no deaths in sparsentan group in PROTECT, and 7 deaths in RGD Study Pool in patients treated with different sparsentan doses, one of them considered related and discussed during the initial MA.

The frequency of TEAEs leading to permanent discontinuation of study medication was comparable in sparsentan, 400/800 mg sparsentan groups and irbesartan groups in PROTECT and RGD Study Pool.

Hepatotoxicity and elevated serum aminotransferases are known side effects of some ERA therapeutics and were pre-defined in the PROTECT and DUPLEX study protocols as adverse events of interest (AEOIs). The frequencies of TEAEs Associated with Abnormal Liver Function Tests were low and comparable in PROTECT and RGD Study Pool (2% in sparsentan group versus 3% in irbesartan group and 2.9% in 400/800 mg sparsentan group versus 2.8% in irbesartan group, respectively). The frequencies of Hepatic Disorders TEAEs were slightly higher in PROTECT and RGD Study Pool (9% in sparsentan group versus 6% in irbesartan group and 7.6% in 400/800 mg sparsentan group versus 5.6% in irbesartan group, respectively). No elevations met criteria for Hy's law. The most common reported PTs ALT increased (2% in each treatment group in PROTECT; 2% in 400/800 mg sparsentan group versus 1.4% in irbesartan group in RGD Study Pool), AST increased (1% in sparsentan group versus 2% in irbesartan group in PROTECT, 1.6% in each treatment group in RGD Study Pool), GGT increased (<1% in sparsentan group versus 1% in irbesartan group in PROTECT, 0.2% in 400/800 mg sparsentan group versus 0.5% in irbesartan group in RGD Study Pool) are listed in currently approved SmPC section 4.8.

Other safety topics of interest included TEAEs discussed below.

In PROTECT, the frequency of cardiac arrhythmia-associated TEAEs was higher in irbesartan group compared with sparsentan (10% versus 6%). In RGD Study Pool, it was comparable between 400/800 mg sparsentan and irbesartan groups (8.3% versus 7.5%).

In both PROTECT and RGD Study Pool, hypotension-associated TEAEs were more frequent in the sparsentan and 400/800 mg sparsentan group, compared to irbesartan. The most frequent PTs reported in both PROTECT and RGD Study Pool were hypotension, orthostatic hypotension, and dizziness. The mentioned PTs are listed in the currently approved SmPC section 4.8. The frequency of the adverse reaction hypotension is updated from common to very common in SmPC Section 4.8.

In PROTECT, TEAEs and serious TEAEs of AKI were more frequent in the sparsentan group, compared to irbesartan (TEAEs: 6% versus 2%; serious TEAEs 2% versus <1%). Treatment-related AKI events were reported in 2% of sparsentan group and 1% of irbesartan group. In RGD Study Pool, TEAEs and TESAEs of AKI were comparable in 400/800 mg sparsentan and irbesartan groups (TEAEs: 4.5% versus 3.8%; serious TEAEs 1.3% versus 1.9%). None of Serious AKIs led to death or required acute dialysis. AKI is listed in the currently approved SmPC section 4.8.

In both PROTECT and RGD Study Pool, the frequency of Fluid retention-associated TEAEs was slightly higher in the sparsentan compared to irbesartan group (18% versus 15%) and 400/800 mg sparsentan group, compared to irbesartan (20% versus 18.6%). Most frequent PT reported in both PROTECT and RGD Study Pool was Peripheral oedema (15% sparsentan versus 12% irbesartan and 16.4% 400/800 mg sparsentan versus 14.4% irbesartan, respectively). Mentioned PT is listed in the currently approved SmPC section 4.8.

In both PROTECT and RGD Study Pool, the frequency of Anaemia-Associated TEAEs was substantially higher in the sparsentan compared to irbesartan group (10% versus 5%) and 400/800 mg sparsentan group, compared to irbesartan (11.4% versus 5.4%). Most frequent PT reported in both PROTECT and

RGD Study was Anaemia (8% sparsentan versus 4% irbesartan, and 9% 400/800 mg sparsentan versus 4% irbesartan, respectively). Mentioned PT is listed in the currently approved SmPC section 4.8.

In both PROTECT and RGD Study Pool, the frequency of Hyperkalaemia-associated TEAEs was substantially higher in the sparsentan compared to irbesartan (17% versus 13%) and 400/800 mg sparsentan group, compared to irbesartan (15.7% versus 11.5%). Most frequent PT reported in both PROTECT and RGD Study was Hyperkalaemia (16% sparsentan versus 13% irbesartan, and 13.9% 400/800 mg sparsentan versus 11.1% irbesartan, respectively), which is listed in currently approved SmPC section 4.8.

The confirmatory safety results from the PROTECT study were consistent with the interim data with no change in the overall safety profile of sparsentan and no new safety concerns identified. The safety profile remains acceptable for sparsentan.

8. PRAC advice

N/A

9. Risk management plan

The MAH submitted an updated RMP version 1.0 with this application. The main proposed RMP changes were the following:

- Submission of final study results for the double-blind phase of PROTECT to address Conditional Marketing Authorisation Specific Obligation enabling conversion to standard Marketing Authorisation
- SIII and SV per up-to-date exposure figures, inclusion of post-marketing methodology SVII.3.1 per final study results (PROTECT) and post-marketing data Part IV/VI: Removal of Specific Obligations (PROTECT)

9.1. Safety Specification

Clinical trial exposure

The clinical trial exposure has been updated in the submitted RMP version 1.0.

The clinical development programme of sparsentan consists of 32 clinical studies (Table 16): 23 Phase 1 clinical pharmacology and safety studies, 5 Phase 2 studies, 2 Phase 3 studies, and 2 Investigator-initiated exploratory studies. The cumulative exposure for all studies by age, sex and racial group is not available:

Table 16 Overview of All Sparsentan Studies

Indication/Special Population	Study	Phase	Number of Patients
IgAN	PROTECT	3	404
	SPARTAN	Investigator sponsored	12
	TVTX-RE021-204; SPARTACUS	2	48
ANCA-vasculitis	SPARVASC~~SPARTAN~~	Investigator sponsored	~~10~~32 planned
FSGS	DUPLEX	3	371
	DUET	2	109
Hypertension	PCO-C-006	2	261
	PCO-C-008	2	113
Healthy ~~Volunteers~~volunteers	PCO-C-001	1	48
	PCO-C-002	1	18
	PCO-C-003	1	40
	PCO-C-004	1	15
	PCO-C-007	1	14
	PCO-C-009	1	8
	PCO-C-010	1	39
	021HVOL16001	1	33
	021HVOL16002	1	Part 1: 9 Part 2: 60
	021HVOL16005	1	8
	021HVOL16006	1	32
	021HVOL16007	1	28
	021HVOL16008	1	28
	021HVOL109	1	16
	021IHFX16009	1	28
	RTRX RE021-101	1	36
	RTRX-RE021-102	1	47
	RTRX-RE021-103	1	36
	TVTX-RE021-106	1	22 ~~enrolled~~
	TVTX-RE021-107	1	23
	TVTX-RE021-108	1	20
	TVTX-RE021-109	1	74
	TVTX-RE021-~~107~~110	1	~~24~~20 planned
Paediatric subjects with selected proteinuric glomerular diseases	~~RTRX~~TVTX-RE021-201; EPPIK	2	~~57~~67 planned

Notes: FSGS=Focal segmental glomerulosclerosis; IgAN=Immunoglobulin A nephropathy.

The efficacy of sparsentan in the IgAN indication is based on the Phase 3 PROTECT study. An exploratory, Investigator-sponsored, open-label study in newly diagnosed treatment-naïve subjects with IgAN is ongoing, SPARTAN. Demographics and baseline characteristics in the PROTECT double-blind period are presented in the Table 17 below:

Table 17 Demographics and Baseline Characteristics (FAS) – PROTECT Double-blind Period

	Sparsentan (N=202)	Irbesartan (N=202)	Total (N=404)
Age at informed consent (years)			
n	202	202	404
Mean (SD)	46.6 (12.76)	45.4 (12.12)	46.0 (12.44)
Min, max	18, 73	19, 76	18, 76
Age group, n (%)			
≤45 years	96 (47.5)	99 (49.0)	195 (48.3)
>45 years	106 (52.5)	103 (51.0)	209 (51.7)
Sex, n (%)			
Male	139 (69)	143 (71)	282 (70)
Female	63 (31)	59 (29)	122 (30)
With childbearing potential[1]	37 (59)	38 (64)	75 (61)
Race[1,2], n (%)			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	67 (33)	48 (24)	115 (28)
Black or African American	1 (<1)	3 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (<1)	1 (<1)
White	130 (64)	142 (70)	272 (67)
Other	4 (2)	9 (4)	13 (3)

1 Percentages for with childbearing potential are based on the female subjects only.
2 Subjects may have selected more than 1 race.
Notes: Percentages are based on all subjects in the ~~primary analysis set~~FAS with non-missing data within each group, unless otherwise specified.
FAS=Full analysis set; n=Number of subjects in sample; N=~~number~~Number of subjects; SD=Standard deviation.

The CKD RCT study pool (rare glomerular disease study pool) includes all subjects with rare glomerular diseases across the 1 IgAN and the 2 FSGS randomised controlled studies (PROTECT, DUPLEX, and DUET), as these subjects share common characteristics associated with the progression of glomerular diseases that are helpful in the assessment of the safety of sparsentan. Each study used irbesartan as comparator and included an open-label extension (OLE) period in which subjects who received either sparsentan or irbesartan in the double-blind period could receive sparsentan.

- Study 021IGAN17001 (PROTECT) – An ongoing, Phase 3 study to determine the efficacy and safety of sparsentan for the treatment of IgAN. The double-blind treatment period comparing sparsentan to irbesartan treatment is complete. The OLE phase to assess the long-term efficacy and safety of sparsentan is ongoing.

- Study 021FSGS16010 (DUPLEX) – An ongoing, Phase 3 study to determine the efficacy and safety of sparsentan for the treatment of FSGS. The double-blind treatment period comparing sparsentan to irbesartan treatment is complete. The OLE phase to assess the long-term efficacy and safety of sparsentan is ongoing.

- Study RET-D-001 (DUET) – An ongoing, Phase 2 study to determine the efficacy and safety of different doses (200 mg, 400 mg, or 800 mg) of sparsentan in FSGS subjects to support the design of the DUPLEX study. The 8-week double-blind treatment period comparing sparsentan to irbesartan treatment is complete. The OLE phase to assess the long-term efficacy and safety of sparsentan is ongoing.

The tables for demographics and baseline characteristics in the CKD RCT study pool (safety analysis set) extent of exposure in the CKD RCT study pool and details of important potential risks have been updated accordingly.

Post-authorisation experience

Post-authorisation Exposure:

As of the date of this submission, sparsentan has only been marketed in the US for the indication of reducing proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-creatinine ratio ≥1.5 g/g. Cumulatively 1,087 patients have been exposed to Filspari since its approval in the US through 16 February 2024 with 410 total patient-years exposure. Additionally, sparsentan was available through Compassionate Use Programme in the US, for the treatment of FSGS with 12 patients treated. In the EU, sparsentan is available to patients in Managed Access Programme (HQ-MAP-SPT-056) in selected countries for the treatment of IgAN. Total of 41 patients were treated in the Managed Access Programme with sparsentan at the time of this report.

Plans for post-authorisation efficacy studies

One post-authorisation efficacy study (PAES) as a condition of the marketing authorisation for sparsentan is in place: Study 021IGAN17001 (PROTECT) is a randomised, multicentre, double-blind, parallel-group, active control study of the efficacy and safety of sparsentan for the treatment of immunoglobulin A nephropathy (IgAN). The double-blind treatment period of this study comparing sparsentan to irbesartan treatment is complete and the results have been submitted within this variation procedure. The OLE phase to assess the long-term efficacy and safety of sparsentan is ongoing.

This PAES has been proposed to be removed from the PART IV in the updated RMP:

Part IV: Plans for Post-Authorisation Efficacy Studies

Table 18 Planned and Ongoing Post-authorisation Efficacy Studies That Are Conditions of the Marketing Authorisation or Specific Obligations

Study (study short name and title), Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
~~Study 021IGAN17001 (PROTECT) A randomised, multicentre, double-blind, parallel-group, active control study of the efficacy and safety of sparsentan for the treatment of immunoglobulin A nephropathy (IgAN) Ongoing~~N/A	~~To confirm the long-term efficacy and safety of sparsentan for the treatment of primary immunoglobulin A nephropathy (IgAN) in adults, and in order to specifically assess the maintenance of the long-term efficacy and safety~~N/A	~~Long-term efficacy~~N/A	~~Final report~~N/A	~~30/09/2024~~N/A

Note: N/A=Not applicable.

Conclusion on the proposed changes in the RMP

The main proposed changes in the submitted updated RMP version 1.0 concerns the removal of the finalised post-authorisation efficacy study 021IGAN17001 (PROTECT) form the PART IV as a specific obligation in the context of a conditional MA, as well as to update the respective tables in the RMP with the results of the double-blind treatment period of this completed study.

RMP version 1.0 is acceptable.

9.2. Overall conclusion on the RMP

☒The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

10. Changes to the Product Information

As a result of this variation, section(s) 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Annex II conditions as detailed in the recommendations section above.

Editorial changes were also made to the SmPC and PL. The PI is brought in line with the latest QRD template version 10.4.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

11. First request for supplementary information

11.1. Major objections

None

11.2. Other concerns

Clinical aspects

Clinical efficacy

1. The annualized differences in eGFR chronic and total slopes between the sparsentan group and irbesartan group with analysis of baseline proteinuria <1.75 g/day and >1.75 g/day subgroups have not been calculated. The MAH is requested to provide missed data.
2. The reversibility of the initial effect of sparsentan after cessation has not fully been clarified. In that sense, the MAH is requested to perform additional analyses and provide a discussion on the reversibility:
    2.1 Analyses on the reversibility of the initial eGFR effects after cessation of treatment. While such analyses have been presented, there were no analyses performed in the subset of patients that have data on both the 110 weeks and 114 weeks visits. Furthermore, the detailed calculation of eGFR to compare data of the week 114 visit with data from the week 106 visit should be presented and discussed.
    2.2 Proteinuria change may be acute and reversible (reflecting functional changes) *vs* chronic and persistent (reflecting structural changes). It is unclear whether the effect on proteinuria persists after the end of the treatment period. Analyses on the reversibility of the effect on proteinuria were not present by MAH. It should be provided using the full data.
3. Additional data from open-label extension (OLE) period of PROTECT study regarding the long-term efficacy (proteinuria, eGFR) has not been submitted by MAH. It is unclear, does the effect on eGFR slope maintain over time?
4. The MAH is requested to provide a detailed analysis of the changes in the proportion of subjects reporting haematuria from baseline over treatment time until week 110. The statistical analysis to investigate patients with haematuria in association with the amount of proteinuria, eGFR and other kidney composite outcomes could be beneficial to find the clinical relevance of haematuria.

Clinical safety

5. The number of subjects with any hypotension-associated TEAEs in both sparsentan and irbesartan groups provided in SCS (data cutoff 07 Sep 2023) is lower than in the interim report (data cutoff 01 Feb 2022). The MAH is asked to clarify this.
6. The MAH is asked to review the comments in SmPC section 4.8 and provide responses to the issues raised.

RMP aspects

The conclusion on the submitted RMP is pending the responses of the MAH to the questions raised by the CHMP and the assessment thereof.

12. Assessment of the responses to the first request for supplementary information

12.1. Major objections

None

12.2. Other concerns

Clinical aspects

Clinical efficacy

Question 1

The annualized differences in eGFR chronic and total slopes between the sparsentan group and irbesartan group with analysis of baseline proteinuria <1.75 g/day and >1.75 g/day subgroups have not been calculated. The MAH is requested to provide missed data.

Summary of the MAH's response

The annualised estimated glomerular filtration rate (eGFR) chronic and total slopes with analysis of baseline proteinuria ⩽1.75 g/day and >1.75 g/day subgroups demonstrated consistency of Sparsentan' s effect across these subgroups, as described in the Clinical Study Report (CSR) (021IGAN17001 Final DB CSR, Section 5.1.5.3.2 and Section 5.1.5.4.2).

As requested by the Agency, the annualised differences in eGFR chronic and total slopes between the Sparsentan group and Irbesartan group with analysis of baseline proteinuria ≤1.75 g/day and >1.75 g/day are presented below.

When assessing the eGFR **chronic slope**, in the subgroup with proteinuria ⩽1.75 g/day, the slope was -3.1 ml/min/1.73 m^2/year (95% confidence interval (CI): -4.16,-2.09) in the Irbesartan group and -2.0 ml/min/1.73 m^2/year (95% CI:-3.03,-1.06) in the Sparsentan group (annualised difference 1.1 ml/min/1.73 m^2/year (95% CI: -0.35, 2.51)).

In the subgroup with proteinuria >1.75 g/day, the slope was -4.7 ml/min/1.73 m^2/year (95% CI: -5.66, -3.69) for Irbesartan and -3.6 ml/min/1.73 m^2/year (95% CI: -4.55, -2.65) for Sparsentan (annualised difference 1.1 ml/min/1.73 m^2/year (95% CI: -0.29, 2.45)).

For the eGFR **total slope**, in the subgroup with proteinuria ⩽1.75 g/day, the slope was -2.9 ml/min/1.73 m^2/year (95% CI: -3.95, -1.94) for Irbesartan and -2.2 ml/min/1.73 m^2/year (95% CI: -3.12, -1.20) for Sparsentan (annualised difference 0.8 ml/min/1.73 m^2/year (95% CI: -0.61, 2.17)).

In the subgroup with proteinuria >1.75 g/day, the slope was -4.9 ml/min/1.73 m^2/year (95%CI: -5.88, -3.93) for Irbesartan and -3.8 ml/min/1.73 m^2/year (95% CI: -4.76, -2.87) for Sparsentan (annualised difference 1.1 ml/min/1.73 m^2/year (95% CI: -0.27, 2.45)).

These results provided above are consistent with what is observed in the overall study population and also across different subgroups.

Assessment of the MAH's response

As presented by the MAH, the eGFR chronic slope was very similar in the subgroups with baseline proteinuria ⩽ 1.75 g/day and >1.75 g/day with the same annualised difference 1.1 ml/min/1.73 m^2/year. This difference between sparsentan and irbesartan was not statistically significant (in the subgroup proteinuria ⩽ 1.75 g/day p-value =0.1366, in the subgroup proteinuria > 1.75 g/day p-value =0.1215) and Treatment-by-prognostic factor interaction effect p-value: 0.7449.

The eGFR total slope was slightly different in the baseline proteinuria subgroups without statistical siginificance: annualised difference 0.8 ml/min/1.73 m^2/year in the subgroup proteinuria ⩽ 1.75 g/day (p =0.2676) and 1.1 ml/min/1.73 m^2/year in the subgroup proteinuria > 1.75 g/day (p= 0.1148) and Treatment-by-prognostic factor interaction effect p-value: 0.9225.

The presented data show that there are no significant differences between sparsentan and irbesartan on eGFR chronic slope and total slope.

Conclusion

The requested data has been presented. Point resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 2

The reversibility of the initial effect of sparsentan after cessation has not fully been clarified. In that sense, the MAH is requested to perform additional analyses and provide a discussion on the reversibility:

2.1 Analyses on the reversibility of the initial eGFR effects after cessation of treatment. While such analyses have been presented, there were no analyses performed in the subset of patients that have data on both the 110 weeks and 114 weeks visits. Furthermore, the detailed calculation of eGFR to compare data of the week 114 visit with data from the week 106 visit should be presented and discussed.

2.2 **Proteinuria change may be acute and reversible (reflecting functional changes) *vs* chronic and persistent (reflecting structural changes). It is unclear whether the effect on proteinuria persists after the end of the treatment period. Analyses on the reversibility of the effect on proteinuria were not present by MAH. It should be provided using the full data.**

Summary of the MAH's response

Response to Question 2.1

The MAH acknowledges the Agency' s comments on the reversibility of the eGFR effect after treatment cessation, that was prespecified to be assessed between end of treatment and 4 weeks after Sparsentan treatment was discontinued and standard of care with renin-angiotensin-aldosterone system (RAAS) inhibition had been resumed.

The MAH extensively reviewed the data to explain the variability found in the Sparsentan group between Week 106 and Week 110 and concluded that there was no pathophysiological mechanism identified underlying the variability of data at Weeks 106 and 110. This change could be due to a few patients having fluctuations in their eGFR during the study, causing some distortion in the mean, since the medians (interquartile range) eGFR change from Week 106-Week 110 are around 0 (-2.0, 3.0) ml/min/1.73 m2.

In addition, the MAH conducted the post-hoc analysis of eGFR slopes excluding Week 110 eGFR from the analysis, as requested by the Agency. The results show slightly less pronounced eGFR slope preservation estimates for Sparsentan compared to the primary analyses. The MAH is of the opinion that arbitrarily discarding data points and comparing data from Week 106 with data at Week 114 is not appropriate.

For this reason, a more appropriate analysis that mitigates the impact of the numerical increase observed at Week 110 was to use the on-study eGFR data up to Week 114, consistent with a treatment policy approach. The results of these post-hoc analyses (Table 1) have shown similar estimates to those obtained from the primary analyses.

Table 1 eGFR Annualised Slope Preservation Estimates (LS Mean, 95% CI) – Full Analysis Set

Endpoint	Irbesartan (N=202)	Sparsentan (N=202)	Sparsentan vs Irbesartan
Primary analysis: chronic slope (on-treatment, Week 6–Week 110)[1]	-3.8 (-4.60, -3.07)	-2.7 (-3.43, -2.05)	1.1 (0.07, 2.12)
Excluding Week 110: chronic slope (on-treatment, Week 6–Week 106)[1]	-3.8 (-4.59, -3.07)	-3.0 (-3.72, -2.34)	0.8 (-0.23, 1.83)
Using on-study eGFR up to Week 114: chronic slope (on-study, Week 6–Week 114)[2]	-4.1 (-4.83, -3.38)	-2.9 (-3.56, -2.16)	1.2 (0.24, 2.26)
Primary analysis: total slope (on-treatment, Day 1–Week 110)[3]	-3.9 (-4.59, -3.13)	-2.9 (-3.58, -2.24)	1.0 (-0.03, 1.94)
Excluding Week 110: total slope (on-treatment, Day 1–Week 106)[3]	-3.9 (-4.59, -3.12)	-3.2 (-3.84, -2.49)	0.7 (-0.30, 1.69)
Using on-study eGFR up to Week 114: total slope (on-study, Day 1–Week 114)[4]	-4.1 (-4.82, -3.41)	-3.0 (-3.69, -2.32)	1.1 (0.13, 2.09)

1 Slopes estimated from random coefficient analysis with 1 slope (no change point) including available on-treatment eGFR data from Week 6 with multiple imputation; ml/min/1.73 m^2 per year; 021IGAN17001 Final DB CSR Table 14.2.2.2.1, Post-hoc Table 14.2.2.2.11 07SEP2023.
2 Slopes estimated from random coefficient analysis with 1 slope (no change point) including available on-study eGFR data from Week 6; ml/min/1.73 m2 per year; Post-hoc Table 14.2.2.2.14 07SEP2023.
3 Slopes estimated from random coefficient analysis with 1 slope (no change point) including available on-treatment eGFR data from Day 1 with multiple imputation; ml/min/1.73 m^2 per year; 021IGAN17001 Final DB CSR Table 14.2.2.4.1, Post-hoc Table 14.2.2.4.11 07SEP2023.
4 Slopes estimated from random coefficient analysis with 1 slope (no change point) including available on-study eGFR data from Day 1; ml/min/1.73 m^2 per year; Post-hoc Table 14.2.2.4.14 07SEP2023.
Notes: CI=Confidence interval; CSR=Clinical Study Report; eGFR=Estimated glomerular filtration rate; LS=Least squares.

Assessment of the MAH's response

The detailed calculation of eGFR to compare data of the week 114 visit with data from the week 106 visit has not been submitted. The MAH is of the opinion that discarding data points and comparing data from Week 106 with data at Week 114 is not appropriate. The MAH submitted analysis that mitigates the impact of the numerical increase observed at Week 110 was to use the on-study eGFR data up to

Week 114. The results of these post-hoc analyses have shown similar estimates to those obtained from the primary analyses.

The MAH extensively reviewed the data to explain the variability found in the Sparsentan group between Week 106 and Week 110 and concluded that there was no pathophysiological mechanism identified underlying the variability of data at Weeks 106 and 110. The MAH is of the opinion that this change is due to a few patients having fluctuations in eGFR.

No new data has been submitted. The reversibility of sparsentan effect on eGFR remains unknown (**OC**).

Conclusion
The point is not resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Response to Question 2.2
The MAH acknowledges the question and would like to remind the Agency that after treatment discontinuation at Week 110, patients returned to standard of care with RAAS inhibition (and the specific RAAS inhibitor and dose was selected at the Investigator' s discretion individual per patient), making the interpretation of reversibility in proteinuria difficult and less accurate during the treatment discontinuation period.

Nevertheless, the MAH conducted a post-hoc analysis based on the request from the Agency. The post-hoc analysis was conducted to assess the percent change from baseline in urine protein-to-creatinine ratio (UP/C) at 4 weeks post-cessation of randomised treatment among subjects who completed the double-blind treatment period (i.e., percent change from baseline in UP/C at Week 114) and although the difference between the treatment groups is smaller, it remains in favour of Sparsentan compared to Irbesartan. The geometric LS means percent change from baseline to Week 114 (95% CI) were -5.38 (-16.46, 7.17) for the Sparsentan group and 5.54 (-7.57, 20.51) for the Irbesartan group, indicating attenuation of effect in proteinuria following discontinuation of study medication and initiation of standard of care treatment: Nevertheless, this does not rule out a persistent effect and the achievement of structural changes, as post treatment biopsies are not available in PROTECT. Moreover, Sparsentan is a non-immunosuppressive drug intended to be used as a chronic treatment and has demonstrated long-term efficacy in the double-blind period of the PROTECT trial, both on proteinuria and on eGFR.

Assessment of the MAH's response
The requested data has been submitted. The post-hoc analysis was conducted in urine protein-to-creatinine ratio (UP/C) at 4 weeks post-cessation of randomised treatment among subjects who completed the double-blind treatment period (i.e., percent change from baseline in UP/C at Week 114). The difference between the treatment groups is smaller and it is not statistically significant (p=0.239), it remains in favour of Sparsentan compared to Irbesartan. However, these data cannot prove that the effect on proteinuria persists after the end of the treatment period (**OC**).

A MS commented also that it appears that the MAH has not fully understood question 2.2 and 2.1 regarding reversibility. The MAH has not provided the requested analyses on reversibility, but instead provided data on eGFR annualized slope preservation and analyses of percent change from baseline in UP/C at Week 114. The raised question was not meant to raise doubt on preservation of beneficial

effects, but rather on understanding the reversibility of the initial eGFR effects after cessation of treatment. Therefore, we are still interested in analyses of the difference in eGFR and UP/C between week 106 (since there are less missing data at this visit as compared to week 110) and week 114.

Conclusion

The point is not resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 3

Additional data from open-label extension (OLE) period of PROTECT study regarding the long-term efficacy (proteinuria, eGFR) has not been submitted by MAH. It is unclear, does the effect on eGFR slope maintain over time?

Summary of the MAH's response

Provided within this submission in the final CSR for the double-blind treatment phase. The MAH acknowledges the Agency's comment about the long-term efficacy of Sparsentan on proteinuria and eGFR, and believes to have fulfilled the commitment of providing the final results of the double-blind period as per agreed specific obligation:

"In order to further characterise the long-term efficacy and safety of Filspari in the treatment of adults with primary immunoglobulin A nephropathy, the MAH shall submit the final results (Clinical Study Report) of the PROTECT study, a randomised, double-blind, active-controlled, multicentre, global phase 3 trial in patients with primary immunoglobulin A nephropathy."

The open-label extension (OLE) period of the study is currently ongoing, and no formal analysis is planned until the end of the study (i.e., after all patients complete up to 156 weeks). In addition, the MAH believes that providing interim OLE data as of today would not provide additional long-term efficacy data as only 39 patients reached the end of the OLE so far (i.e., 3 years). Providing data based on a shorter timepoint (i.e., 1 year) is not considered scientifically relevant to show long-term efficacy as the study is ongoing and not all the patients reached the end of the study. Moreover, all patients in the OLE are on Sparsentan treatment, but half of them were on Irbesartan during the double-blind period, and the exposure time would not allow to make a relevant conclusion on eGFR as 1 year is not considered sufficient to show a robust effect on the eGFR slope. To provide further long-term data on treatment effect of Sparsentan, the MAH commits to submit the final OLE CSR once available.

To further characterise the long-term efficacy on the double-blind period, additional analyses have been conducted on the eGFR chronic slope (first confirmatory endpoint) and eGFR total slope (second endpoint tested at the confirmatory analysis in the statistical hierarchy). The additional data are provided below and the MAH believes that the data strengthen the results found on eGFR total slope, which are supportive and aligned with the results found for the confirmatory endpoint in the European Union (i.e., eGFR chronic slope).

In the original analysis following the statistical analysis plan, only on-treatment data were used regardless of rescue medication use. Missing data were imputed under missing at random assumption for the monotone missing pattern. In the PROTECT study, there was an imbalance in intercurrent events: required rescue immunosuppression and discontinued treatment were more frequent in patients on

Irbesartan.

Pre-specified sensitivity analyses were performed using all observed data during the double-blind period showing results that were consistent with the primary analysis for both eGFR chronic and total slopes (see Table 2).

Table 2 Pre-specified Sensitivity Analyses: Summary of eGFR Chronic and Total Slopes Through Week 110 Using Observed Data During the Double-blind Period Including Premature Treatment Discontinuation (No Imputation of Missing Data) – Full Analysis Set

eGFR Endpoint	Irbesartan (N=202) LS Mean (95%CI)	Sparsentan (N=202) LS Mean (95%CI)	Difference (Sparsentan–Irbesartan) (95%CI)
eGFR chronic annualised slope[1] (ml/min/1.73 m^2 per year)	–4.2 (-4.92, -3.51)	–2.9 (-3.56, -2.19)	1.3 (0.36, 2.32) p=0.0076
eGFR total annualised slope[2] (ml/min/1.73 m^2 per year)	–4.2 (-4.91, -3.53)	–3.0 (-3.70, -2.36)	1.2 (0.23, 2.16) p=0.0157

1 Rate of change in eGFR over 104 Weeks (Week 6 to Week 110) for FAS. Estimates are calculated from a mixed random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomisation stratification factors as fixed effects, random intercept and random slope per patient. An unstructured covariance structure is used in the model.

2 Rate of change in eGFR over 110 weeks (Day 1 to Week 110) for FAS. Estimates are calculated from a mixed random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomisation stratification factors as fixed effects, random intercept and random slope per patient. An unstructured covariance structure is used in the model.

Notes: CI=Confidence interval; eGFR=Estimated glomerular filtration rate; FAS=Full analysis set; LS=Least squares.

Source: 021IGAN17001 Final DB CSR Table 14.2.2.2.8, 021IGAN17001 Final DB CSR Table 14.2.2.4.8.

An additional post-hoc analysis, not included in the initial submission, was conducted and is provided within this response. The results of this analysis for eGFR chronic slope, eGFR total slope, and change from baseline in eGFR at Week 110, using all observed data during the double-blind period are presented in Table 3. The intercurrent events and approach for handling missing data are described in Table 4. Intercurrent events, summarised in Table 5, were more frequent in the Irbesartan group.

Table 3 Additional Analysis 1 - Summary of eGFR Chronic Slope, Total Slope, and Change from Baseline at Week 110 Using Observed Data During the Double-blind Period Including After Premature Treatment Discontinuation with Any New Systemic Immunosuppressive Therapy for Renal Indication as Intercurrent Event – Full Analysis Set

eGFR Endpoint[1]	Irbesartan N=202 LS Mean (95% CI)	Sparsentan N=202 LS Mean (95% CI)	Difference (Sparsentan-Irbesartan) (95% CI)
eGFR chronic annualised slope[2] ($ml/min/1.73\ m^2$ per year)	-4.2 (-4.90, -3.47)	-2.9 (-3.55, -2.18)	1.3 (0.33, 2.31) p=0.0087
eGFR total annualised slope[3] ($ml/min/1.73\ m^2$ per year)	-4.2 (-4.89, -3.50)	-3.0 (-3.69, -2.36)	1.2 (0.21, 2.13) p=0.0168
LS mean change from baseline at Week 110[4] ($ml/min/1.73\ m^2$)	-9.9 (-11.54, -8.31)	-6.1 (-7.65, -4.54)	3.8 (1.59, 6.08) p=0.0008

1 One hundred imputed datasets were created by assuming missing at random to create monotone missing pattern for all subjects, followed by multiple imputation procedure under the assumption of missing at random for subjects without intercurrent event of premature treatment discontinuation, new use of any systemic immunosuppressive therapy for renal indication, RRT, or death; jump to reference imputation for subjects with intercurrent event of premature treatment discontinuation or new use of any systemic immunosuppressive therapy for renal indication and without RRT or death; and by drawing from observed eGFR data less than or equal to the 1st percentile for subjects with RRT or death.

2 Rate of change in eGFR over 104 weeks (Week 6 to Week 110) for FAS. Within each imputed dataset, the estimates of the annualised slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomisation stratification factors as fixed effects, random intercept and random slope per patient. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall are estimates for slopes, 95% CIs, and the p-value. An unstructured covariance structure is used in each model.

3 Rate of change in eGFR over 110 weeks (Day 1 to Week 110) for FAS. Within each imputed dataset, the estimates of the annualised slopes and slope difference are calculated using a mixed model random coefficients model with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit, randomisation stratification factors as fixed effects, random intercept and random slope per patient. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall are estimates for slopes, 95% CIs, and the p-value. An unstructured covariance structure is used in each model. Baseline (Day 1) eGFR is excluded as a response variable.

4 Within each imputed dataset, results are based on a MMRM model on the change from baseline in eGFR with treatment, baseline eGFR, analysis visit, treatment-by-analysis visit interaction, and randomisation stratification factors as fixed effects, and patient as a random effect. eGFR results through Week 110 are included in the model. An unstructured covariance structure is used in each model.

Notes: CI=Confidence interval; eGFR=Estimated glomerular filtration rate; FAS=Full analysis set; LS=Least squares; MMRM=Mixed model repeated measures; RRT=Renal replacement therapy.

Source: T1.2_IR9-RateChg110EGFRMI rtf, T3.2_IR9-ChgEGFRMI.rtf, T2.2_IR9-RateChg110EGFRMI.rtf.

Table 4 Additional Analysis 1 – Approach for Intercurrent Events and Missing Data

Intercurrent Events	Strategy	Missing Data Imputation	
		Intermittent Missing Data	Remaining Missing Data up to Week 110
Premature treatment discontinuation and rescue medication use for renal indication	Treatment policy strategy	MAR	J2R multiple imputation (MNAR)
eGFR drop to below 15 ml/min/1.73 m^2	Treatment policy strategy	MAR	MAR
RRT and death	Hypothetical strategy	MAR	Randomly drawing data less than or equal to the 1 percentile of all observed eGFR data regardless of visit week

Notes: The J2R imputation method imputes missing data assuming patients jump to behave like those in the specified reference group (including monotone missing pattern data from all Irbesartan patients and data from the Sparsentan patients who prematurely discontinued treatment or used rescue medication initiation for renal indication excluding RRT and death) following their last observed time point.
eGFR=Estimated glomerular filtration rate; J2R=Jump to reference; MAR=Missing at random; MNAR=Missing not at random; RRT=Renal replacement therapy.

Table 5 Additional Analysis 1 – Summary of Missing Data by Intercurrent Event Using Observed Data During the Double-blind Period – Full Analysis Set

		Irbesartan (N=202) n (%)	Sparsentan (N=202) n (%)
No intercurrent event			
	Week 110 observed	132 (65)	156 (77)
	Week 110 missing	12 (6)	13 (6)
Premature treatment discontinuation or rescue medication initiation without RRT and death[a]			
	Week 110 observed	23 (11)	15 (7)
	Week 110 missing	29 (14)	13 (6)
RRT and death			
	Week 110 observed	0 (0)	0 (0)
	Week 110 missing	6 (3)	5 (2)

1 Rescue medication: systemic immunosuppressive agents for renal indication. Only initiations within the double-blind period were considered.
Note: RRT=Renal replacement therapy.
Source: IR9 Table 6.2 (T6.2_IR9-PopCnt.rtf).

The analysis shown in Table 3 (inclusion of all observed data regardless of treatment discontinuation) was applied for eGFR chronic slope and the analysis of the United States confirmatory endpoint, the eGFR total slope.

The LS mean eGFR chronic slope from Week 6 to Week 110 was -2.9 ml/min/1.73 m^2/year for Sparsentan and -4.2 ml/min/1.73 m^2/year for Irbesartan, with a treatment effect of 1.3 ml/min/1.73 m^2/year (95% CI: 0.33, 2.31, p=0.0087). This analysis is supportive of the primary analysis of the eGFR chronic slope. The LS mean eGFR total slope from baseline to Week 110 was -3.0 ml/min/1.73 m^2/year for Sparsentan and -4.2 ml/min/1.73 m^2/year for Irbesartan, corresponding to a treatment effect of 1.2

ml/min/1.73 m^2/year (95% CI: 0.21, 2.13; p=0.0168). This differs from the primary analysis of the eGFR total slope, which narrowly missed statistical significance, but is consistent with a prespecified sensitivity analysis including data after treatment discontinuation (as shown in Table 2) and provides additional data supporting the long-term efficacy of Sparsentan.

Based on the clinical relevance and importance of the presented additional analysis that reflects what happens in clinical practice under the use of standard of care, the MAH considers that the addition of these analyses, including patient data after premature discontinuation and imputing data for those initiating immunosuppression for renal indication in the Summary of Product Characteristics (SmPC), is critical for prescribers.

As such, the MAH proposes some changes to Section 5.1 of the SmPC as follows

(*in italic*):

Estimated GFR

At the time of confirmatory analysis, the improvement in 2 year eGFR chronic slope (from 6 weeks onwards) was 1.1 ml/min/1.73 m^2 per year with Sparsentan compared to Irbesartan (95% CI: 0.07, 2.12; p=0.037), and the corresponding improvement in 2 year eGFR total slope (from baseline onwards) was 1.0 ml/min/1.73 m^2 per year (95% CI: 0.03, 1.94; p=0.058). The absolute change from baseline in eGFR at 2 years was -5.8 ml/min/1.73 m^2 (95% CI: -7.38, -4.24) for Sparsentan compared to -9.5 ml/min/1.73 m^2 (95% CI: - 11.17, -7.89) for Irbesartan.

In a post-hoc analysis on all observed data and imputed data after treatment discontinuation or initiation of rescue immunosuppressive therapy, the improvement in 2 year eGFR chronic slope (from 6 weeks onwards) was 1.3 ml/min/1.73 m^2 per year in favor of Sparsentan compared to Irbesartan (95% CI: 0.33,2.31); p=0.0087), and the corresponding improvement in 2 year eGFR total slope (from baseline onwards) was 1.2 ml/min/1.73 m^2 per year (95% CI: 0.21,2.13; p=0.0168). The absolute change from baseline in eGFR at 2 years was -6.1 ml/min/1.73 m^2 (95% CI: -7.65, -4.54) for Sparsentan compared to -9.9 ml/min/1.73 m^2 (95% CI: -11.54, -8.31) for Irbesartan.

Assessment of the MAH's response

The MAH submitted explanation for not providing the long-term efficacy data. The OLE period of the study is currently ongoing, and interim OLE data would not provide additional long-term efficacy data as only 39 patients reached the end of the OLE so far (i.e., 3 years). To provide further long-term data on treatment effect of Sparsentan, the MAH commits to submit the final OLE CSR once available. The explanation of the MAH is acceptable.

The long-term efficacy remains unknown. It is unclear whether the effect on eGFR slope is maintained over time.

The MAH provided additional post-hoc analysis within this response. The results of this analysis for eGFR chronic slope, eGFR total slope to Week 110, using all observed data during the double-blind period including After Premature Treatment Discontinuation with Any New Systemic Immunosuppressive Therapy for Renal Indication as Intercurrent Event are presented. This additional analysis is not related to the question, and it is therefore not assessed, and the proposed update of SmPC Section 5.1 is not agreed.

Conclusion

The point has been deferred until the end of the OLE study.

The initial specific obligation to submit the final results (Clinical Study Report) of the PROTECT study, a

randomised, double-blind, active-controlled, multicentre, global phase 3 trial in patients with primary immunoglobulin A nephropathy has been fulfilled. However, it is unclear, does the effect on eGFR slope maintain over time? The following measures necessary to address the mentioned issue: the MAH should submit the final OLE CSR.

The MAH has provided a draft letter to provide commitment to the provision of the OLE results for the PROTECT study, as follows:

In order to further characterise the long-term efficacy of Filspari in the treatment of adults with primary immunoglobulin A nephropathy, the MAH shall submit the final results (Clinical Study Report) of Phase 3 PROTECT open label extension study.

Due date: 31 October 2027.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 4

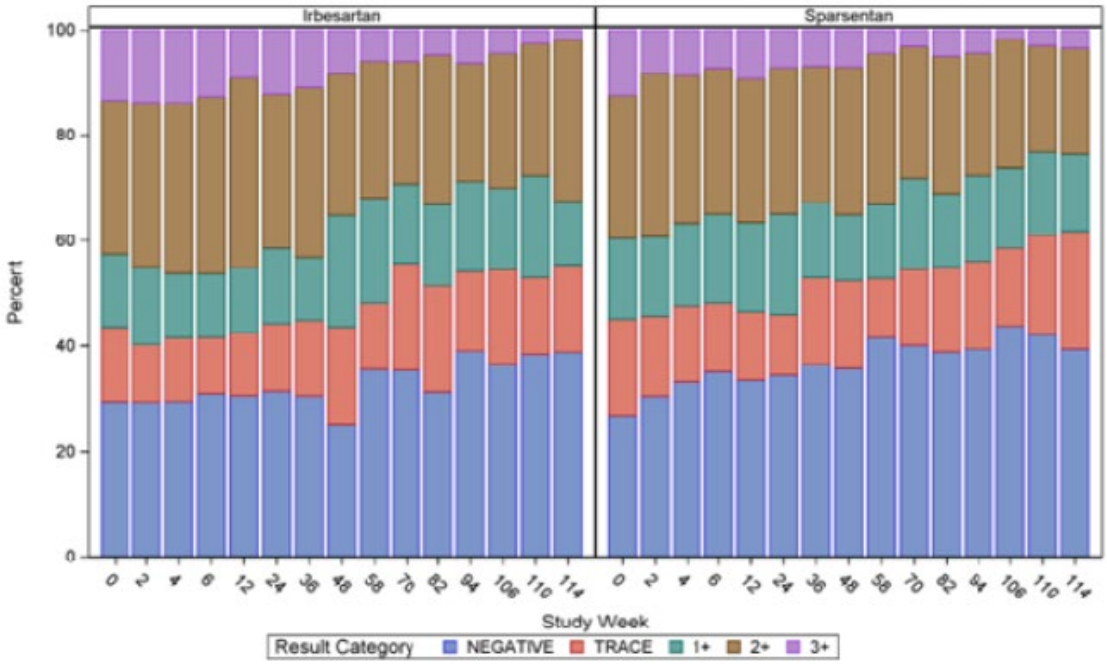
The MAH is requested to provide a detailed analysis of the changes in the proportion of subjects reporting haematuria from baseline over treatment time until week 110. The statistical analysis to investigate patients with haematuria in association with the amount of proteinuria, eGFR and other kidney composite outcomes could be beneficial to find the clinical relevance of haematuria.

Summary of the MAH's response

At baseline, the proportion of subjects with haematuria were similar in both treatment groups (54.4% of subjects in the Sparsentan group and 59.8% of subjects in the Irbesartan group). There was an observed reduction in the proportion of subjects reporting haematuria for both treatment groups across the study with 39.0% of patients experiencing haematuria in the Sparsentan group, and 47.0% in the Irbesartan group at Week 110.

This reduction is a numerical trend and should be interpreted with caution (Figure 1).

Figure 1 **Stacked Bar Chart of Percent of Subjects with Haematuria Categorical Result by Study Week - Full Analysis Set**



A post-hoc analysis assessed outcomes of proteinuria according to the presence or absence of haematuria at baseline. In the group with haematuria at baseline, a significant decrease in UP/C was observed in the Sparsentan group at all time points, with a geometric LS mean percent change from baseline to Week 110 of -8.76 (95% CI:-24.10, 9.69) in the Irbesartan group, and -43.57 (95% CI: -52.86, -32.46) in the Sparsentan group, p=0.0003, see post-hoc Table 14.2.12.1.19. Similar results were observed in patients without haematuria at baseline, with a significant decrease in the Sparsentan group at all time points (geometric LS mean percent change from baseline to Week 110 of 0.13 (95% CI: -17.11, 20.95) in the Irbesartan group, and -41.91 (95% CI: -51.28, -30.73) in the Sparsentan group, p<0.0001).

Another post-hoc subgroup analysis assessed outcomes on eGFR slope in patients with and without baseline haematuria. The eGFR chronic slope numerically favoured Sparsentan in patients with haematuria (annualised slope difference of 0.8 ml/min/1.73 m2, p=0.2785) and significantly favoured Sparsentan in patients without haematuria (annualised slope difference of 1.3 ml/min/1.73 m2, p=0.0378), see post-hoc Table 14.2.12.3.19. When a similar analysis was done for the eGFR total slope, consistent results were observed; patients with baseline haematuria had an annualised slope difference of 0.7 ml/min/1.73 m2 in favour of Sparsentan (p=0.3344), while patients without haematuria at baseline had an annualised slope difference of 1.1 ml/min/1.73 m2 (p=0.0692), also favouring Sparsentan.

A post-hoc analysis assessing change from baseline in eGFR by presence or absence of haematuria at baseline also resulted in similar conclusions, with a difference in LS mean change from baseline in eGFR of 3.3 ml/min/1.73 m2 at Week 110 (p=0.0676) in favour of Sparsentan in patients with haematuria at baseline, and in a difference in LS mean change from baseline in eGFR of 4.0 ml/min/1.73 m2 at Week 110 (p=0.0041) in favour of Sparsentan in patients without haematuria at baseline.

All these analyses demonstrate the favourable treatment effect of Sparsentan, regardless of the presence or absence of haematuria.

Assessment of the MAH's response

The MAH submitted analysis assessing change from baseline in eGFR and UP/C by presence or absence of haematuria at baseline. All these analyses demonstrate the favourable treatment effect of Sparsentan, regardless of the presence or absence of haematuria. The positive effect of sparsentan on eGFR slope was statistically significant for patients without haematuria and it was statistically insignificant for patients with haematuria. However, this difference cannot be recognized as substantively changing aspect. It can be agreed that baseline haematuria is not a prognostic factor for successful treatment with sparsentan.

The statistical analysis to investigate patients with haematuria changes over the treatment with sparsentan in association with the amount of proteinuria and eGFR changes have not been provided. The mentioned analysis is not expected to reveal any new findings.

The point is partially resolved. This issue is not pursued further.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Clinical safety

Question 5

The number of subjects with any hypotension-associated TEAEs in both sparsentan and irbesartan groups provided in SCS (data cutoff 07 Sep 2023) is lower than in the interim report (data cutoff 01 Feb 2022). The MAH is asked to clarify this.

Summary of the MAH's response

The MAH acknowledges the Agency´s comment about the difference in the number of subjects with any hypotension-associated treatment-emergent adverse events (TEAEs) in both Sparsentan and Irbesartan groups provided in the Summary of Clinical Safety (data cutoff 7 September 2023) compared to the interim report (data cutoff 1 February 2022) and provides clarification further below on the different preferred terms (PTs) included in the search strategies for hypotension-associated TEAEs and symptomatic hypotension-associated TEAEs presented in the respective documents.

The data, presented in Table 6 (PROTECT study with a data cutoff 7 September 2023) referenced in the Summary of Clinical Safety, shows hypotension-associated TEAEs reported in 16% and 6% of Sparsentan and Irbesartan-treated subjects, respectively. The hypotension-associated TEAEs were determined by a medical monitor and the table includes PTs of hypotension, orthostatic hypotension and blood pressure systolic decreased.

Table 6 Hypotension-Associated TEAE Events During the Double-blind Period by Preferred Term (SAS) (Data Cutoff 7 September 2023)

Preferred Term	Sparsentan (N=202) n (%) (Event)	Irbesartan (N=202) n (%) (Event)	Total (N=404) n (%) (Event)
Subjects with any hypotension-associated TEAEs[1]	33 (16) (46)	13 (6) (15)	46 (11) (61)
Hypotension	26 (13) (35)	8 (4) (10)	34 (8) (45)
Orthostatic hypotension	8 (4) (10)	5 (2) (5)	13 (3) (15)
Blood pressure systolic decreased	1 (<1) (1)	0 (0) (0)	1 (<1) (1)

1 TEAE is defined as any adverse event that newly appears, increases in frequency, or worsens in severity following initiation of study medication.

Notes: Percentages are based on all subjects in the SAS within each group.
Adverse events are coded with MedDRA Version 23.0.
If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.
Hypotension-associated TEAEs were determined by the medical monitor based on a review of event terms related to hypotension.
MedDRA=Medical Dictionary for Regulatory Activities; n=Number of subjects in the sample; N=Number of subjects; SAS=Safety analysis set; TEAE=Treatment-emergent adverse event.

Source: 021IGAN17001 Final DB CSR Table 14.3.1.21.1.

In contrast, Table 7 below (PROTECT study with a data cutoff 1 February 2022) shows that symptomatic hypotension-associated TEAEs were reported in 26% and 11% of Sparsentan and Irbesartan-treated subjects, respectively; however, PTs presented in the table include hypotension, dizziness, orthostatic hypotension, dizziness postural, syncope, and blood pressure systolic decreased.

Table 7 Incidence of Symptomatic Hypotension-associated TEAE (Primary Analysis Set) (Data Cutoff 1 February 2022)

Preferred Term	Irbesartan (N=202) n (%) (Event)	Sparsentan (N=202) n (%) (Event)	Total (N=404) n (%) (Event)
Any symptomatic hypotension-associated TEAE	22 (11) (37)	52 (26) (79)	74 (18) (116)
Mild	21 (10) (31)	40 (20) (58)	61 (15) (89)
Moderate	4 (2) (6)	18 (9) (20)	22 (5) (26)
Severe	0 (0) (0)	1 (<1) (1)	1 (<1) (1)
Drug-related	14 (7) (20)	35 (17) (52)	49 (12) (72)
Serious	1 (<1) (1)	3 (1) (3)	4 (1) (4)
Leading to dose change/interruption	6 (3) (6)	13 (6) (19)	19 (5) (25)
Leading to drug discontinuation	0 (0) (0)	3 (1) (3)	3 (1) (3)
Resulting in death	0 (0) (0)	0 (0) (0)	0 (0) (0)

Notes: Preferred terms include: Blood pressure systolic decreased, dizziness, dizziness postural, hypotension, orthostatic hypotension, syncope.
n=Number of subjects in the sample; N=Number of subjects; TEAE=Treatment-emergent adverse event.

Source: Table 10.1 (data cutoff 1 February 2022)

In summary, the difference observed between the number of subjects with any hypotension-associated TEAEs in Sparsentan and Irbesartan groups provided in the Summary of Clinical Safety (data cutoff 7 September 2023) and in the interim report (data cutoff 1 February 2022) corresponds to the different PTs included in the categories of hypotension-associated TEAEs and symptomatic hypotension-associated TEAEs. Namely, the symptomatic hypotension associated TEAEs comprise an extended list of PTs,

compared to the hypotension-associated TEAEs, including the PTs dizziness, dizziness postural and syncope.

Assessment of the MAH's response

The number of subjects with any hypotension-associated TEAEs in both sparsentan and irbesartan groups provided in SCS (data cutoff 07 Sep 2023) is lower than in the interim report (data cutoff 01 Feb 2022) due to the different PTs included in the categories of hypotension-associated TEAEs and symptomatic hypotension-associated TEAEs. In the interim report, more extended list of PTs were included in the symptomatic hypotension-associated TEAEs. It is acceptable.

Conclusion

Issue is resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 6

The MAH is asked to review the comments in SmPC section 4.8 and provide responses to the issues raised.

Summary of the MAH's response

For the response to the percentage on acute kidney injury and the number of patients exposed to Sparsentan in chronic kidney disease population including immunoglobulin A nephropathy and focal segmental glomerular sclerosis, please refer to response provided in Section 4.8 of the SmPC (annotated version).

Regarding hypotension update in Section 4.8 of the SmPC, the data was updated to reflect the 2-year PROTECT data based on language added during the initial procedure by the Agency, which was not part of the initial subgroup analysis. As shown in post-hoc Table 3.1.1, a subgroup by age analysis based on the 2-year PROTECT data showed that hypotension was reported in 20 (11%) subjects <65 years of age receiving Sparsentan and in 6 (40%) subjects between 65 to 74 years of age (Source: Table 3.1.1 Subgroup Analysis: Treatment-Emergent Adverse Events During the Double-Blind Period by Age Group (data cutoff 7 September 2023)).

Assessment of the MAH's response

The MAH provided the source of amended numbers in section 4.8 of SmPC. It is acceptable.

Conclusion

Issue is resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

Question X

None

Summary of the MAH's response

N/A

Assessment of the MAH's response

N/A

Conclusion

The conclusion on proposed changes to specific obligations of MA in the RMP is pending the final assessment of the CHMP on the fulfilment of the PAES regarding long-term efficacy data.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

13. Second request for supplementary information

13.1. Major objections

None

13.2. Other concerns

1. The reversibility of the initial effect of sparsentan (~deterioration between week 0 and 8) after cessation has not fully been clarified. Although patients will have returned to standard of care RAASi therapy after cessation of the study treatment, the difference in eGFR and UP/C between week 106 and week 114 can provide information about the reversibility of the initial effect of sparsentan after cessation. The MAH is requested to analyze the difference in eGFR and UP/C between week 106 (since there are less missing data here as compared to week 110) and week 114, for both the sparsentan group and irbesartan group, and discuss the results. In addition, the number of subjects evaluated at week 110 for eGFR and UP/C was low as compared with number of subjects at weeks 106 and 114, and MAH should clarify reasons and impact on point-estimates for eGFR and UP/C.

14. Assessment of the responses to the second request for supplementary information

14.1. Major objections

None

14.2. Other concerns

Clinical aspects

Question 1

The reversibility of the initial effect of sparsentan (~deterioration between week 0 and 8) after cessation has not fully been clarified. Although patients will have returned to standard of care RAASi therapy after cessation of the study treatment, the difference in eGFR and UP/C between week 106 and week 114 can provide information about the reversibility of the initial effect of sparsentan after cessation. The MAH is requested to analyze the difference in eGFR and UP/C between week 106 (since there are less missing data here as compared to week 110) and week 114, for both the sparsentan group and irbesartan group, and discuss the results. In addition, the number of subjects evaluated at week 110 for eGFR and UP/C was low as compared with number of subjects at weeks 106 and 114, and MAH should clarify reasons and impact on point-estimates for eGFR and UP/C.

Summary of the MAH's response

As requested by the Committee for Medicinal Products for Human Use, the Applicant analysed the difference in estimated glomerular filtration rate (eGFR) and urine protein-to-creatinine ratio (UP/C) between week 106 and week 114 for both treatment groups on subjects with data available at both week 106 on-treatment and week 114 (4 weeks post treatment cessation).

As it has been shown in the final PROTECT Clinical Study Report (CSR), the initial acute effect of randomized therapy in eGFR reduction at Week 6 was comparable between the sparsentan and irbesartan treatment group (021IGAN17001 Final DB CSR, Table 14.2.2.8.1). At Week 6, the least squares (LS) mean change from baseline (95%, confidence interval (CI)) was –1.2 (-2.17, -0.27) mL/min/1.73 m2 for the sparsentan group and -1.6 (-2.56, -0.65) mL/min/1.72 m2 for the irbesartan group. Based on this mild magnitude of the initial acute effect, the Applicant did not anticipate a reversibility on eGFR.

Looking at the change in eGFR from week 106 on-treatment to week 114, eGFR remained stable in both treatment groups post-cessation of randomized treatment with a LS mean change from week 106 to 114 (95% CI) of -0.1 (-1.16, 0.86) mL/min/1.73 m2 for the sparsentan group and -0.2 (-1.36, 0.88) for the irbesartan group. The post-hoc analysis confirms accrual of the benefit of sparsentan treatment on eGFR over time that remained after treatment discontinuation. Similar results are observed on the change in eGFR from week 106 on-study to week 114.

Table 1 Change in eGFR from Week 106 to Week 114 of Randomized Treatment - Full Analysis Set (Subjects who had Week 106 On-Treatment eGFR data and Week 114 eGFR data)

eGFR (mL/min/1.73m^2)	Irbesartan (N=131)	Sparsentan (N=161)
Week 106		
n	131	161
Mean (SD)	49.9 (24.97)	51.5 (24.72)
SE	2.18	1.95
Median	46.0	45.0
Q1, Q3	30.0, 62.0	33.0, 69.0
Min, Max	10, 120	11, 126
Week 114		
n	131	161
Mean (SD)	49.7 (26.08)	51.4 (25.18)
SE	2.28	1.98
Median	44.0	45.0
Q1, Q3	30.0, 61.0	32.0, 68.0
Min, Max	6, 121	8, 127
Change from Week 106 to Week 114		
n	131	161
Mean (SD)	-0.2 (5.72)	-0.2 (7.02)
SE	0.50	0.55
Median	-1.0	-1.0
Q1, Q3	-3.0, 2.0	-4.0, 2.0
Min, Max	-15, 29	-16, 39
ANCOVA Results [a]		
LS Mean Change from Week 106	-0.2	-0.1
SE	0.57	0.51
95% CI for LS Mean Change	(-1.36, 0.88)	(-1.16, 0.86)

[a] Results are based on an ANCOVA model on the change in eGFR from Week 106 to Week 114, Week 106 eGFR, and randomization stratification factors as fixed effects.
Notes: The estimated glomerular filtration rate (eGFR) is determined using the CKD-EPI equation.
ANCOVA=Analysis of covariance; eGFR=Estimated glomerular filtration rate; LS=Least squares; CKD-EPI=Chronic kidney disease epidemiology.
Source: Post-hoc Table 14.2.2.7.10.2

The difference in UP/C was also assessed comparing on treatment data at week 106 and data at week 114. The Applicant had already provided information (Response to Request for Supplementary Information submitted in November 2024) showing that there was an attenuation of the effect in proteinuria following discontinuation of study medication at week 110 and initiation of standard of care treatment.

The new post-hoc analysis shows an increase in proteinuria in both treatment groups after randomized treatment discontinuation (between week 106 on-treatment data and week 114 data) with a geometric LS mean percent change from week 106 to 114 (95% CI) of 64.65 (51.68, 78.73) % for the sparsentan group and 34.30 (22.46, 47.28) % for the irbesartan group . Similar results are observed on the change in UP/C from week 106 on-study to week 114 (Post-hoc analysis, Table 14.2.3.1.5.2).

Table 2 **Percent Change in UP/C from Week 106 to Week 114 of Randomized Treatment - Full Analysis Set (Subjects who had Week 106 On-Treatment UP/C data and Week 114 UP/C data)**

UP/C (g/g)	Irbesartan (N=129)	Sparsentan (N=162)
Week 106		
n	129	162
Mean (SD)	1.35 (1.011)	0.99 (0.967)
SE	0.089	0.076
Median	1.18	0.72
Q1, Q3	0.62, 1.86	0.31, 1.40
Min, Max	0.1, 5.2	0.1, 6.6
Geometric Mean	0.98	0.64
Geometric CV (%)	109.7	128.7
Week 114		
n	129	162
Mean (SD)	1.68 (1.339)	1.56 (1.182)
SE	0.118	0.093
Median	1.37	1.29
Q1, Q3	0.73, 2.28	0.67, 2.31
Min, Max	0.1, 8.7	0.1, 6.2
Geometric Mean	1.23	1.11
Geometric CV (%)	106.5	114.6
Percent Change from Week 106 to Week 114		
n	129	162
Mean (SD)	44.87 (90.131)	114.46 (183.838)
SE	7.936	14.444
Median	23.95	63.81
Q1, Q3	-5.49, 71.01	13.52, 152.38
Min, Max	-70.3, 632.2	-74.2, 1578.3
Geometric LS Mean Percent Change from Week 106	34.30	64.65
95% CI for Geometric LS Mean Percent Change	(22.46, 47.28)	(51.68, 78.73)

Notes: Results are based on an ANCOVA model on the natural log(change in UP/C from Week 106 to Week 114), Week 106 log (UP/C), and randomization stratification factors as fixed effects. Estimated LS Mean and 95% CIs are converted to percentages as follows: [exp(least squares mean change in natural log(UP/C)) - 1] x 100.
LS=Least squares; UP/C=Urine protein/creatinine ratio.
Source: Post-hoc Table 14.2.3.1.4.2

This attenuation in the antiproteinuric effect at week 114 does not rule out a persistent effect and the achievement of structural changes, as post treatment biopsies are not available in the PROTECT trial.

Moreover, sparsentan is a non-immunosuppressive drug intended to be used as a chronic treatment that can be continued until advanced stages of chronic kidney disease and has demonstrated long-term efficacy in the double-blind period of the PROTECT trial, both on proteinuria and on eGFR.

Finally, the Applicant would like to provide further clarification on the lower number of subjects evaluated at week 110 for eGFR and UP/C compared to weeks 106 and 114. The main reasons to have missing eGFR or UP/C data at the analysis week 110 visit for subjects who completed double-blind treatment were missed samples collection, or sample collection dates outside of the pre-specified analysis window of 4 weeks (between days 758 – 785 for the analysis week 110 visit) as shown in Table 3 and Table 4. For the purposes of the efficacy analyses (using on-treatment data), an assessment was considered "on treatment" if it occurred after the first dose of randomized treatment and no more than 3 days after the date of last dose of randomized treatment for the subject (021IGAN17001 Statistical analysis plan, version 3.0, 12 July 2021) which narrowed the treatment window for the analysis week 110. Additionally, treatment completion was expected by day 785 (upper bound of the analysis week 110), subjects who remained on treatment longer had their on-treatment results mapped to week 114, which was not anticipated. Both rules may have prevented subjects from having their week 110 visits on time.

Table 3 Reason for missing on-treatment eGFR at Week 110 - Full Analysis Set (Subjects who completed treatment during Double-Blind period)

	Irbesartan (N=154)	Sparsentan (N=174)	Overall (N=328)
Patients with missing eGFR on-treatment data at Analysis Week 110	16 (10.4)	15 (8.6)	31 (9.5)
Patients with eGFR on-treatment data at Analysis Week 110	138 (89.6)	159 (91.4)	297 (90.5)
Patients with treatment duration < 758 days*	10 (6.5)	5 (2.9)	15 (4.6)
Patients with eGFR on-treatment Analysis Week 110 data**	2 (1.3)	1 (0.6)	3 (0.9)
Patients with missing eGFR on-treatment Analysis Week 110	8 (5.2)	4 (2.3)	12 (3.7)
Patients with eGFR data outside of visit window*	8 (5.2)	4 (2.3)	12 (3.7)
Patients with missing eGFR data collection	0	0	0
Patients with treatment duration >= 758 days	144 (93.5)	169 (97.1)	313 (95.4)
Patients with eGFR on-treatment Analysis Week 110 data**	136 (88.3)	158 (90.8)	294 (89.6)
Patients with missing eGFR on-treatment Analysis Week 110	8 (5.2)	11 (6.3)	19 (5.8)
Patients with eGFR data outside of visit window*	5 (3.2)	8 (4.6)	13 (4.0)
Patients with missing eGFR data collection	3 (1.9)	3 (1.7)	6 (1.8)

* Day 758 is the lower limit of Week 110 analysis window (758-785 days).
** As per SAP, on-treatment definition includes data collected up to date of last dose + 3 days.
Notes: eGFR=Estimated glomerular filtration rate; SAP=Statistical analysis plan.

Table 4 Reason for missing on-treatment UP/C at Week 110 - Full Analysis Set (Subjects who completed treatment during Double-Blind period)

	Irbesartan (N=154)	Sparsentan (N=174)	Overall (N=328)
Patients with missing UP/C on-treatment data at Analysis Week 110	21 (13.6)	18 (10.3)	39 (11.9)
Patients with UP/C on-treatment data at Analysis Week 110	133 (86.4)	156 (89.7)	289 (88.1)
Patients with treatment duration < 758 days*	10 (6.5)	5 (2.9)	15 (4.6)
Patients with UP/C on-treatment Analysis Week 110 data**	2 (1.3)	1 (0.6)	3 (0.9)
Patients with missing UP/C on-treatment Analysis Week 110	8 (5.2)	4 (2.3)	12 (3.7)
Patients with UP/C data outside of visit window*	8 (5.2)	3 (1.7)	11 (3.4)
Patients with missing UP/C data collection	0	1 (0.6)	1 (0.3)
Patients with treatment duration >= 758 days	144 (93.5)	169 (97.1)	313 (95.4)
Patients with UP/C on-treatment Analysis Week 110 data**	131 (85.1)	155 (89.1)	286 (87.2)
Patients with missing UP/C on-treatment Analysis Week 110	13 (8.4)	14 (8.0)	27 (8.2)
Patients with UP/C data outside of visit window*	7 (4.5)	8 (4.6)	15 (4.6)
Patients with missing UP/C data collection	6 (3.9)	6 (3.4)	12 (3.7)

* Day 758 is the lower limit of week 110 analysis window (758-785 days).
** As per SAP, on-treatment definition includes data collected up to date of last dose + 3 days.
Notes: SAP=Statistical analysis plan; UP/C=Urine protein/creatinine ratio.
Source: Post-hoc Table 14.1.0.2

Assessment of the MAH's response

The MAH submitted analysis assessing change in eGFR and UP/C between week 106 and week 114 for both treatment groups on subjects with data available at both week 106 on-treatment and week 114 (4 weeks post treatment cessation).

eGFR remained stable in both treatment groups post cessation of randomized treatment with a LS mean change from week 106 to 114 of -0.1 mL/min/1.73 m^2 for the sparsentan group and -0.2 for the irbesartan group. The initial decline in eGFR following the initiation of sparsentan remains not fully understood, since no increase of eGFR following discontinuation and thus no reversibility is established, that would be in support of a haemodynamical mechanism. However, similar absence of increase of eGFR is seen following discontinuation of irbesartan, which may be related to the duration of the

interval between initiation and discontinuation of irbesartan and sparsentan.

In addition, an increase in proteinuria and UP/C in both treatment groups after randomized treatment discontinuation (between week 106 on-treatment data and week 114 data) has been observed: in UP/C a geometric LS mean percent change of 64.65 % for the sparsentan group and 34.30 % for the irbesartan group. These findings show that the benefit of sparsentan treatment on UP/C after discontinuation is reversible. A pronounced effect of discontinuation of sparsentan on proteinuria may be a signal of haemodynamical or functional changes, as opposed to structural changes.

The MAH has also provided clarification on the lower number of subjects evaluated at week 110 for eGFR and UP/C compared to weeks 106 and 114. The main reasons to have missing eGFR or UP/C data at the analysis week 110 visit for subjects who completed double-blind treatment were missed samples collection, or sample collection dates outside of the pre-specified analysis window of 4 weeks (between days 758 – 785 for the analysis week 110 visit).

Conclusion

The requested data has been provided. The point is resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

15. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 27 February 2025.