22 February 2024
EMA/106429/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Filspari

International non-proprietary name: sparsentan

Procedure No. EMEA/H/C/005783/0000

Note

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

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List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
DBP	diastolic blood pressure
DEARA	dual endothelin angiotensin receptor antagonist
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
ET-1	endothelin-1
ETAR	endothelin type A receptor
ETBR	endothelin type B receptor
FAS	full analysis set
FDA	Food and Drug Administration
FSGS	focal segmental glomerulosclerosis
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgAN	immunoglobulin A nephropathy
IRT	interactive randomization technology
KDIGO	Kidney Disease Improving Global Outcomes
LS	least squares
MAA	Marketing Authorisation Application
MMRM	mixed model repeated measures
OLE	open-label extension
PAS	primary analysis set
PI	principal investigator
PK	pharmacokinetic
PPPA	Per protocol at Primary Analysis
RAAS	Renin-angiotensin-aldosterone system
RCT	randomized control study
SAE	serious adverse event
SBP	systolic blood pressure
UA/C	urine albumin/creatinine ratio
UP/C	urine protein/creatinine ratio

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vifor France submitted on 20 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Filspari, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 October 2020.

Sparsentan was designated as an orphan medicinal product EU/3/20/2345 on 19 October 2020 in the following condition: Treatment of primary IgA nephropathy.

The applicant applied for the following indication:

Filspari is indicated in adults for the treatment of primary immunoglobulin A nephropathy (IgAN).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0024/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0024/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active substance status

The applicant requested the active substance sparsentan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance/Scientific advice

Date	Reference
11/04/2018	EMEA/H/SA/3469/2/2018/II
15/01/2020	EMEA/H/SA/3469/3/2019/PED/III
15/10/2020	EMEA/H/SA/3469/4/2020/PA/I; CMC

The applicant received Scientific Advice as mentioned above for the development of Filspari for treatment of primary immunoglobulin A nephropathy (IgAN). The Scientific Advice pertained to the following quality, pre-clinical and clinical aspects:

- Designated starting materials for the synthesis of the drug substance (DS); DS and drug product (DP) control specifications and methods in support the planned MAA. Dissolution method to control the quality of the commercial DP. Agreement on bioequivalence between the 200 mg tablets to be commercialised and the over-encapsulated 200 mg tablets used in the blinded phase of the clinical study based on the results of an in vitro dissolution comparison study. Sufficiency of the stability package for the DP
- Non-clinical evidence to support 2 years of age as a safe and appropriate lower age limit for paediatric development
- Phase 3 clinical development programme: number of confirmatory studies, study population, primary and secondary efficacy endpoints, sample size, statistical analysis plan
- Acceptability of the proposed paediatric development (clinical study design and extrapolation concept):
    - renal conditions for inclusion
    - age range
    - single arm design
    - need for biopsy
    - line of treatment
    - PK investigations, PopPK and PBPK modelling

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Vilma Petrikaite Co-Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	20 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 November 2022

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 November 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 November 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	01 December 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	17 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	25 September 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	06 October 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	11 October 2023
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	07 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 November 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	07 December 2023
The CHMP agreed on a 3rd list of outstanding issues in writing to be sent to the applicant on	14 December 2023

The applicant submitted the responses to the 3rd CHMP List of Outstanding Issues on	22 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 February 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	15 February 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to FILSPARI on	22 February 2024
The CHMP adopted a report on similarity on (see Appendix on similarity)	22 February 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	22 February 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Immunoglobulin A Nephropathy (IgAN), categorised as a rare disease affecting the kidneys, is a serious, progressive, and life-limiting disease with a poor prognosis and high unmet medical need in Europe and worldwide. IgAN is a form of glomerulonephritis (GN) diagnosed from a kidney biopsy and characterised by the findings of immune deposits, predominantly containing polymeric immunoglobulin A, in the glomerular mesangium of the kidney.

2.1.2. Epidemiology

Between 40% and 50% of patients present one or more recurrent episodes of visible haematuria, usually following an upper respiratory tract infection. Less than 10% of patients present nephrotic syndrome or acute, rapidly progressing GN, and in rare instances, may present malignant hypertension. The remainder of patients (30% to 40%) present persistent proteinuria that is accompanied by microscopic haematuria, which can be detected during a routine examination. This group is the target patient population for treatment with sparsentan and is described in detail by the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline on Glomerular Diseases (KDIGO 2021).

In IgAN, up to 40% of patients progress to end-stage kidney disease (ESKD) within 10 to 20 years after diagnosis. It can occur at any age, but clinical onset is common during the third decade of life. Thus, most patients are diagnosed in their 20s or 30s, and face the prospect of dialysis or kidney transplantation in the prime of their lives. A retrospective analysis of IgAN subjects across 4 countries on 3 continents (Europe, North America, and Australia) assessing long-term outcome found the overall 10-, 15-, and 20-year actuarial renal survival rates were 78%, 70%, and 55%, respectively. Following kidney transplantation, the recurrence of IgAN is variable, with an incidence of around 10% to 30% in studies done with for-cause biopsies, and 25% to 35% in studies based on protocol biopsies. The estimated 10-year incidence of graft loss due to IgAN recurrence is uncertain. Data from European Registry analysis suggest similar graft survival in the first 10 years after transplant for IgAN in comparison with diseases in which the native kidney primary disease does not recur, while the risk of graft loss increases after this period for patients with IgAN. In addition, survival in patients who receive a kidney transplant is lower compared to the general population, and in men and women 50-54 years of age at the time of transplant, their life span is reduced by 7.1 and 9 years, respectively.

2.1.3. Aetiology and pathogenesis

IgAN is a form of GN diagnosed from a kidney biopsy and characterised by the finding of immune deposits, predominantly containing polymeric immunoglobulin A, which cause a cascade of events that include the proliferation of the mesangial cells, synthesis of extracellular matrix, and excess production of inflammatory cytokines, resulting in damage to the glomerular filtration barrier, proteinuria, haematuria, and decreased glomerular filtration rate. Persistent proteinuria, which causes tubular cell injury, tubulointerstitial inflammation, fibrosis, and scarring, is the strongest predictor of future kidney failure for patients with IgAN.

Focal Segmental Glomerulosclerosis (FSGS), categorised as a rare disease affecting the kidneys, is a serious, progressive, and life-limiting disease with a poor prognosis and high unmet medical need in Europe and throughout the world. It is a histological lesion characterised by segmental accumulation of the glomerular extracellular matrix, resulting in glomerular scarring and capillary obliteration. The applicant is investigating sparsentan as a potential treatment for FSGS and hence, in this submission, clinical pharmacology and safety data from patients with FSGS treated with sparsentan are provided to contribute to the overall understanding of the pharmacokinetic and safety profiles of the product.

2.1.4. Clinical presentation, diagnosis

IgAN can be classified as primary (idiopathic) or secondary to other diseases such as IgA vasculitis, cirrhosis, autoimmune diseases to chronic infections, and neoplasms. There are no specific histologic features in the renal biopsy that differentiates primary from secondary IgAN. Patients with secondary IgAN usually present with hypertension, haematuria with proteinuria, and chronic, slowly progressive renal injury. Mesangial hypercellularity and expansion of the matrix is also observed in secondary IgAN.

2.1.5. Management

There are limited approved treatments for IgAN in the EU. The current treatment strategy is aimed at preventing or delaying ESKD. The main clinical predictor of disease progression in patients with IgAN is proteinuria. Standard-of-care treatment for IgAN patients consists of renin-angiotensin-aldosterone system (RAAS) inhibitors (angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers [ARBs]) to reduce proteinuria and manage blood pressure, along with supportive interventions such as dietary and lifestyle modifications (KDIGO 2021). Clinical trials have shown that ACEIs/ARBs successfully reduce proteinuria and blood pressure and slow the estimated glomerular filtration rate (eGFR) decline.

However, despite optimised RAAS blockade therapy and blood pressure control, persistent proteinuria remains in many patients, concurrent with renal function loss and progression to ESKD. In a reported retrospective study, the majority (>70%) of whom were receiving RAAS inhibitors, the 5-, 10-, 15-, and 20-year renal survival rates were 94.1%, 82.1%, 73.1%, and 60.3%, respectively. In the pan-European Validation study of the Oxford Classification of IgAN cohort, the 10-year rate of ESKD (defined as a 50% decrease in eGFR or <15 mL/min/1.73 m^2) was 74%.

Treatment with glucocorticoids may be considered for patients with persistent proteinuria >1 g/day despite maximised ACEI/ARB treatment who are at risk for progression to ESKD. However, the indication for steroid treatment must be carefully considered in individual patients due to the well-described, serious side effects of systemic corticosteroid treatment. The available evidence on the efficacy of immunosuppressants in IgAN is limited and based on a small number of clinical studies that did not utilise the current standard of care. The STOP-IgAN study showed little benefit of immunosuppressive agents over supportive therapy, where patients received corticosteroids or cyclophosphamide and corticosteroids or continued supportive management for 3 years. The randomised, controlled TESTING trial of the systemic corticosteroid methylprednisolone for the treatment of IgAN demonstrated a benefit of treatment *vs* placebo. However, it was noted that the reduction in proteinuria was no longer apparent 36 months after randomisation and *post hoc* analyses suggest that the benefit on other outcomes may diminish over time.

For the minority of IgAN patients who experience nephrotic syndrome, ciclosporin may be a treatment option, especially for patients with steroid-resistant or steroid-dependent nephrotic syndrome.

However, calcineurin inhibitors, such as ciclosporin, are not recommended for the entire treatment of IgAN because there is no documented evidence of efficacy (KDIGO 2021).

Budesonide (Kinpeygo) is approved in the EU for the treatment of primary IgAN in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g. Nevertheless, considering the progressive nature of IgAN and the comorbidities associated with complications of the disease or with the use of steroids, a high unmet medical need remains for patients with persistent proteinuria >1 g/day, as claimed by the applicant. This is the population with the highest risk for progression to ESKD, requiring dialysis or a kidney transplant, which is associated with a reduced quality of life and a shorter survival.

2.2. About the product

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a conditional marketing authorisation (CMA) in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

The applicant is seeking CMA and subsequent full marketing authorisation of sparsentan for the treatment of IgAN based on:

  - Positive results from the primary efficacy endpoint analysis of change from baseline in urine protein-to-creatinine ratio (UP/C) at Week 36 in the Phase 3 PROTECT study, comparing sparsentan to irbesartan, based on the data cutoff date of 01 Aug 2021;
  - Preliminary eGFR data showing a consistency in total and chronic eGFR slope, which are indicative of slower rate of decline in eGFR in sparsentan-treated subjects relative to irbesartan-treated subjects. The safety profile of sparsentan is manageable with standard therapies, if needed.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant claimed that the ongoing PROTECT study is fully recruited and will complete with confirmatory results available in 2023. Based on these timelines, the applicant assumed to be positioned to submit the confirmatory data in 2024 to enable the transition of the sparsentan CMA (if granted) to a full marketing authorisation. As claimed, access to sparsentan through CMA, rather than delay until full data are available from the PROTECT, will provide a new treatment option for primary IgAN, a life-threatening orphan condition with high unmet medical need, but with low inherent risk from the incomplete dataset.

- Unmet medical need will be addressed.

At the time of this submission, budesonide (Kinpeygo) had received a positive CHMP opinion for the treatment of primary IgAN in adults at risk of rapid disease progression with a UP/C ≥1.5 g/g. However, as claimed by the applicant, the indication for steroid treatment must be carefully considered in individual patients due to well-described, serious side effects of systemic corticosteroid treatment. The available evidence on the efficacy of immunosuppressants in IgAN is limited and based on a small number of clinical studies that did not utilise the current standard of care.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The applicant states that results from the sparsentan clinical studies demonstrate that it can provide a

significant improvement in the treatment of IgAN and that immediate availability to patients through CMA outweighs the uncertainty of pending confirmatory data from the PROTECT study. The totality of data from the sparsentan studies also should be considered in the context of the paucity of approved medicinal products for treatment of IgAN, the improved response with a novel mechanism of action, and the significant side effects with the use of immunosuppressants. As claimed, the timely availability of sparsentan to patients with primary IgAN through conditional approval outweighs the uncertainty of pending confirmatory clinical data. The uncertainties in the 2-year eGFR efficacy data are considered small and of low risk given the predictive nature of proteinuria reduction on clinical outcome and the supportive trend seen with 1-year eGFR data. Given the size and duration of exposure in the existing safety database, the uncertainties in safety data are not considered major. The AE profile to date is expected and in line with the pharmacological activity of sparsentan and with other drug products with similar pharmacological properties that are approved, with well-established safety profiles for long-term treatment, as claimed by the applicant.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a film-coated tablet containing 200 mg or 400 mg of sparsentan as active substance.

Other ingredients are:

- Tablet core: silicified microcrystalline cellulose (microcrystalline cellulose and colloidal anhydrous silica); lactose; sodium starch glycolate; colloidal anhydrous silica; magnesium stearate.
- Film coating: polyvinyl alcohol; macrogol; talc; titanium dioxide (E171).

The product is available in high-density polyethylene (HDPE) bottle with child-resistant polypropylene cap as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of Sparsentan is 2-[4-[(2-butyl-4-oxo-1,3-diazaspiro [4.4]non-1-en-3-yl)methyl]-2-(ethoxymethyl)phenyl]-N-(4,5-dimethyl-1,2-oxazol-3-yl)benzenesulfonamide corresponding to the molecular formula $C_{32}H_{40}N_4O_5S$. It has a relative molecular mass of 592.76 g/mol and the following structure:

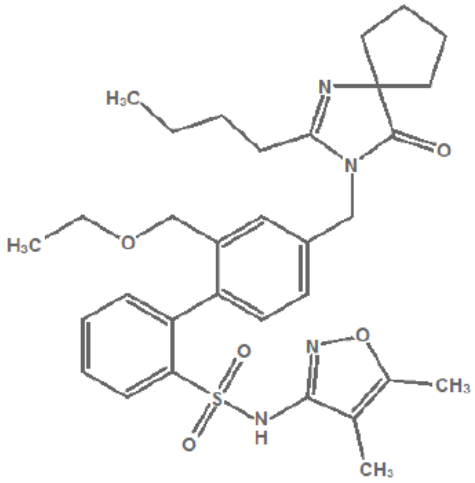


Figure 1. Active substance structure

The chemical structure of sparsentan was elucidated by a combination of structural elucidation techniques: proton NMR, ^{13}C-NMR, MS, FTIR spectroscopy, single crystal X-ray crystallography, UV-vis, Polymorph screen (XRPD, NMR spectroscopy). The solid-state properties of the active substance were measured by elemental analysis, thermal analysis by DCS, aqueous solubility in biorelevant media measured by HPLC, pKa determination, LogP determination.

Sparsentan is a white to off-white powder. The free base form is a crystalline, non-solvated and non-hygroscopic solid. Sparsentan is practically insoluble in water at 37°C ± 2°C, pH 7.0; and slightly soluble in sodium bicarbonate 4% w/v (6 mg/mL) and in 0.1N HCl, pH 1.23.

Sparsentan has a non-chiral molecular structure.

Polymorphism has not been observed for sparsentan. Only one crystalline non-solvated form has been observed with polymorph screen. No form changes were observed on stability or during batch analysis by PXRD.

2.4.2.2. Manufacture, characterisation and process controls

Sparsentan is manufactured at two sites for which the applicant provided adequate evidence of GMP compliance.

Sparsentan is synthesized in 6 main steps using 3 well defined starting materials with acceptable specifications.

The selected starting materials are well justified and acceptable. The provided information on control of materials is of satisfactory quality, a discussion on related impurities in starting materials and their impact on the final active substance is provided.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities of the active substance and residual solvents were well discussed with regards to their origin and characterised. Information on the evaluation of possible genotoxicity and information on elemental impurities and nitrosamine forming was provided.

The active substance has identified process related impurities. Structurally related potential degradation impurities were found when exposed to extreme conditions. Genotoxicity evaluation was conducted on process related impurities and potential degradation impurities.

Limits for residual solvents used in the manufacturing process are controlled as per ICH Q3C guideline recommendations.

The elemental impurities risk analysis revealed no other risk than palladium, which proposed limit has been considered acceptable.

The provided nitrosamine risk assessment concluded that the risk of presence of nitrosamine impurities in the active substance is very low. No further action was necessary.

Adequate in-process controls are applied during the stages of the synthesis: reaction endpoints, residual solvents, residual water, residual metal (palladium), purity and impurity levels, intermediates are controlled by IPC at each stage of the manufacturing process. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Sparsentan is packaged and stored in double, low-density polyethylene (LDPE) bags, with each bag closed with a plastic twist tie and placed in a high-density polyethylene (HDPE) or fiber drum. The LDPE bags, as primary packaging, are food grade and are manufactured in compliance with European Pharmacopoeia monograph 3.1.3 – Polyolefins and Commission Regulation (European Union) 10/2011 - Plastic Materials and Articles Intended to Come into Contact with Food.

The suitability of LDPE bags as the primary packaging and storage of sparsentan is demonstrated by stability studies. The available stability data have shown that sparsentan drug substance is stable when packaged in double LDPE bags and stored at 25°C/60% relative humidity (RH), 30°C/65% RH, or 40°C/75% RH.

2.4.2.3. Specification

The active substance specification shown includes tests for: appearance (visual), identification (IR spectroscopy, HPLC), organic impurities (HPLC), assay (HPLC), elemental impurities (ICP-MS), residue on ignition/sulfated ash (Ph. Eur.), microbial limits (Ph. Eur.), residual solvents (GC, GC-MS), water content (KF), and particle size distribution (laser diffraction).

Each specification parameter has been justified individually. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The certificates of analysis of pilot and commercial batches (batches from former manufacturing sites and batches from current manufacturing sites) are provided and demonstrate that the results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from clinical and commercial batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 60 months under long term

conditions (25 ºC / 60% RH); and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Stability data from clinical batch of active substance from a proposed manufacturer stored in the intended commercial package for up to 48 months under intermediate conditions (30ºC/65% RH) were also provided.

Photostability testing following the ICH guideline Q1B was performed comparing respectively 1 solid and 1 liquid sample exposed to light to 1 solid and 1 liquid sample protected from light. Results of forced degradation studies under acid, alkaline, oxidation, high-temperature, and humidity stress conditions were provided for the active substance for each stress condition.

The following parameters were tested: appearance, organic impurities, assay, microbial testing, water content. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long-term, intermediate, and accelerated storage conditions. No trends or significant changes have been observed. The active substance also remains stable under light exposure.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period with no special storage precautions required in the proposed container.

2.4.2.5. Comparability exercise for Active Substance

Not applicable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Sparsentan is provided as white to off-white film-coated tablets, plain on one side and with debossed number on other side (200 mg: '105'; 400 mg: '021'). Tablet dimensions are approximately 13 mm × 7 mm for the 200-mg tablets and 18 mm × 8 mm for the 400-mg tablets. The two tablet strengths have the same shape and colour but are considered sufficiently visually distinguishable by the difference in size and debossing.

The composition, function, and quality standards of the components of the finished product are presented.

The active substance is sparsentan. The other ingredients are: microcrystalline cellulose, lactose, sodium starch glycolate (type A), colloidal anhydrous silica, magnesium stearate, poly(vinyl alcohol), macrogol, talc, titanium dioxide (E171).

The active substance is poorly soluble in bio-relevant media and is regarded as a Class II drug with respect to the Biopharmaceutical Classification System. The impact of particle size distribution on the finished dosage form performance in releasing the active substance has been assessed and the results indicate that larger particle size, specifically at the 90th percentile (D90) influences the dissolution rate.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A compatibility study of sparsentan active substance with commonly used excipients for oral solid dosage form formulation was performed and placed on accelerated stability. The studies demonstrated that sparsentan is chemically compatible with the excipients.

The commercial manufacturing process is a typical tableting process, namely blending, granulation, final blending, tableting, and coating. A process risk assessment was performed to map the relationship between various process steps and quality attributes in terms of risk to the safety, efficacy, and/or performance of the drug product. The manufacturability of the product is affected by the high quantity of the active substance in the finished product.

A Quality Target Product Profile (QTPP) was defined for the Filspari 200-mg and 400-mg tablets, and critical quality attributes identified. Initially, the sparsentan base in a powder-in-a-bottle (PIB) formulation was used for the initial clinical studies. Sparsentan base was provided in 1 bottle, and a formulated vehicle was provided in a separate bottle; the 2 were combined and mixed just prior to dosing.

In the following phase a 100-mg capsule dosage form developed, and the resulting capsules showed acceptable content uniformity (CU) and dissolution profiles; this process was selected and used in the Phase 2 blinded and open-label extension program of the DUET study.

Additional formulation work was conducted, resulting in 400-mg tablet formulation to minimise the number of capsules used by patients.

Using the same formulation, 200-mg tablets were also successfully manufactured for Phase 3 clinical studies. The 200-mg tablets were over-encapsulated (OE) in Size 00 grey gelatin capsules using microcrystalline cellulose (MCC). The 200-mg and 400-mg tablets are the proposed commercial formulation.

Bioequivalence studies were performed showing bioequivalence between the clinical formulations (PIB and 100-mg dosage form) and the proposed commercial formulations (200-mg and 400-mg tablets).

A formulation robustness study was conducted. The formulation robustness DOE study showed that the formulation components do not have significant effects on content uniformity and dissolution; implying that the current formulation of sparsentan 400-mg tablets is robust to controlled variations in formulation composition.

The dissolution method was assessed, and more information was requested. The provided updated dissolution data by the applicant was considered acceptable.

The primary packaging is a high-density polyethylene (HDPE) bottle with child-resistant polypropylene cap containing 30 film-coated tablets. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The commercial manufacturing process consists of six main steps: (1) pre-granulation mixing, (2) granulation, (3) final blend mixing, (4) tablet compression, (5) film coating, and (6) packaging. The process is considered to be a standard manufacturing process.

Critical process parameters have been defined for both finished product strengths.

The manufacturing process for both dosage strengths was successfully validated through Process Performance Qualification (PPQ) consisting of enhanced monitoring, sampling, and testing of three consecutive commercial-scale lots of finished product manufactured per current Good Manufacturing

Practices and the proposed commercial process. Manufacturing hold times were verified during process performance qualification (PPQ) to confirm that the product at various stages throughout manufacturing may be held for an extended period of time.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release and shelf-life specifications shown include appropriate tests for this kind of dosage form, namely: appearance (visual); identification (HPLC, UV spectrum); assay (HPLC); impurities (HPLC); uniformity of dosage units (Ph. Eur.); water content (Ph. Eur.); dissolution (Ph. Eur.); microbial enumeration (Ph. Eur.); and microbial examination (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on PPQ batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

During the procedure, a risk assessment concerning the potential presence of nitrosamine impurities in the finished product was requested as part of a MO to the applicant since it was not included in the Module 3. The applicant responded adequately, and the issue was resolved. The risk assessment concerning the potential presence of nitrosamine impurities in the finished product has therefore been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. No additional reference standards were used for the testing of the finished product than those used for the testing of the active substance.

Batch analysis results are provided, thus confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification with the intended commercial batch size.

2.4.3.4. Stability of the product

Stability data from pilot and commercial batches of the 200-mg finished product strength and of 400-mg finished product strength stored for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability data from the same batches were also obtained up to 60 months under intermediate conditions (30°C/75% RH) to support stability Zone IV.

Samples were tested for appearance, assay, individual impurity and total impurities, water content, dissolution, microbial enumeration TAMC and TYMC, and microbial examination for *E. coli*. The analytical procedures used are stability indicating.

No OOS, nor significant changes or trends have been observed. All results met the proposed commercial specification.

An in-use stability study was performed for 200-mg strength and 400-mg strength and showed no significant changes or relevant deterioration. Therefore, an in-use shelf-life is not necessary according to the EMA Q&A section Quality of medicines questions and answers: Part 2.

In addition, 200-mg strength and 400-mg strength batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability study demonstrated that the product is not sensitive to light exposure.

Based on available stability data, the proposed shelf-life of 4 years without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Comparability exercise for finished medicinal drug product

Not applicable.

2.4.3.6. Adventitious agents

Lactose is the only excipient used in the finished product which is from animal origin.

The lactose is manufactured in compliance with the EMA Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev. 3) and the respective Monograph Ph. Eur. 5.2.8. Notably, it is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During evaluation, 2 major objections (MOs) were raised by the CHMP in relation to proposed dissolution limits and risk assessment of nitrosamines. The responses from the applicant to the MOs were considered satisfactory and all the issues were considered to be resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Sparsentan is a novel, first-in-class, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA) being developed for the treatment of immunoglobulin A (IgA) nephropathy (IgAN). Sparsentan is a highly selective antagonist for endothelin type A receptor (ETAR) and angiotensin II (Ang II) type 1 receptor (AT1R), which are both involved in mechanisms underlying the pathophysiology of rare proteinuric glomerular diseases.

In scope of the non-clinical development programme for Filspari, a series of PD/PK studies were carried out by the company Cetero, that was found to falsify data, and accordingly, results obtained in period April 2005-June 2010 cannot be considered reliable (Art. 31 referral for Cetero). Nevertheless, the applicant presented those data with justification that the calculated parameters are consistent with data generated by GLP-compliant laboratories. The CHMP considered this approach convenient because more experimentations data widens knowledge about the test article. The applicant's justification concerning Cetero studies results deviations were considered when assessing relevant assay data. Such data were interpreted as supportive and informative, but not decisive.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The applicant performed and presented 8 *in vitro* studies evaluating receptor specificity, selectivity, potency, and receptor function, using human and murine cell lines.

The *in vitro* studies demonstrated that sparsentan functions as a high-affinity, dual-acting antagonist of both the human ET_AR (inhibitory constant [Ki] = 12.8 nM) and AT_1R (Ki = 0.36 nM), with greater than 500-fold selectivity over endothelin type B receptor (ET_BR) and angiotensin II type 2 receptor (AT_2R), respectively. It has approximately 36-fold higher affinity for AT_1R than ET_AR.

In competitive radioligand binding assays for 105 different human G-protein coupled receptors, sparsentan demonstrated significant binding for only 3 of the 105 receptors evaluated: ET_AR, AT_1R, and AT_2R. Follow-up binding studies for these 3 receptors determined that sparsentan had Ki values for ET_AR = 43.2 nM, AT_1R = 0.98 nM, and inhibition of ligand binding to AT_2R by 90% at 10 µM, confirming higher affinity of sparsentan for AT_1R than for ET_AR. Sparsentan did not bind to selected receptors, ion channels, or transporters associated with abuse potential. Sparsentan has a higher affinity for the rat AT_1R (Ki = 11 nM) than the ET_AR (Ki = 110 nM). The affinity of sparsentan at the rat ET_AR is approximately 10-fold lower, and for the rat AT_1R approximately 30-fold lower than for the respective human receptors.

Sparsentan binding of ET_AR and AT_1R demonstrated a dose-dependent inhibition of receptor function in intracellular signalling, inhibiting both endothelin-1 (ET-1) and angiotensin II (Ang II)-stimulated calcium mobilization and β-arrestin translocation in human cells *in vitro*.

Schild's analysis of sparsentan antagonism of ET-1 and Ang II-stimulated inositol monophosphate (IP1) is consistent with sparsentan acting as an antagonist of both ET_AR and AT_1R. However, whereas sparsentan behaves as a simple competitive antagonist of AT_1R, the slope following Schild analysis of the ET-1 IP1 data of less than unity suggests that sparsentan may be a negative allosteric modulator of the ET_AR.

Sparsentan pharmacology was evaluated in the battery of *in vivo* studies: 15 studies with mice and rats representing a range of nonclinical models of renal conditions. Animal species choice is consistent with valid guidelines.

In vivo PD assays: After intravenous injection of the vasoactive peptides, ET-1 or Ang II, in rats, increased blood pressure primarily due to interaction with their respective receptors (ET_AR and AT_1R). Sparsentan appeared to be a potent antagonist of both ET_AR and AT_1R *in vivo*, inhibiting ET-1- and Ang II-mediated pressor responses in the male rat.

Sparsentan demonstrated efficacy in a range of nonclinical animal models of kidney disease. Physiological mechanisms of disease amelioration demonstrated in one or more of these models include attenuated development of proteinuria, reduced inflammatory cell infiltrate and mesangial cell activation and/or proliferation, amelioration of glomerulosclerosis, protection of podocytes, reduced tubulointerstitial fibrosis, reduced vasoconstriction increasing afferent and efferent arteriole dilation, and attenuation of decline in GFR. Hence, sparsentan might provide benefits across a spectrum of glomerular diseases.

The test article has demonstrated efficacy in 2 rodent models of IgAN (also known as Berger's disease) - the grouped Deutschland, Denken, and Yoken (gddY) mouse model and an engineered immune complex (EIC)-induced "passive IgAN" mouse model - and in a model of mesangial proliferative glomerular nephritis - the anti-Thymocyte (Thy-1) rat (ATS) model. Sparsentan attenuated the development of proteinuria in the gddY and ATS models, glomerular sclerosis in the gddY mice, mesangial cell activation and cellularity (proliferation) in the passive IgAN and ATS models, and macrophage infiltration in the ATS model.

Alport syndrome (AS), characterised by renal injury, hearing loss, and ocular abnormalities, is a result of mutations in the genes that encode the type IV collagen α3, α4, and α5 chains, which are major structural components of the glomerular basement membrane (GBM) and the strial capillary basement membrane (BM) in the inner ear. The clinical course of AS may begin with asymptomatic microscopic haematuria and proteinuria, progressing to decreases in GFR and eventually end-stage kidney disease. Experimental mouse models have suggested that in addition to GBM dysregulation, AS also results in podocyte injury. Sparsentan dose-dependently attenuated disease-mediated increases in the urinary protein-to-creatinine ratio (UP/C) and GS, and completely prevented the onset of tubulointerstitial fibrosis (TIF) without a significant reduction in systolic blood pressure (SBP) in AS mice. Sparsentan also prevented the decline in GFR seen in vehicle treated AS mice.

In vivo modelling of PK/PD: Using a sigmoidal maximum effect (E_{max}) model to examine pharmacokinetic (PK)/PD relationships, it was found that higher sparsentan plasma concentrations are required to inhibit ET-1-stimulated MAP increases compared to those needed to inhibit Ang II-stimulated MAP increases. This is consistent with the higher affinity of sparsentan to the AT_1R compared to that for the ET_AR.

The inhibitory effect I_{max} model described the relationship between plasma concentration and efficacy measures in the ATS rat model. The predicted half-maximal inhibitory concentration (IC_{50}) estimates

suggested that sparsentan has similar potency for lowering mesangial cell activation and proliferation and proteinuria. Based on the model, a relatively higher plasma concentration was required to attenuate macrophage infiltration.

Modelling ET_AR and AT_1R receptor occupancies and proteinuria in the ATS rat model showed an attenuation in proteinuria as the 50% receptor occupancy (RO) of AT1R is reached with further attenuation as the 50% RO of ETAR is approached. This is consistent with the hypothesis that greater attenuations in proteinuria with dual antagonism of ETAR and AT1R is achieved than with antagonism on a single receptor alone.

2.5.2.2. Secondary pharmacodynamic studies

The applicant did not present a dedicated secondary pharmacodynamics study and relayed on primary pharmacology receptor binding assays. No significant inhibition or stimulation of binding of the radioactive ligands was observed for a subset of receptors, ion channels, or transporters associated with abuse potential. This is acceptable to the CHMP.

2.5.2.3. Safety pharmacology programme

Results of three *in vitro* and three *in vivo* studies were presented. Dedicated studies revealed minimal changes (<8%) in transmembrane action potential in isolated rabbit Purkinje fibres at concentrations up to 30 µM. Inhibition of rapidly activating inward rectifying current (IKr) conducted by cardiac potassium channels encoded by the human ethera-go-go related gene (hERG) in human embryonic kidney-293 (HEK-293) cells by sparsentan was 7% at 500 µM, approximately 3900 times higher than the geometric mean maximum plasma concentration (C_{max}) of unbound sparsentan at the 800 mg human efficacious dose. Non-adverse decreases in BP without compensatory increases in heart rate were observed in monkeys administered single oral doses of sparsentan up to 1000 mg/kg. However, there were no effects on electrocardiogram parameters or core body temperature. Sparsentan did not affect the CNS or pulmonary function in rats administered single oral doses of up to 1000 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

No non-clinical PD drug interaction studies were performed and a justification that PD interactions of endothelin antagonists and angiotensin receptor blockers with other drugs have been well characterised in the past was provided. The approach is acceptable to the CHMP.

2.5.3. Pharmacokinetics

Concentrations of sparsentan were quantified in rat, rabbit and monkey blood plasma using liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical methods in non-GLP and GLP toxicokinetic (TK) studies. Qualified and partially validated methods were developed to support single-dose, dose range finding, and pilot studies, and the validation reports were presented in the dossier. Obtained results were regarded as reliable.

The study of transcellular permeability through a human colon adenocarcinoma cell line (Caco-2) revealed that sparsentan under gastrointestinal (GI)-relevant conditions demonstrated ≥233 nm/s apical-to-basolateral uptake depending on medium pH and suggested bigger than 50% oral absorption.

The applicant submitted seven studies evaluating absorption after a single dose and additional studies evaluating absorption after a repeat dose from dedicated PK assays and bridging data from toxicology

tests. The PK profile of sparsentan was assessed in a series of *in vitro* studies in mice, rats, dogs and monkeys.

After oral administration in mice, rats, dogs, and monkeys, sparsentan is readily absorbed, as indicated by the 1-2 hours T_{max} and showed moderate oral bioavailability (F - 32% in monkeys to 56% in rats). In certain studies, exposure to sparsentan was higher in female rodents compared to males, with >2-fold observed. There were no consistent gender differences in exposure in monkeys. Following repeated dosing, the systemic exposure of sparsentan increased in a dose-dependent manner and was less than dose-proportional at high doses. There was little evidence of drug accumulation in rodents, but some evidence in monkeys following repeated oral administration was observed. In some rodent studies, decreased exposure was observed after repeat dosing, but this was not the case for monkeys.

Following IV or IA administration to rats and monkeys, sparsentan plasma concentrations declined in a biphasic manner, with a rapid distribution phase followed by a slower elimination phase. The plasma half-life (t½) was approximately 3 hours in rats and 5.6 hours in monkeys. The volume of distribution was approximately 440 mL/kg in rats and monkeys and, thus, less than total body water, suggesting that the distribution of sparsentan was not very extensive, consistent with being highly protein bound. Systemic clearance was approximately 197 and 777 mL/kg·h in rats and monkeys, respectively, both less than hepatic blood flow, indicating low-to-moderate clearance in these species.

The applicant presented four *in vitro* and *in vivo* studies on distribution. The *in vitro* study assessed plasma protein binding of sparsentan using equilibrium dialysis in pooled rats, monkeys, and human blood plasma. Sparsentan appeared highly protein bound (97.2% to >99%), leading at 10 µM (5.9 µg/ml) to an unbound fraction (%) of 0.4%, 0.8% and 1.2% in rats, monkeys, and human, respectively. At a 10-fold higher concentration, however, the free fraction increased to ~2.7% in rats, monkeys and humans. Overall, in rat, monkey, and human plasma, sparsentan (1 to 100 µM) was highly bound to plasma proteins (≥97.2%) in a concentration-independent manner, as well as to human serum albumin (HSA) and human α1-acid glycoprotein (AAG). Blood-to-plasma distribution ratio in humans in vitro ranged from 0.579 to 0.674 across a concentration range of 0.1 to 100 µM (0.059 to 59 µg/mL), indicating low affinity of sparsentan to red blood cells.

The highest radioactivity was found in bile, blood, and urine, followed by the liver, arterial walls, lungs, renal cortex, and intervertebral discs. The lowest amount of radioactivity was in the non-circumventricular CNS tissues, bones, seminal vesicles, abdominal fat, and eyes. The radioactivity that did distribute across the blood:brain barrier was measurable at 1.8 times the lower level of quantitation but was not detectable after 2 hours. In all tissues, the elimination of ^{14}C-sparsentan–derived radioactivity was complete by 168 hours after a single oral dose.

Sparsentan undergoes moderate metabolism in hepatocytes and liver microsomes isolated from mice, rats, dogs, monkeys, and humans. The majority of metabolism is the result of hydroxylation (mono- and dihydroxylation), with metabolites formed in human hepatocytes consisting of either monohydroxylated (M19, M20, M21, M22, and M24) or keto (M25) forms. No human-specific metabolites were formed in human hepatocytes. All the metabolites were detected in one or more animal species at proportionate levels, and no metabolite was observed to be ≥10% of total sparsentan-related exposure. CYP3A4 is the primary enzyme responsible for sparsentan metabolism, with a relatively minor contribution by CYP2C8 and CYP2C9.

Overall, incubation with hepatocytes and liver microsomes from mice, rats, dogs, monkeys, and humans showed that sparsentan was moderately to extensively metabolised (16% to 54%), with hydroxylation (mono- and dihydroxylation) identified as one of the main metabolic biotransformations. *In vivo*, the biotransformation of sparsentan was assessed in rats, where sparsentan was the major component in plasma (80-37%) with 6 metabolites above 1% of total label in plasma. Metabolites formed in human hepatocytes consist of either monohydroxylated (M19, M20, M21, M22, and M24) or

keto (M25) forms. The metabolic profile was qualitatively similar in general across species, and there were no major unique human metabolites observed. Comparing recombinant human cytochrome P450 enzymes, sparsentan was primarily metabolised by CYP3A4, with possible CYP2C8 or CYP2C9 contribution. Hepatic intrinsic clearance was 79.1 to 94.5 mL/min/kg and 29.6 to 33.9 mL/min/kg at 1 and 5 µM of sparsentan, respectively, in pooled human liver microsomes. The lower clearance rate at higher sparsentan concentration indicates saturation and/or inhibition of CYP3A4. All metabolites in humans were detected in 1 or more animal species.

In excretion testing in rats, the radioactivity occurred predominantly in faeces, with mean recoveries of 93.7% and 1.96% of the total dose from faeces and urine, respectively, through 336 hours post-dose. Urine was shown to be a minor elimination pathway. Excretion of sparsentan was also evaluated in bile-duct cannulated rats after a single oral dose of ^{3}H-sparsentan, where biliary excretion accounted for approximately 72% of the dose within 12 hours post-dose. The main sparsentan components in the bile were mono-oxygenated metabolites, with the parent drug accounting for <1% of the radioactivity, indicating that biliary excretion is not a clearance route for sparsentan. This suggests that the primary clearance pathway for sparsentan is CYP3A-mediated metabolism followed by biliary excretion and faecal elimination.

PK drug interactions studies were performed *in vitro*. It was shown that sparsentan inhibits CYP2C8 and CYP3A4/5 and exhibits metabolism-dependent inhibition of CYP3A4, suggesting it may potentially interact with substrates of CYP2C8 or CYP3A4. Sparsentan was an inducer of CYP2B6, CYP3A4, CYP2C9, and CYP2C19, suggesting potential drug interaction with substrates of those CYPs. Transporter interaction studies indicated that sparsentan was a substrate and inhibitor of permeability-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Sparsentan was not a substrate for organic anion transporter protein (OATP)1B1 or OATP1B3. Sparsentan inhibited bile salt export pump (BSEP), BCRP organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug resistance-associated protein (MRP)3, OATP1B1, OATP1B3, OATP2B1, and sodium taurocholate transporting polypeptide (NTCP). Sparsentan was not an *in vitro* inhibitor of MATE2-K and was at most a weak inhibitor of MATE1. Relevant findings are adequately reflected in section 4.5 of the SmPC.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Two single-dose, 14-day toxicity studies in mice and rats were presented, both GLP compliant. The maximum dose (oral administration) in both species was 2 000 mg/kg, and it was well tolerated. The acute toxicity was limited to decreased activity and one death in mice at 2 000 mg/kg and transient decreases in body weight gain in rats at ≥1000 mg/kg. No drug-related changes were noted in mice given sparsentan as single oral doses of 250, 500, or 1000 mg/kg and in rats given sparsentan at 250 or 500 mg/kg.

2.5.4.2. Repeat dose toxicity

Several repeat dose toxicity studies in mouse, rat, and monkey were presented. All of them, except a 2-week study in rat, are GLP compliant, which is the supportive data source for determining toxicological profile of sparsentan.

In 28-day and 13-week toxicity studies in mice based on clinical signs, body weight changes, a higher degree of severity of hepatocellular hypertrophy, and single-cell necrosis of hepatocytes at 750

mg/kg/day, the NOAEL in the CD-1 mice was determined as 200 mg/kg/d (13-week study). Associated Day 91 $AUC_{0\text{-last}}$ values were 321,000 h·ng/mL in males and 427,000 h·ng/mL in females.

Two-week and 1-, 3-, and 6-month repeat-dose toxicity studies were conducted in rats administered dose levels from 15 to 400 mg/kg/d. Recovery of sparsentan-related changes was assessed after 1 month in the 1- and 3-month studies and after 2 months in the 6-month study. There were no sparsentan-related deaths. Alopecia and salivation were observed in the 3-month study at all dose levels (15, 80, and 320 mg/kg/d), and salivation and porphyrin staining were observed at ≥80 mg/kg/d in the 6-month study. Decreases in body weight were observed in all studies, generally at ≥80 mg/kg/d, and were often accompanied by decreases in food consumption. Red cell mass was decreased in all studies at ≥80 mg/kg/d, but no corresponding changes in bone marrow were noted. Urea nitrogen was increased in most studies at ≥80 mg/kg/d, with increases in creatinine at 320 mg/kg/d. Increased liver weight, hepatocellular hypertrophy, was observed at ≥80 mg/kg/d in all studies. JGA hypertrophy/hyperplasia were observed at all dose levels in the 3- and 6-month studies and the incidence and severity of renal tubular degeneration/fibrosis were increased at 320 mg/kg/d in the 6-month study. All sparsentan-related changes were reversible, except decreases in body weight. Based on irreversible changes in body weight, the magnitude of clinical laboratory changes, and the incidence and severity of multifocal renal tubular degeneration and fibrosis at 320 mg/kg/d, the NOAEL in rats in the 6-month study was 80 mg/kg/d. At the NOAEL, the associated Day 182 $AUC_{0\text{-last}}$ values were 318,000 h·ng/mL in males and 99,700 h·ng/mL in females (or 3.3 and 1.0 times, respectively, the $AUC_{0\text{-}24}$ in humans at the 800 mg clinical dose).

One-, three-, and nine-month repeat-dose toxicity studies were conducted in monkeys with dose levels 10 mg/kg/d to 250 mg/kg/d. Tail lesions, necessitating amputation in some animals, emesis and decreased body weight and food consumption were observed at 250 mg/kg/d in the 3-month study and at ≥10/125 mg/kg/d in the 9-month study. Soft and/or discoloured faeces were also noted. Red cell mass was decreased in the 1- and 3-month studies at 250 mg/kg/d and in the 9-month study at ≥10/125 mg/kg/d; this was correlated with bone marrow hypocellularity in the 3- and 9-month studies. Increases in urea nitrogen and creatinine were observed at 250 mg/kg/d in the 1- and 3-month studies and at 200 mg/kg/d in the 9-month study. Juxtaglomerular apparatus hypertrophy/hyperplasia was observed at 250 mg/kg/d in the 1-month study and at all dose levels (≥10 mg/kg/d) in the 3- and 9-month studies. Renal cortical interstitial fibrosis was observed in the 9-month study at ≥10/125 mg/kg/d. All sparsentan-related changes were reversible or reversing at the end of the 1-or 2-month recovery periods. The NOAEL in the monkeys in the 9-month study was 50 mg/kg/d. At the NOAEL, the associated Week 39 AUC0-last values were 16,700 h·ng/mL in males and 12,700 h·ng/mL in females or 0.2 and 0.1 times, respectively, the AUC0-24 in humans at 800 mg clinical dose.

The design, duration, methodology and the number of repeat-dose studies, as well as the number of animals tested are considered sufficient to characterise the toxicological profile of sparsentan. The selection of three main animal species (one of them non–rodent) is justified.

2.5.4.3. Genotoxicity

Standard test battery was performed: assessment of mutagenicity in a bacterial reverse gene mutation test (in four Salmonella typhimurium strains and one Escherichia coli strain), chromosome aberration in mammalian cells assay *in vitro* (human peripheral lymphocytes), analysis of micronuclei in erythrocytes in the bone marrow of rats. This is acceptable according to ICH guideline S2 (R1). The set of bacterial strains were also chosen according to recommendations of ICH guideline S2 (R1).

Sparsentan showed no mutagenic effects in the *in vitro* bacterial reverse mutation and human peripheral lymphocyte cells assay and no genotoxic effects in an *in vivo* bone marrow micronucleus assay in rats up to an exposure margin of 9-fold exposure at MRHD.

2.5.4.4. Carcinogenicity

Two GLP-compliant dose finding 4-week carcinogenicity studies were performed in mice to evaluate potential toxicity and toxicokinetics of sparsentan in wild-type CByB6F1-Tg (HRAS)2Jic mice after oral administration for 4 weeks and to assist in the dose level selection for a subsequent 6-month carcinogenicity study in transgenic mice (RasH2). Initially, during the 4-week DRF study mice were dosed once daily via oral gavage with sparsentan at 1000 or 3000 mg/kg/day. But due to the high toxicity, especially in male mice, the other 4-week DRF study was initiated, were mice received the highest dose at 450 mg/kg/d. Toxicokinetic parameters were assessed in both studies and were independent of sex but showed increased exposure with increasing dose in a greater than dose-proportional manner and appeared to decrease following repeated administration.

Long-term carcinogenicity studies were conducted in mice (26 -week duration) and one in rats (104-week duration). Both sexes of animals were involved in the studies. During the 26-week study, in mice the maximal dose used was 600 mg/kg/day; in the 104-week study, in rats 320 mg/kg/day. Sparsentan was not carcinogenic in transgenic mice administered up to 600 mg/kg/day for 26 weeks, with Day 182 $AUC_{0\text{-last}}$ values of 376,000 h·ng/mL in male mice and 549,000 h·ng/mL in female mice 3.9 and 5.7 times, respectively, the $AUC_{0\text{-}24}$ in humans at 800 mg clinical dose. Sparsentan toxicity to the liver and kidney during this study was similar to what was revealed in repeat dose toxicity studies.

Once daily oral gavage administration of sparsentan for 93 weeks in a rat study was tolerated in males at a dose level of 15 mg/kg/day and in females for up to 92 weeks at dose levels of 15, 60, and 240 mg/kg/day, due to lower body weights and body weight gains, males given 60 or 240 mg/kg/day were euthanised during Week 29. Thin appearance, lower body weight, decreased food consumption, and microscopic findings in the kidneys were considered sparsentan-related in males at 15 mg/kg/day and females at ≥15 mg/kg/day. However, there were no increases in any tumour type, and all tumours were considered incidental to the administration of sparsentan. Therefore, sparsentan was not carcinogenic in rats with Day 198 $AUC_{0\text{-last}}$ values of 453,000 h·ng/mL in males and with Day 363 $AUC_{0\text{-last}}$ values of 2,030,000 h·ng/mL in females or 4.7 and 21.3 times, respectively, the $AUC_{0\text{-}24}$ in humans at 800 mg clinical dose.

2.5.4.5. Reproductive and developmental toxicity

The reproductive and developmental toxicity studies were performed in line with GLP requirements. The studies evaluated ICH Harmonised Tripartite Guideline stages A and B of the reproductive process in rats, stages C to D of the reproductive process in rats and rabbits, and stages C to F of the reproductive process in rats. Toxicity to juvenile rats was assessed in 4 separate 14-day, 10-, 11-, 12-week studies starting exposure PND 7 or PND22. Selected species (rat and rabbit) for reproductive and developmental toxicity studies are acceptable.

There were no adverse effects on any fertility or early embryonic development reproductive parameters evaluated in male or female rats up to the highest tested dose (320mg/kg/day) at approximately 26- and 31-times exposure margin, respectively, the $AUC_{0\text{-}24}$ in humans at 800 mg clinical dose. Developmental toxicities occurred in rats and rabbits, which were consistent with class effects for approved ARBs and/or ERA receptor antagonist products. In rats, teratogenic effects and other forms of developmental toxicity were observed in the EFD studies below the lowest dose (<80 mg/kg/d) associated with 8.4 times higher $AUC_{0\text{-}24}$ than in humans at clinical dose, in rabbits at a very

low dose associated with the AUC0-24 0.1 times of human clinical dose. In a pre- and postnatal development study a reduction in pup survival occurred. Therefore, sparsentan induced teratogenicity and/or developmental toxicity, which has been stated in SmPC.

Juvenile toxicity studies were conducted in rats to evaluate the effects of sparsentan treatment across several different developmental stages. In general, the studies showed increased sensitivity to the supra-pharmacological effects of sparsentan in Postnatal Day (PND) 7 rats (equivalent to a newborn human infant) that were negligible with older juvenile rats (PND 14, 21/22, or 28). Clear age-related toxicities occurred in the kidney and vasculature systems, which were present when dosing started on PND 7 and minimal or absent when dosing started on PND 14 and later. At older ages, kidney changes were considered an exacerbation of chronic progressive nephropathy (CPN), which occurred as a non-adverse finding at ≥10 mg/kg/d when dosing started on PND 14 or PND 22. Vascular toxicity occurred only in the juvenile study starting on PND 7 at 10 mg/kg/d. This finding was not observed at the terminal necropsy but only after the 4-week recovery period. Importantly, no vascular toxicity and secondary toxicity related to vascular changes were seen in juvenile studies starting on PND 14 or later, supporting that these effects were age-related. These findings were adequately reflected in SmPC section 5.3.

2.5.4.6. Toxicokinetic data

Following repeated oral administration of sparsentan, systemic exposure increased in a dose-dependent manner across species over a limited dose range, beyond which the exposure generally increased in a less-than-proportional manner with dose. There was little evidence of drug accumulation, as the exposure was generally observed to remain the same or decrease at high doses. The exposure at lower doses was higher in female rodents (mice and rats) compared to males. There was no consistent difference in exposure between sexes in monkeys.

2.5.4.7. Local Tolerance

Not applicable.

2.5.4.8. Other toxicity studies

Studies on impurities: None of the synthetic intermediates of sparsentan evaluated contained structural alerts for mutagenicity except two. One was evaluated in a bacterial mutagenicity assay and was negative; reverse bacterial mutagenicity testing was not performed for the second and will be treated as a Class 2 impurity. Impurities were not mutagenic in bacteria with or without metabolic activation. No differences in toxicity profile were observed in a 13-week repeat-dose toxicity study in rats between sparsentan containing the standard level of impurity (0.11%) and a higher level of impurity (0.2%).

2.5.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name):Sparsentan			
CAS-number (if available): 254740-64-2			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	Shake flask method	3.95 pH 5 2.28 (pH 7 (neutral) 0.60 pH 9	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.95 pH 5 2.28 pH 7 0.60 pH 9	Not B
	BCF	not required	
Persistence	ready biodegradability	not readily biodegradable	potentially P
	DT50 (at12°C)	DT50 sediment = 274 d (1), 301 d (2)	vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥65 mg/L ≥9.04 mg/L ≥10.4 mg/L	not T
	CMR	not investigated	potentially T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (prevalence)	0.22	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{Foc}= 320 L/kg Loamy sand 223 L/kg Silty sand 81.3 L/kg Clayey loam 169 L/kg Sludge 153 L/kg SludgeK_{oc} <10,000 ml/g	Geometric mean for soil: 180 L/kg Geometric mean for sludge: 161 L/kgList all values
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ = 12.8 d (1), 15 d (2) $DT_{50\ sediment}$ = 129 d (1), 142 d (2) $DT_{50\ system}$ >10 000 d (1), >10 000 d (2) 1 = Calwich Abbey lake sediment 2 = Middle Pond sediment shifting to sediment: 40% %CO_2 = 2.6% (1),3.1% (2) %NER = 14% (1), 12% (2) Transformation products>10% = YES WS1 57%, DT50 75 d WS2 19%, DT50 <10000 d	
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC	≥65	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥9.04	mg/L	reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	≥10.4	mg/L	reproduction
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	≥4014	Mg/kg oc	normalised to 10% oc; mean measured

Phase I PECSW for sparsentan for combined indications of FSGS and IgAN (0.22 µg/L) exceeds the limit of 0.01 µg/L. Therefore, a Phase II evaluation was performed by testing the effects of sparsentan on aquatic receptors. The log DOW value at pH 7 was estimated to be below the trigger value of 3; therefore, a bioaccumulation study was not warranted. However, the requirement for a bioconcentration study according to OECD 305 is based on the Guideline EMEA/CHMP/SWP/4447/00 Corr 2. Risks associated with the use and release of sparsentan were determined through comparison of the PECs in surface water, STP, groundwater, and sediment to PNECs for various aquatic receptors. The PECs for sparsentan are several orders of magnitude less than the PNECs estimated for aquatic organisms, STP microorganisms, and sediment invertebrates. Thus, based on this ERA, the available data do not allow to conclude on the potential risk of sparsentan to the aquatic environment. It appears that sparsentan is not considered PBT or vPvB. A risk to the STP, surface water, groundwater, sediment, and terrestrial compartment is not anticipated based on the prescribed use of sparsentan.

2.5.6. Discussion on non-clinical aspects

Based on the observations in the non-clinical pharmacology studies, sparsentan revealed to function as a high-affinity, dual-acting antagonist of both human ETAR and AT1R, with greater than 500-fold selectivity over ETBR and AT2R, respectively. The affinity of sparsentan for the rat ETAR and AT1R was also demonstrated. Receptor homology ranges from 99% identity to human for both ETAR and AT1R in monkeys and to 92% and 94% identity for ETAR and AT1R, respectively, in mice. The results of these studies and associated PK modelling support the relative potency from *in vitro* sparsentan studies for ETAR and AT1R.

As sequence similarity of monkey ETAR and AT1R to human ETAR and AT1R is relatively high, anticipated pharmacology is observed in the monkey safety pharmacology and repeat dose toxicity studies, and considering that pharmacological activity, metabolic profile, and toxicological findings in monkeys are consistent with observations in the rat, it can be accepted that Ki values of sparsentan for monkey ETAR and AT1R are not present in the dossier.

In a battery of *in vivo* PD studies using multiple rodent models of kidney damage, treatment with sparsentan resulted in attenuation of the development of proteinuria, amelioration of glomerulosclerosis, protection of podocytes, reduced TIF, reduction of inflammatory cell infiltrate and mesangial cell activation and attenuation of decline in GFR. These effects can be attributed to dual ETAR and AT1R antagonism of sparsentan, which consequently may provide benefits across a spectrum of glomerular diseases and greater disease amelioration than therapies inhibiting only 1 of these 2 receptors.

The safety pharmacology studies *in vitro* and *in vivo* revealed that sparsentan had minimal effects on the human hERG cardiac potassium channel current and no biologically significant effects on Purkinje fiber action potential duration at concentrations up to the highest concentration tested. Sparsentan, at doses up to 1000 mg/kg, did not show statistically significant or biologically relevant AEs on the CVS (monkeys) or the respiratory and CNS (rats).

The non-clinical PK profile of sparsentan was assessed in a series of *in vitro* studies and evaluated in mice, rats, and monkeys. After oral administration, sparsentan was readily absorbed in rats and monkeys. The t½ of orally administered sparsentan in rats and monkey supports QD dosing. Sparsentan is highly bound to rat, monkey, and human plasma protein, as well as to HSA and AAG. There were no consistent gender differences in exposure in monkeys. Following repeated dosing, the systemic exposure of sparsentan increased in a dose-dependent manner and was less than dose-proportional at high doses. There was little evidence of drug accumulation in rodents, but some accumulation occurred in monkeys following repeated oral administration. Exposure to sparsentan was lower following repeat dosing, especially at high doses.

In vitro metabolism studies in human, monkey, dog, rat, and mouse hepatocytes generated qualitatively similar metabolic profiles. No major unique metabolites were formed in human hepatocytes. Sparsentan is likely to inhibit CYP3A4/5 *in vivo* but not likely to inhibit other CYP enzymes. It is an inducer of CYP2B6, CYP3A4, CYP2C9, and CYP2C19, suggesting potential drug interaction with substrates of those CYPs.

The applicant stated that the absence of histological evidence of structural degeneration and necrotic changes and the absence of significant and consistent increases in clinical pathology parameters are supportive of the liver changes in mice and rats being an adaptive, physiological response to a xenobiotic. Also, no liver findings were recorded in any repeat-dose toxicity study in the monkey up to the dose of 250 mg/kg/day, 4 and 3 times the human exposure. Hence, hepatocellular hypertrophy in this context is likely a result of enzyme induction due to chemical stress and not of relevance at clinically relevant exposures. However, in the clinical setting, liver enzyme elevations and hepatic AEs will be monitored as part of standard care. Recommendations for health care professionals are included in the SmPC and RMP.

Sparsentan showed no mutagenic effects in *in vitro* bacterial reverse mutation and human peripheral lymphocyte cells assays and no genotoxic effects in an *in vivo* bone marrow micronucleus assay in rats. The duration of the carcinogenicity studies is appropriate. Sparsentan’s toxicity to the liver and kidney was similar as observed in repeat dose toxicity studies. There were no increases in any tumour type, and all tumours were considered incidental to the administration of sparsentan.

There were no AEs on any fertility or early embryonic development reproductive parameters evaluated in male or female rats up to the highest tested dose. In rats and rabbits, teratogenic effects and other forms of developmental toxicity were observed in the EFD studies below the lowest dose. Section 5.3 of the SmPC includes the relevant information for the treating physician. Furthermore, the patient will carry a patient card with description of the teratogenic risk associated with the use of Filspari and relevant instructions.

The current ERA data for sparsentan do not suggest a potential risk to the environment. Sparsentan is not a PBT substance and is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the presented non-clinical programme provides an adequate characterisation of the PD, PK and toxicology profile of sparsentan.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifier and Site Locations	Location of Study Report Within Application	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status Type of Report
Phase 1 Studies								
PCO-C-001[a] USA	5.3.3.1	Safety, tolerability, and single-dose PK profile	SC, R, DB, PC, SAD	Placebo or sparsentan (suspension) 20, 50, 100, 250, 500, or 1000 mg Oral administration	48	Healthy subjects	Single dose	Complete CSR
PCO-C-002[a] UK	5.3.4.1	Safety, tolerability, and single-dose PK profile	SC, CR, R, DB, PC	Placebo, irbesartan 300 mg, or sparsentan (suspension) 20, 100, 250, or 500 mg Oral administration	18	Healthy subjects	Single dose	Complete CSR
PCO-C-003[a] USA	5.3.3.1	Safety, tolerability, and multiple-dose PK profile	SC, DB, R, PC, MAD	Placebo or sparsentan (suspension) 50, 100, 250, 500, or 1000 mg Oral administration	40	Healthy subjects	QD for 14 days	Complete CSR
PCO-C-004[a] USA	5.3.1.2	Relative bioavailability of capsule vs suspension formulations; safety and tolerability	SC, OL, SD, R, 2-treatment, 2-way CR	100 mg sparsentan capsule (Test) 100 mg sparsentan suspension (Reference) Oral administration	15	Healthy subjects	Single dose	Complete CSR
PCO-C-007[a] USA	5.3.3.4	Effect of a high-fat meal on the PK profile of sparsentan; safety	SC, OL, SD, R, 2-treatment, 2-period CR	5 x 100 mg sparsentan (fed) 5 x 100 mg sparsentan (fasted) Oral administration	14	Healthy subjects	Single dose	Complete CSR

Study Identifier and Site Locations	Location of Study Report Within Application	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status Type of Report
PCO-C-009[a] USA	5.3.3.1	Mass balance recovery and metabolite profiling; safety, tolerability, and PK	SC, OL, SD, NR	500 mg sparsentan and 200 nCi of [^{14}C]sparsentan (suspension) (fasted) Oral administration	8	Healthy subjects	Single dose	Complete CSR
PCO-C-010[a] USA	5.3.3.3	Effect of age and sex on the single-dose PK profile of sparsentan; effect of age and sex on safety and tolerability	SC, OL, SD, NR	500 mg sparsentan (suspension) with approximately 1 µCi of [^{14}C]sparsentan Oral administration	39	Healthy subjects	Single dose	Complete CSR
021HVOL16001 USA	5.3.1.2	Relative bioavailability of tablet vs capsule formulations; safety and tolerability	SC, OL, SD, R, CR	1 x 400 mg sparsentan tablet (Test) 4 x 100 mg sparsentan capsules (Reference) Oral administration	33	Healthy subjects	Single dose	Complete CSR

Study Identifier and Site Locations	Location of Study Report Within Application	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status Type of Report
021HVOL16002 USA	5.3.4.1	QT interval (TQT), safety, tolerability, and PK Part 1: MTD Part 2: 4-arm, 4-period crossover	SC, DB, R, PC/AC, SD	Part 1: 1200 mg sparsentan 1600 mg sparsentan Single oral dose Part 2: 800 mg sparsentan 1600 mg sparsentan Moxifloxacin Single oral dose	Part 1: 9 Part 2: 60	Healthy subjects	Single dose	Complete CSR
021HVOL16005 USA	5.3.3.1	Mass balance and routes of elimination, metabolite profiling, safety, tolerability, and PK	SC, OL, SD, NR	400 mg sparsentan (suspension) with approximately 1 µCi of [^{14}C]sparsentan Oral administration	8	Healthy subjects	Single dose	Complete CSR

021HVOL16006 USA	5.3.3.4	Safety, efficacy, tolerability, and PK profile	SC, OL, PR, 2-sequence, 3-treatment study	200 mg sparsentan (capsule) single dose (Reference); 600 mg cyclosporine, (capsule) + 200 mg sparsentan (capsule) single dose (Test 1); 200 mg itraconazole (solution) BID Day 1 and QD Days 2 to 10 + 200 mg sparsentan (capsule) single dose Day 6 (Test 2) Oral administration	32	Healthy subjects	39 days	Complete CSR

Study Identifier and Site Locations	**Location of Study Report Within Application**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) and Dosage Regimen** **Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treatment**	**Study Status** **Type of Report**
021HVOL16007 USA	5.3.3.4	Safety, tolerability, and PK profile	SC, OL, R, 2-period, 2-sequence, CR, DDI	Pitavastatin (tablet) 4 mg single dose Days 1 and 8 + sparsentan 800 mg (2 x 400 mg tablets) QD Days 7 through 10 Pitavastatin (tablet) 4 mg single dose Days 2 and 8 + sparsentan 800 mg (2 x 400 mg tablets) QD Days 1 through 4 Oral administration	28	Healthy subjects	Approx. 46 days	Complete CSR

021HVOL16008 USA	5.3.3.4	Safety, tolerability, efficacy, and PK profile	SS, CR, OL, 2-period, SD	Midazolam: 1 mL single dose of 2 mg/mL syrup on Days 1 and 14 Bupropion: 150 mg (2 x 75 mg tablets) single dose on Days 3 and 16 Sparsentan: 800 mg (2 x 400 mg tablets) QD on Days 7 through 19 Oral administration	28	Healthy subjects	Up to 55 days	Complete PK Report

021HVOL109 USA	5.3.3.4	Safety, efficacy, tolerability, and PK profile	OL, R, SD, 4-period, CR	A: 200 mg sparsentan tablet with 10-hour fast B: 200 mg sparsentan tablet with high-fat meal C: 2 x 400 mg sparsentan tablets with 10-hour fast D: 2 x 400 mg sparsentan tablets with high-fat meal Oral administration	16	Healthy subjects	Single dose	Complete CSR
021IHFX16009 USA	5.3.3.3	Safety, tolerability, and PK profile	MC, PG, OL, SD	Sparsentan 400 mg single dose Oral administration	28	Subjects with mild or moderate hepatic impairment or with normal hepatic function	Single dose	Complete CSR

RTRX-RE021-101 USA	5.3.1.2	Bioequivalence	SC, OL, R 2-period, 2-way crossover	Sparsentan 400 mg tablet Sparsentan 200 mg tablet Oral administration	36	Healthy subjects	Single dose	Complete CSR
RTRX-RE021-102 UK	NA[b]	PK of SD in fasted and fed states PK after a standard high-fat breakfast PK of MD in fed state	OL, R, SD, MD, 3-way sequential	Sparsentan 200, 400, and 800 mg Oral administration	47	Healthy subjects	29 days	Complete CSR
RTRX-RE021-103 USA	5.3.3.1	PK of SD in fasted and fed states PK after 7 and 14 days repeat dosing Safety and tolerability, BP, HR, and QTc	SC, OL, PG, MAD	Sparsentan 50, 100, 200, 400, 800, and 1600 mg Single dose in fasted and fed states Multiple doses in fasted state Oral administration	36	Healthy subjects	14 days	Complete CSR

TVTX-RE021-106	NA[c]	Effect of multiple-dose sparsentan on the PK of single-dose dapagliflozin Safety and tolerability	OL, DDI, 1-sequence, 2-period crossover	Sparsentan 800 mg and once daily sparsentan for 10 days following single administration of 10 mg dose of dapagliflozin Oral administration	22 enrolled	Healthy subjects	22 days	Ongoing
TVTX-RE021-107	NA[c]	PK of single and multiple dose of sparsentan Dose proportionality, safety, and tolerability	SC, OL, SD, and MD	1: 200 mg fasted for 15 days 2: 400 mg fasted for 15 days 3: 800 mg fasted for 15 days 4: 400 mg fasted for 15 days Cohorts 1 to 3 in first-generation Japanese males; Cohort 4 in non-Asian males Oral administration	24 planned	Healthy subjects	22 days	Ongoing
Phase 2 Studies								
PCO-C-006 USA	5.3.5.4	Safety and efficacy	MC, R, DB, PC, AC, PG	100 mg sparsentan 300 mg irbesartan or placebo Oral administration	261	Subjects with hypertension	4-week SB placebo run-in period 12-week DB treatment period 3-day withdrawal period	Complete CSR
PCO-C-008 USA	5.3.5.4	Safety and efficacy	MC, R, DB, PC, PG	2 x 100 mg or 5 x 100 mg sparsentan Oral administration	113	Stage 1 and 2 hypertension	3- to 4-week SB placebo run-in 4-week DB period (<28 days)	Complete CSR
RET-D-001; DUET USA, Italy, and Czech Republic	NA[c]	Safety and efficacy	MC, R, dose escalation with an 8-week DB, AC treatment period, followed by an OL period	Sparsentan 200, 400, or 800 mg QD or irbesartan 300 mg QD for 8 weeks Followed by open-label sparsentan 200, 400, or 800 mg QD Oral administration	109 enrolled	Subjects with FSGS	8 weeks in the DB period	Ongoing (OLE) Interim CSR
RTRX-RE021-201; EPPIK	NA[b]	Safety, efficacy, and PK in pediatric	MC, R, OL	Sparsentan suspension (80 mg/mL) Oral administration	57 planned	Pediatric subjects with selected proteinuric glomerular diseases	108 weeks	Ongoing

Phase 3 Studies								
021FSGS16010; DUPLEX North America, Europe, Asia-Pacific, and South America	NA[c]	Safety, efficacy, and tolerability	MC, R, DB, AC, OL	Sparsentan 400 mg QD for 2 weeks, titrating to 800 mg QD Irbesartan 150 mg QD for 2 weeks, titrating to 300 mg QD Oral administration	371 enrolled	Subjects with FSGS	268 weeks (112 weeks followed by an OLE of up to 156 weeks)	Ongoing Interim CSR
021IGAN17001 (PROTECT) North America, Europe, and Asia-Pacific	5.3.5.1	Safety and efficacy	R, MC, DB, PG, AC	Sparsentan 200 mg QD for 2 weeks titrating to 400 mg QD Irbesartan 150 mg QD for 2 weeks, titrating to 300 mg QD OLE period of up to 156 weeks Oral administration	406 enrolled	Subjects with IgAN	270 weeks (114 weeks followed by an OLE of up to 156 weeks)	Ongoing Interim CSR

Study Identifier and Site Locations	**Location of Study Report Within Application**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) and Dosage Regimen** **Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Subjects**	**Duration of Treatment**	**Study Status** **Type of Report**
Investigator Study								
SPARTAN University of Leicester (Travere funded)	NA[c]	Safety and exploratory activity	SC, NR, OL	Sparsentan 200 mg QD for 2 weeks, titrating to 400 mg QD Oral administration	10 planned	Subjects with IgAN	110 weeks	Ongoing

[a] PK data derived from samples analyzed by the bioanalytical facility of Cetero Research were excluded from the evaluation of the PK and clinical pharmacology of sparsentan due to US FDA identified significant instances of misconduct and violations of federal regulations.
[b] This study is relevant to pediatric studies only and is not included in the FDA submission for adult administration.
[c] This study is not included in the FDA submission as study is ongoing.
AC = active-controlled; BID = twice daily; BP = blood pressure; CR = crossover; CSR = clinical study report; DB = double-blind; DDI = drug-drug interaction; HR = heart rate; FSGS = focal segmental glomerulosclerosis; IgAN = immunoglobulin A nephropathy; MAD = multiple ascending dose; MC = multi-center; MD = multiple dose; MTD = maximum tolerated dose; NA = not applicable; NR = non-randomized; OL = open-label; OLE = open label extension; PC = placebo controlled; PG = parallel group; PK = pharmacokinetic(s); PR = partially randomized; QD = daily; QTc = QT corrected for heart rate; R = randomized; SAD = single ascending dose; SB = single blind; SC = single-center; SD = single dose; SS = single sequence; TQT = QT interval; UK = United Kingdom; USA = United States of America; vs = versus

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of sparsentan was investigated in 13 clinical studies in healthy volunteers or patients with IgAN or FSGS. PopPK analysis was used to identify significant covariates (gender and age). Furthermore, *in vitro* studies were conducted to investigate the permeability, plasma protein binding, the blood-to-plasma ratio, metabolism, enzyme identification, substrate for transporters, CYP inhibition and induction, transporter inhibition, and the effect of other drugs on the metabolism of sparsentan. Clinical studies were conducted and analysed at Cetero research (studies PCO-C-001, PCO-C-002, PCO-C-003, PCO-C-004, PCO-C-007, PCO-C-009 and PCO-C-010). In 2011, the FDA identified significant instances of misconduct and violations of federal regulations, including falsification of documents and manipulation of samples. The EMA concluded that clinical PK data generated at the

Cetero Houston facility from 01 April 2005 to 15 June 2010 need to be excluded. Therefore, the PK outcome of these studies is not included in the assessment. The clinical PK studies were repeated and are included as part of the MAA. This approach to exclude PK data from studies with unreliable analytical analysis is acceptable. Sparsentan treatment for IgAN is initiated at a dose of 200 mg once daily for 14 days and then increased to a maintenance dose of 400 mg once daily, as tolerated.

The below Table 1 reflects the conducted PK studies.

Table 1. Pharmacokinetic studies

Study	Description	Dose
Studies in healthy volunteers		
021HVOL16005	Investigation of sparsentan absorption, metabolism, and excretion	Single dose of 400 mg
RTRX-RE021-103	Single (under fasted and fed condition) and multiple ascending dose study of sparsentan safety, tolerability, and PK	Single dose of 50, 100, 200, 400, 800 or 1600 mg Repeated dose of 50, 100, 200, 400, 800 or 1600 mg once daily
021HVOL109	Effect of food on the PK of sparsentan	Single dose of 200 mg and 800 mg
021HVOL16002	Effect of sparsentan on QT interval	
021HVOL16001	Comparative bioavailability of sparsentan tablet versus sparsentan capsule	Single dose with 4 × 100 mg capsule or 1 × 400 mg tablet
RTRX-RE021-101	Bioequivalence study of 200 mg sparsentan tablet versus 400 mg sparsentan tablet	Single dose with 2 × 200 mg or 1 × 400 mg tablet
Studies in patients		
021IGAN17001 (PROTECT)	Phase 3 study of sparsentan efficacy in subjects with IgAN versus active control	Repeated dose of 200 mg once daily for 2 weeks followed by 400 mg once daily for up to 110 weeks
021FSGS16010 (DUPLEX)	Phase 3 study of sparsentan efficacy in subjects with FSGS versus active control	Repeated dose of 400 mg once daily for 2 weeks followed by 800 mg once daily
RET-D-001 (DUET)	Phase 2 study of sparsentan efficacy and safety in subjects with FSGS	Repeated dose of 200 mg, 400 mg or 800 mg once daily
Special populations		
021IHFX16009	Effect of hepatic impairment on the PK of sparsentan	Single dose of 400 mg
DDI studies as victim		
021HVOL16006	Effect of cyclosporine and itraconazole on the PK of sparsentan	Single dose of 200 mg
DDI studies as perpetrator		
021HVOL16007	Effect of sparsentan on the PK of pitavastatin	Repeated dose of 800 mg once daily for 4 days
021HVOL16008	Effect of sparsentan on the PK of midazolam and bupropion	Repeated dose of 800 mg once daily for 13 days

Absorption

Following oral administration, the rate of absorption of sparsentan was moderate, with a median time to maximum plasma concentration (t_{max}) of approximately 3 hours. Following a single dose of 400 mg sparsentan, the C_{max} and $AUC_{0\text{-}inf}$ were 6.97 µg/mL (CV%=34) and 83.0 µg × h/mL (CV%=46), respectively, and after a single dose of 800 mg sparsentan, the C_{max} and $AUC_{0\text{-}inf}$ were 8.62 µg/mL (CV%=21) and 161 µg × h/mL (CV%=27), respectively. Following multiple doses of 400 mg once daily sparsentan for 14 days, the C_{max} and $AUC_{0\text{-}inf}$ were 6.47 µg/mL (CV%=35) and 63.6 µg × h/mL (30%), respectively, and after multiple doses of 800 mg once daily sparsentan for 14 days, the C_{max} and $AUC_{0\text{-}inf}$ were 9.81 µg/mL (CV%=19) and 96.9 µg × /mL (CV%=19), respectively.

The PK of sparsentan is less than dose-proportional over the dose range of 200 mg to 400 mg. This is most likely due to the poor solubility of sparsentan. No accumulation was observed following once-daily dosing with 200 mg and 400 mg sparsentan. A steady state is reached within 7 days.

Following administration of a single dose of sparsentan at 200 mg, a high-fat meal (1000 calories, 50% fat) had minimal effect on sparsentan exposure, with C_{max} increased by 22% and AUC decreased by 14% when compared to the fasted state. Following the administration of a single dose of sparsentan at 800 mg, a high-fat meal (1000 calories, 50% fat) increased C_{max} and AUC by 108% and 22%, respectively, when compared to the fasted state. In another study, the effect of food on a single oral dose of 50, 100, 200, 400, 800, and 1600 mg sparsentan using crushed tablets was investigated. The C_{max} increased 1.07-fold at 200 mg, 1.16-fold at 400 mg and 2.01-fold at 800 mg under fed conditions compared to fasted conditions. AUC decreased at 200 and 400 mg and increased 1.1-fold at 800 mg. The effect of food on the exposure is dependent on the administered dose, with a high effect at 800 mg and no effect at 200 mg and 400 mg doses. Sparsentan can be taken with or without food with the current posology as reflected in the SmPC.

Distribution

The plasma protein binding is high (≥97% *in vitro* and ≥99% *ex vivo*) and sparsentan is mainly bound to albumin. The blood-to-plasma ratio is <1, indicating that sparsentan is mainly in plasma and not in the erythrocytes. The apparent volume of distribution is 61.4 L at a clinically relevant dose of 400 mg, indicating some distribution outside the blood compartment. Subject type (IgAN versus healthy) had no clinically relevant impact on the sparsentan PK exposure. Sparsentan CL in subjects with IgAN was approximately 16% lower than in healthy subjects, with no statistically significant impact on PK.

Elimination

Sparsentan is mainly metabolised by CYP3A4, with a minor contribution of CYP2C8, 2C9 and 3A5. Following oral administration, nine metabolites were identified across plasma, faeces, and urine. In human plasma, sparsentan accounted for approximately 90% of the radioactivity; a minor hydroxylated metabolite was the only metabolite in plasma that accounted for >1% of the sample radioactivity (approximately 3%). Following single oral administration of [^{14}C]-sparsentan, faecal excretion was the predominant route of elimination of the radioactive dose; 80.2% and 2.3% of the dose were recovered in faeces and urine. At the maximal clinical dose of 400 mg, the elimination half-life is 10.2 h following a single dose and 10.8 h following repeated dosing. Based on popPK analysis, the apparent clearance is 3.88 L/h, increasing to 5.11 L/h at steady state.

Special populations

A clinical study was conducted to investigate the effect of hepatic impairment on the PK of sparsentan. The effect of renal function, gender, age, and race was investigated using PopPK modelling.

No PK studies were performed investigating the effect of renal function on the PK of sparsentan. Mild and moderate renal impairment is not expected to affect the PK of sparsentan, because renal elimination is very limited. However, severe renal impairment may affect the PK of sparsentan because

it may lead to metabolic changes. Based on population PK analysis in chronic kidney disease patients with mild or moderate kidney disease, there was no clinically meaningful effect of kidney impairment on PK as compared to normal kidney function. As there is limited clinical experience in patients with severe kidney disease, sparsentan is not recommended in these patients. No data are available in patients with end-stage kidney disease. Sparsentan has not been studied in patients who have received a kidney transplant, therefore sparsentan should be used with caution is these patients. Similarly, it was not been studied in patients undergoing dialysis and initiation of sparsentan is not recommended in these patients.

Mild hepatic impairment does not have an effect on the PK of sparsentan. However, the C_{max} and AUC is increased in subjects with moderate hepatic impairment. In addition, the free fraction in subjects with moderate hepatic impairment is significantly higher than in subjects with normal hepatic function. This results in a 2.2-fold increase in $C_{max,unbound}$ and a 2.0-fold increase in $AUC_{0\text{-}36h,unbound}$. Based on the therapeutic window, no dose adjustment is needed in patients with moderate hepatic impairment. However, sparsentan should be used with caution in patients with moderate hepatic impairment, see SmPC. No information is available on the effect of severe hepatic impairment on the PK of sparsentan, sparsentan is therefore not recommended in these patients.

The effect of gender on the PK of sparsentan is limited (<20% on AUC, <10% on C_{max}, and <40% on C_{trough}) and is most likely due to the on average lower body weight in females compared to males. There was a low to modest effect of race (White, Black, and Asian) on sparsentan Vc/F and PK variability and is considered not clinically meaningful. No effect of age >65 years was observed with the PopPK model, but this is based on limited data (no patients aged 75 years and older were included and 35 [9% of total population] patients aged 65-74 years were included in the studies).

Simulations of exposure of sparsentan in subjects with immunoglobulin A nephropathy (IgAN) at 200 mg and 400 mg in 4 weight categories show that body weight does not appear to affect the exposure of sparsentan to a major extent. Therefore, dose adjustments based on body weight appear not necessary for the IgAN population.

Pharmacokinetic interaction studies

Sparsentan as perpetrator: At maximal intestinal concentrations, sparsentan is an *in vitro* inhibitor of CYP3A4, P-glycoprotein, BCRP and MRP2. At maximal portal vein concentrations, sparsentan is an *in vitro* inhibitor of OATP1B3 and OATP2B1. In a clinical DDI study with 800 mg sparsentan co-administered with pitavastatin (substrate of OATP1B1 and 1B3), C_{max} was increased by 1.2-fold and $AUC_{0\text{-}inf}$ by 1.4 fold which was not considered clinically relevant. Thus, at clinical dosages, sparsentan is not an inhibitor of OATP1B3. The clinical relevance of the observed *in vitro* OAPT2B1 inhibition is unknown.

At maximal systemic concentrations, sparsentan is an *in vitro* direct and time-dependent inhibitor of CYP3A4 and an inhibitor of OATP1B3, OAT1, OAT3 and BSEP. Furthermore, sparsentan is an inducer via CAR and PXR. The applicant is investigating whether sparsentan is an *in vitro* inhibitor of OCT1 as a post-authorisation measure (PAM) and is requested to submit the final study report by Q2 of 2024. Sparsentan was found to have no effect on serum bile acids, which are substrates of BSEP, indicating that sparsentan has no clinically relevant effect on BSEP *in vivo*. Furthermore, sparsentan had no effect on 6β hydroxycortisol (substrate of OAT3) clearance, indicating that sparsentan has no clinically relevant effect on OAT3 *in vivo*. However, the inhibition effect of sparsentan following a single dose on the PK of a substrate of CYP3A was not investigated. The applicant plans to conduct a clinical DDI study to investigate the CYP3A4 inhibition potential of sparsentan. Furthermore, the applicant will investigate the *in vivo* induction potential of sparsentan on CYP2C9 following multiple dosing as a PAM.

Sparsentan as victim: Sparsentan is mainly metabolised by CYP3A4 with minor contribution from CYP2C8, CYP2C9 and CYP3A5. Sparsentan was a substrate of P-glycoprotein and BCRP. The less than dose-proportional increase in exposure of sparsentan over the clinical dose range of 200 mg to 400 mg indicates that efflux in the intestine by P-glycoprotein and BCRP does not significantly affect the absorption and is most likely saturated at clinically relevant doses. Therefore, no clinical DDI studies with inhibitors of P-glycoprotein and BCRP are warranted.

Co-administration with a strong CYP3A4 inhibitor (itraconazole) caused an increase in sparsentan exposure (C_{max} by 1.3-fold and $AUC_{0\text{-}inf}$ by 2.7-fold). Co-administration with a moderate CYP3A4 inhibitor (cyclosporine) caused an increase in sparsentan exposure (C_{max} by 1.4-fold and $AUC_{0\text{-}inf}$ by 1.7-fold). Overall, the C_{max} is affected similarly by strong and moderate CYP3A4 inhibitors, indicating that at dosing, not only CYP3A4 is involved in the metabolism of sparsentan and also CYP2C8 and 2C9 may be involved. Furthermore, a strong CYP3A4 inhibitor resulted only in a 2.7-fold increase in exposure of sparsentan.

In the SmPC section 4.5 concomitant use with strong and moderate CYP3A4 inducers is not recommended. This is agreed for strong inducers due to most likely lack of efficacy. However, current administered co-medication includes moderate CYP3A4 inducer. Therefore, recommendation not to use moderate CYP3A4 inducers would lead to a subpopulation not been able to be treated. It is therefore important to know if concomitant administration with a moderate PXR inducer will have a clinically significant effect on the PK of sparsentan or not. The applicant will investigate the effect of a moderate PXR inducer on the PK of sparsentan as a PAM. Until the study results become available the recommendation to not use moderate CYP3A4 inducers concomitantly with sparsentan is agreed.

2.6.2.2. Pharmacodynamics

Mechanism of action

Glomerular injury and scarring are the hallmark of CKD progression regardless of the underlying disease, and increased production of ET-1 has been found in multiple diseases associated with CKD, including IgAN. ET synthesis is upregulated by gene transcription induced by angiotensin, vasopressin, interleukin-1, and low extracellular pH. Angiotensin II triggers the release of aldosterone from the adrenal cortex, which in turn increases renal ET-1 expression. Angiotensin II also directly triggers the contraction of the vascular smooth muscle of both afferent and efferent arterioles. This eventually leads to decreased renal blood flow, as well as glomerular capillary hypertension. ET-1 is a growth factor that acts via its two receptors, endothelin-A (ETAR) and endothelin-B (ETBR) receptor. It may have several deleterious effects on the kidney, including vasoconstriction, mesangial cell proliferation, podocyte disruption, production of extracellular matrix, inflammation, and fibrosis. Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) inhibits activation of both ETAR and AT1R, thereby reducing proteinuria, and is expected to slow the progression of kidney disease.

Primary and Secondary pharmacology

Pharmacology of sparsentan was investigated in the following studies:

Study PCO-C-002 was a randomised, controlled study of angiotensin II blockade by single doses of sparsentan in healthy subjects compared with placebo and irbesartan. The objectives of the study were to provide an effective antihypertensive dose in man by studying the ability of sparsentan compared with placebo and irbesartan to antagonize the pressor effect of exogenously administered angiotensin II (AII). The subjects received 20, 100, 250 and 500 mg single dose of sparsentan or 300 mg single dose of irbesartan.

To the AII challenge, all doses of sparsentan and irbesartan had clinically and statistically important inhibition of SBP and DBP compared to placebo. Placebo had no effect on SBP and DBP. The effect was sustained for at least 24 hours after sparsentan administration.

RTRX-RE021-103 study was an open-label, parallel-group, fixed single and multiple dose study to evaluate the PK, safety, and tolerability of sparsentan in healthy males and females. One of the exploratory endpoints was to evaluate changes in concentrations of ET-1 following single-dose administration of sparsentan.

There were minor changes in mean baseline plasma ET-1 concentrations following the administration of single oral doses of 50, 100, 200, 400, 800, and 1600 mg sparsentan under fasting conditions. No clear increase or decrease is plasma ET-1 levels was observed taking different doses of sparsentan. ET-1 concentrations were not observed in healthy patients not taking the study drug. The relationship between sparsentan plasma concentrations and dQTc was assessed using a linear mixed-effect model by evaluating the retrieved data from the current study on dQTc on time-matched sparsentan concentrations. Based on this model, the predicted maximum dQTcF at the geometric mean C_{max} of plasma sparsentan under fasted conditions ranged from 0.013ms (50 mg sparsentan) to 3.070ms (1600 mg sparsentan). The upper bound of the 90% CI ranged from -0.370ms (50 mg sparsentan) to 3.637ms (1600 mg sparsentan).

In the Phase 2 RET-D-001 (DUET) study and Phase 3 021FSGS16010 (DUPLEX) and 021IGAN17001 (PROTECT) studies in patients with IgAN and FSGS, sparsentan tablets were effective in reducing proteinuria compared with irbesartan tablets.

PCO-C-006 study was a randomised, double-blind, placebo- and active-controlled, parallel-group study to evaluate the dose-related efficacy and safety of sparsentan in subjects with hypertension. Patients' mean seated SBP had to be ≥140 mmHg and ≤179 mmHg and mean seated DBP had to be ≥90 mmHg and ≤109 mmHg. Patients were weaned off all antihypertensive medications and randomised to receive sparsentan at daily doses of 200, 400, or 800 mg, irbesartan 300 mg, or a matching placebo. After 12 weeks of treatment in sparsentan group, mean decrease in seated SBP in 200 mg dose was 13.2 mmHg and in 400 mg dose -14.2 mmHg. The decrease in seated mean SBP was statistically significant compared to placebo in the FAS group. After 12 weeks of treatment, in the sparsentan group mean decrease in seated DBP in 200 mg dose was 7.2 mmHg and in 400 mg dose -9.2 mmHg. The decrease in seated mean DBP was statistically significant when compared to placebo in the FAS population.

PCO-C-008 study was a prospective, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of sparsentan in subjects with stage I and stage II hypertension. Included patients' mean seated SBP had to be ≥150 mmHg and ≤179 mmHg and mean seated DBP had to be ≤110 mmHg and they were weaned off all antihypertensive medications. 113 patients were included in the primary analysis and randomised to receive sparsentan at doses of 200 or 500 mg or a matching placebo taken once daily. After 4 weeks of treatment, the mean SBP decrease was 12.2 mmHg in the 400 mg dose group and 14.8 mmHg in the 500 mg dose group. The decrease in mean ASBP was statistically significant when compared with placebo. After 4 weeks of treatment in sparsentan group mean decrease in ADBP in 200 mg dose was 9.3 mmHg and in 500 mg dose - 10.1 mmHg. The decrease in mean ADBP was statistically significant when compared with placebo.

021HVOL16002 study was a 2-center, 2-part randomised, blinded, placebo- and active-controlled study to evaluate the QT/QTc interval prolongation potential of sparsentan when administered to healthy subjects. Part 1 was a single ascending dose (SAD) evaluation of the safety and tolerability of 1200 mg and 1600 mg—of sparsentan compared to placebo. Part 2 was to explore the effect of

sparsentan on cardiac repolarization (QTc duration) using single oral therapeutic dose 800 mg and a single safe supratherapeutic dose 1600 mg.

In sparsentan group, mild QTcF prolongation with a peak effect at 5 hours post-dose was observed in 800 mg (8.8 msec, 90% CI 5.93; 11.76) and 1600 mg (8.1 msec, 90% CI 5.22; 10.96) dose groups compared to a larger effect on QTcF prolongation in 400 mg moxifloxacin group. There were no subjects with QTcF >480 msec at any timepoint.

2.6.3. Discussion on clinical pharmacology

In vitro and clinical studies were conducted with sparsentan. PopPK modelling was used to investigate the effect of different intrinsic and extrinsic factors on the PK of sparsentan. In general, the PK has been sufficiently characterised.

The applicant will investigate *in vitro* if sparsentan is an inhibitor of OCT1 as PAM. Furthermore, the applicant plans to provide results from a clinical DDI study investigating the relevance of the inhibition towards CYP3A4 following a single dose of sparsentan and will also conduct a clinical DDI study towards the CYP2C9 induction potential of sparsentan. Additional investigations will examine the effect of a moderate PXR inducer on the PK of sparsentan (single dose) in a clinical DDI study (PAM).

Sparsentan inhibits the activation of both ETAR and AT1R, thereby reducing proteinuria and slowing the progression of kidney disease. The effect on inhibition of angiotensin II was presented in PCO-C-002 study and is acceptable. No effect on ET1 concentrations was found, which can be explained by sparsentan preferably binding to ET_A receptors, whereas ET_B receptors mediated the majority of the systemic ET-1 clearance. Sparsentan showed a positive effect on reducing SBP and DBP in subjects with hypertension and hypertension due to exogenously administered angiotensin II in three clinical studies (PCO-C-002, PCO-C-006 and PCO-C-008).

In study RTRX-RE021-103, the applicant performed a PK study investigating a range of sparsentan doses, including QTc analyses. However, this study was limited as there was no positive control nor a placebo group, the dose proportionality of the peak QTc effect was not adequately demonstrated. Lastly, the concentration-effect analyses appear to focus on multiple time points rather than the time points with the peak QTc effect. Overall, the results from study RTRX-RE021-103 are considered of lesser relevance than those of the thorough QT/QTc study 021HVOL16002, in which the applicant performed an extensive QT/QTc testing. It was a double-blind (except for moxifloxacin), randomised QT trial study. Sparsentan at 800- and 1600-mg doses caused mild QTcF prolongation with a peak effect at 5 hours post dosing. The ΔΔQTcF was comparable in both sparsentan periods without clear dose dependency.

2.6.4. Conclusions on clinical pharmacology

In general, the clinical pharmacology profile of sparsentan was sufficiently characterised. Data have been presented on the mechanism of action of sparsentan, on ET concentrations and on blood pressure. Furthermore, secondary pharmacology, including evaluation of QT prolongation, have been discussed. The applicant committed to further investigate sparsentan's interaction profile in the post-marketing setting.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

1. Since moderate PXR inducers are known to be co-administered with sparsentan (e.g. corticosteroids) and not recommending co-administration would lead to a subpopulation that cannot be

treated with sparsentan. the applicant is requested to conduct a clinical DDI study with moderate PXR inducers. Due date: 30 June 2025

2. The applicant will investigate in vitro if sparsentan is an inhibitor of OCT1. Due date: 30 July 2024.

3. The applicant will investigate the in vivo induction potential of sparsentan towards CYP2C9 following multiple dosing. 30 June 2025

4. The applicant will perform a clinical DDI study to investigate the clinical relevance of the inhibition towards CYP3A following a single dose of sparsentan. Due date: 30 June 2025

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dose-ranging study was conducted in subjects with IgAN. The selection of the target dose of 400 mg QD for the PROTECT study in subjects with IgAN was based on the similar exposure to sparsentan and reduction in UP/C between 400 mg QD and 800 mg QD observed in the DUET study in subjects with FSGS.

Study RET-D-001 (DUET) was a phase 2, randomised, double-blind, active-control, dose-escalation study with an open-label extension period in subjects with FSGS. Subjects aged 8 to 75 years (United States) or 18 to 75 years (Europe) with biopsy-proven primary FSGS (or documentation of a genetic mutation in a podocyte protein associated with the disease) with a UP/C at or above 1.0 g/g and estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 were enrolled in the study. Subjects were randomised to receive either a sparsentan dose (200mg, 400mg or 800mg once daily (QD)), or comparator irbesartan (300mg QD).

The results demonstrated a statistically significant greater reduction in UP/C among pooled (all doses combined) sparsentan-treated subjects compared with irbesartan-treated subjects at Week 8. Reduction in UP/C appeared to reach a plateau between 400 mg and 800 mg, as evidenced by the ratio (sparsentan/ irbesartan) for change from baseline in 24-Hour Urinary Protein Excretion (mg/24 hours) at Week 8, which was 1.1 (95% CI 0.7, 1.8) for 200 mg, 0.4 (95% CI 0.2, 1.2) for 400 mg and 0.4 (95% CI 0.2, 1.1) for 800 mg Sparsentan. Similarly, following multiple oral administration of sparsentan to subjects with FSGS, systemic exposure (based on the AUC from time 0 to 24 hours postdose [AUC_{0-24}] and C_{max}) increased in a less than dose-proportional manner over the 200-800 mg dose range at steady state, and with the last dose-proportional increase between 400 and 800 mg, see Table 2 below.

Table 2. Effects of increasing dose on the pharmacokinetics of sparsentan in the DUET Study

Day		200 mg	400 mg	800 mg
Day 1	Dose increment	-	2.00	2.00
	Increase in $AUC_{(0-24)}$	-	1.55	1.37
	Increase in C_{max}	-	1.61	1.37
Day 57	Dose increment	-	2.00	2.00
	Increase in $AUC_{(0-24)}$	-	1.65	1.16
	Increase in C_{max}	-	1.65	1.06

Dose proportionality based on the preceding dose level

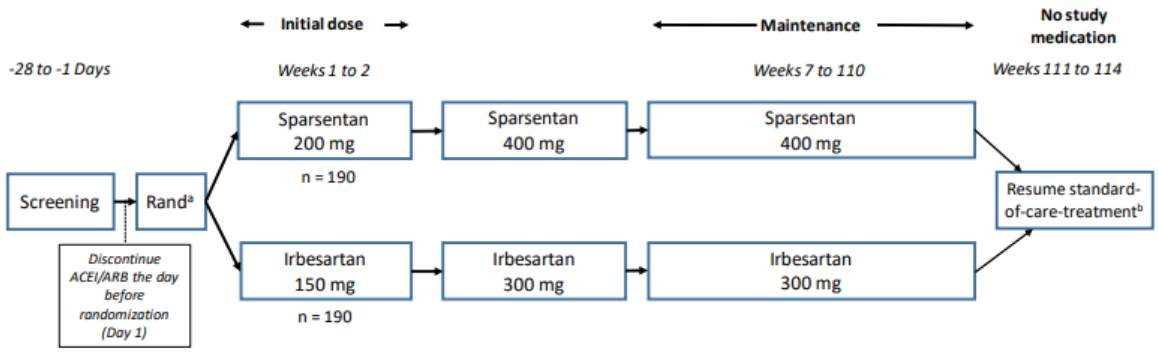
2.6.5.3. Main study

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
021IGAN17001 (PROTECT) Phase 3	156 centres in Europe North America, and Asia-Pacific	Randomised, double-blind, parallel-group, active control study, followed by an OLE phase	Sparsentan: initial 200 mg qd for 2 weeks, titrating to 400 mg qd Irbesartan: initial 150 mg qd, titrating to 300 mg qd	Efficacy, safety	404 RCT phase: Sparsentan: 202 Irbesartan: 202 21 OLE phase: Sparsentan	11 December 2018 to 08 Sep 2020 (RCT phase interim; OLE ongoing)	The mean age was 46.6 years (range: 18 to 73 years) in the sparsentan group and 45.4years (range: 19 to 76 years) in the irbesartan group. 139 (69%) in the sparsentan group and 143 (71%) in the irbesartan group were male.	IgAN patients biopsy - proven. urine protein excretion value ≥1.0 g/day eGFR ≥30 mL/min/ 1.73 m2	Percent Change from Baseline in UP/C at 36 Weeks: Sparsentan: -49.77% (95% CI: -54.98, -43.95) Irbesartan: -15.05% (95% CI: -23.72, -5.39)

Title of study

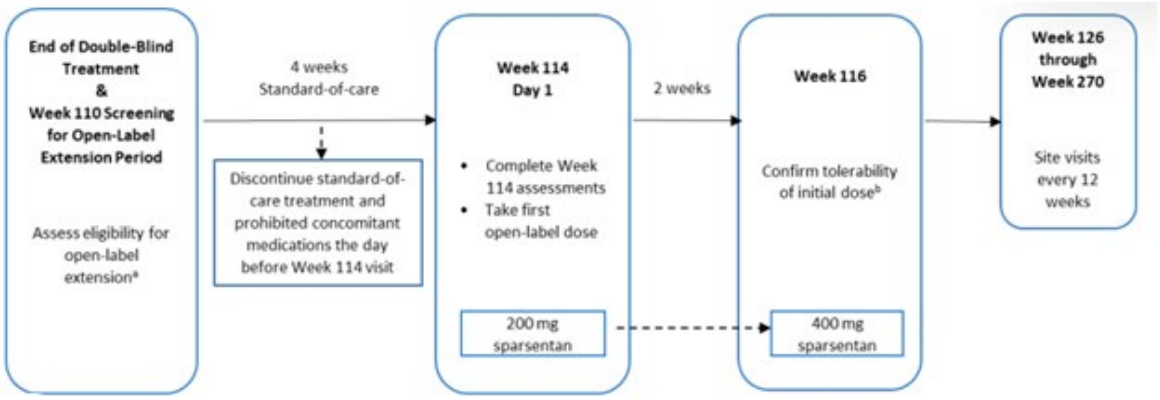
Study 021IGAN17001 (PROTECT) is a 114-week,randomised, multicenter, double-blind, parallel-group, active-control study with an open-label extension period of up to 156 weeks, for a total duration of up to 270 weeks in patients with IgAN who have persistent overt proteinuria and remain at high risk of disease progression despite being on a stable dose (or doses) of an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB) that is a maximum tolerated dose that is at least one half of the maximum labelled dose (MLD) according to approved labelling.

Figure 2. Study 021IGAN17001 (PROTECT) double -blind period overview



[a] On Day 1, subjects were randomized 1:1 to sparsentan or irbesartan, stratified by eGFR value (30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and urine protein excretion (≤1.75 g/day and >1.75 g/day).
[b] Resume standard-of-care treatment, including RAAS inhibitor treatment. Where possible, the same treatment regimen the subject was on at study entry (ie, the same ACEI and/or ARB at the same dose[s]) should be used, unless in the Investigator's opinion, an alternative treatment approach is warranted.

Figure 3. Study 021IGAN17001 OLE period



Methods

- **Study Participants**

Adults ≥ 18 years of age with IgAN (biopsy-proved), who had urine protein excretion value ≥1.0 g/day, eGFR ≥30 mL/min/1.73 m^2, were on a stable dose of ACEI and/or ARB therapy for at least 12 weeks and had well managed BP (SBP ≤ 150 mm Hg and DBP ≤100 mm Hg).

Patients were excluded if they had secondary IgAN or Henoch-Schonlein purpura, glomerular crescents present in >25% of glomeruli in a biopsy, CKD not associated with IgAN, any organ transplant (except corneal transplant), have been taking prohibited concomitant medications or/and systemic immunosuppressive medications or/and corticosteroids for >2 weeks for the last 3 months, had heart failure (NYHA class II-IV), other clinically significant disorders (cerebrovascular, coronary artery disease, jaundice, hepatitis, hepatobiliary disease, malignancy other than adequately treated basal cell or squamous cell skin cancer or cervical carcinoma), abnormal laboratory tests (ALT and/or AST >2 UNL, haematocrit value <27% (0.27 V/V) or haemoglobin value <9 g/dL (90 g/L), potassium value of >5.5 mEq/L (5.5 mmol/L)), allergy or hypersensitivity to any of the tested compounds or materials.

In the OLE phase, patients were those who completed the double-blind period, including the Week 114

visit, and those who did not permanently discontinue study medication during the double-blind period. Patients were excluded if they had progressed to end-stage renal disease requiring renal replacement therapy, developed any criteria for discontinuation of study medication or discontinuation from the study between Week 110 and Week 114, were unable to initiate, or developed contraindications to, treatment with RAAS inhibitors between Week 110 and Week 114, had an eGFR value of ≤20 mL/min/1.73 m^2 at Week 110, had a potassium value of >5.5 mEq/L (5.5 mmol/L).

- **Treatments**

RCT phase: Sparsentan tablets (FILSPARI) were titrated from 200 mg once daily (for the first 2 weeks after randomisation) to 400 mg once daily if the patient tolerated the drug. Dose tolerance after 2 weeks of treatment is characterised as SBP >100 mm Hg and DBP >60 mm Hg, no AEs and no laboratory findings. 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. Upon Investigator's evaluation, patients who continued the initial dose after 2 weeks of treatment could be titrated to the dose of 400mg once daily. Sparsentan was taken prior to the morning meal except on the day of a study visit.

Reference irbesartan tablets were taken in the same manner as sparsentan tablets. Irbesartan was titrated from 150 mg once daily (for the first 2 weeks after randomisation) to 300 mg once daily, if tolerated.

OLE phase: Sparsentan was titrated from 200mg at Week 114 to 400mg at Week 116 once daily if the drug was tolerated. If the patient tolerated the drug but had asymptomatic hypotension or orthostatic hypotension symptoms, patient continued initial dose of 200mg once daily. If the patient had an eGFR value of <30 mL/min/1.73m^2 at Week 110, any dose titration at Week 116 was at the Investigator's discretion. If the sparsentan dose was titrated to 400 mg at Week 116 and patients had an eGFR value of <30 mL/min/1.73 m^2, they were contacted by the Investigator at Week 118 to assess tolerance of the higher dose.

- **Objectives**

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 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.

- **Outcomes/endpoints**

The primary efficacy endpoint was the change from baseline in the UP/C based on a 24-hour urine sample at Week 36. Based on the EMA Scientific Advice (see section 1.6), the primary efficacy endpoint of a certain reduction of proteinuria cannot be sufficient as a surrogate endpoint alone, the reduction of proteinuria should be a combined endpoint with clear clinically meaningful benefit in GFR slopes. The applicant chose the rate of change in eGFR as a key secondary endpoint. According to EMA guideline on the clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency (EMA/CHMP/500825/2016) primary efficacy endpoint should be the prevention or slowing of decline in the level of renal function, defined as a clinically meaningful and stable GFR loss rate with or without one of co-primary endpoint, in this case, prevention of proteinuria/albuminuria.

Key secondary efficacy endpoints were as follows:

1. Rate of change in eGFR over a 52-Week (Week 6 to Week 58) period following the acute effect of randomised therapy at the primary analysis. Acute effect is described as the first 6 weeks of randomised treatment with study drug.

2. Rate of change in eGFR over a 104-Week period following the acute effect of randomised therapy at the final analysis.
3. Rate of change in eGFR over a 110-Week period following the initiation of randomised therapy at the final analysis.

Other secondary efficacy endpoints were:

1. The mean change from baseline in eGFR and selected proteinuria variables over time based on a 24-hour urine sample (urine protein excretion, urine albumin excretion, urine albumin/creatinine ratio [UA/C] and UP/C) through Week 110 (interim analysis was done through Week 94).
2. The proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death. ESRD was defined as initiation of renal replacement therapy or sustained eGFR value of <15 mL/min/1.73 m^2.

Data on adverse reactions, vital signs, physical examination, and clinical laboratory assessments were also collected during this study.

Endpoints in the OLE phase were:

1. The absolute and percent change from Week 114 in eGFR at each visit
2. The percent change from Week 114 in UP/C at each visit
3. Changes from Week 114 in QoL at each visit
4. Changes from Week 114 in body weight, vital signs, physical examinations, peripheral oedema, and clinical laboratory parameters
5. Changes from Week 114 in lipid profile (total cholesterol and triglycerides, low-density lipoprotein C, and high-density lipoprotein C)
6. The incidence of TEAEs during the open-label extension period

- **Sample size**

The sample size (380 subjects) was calculated based on The Tufts University/University of Utah trial-level analysis, which indicated that a 40% relative treatment effect on change in proteinuria at 9 months can predict a treatment effect of approximately 2.9 mL/min/1.73 m^2/year on the total slope of eGFR over 2 years, with 90% power. In addition, approximately 380 patients provide 80% power to detect a smaller treatment effect on eGFR slope at 2 years of 2.55 mL/min/1.73 m^2 per year. Consequently, approximately 380 patients provide more than 90% power to detect an underlying treatment effect in the rate of change in eGFR over 104 weeks following the initial acute effect of randomised therapy (eGFR chronic slope at 2 years) of 3.15 mL/min/1.73 m^2 per year.

- **Randomisation and Blinding (masking)**

Patients were randomised in a 1:1 ratio using an interactive response technology system based on a permuted-block randomisation method to receive either sparsentan or irbesartan. The study utilised a centralised stratified randomisation 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). Treatment allocation was not revealed before database lock for the entire study. All patients, investigators, and study personnel involved in the study were blinded to treatment assignment except for a Data Monitoring Committee, study drug supply, SAE reporting contact, independent statistical team, and the team of individuals prespecified in the data analysis and dissemination plan. The

randomisation code and corresponding treatment assignments were maintained by the interactive randomisation technology (IRT).

OLE FAS: This population includes all patients who received at least 1 dose of sparsentan during this phase.

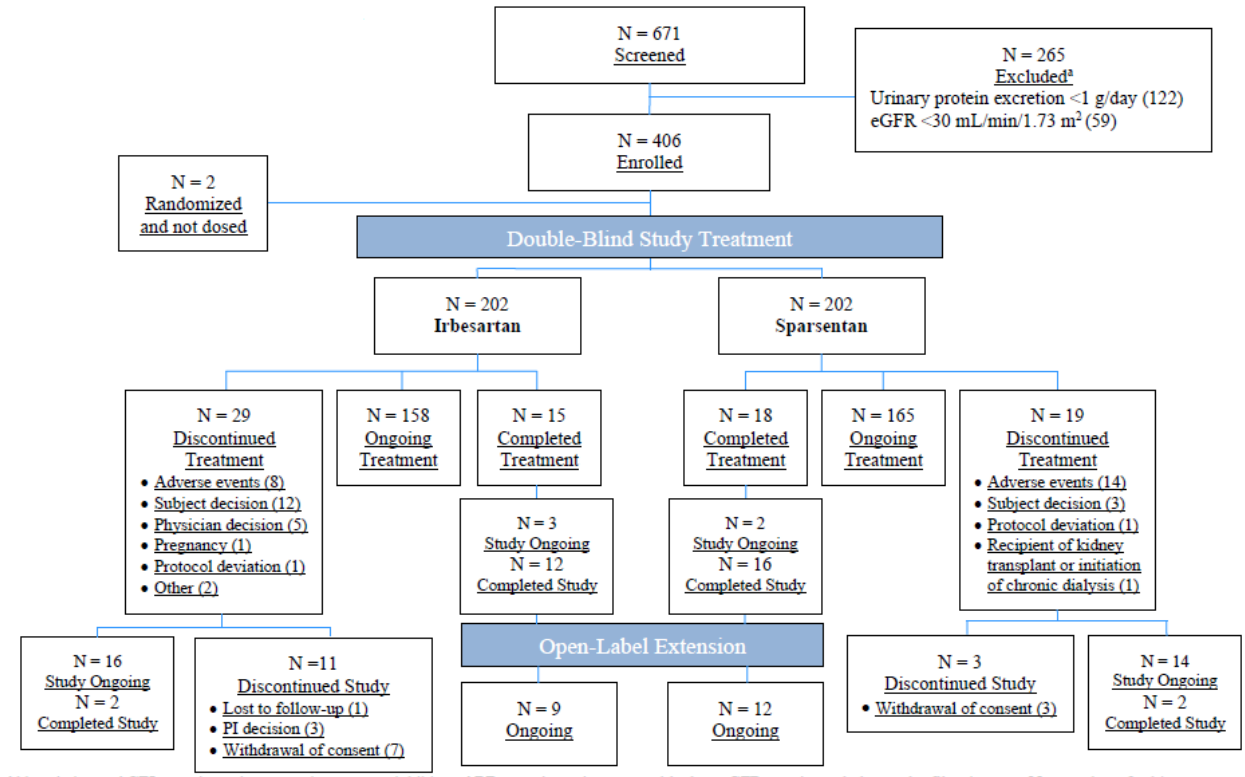
- **Statistical methods**

The primary efficacy endpoint in the key study was the change from baseline in the UP/C based on a 24-hour urine sample at Week 36, 236 patients were evaluated for the primary efficacy endpoint, with 136 patients in sparsentan group and 127 in irbesartan group. The test of the primary endpoint was least squares means at week 36 between sparsentan and irbesartan, adjusted for baseline proteinuria (UP/C) using MMRM analysis. Additional subgroup analysis was performed for gender, region, age, baseline characteristics, randomisation strata, baseline eGFR and urine protein.

Results

- **Participant flow**

Patient Disposition During the 021IGAN17001 (PROTECT) study (404 patients were included in FAS, PAS and Safety Analysis Set (202 patients in each treatment group)).



Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; N = number of subjects.
[a] The most common reasons for subjects' exclusion were due to the inclusion criteria of urinary protein excretion ≥1 g/g (N = 122), eGFR ≥30 mL/min/1.73 m² (N = 59), and on a stable dose of ACEI and/or ARB for at least 12 weeks that is the subject's maximum tolerated dose and at least one-half of the maximum label dose at screening (N = 44). Counts across reasons for screen failures were not unique.

In total, 193 patients in the sparsentan group and 187 in the irbesartan group were included in the Per Protocol set at Primary Analysis; 24 patients were excluded from this analysis due to protocol deviations (Figure 4).

Figure 4. Analysis Sets

Analysis Sets (Randomized Subjects at Primary Analysis)

	Irbesartan (N = 203) n (%)	Sparsentan (N = 203) n (%)	Total (N = 406) n (%)
Full Analysis Set[a]	202 (>99)	202 (>99)	404 (>99)
Primary Analysis Set[b]	202 (>99)	202 (>99)	404 (>99)
Per Protocol Analysis Set at Primary Analysis[c]	187 (92)	193 (95)	380 (94)
Safety Analysis Set[d]	202 (>99)	202 (>99)	404 (>99)
Pharmacokinetic Analysis Set[e]	166 (82)	174 (86)	340 (84)
Open-Label Full Analysis Set[f]	9 (4)	12 (6)	21 (5)

- **Recruitment**

The PROTECT study was conducted in Europe, North America, Asia and Australia. Study Period: 114 weeks, approximately 2 years (core study); Initiation Date: 11 December 2018 (first subject enrolled); Completion Date: November 2023; Cut-off date for interim analysis: 01 Aug 2021 (core study). Follow-up period: in double blind-period the patients will discontinue treatment at 110-week, the treatment will be discontinued for 4 weeks. Following completion of double-blind period, patients could entry into the OLE study to receive sparsentan tablets for up to 156 weeks.

- **Conduct of the study**

Amendments to the protocols were the addition of orthostatic hypotension blood pressure measurements, enlarged sample size from 280 to 380 subjects, COVID-19 pandemic-related contingency procedures, and inclusion of interim analysis. The protocol amendments were described appropriately and do not seem to impair the overall validity of the clinical trial.

- **Baseline data**

The patient's mean age at screening for the double-blind study was 46 years. Most patients were White (67%), and about two-thirds were male (70%). The mean eGFR was 57.0 mL/min/1.73 m^2, the median UP/C was 1.24 g/g, and the median urinary protein excretion was 1.79 g/day. The demographic and baseline characteristics were well balanced between the sparsentan and the irbesartan group. The IgAN disease's baseline characteristics were as follows: the mean age at IgAN diagnosis was 39.6 years and the mean year since renal biopsy was done was 6.4 years. The baseline characteristics of IgAN disease were well balanced between the sparsentan tablets group and the irbesartan tablets group see Table 3.

Table 3. Baseline IgAN disease characteristics

	Irbesartan (N = 202)	Sparsentan (N = 202)	Total (N = 404)
Age at IgAN Diagnosis (years)[1]			
Mean (SD)	39.0 (12.38)	40.2 (13.35)	39.6 (12.87)
Min, Max	8, 75	10, 72	8, 75
Age at IgAN Diagnosis Group, n (%)			
≤18 Years	5 (2)	9 (4)	14 (3)
>18 to ≤40 Years	109 (54)	102 (50)	211 (52)
>40 Years	88 (44)	91 (45)	179 (44)

Years Since Renal Biopsy[2]			
Mean (SD)	6.4 (7.10)	6.4 (6.48)	6.4 (6.79)
Min, Max	0, 36	0, 33	0, 36

Abbreviations: IgAN = immunoglobulin A nephropathy; SD = standard deviation.
Note: Percentages are based on all patients in the Primary Analysis Set with non-missing data within each group.
[1] Age at IgAN Diagnosis is derived based on the year of IgAN diagnosis and year of birth.
[2] Years Since Renal Biopsy is derived based on the year of the initial renal biopsy and year of informed consent signed.

- **Numbers analysed**

Table 4. Patient Disposition (Screened Patients at Final Analysis)

	Sparsentan n (%)	**Irbesartan n (%)**	**Total n (%)**
Screened			669
Failed Screening			263
Enrolled/Randomised	203 (100)	203 (100)	406 (100)
Received Study Medication	202 (>99)	202 (>99)	404 (>99)
Completed Treatment in the Double-Blind Period	174 (86)	154 (76)	328 (81)
Primary Reasons for Discontinuing Study Medication in the Double-Blind Period	28 (14)	48 (24)	76 (19)
Adverse Event/Adverse Event of Interest	19 (9)	18 (9)	37 (9)
Death	0 (0)	0 (0)	0 (0)
Diagnosis of Class II-IV CHF	0 (0)	0 (0)	0 (0)
Hyperkalaemia Resistant to Treatment	0 (0)	0 (0)	0 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Patient Decision	5 (2)	21 (10)	26 (6)
Physician Decision	0 (0)	7 (3)	7 (2)
Pregnancy	1 (<1)	1 (<1)	2 (<1)
Protocol Deviation	1 (<1)	1 (<1)	2 (<1)
Receipt of Kidney Transplant or Initiation of Chronic Dialysis	2 (1)	0 (0)	2 (<1)
Site Terminated by Sponsor	0 (0)	0 (0)	0 (0)
Study Terminated by Sponsor	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)
Completed the Planned Study Duration of 114 Weeks in the Double-Blind Period	199 (98)	191 (94)	390 (96)
Discontinued from the Study During the Double-Blind Period	4 (2)	12 (6)	16 (4)
Reason for Study Discontinuation			
Death	0 (0)	1 (<1)	1 (<1)
Lost to Follow-Up	0 (0)	1 (<1)	1 (<1)
Physician Decision	0 (0)	1 (<1)	1 (<1)
Study Terminated by Sponsor	0 (0)	0 (0)	0 (0)
Withdrawal of Consent	4 (2)	9 (4)	13 (3)

	Sparsentan n (%)	Irbesartan n (%)	Total n (%)
Enrolled in the Open-Label Extension	155 (76)	128 (63)	283 (70)
Discontinued in the Open-Label Extension[a]	8 (5)	13 (10)	21 (7)
Reason for Open-Label Extension Discontinuation			
Adverse Event/Adverse Event of Interest	2 (1)	5 (4)	7 (2)
Death	0 (0)	0 (0)	0 (0)
Diagnosis of Class II-IV CHF	1 (1)	0 (0)	1 (<1)
Hyperkalaemia Resistant to Treatment	0 (0)	0 (0)	0 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Patient Decision	4 (3)	5 (4)	9 (3)
Physician Decision	0 (0)	3 (2)	3 (1)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol Deviation	0 (0)	0 (0)	0 (0)
Receipt of Kidney Transplant or Initiation of Chronic Dialysis	1 (1)	0 (0)	1 (<1)
Study Terminated by Sponsor	0 (0)	0 (0)	0 (0)
Site Terminated by Sponsor	0 (0)	0 (0)	0 (0)
Ended Study Participation during the Open-Label Extension Period[a]	8 (5)	13 (10)	21 (7)
Ongoing in the Open-Label Extension Period[a]	147 (95)	115 (90)	262 (93)

Abbreviations: CHF = congestive heart failure.
Notes: Screened patients are those who signed informed consent and they are counted once regardless of the number of times they rescreened. Percentages are based on the randomised patients within each treatment group.
[a]. Percentages for open-label extension discontinuations, ending participation and ongoing are based on patients who enrolled in the open-label extension.

- **Outcomes and estimation**

Primary endpoint results

In the interim analysis, the primary efficacy endpoint was analysed in 263 patients, 136 patients in the sparsentan group and 127 in the irbesartan group. The primary efficacy endpoint was the change from baseline in the UP/C based on a 24-hour urine sample at Week 36. Overall, in the sparsentan group geometric LS mean percent change from baseline in UP/C was -49.8 % (95% CI: -54.98, -43.95) and in the irbesartan group -15.1 % (95% CI: -23.72, -5.39). A sensitivity analyses demonstrated that the treatment difference of decrease in proteinuria from baseline was similar when urinary protein excretion rather than UP/C was used, see below.

Table 5. Percent change from baseline in UP/C using a MMRM with multiple imputation at Week 36

UP/C (g/g)	Irbesartan (N = 202)	Sparsentan (N = 202)
Percent Change From Baseline to Week 36		
n	127	136
Mean (SD)	4.03 (81.841)	-29.02 (53.905)
SE	7.262	4.622
Median	-8.65	-44.06
Q1, Q3	-43.83, 28.19	-65.13, -9.93
Min, Max	-83.9, 581.8	-92.4, 168.2
MMRM Results at Week 36[a]		
Geometric LS Mean Percent Change From Baseline	-15.05	-49.77
95% CI For Geometric LS Mean Percent Change	(-23.72, -5.39)	(-54.98, -43.95)
Ratio (sparsentan/irbesartan)		0.59
95% CI for Ratio		(0.51, 0.69)
P-value		<0.0001

Abbreviations: CI = confidence interval; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; Q = quartile; SD = standard deviation; SE = standard error; UP/C = urine protein/creatinine ratio.

Notes: Baseline is defined as the last nonmissing observation on or prior to the start of the dosing. Only results through Week 94 are included.

[a] Thirty imputed datasets are created by a multiple imputation procedure under the assumption of Missing at Random. Within each imputed dataset, the estimates of the LS mean for change from baseline to each visit are calculated using a MMRM model on the natural log (change from baseline in UP/C) with treatment, baseline log (UP/C), analysis visit, treatment-by-analysis interaction, and randomization stratification factors as fixed effects, and patient as random effect. Using Rubin's approach, the estimated treatment effects are combined across all imputations to obtain the overall estimates for LS means, 95% CIs, and the p-value. Estimated LS means and 95% CIs are back-transformed to the ratio scale. Estimated LS mean and 95% CIs are converted to percentages as follows: [exp (least squares mean change from baseline in natural log (UP/C)) – 1] × 100. An unstructured covariance structure is used in each model.

Source: Table 14.2.1.1.1.

Reduction in proteinuria remained sustained till the end of the study (week 110), see Figure 5.

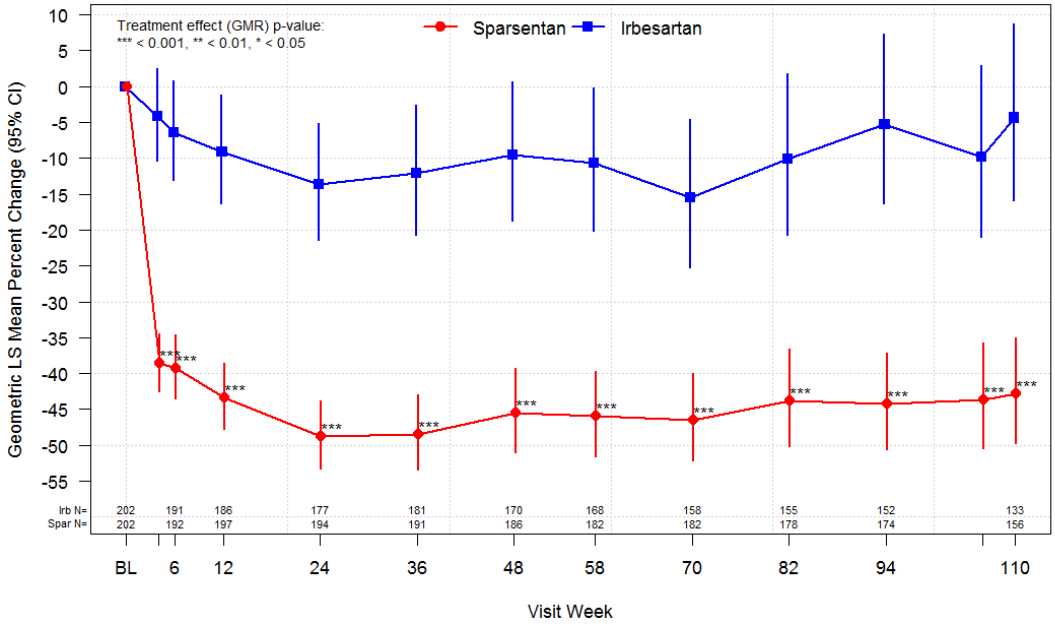


Figure 5. Percent Change from Baseline UP/C Using an MMRM with Multiple Imputation by Visit to Week 110

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

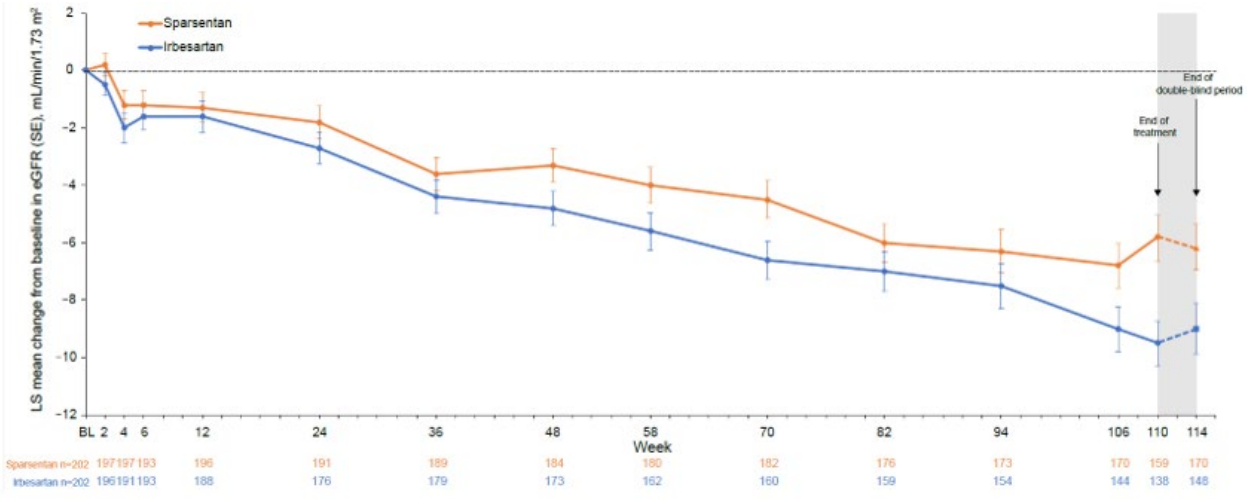
In the interim analysis, only one key secondary efficacy endpoint was analysed, it was analysed in 190 patients, 102 patients in the sparsentan group and 88 in the irbesartan group. The key secondary efficacy endpoint was the rate of change in eGFR over a 52-Week (Week 6 to Week 58) period following the acute effect of randomised therapy (eGFR Chronic Slope at 1 Year) at the primary analysis. In the sparsentan group, the annualised eGFR chronic slope at 1 year was -3.4 (95% CI: -4.77, -2.09) mL/min/1.73 m^2/year, and in the irbesartan group, -4.9 (95% CI: -6.28, -3.48) mL/min/1.73 m^2/year. The annualised difference in chronic slopes at 1 year between treatment groups was 1.4 (95% CI: -0.36, 3.26; p = 0.1167) mL/min/1.72 m^3/year in the sparsentan group's favour.

In the sparsentan group, the annualised eGFR chronic slope at 1 year was -3.7 (95% CI: -5.08, -2.29) mL/min/1.73 m^2/year, and in the irbesartan group, -5.1 (95% CI: -6.48, -3.63) mL/min/1.73 m^2/year in the s PAS subjects who completed Week 58 or early terminated but were expected to complete Week 58. The annualised difference in chronic slopes at 1 year between treatment groups was 1.4 (95% CI: -0.63, 3.38; p = 0.1791) mL/min/1.72 m^3/year in the sparsentan group's favour. In the sparsentan group, the annualised eGFR total slope at 1 year was -3.7 (95% CI: -4.87, -2.47) mL/min/1.73 m^2/year and in the irbesartan group -4.7 mL/min/1.73 m^2/year (95% CI: 6.03, 3.46). The annualised difference in total slopes at 1 year between treatment groups was 1.1 (95% CI: -0.59, 2.75; p = 0.205) mL/min/1.72 m^3/year favouring sparsentan.

On CHMP's request, the applicant provided longer term follow-up data on eGFR slopes. The eGFR chronic slope (Week 6 to Week 110) showed a significant treatment difference that was 1.1 mL/min/1.73 m^2 per year in favour of sparsentan compared to the active comparator irbesartan. eGFR total slope was the second endpoint tested at the confirmatory analysis in the statistical hierarchy. The difference in eGFR total slope between sparsentan and the active comparator irbesartan was 1.0 mL/min/1.73 m^2 per year, consistent with the confirmatory endpoint of eGFR chronic slope and supportive of the overall results of PROTECT, but not significant, see Table 6, Figure 6.

Table 6. eGFR Endpoints with the 2-year follow-up data

eGFR Endpoint	Sparsentan (N=202)	Irbesartan (N=202)	Difference (Sparsentan – Irbesartan) (95%CI)
eGFR Chronic Slope[a] (mL/min/1.73 m^2 per year)	–2.7 (-3.43, -2.05)	–3.8 (-4.60, -3.07)	1.1 (0.07, 2.12) p=0.037
eGFR Total Slope[b] (mL/min/1.73 m^2 per year)	–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[c] (mL/min/1.73 m^2)	–5.8 (-7.38, -4.24)	–9.5 (-11.17, -7.89)	3.7 (1.45, 5.99)
Change from baseline to 4 weeks post-cessation of randomised treatment [d] (mL/min/ Sparsentan LS Mean change Irbesartan LS Mean change Difference 95% confidence interval -1.2 -1.6 0.4 -1 to -1.7 Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least squares. 1.73 m^2)	–6.1 (-7.74, -4.48)	–9.0 (-10.71, -7.21)	2.9 (0.45, 5.25)



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Sparsentan LS Mean change	-1.2	-4.0	-5.8	-6.1
Irbesartan LS Mean change	-1.6	-5.6	-9.5	-9.0
Difference	0.4	1.7	3.7	2.9
95% confidence interval	-1 to -1.7	-0.1 to 3.5	1.5 to 6	0.5 to 5.3

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

Figure 6. Change from Baseline in eGFR (mL/min/1.73 m^2) by Visit

There was variability of eGFR in the sparsentan group between Week 106 and Week 110. The mean increase among patients on sparsentan between week 106 and week 110 is approximately 1 mL/min/1.73 m^2. This may be driven by a few patients with some fluctuations in their eGFR during the

study, causing some distortion in the mean, since the median (interquartile range) eGFR changes from week 106 to week 110 are around 0 (-2.0, 3.0) mL/min/1.73m^2.

Secondary endpoint results

In the interim analysis, one secondary efficacy endpoint was analysed, which was the proportion of patients reaching a confirmed 40% reduction in eGFR, ESRD, or death. 20 subjects achieved the endpoint of a confirmed 40% reduction in eGFR, ESRD, or death in the sparsentan group 7 patients (3.5%) and in the irbesartan group, 13 patients (6.4%). These analyses were primarily driven by a difference in 40% reduction in eGFR (7 (3%) in the sparsentan group versus 11 (5%) in the irbesartan group), with less difference in reaching ESRD (4 (2%) in the sparsentan group versus 5 (2%) in the irbesartan group) and no deaths in both groups. In response to the CHMP's request, the applicant provided updated analyses of the proportion of subjects reaching a confirmed 40% reduction in eGFR, ESRD, or death, see Table 7.

Table 7. Proportion of Patients Reaching a Confirmed 40% Reduction in eGFR, ESRD, or Death (FAS) at 2-year follow-up

	Sparsentan (N=202)	**Irbesartan (N=202)**
Confirmed 40% reduction in eGFR, ESRD, or death		
Event, n (%)	18 (8.9)	26 (12.9)
Relative risk for events (sparsentan/irbesartan)	0.68	
95% CI	(0.37, 1.24)	

Abbreviations: CI=confidence interval; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; FAS = Full Analysis Set; RRT = renal replacement therapy.
Notes: - Percentages are based on all patients in the Full Analysis Set within each group.
- N = Full Analysis Set; n = patients meeting events criteria.
- eGFR was determined using the CKD-EPI equation.
- Reduction in eGFR required confirmation by a consecutive value at least 4 weeks after the initial value.
- ESRD was defined as initiation of renal replacement therapy (RRT), or sustained eGFR <15 mL/min/1.73 m^2 during the study (confirmed after repeat assessment).
- Patients with events were those who met the indicated criteria.
- Relative risk of events and 95% CI was estimated from a Poisson regression model with log link and the same fixed effects as the logistic regression model.

- **Ancillary analyses**

The results of the sensitivity analyses in completers only, PAS, observed data on treatment, exclusion of assessments after initiation of IST, observed data during double-blind period, multiple imputation per protocol analysis set populations assessed the robustness of the primary analysis to show sparsentan superiority of primary endpoint. The results of these subgroup analyses did not show any major differences between subgroups. Only the baseline eGFR ≥90 mL/min/1.73 m^2 and ≤18 years age at IgAN diagnosis subgroups of irbesartan had a greater reduction in UP/C from baseline compared to the overall primary analysis, though the group of ≤18 years age at IgAN diagnosis includes only 8 subjects (2 in irbesartan group and 6 in sparsentan group).

Sensitivity Analyses of Chronic eGFR Slope and Total eGFR Slope at 1 Year

The impact of missing data and premature discontinuations (including those due to COVID-19) on the robustness of the primary analysis of chronic slope at 1 year was assessed through various prespecified sensitivity analyses, such as analyses using only observed data on treatment, using only data for those who complete the Week 36 visit, including local laboratory results in lieu of missing central laboratory results, using available data in the study including posttreatment discontinuation,

and excluding data after initiation of immunosuppressive treatments for any indication or for kidney indication. An additional sensitivity analysis to estimate chronic slope using all available on-treatment data from Day 1 to Week 58 was conducted via a mixed model random coefficients analysis with a change point at Week 6 (i.e., 2-slope model). Sensitivity analysis of the chronic slope focused only on completers of the 58-week double-blind period demonstrates a slope difference of 0.5 (95% CI: -1.6 – 2.5; p = 0.66) ml/min/1.73m^2/year. The applicant explained that the eGFR slopes for subjects on sparsentan were consistent across completers, ongoing non completers, and discontinued non-completers. Nevertheless, subjects on irbesartan who were discontinued non-completers tended to have worse eGFR slopes compared to the rest of the population. Therefore, the removal of patients with worse eGFR slopes in the control arm may lead to more optimistic effect in the control arm regarding eGFR slope. Consequently, the treatment effect of sparsentan over irbesartan may be lower in this sensitivity analysis. It is agreed that this may in part explain the lower treatment effect size in the sensitivity analyses of completers only.

The sensitivity analyses of chronic eGFR slope generally support the results of the primary analysis of chronic slope at 1 year, indicating a slower rate of decline in eGFR in the sparsentan group. While point estimates for the chronic slope at 1 year within the sparsentan group showed some variability across sensitivity analyses, these results are within range of the primary analysis results. In addition, all sensitivity analyses showed a treatment effect in favour of sparsentan. Given the nonsignificant *p*-value for this key secondary endpoint, the results of the tipping point analysis are not relevant since tipping point analysis assumes a significant *p*-value before adjustment. The sensitivity analyses of total eGFR slope generally support the results of the primary analysis of total slope at 1 year, indicating a slower rate of decline in eGFR in the sparsentan group, although overall the effect sizes are smaller.

The robustness of the effects of total eGFR slope were demonstrated by using a variety of eGFR equations based on either creatinine and/or cystatin C, as well as analyses using creatinine clearance (see tables 8 and 9).

Table 8. Creatinine Clearance and eGFR Slopes Calculated Using Creatinine, Cystatin C, and Creatinine-Cystatin C Formulas (Weeks 1 to 58)

Annualised Slope	Irbesartan	Sparsentan
Creatinine Clearance (mL/min per year) (Weeks 1–58)[a]		
n	85	103
LS Mean (95% CI)	–10.4 (–14.80, –5.98)	–4.7 (–8.83, –0.51)
Slope Difference		5.7 (–0.34, 11.78)
eGFR (mL/min/1.73 m^2 per year) Using Creatinine (2021) (Weeks 1–58)[b]		
n	89	105
LS Mean (95% CI)	–5.0 (–6.29, –3.62)	–4.2 (–5.43, –2.87)
Slope Difference		0.8 (–1.05, 2.65)
eGFR (mL/min/1.73 m^2 per year) Using Cystatin C (2012) (Weeks 1–58)[b]		
n	90	106
LS Mean	–3.9 (–5.11, –2.77)	–2.9 (–4.05, –1.81)
Slope Difference		1.0 (–0.62, 2.63)
eGFR (mL/min/1.73 m^2 per year) Using Creatinine-Cystatin C (2021) (Weeks 1–58)[b]		
n	89	105
LS Mean (95% CI)	–4.5 (–5.71, –3.37)	–3.5 (–4.60, –2.35)
Slope Difference		1.1 (-0.56, 2.69)
eGFR (mL/min/1.73 m^2 per year) Using Creatinine-Cystatin C (2012) (Weeks 1–58)[b]		
n	89	105
LS Mean (95% CI)	–4.3(–5.48, –3.22)	–3.4 (–4.47, –2.30)
Slope Difference		1.0 (–0.60, 2.53)

Table 9. Sensitivity Analyses for Total eGFR Slope (Weeks 1 to 58)

Annualised eGFR Total Slope (Weeks 1–58)	**Irbesartan**	**Sparsentan**
Overall Observed Data on Treatment[a]		
n	89	105
LS Mean (95% CI)	–4.9 (–6.15, –3.57)	–4.1 (–5.32, –2.84)
Slope Difference (95% CI)		0.8 (–1.01, 2.57)
Completers[a,b]		
n	89	105
LS Mean (95% CI)	–4.4 (–5.81, –3.06)	–4.1 (–5.45, –2.83)
Slope Difference (95% CI)		0.3 (–1.61, 2.19)
Exclusion of Assessments After Immunosuppressive Medication[b]		
n	85	98
LS Mean (95% CI)	–4.7 (–6.07, –3.42)	–4.0 (–5.24, –2.71)
Slope Difference (95% CI)		0.8 (–1.06, 2.61)
Exclusion of Assessments After Immunosuppressive Medication with Renal Indication[a]		
n	88	104
LS Mean (95% CI)	–4.8 (–6.11, –3.50)	–4.0 (–5.28, –2.79)
Slope Difference (95% CI)		0.8 (–1.04, 2.57)
Inclusion of Local Lab Data[a]		
n	90	109
LS Mean (95% CI)	–4.9 (–6.21, –3.57)	–4.1 (5.38, –2.84)
Slope Difference (95% CI)		0.8 (–1.05, 2.61)
Includes Data After Premature Discontinuation[a]		
n	95	110
LS Mean (95% CI)	–4.8 (–6.11, –3.54)	–4.2 (–5.43, –2.92)
Slope Difference (95% CI)		0.6 (–1.15, 2.44)
Multiple Imputation – Per Protocol Analysis Set[c]		
n	83	99
LS Mean (95% CI)	–4.6 (–6.07, –3.21)	–3.8 (–4.97, –2.60)
Slope Difference (95% CI)		0.9 (–1.03, 2.73)

Sensitivity analyses on 2-year eGFR slope data

During the evaluation phase, the applicant provided the following sensitivity analyse on the 2-year eGFR slope data, see Figure7 and Figure 8.

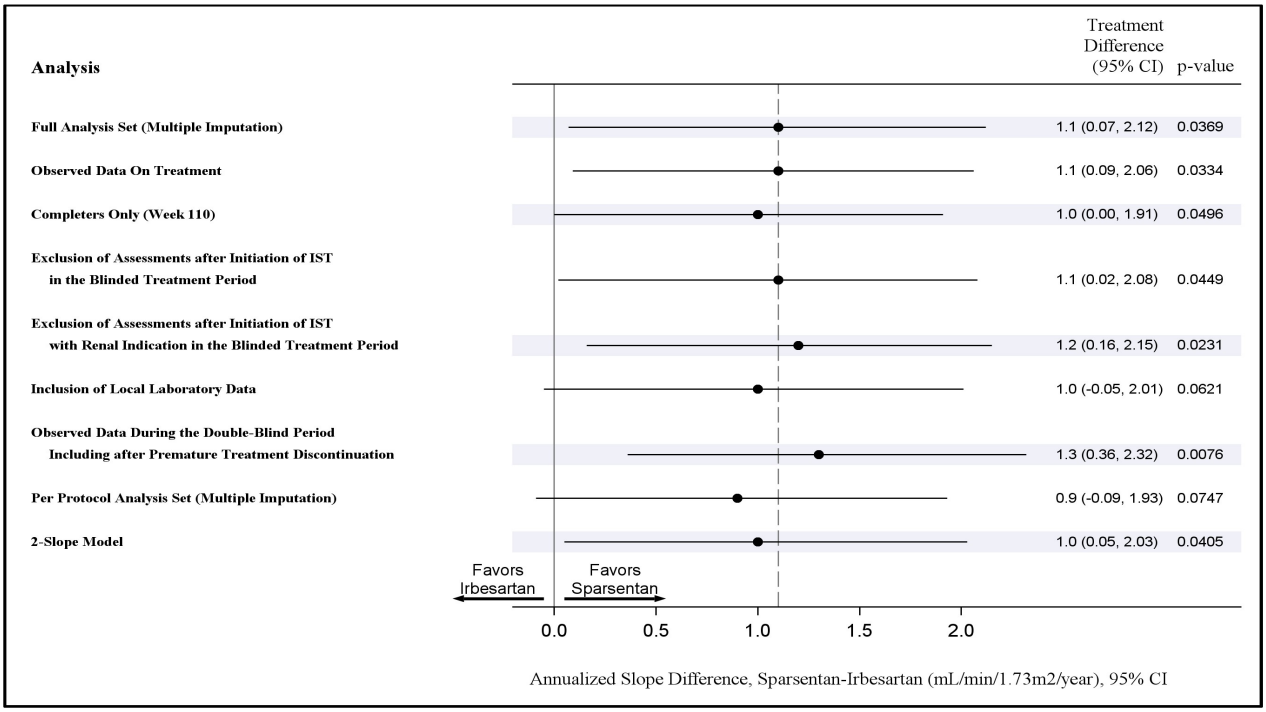

Figure 7. Chronic Slope Forest Plot of Sensitivity Analysis: Rate of Change in eGFR Over 104 Weeks (Week 6 to Week 110) Following Acute Effect of Randomised Therapy – Annualised Slope Difference

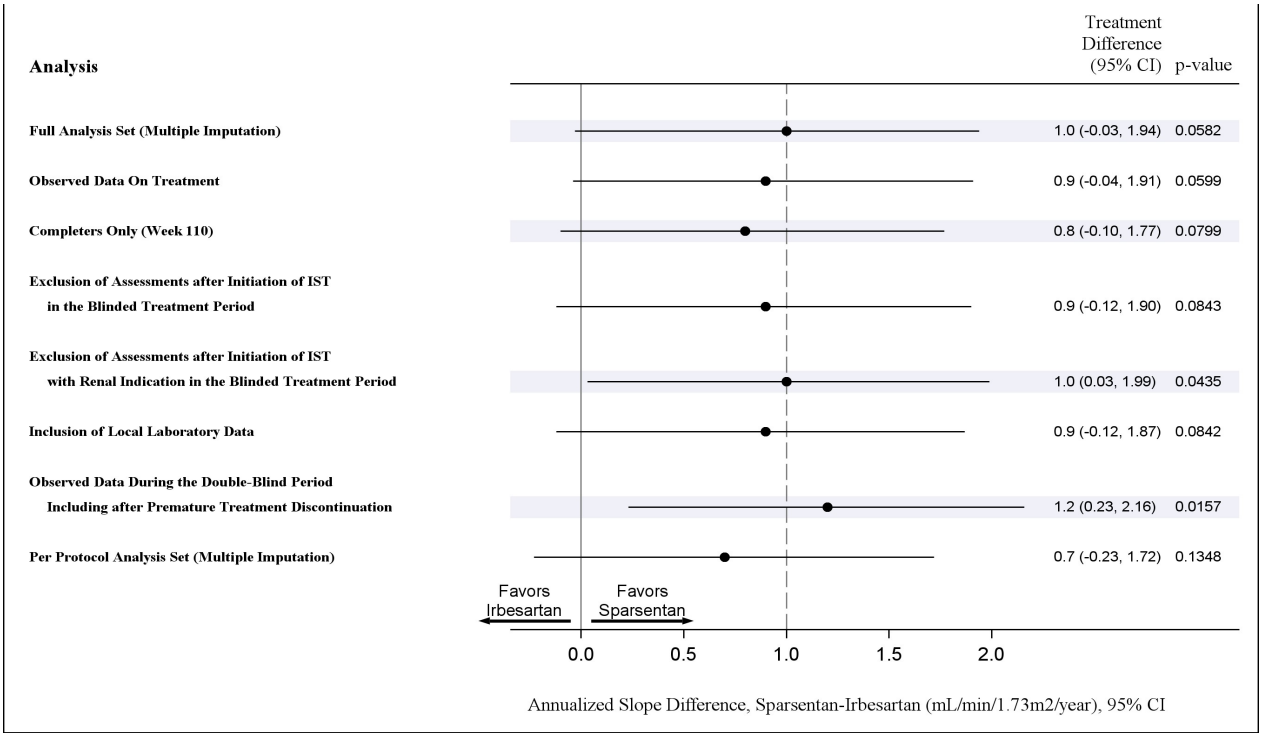

Figure 8. Total Slope Forest Plot of Sensitivity Analysis: Rate of Change in eGFR Over 110 Weeks (Day 1 to Week 110) Following Initiation of Randomisation Therapy – Annualised Slope Difference

Subgroup analyses of 1-year chronic eGFR slope and total eGFR slope: The eGFR chronic slope at 1 year within the sparsentan treatment group was generally consistent with the primary analysis across baseline subgroups, albeit with noticeably higher variability in the subgroups, even in those with a modest sample size (approximately 50 subjects). The impact of this larger variability within treatment groups was large variability in the estimated treatment effect, making the interpretation difficult. Generally, for both the chronic eGFR slope and total eGFR slope the estimate of the treatment effect was consistent with the primary analysis across most subgroups, i.e., in favour of sparsentan. An important exception is the subgroup analyses according to baseline proteinuria.

Subgroup analyses according to baseline proteinuria demonstrated an annualised chronic eGFR slope difference of 0.1 (-2.83 to 3.06) ml/min/1.73m^2/year (in favour of irbesartan) in patients with a baseline proteinuria <=1.75g/day and an annualised chronic eGFR slope difference of 2.0 (-0.56 to 4.47) ml/min/1.73 m^2/year (in favour of sparsentan) in patients with a baseline proteinuria > 1.75 g/day.

Preliminary subgroup analyses for 2-year eGFR slope analyses

In response to the of the CHMP, subgroup analyses on 2-year chronic and total eGFR slope according to baseline proteinuria and baseline eGFR were submitted, see Table 10.

Table 10. Chronic Slope Subgroup Analysis of Baseline eGFR and Proteinuria: Rate of Change in eGFR Over 104 Weeks (Week 6 to Week 110) Following the Acute Effect of Randomised Therapy (FAS)

Subgroup	Statistic	Sparsentan (N=202)	Irbesartan (N=202)	Difference (Sparsentan – Irbesartan)
Baseline eGFR <60 mL/min/1.73 m²	n	127	129	
	LS Mean (95% CI)	-2.9 (-3.61, -2.15)	-3.8 (-4.53, -3.03)	0.9 (-0.15, 1.94)
Baseline eGFR ≥60 mL/min/1.73 m²	n	75	73	
	LS Mean (95% CI)	-2.8 (-4.16, -1.39)	-4.2 (-5.65, -2.72)	1.4 (-0.61, 3.43)
Baseline Urine Protein ≤1.75 g/day	n	98	93	
	LS Mean (95% CI)	-2.0 (-3.03, -1.06)	-3.1 (-4.16, -2.09)	1.1 (-0.35, 2.51)
Baseline Urine Protein >1.75 g/day	n	104	109	
	LS Mean (95% CI)	-3.6 (-4.55, -2.65)	-4.7 (-5.66, -3.69)	1.1 (-0.29, 2.45)

Table 11. Total Slope Subgroup Analysis of Baseline eGFR and Proteinuria: Rate of Change in eGFR Over 110 Weeks (Day 1 to Week 110) Following the Initiation of Randomised Therapy (FAS)

Subgroup	Statistic	Sparsentan (N=202)	Irbesartan (N=202)	Difference (Sparsentan – Irbesartan)
Baseline eGFR <60 mL/min/1.73 m²	n	127	129	
	LS Mean (95% CI)	-2.9 (-3.64, -2.14)	-3.9 (-4.62, -3.08)	1.0 (-0.12, 2.03)

Subgroup	Statistic	Sparsentan (N=202)	Irbesartan (N=202)	Difference (Sparsentan – Irbesartan)
Baseline eGFR ≥60 mL/min/1.73 m²	n	75	73	
	LS Mean (95% CI)	-3.2 (-4.54, -1.88)	-4.2 (-5.62, -2.80)	1.0 (-0.94, 2.94)
Baseline Urine Protein ≤1.75 g/day	n	98	93	
	LS Mean (95% CI)	-2.2 (-3.12, -1.20)	-2.9 (-3.95, -1.94)	0.8 (-0.61, 2.17)
Baseline Urine Protein >1.75 g/day	n	104	109	
	LS Mean (95% CI)	-3.8 (-4.76, -2.87)	-4.9 (-5.88, -3.93)	1.1 (-0.27, 2.45)

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main studies supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of main efficacy results (interim results only)

Title: A Randomised, Multicenter, Double-Blind, Parallel-Group, Active Control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy			
Study identifier	021IGAN17001		
Design	This is an ongoing 114-week, randomised, multicenter, double-blind, parallel-group, active control study, with an OLE period of up to 156 weeks for a total study duration of up to 270 weeks. This summary presents the results for interim analysis at Week 36.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	114 weeks (interim analysis at Week 36, double-blind treatment period at 110 weeks) Not applicable 156 weeks (OLE)	
Hypothesis	Superiority of sparsentan compared to irbesartan		
Treatment groups	Sparsentan	An initial starting dose of 200 mg daily for 2 weeks, titrating up to a target dose of 400 mg daily	
	Irbesartan	An initial starting dose of 150 mg daily for 2 weeks, titrating up to a target dose of 300 mg daily	
Endpoints and definitions	**Primary (Efficacy) Endpoint**	UP/C ratio analyses at Week 36	Percent change from baseline in UP/C based on a 24-hour urine sample at Week 36
	Key Secondary Efficacy Endpoint	Chronic eGFR slope over a 52-week (Week 6 to Week 58) period following the initial acute effect of randomised therapy	Rate of change in eGFR over a 52-week (Week 6 to Week 58) period (eGFR chronic slope at 1 year)

		Chronic eGFR slope over a 104-week (approximately 2 years) period following the initial acute effect of randomised therapy (6 weeks post-randomisation to 110 weeks post-randomisation)	Rate of change in eGFR over a 104-week (Week 6 to Week 110) period (eGFR chronic slope at 2 years)
		eGFR over a 110-week (approximately 2 years) period following the initiation of randomised therapy	Rate of change in eGFR over a 110-week (Day 1 to Week 110) period (eGFR total slope at 2 years)
	Other Secondary Efficacy Endpoints	Mean change from baseline over time in eGFR and selected proteinuria variables based on a 24-hour urine sample (eg, urine protein excretion, urine albumin excretion, UP/C and urine albumin/creatinine ratio [UA/C]) through Week 110 (data in this interim CSR are through Week 94).	Change from baseline by visit through Week 94 for selected proteinuria variables (UA/C and UP/C)
		First confirmed 40% reduction in eGFR, ESRD, or death	Proportion of subjects reaching a confirmed 40% reduction in eGFR, ESRD, or death
	Exploratory Endpoints	Total slope of eGFR over 58 weeks (Day 1 to Week 58)	Change in eGFR over a 58-week period following the initiation of randomised therapy (total slope)
		UP/E of <0.3 g/day (complete remission) up to Week 110	Proportion of subjects achieving UP/E <0.3 g/day up to Week 110
		UP/E of <1.0 g/day (partial remission) up to Week 110	Proportion of subjects achieving UP/E <1.0 g/day up to Week 110
		Haematuria at each visit through Week 94	Proportion of subjects with haematuria through Week 94
		Blood pressure through Week 94	Change from baseline for blood pressure results through Week 94
		Subjects with intensification of immunosuppressive medication	Proportion of subjects with use of systemic immunosuppressive medication during the study

Database lock	Interim analysis 01 Aug 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The Primary Analysis Set (PAS) is the subset of the FAS (all subjects who were randomised and took at least 1 dose of randomised therapy) at the time of the data extraction for primary analysis. Subjects in the PAS are analysed according to randomised treatment assignment. Because the study was fully enrolled at the time of the primary analysis, the PAS is equivalent to the FAS. All efficacy analyses are based on the PAS.		
Descriptive statistics and estimate variability	Treatment group	Sparsentan	Irbesartan
	Number of subjects	202	202
	Percent Change From Baseline in UP/C at Week 36 (Mixed Model Repeated Measures) Geometric LS Mean	-49.77%	-15.05%
	95% CI	(-54.98, -43.95)	(-23.72, -5.39)
	p-value	<0.0001	
	Chronic eGFR slope over 52-weeks (Week 6 to Week 58) Mean annualized change from Week 6 at Week 58	-3.6 mL/min/1.73 m2/year	-4.3 mL/min/1.73 m2/year
	SD	8.55	7.92
	Absolute change in eGFR (Baseline through Week 94) Mean eGFR at Week 94	-5.6 mL/min/1.73 m^2 48.2 mL/min/1.73 m2	-7.9 mL/min/1.73 m^2 48.0 mL/min/1.73 m2
	SD	8.65 23.40	10.51 26.98
	UP/C change from baseline by visit through Week 94 Mean UP/C at Week 94	0.97 g/g	1.48 g/g
	SD	0.809	1.117
	Mean at UA/C Week 94	0.78 mg/day	1.18 mg/day
	SD	0.651	0.877
	Subjects reaching confirmed 40% reduction in eGFR, ESRD, or death n/N (%)	7/202 (3.5%)	13/202 (6.4%)

	eGFR total slope over a 58-week (Day 1 to Week 58) period Mean annualized change from baseline at Week 58	-4.3 mL/min/1.73 m^2/year	-5.2 mL/min/1.73 m^2/year
	SD	8.12	6.87
	Urinary protein excretion <0.3 g/day (complete remission) at any time on treatment n/N (%)	42/202 (20.8%)	16/202 (7.9%)
	Urinary protein excretion <1.0 g/day (partial remission) at any time on treatment n/N (%)	142/202 (70.3%)	89/202 (44.1%)
	Hematuria at each visit through Week 94 n/N (%) at Week 94	18/50 (36.0%)	18/38 (47.4%)
	Change from baseline in blood pressure over time Mean (SD) for systolic blood pressure at Week 6 and Week 94	-4.5 (12.53) mmHg -1.9 (11.85) mmHg	-3.3 (11.24) mmHg -3.1 (16.08) mmHg
	Mean (SD) for diastolic blood pressure at Week 6 and Week 94	-4.2 (8.41) mmHg -2.5 (8.89) mmHg	-0.4 (10.08) mmHg -1.8 (11.76) mmHg
	Initiation or intensification of immunosuppressive medication at any time on treatment n/N (%)	14/202 (6.9%)	20/202 (9.9%)
Effect estimates per comparison	**Primary Endpoint** Percent change from baseline in UP/C at Week 36	Comparison groups	Sparsentan *vs* Irbesartan
		LS mean percent change from baseline, 95% CI	-49.77% (-54.98, -43.95) vs -15.05% (-23.72, -5.39)
		Ratio (Sparsentan/Irbesartan)	0.59 (0.51, 0.69)
		p-value	<0.0001
	Secondary Endpoints Chronic eGFR slope over 52 weeks (Week 6 to Week 58)	Comparison groups	Sparsentan *vs* Irbesartan
		LS mean (95% CI)	-3.4 mL/min/1.73 m^2/year (-4.77, -2.09) vs -4.9 mL/min/1.73 m^2/year (-6.28, -3.48)

		Slope difference, Week 6 to Week 58, Estimate (95% CI)	1.4 (-0.36, 3.26)
		p-value	0.1167
	Absolute change in eGFR (Baseline through Week 94)	Comparison groups	Sparsentan *vs* Irbesartan
		LS mean change from baseline (95% CI)	-7.2 mL/min/1.73 m^2 (-9.39, -4.99) vs -8.7 mL/min/1.73 m^2 (-11.04, -6.29)
		Difference (Sparsentan-Irbesartan)	1.5
		95% CI for difference	-1.77, 4.70
		p-value	0.3709
	UP/C change from baseline by visit through Week 94 for selected proteinuria variables Week 94 values	Comparison groups	Sparsentan *vs* Irbesartan
		Geometric LS mean percent change from baseline (95% CI)	-52.57% (-61.55, -41.49) vs -11.17% (-28.24, 9.98)
		Ratio (Sparsentan/Irbesartan)	0.53
		95% CI for ratio	(0.39, 0.73)
		p-value	0.0002
	UA/C change from baseline by visit through Week 94 for selected proteinuria variables Week 94 Values	Comparison groups	Sparsentan *vs* Irbesartan
		Geometric LS mean percent change from baseline (95% CI)	-58.71% (-66.04, -49.79) vs -23.71% (-38.03, -6.09)
		Ratio (Sparsentan/Irbesartan)	0.54
		95% CI for ratio	(0.41, 0.72)
		p-value	<0.0001
	Subjects reaching confirmed 40% reduction in eGFR, ESRD, or death	Comparison groups	Sparsentan *vs* Irbesartan
		Difference in rates of no events (Sparsentan-Irbesartan)	1.46
		95% CI for difference	(-0.60, 3.51)
	Exploratory Endpoints		
	eGFR total slope over a 58-week period following initiation of randomised therapy from Day 1 to Week 58	Comparison groups	Sparsentan *vs* Irbesartan
		LS mean (95% CI)	-3.7 (-4.87, -2.47) mL/min/1.73 m^2/year vs -4.7 mL/min/1.73 m^2/year (-6.03, -3.46)
		Slope difference, Day 1 to Week 58, Estimate (95% CI)	1.1 (-0.59, 2.75)
		p-value	0.2053

	UP/E <0.3 g/day (complete remission) Up to Week 110	Comparison groups	Sparsentan *vs* Irbesartan
		Relative risk, 95% CI	2.45 (1.37, 4.38)
		Odds ratio, 95% CI	3.08 (1.63, 5.82)
		p-value	0.0005
	UP/E <1.0 g/day (partial remission) Up to Week 110	Comparison groups	Sparsentan *vs* Irbesartan
		Relative risk, 95% CI	1.54 (1.18, 2.01)
		Odds ratio, 95% CI	4.54 (2.72, 7.59)
		p-value	p<0.0001
	Hematuria at each visit through Week 94	Comparison groups	Sparsentan *vs* Irbesartan
		Proportion of subjects with hematuria	44.4% vs 50.8%
	Change from baseline in blood pressure over time Systolic blood pressure at Week 94	Comparison groups	Sparsentan *vs* Irbesartan
		LS mean change from baseline (95% CI)	-2.8 mmHg (-5.69, 0.16) vs -2.4 mmHg (-5.60, 0.79)
		Difference (Sparsentan-Irbesartan)	-0.4
		95% CI for difference	(-4.70, 3.97)
		p-value	0.8679
	Diastolic blood pressure at Week 94	Comparison groups	Sparsentan *vs* Irbesartan
		LS mean change from baseline (95% CI)	-2.8 mmHg (-5.10, -0.59) vs -0.9 mmHg (-3.39, 1.56)
		Difference (Sparsentan-Irbesartan)	-1.9
		95% CI for difference	(-5.27, 1.42)
		p-value	0.2562
	Initiation or intensification of immunosuppressive medication at any time on treatment	Comparison groups	Sparsentan *vs* Irbesartan
		Proportion of subjects with use of systemic immunosuppressive medication	6.9% vs 9.9%
Notes	[a] Other secondary endpoints as per protocol to be assessed in the final analysis. Abbreviations: CI = confidence interval; CSR = clinical study report; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FAS = Full Analysis Set; IgAN = immunoglobulin A nephropathy; LS = least squares; OLE = open-label extension; PAS = Primary Analysis Set; SD = standard deviation; UA/C = albumin/creatinine ratio; UP/C = urine protein/creatinine ratio; UP/E = urinary protein excretion.		

2.6.5.4. Clinical studies in special populations

The phase 1 study PCO-C-010 evaluated the effects of age and gender on the single-dose PK of sparsentan. Systemic exposure to sparsentan was higher in elderly patients (≥ 65 years) compared

with younger patients (18 - 40 years). Based on AUC_{0-t} and $AUC0_{-inf}$, older patients had 65 - 67% higher exposure compared to young patients; however, 90% CI was wide. Phase 3 clinical study (DUPLEX) enrolled 35 patients 8-17 years of age (16 in the sparsentan group and 19 in the irbesartan group) with FSGS; no sparsentan efficacy differences were seen compared to adults.

2.6.5.5. Supportive studies

021FSGS16010 (DUPLEX) study: A randomised, multicenter, double-blind, parallel, active-control study of sparsentan and irbesartan's effects on renal outcomes in patients with primary FSGS.

In the sparsentan group, the change in eGFR over the Week 6 to Week 60 period (eGFR chronic slope at 1 year) was -6.9 (95% CI: -10.12, -3.66) mL/min/1.73 m^2/year and in the irbesartan group -7.4 (95% CI: -10.66, -4.19) mL/min/1.73 m^2/year. The annualised difference in chronic slopes at 1 year between treatment groups was 0.5 (95% CI: -4.03, 5.10; p=0.8172) mL/min/1.72 m^3/year in sparsentan group's favour and it is not statistically significant. The annualised difference in total eGFR slope between the sparsentan group and irbesartan group (sparsentan-irbesartan) was -1.3 (95% CI: -5.2, 2.6; p = 0.51) mL/min/1.73 m^2/year. This difference indicates a slower rate of decline in eGFR in irbesartan-treated subjects relative to sparsentan-treated subjects over the entire duration (Day 1 to Week 60).

RET-D-001 (DUET study): A randomised, double-blind, active-control, dose-escalation study to evaluate the efficacy and safety of sparsentan and irbesartan in patients with primary FSGS.

All pooled doses of sparsentan (200 mg to 800 mg) showed a significant reduction in UP/C compared to irbesartan 300 mg after 8 weeks of treatment (p = 0.006). The 2 higher sparsentan doses pooled (400 mg and 800 mg) also showed a reduction in proteinuria compared to irbesartan 300 mg after 8 weeks of treatment (p = 0.011). The subjects achieving FPRE (UP/C ≤1.5 g/g and >40% reduction from baseline) was 28.13% in 200 mg, 400 mg, 800 mg dose (pooled) sparsentan group and 9.38% in the irbesartan group (p= 0.040) after 8 weeks of treatment.

Relevance of proteinuria as a possible surrogate: In the current development programme for sparsentan, a strong effect was shown on proteinuria, but the effects on the total slope are not sufficient to facilitate the full approval and hence a CMA is requested, as it cannot be ascertained that lowering albuminuria will decrease the risk of the progression of kidney disease long term. A clear and evident confirmatory effect on the eGFR slope is necessary, see discussion on CMA below.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Clinical efficacy data was collected mainly from the phase 3 trial (PROTECT). It is a randomised, multicenter, double-blind, parallel-group, active-control study in subjects with IgAN, followed by an OLE phase trial. Irbesartan was chosen as an active comparator as the KDIGO guideline recommends RAAS inhibitors as the standard of care for IgAN, and due to the fact that it seems to have kidney protection properties and is commercially available in all countries where PROTECT was conducted.

The key inclusion for the PROTECT study included aged ≥18 years, biopsy-proven IgAN, a urinary protein excretion ≥ 1.0 gram/day, an eGFR ≥30 mL/min/1.73 m^2, a stable dose of ACEI or ARB at the maximum tolerable dose (at least 50% of maximal labelled dose) for at least 12 weeks. Following the CHMP's questioning the broad indication applied for initially, the applicant reworded the indication to reflect the proteinuria measurement that was used in the PROTECT study, which is the urinary protein excretion in grams per day and the UP/C ratio.

The originally claimed indication was:

"Filspari is indicated in adults for the treatment of primary immunoglobulin A nephropathy (IgAN)"

The revised indication following CHMP assessment is:

"Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥ 1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g, see section 5.1)."

The key exclusion criteria for the PROTECT study were IgAN secondary conditions, concomitant other chronic kidney diseases, previous organ transplantation, heart failure, severe hepatic impairment, recent cerebrovascular disease, recent coronary artery disease, malignancies, pregnancy and hyperkalaemia. The applicant stated that IgAN presents in 1 of 3 ways, with 40-50% presenting with visible haematuria, 10% presenting with nephrotic syndrome or rapidly progressing glomerulonephritis and 30-40% presenting with persistent proteinuria accompanied with microscopic haematuria. Hence, a substantial subset of IgAN patients will eventually develop proteinuria, despite the current standard of care. The fact that sparsentan is proposed to be indicated only for patients with a high degree of proteinuria is reflected by including the proteinuria level in the indication of the labelling, which was amended on request of the CHMP, see below.

The primary endpoint of change in baseline urinary protein/creatinine ratio in 24 hours per week is an acceptable biomarker to evaluate the early onset of effect within the context of IgAN. In IgA nephropathy, proteinuria is believed to be in the disease pathway toward kidney damage, and the marker is used in clinical practice to monitor disease severity (episodes) and treatment success. However, proteinuria has currently not been accepted as a surrogate for (long-term) kidney damage. Therefore, in previous scientific advice regarding the PROTECT study, additional confirmation has been requested by using a confirmatory endpoint of eGFR change over time as assessed over a 2-year period. This is another reasonable surrogate for monitoring kidney progression if the pattern of the eGFR slope is sufficiently characterised and understood.

Regarding the evaluation of the key secondary endpoint of the eGFR slope, it is noted that the rate of eGFR change is currently limited to over a 52-week period following the initial acute effect of randomised therapy. It thus provides less confidence to the concept of reasonably likely surrogate defined as minimum of 2 years of the slope. Furthermore, the use of the total slope is strongly favoured over a chronic slope. This reflects eGFR change during the entire study period, minimises possible bias introduced by post-randomisation events and has a lower risk for false-positive findings, particularly in a setting of an acute decline in eGFR when initiating treatment. Upon CHMP's request, it was agreed to add total eGFR slope as key secondary endpoint. The preferable primary endpoint is the combination of a benefit on proteinuria reduction and total eGFR slope. Moreover, full understanding of the acute effect and its reversibility is needed. The applicant claimed that at this point the reversibility of eGFR effect after stopping the treatment cannot be addressed as there is a small number of patients who finished the double-blind period. However, they will provide such analyses when the final CSR is available (by 30 Sep 2024).

Other factors which may importantly influence the eGFR slope are to be appropriately accounted for, especially in the case where treatment effect differences may not be that substantial (though potentially clinically relevant). In this context, the applicant adequately demonstrated that sparsentan did not affect muscle mass by comparing 24-hour creatinine excretion at baseline and the change from baseline. Some uncertainty was expressed from a methodological point of view on defining the appropriate estimand with possibly too optimistic analysis approach (see below). In response, the applicant provided robust analyses using estimated cystatin C, creatinine-cystatin C, creatinine-cystatin C, creatinine eGFR total and chronic slopes show consistent results. The differences between

treatment groups are small, ranging from 0.8 to 1.3 mL/min/1.73 m^2/year. Exploratory outcomes, including partial and full remission, haematuria, and blood pressure are informative and further support the primary and secondary findings.

The assumptions of the sample size calculation and original sample size re-estimation appear reasonable, and the calculations are accepted.

Randomised subjects were stratified by their screening eGFR value (30 to <60 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) and screening urine protein excretion (≤1.75 g/day and >1.75 g/day). The patient's treatment allocation for the double-blind period remained blinded to all parties involved with the study throughout its course, which is adequate. The definition of the analysis populations is standard and acceptable. The model included treatment, time, treatment-by-time interaction, baseline UP/C and randomisation strata, and an unstructured covariance matrix was used. Due to skewness, the UP/C measurements were log-transformed. This is adequate. The key secondary endpoint was analysed with a similar model as for the primary endpoint but including random intercept and slope, which is acceptable.

Missing data was imputed using multiple imputation, assuming missing at random, an acceptable approach for intermittent missing data. However, after treatment or study discontinuation, it is unlikely that missing data are random. To test the MAR assumption, the applicant performed several sensitivity analyses, of which the tipping point approach, varying missing data handling from MAR to MNAR, is most useful. Other secondary and exploratory endpoints were analysed appropriately. Multiplicity is handled by gatekeeping and fixed sequence testing. This will protect the type I error rate and is acceptable.

Efficacy data and additional analyses

A total of 406 patients enrolled in the PROTECT study, of which 202 were randomised to sparsentan and 202 to irbesartan. As of the data cut-off date (01 August 2021), 33 patients (18 in the sparsentan group and 15 in the irbesartan group) completed treatment in the double-blind period. The primary efficacy endpoint in the interim analysis shows superiority over irbesartan in reducing proteinuria at week 36 of treatment. The results of the primary efficacy endpoint are clinically and statistically significant. Proteinuria change may be acute and reversible *vs* chronic and persistent. However, this needs to be confirmed in the final CSR (Specific obligation, Annex II.E).

Although only limited number of patients > 65 years were included, results were consistent with overall data. Sensitivity analyses showed consistency with the primary effect. No dose adjustment is necessary in the elderly, as reflected in the SmPC.

Total slope is generally considered the preferred analysis but was included as an exploratory analysis and demonstrated an annualised numerical difference of 1.1 (95% CI: -0.59, 2.75; p = 0.21) mL/min/1.73 m^2/year for the interim results; however, this was not significant. Upon CHMP's request, the applicant agreed to upgrade total eGFR slope to a key secondary endpoint. This effect was inflated by the analysis of the secondary endpoint of chronic slope over a 52-week period with a difference of 1.4 (95% CI: -0.36, 3.26; p = 0.12) mL/min/1.73 m^2/year (-3.4 (95% CI: -4.77, -2.09) mL/min/1.73 m^2/year *vs* -4.9 (95% CI: -6.28, -3.48) mL/min/1.73 m^2/year). Regardless of the chosen slope, the analysis did not reach statistical significance and can be considered as a failed first-year analysis. It was uncertain whether the current total eGFR slope of 1.1 (95% CI: -0.6, 2.8) mL/min/1.73m^2/year will evolve into the total eGFR slope specified in the SAP of 2.55 mL/min/1.73 m^2 per year (to be detected with 80% power based on this sample size) at the 2 years analysis. Therefore, in response to the CHMP's request, the applicant provided top line results from 2-year analyses on the confirmatory eGFR slope and analyses regarding the risk of a composite outcome of 40% reduction in eGFR, ESRD, or death. For the confirmatory outcome of chronic eGFR slope and total slope, the applicant

demonstrated a treatment difference of 1.1 mL/min/1.73 m^2 per year (95% CI: 0.07, 2.12; p=0.037) and 1.0 mL/min/1.73 m^2 per year (95% CI: –0.03, 1.94; p=0.058), respectively, in favour of sparsentan compared to the active comparator irbesartan. This treatment difference can be considered clinically meaningful, as this is higher than the 0.75 mL/min/1.73m^2 per year level regarded as a clinically meaningful predictor of benefit on CKD progression. Furthermore, sensitivity analyses were generally consistent with the main findings. Confidence in the long-term beneficial effect of sparsentan is also gained from the effect on the absolute difference in eGFR at 2 years showing less decline in sparsentan *vs* irbesartan (2 -year decline in eGFR of –5.8 mL/min/1.73m^2 per year for sparsentan *vs* -9.5 mL/min/1.73m^2 per year for irbesartan, mean difference of 3.7 mL/min/1.73m^2 per year, 95% CI 1.45 to 5.99). Moreover, a numerical improvement for the clinical endpoint of confirmed 40% reduction in eGFR and further exploratory support comes from a lower need for immunosuppressive rescue therapy for sparsentan (3% *vs* 7.4%).

Despite these positive initial findings, the following aspects should be considered:

Firstly, as previously stated, the use of the total slope is commonly favoured over a chronic slope as total slope reflects eGFR change during the entire study period and has a lower risk for false-positive findings, particularly in a setting of an acute decline in eGFR when initiating treatment. It should be noted that this of particular interest in a placebo-controlled study, where only the treatment under investigation is expected to have an acute decline in eGFR. For the PROTECT study, this may be of less importance, as both the sparsentan and irbesartan arm demonstrated a comparable acute eGFR decline at 6 weeks post-baseline (-1.1 mL/min/1.73m^2 for sparsentan and -1.4 mL/min/1.73m^2 for irbesartan). In this scenario, the acute eGFR decline may increase variability in the slope analyses and limit the sensitivity for detecting a treatment effect. Therefore, it is considered more important that both chronic and total eGFR slope are comparable in terms of the point estimates which has been demonstrated in current PROTECT study.

It is also noted that there was an unexpected increase in eGFR between week 106 and 110 in the sparsentan arm. The applicant investigated different causes of this observed pattern and did not find any confounders or pathophysiological mechanisms, concluding that it reflects inherent variability and data at each timepoint are equally reliable. Therefore, the basis for interpretation should be the primary prespecified analysis, which demonstrated a clinically relevant and statistical effect on the chronic eGFR slope in favour of sparsetan.

Although the acute eGFR effects of sparsentan were mild, a reversibility of this acute effect was expected after cessation of therapy. However, this was not observed between week 110 and week 114. The applicant argued that the effect may be beyond a haemodynamic effect. Although possible, this cannot be concluded based on the current data, also given the variability between the week 106 and week 110 data in the sparsentan arm. In fact, if the eGFR of week 114 is compared to week 106 (rather than week 110), there appears a small increase in eGFR at week 114. Given that both timepoints have data of 170 participants in the sparsentan arm, this would plead for a small reversibility of the acute effect.

In addition, both the preliminary treatment effects on chronic and total eGFR slope are smaller than anticipated (in the SAP a treatment effect on eGFR total slope of 2.55 mL/min/1.73 m^2 per year was assumed). The applicant argues that this could be related to the fact that PROTECT was conducted with the active comparator irbesartan titrated to the maximum labelled dose (MLD). Despite high baseline risk of disease progression, and likely due to the maximum dose of irbesartan, the active control arm of PROTECT performed well and notably better than the placebo + standard of care arms in recent trials. In the irbesartan arm of PROTECT the total eGFR slope of the irbesartan arm was –3.9 ml/min/1.73m^2 per year. In the PROTECT study 95% of the patients were on the maximum labelled dose, whereas in other trials, 20% of patients were on less than 50% of the maximum labelled dose

RAS-inhibitor and 30% were between 50 and 80% of the maximum labelled dose. It is therefore possible that the design of the PROTECT study with an actively titrated control arm led to a lower treatment difference in the comparison of sparsentan and irbesartan, which limits the sensitivity of the study to demonstrate a significant reno-protective effect, as this was not anticipated in the sample size calculations of PROTECT.

Overall, although the interim analyses appeared to demonstrate an effect modification according to baseline proteinuria for both chronic and total eGFR slope, no strong effect modification according to baseline proteinuria for chronic and total eGFR slope was found in the final analyses. While it is not understood why the final analyses differ from the interim analyses results, 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. The CHMP has requested the applicant to provide the full analyses and data from the recently completed PROTECT trial in frame of the conditional marketing authorisation. The data are needed to confirm the long-term efficacy and safety of sparsentan on the IgAN patients. The applicant accepted this specific obligation.

Additional efficacy data needed in the context of a conditional MA

The sought CMA is acceptable as it meets all scientific and regulatory criteria, see section 3.7.3. Sparsentan is intended for the treating a seriously debilitating disease and is designated as an orphan medicinal product. There is currently an unmet medical need, since only budesonide, a steroid-based treatment is authorised, which has its limitations, especially safety-related. Other treatments, used as the standard-of-care, are not officially approved.

The CHMP concluded that there is positive benefit-risk based on the currently available preliminary data, which show that the pivotal study met its primary endpoint in mean percent change in UP/C and the rate of eGFR decline is slower with sparsentan than with irbesartan. The applicant also provided top line data from the recently completed 2-year study, including the analyses of eGFR slopes and other key secondary endpoints. These appear to be indicative of the positive long-term effects. Hence, the benefits of making sparsentan already available for treatment outweigh the risks associated with the current lack of comprehensive data.

The applicant has committed to submit the full analyses of the PROTECT trial in the post-marketing setting in fulfilment of the condition to the marketing authorisation. Therefore, it is considered that all four CMA criteria are satisfied.

2.6.7. Conclusions on the clinical efficacy

Sparsentan demonstrated a large and sustained effect on proteinuria as well as a significant and clinically relevant treatment effect on chronic eGFR slope over 2 years, based on the interim analysis and the top line results from the recently completed PROTECT trial. Total eGFR slope analyses narrowly missed statistical significance, but the effect size was similar to that of chronic eGFR slope. Other efficacy endpoints, including use of rescue immunosuppressive medication and hard renal outcomes favoured sparsentan. Given the fact that both sparsentan and irbesartan demonstrated a comparable acute eGFR decline, the use of chronic slope can be considered as acceptable in this scenario. The lower effect size than anticipated is likely attributable to the fact that the active control arm was actively titrated to maximum labelled dose in more than 95% of patients. This approach differs from other previous interventional trials in IgAN. Re-confirmation of the positive benefit-risk is expected in the post-marketing setting in frame of the fulfilment of the imposed condition: In order to confirm the long-term efficacy and safety of sparsentan for the treatment of IgAN in adults, and in order to specifically assess the maintenance of the long-term efficacy and safety, the MAH will submit the detailed complete study report of the PROTECT trial, a randomised, double-blind, active-controlled,

multicentre, global phase 3 trial in patients with IgAN, along with an updated clinical overview, summaries of clinical pharmacology, efficacy and safety as well as the underlying integrated analyses. This will include the final complete efficacy and safety results and key outcomes and/or endpoints with analyses of safety (with special focus on AKI-associated adverse events and hepatic-associated adverse events) during long-term use and proof of maintenance of efficacy and analyses of safety and efficacy in relevant patient sub-groups.

The CHMP considers the following specific obligation necessary to address the missing long-term efficacy and safety data in the context of a conditional MA:

> *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. Fulfilment by 30 September 2024.*

2.6.8. Clinical safety

Clinical safety information is based on the following safety sets:

- The phase 3 PROTECT study in IgAN patients (n=404).
- Pooled data from the PROTECT study in IgAN, and the phase 2 DUET and ongoing phase 3 DUPLEX studies in FSGS (n= 884). Further, within this pool, a sub-pool of open-label data of patients with exposure up to 7 years, has been described (sparsentan group).
- Hypertension study pool including 2 completed Phase 2 studies in subjects with hypertension (PCO-C-006 (n=261) and PCO-C-008 (n=113)).
- Healthy volunteers study pool, which contains all subjects treated in any Phase 1 study of sparsentan (n=554).

The key safety information for the indication IgAN is based on the PROTECT study, a Phase 3 randomised double-blind study in IgAN. Supportive safety data are retrieved from the CKD RCT study pool, covering 3 RCTs in rare glomerular disease, including the PROTECT study in IgAN and the phase 2 DUET and a phase 3 DUPLEX studies in FSGS (Table 13).

Table 12. Number of Subjects in Each Study by Study Pool and Treatment Group (Safety Analysis Set)

	Double-Blind				
	Placebo n (%) (N = 95)	Sparsentan n (%) (N = 680)	Irbesartan n (%) (N = 483)	All Sparsentan n (%) (N = 1249)	All Subjects n (%) (N = 1813)
IgAN Study Pool	NA	202 (29.7)	202 (41.8)	212 (17.0)	405 (22.3)
PROTECT	NA	202 (29.7)	202 (41.8)	211 (16.9)	404 (22.3)
SPARTAN001	NA	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
CKD RCT Study Pool[a]	NA	459 (67.5)	425 (88.0)	504 (40.4)	884 (48.8)
Hypertension Study Pool	95 (100.0)	221 (32.5)	58 (12.0)	221 (17.7)	374 (20.6)
PCO-C-006	59 (62.1)	144 (21.2)	58 (12.0)	144 (11.5)	261 (14.4)
PCO-C-008	36 (37.9)	77 (11.3)	NA	77 (6.2)	113 (6.2)
Healthy Volunteers Study Pool	NP	NP	NP	523 (41.9)	554 (30.6)
Hepatic Impaired Cohort	NA	NA	NA	16 (1.3)	16 (0.9)
Healthy Subjects[b]	NP	NP	NP	507 (40.6)	538 (29.7)

Abbreviations: CKD = chronic kidney disease; FSGS = focal segmental glomerulosclerosis; GD = glomerular diseases; IgAN = immunoglobulin A nephropathy; n = number of subjects in sample; N = number of subjects; NA = not applicable; NP = not presented; RCT = randomized controlled trial.

2.6.8.1. Patient exposure

Across all data pools, the median duration of exposure for all studies in the Safety Analysis Set was 30 days for all subjects who received sparsentan (n = 1249), with 787.56 total subject-years. Median exposure to treatment was 64 weeks for all subjects in the PROTECT study and 403 days for all subjects on sparsentan in the CKD (rare GD) RCT pool. In the CKD RCT study pool, overall exposure to sparsentan included exposure in the DUET study OLE; thus, median exposure was longer in subjects treated with sparsentan (414 days) than subjects treated with irbesartan (339 days); the median duration of exposure for subjects treated with 400/800 mg sparsentan was 337 days and, therefore, the DB 400 mg/800 mg sparsentan group was used for comparison.

PROTECT study: Enrolment in the PROTECT study closed on 26 May 2021, and the data cutoff date for the initial submission was 01 August 2021. Additional safety data with an updated data cutoff date of 01 February 2022 were also submitted for the PROTECT study as there was an additional 6 months of exposure for those already enrolled in the double-blind period. The mean (standard deviation [SD]) and median (first quartile [Q1], third quartile [Q3]) duration of exposure were 81.8 (30.6) and 96.5 (51.9, 110.0) weeks in the sparsentan treatment group, respectively, and 77.6 (32.6) and 84.5 (47.1,109.9) weeks in the irbesartan treatment group, respectively. A total of 95.0% of subjects was titrated to the target dose in both treatment arms.

IgAN study pool: In the IgAN Study Pool, mean (SD) exposure for the 405 subjects who received sparsentan or irbesartan was 434 (252) days, and median (range) exposure was 436 (1 to 870) days; in total, there were 481.5 subject-years of exposure.

CKD RCT Study Pool: For the CKD RCT Study Pool, as of the updated data cutoff date (01 Feb 2022), only data from subjects enrolled in the 400 mg sparsentan and irbesartan treatment groups, as well as those who then rolled over into the OLE are included. The extent of exposure in the double-blind periods was similar in subjects treated with irbesartan and subjects treated with sparsentan 400/800 mg.

The median (Q1, Q3) duration of exposure for subjects treated with irbesartan (n = 425) was 339.0 (1 to 826) days, with 437.2 total subject-years. The median (Q1, Q3) duration of exposure for subjects treated with 400/800 mg sparsentan (n = 446) was 336.5 (1 to 813) days, with 448.98 total subject-years (see Table 13).

Table 13. Extent of Exposure (CKD RCT Study Pool) (Safety Analysis Set)

	Data cutoff[a]: 01 Aug 2021					Data cutoff[b]: 01 Feb 2022				
	Double-blind					Double-blind				
	Irbesartan (N=425)	400 mg Sparsentan (N=228)	800 mg Sparsentan (N=218)	400/800 mg Sparsentan (N=446)	All Sparsentan (N=504)	Irbesartan (N=425)	400 mg Sparsentan (N=228)	800 mg Sparsentan (N=218)	400/800 mg Sparsentan (N=446)	All Sparsentan (N=537)
Number of Days Exposed										
n	425	228	218	446	504	425	228	218	446	537
Mean (SD)	324.3 (247.21)	398.6 (263.28)	233.1 (210.88)	317.7 (252.80)	538.6 (541.25)	***375.5 (264.28)***	***495.9 (262.93)***	233.1 (210.88)	***367.4 (272.50)***	***566.4 (532.17)***
SE	11.99	17.44	14.28	11.97	24.11	***12.82***	***17.41***	14.28	***12.90***	***22.96***
Median	283.0	413.0	143.5	254.0	403.0	***339.0***	***538.0***	143.5	***336.5***	***414.0***
Q1, Q3	81.0, 533.0	123.5, 649.0	56.0, 374.0	69.0, 547.0	130.5, 680.5	***101.0, 614.0***	***278.5, 761.5***	56.0, 374.0	***71.0, 639.0***	***172.0, 770.0***
Min, Max	1, 796	1, 790	4, 758	1, 790	1, 2403	***1, 826***	***1, 813***	4, 758	***1, 813***	1, 2403
Total Subject-Years[c]	377.57	248.98	139.20	388.18	743.69	***437.18***	***309.78***	139.20	***448.98***	***833.27***
Exposure Days Categories, n (%)										
1 day (single dose)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)
2 to 7 days	2 (0.5)	0 (0.0)	1 (0.5)	1 (0.2)	1 (0.2)	2 (0.5)	0 (0.0)	1 (0.5)	1 (0.2)	1 (0.2)
8 to 14 days	1 (0.2)	1 (0.4)	1 (0.5)	2 (0.4)	2 (0.4)	1 (0.2)	***2 (0.9)***	1 (0.5)	***3 (0.7)***	***4 (0.7)***
15 to 21 days	6 (1.4)	0 (0.0)	2 (0.9)	2 (0.4)	2 (0.4)	***7 (1.6)***	0 (0.0)	2 (0.9)	2 (0.4)	***6 (1.1)***
22 to 28 days	4 (0.9)	2 (0.9)	4 (1.8)	6 (1.3)	7 (1.4)	4 (0.9)	***1 (0.4)***	4 (1.8)	***5 (1.1)***	***7 (1.3)***
29 to 56 days	51 (12.0)	20 (8.8)	52 (23.9)	72 (16.1)	39 (7.7)	51 (12.0)	20 (8.8)	52 (23.9)	72 (16.1)	***44 (8.2)***
57 to 84 days	46 (10.8)	19 (8.3)	27 (12.4)	46 (10.3)	33 (6.5)	***34 (8.0)***	***9 (3.9)***	27 (12.4)	***36 (8.1)***	***20 (3.7)***
85 to 168 days	49 (11.5)	25 (11.0)	30 (13.8)	55 (12.3)	59 (11.7)	***25 (5.9)***	***1 (0.4)***	30 (13.8)	***31 (7.0)***	***47 (8.8)***
169 to 336 days	82 (19.3)	34 (14.9)	32 (14.7)	66 (14.8)	78 (15.5)	***86 (20.2)***	***40 (17.5)***	32 (14.7)	***72 (16.1)***	***97 (18.1)***
337 to 504 days	62 (14.6)	25 (11.0)	37 (17.0)	62 (13.9)	72 (14.3)	***74 (17.4)***	***35 (15.4)***	37 (17.0)	***72 (16.1)***	***82 (15.3)***
505 to 672 days	67 (15.8)	57 (25.0)	21 (9.6)	78 (17.5)	79 (15.7)	***47 (11.1)***	***24 (10.5)***	21 (9.6)	***45 (10.1)***	***46 (8.6)***
673 to 840 days	54 (12.7)	44 (19.3)	11 (5.0)	55 (12.3)	58 (11.5)	***93 (21.9)***	***95 (41.7)***	11 (5.0)	***106 (23.8)***	***77 (14.3)***
841 to 1008 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	***39 (7.3)***
>1008 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	62 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	***66 (12.3)***

Abbreviations: CKD = chronic kidney disease; ISS = Integrated Summary of Safety; max = maximum; min = minimum; n = number of subjects in sample; N = number of subjects; Q1 = first quartile; Q3 = third quartile; RCT = randomised controlled trial; SD = standard deviation; SE = standard error.
Note: Changes from the original MAA to this addendum are indicated with ***bold and italic*** font.
Note: All Sparsentan column includes subjects who received at least one 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 continued to receive sparsentan during the open-label extension.
Note: All Subjects column includes subjects who received at least one dose of study drug during any treatment period.
Note: Percentages are based on all subjects in the Safety Analysis Set with non-missing data within each group.
[a] Data cutoff dates were 22 Jan 2021 for DUPLEX and 05 Feb 2021 for DUET, and 01 Aug 2021 for PROTECT.
[b] Data cutoff dates were 22 Jan 2021 for DUPLEX and 05 Feb 2021 for DUET, and 01 Feb 2022 for PROTECT.
[c] Total Subject-Years are calculated as sum of total number of dosed days across all subjects/365 days.
Source: ISS Table 1.5.4 (data cutoff 01 Aug 2021) and ISS Table 1.5.4 (data cutoff 01 Feb 2022)

Hypertension Study Pool: Mean (SD) and median (range) duration of exposure were very similar in the key groups for comparison, namely irbesartan and sparsentan, at any dose. The duration of exposure in the placebo group was lower than in any of the active treatment groups.

Healthy Volunteer Study Pool: In the HV Study Pool, mean (SD) exposure of the 523 subjects who received sparsentan was 5.4 (5.8) days, and median (range) exposure was 2 (1 to 16) days; in total, there were 7.68 subject-years of exposure.

2.6.8.2. Adverse events

An overview of TEAEs in the double-blind period of the PROTECT study as of the updated data cutoff (01 Feb 2022) has been provided:

PROTECT study: Overall, in the PAS, 336 (83%) subjects experienced at least 1 TEAE, and 153 (38%) subjects experienced a treatment related TEAE during the double-blind study period.

For subjects receiving sparsentan, 177 (88%) subjects experienced at least 1 TEAE, and 86 (43%) subjects experienced a treatment related TEAE. For subjects receiving irbesartan,159 (79%) subjects experienced at least 1 TEAE, and 67 (33%) subjects experienced a treatment related TEAE.

Overall, for the PAS, 42 (10%) subjects reported AEs that were considered severe (16 (8%) subjects receiving sparsentan, 26 (13%) subjects receiving irbesartan), 84 (21%) subjects experienced a serious adverse event (SAE) (43 (21%) subjects receiving sparsentan, 41 (20%) subjects receiving irbesartan), and 25 subjects (6%) experienced TEAEs that lead to treatment discontinuation (15 subjects [7%] receiving sparsentan, 10 subjects [5%] receiving irbesartan).

CKD RCT Study Pool: In the CKD RCT study pool, 364 (81.6%) subjects in the sparsentan (400/800 mg) group and 321 (75.5%) subjects in the irbesartan group experienced treatment-emergent adverse events (TEAEs). One hundred seventy-seven/44 6 (39.7%) of subjects in the sparsentan group and 135/425 (31.8%) of subjects in the irbesartan group experienced a treatment-related adverse event.

- 41/446 (9.2%) of subjects on sparsentan, and 35/425 (8.2%) of subjects on irbesartan experienced a severe treatment-emergent adverse event.
- 68/446 (15.2%) of subjects in the sparsentan group and 63/425 (14.8%) of subjects in the irbesartan group experienced serious adverse events.
- 34/446 (7.6%) of subjects on sparsentan and 20/425 (4.7%) of subjects on irbesartan experienced TEAEs that lead to treatment discontinuation.

Most common adverse events

PROTECT study: Most common TEAEs in sparsentan group were dizziness (28 subjects, 14%), peripheral oedema (29 subjects, 14%), headache (22 subjects, 11%), hyperkalemia (27 subjects, 13%), hypotension (22 subjects, 11%). After completion of the PROTECT study, with data cutoff date 7 Sept 2023, in general frequencies of common TEAEs were slightly increased as compared with previous data, though with comparable distribution for the sparsentan and irbesartan subgroup. More frequently reported for sparsentan were hypotension, dizziness, AKI and anaemia.

CKD RCT Study Pool: In the CKD RCT study pool, the most common TEAEs (≥5% of subjects) that occurred during the double-blind period in subjects who received sparsentan 400/800 mg vs irbesartan were peripheral oedema, headache, hypotension, hyperkalaemia, dizziness, and diarrhoea. TEAEs that occurred in ≥5% of subjects who received sparsentan 400/800 mg but occurred in <5% of subjects who received irbesartan were fatigue and nausea.

Adverse events by severity

PROTECT Study: Throughout the double-blind PROTECT study period, most subjects had TEAEs that were mild or moderate in severity in both treatment groups. Overall, in the PAS, 42 (10%) subjects had at least 1 TEAE that was severe (16 subjects [8%] receiving sparsentan, 26 subjects [13%] receiving irbesartan). The most commonly reported severe TEAEs were from SOC renal and urinary disorders, and the distribution was similar across groups (2% of subjects in each).

CKD RCT Study Pool: In the CKD RCT study pool, a total of 41 (9.2%) subjects who received sparsentan 400/800 mg and 35 (8.2%) subjects who received irbesartan had at least 1 TEAE that was severe during the double-blind period. Renal and urinary disorders accounted for the most reported severe TEAEs across the groups. AKI was reported as severe in 6 (1.3%) subjects who received sparsentan 400/800 mg and in 1 (0.2%) subject who received irbesartan.

Treatment related adverse events

PROTECT Study: Overall, in the PAS, 153 (38%) subjects experienced at least 1 treatment related TEAE (86 [43%] subjects who received sparsentan and 67 (33%) subjects receiving irbesartan). Treatment-related TEAEs by SOC reported in ≥10% of subjects were noted in nervous system disorders (10%) and metabolism and nutrition disorders (10%). At the initial analysis after completion of the PROTECT study, with cutoff date 7 Sept 2023, in general frequencies of TEAEs were

slightly increased as compared with previous data, though with comparable distribution for the sparsentan and irbesartan subgroup.

CKD RCT Study Pool: Treatment-related TEAEs by PT in ≥3% of subjects in the CKD RCT Study Pool are summarised in Table 15.

Table 14. Treatment-Related Adverse Events During the Double-Blind Period by Preferred Term Reported in ≥3% of Subjects in Any Treatment Group (CKD RCT Study Pool) (Safety Analysis Set) (data cutoff date 01 Feb 2022)

System Organ Class/ Preferred Term	Double-blind				All Sparsentan n (%) (N=537)
	Irbesartan n (%) (N=425)	400 mg Sparsentan n (%) (N=228)	800 mg Sparsentan n (%) (N=218)	400/800 mg Sparsentan n (%) (N=446)	
Any Treatment-Related TEAEs[a]	135 (31.8)	95 (41.7)	82 (37.6)	177 (39.7)	230 (42.8)
Gastrointestinal disorders	25 (5.9)	17 (7.5)	19 (8.7)	36 (8.1)	48 (8.9)
Nausea	6 (1.4)	6 (2.6)	8 (3.7)	14 (3.1)	18 (3.4)
General disorders and administration site conditions	26 (6.1)	19 (8.3)	23 (10.6)	42 (9.4)	50 (9.3)
Oedema peripheral	10 (2.4)	14 (6.1)	6 (2.8)	20 (4.5)	27 (5.0)
Fatigue	7 (1.6)	5 (2.2)	7 (3.2)	12 (2.7)	12 (2.2)
Investigations	20 (4.7)	24 (10.5)	14 (6.4)	38 (8.5)	59 (11.0)
Blood creatinine increased	7 (1.6)	5 (2.2)	3 (1.4)	8 (1.8)	16 (3.0)
Metabolism and nutrition disorders	31 (7.3)	22 (9.6)	18 (8.3)	40 (9.0)	65 (12.1)
Hyperkalaemia	23 (5.4)	18 (7.9)	12 (5.5)	30 (6.7)	50 (9.3)
Nervous system disorders	33 (7.8)	32 (14.0)	21 (9.6)	53 (11.9)	64 (11.9)
Dizziness	19 (4.5)	21 (9.2)	11 (5.0)	32 (7.2)	38 (7.1)
Headache	9 (2.1)	9 (3.9)	11 (5.0)	20 (4.5)	24 (4.5)
Vascular disorders	30 (7.1)	27 (11.8)	30 (13.8)	57 (12.8)	73 (13.6)
Hypotension	22 (5.2)	17 (7.5)	23 (10.6)	40 (9.0)	52 (9.7)
Orthostatic hypotension	3 (0.7)	5 (2.2)	7 (3.2)	12 (2.7)	14 (2.6)

Abbreviations: CKD = chronic kidney disease; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in sample; N = number of subjects; OLE = open-label extension; RCT = randomised controlled trial; TEAE = treatment-emergent adverse event.

Note: Data cutoff dates were 22 Jan 2021 for DUPLEX and 05 Feb 2021 for DUET, and 01 Feb 2022 for PROTECT.

Note: All Sparsentan column includes subjects who received at least one 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 continued to receive sparsentan during the OLE.

Note: Percentages are based on all subjects in the Safety Analysis Set within each group.

Note: TEAE is defined as any adverse event that newly appears, increases in frequency, or worsens in severity following initiation of study medication, but within 30 days after the last dose.

Note: Adverse events are coded with MedDRA Dictionary Version 23.0.

Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

[a] Related TEAEs are defined as TEAEs that are deemed to be 'possibly related', 'probably related' or 'related' to the study medication by the investigator. Adverse events with missing relationship are counted under 'Related'.

Source: ISS Table 2.5 (data cutoff 01 Feb 2022)

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

PROTECT Study: The overall incidence of SAEs was comparable between the PROTECT treatment groups: 43 (21%) subjects in the sparsentan group and 41 (20%) subjects in the irbesartan group. Per the study protocol, all symptomatic COVID 19 events were reported as serious. As of the updated cutoff date of 01 Feb 2022, a total of 23 subjects (11 subjects in the sparsentan group and 12 subjects in the irbesartan group) had experienced COVID-19 events. One event of COVID-19 in the irbesartan group was considered related to study medication by the investigator. One subject in the sparsentan group and one subject in the irbesartan group who experienced COVID 19 also experienced COVID 19 pneumonia.

AKI was reported more frequently in the sparsentan treatment group than irbesartan (in 4 versus 0 subjects, respectively). CKD (2 versus 1 subjects) and dizziness (2 versus 1 subjects) were the only other serious TEAE reported more frequently in the sparsentan arm than irbesartan. Cases of AKI were reported based on changes in serum creatinine between study visits that were usually several weeks apart, rather than in an acute hospital setting and, therefore, may have been representative of a gradual decline of kidney function rather than AKI.

CKD RCT Study pool: 53 subjects in both groups experienced any SAEs. A total of 103 (19.2%) subjects who received any dose of sparsentan had a serious TEAE, which includes subjects in DUET OLE study with long-term sparsentan exposure of up to 7 years. At data cutoff date of 01 Feb 2022, the overall incidence of SAEs was comparable between the 400/800 mg sparsentan and irbesartan groups: 68 (15.2%) subjects in the 400/800 mg sparsentan group and 63(14.8%) subjects in the irbesartan group.

The frequency of SAEs can partially be attributed to COVID-19. Per the study protocol, all symptomatic COVID-19 events were reported as serious. As of the cutoff date of 01 Feb 2022, TEAEs of COVID-19 were reported for 11 subjects in the 400/800 mg sparsentan group and 16 subjects in the irbesartan group).

Renal and urinary disorders accounted for the most reported serious TEAEs across groups in 8 (3.5%) subjects on sparsentan 400 mg, 4 (1.8%) subjects on sparsentan 800 mg vs 15 (3.5%) subjects on irbesartan. Serious infections and infestations were reported in 24 (5.4%) subjects who received sparsentan 400/800 mg and in 26 (6.1%) subjects who received irbesartan; serious gastrointestinal disorders in 8 (1.8%) and 2 (0.5%) subjects, respectively; metabolism and nutritional disorders in 5 (1.1%) and 4 (0.9%) subjects, respectively; and serious investigations in 5 (1.1%) and 5 (1.2%) subjects, respectively.

Deaths

At the time of the interim analysis, there were no deaths in the PROTECT study. One fatal event was reported in the DUPLEX study. The death was not of a study subject but of an infant born to a female subject in the irbesartan group. The infant was born prematurely with intestinal perforation (reported as possibly related to study medication), resulting in neonatal death.

Since the interim analyses through 01 April 2022, 1 fatal, possibly related SAE has been reported from each of the PROTECT and DUPLEX studies. Both have been submitted as suspected, unexpected, serious adverse reactions. No fatal cases have been reported from DUET through 01 April 2022.

One subject in the irbesartan arm experienced a fatal SAE reported as death after the original conditional MAA data cutoff date (01 Aug 2021). No other TEAEs led to death in the PROTECT study or the CKD RCT study pool as of the updated data cutoff date [data cutoff 01 Feb 2022]).

In the PROTECT study (interim analysis cutoff date of 01 April 2022 for fatal events), a 64-year-old subject with a history of left bundle branch block, respiratory distress, peripheral oedema, and type 2 diabetes died while sleeping approximately 18 months after starting study medication. The subject was positive for coronavirus disease 2019 that is caused by the SARS-Cov-2 virus (COVID-19) infection 3 months earlier, and 1 month later, was hospitalised with respiratory distress, fatigue, and a cardiac episode. An extensive workup showed a reduced ejection fraction and a dilated left ventricle with severely reduced systolic function. On discharge 5 days later, the subject was diagnosed with coronary artery disease, dyspnea, hypoxia, pulmonary oedema, acute kidney injury (AKI), and hyperlipidemia, and was appropriately treated with instructions to follow up with the nephrologist and cardiologist. The subject passed away 3 weeks later. The cause of death was not provided. The subject was randomised to receive irbesartan.

The investigator assessed the event of death as possibly related to the study medication. The applicant agreed with the investigator's causality assessment for the event of death as possibly related to the study medication.
In addition to the single death in the PROTECT study, 1 death was reported in the DUPLEX study in the interim analysis. A 74-year-old subject experienced gradual weight loss of approximately 17 kg over 6 months after starting study medication as well as loss of appetite andgastrointestinal discomfort. A computed tomography (CT) scan showed multiple masses in the right liver lobe consistent with metastatic disease; whole body positron emission tomography showed extensive metastatic disease involving the adrenal glands and liver. The neuroendocrine large cell carcinoma was believed to have originated in the lungs and had metastasised to the bone, adrenals, and liver. Study medication was stopped, and the subject completed 3 cycles of chemotherapy but elected to stop treatment given the prognosis. The subject died 1 month later, with the cause of death being metastatic cancer. The subject was randomised to receive sparsentan. The investigator assessed the fatal event of high-grade neuroendocrine large cell carcinoma as severe in intensity and possibly related to the study medication, since the possibility that the current clinical presentation was a consequence of the study medication could not be excluded. The possible cause of the event was noted as "other" - high-grade neuroendocrine carcinoma.

Other significant events

Several significant AEs have been evaluated in the PROTECT study, see Table 16:

Table 15. Safety Topics of Interest (Primary Analysis Set) – PROTECT (data cutoff date 01 Feb 2022)

	Irbesartan (N = 202) n (%) [event]	**Sparsentan (N = 202) n (%) [event]**	**Total (N = 404) n (%) [event]**
Subjects with Any Cardiovascular-Associated TEAEs	47 (23) [78]	53 (26) [86]	100 (25) [164]
Subjects with Any Cardiac Arrhythmia-Associated TEAEs	16 (8) [23]	11 (5) [12]	27 (7) [35]
Subjects with Any Symptomatic Hypotension-Associated TEAEs	22 (11) [37]	52 (26) [79]	74 (18) [116]
Subjects with Any Hepatic Disorder TEAEs	8 (4) [19]	14 (7) [33]	22 (5) [52]
Subjects with Acute Kidney Injury TEAEs	3 (1) [3]	9 (4) [10]	12 (3) [13]
Subjects with Any Pancreatic Enzyme-Associated TEAEs	9 (4) [14]	13 (6) [24]	22 (5) [38]
Subjects with Any Fluid Retention-Associated TEAEs	26 (13) [32]	32 (16) [47]	58 (14) [79]

	Irbesartan (N = 202) n (%) [event]	Sparsentan (N = 202) n (%) [event]	Total (N = 404) n (%) [event]
Subjects with Any Anaemia-Associated TEAEs	8 (4) [8]	15 (7) [16]	23 (6) [24]
Subjects with Any Hyperkalaemia-Associated TEAEs	22 (11) [30]	29 (14) [37]	51 (13) [67]

Cardiovascular-associated TEAEs: At least one cardiovascular-associated TEAE was experienced by 53 (26%) subjects in the sparsentan group and 47(23%) of subjects in the irbesartan group. There was no evidence of heart failure. The most commonly experienced TEAEs were hypertension (39(10%) subjects) and hypotension (29 (7%) subjects). There was 1 serious TEAE in the sparsentan group (hypotension), and 3 across 2 (1%) subjects) in the irbesartan group (angina pectoris, coronary artery occlusion, and deep vein thrombosis).

Cardiac arrhythmia associated TEAEs: In the same study, 27 subjects (7%) experienced at least 1 cardiac arrhythmia associated TEAE, with a higher incidence in subjects receiving irbesartan (16; 8% subjects) than subjects receiving sparsentan (11; 5% subjects). The most commonly experienced cardiac arrhythmia associated TEAE was palpitations, reported by 5 (2%) subjects on sparsentan and 7(3%) subjects on irbesartan. Cardiac arrhythmia associated TEAEs were related to treatment in 9 (2%) subjects, including 3 (1%) subjects on sparsentan and 6 (3%) subjects on irbesartan. In the sparsentan treatment group, palpitations (1 subject) and increased heart rate (2 subjects) were reported; in the irbesartan treatment group, palpitations were experienced by 3 subjects, sinus tachycardia, syncope, and tachycardia, each experienced by 1 subject each. There were no cases of ventricular tachycardia or torsade de pointes in either treatment group and no evidence of any symptomatic elevations or evidence of heart failure.

Symptomatic hypotension associated TEAEs were reported in 52 (26%) and 22 (11%) of subjects in the sparsentan and irbesartan groups, respectively. Three subjects who received sparsentan and 1 subject who received irbesartan reported serious symptomatic hypotension associated TEAEs. Symptomatic hypotension associated TEAEs led to treatment dose changes or interruptions in 13 of 52 subjects in the sparsentan group and in 6 of 22 subjects in the irbesartan group. Three subjects in the sparsentan and no subjects in the irbesartan group discontinued the drug due to symptomatic hypotension associated TEAEs. The majority of these TEAEs were reported in the first 24 weeks of treatment.

Hepatic-associated TEAEs: In the PROTECT study, hepatic-associated TEAEs were experienced in more subjects in the sparsentan treatment group, in 14 (7%) *vs* 8 (4%) subjects. The majority of these AEs were based on laboratory results. In the sparsentan group: increased ALT (n=8; 4%), increased AST (n=4; 2%) and gamma glutamyl transferase (GGT) (n=7; 3%). In the irbesartan group increased ALT (n=7; 3%), increased AST (n=6; 3%) and GGT (n=4; 2%). In the sparsentan group, additional hepatic associated TEAEs were abnormal alkaline phosphatase (n=1), cholestasis (n=1), hepatic steatosis (n=1), hepatitis (n=2), and hypoalbuminemia (n=1). These additional hepatic associated TEAEs were not noted in the irbesartan treatment group. Treatment-related hepatic disorder TEAEs occurred in 3% of subjects in the sparsentan group and 1% of subjects in the irbesartan group.

No subjects in either group experienced elevations in bilirubin that met the criteria for Hy's law. A total of 6 subjects in the sparsentan group and 4 subjects in the irbesartan group met Temple's Corollary (ALT or AST >3 x ULN without increased bilirubin). The elevated liver transaminases occurred between day 168 and 407, and were graded mild in 4 cases, moderate in 1 case and severe in 1 case. No clinical symptoms of hepatic injury were observed. Liver transaminases returned to baseline values upon discontinuation of sparsentan in all cases. Rechallenge was performed in 5 out of 6 cases, with

treatment permanently restarted in 3, and recurrence of elevated liver transaminases in 2 cases, leading to permanent discontinuation of sparsentan.

In the PROTECT study, prior to initiation of study treatment, the incidence of peripheral oedema was 10% in the sparsentan group and 4% in the irbesartan group. The percentage of subjects with fluid retention-associated TEAEs was higher in the sparsentan group compared with the irbesartan group, 47 events in 32 (16%) sparsentan-treated subjects compared with 32 events in 26 (13%) irbesartan-treated subjects. Oedema peripheral was experienced by 14% of subjects in the sparsentan treatment group and 11% of subjects in the irbesartan treatment group.

Pancreatic Enzyme associated TEAEs: In the PROTECT study, pancreatic-associated disorder TEAEs were reported in a larger proportion of subjects in the sparsentan group than in the irbesartan group (6% versus 4% of subjects, respectively). The PTs reported in more than 1 subject in either the sparsentan or irbesartan groups were lipase increased (5% and 3% of subjects, respectively) and amylase increased (3% and 2% of subjects, respectively). No serious pancreatic enzyme associated TEAEs were reported in either of the treatment groups.

Acute Kidney Injury associated TEAEs: In the PROTECT study, AKI-associated TEAEs were reported in 9 (4%) subjects in the sparsentan group and 3 (1%) subjects in the irbesartan group. TEAEs of AKI were assessed by the Investigator as related or possibly related in 4 (2%) subjects in the sparsentan group and 2 (1%) subjects in the irbesartan group. Study medication was discontinued in 3 (1%) sparsentan-treated subjects and no irbesartan-treated subjects. The AKI-associated TEAE was graded seriously in 4 (2%) subjects on sparsentan and no subject on irbesartan The Investigator assessed AKI-associated TEAEs as possibly related in 3 subjects in the sparsentan group and no subject in the irbesartan group. Of these events, the drug was withdrawn in 1 subject in the sparsentan group on Study Day 745; in the remaining sparsentan cases, study medication was interrupted, or the dose was reduced, and the AE outcome was recovered/resolved. None of the subjects required dialysis.

Fluid-retention associated TEAEs: A fluid retention-associated TEAE that was related to study medication, was experienced by 13 subjects (6%) in the sparsentan subgroup and 5 subjects (2%) in the irbesartan subgroup. The most common related TEAE was oedema peripheral (12 [6%] subjects on sparsentan and 4 [2%] subjects on irbesartan). Only 1 subject (<1%) in the sparsentan treatment group experienced treatment-related joint swelling, and 1 subject (<1%) experienced peripheral swelling related to sparsentan. Treatment-related lymphoedema was experienced by 1 subject (<1%) in the irbesartan treatment group.

The assessment score profile of peripheral oedema was comparable between the 2 study treatment groups. Grade 3 or 4 peripheral oedema assessments were reported in 4 subjects treated with sparsentan versus 8 subjects treated with irbesartan. At baseline in the PROTECT study, similar percentages of subjects in the sparsentan (15%) and irbesartan (16%) groups had diuretics reported as a prior concomitant medication. Initiation of concomitant diuretic treatment was also similar between subjects in the sparsentan (18%) and irbesartan (19%) groups.

Anaemia-associated TEAEs: In the PROTECT study, Anaemia-associated TEAEs were reported in 15 (7%) subjects on sparsentan and 8 (4%) subjects on irbesartan. In 3 subjects on sparsentan and 2 subjects on irbesartan, the anaemia-related TEAE was considered treatment-related. In one subject (on sparsentan) the anaemia associated TEAE was serious. Generally, the frequency of anaemia associated TEAEs is slightly increased in the subgroup on sparsentan. Overall, the majority of AEs reported as anaemia are based on decreases in haemoglobin rather than representing severe clinical anaemia that requires intervention in the form of transfusion.

Hyperkalaemia-associated TEAEs: In the PROTECT study, 51 (13%) subjects experienced at least 1 hyperkalaemia-associated TEAE: 29 (14%) subjects in the sparsentan treatment group and 22 (11%)

subjects in the irbesartan treatment group. Hyperkalaemia-associated TEAEs leading to dose change/interruption occurred in 6 of 29 subjects in the sparsentan group and 2 of 22 subjects in the irbesartan treatment group. One subject (<1%) who received irbesartan reported a serious event of hyperkalaemia (none in the sparsentan group). No subjects in either treatment group discontinued from treatment due to hyperkalaemia associated related TEAEs. The majority of hyperkalaemia associated TEAEs were considered as recovered/resolved.

Further details on the laboratory findings are given in sections below.

2.6.8.4. Laboratory findings

Haematology

At the interim analysis in the PROTECT study, there were no clinically relevant trends or changes over time in any haematology parameters, except for haemoglobin levels and haematocrit with moderate decreases in the sparsentan group from baseline (haemoglobin: 137.5 [15.52] and 138.0 g/L; haematocrit: 0.416 [0.0445] and 0.420 v/v) to Week 6 (haemoglobin: 129.0 [15.08] and 128.0 g/L; haematocrit: 0.391 [0.0450] and 0.390 v/v) that were stable through Week 94 (haemoglobin: 132.3 [19.56] and 131.5 g/L; haematocrit: 0.405 [0.0585] and 0.405 v/v).

Pancreatic enzymes

PROTECT study: Asymptomatic elevations in amylase and lipase were observed across both treatment groups, as frequently seen in patients with CKD. Post-baseline elevations in amylase and lipase were observed in 133 and 135 of 202 sparsentan-treated subjects, respectively, and 114 and 120 of 202 irbesartan-treated subjects, respectively, in the PROTECT study. Seven subjects in the sparsentan group and 6 subjects in the irbesartan group had elevations in amylase ≥3x ULN, and 19 subjects in the sparsentan group and 20 subjects in the irbesartan group had elevations in lipase ≥3x ULN.

DUPLEX study: In the DUPLEX study, postbaseline elevations in amylase were observed in 53.3% and 55.6% of subjects in the sparsentan and irbesartan groups, respectively. Post-baseline elevations in lipase were observed in 43.5% and 43.3% of subjects in the sparsentan and irbesartan groups, respectively.

Potassium

PROTECT study: An early, small increase in potassium levels was observed in both treatment groups that then stabilised with a mean increase of <0.1 mmol/L through Week 82 and a maximum of 0.26 mmol/L at Week 106 in the sparsentan group and 0.17 mmol/L in irbesartan subjects.

DUPLEX study: Increases in mean potassium levels were reported with acute changes by Week 6 or Week 8 that were sustained through Week 60 in both treatment groups. In the sparsentan group, there were increases in potassium levels (mean [SD] and median) from baseline (4.32 [0.463] and 4.35 mmol/L) to Week 2 (4.64 [0.469] and 4.60 mmol/L) and at Week 8 (4.60 [0.429] and 4.60 mmol/L). Overall, the increase in potassium levels occurred early and then stabilised (mean and median increase of approximately 0.3 mmol/L at Week 2). Similarly, in the irbesartan group, there were increases in potassium levels (mean [SD] and median) from baseline (4.31 [0.442] and 4.30 mmol/L) to Week 2 (4.53 [0.503] and 4.5 mmol/L) and at Week 8 (4.54 [0.573] and 4.50 mmol/L). After Week 8, mean potassium levels remained stable through Week 60 in both treatment groups.

B-type natriuretic peptide (BNP)

Elevations in BNP are associated with renal impairment, and elevations in N-terminal-pro hormone BNP (NT-proBNP) were consistent between the sparsentan and irbesartan treatment groups in the PROTECT

study. NT-proBNP elevations >400 pg/mL were observed in 30 (14.9%) subjects who received sparsentan and 33 (16.3%) subjects who received irbesartan.

Serum albumin

PROTECT study: Shifts in serum albumin levels were observed in postbaseline maximum results as follows: low serum albumin levels shifted to normal in 6 (3%) subjects in the sparsentan 400 mg group and 4 (2%) subjects in the irbesartan group; low serum albumin levels remained low in 2 (1%) subjects in the sparsentan 400 mg and in 5 (2%) subjects in the irbesartan group. There were no normal to low serum albumin shifts in the sparsentan 400 mg group; normal serum albumin shifted to low in 1 (<1%) subject in the irbesartan group.

CKD RCT Study pool: Shifts in serum albumin levels were observed in postbaseline maximum results as follows: low serum albumin levels shifted to normal in 45 (10.2%) subjects in the sparsentan 400/800 mg group and 36 (8.7%) subjects in the irbesartan group; low serum albumin levels remained low in 61 (13.8%) subjects in the sparsentan 400/800 mg group and in 53 (12.8%) subjects in the irbesartan group. Normal serum albumin levels shifted to low in 1 (0.2%) subject in the sparsentan 400/800 mg group and in 2 (0.5%) subjects in the irbesartan group.

Creatine Kinase

In the PROTECT study, shifts in CK were similar across both treatment arms, with postbaseline maximums shifting from normal to high in 52 (26%) subjects in the sparsentan 400 mg group and 49 (24%) subjects in the irbesartan group.

In the CKD RCT study pool, shifts in CK were similar across both treatment arms, with postbaseline maximums shifting from normal to high in 99 (22.3%) subjects in the sparsentan 400/800 mg group and 90 (21.7%) subjects in the irbesartan group. A limited number of sparsentan- and irbesartan-treated subjects in the CKD RCT study pool had CK values of >5000 U/L (3 subjects each).

Urinalysis

PROTECT study: During the interim analysis, there were no clinically relevant trends or changes over time through Week 94 in either PROTECT study treatment group in any urinalysis parameters, except for measures of protein and albumin in the urine.

CKD RCT Study pool: In the CKD RCT Study Pool, shifts in albumin levels were observed in post-baseline maximum results, with low albumin levels shifting to normal in 45 (10.2%) subjects in the sparsentan 400/800 mg group and 36 (8.7%) subjects in the irbesartan group.

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

Blood pressure: In the PROTECT study, sparsentan treatment led to an initial decrease in LSM systolic and diastolic blood pressure (DBP) (approximately 5 mmHg each), with subsequent stabilization starting at Week 12. Irbesartan treatment led to an initial LSM decrease only in systolic blood pressure (SBP) (approximately 3 mmHg) with subsequent stabilisation starting at Week 12 (Figures 9 and 10).

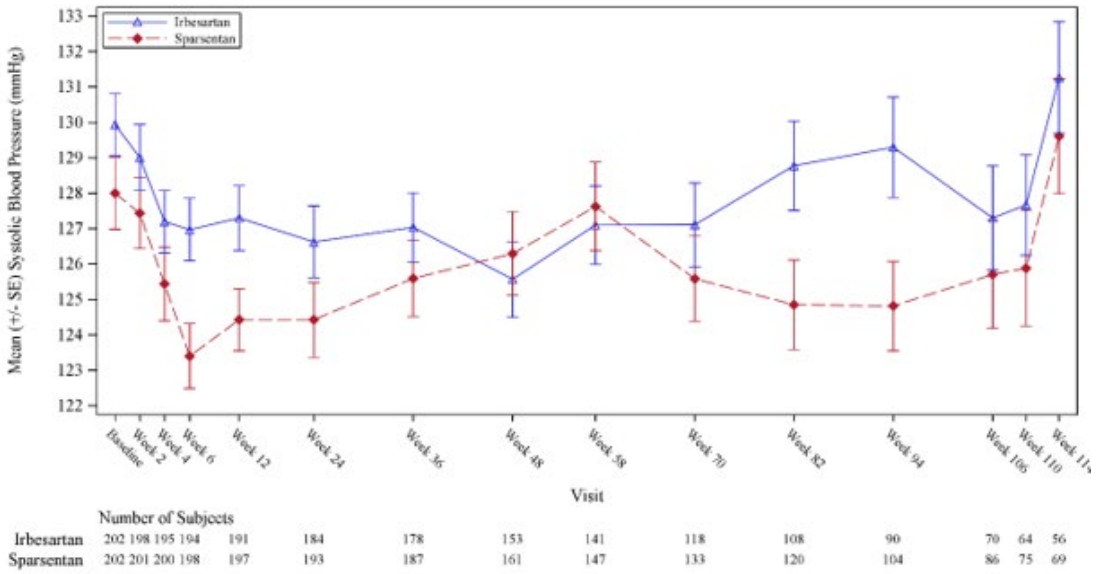

Figure 9. Systolic Blood Pressure over time (mean, SE; PROTECT study, data cutoff date 01 Feb 2022)

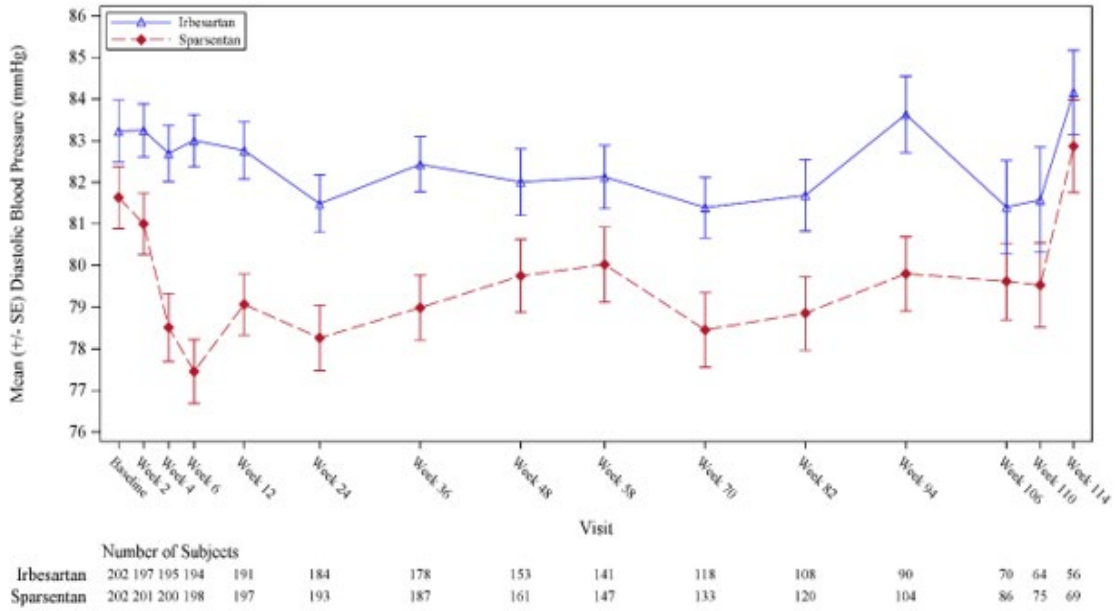

Figure 10. Diastolic Blood Pressure over Time (mean + SE, PROTECT study, data cutoff date 01 Feb 2022)

In the CKD RCT Study pool, changes in DBP were more common among subjects than changes in SBP. A SBP ≤100 mmHg was reported in 27 (11.8%) on sparsentan 400 mg, 44 (20.3%) on sparsentan 800 mg, and 56 (13.3%) on irbesartan, and a decrease in SBP from baseline >30 mmHg was reported in 16 (7.0%), 50 (23.0%) and 46 (10.9%) subjects. A DBP <=60 mmHg was reported in 38 (16.7%), 67 (30.9%), and 48 (11.4%) of subjects, respectively. A decrease in DBP from baseline > 20 mmHg was reported in 33 (14.5%), 85 (39.2%) and 64 (15.2%) subjects, respectively. Abnormal heart rates 120 bpm were infrequent in subjects across groups. Increases in heart rate from a baseline of more than

20 bpm occurred in 78 (17.5%) subjects who received sparsentan 400/800 mg and in 73 (17.3%) subjects who received irbesartan.

Electrocardiogram: A thorough QT/QTc (TQT) study was conducted in study 021HVOL16002, in 60 participants randomised to receive a treatment sequence including placebo and positive control moxifloxacin. Sparsentan at 800- and 1600-mg doses caused mild heart-rate corrected QT interval calculated using Fridericia's equation (QTcF) prolongation with a peak effect at 5 hours post-dose reaching 8.8 ms (90% confidence interval [CI]: 5.9 to 11.8) at 800 mg and 8.1 ms (90% CI: 5.2 to 11.0) at 1600 mg, without clear dose dependency (RTRX-RE021-104). ΔΔQTcF exceeding 10 ms could not be excluded in the by-timepoint analysis.

A thorough follow-up evaluation was performed by C-QT/E-R modelling approach in study RTRX-RE021-103, evaluating the effects of single doses (fasted and fed) of sparsentan at doses up to 1600 mg in healthy males and females. Holter monitors were used to collect continuous 12-lead ECG data for at least 24 hours on Days -1, 1, 4, and 5. The potential relationship between sparsentan plasma concentrations and ΔQTc was analyzed using E-R modelling and included assessment of hysteresis and goodness of fit (GoF). The predicted maximum ΔQTcF at the geometric mean C_{max} of plasma sparsentan under fasting conditions ranged from a mean of 0.013 ms to 3.070 ms. The upper bound of the 90% CI ranged from -0.370 ms to 3.637 ms. The predicted maximum ΔQTcF at the geometric mean C_{max} of plasma sparsentan under fed conditions ranged from 0.0002 ms to 8.292 ms. The upper bound of the 90% CI ranged from -0.382 ms to 9.896 ms. The upper 90% CI for all ΔQTcF predictions at geometric mean C_{max} was <10 ms, indicating there is no QTc prolongation of concern within the range of exposures in this study.

In the PROTECT study, post-baseline ECG assessments were not collected in the study except at sites in Germany. QTcF outlier analysis in the FSGS study pool (i.e., DUPLEX and DUET studies) found similar incidences of QTcF values >500 msec between the sparsentan and irbesartan treatment groups. Shift analyses in ECG results from the FSGS study pool found a similar incidence of shifts from normal to abnormal (not clinically significant) and abnormal (clinically significant) between the sparsentan (22.9% and 0.7%, respectively) and irbesartan (19.0% and 1.5%, respectively) groups.

2.6.8.6. Safety in special populations

Age: The PROTECT study enrolled subjects ≥18 years of age, the age range in the sparsentan group was 18 to 73 years, with 52.5% of the subjects >45 years of age, and the age range in the irbesartan group was 19 to 76 years, with 51.0% of the subjects >45 years of age. The 2 age groups had similar proportions of sparsentan-treated subjects who experienced AEs. The Preferred Terms (PTs) of AEs reported in sparsentan-treated subjects were generally consistent for subjects in the ≤45 years age group as compared to those in the >45 years age group, though headache, dizziness, and oedema peripheral occurred more frequently in the ≤45 years age group and hypotension occurred more frequently in the >45 years age group.

In the PROTECT study, a limited number of 24 subjects who are > 65 years of age were included. Summaries of treatment-emergent adverse events (TEAEs) by age group < 65 yrs, 65-74 yrs and 75-84 yrs for subjects in the sparsentan groups are provided in Table 22 for the PROTECT study. These include additional safety data from the PROTECT study based on a data cutoff date of 01 Feb 2022.

Table 16. TEAEs by Age Group (PROTECT) (Primary Analysis Set) - data cutoff date of 01 Feb 2022

	Age <65 Years		**Age 65-74 Years**		**Age 75-84 Years**	
	Irbesartan (N = 193)	**Sparsentan (N = 187)**	**Irbesartan (N = 7)**	**Sparsentan (N = 15)**	**Irbesartan (N = 2)**	**Sparsentan (N = 0)**

	n (%) [Event]	n (%) [Event]	n (%) [Event]	n (%) [Event]	n (%) [Event]	n (%) [Event]
Any TEAEs[a]	153 (79) [883]	162 (87) [944]	5 (71) [46]	15 (100) [108]	1 (50) [22]	0 (NC) [0]
Any related TEAEs[b]	65 (34) [157]	75 (40) [183]	2 (29) [9]	11 (73) [38]	0 (0) [0]	0 (NC) [0]
Any severe TEAEs	24 (12) [33]	13 (7) [19]	2 (29) [2]	3 (20) [7]	0 (0) [0]	0 (NC) [0]
Any SAEs	39 (20) [63]	40 (21) [51]	2 (29) [2]	3 (20) [7]	0 (0) [0]	0 (NC) [0]
Any SAEs with congenital anomaly or birth defect	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Any SAEs resulting in death	1 (1) [1]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Any SAEs requiring initial or prolonged hospitalisation	28 (15) [45]	27 (14) [37]	1 (14) [1]	2 (13) [5]	0 (0) [0]	0 (NC) [0]
Any SAEs that are life threatening	2 (1) [2]	3 (2) [4]	1 (14) [1]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Any SAEs persistent or significant disability/incapacity	3 (2) [4]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Any SAEs with other medically important event	17 (9) [19]	21 (11) [21]	0 (0) [0]	2 (13) [6]	0 (0) [0]	0 (NC) [0]
Any AEOIs[c]	4 (2) [10]	4 (2) [7]	0 (0) [0]	1 (7) [3]	0 (0) [0]	0 (NC) [0]
Any TEAEs leading to treatment discontinuation	9 (5) [12]	13 (7) [15]	1 (14) [1]	2 (13) [5]	0 (0) [0]	0 (NC) [0]
Any TEAEs leading to death	1 (1) [1]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Psychiatric disorders[d]	15 (8) [18]	15 (8) [18]	0 (0) [0]	1 (7) [1]	1 (50) [2]	0 (NC) [0]
Nervous system disorders[e]	45 (23) [75]	55 (29) [89]	1 (14) [1]	4 (27) [10]	1 (50) [2]	0 (NC) [0]
Accidents and injuries[f]	28 (15) [39]	17 (9) [25]	0 (0) [0]	2 (13) [2]	0 (0) [0]	0 (NC) [0]
Cardiac disorders[g]	16 (8) [21]	8 (4) [10]	1 (14) [2]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Vascular disorders[h]	32 (17) [44]	42 (22) [63]	2 (29) [2]	6 (40) [10]	0 (0) [0]	0 (NC) [0]
Cerebrovascular disorders[i]	1 (1) [1]	1 (1) [1]	0 (0) [0]	0 (0) [0]	1 (50) [0]	0 (NC) [0]
Infections and infestations[j]	80 (41) [123]	71 (38) [113]	3 (43) [3]	5 (33) [5]	0 (0) [0]	0 (NC) [0]
Anticholinergic syndrome[k]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Quality of life decreased[l]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (NC) [0]
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[m]	28 (15) [43]	41 (22) [58]	0 (0) [0]	2 (13) [4]	0 (0) [0]	0 (NC) [0]
TEAEs appearing more frequently in older patients by PT						
Oedema peripheral	20 (10) [22]	26 (14) [37]	2 (29) [2]	3 (20) [3]	0 (0) [0]	0 (NC) [0]
Hypotension	6 (3) [8]	17 (9) [24]	1 (14) [1]	5 (33) [7]	0 (0) [0]	0 (NC) [0]

Source: Table 2.1, Table 2.3, and Table 3.1.1

In the CKD RCT study pool, in the All Sparsentan group, there were no meaningful differences in overall AE incidence across age groups. There was a total of 39 subjects aged ≥65 years, and 92.3% of subjects had at least 1 TEAE. Approximately 80% of subjects aged 18 to < 65 years had at least 1 TEAE, and 85.3% of subjects aged < 18 years had at least 1 TEAE.

There were some differences in specific AE incidence among subjects < 18, 18 to < 65, and ≥65 years. Across these 3 groups, compared with the 18 to < 65 groups anaemia was most common in subjects < 18 years (17.6%), and peripheral oedema was most common in subjects ≥65 years (28.2%). Headache occurred in 26.5% of subjects aged <18 years, while hypotension occurred in 28.2% of subjects aged ≥65 years.

In the CKD RCT study pool, the inclusion criteria for the DUPLEX and DUET studies limited enrolment to subjects who were up to 75 years of age. A total of 497 subjects were <65 years of age and 40 subjects were 65 to 74 years of age in the All Sparsentan group, see Table 23. There were no subjects ≥75 years of age in the sparsentan group. In the irbesartan group, 402 subjects were <65 years of age, 19 subjects were 65 to 74 years of age, and 4 subjects were 75 to 84 years of age.

Table 17. TEAEs by Age Group (CKD RCT Study Pool) (Safety Analysis Set) data cutoff date of 01 Feb 2022

	Age <65 Years			**Age 65-74 Years**			**Age 75-84 Years**		
	Double-Blind			**Double-Blind**			**Double-Blind**		
	Irbesartan n (%) (N = 402)	**400/800 mg Sparsentan n (%) (N = 409)**	**All Sparsentan n (%) (N = 497)**	**Irbesartan n (%) (N = 19)**	**400/800 mg Sparsentan n (%) (N = 37)**	**All Sparsentan n (%) (N = 40)**	**Irbesartan n (%) (N = 4)**	**400/800 mg Sparsentan n (%) (N = 0)**	**All Sparsentan n (%) (N = 0)**
Any TEAEs	303 (75)	329 (80)	393 (79)	15 (79)	35 (95)	37 (93)	3 (75)	0 (NC)	0 (NC)
Any related TEAEs[a]	129 (32)	156 (38)	206 (41)	6 (32)	21 (57)	24 (60)	0 (0)	0 (NC)	0 (NC)
Any severe TEAEs	32 (8)	35 (9)	51 (10)	3 (16)	6 (16)	8 (20)	0 (0)	0 (NC)	0 (NC)
Any SAEs	57 (14)	60 (15)	93 (19)	5 (26)	8 (22)	10 (25)	1 (25)	0 (NC)	0 (NC)
Any SAEs with congenital anomaly or birth defect	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (NC)	0 (NC)
Any SAEs resulting in death	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (NC)	0 (NC)
Any SAEs requiring initial or prolonged hospitalisation	44 (11)	44 (11)	70 (14)	4 (21)	6 (16)	8 (20)	1 (25)	0 (NC)	0 (NC)
Any SAEs that are life threatening	2 (<1)	4 (1)	4 (1)	1 (5)	1 (3)	1 (3)	0 (0)	0 (NC)	0 (NC)
Any SAEs persistent or significant disability/incapacity	4 (1)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (NC)	0 (NC)
Any SAEs with other medically important event	20 (5)	25 (6)	34 (7)	0 (0)	3 (8)	3 (8)	0 (0)	0 (NC)	0 (NC)
Any TEAEs leading to discontinuation of study medication	17 (4)	29 (7)	52 (10)	2 (11)	5 (14)	6 (15)	1 (25)	0 (NC)	0 (NC)
Any TEAEs leading to dose interruption	36 (9)	52 (13)	65 (13)	6 (32)	5 (14)	7 (18)	0 (0)	0 (NC)	0 (NC)

Psychiatric disorders[b]	26 (6)	25 (6)	40 (8)	0 (0)	3 (8)	4 (10)	1 (25)	0 (NC)	0 (NC)
Nervous system disorders[c]	88 (22)	106 (26)	131 (26)	4 (21)	7 (19)	9 (23)	1 (25)	0 (NC)	0 (NC)
Accidents and injuries[d]	35 (9)	24 (6)	54 (11)	1 (5)	3 (8)	5 (13)	0 (0)	0 (NC)	0 (NC)
Cardiac disorders[e]	20 (5)	19 (5)	32 (6)	2 (11)	5 (14)	8 (20)	0 (0)	0 (NC)	0 (NC)
Vascular disorders[f]	57 (14)	81 (20)	117 (24)	2 (11)	12 (32)	14 (35)	0 (0)	0 (NC)	0 (NC)
Cerebrovascular disorders[g]	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (25)	0 (NC)	0 (NC)
Infections and infestations[h]	130 (32)	116 (28)	177 (36)	6 (32)	12 (32)	15 (38)	0 (0)	0 (NC)	0 (NC)
Anticholinergic syndrome[i]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (NC)	0 (NC)
Quality of life decreased[j]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (NC)	0 (NC)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[k]	51 (13)	72 (18)	86 (17)	2 (11)	4 (11)	4 (10)	0 (0)	0 (NC)	0 (NC)
TEAEs appearing more frequently in older patients by PT									
Oedema peripheral	40 (10)	52 (13)	74 (15)	3 (16)	10 (27)	11 (28)	2 (50)	0 (NC)	0 (NC)
Hypotension	23 (6)	43 (11)	55 (11)	1 (5)	9 (24)	11 (28)	0 (0)	0 (NC)	0 (NC)

Abbreviations: CKD = chronic kidney disease; MedDRA = Medical Dictionary for Regulatory Activities; NC = not calculated; PT = preferred term; RCT = randomised clinical trial; TEAE(s) = treatment-emergent adverse event(s); SAE(s) = serious adverse event(s); SMQ = standardised MedDRA query; SOC = System Organ Class; ULN = upper limit of normal.
Note: Data cutoff dates were 22 Jan 2021 for DUPLEX, 05 Feb 2021 for DUET, and 01 Feb 2022 for PROTECT.
Note: All Sparsentan column includes 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 continued to receive sparsentan during the open-label extension.
Note: Percentages are based on all subjects in the Safety Analysis Set within each group.
Note: TEAE is defined as any adverse event that newly appears, increases in frequency, or worsens in severity following initiation of study medication, but within 30 days after the last dose.
Note: Adverse events are coded with MedDRA Dictionary Version 23.0.
a Related TEAEs are defined as TEAEs that are deemed to be "possibly related," "probably related," or "related" to the study medication by the Investigator. Adverse events with missing relationship are counted under "related."
b Includes all events in the MedDRA Psychiatric disorders SOC.
c Includes all events in the MedDRA Nervous system disorders SOC.
d Includes all events in the MedDRA Injury, poisoning and procedural complications SOC.
e Includes all events in the MedDRA Cardiac disorders SOC.
f Includes all events in the MedDRA Vascular disorders SOC.
g Includes all events in the MedDRA Central nervous system vascular disorders High Level Group Term.
h Includes all events in the MedDRA Infections and infestations SOC.
i Includes all events in the Anticholinergic system SMQ using a broad algorithmic search.
j Includes the preferred terms "Impaired quality of life" and "Quality of life decreased."
k Includes the following observed preferred terms: Ankle fracture, Bursitis, Dizziness, Dizziness postural, Fall, Fibula fracture, Foot fracture, Hand fracture, Hip fracture, Humerus fracture, Jaw fracture, Joint dislocation, Joint injury, Meniscus injury, Orthostatic hypotension, Pseudarthrosis, Radius fracture, Rotator cuff syndrome, Stress fracture, Syncope, Ulna fracture, and Wrist fracture.
Source: Table 2.2, Table 2.4, and Table 3.2.1

No new safety concerns were identified in patients older than 65 years, and overall, sparsentan safety profile was consistent across all age groups. Nevertheless, conclusions on some differences in the incidences of specific TEAEs are limited, due to the small number of patients of ≥ 65years.

Gender

There were no noteworthy differences in the incidence of AEs by type between the gender subgroups the PROTECT study.

Overall, in the pooled analysis, the incidence of AEs was slightly higher in females than in males (84.7% versus 77.2%, respectively). TEAEs include headache, peripheral oedema, hypotension, dizziness, diarrhoea, vomiting, nausea, hypertension, anaemia, orthostatic hypotension, urinary tract infection, nasopharyngitis, proteinuria, dyspepsia, pruritus, and pyrexia were more common in female

subjects taking any dose of sparsentan. TEAEs of hyperkalaemia, fatigue, blood creatine phosphokinase increased, gout, muscle spasms, blood creatinine increased, and AKI were more common in male than in female subjects overall.

Race and ethnicity

There were no noteworthy differences in the incidence of AEs by type between the different race groups in PROTECT, DUPLEX and DUET studies.

Use in pregnancy and lactation

Both ARB and ERA classes are known to be teratogenic. As sparsentan shares a mechanism of action with both classes of drugs, it is also expected to have teratogenic effects. Teratogenic effects have been observed in animal studies with sparsentan. Therefore, the patients will be issued with dedicated patient card with description of the teratogenic risk associated with the use of Filspari and relevant instructions.

The use of sparsentan during pregnancy is therefore contraindicated, and females of child-bearing potential must use effective contraception while being treated with sparsentan. There is no information on the presence of sparsentan in human breast milk, the effects on the breastfed infant, or human breast milk production. As sparsentan is highly protein-bound, it is reasonable to assume that it would be present in breast milk. Therefore, sparsentan should not be given to a breastfeeding mother.

Twelve pregnancies have been reported in subjects receiving sparsentan or enrolled in a sparsentan study to date. A total of 5 pregnancies occurred in subjects enrolled in the IgAN PROTECT study, 6 pregnancies occurred in subjects enrolled in FSGS studies (5 DUET study subjects and 1 DUPLEX study subject), and 1 pregnancy occurred in a subject receiving sparsentan through a compassionate use program. All subjects with a positive pregnancy test stopped treatment as soon as the pregnancy was discovered. No congenital anomalies have been reported following any pregnancy during the study.

Baseline eGFR

In the PROTECT study, no noteworthy difference was seen for the TEAEs experienced related to baseline eGFR (ranging from <60 ml/min/1/73m^2 to > 90 ml/min/1.73 m^2) comparing both treatment groups. In all categories, slightly more TEAEs were experienced on sparsentan vs irbesartan (77-83% *vs* 64-76%). At baseline eGFR >90 ml/min/1.73m^2, the incidence of severe TEAEs was increased in subjects on sparsentan (8 *vs* 0%), but in the other stages of renal insufficiency, the frequency of SAE was similar for sparsentan and irbesartan.

In the CKD RCT study pool, based on a data cut-off date of 01 February 2022, some differences in the incidences of specific TEAEs were seen: the relative incidences of aspartate aminotransferase increased, CKD, fatigue, GGT increased, GFR decreased, and hyperkalaemia were higher among subjects with lower eGFR, while dizziness and headache were higher among subjects with higher baseline eGFR.

Baseline proteinuria

In the PROTECT study, in subjects with a baseline proteinuria less than 1.75 g/day, TEAEs, treatment related TEAEs and SAEs were reported more often on sparsentan. In subjects with a baseline UPE of >1.75 g/day, TEAEs and treatment related TEAEs were reported more often on sparsentan, whereas SAEs occurred more often on irbesartan.

In the CKD RCT study pool, based on a data cutoff date of 01 February 2022, the TEAEs by incidence were similar across baseline UP/C subgroups. In subjects with a high baseline proteinuria, TEAEs occurring more frequently as compared with low baseline proteinuria were acute kidney injury, blood creatine phosphokinase increased, diarrhoea, hypotension, muscle spasms, nausea, and vomiting.

However, like the eGFR subgroups, uneven subject distribution across UP/C subgroups does limit the conclusions that can be made from this comparative analysis.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Please refer to section 2.6 (Clinical Pharmacology).

2.6.8.8. Discontinuation due to adverse events

PROTECT Study: In the primary analysis set, 15 (7%) subjects who received sparsentan and 10 (5%) subjects who received irbesartan experienced TEAEs leading to treatment discontinuation. TEAEs leading to discontinuation of more than 1 subject in the sparsentan group were AKI (3 subjects, 1%), CKD (2 subjects, 1%), and ALT increase (2 subjects, 1%). In the irbesartan treatment group, the TEAE leading to discontinuation of more than 1 subject was renal impairment (2 subjects, 1%). All other TEAEs leading to study discontinuation were reported in a single subject.

In the CKD RCT study pool, 34 (7.6%) subjects who received sparsentan and 20 (4.7%) subjects who received irbesartan had a TEAE leading to discontinuation of study medication. The most common SOCs leading to study medication discontinuation were investigations (7; 1.6% subjects on sparsentan *vs* 2; 0.5% subjects on irbesartan) and renal and urinary disorders (9; 2.0% *vs* 7; 1.6%).

Treatment-Emergent Adverse Events that led to interruption of study drug

In the PROTECT study, in the sparsentan group, the mean (SD) and median total duration of study medication interruption among subjects with an interruption were 48.8 (76.6) and 23.0 days. In the irbesartan group, the mean (SD) and median total duration of study medication interruption among subjects with an interruption were 31.4 (38.57) and 13.0 days.

Symptomatic hypotension associated TEAEs led to treatment dose change or interruptions in 12 of 50 subjects in the sparsentan treatment group that experienced any symptomatic hypotension associated TEAE, and 5 of 21 subjects in the irbesartan treatment group.

AKI led to treatment dose change or interruptions in 4 out of 8 subjects and discontinuation in 3 out of 8 subjects in the sparsentan treatment group that experienced any AKI associated TEAE, and 1 out of 3 and 0 out of 3 subjects in the irbesartan treatment group. Hyperkalaemia-associated TEAEs leading to dose change/interruption occurred in 6 of 23 subjects in the sparsentan group and 2 of 19 subjects in the irbesartan treatment group. There were no permanent drug discontinuations due to hyperkalaemia associated TEAEs in either PROTECT study treatment group.

In the CKD RCT study pool, the incidence of TEAEs leading to dose interruptions was consistent across groups.

2.6.8.9. Post marketing experience

There is no information on the use of sparsentan in the applied indication in the EU.

2.6.9. Discussion on clinical safety

The safety database of sparsentan is primarily based on the data of the phase 3 PROTECT study in IgAN patients. At initial data base cut-off date 01 August 2021, 202 subjects with IgAN were exposed to sparsentan with a median (range) duration of exposure limited to 73.4 (32.6, 115.9) weeks overall

and 52.2 (0.0, 110.9) weeks for the target dose of 400 mg, and only 33/404 subjects had completed the DB treatment period.

To further characterise the safety of sparsentan, data of the PROTECT study was pooled with results in FSGS patients, including a phase 2 DUET study (study RET D-001) and phase 3 DUPLEX study (study 021FSGS16010). The applicant provided updated safety data based on an updated data cut-off date of 01 Feb 2022. In the PROTECT study, the median (range) duration of exposure to sparsentan was 96.50 (51.9-110.0) weeks overall and 69.1 (36.1-104.6) weeks for the target dose of 400 mg. At the data cut-off date of 01 Feb 2022, 123/404 subjects had completed the DB treatment period. For the CKD RCT study pool median (range) exposure in the DB period is extended by 6 months to 602 (1 to 813) days in the 400 mg sparsentan group and 566.0 (1 to 826) days in the irbesartan group. In the PROTECT trial as well as in the CKD RCT study pool, overall findings on safety were consistent with those reported originally. No new safety concerns for sparsentan were identified. Finally, a brief summary of safety data consisting of frequencies of TEAEs, common TEAEs and treatment related TEAEs with data cut-off date 7 Sept 2023 were provided and the PI was updated accordingly.

In the PROTECT study, the most common TEAEs in the sparsentan group were dizziness (14%), peripheral oedema (14%), headache (11%), hyperkalaemia (13%), and hypotension (11%). Common TEAEs of dizziness (14% *vs* 5%), fatigue (7% *vs* 4%), hypotension (11% *vs* 3%), peripheral oedema (14% *vs* 11%), hyperkalaemia (13% *vs* 10%), hepatic-associated events (7% *vs* 4%) and increased lipase (5% *vs* 3%) were reported with numerically increased frequency for sparsentan *vs* irbesartan. Similar findings were seen in the CKD RCT study pool, and no large differences in the distribution of treatment-related AEs have been found.

Sparsentan was associated with a slightly larger initial BP lowering effect *vs* irbesartan. Despite up-titration, this resulted in symptomatic hypotension reported more frequently for sparsentan. Also, dizziness and fatigue have been commonly and could be associated with a BP-lowering effect. However, hypotension was serious in very limited cases, led to change of dose or interruption in a limited number of subjects and to discontinuations in only a very small proportion of patients. This has been appropriately addressed in the SmPC, section 4.4.

Furthermore, cases of acute kidney injury (AKI) were limited but slightly increased with sparsentan and led to discontinuation in a small number of cases. In the larger CKD RCT study pool, serious cases of AKI were also limited. From longer-term data, 26 (4.8%) subjects had at least 1 TEAE of AKI, including 23 events in 18 (3.6%) subjects graded moderate or severe. Most cases of AKI occurred during a concomitant intercurrent co-morbidity. Hence, section 4.4 of the SmPC advises that periodic monitoring of serum creatinine and serum potassium levels should be performed in patients at risk. Sparsentan is to be used with caution in patients with bilateral renal artery stenosis.

Overall, 6 deaths have been reported, one death in the PROTECT study (irbesartan arm) after the *interim* period, and in the CKD RCT study pool (DUPLEX study) one in the sparsentan arm, including a newborn with a congenital anomaly of the bowel, of whom the mother was randomised to irbesartan, and one in the sparsentan arm after the interim period. Furthermore, four additional cases in the DUPLEX study have been reported without mentioning the treatment. In none of the cases, a causal relation to sparsentan was deemed likely.

The frequency of any AEs related to fluid-retention was increased for sparsentan, with peripheral oedema as the most frequent increased AE. The majority of fluid retention-associated events (approximately 70% for sparsentan and 56% for irbesartan) were not linked with initiation of a new diuretic treatment or an increase of dose of prior concomitant diuretic treatment. Similar results were seen in the CKD RCT study pool. Overall, fluid retention associated TEAEs were generally well manageable, using diuretic treatment as needed in a minority of subjects. The risk of fluid retention

with sparsentan, and the lack of data in subjects with heart failure, have been appropriately mentioned in the SmPC section 4.4.

In the PROTECT study, the AEs associated with hyperkalaemia lead to a change of dose or interruption in a small number of patients. No discontinuations due to hyperkalaemia were reported. In the CKD RCT study pool, the number of subjects experiencing at least 1 hyperkalaemia associated TEAE during the DB treatment period was higher on sparsentan 400/800 mg (n=48; 11%) than on irbesartan (n=34; 8%). The frequency in the sparsentan group increased from 7.1% at eGFR 60-90 ml/min/1.73m^2 to 10.9% at 30-60 ml/min/1.73m^2 and 36.0% at eGFR < 30 ml/min/1.73m^2. For irbesartan, these frequencies were 2.7%, 11.1% and 14.3% respectively. Accordingly, this risk has been addressed in the agreed SmPC.

Hepatotoxicity and elevated serum aminotransferases are known side effects of some ERA therapeutics. The majority of these AEs were reported based on enzyme elevations. However, the adverse event of interest of abnormal liver test results, defined as an elevation of ALT/AST > 3 x ULN, or 2-fold increase of ALT/AST above baseline, were sparsely observed and at a similar frequency for sparsentan and irbesartan. Reassuringly, no subjects experienced an event of AST or ALT elevation > 3 × ULN accompanied by concurrently elevated bilirubin that met Hy's law criteria. Likewise, in the CKD RCT Study Pool, increased liver enzymes were reported only for ALT (ALT 3.1% *vs* 1.8%, AST 1.8% *vs* 1.6%, GGT 1.8% *vs* 1.0% and total bilirubin 0% *vs* 1.0%); cases of Hy's law were not observed. Comparable results were observed during the longer-term OLE period. In the PROTECT study, a total of 6 subjects in the sparsentan group and 4 subjects in the irbesartan group met Temple's Corollary, after receiving study medication for 168 to 407 days. No clinical symptoms of hepatic injury were observed. Four of the 6 sparsentan-treated subjects had dose interruptions or discontinued study medication due to the events, resulting in liver transaminases returning to baseline. Only 1 subject received remedial treatment. Based on hepatic findings, advice is included in the SmPC for periodic monitoring of serum transaminases and total bilirubin every 3 months during treatment.

The combination of ACE inhibitors and ARB is used in clinical practice in patients with IgAN, and in the PROTECT study 9 (2%) subjects were taking both drug classes at screening. The use of ACE-inhibitors was not allowed during the studies and therefore no data on the combined use are available. In general, the combined use of ACE-inhibitors and ARBs is not advised because of an increased risk of adverse events like hyperkalaemia, hypotension and deterioration of renal function due to impaired glomerular perfusion. However, in some cases e.g. difficult to manage severe proteinuria ACE-inhibitors and ARBs are prescribed concomitantly. The risks and precautionary measures when combining sparsentan with an ACE inhibitor were adequately described in the SmPC.

Sparsentan is contraindicated in pregnancy due to a possible teratogenic effect. In addition, patients will carry a patient card with description of the teratogenic risk associated with the use of Filspari and relevant instructions (see additional risk minimisation measures below).

Furthermore, the SmPC recommends that physicians treat and up titrate the dose for patients older than 65 years of age with caution and as tolerated.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

To confirm the long-term safety of sparsentan for the treatment of primary IgAN in adults, and in order to specifically assess the long-term safety, the applicant will submit the detailed complete study report of the PROTECT trial, a randomised, double-blind, active-controlled, multicentre, global phase 3 trial in patients with IgAN. The key outcomes and/or endpoints will include analyses of safety (with special focus on AKI-associated adverse events and hepatic-associated adverse events) during long-term use

and analyses of safety and efficacy in relevant patient sub-groups. The results of the study will be provided in 3Q 2024.

2.6.10. Conclusions on the clinical safety

The safety profile of sparsentan has mainly been investigated in active-controlled studies in IgAN and FSGS, with irbesartan as an active comparator. Due to the lack of a placebo-controlled trial, the background population's frequencies of adverse events are unavailable. The available safety database for sparsentan in the long-term treatment of patients with IgAN is considered somewhat limited, especially for detecting rare or long-term safety issues. Frequency of AEs related to hypotension and AKI is increased. Furthermore, an increased frequency of AEs in subgroups (symptomatic hypotension in elderly, and hyperkalaemia in more severely impaired eGFR) is appropriately addressed in the SmPC.

Overall, adverse drug reactions include hypotension, hyperkalaemia, AKI, fluid retention, hepatotoxicity, and anaemia. The most common serious adverse reactions are listed in section 4.8 of the SmPC. Advice on periodic monitoring liver transaminases and bilirubin was also included in the SmPC. Further confirmation of the positive benefit-risk is expected in the post-marketing setting.

The CHMP considers the following measures necessary to address the missing efficacy and safety data in the context of a conditional MA:

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. Completion by 30 September 2024.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Drug-induced liver injury Teratogenicity
Missing information	Use in patients with heart failure Use in patients with severe hepatic impairment Use during breastfeeding Use in patients after renal transplantation

Safety specifications proposed by the applicant following the assessment of the responses to the CHMP's questions are acceptable. It is agreed that male infertility as a class effect of ERAs may not be applicable to sparsentan and therefore, does not need to be included as an important potential risk into the RMP or the product information. This theoretical risk will be considered as potential risk in upcoming PSURs to obtain further information in this regard.

2.7.2. Pharmacovigilance plan

There are no additional PhV activities for the safety concerns. The PRAC and CHMP, having considered the data submitted, are of the opinion that routine pharmacovigilance including specific follow-up

questionnaires for teratogenicity and drug-induced liver injury is sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

Table 18. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Drug-induced liver injury	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Legal status: subject to medical prescription Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Questionnaire - Drug-induced liver injury Additional pharmacovigilance activities: None
Teratogenicity	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • Legal status: subject to medical prescription Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Questionnaire - Teratogenicity Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with heart failure	Routine risk minimisation measures: • SmPC Section 4.4 • Legal status: subject to medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with severe hepatic impairment	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 5.2 • Legal status: subject to medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use during breastfeeding	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 • Legal status: subject to medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients after renal transplantation	Routine risk minimisation measures: • SmPC Section 4.2 • Legal status: subject to medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.6 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17 February 2023. The new EURD list entry will therefore use the IB} to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, FILSPARI (sparsentan) is included in the additional monitoring list as it contains a new active substance which was not contained in any medicinal product authorised in the EU. Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an

inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

The IgAN, categorised as a rare disease affecting the kidneys, is a serious, progressive, and life-limiting disease with a poor prognosis and high unmet medical need in Europe. IgAN is a form of glomerulonephritis (GN) diagnosed from a kidney biopsy and characterised by the finding of immune deposits, predominantly containing polymeric immunoglobulin A, in the glomerular mesangium of the kidney. Up to 40% of patients progress to end-stage kidney disease (ESKD) within 10 to 20 years after diagnosis.

3.1.2. Available therapies and unmet medical need

There are limited approved treatments for IgAN in the EU. The current treatment strategy is aimed at preventing or delaying ESKD. The main clinical predictor of disease progression in patients with IgAN is proteinuria. Standard-of-care for IgAN patients consists of RAAS inhibitors to reduce proteinuria and manage blood pressure, along with supportive interventions such as dietary and lifestyle amendments. Treatment with glucocorticoids may be considered for patients with persistent proteinuria >1 g/day despite maximised ACEI/ARB treatment who are at risk for progression to ESKD. For the minority of IgAN patients who experience nephrotic syndrome, ciclosporin may be a treatment option. Budesonide (Kinpeygo) is approved in the EU for the treatment of primary IgAN in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

Considering the progressive nature of IgAN and the comorbidities associated with complications of the disease or from the use of steroids, unmet medical need remains for patients with persistent proteinuria >1 g/day. This is the population with the highest risk for progression to ESKD, requiring dialysis or a kidney transplant, which is associated with a reduced quality of life and a lower survival.

3.1.3. Main clinical studies

The main evidence of efficacy was based on an interim analysis of the PROTECT study (Study 021IGAN17001) and high-level 2-years data. PROTECT is a global, Phase 3, multicenter, randomised, 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 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 biopsy-proven IgAN with persistent overt proteinuria (≥ 1 g/24 h) and therefore remained at high risk of disease progression despite being on a stable dose of an ACEI and/or ARB at a maximum tolerated dose that is at least one-half of the maximum labelled dose. Patients were randomised to sparsentan or irbesartan (active control). The starting dose was 200 mg once daily for sparsentan and 150 mg once daily for irbesartan, which if tolerated after two weeks, were up-titrated to 400 mg once daily for sparsentan and 300 mg once daily for irbesartan. The primary endpoint was the change from baseline (Day 1) in the UP/C ratio based on a 24-hour urine sample at Week 36. The key secondary endpoint was the rate of change in eGFR over a 52-week period following the initial acute effect of randomised

therapy (chronic slope). The analysis and benefit-risk assessment is based on data from an unblinded interim analysis (cut-off 01 Aug 2021) performed 36 weeks after randomising at least 280 patients, as well as on the 2-years high-level data, which were submitted on request of the CHMP. At the time of the primary interim analysis, more than 50% of subjects have been on randomised treatment longer than 58 weeks. Median durations of exposure were 73.43 (32.57, 95.71) weeks and 60.86 (27.00, 93.57) weeks in the sparsentan and irbesartan treatment group, respectively.

The safety database of sparsentan is primarily based on the interim-data (cut-off 01 Feb 2022) from the PROTECT study, supported by data from the CKD RCT study pool, that included the PROTECT study and two studies in FSGS, phase 2 DUET dose-finding study and phase 3 DUPLEX study. Top line results from the 2-year PROTECT study also reflect the initial safety observations.

3.2. Favourable effects

The main study met its primary endpoint. The geometric least squares mean percent change in UP/C from baseline at week 36 was -49.8% (95%CI: -54.98, -43.95) in the sparsentan arm *vs* -15.1% (95%CI: -23.72, -5.39) in the irbesartan arm (p<0.0001). In the latest analysis based on the top line results from the PROTECT trial, sparsentan treatment suggested a rapid and durable antiproteinuric treatment effect over 2 years, with a 43% mean reduction from baseline compared to 4% for irbesartan. This effect appeared to be consistent across sensitivity and subgroup analyses, which was supported by the exploratory analyses. A considerably higher proportion of patients on sparsentan than irbesartan achieved complete remission of proteinuria (urinary protein excretion <0.3 g/day) at any time while on double-blind treatment.

For the confirmatory outcome of chronic eGFR slope and total eGFR slope (cut-off date Sept 2023) a treatment difference of 1.1 mL/min/1.73 m^2 per year (95% CI: 0.07, 2.12; p=0.037) and 1.0 mL/min/1.73 m^2 per year (95% CI: –0.03, 1.94; p=0.058), respectively, in favour of sparsentan was demonstrated. This can be considered clinically meaningful as this is higher than the 0.75 mL/min/1.73 m^2 per year level (overall regarded as predictor of benefit on CKD progression). Furthermore, sensitivity analyses were generally consistent with the main findings. Confidence in the long-term beneficial effect of sparsentan is further gained from the benefit of the absolute difference in eGFR at 2 years showing less decline in sparsentan *vs* irbesartan (2-year decline in eGFR of – 5.8 mL/min/1.73m^2 per year for sparsentan *vs* -9.5 mL/min/1.73 m^2 per year for irbesartan, mean difference of 3.7 mL/min/1.73 m^2 per year, 95% CI 1.45 to 5.99).

3.3. Uncertainties and limitations about favourable effects

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, as might have been anticipated. Data from the DUPLEX study, although in a smaller group of the FSGS population, further increase the uncertainty regarding the eGFR slope treatment effect, since these demonstrated that the total eGFR slope (day 1 to week 60) in the sparsentan group was larger than in the irbesartan group (annualised difference was -1.3 (95% CI: -5.2, 2.6; p = 0.51) mL/min/1.73 m^2/year, in favour of irbesartan).

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.

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 this finding is still unclear.

Full analyses and data from the PROTECT study are expected to be provided by the applicant in the fulfilment of the imposed condition in frame of the conditional marketing authorisation for Filspari.

3.4. Unfavourable effects

In the PROTECT study, AEs were reported more frequently with sparsentan than irbesartan (88% *vs* 79%), including treatment-related AEs (43% vs 30%). However, no increase in frequency of severe (8% v*s* 13%) and serious AEs (21% *vs* 20%) was seen. The results from the supportive CKD RCT study pool were comparable.

Also, in the PROTECT study, a large patient proportion could be up-titrated to the target dose (95% *vs* 95%). Nevertheless, dose reductions after titration to the target dose occurred more frequently on sparsentan (15.3% *vs* 11.9%), most commonly due to hypotension (4.0 % *vs* 1.5%) and hyperkalaemia (2.0% *vs* 0.5 %). Furthermore, the frequency and duration of study medication interruption were slightly higher for sparsentan (16.3% (mean 27.0 (1, 332) days) *vs* 13.4% (16.0 (1, 134) days)). Discontinuation due to AEs was also slightly increased (7% *vs* 5%), mostly due to AKI (1% *vs* 0%), renal impairment (0.5% *vs* 1%), CKD (1 % *vs* 0%), and ALT increase (1% *vs* 0%).

The blood pressure lowering effect was more pronounced in the sparsentan *vs* irbesartan group, especially at the initiation (CFB of SBP and DBP (LSM) at week 6 -4.9 mmHg and -4.5 mmHg for sparsentan *vs* -2.7 mmHg and no effect on DBP for irbesartan), leveraging after 12 weeks of treatment. Despite a careful up-titration, AEs related to symptomatic hypotension (26% *vs* 11%), dizziness (14% *vs* 5%) and fatigue (7% *vs* 4%) have been commonly reported and could be associated with a BP lowering effect. Although symptomatic hypotension was largely reported in the first 24 weeks of treatment, it could still sparsely occur during an extended period of treatment, which means a frequent monitoring of BP status, volume status, and possible dose reductions or dose interruptions during chronic treatment.

Cases of AKI reported in the PROTECT study were limited but slightly increased with sparsentan compared to irbesartan (4% *vs* 1%), with serious AKI cases occurring at 2% *vs* 0%, and leading to discontinuation in a limited number of cases (1.5% *vs* 0%). In the larger CKD RCT study pool, serious cases of AKI were also limited (1.3% *vs* 0.2%). Longer-term data indicated that AKI could occur at every stage during long-term treatment. These events can be managed by treatment of intercurrent comorbidities and (temporary) interruption of sparsentan.

An increased frequency of events related to fluid-retention was reported for sparsentan (16% *vs* 13%), but this was not associated with an increase in severe peripheral oedema (2% *vs* 4%) and no case of heart failure was reported. With exclusion of hyperkaliaemic patients, monitoring of potassium levels and up-titrating accounting for potassium increase, hyperkalaemia occurred at an increased frequency in the sparsentan group (14% *vs* 11%). Based on open-label data from the CKD RCT study pool, hyperkalaemia appears to occur with increased frequency with lower eGFR (7.1% at CKD stage 1 to 36.0% at CKD stage 4). A substantial proportion of subjects on sparsentan experienced liver associated TEAEs (7% *vs* 4% on irbesartan). Hepatic events qualified as Temple's corollary occurred in 6 (3%) subjects on sparsentan *vs* 4 (2%) on irbesartan, without clinical symptoms of hepatic injury, with liver transaminases returning to baseline values upon discontinuation of sparsentan in all cases. Of note, the rechallenge resulted in repeat elevation of liver transaminases in 2 out of 6 subjects. Pancreatic enzymes were elevated in 57% of subjects at the baseline. However, elevations in amylase or lipase > 3 x ULN were reported at a comparable frequency in sparsentan and irbesartan. In the CKD

RCT study pool, similar results were reported. Anaemia-associated adverse events have been reported more frequently for sparsentan (7% vs 4%).

Malignancy was diagnosed in 3 subjects in the DB treatment periods of the PROTECT study but with no causal relation to trial medication.

The safety profile was similar at baseline eGFR subgroups, though the relative incidences of hyperkalaemia, decreased GFR and CKD were higher among subjects with lower eGFR. An increased frequency of hypotension in elderly patients aged 65-74 years was reported (n=9; 24% *vs* n=1; 5% on irbesartan).

Sparsentan is contraindicated in pregnancy due to a possible teratogenic effect and the special patient card with relevant information is included in the product package.

3.5. Uncertainties and limitations about unfavourable effects

The available safety data are still limited and based on a prespecified interim analysis in the main study. At the data cut-off of the pivotal PROTECT study, 1 Feb 2022, 123 (30%) of subjects had completed the double-blind treatment period of 110 weeks and median exposure was 96.5 weeks. Additional safety data retrieved from the CKD RCT study pool, were also limited. However, in fulfilment of the imposed specific obligation, long-term data are expected to be submitted.

In the performed studies, irbesartan was used as an active comparator. Due to the lack of a placebo-controlled trial data, absolute frequencies of AEs in the study population could not be established. Subjects with an established risk for developing hyperkalaemia, fluid retention, or liver test abnormalities were excluded. Furthermore, only patients who tolerated previous RAASi therapy were included. Therefore, the study population is likely to be a selection - at a reduced risk for several of these AEs. Serious AEs of gastrointestinal disorders were slightly increased (5 (2%) *vs* 1 (1%) in PROTECT and 8 (1.8%) *vs* 2 (0.5%) in the CKD study pool, but without any difference for a single type of GI events.

Malignancy was diagnosed in 3 subjects in the DB treatment periods of the PROTECT study (n=2 on sparsentan, n=1 on irbesartan), in 3 subjects in the DUPLEX study (n=2 *vs* n=1) and in 3 subjects in the DUET study (n=2 *vs* n=1), with no causal relation to trial medication. So far, no signal of a potential carcinogenic risk of sparsentan was seen during the limited time of follow-up and further data will be reported in post-marketing setting.

3.6. Effects table

Effects Table 1 for Filspari indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion $\geq$1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
UP/C ratio	UP/C from baseline at week 36	Ratio, LSM percent change	-49.8 (-55, -44)	-15.1 (-24, -5)	**Unc:** Relative reduction geometric mean ratio of 0.59 (0.51, 0.69); p <0.0001. **SoE:** Consistent among sensitivity analyses and subgroup analyses.	PROTECT study
Total eGFR slope at one year	Rate of change in eGFR over a 110 Week Period (Day 1 to Week 110)	mL/min/1.73m^2/year (95% CI)	−2.9 (-3.58, -2.24)	−3.9 (-4.59, -3.13)	**Unc:** Annualised difference in slope was not significant for total slope: 1.0 (95% CI: -0.03, 1.94) mL/min/1.73 m^2/year, p=0.058. The total eGFR slope did not evolve into the total eGFR slope specified in the SAP of 2.55 mL/min/1.73 m^2 per year (to be detected with 80% power based on this sample size) at the 2 years analysis. **SoE**: Difference in eGFR chronic slope was significant between sparsentan and irbesartan groups: 1.1 (0.07, 2.12) mL/min/1.73 m^2/year, p = 0.037.	
Unfavourable Effects						
Symptomatic hypotension		n (%)	52 (26)	22 (11)	**SoE:** Change in SBP, DBP (wk6): -4.9 and -4.5 mmHg vs -2.7 mmHg and no effect on DB; Dizziness (14% vs 5%) and fatigue (7% vs 4%) were also increased	PROTECT study Data cutoff date 01 Feb 2022
Peripheral oedema		n (%)	29 (14)	22 (11)		
Hyperkalemia	Serum potassium > 5.5 mmol/l	n (%)	27 (13)	21 (10)		

AKI	Acute kidney injury	n (%)	9 (4)	3 (1)	**SoE:** Similar observations in the CKD study pool. Manageable by treatment of intercurrent comorbidities and (temporary) interruption of sparsentan.	
Hepatotoxicity	Increased ALT, AST, GGT, AF; or cholestasis, hepatic steatosis, hepatitis, hypo-albuminaemia	n (%)	14 (7)	8 (4)	**SoE:** Detected by screening at day 168-407 liver transaminases returning to baseline values upon discontinuation in all cases, rechallenge resulting in repeat elevation of liver transaminases in 2 out of 6 subjects.	

Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, AKI = acute kidney injury (acute loss of renal function, within 2 weeks, increased serum creatinine >= 0.3 mg/dl or 26.5 mumol/l; rise serum creatinine >= 1.5 BL), ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma-glutamyltransferase; AF = Blood Alkaline phosphatase

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with sparsentan is aimed at patients with IgAN that maintain overt proteinuria (≥ 1 g/24 h) and therefore remain at high risk of disease progression despite being on a stable dose of an ACEI and/or ARB. Proteinuria is thought to be part of the causal pathway of kidney dysfunction in IgA nephropathy, eventually leading to end-stage kidney disease, supported by trial-level meta-regression analyses of RCTs demonstrating that proteinuria reduction is associated a protective effect on eGFR slope. In this respect, the effect of sparsentan on proteinuria compared to irbesartan can be considered relevant.

However, data on the direct disease-specific evidence establishing a causal role of proteinuria in the pathogenesis of progressive kidney dysfunction in IgAN are limited, which precludes using proteinuria as the sole basis to demonstrate reno-protective efficacy. To obtain confidence in the potential reno-protective effects of sparsentan, an effect on proteinuria should be accompanied by a significant beneficial effect on the eGFR slope in the longer term. In this context, a 2-years eGFR slope has been regarded as a reasonably likely surrogate for a clinically relevant benefit. The approach has also been adopted as a demonstration of a treatment effect on the endpoints that are not considered feasible to be established in the context of clinical studies due to the need for large patient number or an extensive follow-up time.

The applicant provided 2-year eGFR data. These show a statistically significant difference between sparsentan and irbesartan (95% CI) 1.1 (0.07, 2.12), p=0.037 of eGFR chronic slope (mL/min/1.73 m^2 per year), a statistically and clinically insignificant difference in eGFR total slope (95%CI, mL/min/1.73 m^2 per year) 1.0 (−0.03, 1.94) p=0.058. The change from baseline at week 110 (mL/min/1.73 m^2) was different between groups in favour of sparsentan 3.7 (95%CI: 1.45, 5.99). Change from baseline to 4 weeks post cessation of treatment (mL/min/1.73 m^2) was not different between the groups 95 % CI 2.9 (0.45, 5.25).

The chronic and total eGFR slope demonstrated an effect size of 1.1 and 1.0 ml/min/1.73m^2/year treatment difference, respectively. This treatment difference can be considered a clinically meaningful predictor of benefit on CKD progression.

Total eGFR slope analyses narrowly missed statistical significance, but the effect size was similar to that of chronic eGFR slope. Other efficacy endpoints, including use of rescue immunosuppressive medication and hard renal outcomes, favoured sparsentan. Given the fact that both sparsentan and irbesartan demonstrated a comparable acute eGFR decline, the use of chronic slope can be considered as acceptable in this scenario. The lower than anticipated effect size is likely attributable to the fact that the active control arm was actively titrated to the maximum labelled dose in more than 95% of patients. The totality of data from PROTECT suggests that sparsentan is an effective and safe treatment for IgA nephropathy that delivers meaningful clinical benefit beyond RAAS inhibition alone.

Based on the currently limited safety database, sparsentan has demonstrated some typical safety issues that can be anticipated based on its mode of action and based on the safety previously seen with endothelin receptor antagonists and angiotensin receptor blockers. Hypotension and hyperkalaemia could be reasonably managed with appropriate monitoring and careful up-titration in the CKD population, which is has an increased risk for such events. Llimited serious adverse effects such as AKI have been reported. A known effect of fluid-retention has been increasingly observed in sparsentan, but this was not serious. Reported asymptomatic liver enzyme elevations are reversible on

discontinuation of sparsentan. This can be managed by regularly monitoring of liver transaminases, as recommended in the Product Information.

3.7.2. Balance of benefits and risks

Sparsentan has demonstrated that it effectively reduces proteinuria and appears to have a desirable effect on the chronic and total eGFR slope, which is considered a reasonable treatment target according to the KDIGO guideline for IgAN. The current analyses are reassuring that treatment with sparsentan will results in a long-term renal protection in the currently proposed target indication including all patients with a baseline proteinuria ≥ 1.0 g/day, which is expected to be provided in the final CSR. Sparsentan appears to be generally well tolerated, providing the precautions as characterised. The applicant committed to provide full long-term data from the PROTECT study in fulfilment of the condition to this conditional marketing authorisation.

Sparsentan appears to be generally well tolerated, providing the precautions as characterised. Overall, based on the demonstrated reno-protective effects so far, the benefit-risk balance of sparsentan in the scenario of a conditional approval is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the prevention and treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed above.

Confirmatory data from PROTECT provided so far continue to support the expected significant and clinically meaningful antiproteinuric effect of sparsentan compared to active control observed in the interim analysis. These findings reflect the potential for long-term nephroprotection, consistent with the body of evidence establishing the association between proteinuria, eGFR slope, and renal outcomes in primary IgAN. The 2-year safety findings are consistent with earlier trial results suggesting that sparsentan is generally safe and well-tolerated. For the management of the most common ADRs, such as hypotension, hyperkalaemia, AKI, peripheral oedema, appropriate advice has been included in the product information that detail their prevention and management.

- It is likely that the applicant will be able to provide comprehensive data.

For the PROTECT study, the last patient's last visit was in Q3 2023 and the applicant provided top line data within the current procedure and these suggest a clinically meaningful reno-protective effect. The CHMP requested the submission of the final, full data package in frame of the conditional approval as a post-marketing commitment, where the already observed clinical benefit of sparsentan is considered likely to be confirmed.

- Unmet medical needs will be addressed.

There are currently limited approved treatments for IgAN in the EU. The present treatment strategy is

aimed at preventing or delaying ESKD. Therapy consists of RAAS blockade therapy and supportive care. Despite optimised RAAS blockade therapy and associated blood pressure control, persistent overt proteinuria remains, in many patients, concurrent with renal function loss and progression to ESKD. Immunosuppression can be considered for patients who maintain a high degree of proteinuria but are often associated with serious adverse events. Budesonide (Kinpeygo) received a conditional marketing authorisation for the treatment of primary IgAN in adults at risk of rapid disease progression with a UP/C ≥1.5 g/g in 2022. Budesonide may not be tolerated for each patient in the IgAN population meeting the indication criteria, due to its typical corticosteroid-like side effects, including increased blood pressure, cushingoid features and indigestion. Also, it should be noted that budesonide treatment is only indicated for a temporary treatment period of 9 months; this temporal nature may suggest a potentially shorter duration of the therapeutic effect. Sparsentan, is proposed to be indicated without restrictions on the treatment period and for a wider range of patients (baseline proteinuria ≥1 g/day). Sparsentan has demonstrated both, reduction in proteinuria as well as reduction in the rate of eGFR decline for the period of 2 years (based on top line data for the PROTECT study). As this is expected to delay the progression to ESKD, sparsentan could fulfil the unmet medical need in the treatment of IgAN.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The immediate availability of sparsentan will allow patients access to this therapy earlier than awaiting the submission and approval of a standard marketing authorisation application upon availability of the final study analyses and report from the PROTECT study. The main benefit of sparsentan to public health is reduction in the risk of disease progression in patients with primary IgAN during the 2-year period, which under the effect size of the chronic eGFR slope of 1.1 ml/min/1.73m^2 per year would translate to up to 2.2 ml/min/1.73m^2 difference in eGFR. This is considered clinically relevant as this is expected to lead to a delay in the time till ESKD for treated patients. Furthermore, the safety results are reassuring.

In light of the above, it is agreed, that the benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of Filspari is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Filspari is not similar to Kinpeygo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix Report on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Filspari is favourable in the following indication:

> *Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g, see section 5.1).*

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to use of Filspari in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The Marketing Authorisation Holder shall ensure that in each Member State where Filspari is marketed, all patients who are expected to use Filspari have access to the following educational material:

Patient card:

- Description of the teratogenic risk associated with the use of Filspari
- Instruction not to take Filspari in case of pregnancy or planning to become pregnant
- For women of childbearing potential recommendation to use effective contraception methods
- Instruction to have pregnancy testing prior starting Filspari
- Instruction to immediately talk to your doctor in case of pregnancy or the suspicion thereof
- Instruction to have regular monitoring of liver function (serum aminotransferase levels and total bilirubin).
- Signs or symptoms of drug-induced liver injury and when to seek attention from a healthcare professional

- **Obligation to conduct post-authorisation measures**

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sparsentan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendices

5.1. CHMP AR on similarity dated 22 February 2024

5.2. CHMP AR on New Active Substance (NAS) dated 22 February 2024