CSL Vifor

EU RISK MANAGEMENT PLAN FOR SPARSENTAN

RMP version to be assessed as part of this application:

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Rationale for Submitting an Updated RMP:	Submission of final study results for the double-blind phase of PROTECT to address Conditional Marketing Authorisation Specific Obligation enabling conversion to standard Marketing Authorisation
Summary of Significant Changes in this RMP:	SIII and SV per up-to-date exposure figures, inclusion of post-marketing methodology SVII.3.1 per final study results (PROTECT) and post-marketing data Part IV/VI: Removal of Specific Obligations (PROTECT)
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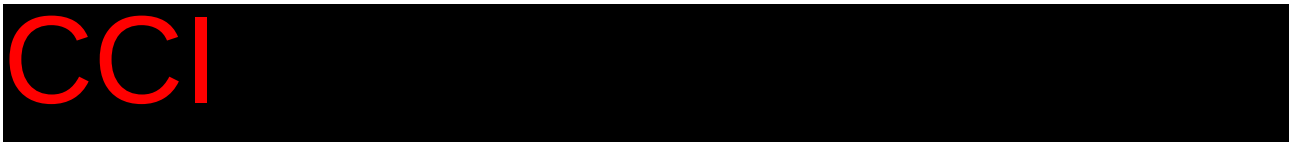
QPPV Name:	Juergen Zorn, EU QPPV
QPPV Oversight Declaration:	The content of this RMP has been reviewed and approved by the Vifor (International) Inc.'s QPPV. The electronic signature is available on file.



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LIST OF ABBREVIATIONS

ACEI	angiotensin converting enzyme inhibitor
ADR	adverse drug reaction
AE	adverse event
AKI	acute kidney injury
ARB	angiotensin receptor blocker
AT_1R	angiotensin II receptor Type 1
AUC	area under the curve
BP	blood pressure
CKD	chronic kidney disease
DILI	drug-induced liver injury
eGFR	estimated glomerular filtration rate
ERA	endothelin receptor antagonist
ESKD	end-stage kidney disease
ET_AR	endothelin Type A receptor
EU	European Union
FSGS	focal segmental glomerulosclerosis
IgAN	immunoglobulin A nephropathy
KDIGO	Kidney Disease Improving Global Outcomes
OLE	open-label extension
PT	preferred term
RAAS	renin angiotensin aldosterone system
RCT	randomised controlled trial
RMP	Risk Management Plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
TQ	Targeted Questionnaire
US	United States

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or Common Name):	Sparsentan
Pharmacotherapeutic Group(s) (ATC Code):	C09XX01
Marketing Authorisation Holder or Applicant:	Vifor France
Medicinal Products to Which This RMP Refers:	1
Invented Name(s) in the EEA:	Filspari™
Marketing Authorisation Procedure:	Centralised
Brief Description of the Product:	Chemical class: Sparsentan is a novel, first-in-class, single-molecule DEARA being developed for the treatment of primary IgAN.
	Summary of mode of action: Sparsentan is a highly selective antagonist for endothelin Type A receptor and angiotensin II Type 1 receptor.
	Important information about its composition: 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. Sparsentan has a molecular weight of 592.76 Daltons and a molecular formula of $C_{32}H_{40}N_4O_5S$. Sparsentan is a white to off-white powder, with a pH of 7.04 in a saturated aqueous solution. The inactive ingredients in Filspari are silicified microcrystalline cellulose, lactose anhydrous, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate. Tablets are coated with Opadry II White.
Hyperlink to the Product Information:	Proposed Product Information
Indication(s) in the EEA:	Approved: Filspari is indicated for the treatment of adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g).
Dosage in the EEA:	Approved: Sparsentan treatment should be initiated at a dose of 200 mg once daily for 14 days and then increased to a maintenance dose of 400 mg once daily, dependent upon tolerability.
Pharmaceutical Form(s) and Strengths:	Approved: Film-coated tablet. Filspari 200 mg film-coated tablets White to off-white, modified oval-shaped, film-coated tablet, debossed with “105” on one side and plain on the other side. The dimensions of the tablets are approximately 13 mm x 7 mm. Filspari 400 mg film-coated tablets White to off-white, modified oval-shaped, film-coated tablet, debossed with “021” on one side and plain on the other side. The dimensions of the tablets are approximately 18 mm x 8 mm.
Is/Will the Product be Subject to Additional Monitoring in the EU?	Yes

Notes: ATC=Anatomical Therapeutic Chemical; DEARA=Dual endothelin angiotensin receptor antagonist; EEA=European Economic Area; IgAN=Immunoglobulin A nephropathy; INN=International Nonproprietary Name; RMP=Risk Management Plan.

PART II: SAFETY SPECIFICATION

SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Epidemiology of the Disease

SI.1.1 Incidence and Prevalence

The estimated incidence of primary IgAN across individual countries in Europe ranges between 1.8 and 27 per million per year [1,2].

The prevalence of primary IgAN is approximately 4 in 10,000 in the European Economic Area. The number of patients affected by the condition is estimated to be 208,000 assessed on the basis of data from the EU 27 and Norway, Iceland, and Liechtenstein and on a total population of 452,500,000 [3].

SI.1.2 Demographics of the Target Population (Age, Sex, Race/Ethnic Origin)

IgAN is a serious, progressive, and life-limiting disease, in which up to 40% of subjects progress to end-stage kidney disease (ESKD) within 10 to 20 years following diagnosis [4-6]. IgAN has a highly variable clinical presentation [7-9], with a heterogeneous risk of progressive kidney function decline to ESKD [10-12]. In a European study including only White patients, approximately 50% of high-risk patients receiving supportive care alone reached a composite endpoint of ESKD, death, or >40% decrease in estimated glomerular filtration rate (eGFR) at a median of 7.4 years [13,14]. IgAN can occur at any age, but clinical onset is most common during the third decade of life [15]. Thus, most patients are diagnosed in their 20s or 30s and face the prospect of dialysis or the need for kidney transplantation in the prime of their lives.

It has been documented that IgAN is most prevalent in people of East Asian descent, followed by Caucasians and is rare in individuals of African descent [16-21], with reports of IgAN being 4 to 13-times less prevalent in Black/African American patients than in Caucasians [16-20]. The prevalence of IgAN in male and female patients differs geographically. The ratios of male to female patients range from less than 2:1 in Asians to as high as 6:1 in patients from Europe and the US [22].

SI.1.3 Risk Factors for the Disease

IgAN is a glomerular disease that is diagnosed from a kidney biopsy and is characterised by the finding of immune deposits, predominantly containing polymeric immunoglobulin A, in the glomerular mesangium of the kidney [23-26]. These immune deposits cause a cascade of events that include proliferation of the mesangial cells, synthesis of extracellular matrix, and excess production of inflammatory cytokines, resulting in damage to the glomerular filtration barrier.

IgAN pathogenesis is incompletely understood; although associations between IgAN and glomerular and circulating markers of complement activation are known, the mechanism of complement activation and contribution to glomerular inflammation and injury are not well defined. More recently, it has been postulated that the renal-gut connection can also play an important role in the pathogenesis of IgAN. In addition to the strong association with genetic factors, there are data on the possible influence of local pathogens in the development of the disease [27,28].

Biopsy studies have shown a substantially higher proportion of patients with serious inflammatory lesions, such as endocapillary hypercellularity and crescent formation, in East Asian populations than in biopsies from European patients [21]. Asian patients with IgAN have been proposed to have a faster progression rate compared to Caucasians [12]. Damage to the glomerular filtration barrier results in proteinuria and haematuria [8,29]. In IgAN, proteinuria is a marker of glomerular injury and amplifies tubulointerstitial fibrosis and tubular cell injury via increased protein filtration, subsequent reabsorption [8,29], and abnormal accumulation of protein in the endolysosomes and endoplasmic reticulum. As a consequence, vasoactive and inflammatory genes are activated within tubular epithelial cells and mediators are released into the interstitium. The inflammatory environment contributes to fibrogenesis via transformation of tubular cells to fibroblasts, fibroblast proliferation, and interstitial inflammation. This culminates in scarring within the kidney and a decline in kidney function [30].

Proteinuria is the most common and well-studied risk factor used to measure the progression of IgAN to ESKD, and it is a reliable predictor of patient outcomes [15,29,31]. According to the current Kidney Disease Improving Global Outcomes (KDIGO) guidelines, high risk of progression in IgAN is defined as proteinuria >0.75-1 g/24 hours despite at least 90 days of optimised supportive care, including maximised renin angiotensin aldosterone system (RAAS) blockade [32]. Sustained (>1 g/24 hours) proteinuria is the strongest single predictor of progressive kidney function decline [15,29,33,34], and each additional daily gram of protein in the urine is associated with a progressively worse kidney survival rate and an increased rate of kidney function decline [15,29,33]. A registry study of patients with biopsy-proven IgAN (n=1,155) that assessed cumulative renal survival rates (10, 15, and 20 years) found that proteinuria >1 g/24 hours at the time of biopsy was significantly associated with kidney failure or a 50% drop in eGFR [26]. In a long-term follow-up (median of 48 months) of IgAN patients (n=921), proteinuria levels of >1 g/24 hours were significantly associated with a higher risk of doubling serum creatinine and a markedly increased risk of kidney failure [35]. Even patients traditionally regarded as being low risk (proteinuria <0.88 g/g) had high rates of kidney failure within 10 years. Importantly, each 10% decrease in proteinuria from baseline was associated with a hazard ratio (95% confidence interval) for kidney failure/death of 0.89 (0.87 to 0.92), after adjusting for age, sex, baseline eGFR, and time from diagnosis to baseline, demonstrating the importance of reducing proteinuria to close to 0.3 g/day in IgAN patients. [36]

In IgAN and across rare proteinuric glomerular diseases, the biological plausibility of proteinuria being on the causal path of the pathological changes and progression to ESKD has been established [31]. A recent analysis of longitudinal observational data from subjects with IgAN found that there was no minimum duration of proteinuria remission required to confer clinical benefit; even remission of proteinuria for only 3 or 6 months was found to be beneficial compared to never achieving proteinuria remission [37]. A set of trial-level meta-regression analyses analogous to those performed on chronic kidney disease (CKD) have been conducted on the subgroup of IgAN randomised controlled trials (RCTs) of the CKD study cohort [31,34,38-40]. These trial-level analyses demonstrate an association between a treatment effect of urine protein/creatinine ratio and a treatment effect on eGFR slope, as well as clinical outcomes.

SI.1.4 Main Existing Treatment Options

The goal of therapy in IgAN, as outlined by the KDIGO guidelines, is to preserve kidney function through management of proteinuria and blood pressure (BP), which is pivotal in slowing progression to kidney failure [32].

Delayed-release budesonide (Kinpegyo®) has received US FDA approval to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression and is authorised for use in Europe to treat patients with proteinuria ≥1.5 g/g. However, considering the immunosuppressive nature of budesonide, the unmet clinical need for steroid-sparing therapeutic options remains; the current treatment strategy is aimed to prevent or delay ESKD.

The standard of care therapy consists of off-label use of RAAS inhibitor therapy (angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) to reduce proteinuria and manage BP [29,32,41,42].

However, despite optimised RAAS blockade therapy, persistent overt proteinuria remains in many patients, concurrent with renal function loss and progression to ESKD. In a retrospective study of 437 subjects performed by Manno et al, 2007 [4], 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 (VALIGA) cohort, the 10-year rate of ESKD (defined as 50% decrease in eGFR or <15 ml/min/1.73 m^2) for subjects receiving RAAS blockade therapy (in the absence of additional immunosuppressive therapy) was 40% [43,44].

In 5 recently conducted RCTs that enrolled subjects with persistent overt proteinuria ≥0.75 g/day or ≥1 g/day despite RAAS blockade therapy (optimised to a maximum tolerated dose), the average annualised loss of eGFR was up to 7 ml/min/1.73 m^2 [45-48].

Treatment with glucocorticosteroids may be considered for subjects with persistent proteinuria >1 g/day despite maximised ACEI/ARB treatment, who are at risk for progression to ESKD [32]. However, the indication for steroid treatment must be carefully considered in individual patients due to well-described, serious side effects of systemic

corticosteroid treatment [32]. The randomised, controlled TESTING trial of the use of systemic corticosteroid methylprednisolone conducted in Asia Pacific and Canada for the treatment of IgAN, demonstrated a benefit of treatment versus placebo. However, the authors noted that the reduction in proteinuria was no longer apparent by 36 months after randomisation, and the incidence of serious adverse events (SAEs) was increased with methylprednisolone, especially with the high dose. Moreover, a post hoc analyses suggest that the benefit on other outcomes may diminish over time [49].

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Patients with IgAN typically present in 1 of 3 ways [11,50]. Between 40% and 50% of patients present with 1 or more recurrent episodes of visible haematuria, usually following an upper respiratory tract infection. Less than 10% of patients present with nephrotic syndrome or acute, rapidly progressing glomerulonephritis and, in rare instances, may present with malignant hypertension. The remainder of patients (30% to 40%) present with persistent proteinuria that frequently is accompanied by microscopic haematuria, which can be detected during routine examination [51,52]. This last group is at risk of progression to ESKD, is described in detail by the KDIGO Clinical Practice Guideline on Glomerular Diseases [32], and is in high need of novel therapeutic approaches.

A retrospective analysis of subjects with IgAN across 4 countries on 3 continents (Europe, North America, and Australia) assessing long-term outcomes found that the overall 10-, 15-, and 20-year actuarial renal survival rates were 78%, 70%, and 55%, respectively [53], which are aligned with Manno's findings.

The incidence of IgAN recurrence following kidney transplantation is variable, being around 10% to 30% in studies done with for-cause biopsies, and 25% to 35% in studies based on protocol biopsies [54-56]; the estimated 10-year incidence of graft loss due to disease recurrence is uncertain. Results of a recent European Registry analysis suggest that 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 [57,58].

SI.2 Important Comorbidities

The most relevant and common comorbidity in patients with IgAN is hypertension. The KDIGO guidelines propose a target systolic BP of less than 120 mmHg in patients with CKD. In addition to kidney disease risk, hypertension is associated with increased risk of stroke, heart failure and coronary artery disease. Therefore, the aim of BP control is to protect against these risks and to delay the progressive loss of glomerular filtration rate [32].

Corticosteroid use is associated with a high risk of adverse events (AEs) in this population, especially those who are older, have hypertension, or with impaired renal function [59].

SII NONCLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 Toxicity

Key safety findings from the nonclinical toxicology programme of sparsentan with relevance to human usage are summarised below in Table 2.

Table 2 Key Nonclinical Safety Findings - Toxicity

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Single-dose Toxicity	
The acute toxicity in mice (DN01026) and rats (DN01027) administered single oral doses of sparsentan up to 2,000 mg/kg was limited to transient decreased activity and 1 death in mice at 2,000 mg/kg and transient decreases in body weight gain in rats at ≥1,000 mg/kg.	No special risk for humans, i.e., the acute oral toxicity of sparsentan is low.
Repeat-dose Toxicity	
Sparsentan-related effects in repeat-dose studies were generally consistent in mice up to 13 weeks (PCO-NC-026), rats up to 6 months (PCO-NC-028), and monkeys up to 9 months (PCO-NC-027). Sparsentan caused reduction of red blood cell parameters (in rat and monkey), hyperplasia/hypertrophy of the juxtaglomerular cells (in mouse, rat and monkey), and increased liver weight accompanied by hepatocellular hypertrophy (in mouse and rat considered adaptive responses to xenobiotic exposure and were not associated with hepatotoxicity). These findings were all largely reversible.	Findings are either consistent with known effects of ARBs and ACE inhibitors or rodent specific. No evidence for any additional risk for humans has been identified.
Genotoxicity	
There was no evidence of genotoxicity in either the bacterial mutagenicity (Ames test; DS01074) or chromosome aberration assays (human peripheral blood lymphocytes, PCO-NC-014). Furthermore, sparsentan was non-genotoxic in the rat bone marrow micronucleus assay following 3 consecutive daily oral doses up to a dose limit of 2,000 mg/kg/day (DS01022).	No evidence for any risk for humans.
Carcinogenicity	
Sparsentan was not carcinogenic when administered at daily oral doses of 60, 200, or 600 mg/kg/day to transgenic rasH2 mice for 26 weeks (RE-021-Report004-2016-CARC). Sparsentan was not carcinogenic in male rats administered the MTD of 15 mg/kg/day for 93 weeks, in female rats administered the MTD of 240 mg/kg/day for up to 89 weeks nor in female rats administered 15 or 60 mg/kg/day for 92 weeks (RE-021-Report056-2016-CARC).	No evidence for any risk for humans.
Reproductive/Developmental Toxicity	
Fertility and Early Embryonic Development: In rats there were no effects on fertility or early embryonic development up to the highest tested dose (320 mg/kg/day) (PCO-NC-021).	The findings observed in embryo-foetal development studies are consistent with the pharmacology of antagonising the ET_AR and AT_1R.

Table 2 Key Nonclinical Safety Findings - Toxicity (Cont'd)

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Reproductive/Developmental Toxicity	
Embryo-foetal Development: In embryo-foetal development studies in rat and rabbit, developmental toxicity was seen in both species, attributed to the pharmacologic action of ET_AR and AT_1R antagonism. In rats, dose-dependent teratogenic effects in the form of craniofacial malformations, skeletal abnormalities, increased embryo-foetal lethality, and reduced foetal weights were observed at all doses of sparsentan tested (RE-021-Report002-2017-RTOX). The lowest dose exposure was ~8 and 10 times the AUC in humans at 800 mg/day and 400 mg/day respectively. In rabbits, there were no foetal malformations or effects on foetal viability or growth at doses tested but an increase in a foetal variation (supernumerary cervical ribs) indicative of developmental toxicity occurred at the highest dose tested (RE-021-Report001-2017-RTOX). Exposure at this dose was approximately 0.10 and 0.1 times the AUC for 800 mg/day and 400 mg/day respectively in humans. Pre- and Post-natal Development: In the pre- and post-natal development study in rat (RE-021-Report003-2017-RTOX), the maternal NOEL for sparsentan was 5 mg/kg/day based on test item-related effects on body weights and food consumption at ≥20 mg/kg/day, and mortality and adverse clinical signs at 80 mg/kg/day. The NOEL for reproduction in the dams and for viability and growth in the F_1 generation was 5 mg/kg/day, based on decreases in pup body weights at ≥20 mg/kg/day, increased pup mortality, and reduced maternal nursing and nesting behaviours at 80 mg/kg/day.	The ERA class has been shown to be teratogenic in animal studies [60] and ERAs are expected to cause foetal harm (harm to a developing embryo), including birth defects and effects on postnatal survival, if given to pregnant women. Similarly, treatment with drugs that act directly on the RAAS during the second and third trimesters of pregnancy have been shown to reduce foetal renal function and increase foetal and neonatal morbidity and death. Potential adverse effects include birth defects, pulmonary hypoplasia, anuria, hypotension, renal failure, and death [61]. As a consequence, teratogenicity is considered as an important potential risk, and sparsentan is contraindicated during pregnancy. In addition, treatment must only be initiated in women of childbearing potential when the absence of pregnancy has been verified and effective contraception is practised during treatment and for 1 month after treatment has stopped. Physicochemical data suggest excretion of sparsentan in human milk. A risk to the newborn cannot be excluded and sparsentan should not be used during breastfeeding.
Juvenile Toxicity	
Juvenile toxicity studies in rat showed an age-dependent increased sensitivity to the suprapharmacological effects of sparsentan in young rats (PND 7, equivalent to a newborn infant) compared with older juvenile rats (PND 14, 21/22, or 28, equivalent to 1-, 2-, and 6-year-old children, respectively). Kidney and vascular toxicities occurred only in juvenile studies starting on PND 7 (RE-021-Report054-2016-TOX). Reduced sperm motility and reproductive function also occurred, which were likely secondary to vascular damage in reproductive organs. There were no effects on reproductive performance or sperm parameters in juvenile studies starting on PND 14 and older (RE-021-Report048-2017-TOXJUV, RE-021-Report019-2018-TOX).	Findings were limited to rat studies where sparsentan dosing started from PND 7 (equivalent to a newborn infant).

Notes: ACE=Angiotensin converting enzyme; ARB=Angiotensin receptor blocker; AT_1R=Angiotensin II receptor Type 1; AUC=Area under the curve; ERA=Endothelin receptor antagonist; ET_AR=Endothelin Type A receptor; F_1=Filial 1 generation; MTD=Maximal tolerated dose; NOEL=No observed effect level; PND=Postnatal day; RAAS=Renin angiotensin aldosterone system.

SII.2 Safety Pharmacology

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Key safety findings from the nonclinical safety pharmacology programme of sparsentan with relevance to human usage are summarised below in Table 3.

Table 3 Key Nonclinical Safety Findings - Safety Pharmacology

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Cardiovascular System	
In vitro data indicate that sparsentan had minimal effect (<8% change) on Purkinje fibre action potentials at concentrations up to 30 µM (PCO-NC-002). Sparsentan had also minimal effect on hERG channel current (7% inhibition at 500 µM, approximately 3,900-fold higher than the geometric mean C_{max} of unbound sparsentan at the human efficacious dose of 800 mg) (RE-021-Report050-2015-SPHARM and BMS-346567-hERG-20060505). No effects on blood pressure or ECG parameters were seen in cynomolgus monkeys that received a single oral dose of sparsentan up to 32 mg/kg (NOEL) (PCO-NC-010). Oral administration of up to 1,000 mg/kg did not adversely alter electrocardiographic intervals, ECG waveforms. However, blood pressure was lowered approximately 10 to 24 hours after dosing, and an expected compensatory increase in heart rate was not observed. The changes in blood pressure and lack of compensatory heart rate changes were not considered adverse and were attributed to pharmacologic activity, therefore, the NOAEL for cardiovascular effects was 1,000 mg/kg. No evidence of ECG alterations was seen in the monkey 1-month (DN01019-erratum), 3-month (PCO-NC-024), or 9-month (PCO-NC-027) general toxicology studies.	No evidence for any risk for humans based on nonclinical cardiovascular safety pharmacology studies.
Respiratory System	
No effects were seen on respiratory parameters (tidal volume, respiratory rate, and derived minute volume) in rats after a single oral administration of sparsentan at doses of up to 1,000 mg/kg (PCO-NC-013). Therefore, the NOAEL was 1,000 mg/kg. These results are consistent with those observed in the 1-month monkey toxicology study (DN01019-erratum) where no effect upon respiratory function (including arterial oxygen saturation) was evident up to and including the high dose of 250 mg/kg/day.	No evidence for any risk for humans based on nonclinical respiratory safety pharmacology studies.
Central Nervous System	
Sparsentan did not affect the behaviour, autonomic function, appearance, or grip strength in rats that received a single oral administration of sparsentan at doses of up to 1,000 mg/kg (PCO-NC-011, PCO-NC-012). Therefore, the NOAEL was 1,000 mg/kg. These results are consistent with those observed in the 1-month monkey toxicology study (DN01019-erratum) where no effect upon neurologic function (including cranial and peripheral nerve functions) was evident up to and including the high dose of 250 mg/kg/day.	No evidence for any risk for humans based on nonclinical safety neuropharmacology studies.

Notes: C_{max}=Maximum plasma concentration; ECG=Electrocardiogram; hERG=Human ether- à-go-go related gene; NOAEL=No observed adverse effect level; NOEL=No observed effect level.

SII.3 Other Toxicity-related Information or Data

Table 4 Other Toxicity-Related Information

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Pharmacokinetic Drug-drug interactions	
Sparsentan is a substrate of CYP3A4, and to a minor degree, possibly also of CYP2C8 or CYP2C9 (PCO-NC-016, RE-021-Report020-2014-DMPK-amend1). Sparsentan exhibited direct inhibition of CYP3A4/5 and metabolism-dependent inhibition of CYP3A4 (RE-021-0007, DH00007-addendum, PCO-NC-017). Sparsentan was an inducer of CYP2B6, CYP2C9, CYP2C19, and CYP3A4 (PCO-NC-015, RE-021-Report016-2016-DMPK, RE-021-0027). Transporter studies indicated that sparsentan was an inhibitor of P-gp and BCRP (PCO-NC-018, RE-021-Report-038-2018-DMPK, PCO-NC-029). Sparsentan inhibited BSEP, OAT3, and OATP1B3. Sparsentan did not inhibit MRP, OATP1B1, NTCP, OCT1, OCT2, OAT1, MATE1, or MATE2-K (PCO-NC-020, RE-021-Report-038-2018-DMPK, PCONC-029, TOX072).	Results from clinical drug-drug interaction studies indicate that sparsentan exposure is affected by strong and moderate CYP3A inhibition. Co-administration with a strong CYP3A inhibitor is not recommended. Co-administration with a moderate CYP3A inhibitor should be used with caution. Sparsentan exposure is predicted to be decreased when co-administered with a strong CYP3A inducer. Concomitant treatment with a strong CYP3A inducer is not recommended. Potential drug interaction from CYP3A4/5 inhibition by sparsentan was evaluated using the CYP3A substrate midazolam in clinical study 021HVOL16008. Co-administration of sparsentan with midazolam had no effect on the systemic exposure of midazolam. The significance of P-gp inhibition by sparsentan has not been evaluated in a clinical study. Results from the drug-drug interaction studies with bupropion and pitavastatin and PBPK modelling indicate that sparsentan is not an inhibitor of OATP1B1, OATP1B3, or BCRP and is a weak inducer of CYP2B6, CYP2C9 and CYP2C19 (021HVOL16007, 021HVOL16008, RE-021-0023). Sparsentan did not affect the exposure of creatinine (endogenous biomarkers for OAT2, OCT2, MATE1, and MATE2K) or 6-β-hydroxycortisol (endogenous biomarkers for OAT3) in a clinical study (021HVOL109). Sparsentan did not affect the exposure of serum bile acids (endogenous biomarkers for BSEP) in a clinical study, RTRX-RE021-103.
Phototoxicity	
Sparsentan does not absorb light between 290 nm and 700 nm. Moreover, no sparsentan-derived radioactivity was present in the eye or in melanin-containing tissues in pigmented rats (RE-021-Report062-2016-DMPK).	No evidence for phototoxic potential.

Notes: BCRP=Breast cancer resistance protein; BSEP=Bile salt export pump; CYP=Cytochrome P450; MATE=Multidrug and toxic extrusion; MRP=Multidrug resistance-associated protein; NTCP=Sodium taurocholate transporting polypeptide; OAT=Organic anion transporter; OATP=Organic anion transporter polypeptide; OCT=Organic cation transporter; PBPK=Physiologically based pharmacokinetic; P-gp=Permeability-glycoprotein.

SIII CLINICAL TRIAL EXPOSURE

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

Table 5 Overview of All Sparsentan Studies

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

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

The efficacy of sparsentan in the IgAN indication is based on the Phase 3 PROTECT study. An exploratory, Investigator-sponsored, open-label study in newly diagnosed treatment-naïve subjects with IgAN is ongoing, SPARTAN.

Demographics and baseline characteristics in the PROTECT double-blind period are presented in Table 6.

Table 6 Demographics and Baseline Characteristics (FAS) – PROTECT Double-blind Period

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

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

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

- Study 021IGAN17001 (PROTECT) – An ongoing, Phase 3 study to determine the efficacy and safety of sparsentan for the treatment of IgAN. The double-blind treatment

period comparing sparsentan to irbesartan treatment is complete. The OLE phase to assess the long-term efficacy and safety of sparsentan is ongoing.

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

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

Demographics and baseline characteristics in the CKD RCT study pool (safety analysis set) are presented in Table 7.

Table 7 Demographics and Baseline Characteristics – CKD RCT Study Pool (Safety Analysis Set)

	Double-Blind			
	400 mg Sparsentan (N=228)	**800 mg Sparsentan (N=218)**	**400/800 mg Sparsentan (N=446)**	**Irbesartan (N=425)**
Age at informed consent (years)				
n	228	218	446	425
Mean (SD)	45.6 (13.49)	40.8 (16.81)	43.2 (15.38)	42.7 (15.22)
Min, max	8, 73	8, 74	8, 74	8, 76
Age group, n (%)				
<18 years	5 (2.2)	21 (9.6)	26 (5.8)	26 (6.1)
≥18 years	223 (97.8)	197 (90.4)	420 (94.2)	399 (93.9)
18 to <45 years	101 (44.3)	107 (49.1)	208 (46.6)	189 (44.5)
≥45 years	122 (53.5)	90 (41.3)	212 (47.5)	210 (49.4)
18 to <65 years	208 (91.2)	175 (80.3)	383 (85.9)	376 (88.5)
≥65 years	15 (6.6)	22 (10.1)	37 (8.3)	23 (5.4)
Gender, n (%)				
Male	156 (68.4)	118 (54.1)	274 (61.4)	261 (61.4)
Female	72 (31.6)	100 (45.9)	172 (38.6)	164 (38.6)
Race[1], n (%)				
American Indian or Alaska Native	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Asian	68 (29.8)	25 (11.5)	93 (20.9)	77 (18.1)
Black or African American	6 (2.6)	20 (9.2)	26 (5.8)	22 (5.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	2 (0.9)	2 (0.4)	1 (0.2)
White	149 (65.4)	163 (74.8)	312 (70.0)	306 (72.0)
Other	5 (2.2)	9 (4.1)	14 (3.1)	24 (5.6)

1 Subjects may have selected more than 1 race.

Notes: Data cut-off dates were 01-Aug-2023 for DUPLEX and DUET, and 07-Sep-2023 for PROTECT.
Percentages are based on all subjects in the safety analysis set with non-missing data within each group.
CKD=Chronic kidney disease; n=Number of subjects in sample; N=Number of subjects; RCT=Randomised controlled trial; SD=Standard deviation.

Table 8 summarises the extent of exposure in the CKD RCT study pool.

Table 8 Extent of Exposure CKD RCT Study Pool (Safety Analysis Set)

	Double-Blind				All Sparsentan (N=736)	All Subjects (N=884)
	400 mg Sparsentan (N=228)	800 mg Sparsentan (N=218)	400/800 mg Sparsentan (N=446)	Irbesartan (N=425)		
Number of days exposed						
n	228	218	446	425	736	884
Mean (SD)	637.7 (257.99)	526.0 (302.16)	583.1 (285.65)	601.6 (267.21)	858.7 (652.98)	1,004.2 (585.81)
SE	17.09	20.46	13.53	12.96	24.07	19.70
Median	767.5	749.5	756.0	756.0	768.5	950.0
Q1, Q3	709.0, 775.0	172.0, 757.0	374.0, 769.0	454.0, 769.0	344.0, 1,234.5	730.0, 1,317.5
Min, max	1, 874	4, 784	1, 874	1, 826	1, 3,291	1, 3,354
Total subject-years[1]	398.32	314.15	712.47	700.55	1,731.59	2,432.14
Exposure days categories, n (%)						
1 day (single dose)	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)
2 to 7 days	0 (0.0)	1 (0.5)	1 (0.2)	2 (0.5)	2 (0.3)	3 (0.3)
8 to 14 days	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)
15 to 21 days	0 (0.0)	2 (0.9)	2 (0.4)	2 (0.5)	4 (0.5)	4 (0.5)
22 to 28 days	1 (0.4)	4 (1.8)	5 (1.1)	2 (0.5)	6 (0.8)	7 (0.8)
29 to 56 days	19 (8.3)	27 (12.4)	46 (10.3)	26 (6.1)	24 (3.3)	14 (1.6)
57 to 84 days	8 (3.5)	12 (5.5)	20 (4.5)	20 (4.7)	9 (1.2)	9 (1.0)
85 to 168 days	1 (0.4)	8 (3.7)	9 (2.0)	7 (1.6)	35 (4.8)	20 (2.3)
169 to 336 days	7 (3.1)	12 (5.5)	19 (4.3)	31 (7.3)	93 (12.6)	57 (6.4)
337 to 504 days	7 (3.1)	14 (6.4)	21 (4.7)	19 (4.5)	77 (10.5)	53 (6.0)
505 to 672 days	8 (3.5)	7 (3.2)	15 (3.4)	19 (4.5)	60 (8.2)	36 (4.1)
673 to 840 days	174 (76.3)	131 (60.1)	305 (68.4)	295 (69.4)	95 (12.9)	135 (15.3)
841 to 1,008 days	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	86 (11.7)	147 (16.6)
>1,008 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	243 (33.0)	395 (44.7)

1 Total subject-years are calculated as sum of total number of dosed days across all subjects/365 days.

Notes: Data cut-off dates were 01-Aug-2023 for DUPLEX and DUET, and 07-Sep-2023 for PROTECT.
All sparsentan columns include 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.
All Subjects column includes subjects who received at least 1 dose of study drug during any treatment period.
Percentages are based on all subjects in the safety analysis set within each group.
CKD=Chronic kidney disease; 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.

SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 9 highlights the populations excluded from clinical trials with sparsentan.

Table 9 Exclusion Criteria

Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information?	Rationale
Subjects with heart failure	ERAs have been associated with an increased risk of fluid retention, therefore subjects with heart failure (New York Heart Association Class II to IV) and/or previous hospitalisation for heart failure were excluded.	Yes	Fluid retention is a known risk in patients with renal impairment. Therefore, the potential for sparsentan to increase fluid retention and worsen heart failure requires further evaluation. If fluid retention develops during treatment with sparsentan, prescribers are directed to determine the cause and the potential need to add or modify the dose of diuretic treatment and then the dose of sparsentan. Peripheral oedema is a recognised ADR for sparsentan and is included in Section 4.8 of the SmPC.
Subjects with severe hepatic impairment	Patients with severe hepatic impairment are at risk of hepatorenal syndrome.	Yes	Sparsentan has not been studied in patients with severe hepatic impairment due to the risk of hepatorenal syndrome and is therefore not recommended in these patients (Child-Pugh Classification C).
Breastfeeding women	Breastfeeding women were excluded from the clinical development programme as physicochemical data suggest excretion of sparsentan in human milk.	Yes	A risk to the newborns/infants cannot be excluded. Sparsentan should not be used during breastfeeding.
Use in patients after renal transplantation	Patients with any organ transplant were excluded from PROTECT as treatment with systemic immunosuppressants is usually required in this population.	Yes	Patients treated with systemic immunosuppressive medications (including corticosteroids) for >2 weeks within 3 months prior to screening was considered as an exclusion criterion in PROTECT.
Pregnant women	Due to the known class effect of ARBs and ERAs and due to the teratogenic potential observed from nonclinical safety data for sparsentan, pregnant women were excluded from the clinical development programme.	No	Pregnancy is contraindicated in Section 4.3 of the SmPC.

Table 9 Exclusion Criteria (Cont'd)

Criteria	Reason for Exclusion	Is it Considered to be Included as Missing Information?	Rationale
Subjects with haematocrit <27% or haemoglobin <9 g/dl at screening	Based on the known effects of ERAs, it was anticipated that sparsentan would reduce haemoglobin, primarily through a haemodilution effect, therefore patients with pre-existing haemoglobin values below 9 g/dl were excluded from the pivotal clinical studies.	No	Anaemia is a recognised ADR for sparsentan and is included in Section 4.8 of the SmPC.
Subjects with serum potassium >5.5 mEq/l at screening	Based on the known effect of RAAS blockade, particularly in patients with impaired renal function, elevations in serum potassium were anticipated with sparsentan treatment. Therefore, patients with pre-existing hyperkalaemia were excluded.	No	Hyperkalaemia is a recognised ADR for sparsentan and is included in Section 4.8 of the SmPC.

Notes: ADR=Adverse drug reaction; ARB=Angiotensin receptor blocker; ERA=Endothelin receptor antagonist; RAAS=Renin angiotensin aldosterone system; SmPC=Summary of Product Characteristics.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions given the size of the population studied.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 10 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Paediatric patients	Children of 8 to 17 years of age were enrolled in the FSGS studies (DUET and DUPLEX), whereas children under 18 years of age were not included in the IgAN study (PROTECT). The paediatric study (EPPIK), a Phase 2, open-label, single-arm, cohort study enrolling children with FSGS from 1 year of age, and children with IgAN from 2 years of age, agreed with PDCO, was initiated on 12-Aug-2021 (first signed informed consent) and is expected to complete in Q3 2025.
Pregnant women	Not included in the clinical development programme based on results from animal studies showing reproductive toxicity including teratogenicity. Nineteen pregnancies have been reported in subjects receiving sparsentan or enrolled in a sparsentan study to date. In all cases, the subjects stopped taking study medication immediately after positive pregnancy test.
Breastfeeding women	Not included in the clinical development programme.
Patients with relevant comorbidities	
Patients with hepatic impairment	Patients with severe hepatic impairment were not included in the clinical development programme.
Patients with renal impairment	Patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) at screening were excluded from the clinical trials; however, data are available in patients with eGFR <30 ml/min who were treated during the course of the trials as their kidney function declined between screening and randomisation. Patients undergoing dialysis or after receiving a kidney transplant were not studied.
Immunocompromised patients	Immunosuppressant use was permitted during the DUPLEX and PROTECT studies, but their use at baseline was not allowed in the PROTECT study.
Population with relevant different ethnic origin	Asian, Black, White and Hispanic subjects were included in the clinical development programme and no notable differences in safety profile were observed.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Notes: Data cut-off dates were 01-Aug-2023 for DUPLEX and DUET, and 07-Sep-2023 for PROTECT.
eGFR=Estimated glomerular filtration rate; FSGS=Focal segmental glomerulosclerosis; IgAN=Immunoglobulin A nephropathy; PDCO=Paediatric Committee.

SV POST-AUTHORISATION EXPOSURE

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Internal tracking database (patient-hub system) has been used as the source for post-authorisation exposure in the US. Database is tracking each individual patient including drug shipments.

SV.1.2 Exposure

As of the date of this submission, sparsentan has only been marketed in the US for the indication of reducing proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-creatinine ratio ≥1.5 g/g.

Cumulatively CCI patients have been exposed to Filspari since its approval in the US through 16 February 2024 with 410 total patient-years exposure.

Additionally, sparsentan was available through Compassionate Use Programme in the US, for the treatment of FSGS with CCI patients treated. In the EU, sparsentan is available to patients in Managed Access Programme (HQ-MAP-SPT-056) in selected countries for the treatment of IgAN. Total of CCI patients were treated in the Managed Access Programme with sparsentan at the time of this report.

SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for Misuse for Illegal Purposes

Based on nonclinical data and the drug mode of action, sparsentan has low potential for misuse for illegal purposes; therefore, no specific risk minimisation measures are deemed necessary.

SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The clinical safety profile for sparsentan is based on 3 clinical trials (all ongoing), a Phase 3 study in subjects with IgAN (PROTECT), a Phase 3 study in subjects with FSGS (DUPLEX), and a Phase 2 study in subjects with FSGS (DUET, with an OLE period (exposure up to 7 years)). In addition, the following pool provides additional analyses of sparsentan safety data:

- The CKD RCT study pool contains all subjects from the studies DUPLEX and DUET (FSGS) and from study PROTECT (IgAN) (446 subjects on sparsentan and 425 subjects on irbesartan).

Clinically Significant Hypotension

Hypotension is an expected effect of drugs that block the AT_1R and the ET_AR. Patients with heart failure or severe volume and/or salt depletion of any aetiology and patients treated with high-dose diuretic therapy are at risk of developing clinically significant hypotension.

In the PROTECT study, symptomatic hypotension-associated treatment-emergent adverse events (TEAEs) were reported in 26% and 11% of subjects in the sparsentan and irbesartan groups, respectively. The most commonly reported symptomatic hypotension-associated TEAE preferred terms (PTs) in sparsentan- and irbesartan-treated subjects were dizziness (14% versus 5%, respectively), hypotension (11% versus 3%, respectively), and orthostatic hypotension (3% versus 2%, respectively). Treatment-related symptomatic hypotension-associated TEAEs occurred in 17% of sparsentan-treated patients and in 7% of irbesartan-treated subjects. Three subjects (1%) who received sparsentan and 1 subject (<1%) who received irbesartan reported serious symptomatic hypotension-associated TEAEs. Three subjects (1%) in the sparsentan group discontinued drug due to symptomatic hypotension-associated TEAEs (none in the irbesartan group). Most subjects reported mild symptomatic hypotension-associated TEAEs. The majority of symptomatic hypotension-associated TEAEs were considered as recovered/resolved. Most of the symptomatic hypotension-associated TEAEs were reported in the first 24 weeks of treatment (18% of the 26% in the sparsentan group and 8% of the 11% in the irbesartan group).

In the CKD RCT study pool, 24% of the subjects who received sparsentan 400/800 mg and 14% of the subjects who received irbesartan had symptomatic hypotension-associated TEAEs. The most commonly reported symptomatic hypotension-associated TEAE PTs in subjects who received sparsentan 400/800 mg versus irbesartan were hypotension (12% versus 6%), dizziness (11% versus 8%), and orthostatic hypotension (4% versus 1%). The

most commonly reported related symptomatic hypotension-associated TEAE PTs in subjects who received sparsentan 400/800 mg versus irbesartan were hypotension (9.0% versus 5.2%), dizziness (7.2% versus 4.5%), and orthostatic hypotension (2.7% versus 0.7%). Serious symptomatic hypotension-associated TEAE PTs in subjects who received sparsentan 400/800 mg versus irbesartan were hypotension (0.2% versus 0.5%), and dizziness (0.4% versus 0.2%). The majority of the TEAEs associated with hypotension were mild or moderate in severity.

In the DUET OLE, the most commonly reported symptomatic hypotension-associated TEAEs (≥5%) were hypotension (20.4%), and dizziness (14.8%). None of the symptomatic hypotension-associated TEAEs were among the most reported serious TEAEs (≥5%).

Due to the fact that sparsentan is a dual endothelin angiotensin receptor antagonist, the potential to result in hypotension is well understood. Therefore, this risk of clinically significant hypotension is not considered as an important identified risk due to the limited impact on overall benefit/risk balance, and is followed up via routine pharmacovigilance activities, namely through signal detection and adverse reaction reporting. Appropriate labelling to guide physicians is included in the SmPC in Section 4.2, Section 4.4 and Section 4.5. Hypotension and orthostatic hypotension are listed as ADRs in the EU SmPC Section 4.8 with common frequency.

Impaired Kidney Function

Acute kidney injury (AKI) is a known risk for ARBs. This risk is accentuated in patients with reduced kidney function, low volume status, or in those receiving higher doses of nonsteroidal anti-inflammatory drugs. Additionally, assessment of AKI-associated events should take into consideration whether the event is true acute deterioration of kidney function due to an identified aetiology, or whether the event represents natural progression of the underlying kidney disease. Outpatient study visits, typically 12 weeks apart, indicate that recent (baseline) laboratory values needed for AKI diagnosis per KDIGO guidelines were not available and that reports of AKI may have been based on the most recently available serum creatinine level preceding the event. Thus, reported AEs of AKI may represent progression of kidney disease or natural fluctuations of S-creatinine concentrations rather than an acute episode of kidney injury. Patients on ARBs and ERAs are at higher risk of AKI when they are hypovolaemic or have an intercurrent illness, such as diarrhoea, vomiting, or viral infection [62]. The risk is increased in patients with bilateral renal artery stenosis and patients who have only 1 kidney, which also has renal artery stenosis. Considering that sparsentan is a dual inhibitor of AT_1R and ET_AR, the risk of pre-renal AKI may be enhanced by a potent effect of the drug on systemic BP.

In the PROTECT study, the impaired kidney function-associated TEAEs in sparsentan- and irbesartan-treated subjects included AKI (4% versus 1%, respectively), blood creatinine increased (5% versus 4%, respectively), and renal impairment (3% versus 3%, respectively). Treatment-related TEAEs in sparsentan- and irbesartan-treated subjects included AKI (2% versus 1%, respectively), renal impairment (2% versus 2%, respectively), and blood

creatinine increased (2% versus 3%, respectively). Four subjects (2%) who received sparsentan reported serious AKI (none in the irbesartan group). None of the serious AKI required acute dialysis. Serious blood creatinine increased was reported in 1 subject (<1%) in the sparsentan group, and in 2 subjects (1%) in the irbesartan group. Serious renal impairment was reported in 2 subjects (1%) in the irbesartan group (none in the sparsentan group). Three subjects (1%) in the sparsentan group experienced TEAEs of AKI that led to treatment discontinuation (none in the irbesartan group). One subject (<1%) in the sparsentan group and 2 subjects (1%) in the irbesartan group experienced TEAEs of renal impairment that led to treatment discontinuation. The majority of impaired kidney function-associated TEAEs were considered as resolved/resolving.

In the CKD RCT study pool, the impaired kidney function-associated TEAEs in sparsentan 400/800 mg- and irbesartan-treated subjects included AKI (3.4% versus 1.4%, respectively), blood creatinine increased (3.6% versus 3.5%, respectively), and renal impairment (2.0% versus 2.1%, respectively). Treatment-related TEAEs in sparsentan 400/800 mg- and irbesartan-treated subjects included AKI (2.0% versus 1.2%, respectively), renal impairment (1.1% versus 1.2%, respectively), and blood creatinine increased (1.8% versus 1.6%, respectively). Serious TEAEs in sparsentan 400/800 mg- and irbesartan-treated subjects included AKI (1.3% versus 0.2%, respectively), renal impairment (0.0% versus 0.5%, respectively), and blood creatinine increased (0.4% versus 0.5%, respectively). The majority of the impaired kidney function-associated TEAEs were moderate in severity.

In the DUET OLE, including subjects with sparsentan exposures of up to 7 years in the all sparsentan group, the most commonly reported impaired kidney function-associated TEAEs (≥5%) were blood creatinine increased (13.9%), and AKI (10.2%). The most commonly reported serious impaired kidney function-associated TEAE (≥5%) was AKI (6.5%).

Although guidance was provided in the study protocols to assist with the definition of AKI, which is based on increases in creatinine during a hospitalisation, AKI was typically reported based on changes in serum creatinine between study visits, which were usually several weeks apart, rather than in a hospital setting, and therefore may have been representative of a gradual decline of kidney function rather than AKI.

The risk is well understood by treating physicians and routine monitoring of serum creatinine and serum potassium levels is standard practice in this patient population. Therefore, this risk of impaired kidney function is not considered as an important identified risk due to the limited impact on overall benefit/risk balance, and is followed up via routine pharmacovigilance activities namely, through signal detection and adverse reaction reporting. Appropriate labelling to guide physicians is included in the SmPC in the sections 4.2, 4.4 and 4.5. Renal impairment, AKI, and blood creatinine increased are listed as ADRs in the EU SmPC Section 4.8 with common frequency.

Hyperkalaemia

Hyperkalaemia is a known risk for ARBs that does not impact the benefit/risk profile and is followed up via routine pharmacovigilance activities namely, through signal detection and adverse reaction reporting.

Hyperkalaemia is an expected effect of drugs that block the AT_1R. Hyperkalaemia in response to sparsentan occurs mainly as a result of the inhibition of aldosterone secretion and also due to its renal haemodynamic action, especially in patients with a history of impaired renal function. Sparsentan use may add a potential risk of AKI due to reductions in intracapillary glomerular pressure and glomerular filtration rate as well as due to reductions of systolic BP. Patients with diabetes, advanced CKD, heart failure, volume depletion and patients taking potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics, and potassium containing salt substitutes) are at risk of developing increased serum potassium.

In the PROTECT study, hyperkalaemia-associated TEAEs in sparsentan and irbesartan-treated subjects included hyperkalaemia (13% versus 10%, respectively) and blood potassium increased (1% versus <1%, respectively). Treatment-related hyperkalaemia-associated TEAEs occurred in 9% of sparsentan-treated subjects and in 8% of irbesartan-treated subjects. One subject (<1%) who received irbesartan reported a serious event of hyperkalaemia (none in the sparsentan group). 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.

In the CKD RCT study pool, 11% of the subjects who received sparsentan 400/800 mg and 8% of the subjects who received irbesartan had hyperkalaemia-associated TEAEs, with the PT of hyperkalaemia reported as the most commonly reported event (10% in the sparsentan group versus 8% in the irbesartan group). Hyperkalaemia drug-related events were reported in 6.7% of subjects who received sparsentan 400/800 mg and in 5.4% of the subjects who received irbesartan. One subject (0.2%) who received irbesartan reported a serious TEAE of hyperkalaemia (none in the sparsentan 400/800 mg group). The hyperkalaemia-associated TEAEs were mild to moderate in severity, none were severe.

In the DUET OLE, hyperkalaemia was reported as a SAE in 2 subjects (1.9%).

Overall, the AEs reported as hyperkalaemia are based on increases in serum potassium from laboratory data rather than clinical consequences of hyperkalaemia that have not been observed in any of the studies of sparsentan in rare glomerular diseases. The number of SAEs, or AEs resulting in discontinuation, is very low indicating that cases of hyperkalaemia were not severe, were reversible and sparsentan treatment was generally well tolerated.

No clear evidence of clinical consequences of hyperkalaemia (including cardiac arrhythmias) has been observed in the clinical development programme to date. The risk may be managed through routine pharmacovigilance activities in association with

appropriate labelling to guide physicians to monitor serum potassium and to avoid drugs that are known to increase potassium (e.g., potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes). The risk is well understood by treating physicians and routine monitoring of serum potassium levels is standard practice in this patient population, and therefore has limited impact on overall benefit/risk balance. Appropriate labelling to guide physicians is included in the SmPC in Section 4.4 and Section 4.5. Hyperkalaemia is listed as an ADR in the EU SmPC Section 4.8 with common frequency.

Anaemia

Anaemia is a known risk for ARBs and ERAs that is followed up via routine pharmacovigilance activities, namely through signal detection and adverse reaction reporting.

Anaemia, including decrease in haemoglobin concentration, has been observed with sparsentan. The effect is likely related to haemodilution and observed primarily in the initial weeks of treatment with sparsentan, then remaining stable. In addition to haemodilution, other mechanisms, such as the effects of AT_1R inhibition on erythropoiesis and multifactorial process associated with decreased kidney function, contribute to lower haemoglobin levels or the development of anaemia in patients in present studies with sparsentan.

In the PROTECT study, there was a low incidence of anaemia-associated TEAEs reported in the sparsentan and irbesartan groups (7% versus 4%), with the PT of anaemia reported as the most commonly related event (5% in the sparsentan group versus 3% in the irbesartan group). Treatment-related anaemia occurred in <1% of sparsentan-treated subjects and in 1% of irbesartan-treated subjects. One TEAE of anaemia in the sparsentan group was serious (none in the irbesartan group), which was considered as recovered/resolved. No subjects in either treatment group discontinued from treatment due to anaemia TEAEs. The majority of anaemia TEAEs were considered as recovered/resolved or recovering/resolving. There were moderate decreases in haemoglobin and haematocrit levels reported in the sparsentan group from baseline to Week 6, which then stabilised through Week 94. No subjects required transfusion to treat anaemia.

In the CKD RCT study pool, 6% of the subjects who received sparsentan 400/800 mg and 3% of the subjects who received irbesartan had anaemia-associated TEAEs, with the PT of anaemia as the most commonly reported event (5% in the sparsentan group versus 2% in the irbesartan group). Anaemia drug-related events were reported in 0.4% of subjects who received sparsentan 400/800 mg and in 0.5% of the subjects who received irbesartan. Two subjects (0.4%) who received sparsentan 400/800 mg reported serious TEAEs of anaemia (none in the irbesartan group). The majority of these events were mild or moderate in severity.

In the DUET OLE, anaemia was reported in 15 subjects (13.9%), and haemoglobin decreased was reported in 6 subjects (5.6%).

The number of SAEs, or AEs resulting in discontinuation, for anaemia is very low, suggesting that it is manageable and well tolerated. 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 a transfusion. The risk may be managed through routine pharmacovigilance activities in association with appropriate labelling. Of note, prior to sparsentan treatment, patients may already display laboratory and/or clinical signs of anaemia due to progression of CKD. The risk is well understood by treating physicians and routine monitoring of haemoglobin is standard practice in this patient population and therefore has limited impact on overall benefit/risk balance. Anaemia is listed as an ADR in the EU SmPC Section 4.8 with uncommon frequency.

Fluid Retention

Fluid retention is a known risk for ERAs that is followed up via routine pharmacovigilance activities, namely through signal detection and adverse reaction reporting.

Fluid retention is associated with rare glomerular diseases, although it is more common in FSGS than IgAN, may occur with drugs that antagonise the ET_AR, and has been observed in clinical studies with sparsentan.

Prior to study treatment the incidence of peripheral oedema was 10% in the sparsentan arm and 4% in the irbesartan arm in the PROTECT study and 13% in each treatment arm in the DUPLEX study.

In the PROTECT study, fluid retention-associated TEAEs were reported in 16% of the subjects in the sparsentan group and in 13% of the subjects in the irbesartan group. The most frequently reported PT (≥5% of subjects in either treatment arm) was oedema peripheral in both sparsentan (14%) and irbesartan (11%) groups. Treatment-related fluid retention-associated TEAEs occurred in 7% of sparsentan-treated subjects and in 3% of irbesartan-treated subjects. Most subjects reported mild fluid retention-associated TEAEs. There was 1 serious TEAE of pleural effusion that was experienced by a subject in the sparsentan group; the event was considered as recovered/resolved and unrelated to study drug by the Investigator. No subjects in either treatment group discontinued from treatment due to fluid retention-associated TEAEs. The majority of fluid retention-associated TEAEs were considered as recovered/resolved. The frequency of fluid retention-associated events was slightly higher in the sparsentan group than in the irbesartan group. However, the incidence of peripheral oedema in the medical history of subjects in the sparsentan treatment arm was higher than the irbesartan treatment arm (10% versus 4%). The fluid retention-associated TEAEs were well-tolerated and managed as needed. Most subjects who experienced fluid retention-associated TEAEs did not require diuretic treatment or were already on diuretic treatment for other reasons without dose change due to these events. No cases of heart failure were reported due to fluid retention.

In the CKD RCT study pool, 17% of the subjects who received sparsentan 400/800 mg and 13% of the subjects who received irbesartan experienced fluid retention-associated TEAEs. The most frequently reported PT (≥5% of subjects in either treatment arm) was oedema peripheral in both sparsentan (14%) and irbesartan (11%) groups. Oedema peripheral drug-related events were reported in 4.5% of subjects who received sparsentan 400/800 mg and in 2.4% of the subjects who received irbesartan. Serious oedema peripheral events were reported in 3 subjects (0.7%) who received irbesartan (none in the sparsentan 400/800 mg group). The majority of these events were mild or moderate in severity.

In the DUET OLE, oedema peripheral was reported in 27 subjects (25%).

The fluid retention-associated TEAEs were well-managed, with a low number of SAEs and AEs leading to discontinuations. The risk may be managed through routine pharmacovigilance activities in association with appropriate labelling. Prior to sparsentan treatment, patients may already display signs of fluid retention due to progression of CKD or due to the disease condition itself. The risk is well understood by treating physicians. As mentioned in the SmPC Section 4.4, if fluid retention develops during treatment with sparsentan, treatment with diuretics is recommended, or the dose of existing diuretics should be increased and then modifying the dose of sparsentan could be considered. If fluid retention develops before starting treatment with sparsentan, treatment with diuretics can be considered. Therefore, fluid retention has limited impact on overall benefit/risk balance. Oedema peripheral is listed as an ADR in the EU SmPC Section 4.8 with common frequency.

Male Fertility

ERAs have been associated with testicular tubular atrophy and decreases in animal male fertility. However, nonclinical studies with sparsentan have not demonstrated toxic effects on the testes or on the spermatogenesis process (see Section SII of this RMP). The effect on male human fertility is not known, but a deterioration of spermatogenesis cannot be excluded. A full package of repeat-dose general toxicity studies, reproductive and developmental toxicity studies, and juvenile toxicity studies have been completed on sparsentan. These studies used the most sensitive methods, histopathologic exam of the testis with proper fixation and staining techniques, to measure the effects on spermatogenesis in animals, according to the International Council for Harmonisation guideline on reproductive toxicity testing (ICH S5(R2), 2005). No effects on spermatogenesis or other evidence of damage to the testis or other male reproductive tissues were observed in any studies. One juvenile toxicity study conducted in young rats (treatment starting on post-natal Day 7, equivalent to a newborn infant) showed effects on sperm/fertility parameters. This generalised effect was considered secondary to vascular damage resulting from an exaggerated pharmacological activity on blood vessels in multiple organs including male reproductive organs. In juvenile studies conducted in older juvenile rats (post-natal Day 14, 21/22, or 28, equivalent to 1-, 2-, and 6-year-old children), there were no vascular effects and no effects on sperm or mating parameters at doses up to 60 mg/kg/day (corresponding to exposures ~1.7 and 2.0 times the AUC in humans at

800 mg/day and 400 mg/day). In adult rats and monkeys, there were no vascular changes and no effects on sperm parameters in rats after up to 6 months of dosing at doses up to 320 mg/kg/day (corresponding to exposures ~8.3 and 9.8 times the AUC in humans at 800 mg/day and 400 mg/day) or in monkeys after 9 months at doses up to 200 mg/kg/day (corresponding to exposures ~1 and 1.2 times the AUC in humans at 800 mg/day and 400 mg/day). In a male and female fertility study in rats, there were no effects on mating performance, sperm assessments, or histopathology changes in the testis or epididymis at doses up to 320 mg/kg/day (corresponding to exposures ~12 times and 14 times the AUC in humans at 800 mg/day and 400 mg/day). In a pre- and post-natal development study in rat, there were no effects on mating and fertility parameters, nor changes in testes, seminal vesicles, or prostate weights at doses up to 80 mg/kg/day (corresponding to exposures ~8 and 10 times the AUC in humans at 800 mg/day and 400 mg/day). There are currently no clinical data to indicate sparsentan negatively impacts male fertility, therefore, this risk is not considered for inclusion in the list of safety concerns.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Potential Risk: Drug-induced liver injury

Benefit/risk impact: Hepatotoxicity and elevated serum aminotransferases are known risks for specific ERAs. In addition, ARBs (including irbesartan) can also cause drug-induced liver injury (DILI) with hepatitis-like syndrome or cholestasis. Although the exact mechanism is unknown, DILI is thought to be due to a combination of host, drug, and environmental factors. The manifestations of DILI are highly variable, ranging from asymptomatic elevations in liver enzymes to cholestasis, jaundice, liver failure, or chronic hepatitis with possible fatal outcome.

During the clinical development programme, hepatic disorder TEAEs have been reported. While these TEAEs have been observed in both treatment arms (sparsentan and irbesartan), their assessment, coupled with data from nonclinical studies and review of the supporting laboratory data, does not indicate that sparsentan treatment is associated with clinically severe cases of hepatoxicity. No subjects met criteria for Hy's law at any point during sparsentan clinical development. The reported hepatic disorder TEAEs concerned mainly hepatic enzymes increased, which were usually mild/moderate and transient in nature, and not associated with clinical symptoms. There was no clinical evidence of hepatotoxicity.

Important Potential Risk: Teratogenicity

Benefit/risk impact: The potential for teratogenicity is a known effect of both ERAs and angiotensin II receptor blockers, through different mechanisms of action. As sparsentan shares a mechanism of action with both classes of drugs, it is also expected to have teratogenic effects.

Nonclinical data demonstrated that exposure to sparsentan in animal reproduction studies in rats and rabbits resulted in teratogenic effects and other forms of foetal toxicity (see Section SII of this RMP).

No congenital abnormalities have been observed following live births from women who have become pregnant while taking sparsentan in clinical trials to date; however data are limited and the subjects stopped taking study medication upon positive pregnancy test in each case which limited exposure. Based on a limited number of pregnancies observed in women exposed to sparsentan, no translation of this risk to humans has been observed. Use of sparsentan during pregnancy is contraindicated. Patients are required to have a negative pregnancy test result prior to starting treatment with sparsentan and must use an effective contraception.

The risk to foetus outweighs the benefit and pregnant women must not take sparsentan. Women of childbearing potential must use an effective method of contraception while taking sparsentan. In addition to routine pharmacovigilance activities and product labelling, this risk will be managed through additional risk minimisation measures including educational material (Patient Card).

Missing Information: Use in Patients with Heart Failure

Benefit/risk impact: Patients with heart failure (New York Heart Association Class II to IV) and/or previous hospitalisation for heart failure were excluded from the pivotal clinical trials. Sparsentan has not been studied in patients with heart failure and the potential for sparsentan to increase fluid retention and worsen heart failure requires further evaluation.

Missing Information: Use in Patients with Severe Hepatic Impairment

Benefit/risk impact: Patients with severe hepatic impairment were excluded from the pivotal clinical trials due to the risk of hepatorenal syndrome. Sparsentan treatment is therefore not recommended in these patients (Child-Pugh Classification C).

Missing Information: Use During Breastfeeding

Benefit/risk impact: Breastfeeding women were excluded from the pivotal clinical trials due to the developmental risks to newborns and infants. It is unknown whether sparsentan is excreted in human breast milk, and the effects of exposure via lactation on a nursing infant are unknown. As physicochemical data suggest excretion of sparsentan in human milk; therefore, as a precautionary measure, sparsentan should not be used during breastfeeding.

Missing Information: Use in Patients After Renal Transplantation

Benefit/risk impact: Patients with any organ transplant were excluded from the pivotal clinical trial, as treatment with systemic immunosuppressants is usually required in this population. Sparsentan has not been studied in patients with a renal transplant, and should be used with caution.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 11 Important Potential Risk: Drug-induced Liver Injury

Important Potential Risk	Drug-induced liver injury
Potential mechanism	Hepatotoxicity and elevated serum aminotransferases are known risks for specific ERAs with unknown mechanism [63-65]. ARBs (including irbesartan) can also cause DILI with hepatitis-like syndrome or cholestasis. The mechanism with irbesartan is not known but resembles idiosyncratic liver injury due to a hypersensitivity reaction [66]. The pathogenesis of DILI is unknown. DILI may be the result of direct toxicity from the administered drug or their metabolites, or injury may result from immune-mediated mechanisms.
Evidence source and strength of evidence	Medicines with the similar mode of action (ERAs and ARBs) are associated with an increased risk of DILI. Pooled data from subjects treated in the sparsentan IgAN and FSGS clinical development programme. Nonclinical data from toxicology studies.
Characterisation of the Risk	
Frequency	**IgAN** In the PROTECT SAS, hepatic disorder TEAEs were reported in more subjects in the sparsentan group than in the irbesartan group (9% versus 6% of subjects, respectively). The PTs reported in more than 1 subject in either the sparsentan or irbesartan groups were ALT increased (5% and 4% of subjects, respectively), AST increased (2% and 4% of subjects, respectively), GGT increased (3% and 2% of subjects, respectively) and hepatic steatosis (1% in the sparsentan group). Treatment-related hepatic disorder TEAEs occurred in 4% of subjects in the sparsentan group and 1% of subjects in the irbesartan group. These included ALT increased (2% and 1% of subjects in the sparsentan and irbesartan groups, respectively), GGT increased (2% and <1% of subjects in the sparsentan and irbesartan groups, respectively), AST increased (1% of subjects in each group), and transaminases increased (<1% of subjects in the sparsentan group).

Incidence of Hepatic Disorder TEAEs (Safety Analysis Set)

	Sparsentan (N=202) n (%) (Events)	Irbesartan (N=202) n (%) (Events)	Total (N=404) n (%) (Events)
Any hepatic disorder TEAE[1]	18 (9) (40)	12 (6) (23)	30 (7) (63)
ALT aminotransferase increased	10 (5) (14)	8 (4) (10)	18 (4) (24)
AST increased	5 (2) (8)	8 (4) (8)	13 (3) (16)
GGT increased	7 (3) (9)	4 (2) (64)	11 (3) (13)
Hepatic steatosis	2 (1) (2)	0 (0) (0)	2 (<1) (2)
Blood alkaline phosphatase abnormal	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Cholestasis	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Hepatitis	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Hypertransaminasaemia	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Liver function test abnormal	0 (0) (0)	1 (<1) (1)	1 (<1) (1)
Liver function test increased	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Hypoalbuminaemia	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Non-alcoholic fatty liver disease	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Related hepatic disorder TEAE[1]	8 (4) (22)	2 (1) (7)	10 (2) (29)
ALT increased	5 (2) (9)	2 (1) (4)	7 (2) (13)

Important Potential Risk	Drug-induced liver injury

Frequency

	Sparsentan (N=202) n (%) (Events)	Irbesartan (N=202) n (%) (Events)	Total (N=404) n (%) (Events)
GGT increased	4 (2) (5)	1 (<1) (1)	5 (1) (6)
AST increased	3 (1) (6)	2 (1) (2)	5 (1) (8)
Hypertransaminasaemia	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Liver function test increased	1 (<1) (1)	0 (0) (0)	1 (<1) (1)
Serious hepatic disorder TEAE[1]	0 (0) (0)	2 (<1) (2)	2 (<1) (2)
ALT increased	0 (0) (0)	1 (<1) (1)	1 (<1) (1)
AST increased	0 (0) (0)	1 (<1) (1)	1 (<1) (1)

1 Hepatic disorder TEAEs comprise terms in the hepatic disorders SMQ.

CKD RCT study pool: Hepatic disorder TEAEs were reported in 7.6% of the subjects who received sparsentan 400/800 mg and 5.6% of the subjects who received irbesartan. The most reported hepatic disorder TEAEs in subjects who received sparsentan 400/800 mg versus subjects who received irbesartan included ALT increased (4.5% versus 2.8%, respectively), AST increased (2.7% versus 3.1% respectively), and GGT increased (2.7% versus 1.4%, respectively). Treatment-related ALT increased occurred in 1.8% of the subjects who received sparsentan 400/800 mg and in 0.7% of the subjects who received irbesartan. Treatment-related AST increased occurred in 1.3% of the subjects who received sparsentan 400/800 mg and in 0.9% of the subjects who received irbesartan. Treatment-related GGT increased occurred in 1.3% of the subjects who received sparsentan 400/800 mg and 0.5% of the subjects who received irbesartan.

In the all sparsentan group[1], 57 (7.7%) subjects reported a total of 115 hepatic disorder TEAEs, with ALT increased being the most common (33 (4.5%) subjects). Twenty-two (3.0%) subjects in the 400/800 mg sparsentan group reported a total of 27 treatment-related hepatic disorder TEAEs.

Post-marketing experience: A total of 44 hepatic disorder cases per 410 total patient-years since its approval in the US through 16-Feb-2024 (11 per 100 patient-years).

Seriousness/outcomes

IgAN

In the PROTECT SAS, 2 subjects in the irbesartan group reported serious hepatic disorder TEAEs: ALT increased and AST increased (1 subject each) (none reported in the sparsentan group). No subjects experienced AST or ALT elevation >3 x ULN accompanied by concurrently elevated bilirubin >2 x ULN. No subjects met the criteria for Hy's law case. In general, elevations in LFTs were asymptomatic transient and there was no other clinical evidence of hepatotoxicity.

Four subjects in the sparsentan group (none in the irbesartan group) discontinued drug due to hepatic disorder TEAEs.

No hepatic disorder TEAEs resulted in death.

CKD RCT study pool: No subject in the 400/800 mg sparsentan group had a serious hepatic disorder TEAE. Five (1.2%) subjects in the irbesartan group reported a serious hepatic disorder TEAE. No subjects experienced an incidence of AST or ALT elevation >3 × ULN accompanied by concurrently elevated bilirubin that met Hy's law criteria.

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

Important Potential Risk	Drug-induced liver injury
	Majority of the hepatic disorder TEAEs were considered as recovered/resolved or recovering/resolving. In the all sparsentan group[(1)], 2 (0.3%) subjects reported serious hepatic disorder TEAEs. Hepatic disorder TEAEs led to permanent discontinuation of study medication for 10 (1.4%) subjects (16 events).
Severity and nature of risk	**IgAN** In the PROTECT SAS, most subjects reported mild to moderate hepatic disorder TEAEs. **CKD RCT study pool:** The majority of the hepatic disorder TEAEs were mild, 29 (6.5%), or moderate, 7 (1.6%), in severity. In the all sparsentan group[(1)], the majority of the hepatic disorder TEAEs were mild, 45 (6.1%), and moderate, 14 (1.9%), in severity.
Risk factors and risk groups	Common risk factors for hepatotoxicity include [67,68]: • Older age • Female gender • Underlying liver diseases (e.g., hepatitis) • Other comorbidities such as acquired immunodeficiency syndrome • Genetic predisposition involving CYP450, HLA alleles and other drug-processing enzymes • Chronic alcohol consumption • Concomitant use of hepatotoxic medications
Preventability	The manifestations of DILI are highly variable. In order to reduce the risk of potential serious hepatotoxicity, serum aminotransferase levels and total bilirubin should be measured prior to initiation of treatment with sparsentan and then continue monitoring every 3 months during treatment. Depending on the clinical assessment, pausing and discontinuation are described in SmPC Section 4.4. Additional risk minimisation measures are proposed to further mitigate this risk including Patient Card that will be provided to inform patients of the risk.
Impact on the benefit/risk balance of the product	The hepatic disorder TEAEs observed during the clinical development concerned mainly hepatic enzymes increased, which were usually mild/moderate and transient in nature. There was no clinical evidence of hepatotoxicity.
Potential public health impact of safety concern	Sparsentan is indicated for the treatment of IgAN, which is a rare disease. The public health impact is anticipated to be negligible.

1 All sparsentan group includes subjects who received at least 1 dose of sparsentan during any treatment period (double-blind or open-label) of PROTECT, DUPLEX, or DUET. Subjects are counted only once regardless of different sparsentan doses received; includes subjects in the DUET OLE study with long-term sparsentan exposure of up to 9 years.

Notes: Data cut-off dates were 01-Aug-2023 for DUPLEX and DUET, and 07-Sep-2023 for PROTECT.
AE=Adverse event; ALT=Alanine aminotransferase; ARB=Angiotensin receptor blocker; AST=Aspartate aminotransferase; CKD=Chronic kidney disease; DILI=Drug-induced liver injury; ERA=Endothelin receptor antagonist; FSGS=Focal segmental glomerulosclerosis; GGT=Gamma glutamyl transferase; IgAN=Immunoglobulin A nephropathy; LFT=Liver function test; OLE=Open-label extension; SAS=Safety analysis set; PT=Preferred term; RCT=Randomised clinical trial; SmPC=Summary of Product Characteristics; TEAE=Treatment-emergent adverse event; ULN=Upper limit of normal.

Table 12 Important Potential Risk: Teratogenicity

Important Potential Risk	Teratogenicity
Potential mechanism	Deleterious class effects on the development of the foetus are known for both ERAs and ARBs. ET_AR antagonists are expected to cause foetal harm (harm to a developing embryo) if given to pregnant women. Similarly, treatment with drugs that act directly on the RAAS during the second and third trimesters of pregnancy has been shown to reduce foetal renal function and increase foetal and neonatal morbidity and death. Potential adverse effects include birth defects, hypoplasia, anuria, hypotension, renal failure, and death.
Evidence source and strength of evidence	Nonclinical studies in which birth defects were observed, demonstrating the potential risk of teratogenicity for sparsentan. Medicines with a similar mode of action are associated with an increased risk of foetal harm during pregnancy.
Characterisation of the Risk	
Frequency	19 pregnancies have been reported in subjects enrolled in sparsentan studies to date, out of which, 15 pregnancies occurred in subjects receiving sparsentan. Total of 9 pregnancies occurred in subjects enrolled in the IgAN PROTECT study, 9 pregnancies occurred in subjects enrolled in FSGS studies (5 DUET subjects and 4 DUPLEX subjects), and 1 pregnancy occurred in a subject receiving sparsentan through a compassionate use programme. All subjects with a positive pregnancy test stopped treatment as soon as the pregnancy was discovered. In PROTECT, there were a total of 8 pregnancies in 7 female subjects and 1 additional pregnancy in a female partner of a male study subject (treated with sparsentan). In the sparsentan treatment group, 1 subject became pregnant and discontinued study medication. After treatment discontinuation, the subject had withdrawal of implanted contraceptive followed by a spontaneous abortion (not related to study medication by the Investigator). The subject did not restart study medication and became pregnant again within 2 months. The pregnancy resulted in live birth at Week 35. Second subject from sparsentan arm, was found to be pregnant approximately 1 year after stopping study medication, outcome was reported as live birth. Third subject treated with sparsentan in OLE, was found to be pregnant while off study medication. Ultrasound showed early embryonic demise with no evidence of birth defect. Fourth subject in the sparsentan arm had a miscarriage on Study Day 1156 at approximately Week 12 of pregnancy. Fifth subject who received sparsentan in OLE, experienced a spontaneous abortion at Week 5 of pregnancy. One subject in the irbesartan group was found to be pregnant 23 days after initiating study medication, which was discontinued the same day, and she experienced a spontaneous abortion 6 weeks later. A second subject in the irbesartan group became pregnant 10 months after starting investigational product, which was stopped following the positive pregnancy test, and the subject had an elective abortion 6 weeks later. Among DUPLEX subjects, there were 4 pregnancies. Two pregnancies occurred in a subject enrolled in the irbesartan arm, one of which resulted in a fatal congenital anomaly. The child was born 3.5 months early with a fatal congenital defect. Another pregnancy in a subject from the irbesartan arm resulted in premature C-section due to pre-eclampsia, both baby and mother are reported as healthy. One pregnancy in a subject (38 years old) from sparsentan arm resulted in a miscarriage; no further details reported. The remaining exposure to sparsentan during pregnancy was reported in a subject in the OLE with no outcome reported.

Important Potential Risk	Teratogenicity
	Among DUET subjects, there were 5 pregnancies. All subjects who experienced a pregnancy stopped treatment immediately on the date of the positive pregnancy test. Two subjects had an elective abortion. One subject had a spontaneous abortion 2 months after the date of their positive pregnancy test. Subject having spontaneous abortion had an ongoing vaginal infection prior to study enrolment and was ongoing at the time of spontaneous abortion. The remaining 2 subjects reported live births: 1 baby was born premature, and the other baby was carried to full-term. Both babies were healthy. No pregnancy-associated adverse events were noted in these patients. The pregnancy in a compassionate-use subject has resulted in full-term live birth without congenital abnormalities reported. Treatment with sparsentan was stopped 6 days after the first dose. None of the reported adverse pregnancy outcomes were assessed as related to sparsentan. Post-marketing reporting included 2 pregnancy cases resulting in treatment interruption. No clinical manifestations were reported.
Seriousness/outcomes	No congenital anomalies have been reported following any pregnancy in subjects receiving sparsentan.
Severity and nature of risk	No congenital anomalies have been reported following any pregnancy in subjects receiving sparsentan.
Risk factors and risk groups	All women of childbearing potential.
Preventability	All women of childbearing potential must take a negative pregnancy test before commencing treatment and use an effective method of contraception during the course of treatment and 1 month after treatment has stopped. Pregnancy is contraindicated in Section 4.3 of the SmPC. Additional risk minimisation measures are proposed to further mitigate this risk including Patient Card that will be provided to inform patients of the risk.
Impact on the benefit/risk balance of the product	The potential risk to foetus outweighs the benefit and pregnant women must not take sparsentan.
Potential public health impact of safety concern	Sparsentan is indicated for the treatment of IgAN, which is a rare disease. The public health impact is anticipated to be negligible.

Notes: Data cut-off dates were 01-Aug-2023 for DUPLEX and DUET, and 07-Sep-2023 for PROTECT.
ARB=Angiotensin receptor blocker; ERA=Endothelin receptor antagonist; ET_AR=Endothelin type A receptor; FSGS=Focal segmental glomerulosclerosis; IgAN=Immunoglobulin A nephropathy; OLE=Open-label extension; RAAS=Renin angiotensin aldosterone system; SmPC=Summary of Product Characteristics.

SVII.3.2 Presentation of the Missing Information

Table 13 Missing Information

Missing Information	What Is Known
Use in patients with heart failure	Population in need of further characterisation: Patients with heart failure (New York Heart Association Class II to IV) and/or previous hospitalisation for heart failure were excluded from the pivotal clinical trials. Sparsentan has not been studied in patients with heart failure and the potential for sparsentan to increase fluid retention and worsen heart failure requires further evaluation. Sparsentan should be used with caution in patients with heart failure
Use in patients with severe hepatic impairment	Population in need of further characterisation: Patients with severe hepatic impairment were excluded from the pivotal clinical trials due to the risk of hepatorenal syndrome. Sparsentan should be used with caution in these patients (Child-Pugh Classification C).
Use during breastfeeding	Population in need of further characterisation: Breastfeeding women were excluded from the pivotal clinical trials due to the developmental risks to newborns and infants. The effects of exposure via lactation on a nursing infant are unknown.
Use in patients after renal transplantation	Population in need of further characterisation: Patients with any organ transplant were excluded from PROTECT due to the required treatment with systemic immunosuppressants. Sparsentan should be used with caution in patients after renal transplantation.

SVIII SUMMARY OF THE SAFETY CONCERNS

Table 14 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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires for Drug-Induced Liver Injury

The follow-up Targeted Questionnaire (TQ) specific for evaluating liver AEs has been incorporated into routine follow-up and is presented in this RMP in Annex 4. All cases of drug-induced liver injury will be carefully followed up and a thorough assessment will be made.

Specific Adverse Reaction Follow-up Questionnaires for Teratogenicity

The follow-up TQ specific for evaluating embryofoetal toxicity/teratogenicity AEs has been incorporated into routine follow-up and is presented in this RMP in Annex 4. All cases of teratogenicity will be carefully followed up and a thorough assessment will be made.

There are no other specific adverse reaction follow-up questionnaires for the other safety concerns listed in this RMP in Table 14.

Other Forms of Routine Pharmacovigilance Activities

Close monitoring of data in Periodic Safety Update Reports and analysis of additional safety data that may arise from any future studies to collect further information related to the following safety concerns:

- Drug-induced liver injury
- Teratogenicity
- Use in patients with heart failure
- Use in patients with severe hepatic impairment
- Use during breastfeeding
- Use in subjects after renal transplantation

III.2 Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities as shown in Table 15.

Table 15 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
N/A	N/A	N/A	N/A	N/A

Note: N/A=Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 16 Planned and Ongoing Post-authorisation Efficacy Studies That Are Conditions of the Marketing Authorisation or Specific Obligations

Study (study short name and title), Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A	N/A	N/A	N/A	N/A
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A

Note: N/A=Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table 17 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Drug-induced liver injury	
Routine risk communication	SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4
Routine risk minimisation activities recommending specific clinical measures to address the risk	Recommendation for liver function test monitoring (serum aminotransferase and total bilirubin) prior to initiation of treatment and every 3 months during treatment is included in the SmPC Section 4.4.
Other routine risk minimisation measures beyond the Product Information	Legal status: subject to medical prescription
Teratogenicity	
Routine risk communication	SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.6 SmPC Section 5.3 PL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Contraindicated in pregnancy. Filspari treatment must only be initiated in women of childbearing potential when the absence of pregnancy has been verified and effective contraception is practised.
Other routine risk minimisation measures beyond the Product Information	Legal status: subject to medical prescription
Use in patients with heart failure	
Routine risk communication	SmPC Section 4.4
Routine risk minimisation activities recommending specific clinical measures to address the risk	Not applicable
Other routine risk minimisation measures beyond the Product Information	Legal status: subject to medical prescription

Table 17 Description of Routine Risk Minimisation Measures by Safety Concern (Cont'd)

Safety Concern	Routine Risk Minimisation Activities
Use in patients with severe hepatic impairment	
Routine risk communication	SmPC Section 4.2 SmPC Section 5.2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Not applicable
Other routine risk minimisation measures beyond the Product Information	Legal status: subject to medical prescription
Use during breastfeeding	
Routine risk communication	SmPC Section 4.6 PL Section 2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Not applicable
Other routine risk minimisation measures beyond the Product Information	Legal status: subject to medical prescription
Use in patients after renal transplantation	
Routine risk communication	SmPC Section 4.2
Routine risk minimisation activities recommending specific clinical measures to address the risk	Not applicable
Other routine risk minimisation measures beyond the Product Information	Legal status: subject to medical prescription

Notes: PL=Package Leaflet; SmPC=Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Patient Card

Objectives

The objectives are to minimise pregnancy exposure, and to minimise the risk of DILI during treatment with sparsentan.

Rationale for the Additional Risk Minimisation activity

Sparsentan has teratogenic potential, and may induce hepatotoxicity, therefore the Patient Card is considered necessary to ensure that patients are aware of these risks and the need to take specific actions.

Target Audience and Planned Distribution Path

The Patient Card is provided as part of the product packaging.

The Patient Card will be developed to inform all patients on the risks of sparsentan teratogenic potential and possible DILI. The following actions are required to minimise these risks:

- A negative pregnancy test is required before starting treatment. Sparsentan treatment must only be initiated in women of childbearing potential when the absence of pregnancy has been verified and effective contraception is practised.
- To use an effective method of contraception before starting, while on therapy and for 1 month after stopping.
- To talk to your doctor if pregnancy is suspected or if a pregnancy test is positive.
- Regular monitoring of liver function (serum aminotransferase levels and total bilirubin) as ordered by the doctor.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success

Effectiveness will be assessed based on routine pharmacovigilance activities to assess compliance with SmPC and Patient Information Leaflet recommendations, through collection of Individual Case Safety Reports. The effectiveness of the programme will be analysed by the Marketing Authorisation Holder and will be reported in Periodic Safety Update Reports.

V.3 Summary of 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
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

Table 18 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern (Cont'd)

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
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

Notes: PL=Package Leaflet; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF THE RMP

Summary of Risk Management Plan for Filspari (Sparsentan)

This is a summary of the Risk Management Plan for Filspari. The Risk Management Plan details important risks of Filspari, how these risks can be minimised, and how more information will be obtained about Filspari's risks and uncertainties (missing information).

Filspari's Summary of Product Characteristics and its Package Leaflet give essential information to healthcare professionals and patients on how Filspari should be used.

This summary of the Risk Management Plan for Filspari should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Filspari's Risk Management Plan.

I. The Medicine and What it is Used for

Filspari is indicated for the treatment of adults with primary IgAN with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥0.75 g/g). It contains sparsentan as the active substance and it is given as 200 mg and 400 mg film-coated tablets.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Filspari, together with measures to minimise such risks and the proposed studies for learning more about Filspari's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and Summary of Product Characteristics addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In the case of Filspari, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Filspari is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Filspari are risks that need special risk management activities to further investigate or minimise the risk so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Filspari. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
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

II.B Summary of Important Risks

Important Potential Risk: Drug-induced liver injury	
Evidence for linking the risk to the medicine	Medicines with the similar mode of action (ERAs and ARBs) are associated with an increased risk of drug-induced liver injury. Pooled data from subjects treated in the sparsentan IgAN and FSGS clinical development programme. Nonclinical data from toxicology studies.
Risk factors and risk groups	Common risk factors for hepatotoxicity include [67,68]: • Older age • Female gender • Underlying liver diseases (e.g., hepatitis) • Other comorbidities such as AIDS • Genetic predisposition involving CYP450, HLA alleles and other drug-processing enzymes • Chronic alcohol consumption • Concomitant use of hepatotoxic medications
Risk minimisation measures	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
Important Potential Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Nonclinical studies in which birth defects were observed, demonstrating the potential risk of teratogenicity for sparsentan. Medicines with a similar mode of action are associated with an increased risk of foetal harm during pregnancy.
Risk factors and risk groups	All women of childbearing potential.
Risk minimisation measures	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: restricted medical prescription Additional risk minimisation measures: Patient Card
Missing Information: Use in patients with heart failure	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • Legal status: restricted medical prescription Additional risk minimisation measures: None

Missing Information: Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 5.2 • Legal status: restricted medical prescription Additional risk minimisation measures: None
Missing Information: Use during breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 • Legal status: restricted medical prescription Additional risk minimisation measures: None
Missing Information: Use in patients after renal transplantation	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 • Legal status: subject to medical prescription Additional risk minimisation measures: None

Notes: ARB=Angiotensin receptor blocker; ERA=Endothelin receptor antagonist; FSGS=Focal segmental glomerulosclerosis; IgAN=Immunoglobulin A nephropathy; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

II.C Post-authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Filspari.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no studies required for Filspari.

PART VII: ANNEXES

CCI

CCI

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Annex 4 Specific Adverse Drug Reaction Follow-up Forms

CSL Vifor

V02

TPLGDS028049: TARGETED QUESTIONNAIRE,

Targeted Questionnaire for Evaluating Liver Adverse Events

CSL Vifor Coding Number:

1. Patient Demography						
Patient initials:	Gender: ☐ Male ☐ Female	Age:	Age group:	Year of Birth:	Weight: ☐ kg ☐ lb	Height: ☐ cm ☐ in

2. Relevant Medical History	
Information on medical history incl. concomitant disorders (diagnoses, family medical history, pregnancies, risk factors, previous hepatic adverse drug reactions, medical history of liver disease, infections etc): Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.	
Risk Factors Alcohol use within 8 weeks prior to adverse event: ☐ Yes Estimated drinks per day: ☐ No ☐ Unknown ☐ Other (please specify)	Chronic Liver Disease Risk Factors: ☐ Diabetes ☐ Hypertriglyceridemia ☐ Obesity ☐ Chronic average alcohol use (past or current) of >1 drink/day for women, >2 drinks/day for men ☐ Other (please specify)

3. Relevant Concomitant Drugs History

Enter medication other than those taken to treat the AE: (If required please complete a separate page or attach the patient's drug list with start and stop dates)

Name of Product (Trade Name or Active Ingredient)	Indication	Dosage Regimen	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

4. Information on Filspari (sparsentan)	
Batch Nr.:	
Indication (with underlying disease):	

Administration:	Start Dose: mg Current dose: mg	Frequency of Administration: Dose taken when liver event first noted: mg	
Start Date: (dd/mmm/yyyy)		End Date: (dd/mmm/yyyy)	
Mode of administration		Date when dose was up titrated	
Was Filspari interrupted due to the liver adverse event?		☐ Yes (specify date) (dd/mmm/yyyy)	☐ No
Was Filspari discontinued due to the liver adverse event?		☐ Yes (specify date) (dd/mmm/yyyy)	☐ No
Was the dose of Filspari reduced due to the liver adverse event?		☐ Yes (please specify date and reduced dose below) (dd/mmm/yyyy) mg	☐ No
If 'Yes' was answered above, please provide the date and dose for all dose changes as a result of this adverse event.			

5. Liver Adverse Event Information

Enter information about liver adverse event(s)

Nr.	Adverse event (AE)	AE Start Date/	AE Stop Date/	Outcome (1)	If outcome was considered as 4 or 6, please specify	Serious (2)	Seriousness Criteria (3)	Causal Relationship to Filspari (4)	Rationale for a causal relationship
I.									
II.									
III.									
IV.									
V.									
VI.									
VII.									
VIII.									

(1) For specifying Outcome, please use the coding system below:
1 = Ongoing, 2 = Recovering, 3 = Recovered without Sequelae, 4 = Recovered with Sequelae, 5 = Fatal, 6 = Unknown

(2) For specifying Serious Assessment for an adverse event, please use the coding system below:
S = Serious; NS = Not serious

(3) For specifying Seriousness Criteria, please use the coding list (1-6) below. According to ICH-E2A guidelines a serious adverse event is any untoward medical occurrence that at any dose:
1 = Results in death; 2 = Life-threatening; 3= Requires inpatient hospitalisation or prolongation of existing hospitalization; 4 = Results in persistent or significant disability/incapacity; 5 = Congenital anomaly/birth defect; 6 = Considered an important medical event (e.g., patient requires intervention to prevent one of the other outcomes listed above)

(4) For specifying Causal Relationship please use the coding system below:
NR = Not related; R = Related

Did the patient die?	☐ Yes	☐ No	
If 'Yes', please enter date: (dd/mmm/yyyy) If 'Yes' please provide details on cause of death:	Was an autopsy performed?	☐ Yes	☐ No
Did the patient require a liver transplant? Outcome:		☐ Yes	☐ No

Medications used to treat the AE

Did patient receive treatment for any of the reported AE(s)? ☐ Yes (please enter AE and medication administered for treatment below) ☐ No

Targeted Questionnaire for Evaluating Liver Adverse Events Version 1.0 (2023.10)
Vifor Coding Number:

Adverse Event (use corresponding roman numerals from table on page 3)	Name of Product (Trade Name or Active Ingredient)	Dosage Regimen	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)

Did this patient receive any non-drug treatment?	☐ Yes	☐ No

If 'Yes' please specify

Please provide a description of the event(s) including outcome, if known.

Signs and symptoms of hepatotoxicity (type and timing to exposure)

6. Laboratory Test and Investigation Results

Please provide SI (International Systems of Units) if available. Otherwise, as reported.
☐ Laboratory Results Attached (tick box if lab results are attached).

Please indicate if any of the following tests have been performed and provide the results. If lab results not obtained, indicate whether lab tests not done, or lab results not yet obtained.
Lab results should be attached whenever possible. If lab results cannot be attached, please **type** (DO NOT handwrite) the results in the space below.

Laboratory test	Baseline Values (Prior to the Event)		Values (At the time of the event/During treatment)		Values (After cessation of treatment)		Reference Range (include units)	Pending?
	Date (dd/mmm/yyyy)	Value (include units)	Date (dd/mmm/yyyy)	Value (include units)	Date (dd/mmm/yyyy)	Value (include units)		
ALT or SGOT								☐ Yes
AST or SGPT								☐ Yes
Direct Bilirubin								☐ Yes
Total Bilirubin								☐ Yes
Albumin (minimum)								☐ Yes
Alkaline Phosphatase								☐ Yes
GGT								☐ Yes
PT/INR								☐ Yes
Other (please specify)								☐ Yes

Investigation	Date of test(s)	Results	
Acute Viral Hepatitis Tests (i e., HAV IgM, HBsAg, anti-HBc IgM, HCV antibody, HCV RNA)			
Other relevant labs (e.g., ANA, anti-smooth muscle, hepatitis E antibodies):			
Relevant Physical Exam Findings:			
Were any of the following procedures performed? **NOTE: If 'Yes' to any of the below, provide copies of the labs and/or imaging results including hospital discharge and autopsy reports. If procedures occurred more than once, please provide information for each individual procedure.**			
Procedure	Date of procedure(s)	Yes or No	Findings
Liver Biopsy		☐ Yes ☐ No	
Liver Ultrasound		☐ Yes ☐ No	
Other Liver Imaging (e.g., MRI, CT)		☐ Yes ☐ No	
Hospitalization		☐ Yes ☐ No	
Other (specify)		☐ Yes ☐ No	

7. Reporter Details			
Name of Reporter:		**Profession of Reporter:**	
Name & Address of the Institution:		**Country:**	
		Telephone:	
		Fax:	
		e-mail:	
Handwritten Signature of Reporting Person: Date: _____ (dd/mmm/yyyy)			
Privacy Notification: The personal data that you provide, such as your name and contact details, will be handled and stored by CSL Vifor. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the CSL Vifor website (www.viforpharma.com/dataprivacy) where you also find contact details if you have questions. NOTE: The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.			

Targeted Questionnaire for Evaluating Embryofoetal toxicity/Teratogenicity Adverse Events

CSL Vifor Coding Number:

1. Patient Demography					
Patient initials:	Age: Age group:	Year of Bir h:	Occupation:	Weight: ☐ kg ☐ lb	Height: ☐ cm ☐ in

2. Relevant Medical History	
Information on maternal medical history incl. concomitant disorders (diagnoses, family medical history (multiple pregnancy, diabetes, hypertension, chromosome or congenital malformations), including pregnancy risk factors, pre-eclampsia, eclampsia, smoking, alcohol intake, environmental & occupational exposures, allergies, exposure to other teratogenic drugs etc.): Please indicate if the following conditions are ei her part of the patient's medical history or are still active conditions.	
Paternal history/drug exposure before a pregnancy is conceived, while trying to conceive pregnancy, or during pregnancy (diagnoses (such as viral infection), drug exposure, exposure to illicit substances (such as alcohol, tobacco, marijuana, opioid misuse etc.), exposure to chemotherapy or radiotherapy, environmental & occupational exposures etc.)	
Past Obstetric History Previous pregnancy: ☐ Yes ☐ No Total no. of pregnancies: Pregnancy outcomes: ☐ Normal delivery or ☐ Cesarean section ☐ Premature delivery (i.e., before 37th week of pregnancy) If premature, gestational age: weeks ☐ Full term ☐ Spontaneous abortion ☐ Induced elective abortion ☐ Ectopic pregnancy ☐ Other (please specify) If multiple pregnancies, please add outcome for each	**Past Gynaecological History** Method of contraception before conception Menstrual history Cervical smear history Surgical history (particularly any pelvic or abdominal surgery) Previous gynaecological problems Other (please specify)

3. Current Pregnancy
Please indicate if any of the following tests have been performed and provide the results. If test results not obtained, indicate whether tests not done, or lab results not yet obtained. Test results should be attached whenever possible. If test results cannot be attached, please **type** (DO NOT handwrite) the results in the space below.

First day of last menstrual cycle (dd/mmm/yyyy) Expected delivery date (dd/mmm/yyyy)
Method of confirmation of pregnancy Date of pregnancy confirmation (dd/mmm/yyyy)

Multiple pregnancy? ☐ Yes ☐ No
If 'Yes', please specify no. of foetuses:

Gestational age of foetus (specify at time of exposure / time of reporting) weeks

Ultrasound performed? ☐ Yes ☐ No
If 'Yes', findings if any including date when performed:

Antenatal test performed? ☐ Yes ☐ No
If 'Yes', findings if any including date when performed:

Amniotic fluid test performed? ☐ Yes ☐ No
If 'Yes', findings if any including date when performed:

Any other tests/ investigations performed? ☐ Yes ☐ No
If 'Yes', findings if any including date when performed:

Any complications, infec ions or illnesses during 1st trimester of pregnancy? ☐ Yes ☐ No
If 'Yes', elaborate:

Any complications, infections or illnesses during 2nd trimester of pregnancy? ☐ Yes ☐ No
If 'Yes', elaborate:

Any complications, infections or illnesses during 3rd trimester of pregnancy? ☐ Yes ☐ No
If 'Yes', elaborate:

Outcome of Current Pregnancy

☐ Normal delivery or ☐ Caesarean section
☐ Full term
☐ Premature delivery (i.e., before 37th week of pregnancy) If premature birth, gestational age: weeks
☐ Spontaneous abortion
☐ Elective abortion Medical Reason? ☐ Yes ☐ No
If 'Yes', please specify:
Complications during labour: ☐ Yes ☐ No
If 'Yes', please specify:
Details / comments (if any):

Maternal Death? ☐ Yes ☐ No
If 'Yes', please enter date: (dd/mmm/yyyy)
If 'Yes', please provide details on cause of death:
If 'Yes', was an autopsy performed? ☐ Yes ☐ No

Is there a suspicion that adverse outcome of pregnancy is related to exposure to Filspari (sparsentan)?
☐ Yes ☐ No
Please elaborate:

Infant Outcome

☐ Healthy baby
☐ Sick baby (e.g., birth trauma, infection etc.)
If checked, please specify
☐ Multiple births
If checked, please specify
☐ Congenital anomaly or birth defect
If checked, please specify
☐ Still birth
☐ Delivery of a small for gestational age infant (low birth weight)

Date of birth (dd/mm/yyyy)
Assigned sex at bir h ☐ Male or ☐ Female
Size: ☐ cm ☐ in
Weight: ☐ gr ☐ oz ☐ lb
Head circumference: ☐ cm ☐ in
APGAR scores, if provided (birth/5/10 mins.) / /
Details / comments (if any):

Is there a suspicion that adverse infant outcome is related to exposure to Filspari (sparsentan)?
☐ Yes ☐ No
Please elaborate:

4. Relevant Concomitant Drugs Exposure during Pregnancy
Please include all drugs administered during pregnancy including those with teratogenic potential.
(If required please complete a separate page or attach the patient's drug list with start and stop dates)

Name of Product (Trade Name or Active Ingredient)	Indica ion	Dosage Regimen	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Route of administra ion

5. **Information on Filspari (sparsentan)**		
Batch Nr.:		
Indication (with underlying disease):		
Administration:	Start Dose: mg Dose taken when pregnancy confirmed: mg	Frequency of administration:
Start Date: (dd/mm/yyyy)		End Date: (dd/mm/yyyy)
Mode of administration		Date when dose was up titrated (dd/mm/yyyy)
Was Filspari discontinued due to the pregnancy?		☐ Yes If 'Yes', please specify date (dd/mm/yyyy) Gestational age: week(s) ☐ No

6. Additional Adverse Event Information

Enter information about any additional adverse event(s) experienced by mother or foetus

Nr.	Adverse event (AE)	AE Start Date/	AE Stop Date/	Outcome (1)	If outcome was considered as 4 or 6, please specify	Serious (2)	Seriousness Criteria (3)	Causal Relationship to Filspari (4)	Rationale for a causal relationship	Maternal or foetal adverse event
I.										
II.										
III.										
IV.										
V.										

(1) For specifying Outcome, please use the coding system below:
1 = Ongoing, 2 = Recovering, 3 = Recovered without Sequelae, 4 = Recovered with Sequelae, 5 = Fatal, 6 = Unknown

(2) For specifying Serious Assessment for an adverse event, please use the coding system below:
S = Serious; NS = Not serious

(3) For specifying Seriousness Criteria, please use the coding list (1-6) below. According to ICH-E2A guidelines a serious adverse event is any untoward medical occurrence that at any dose:
1 = Results in death; 2 = Life-threatening; 3= Requires inpatient hospitalisation or prolongation of existing hospitalization; 4 = Results in persistent or significant disability/incapacity; 5 = Congenital anomaly/birth defect; 6 = Considered an important medical event (e g., patient requires intervention to prevent one of the other outcomes listed above)

(4) For specifying Causal Relationship please use the coding system below:
NR = Not related; R = Related

Medications used to treat the AE

Did patient receive treatment for any of the reported AE(s)? ☐ Yes (please enter AE and medication administered for treatment below) ☐ No

Adverse Event (use corresponding roman numerals from table above)	Name of Product (Trade Name or Active Ingredient)	Dosage Regimen	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)

Did this patient receive any non-drug treatment?	☐ Yes	☐ No
If 'Yes', please specify		
Please provide a description of the event(s) including outcome, if known.		

7. Clinically Significant Laboratory Tests / Investigation Results

Please provide SI (International Systems of Units) if available. Otherwise, as reported.

☐ Laboratory Results Attached (tick box if lab results are attached).

Please indicate if any of the following tests have been performed and provide the results in regard to maternal or infant adverse outcomes. If lab results not obtained, indicate whether lab tests not done, or lab results not yet obtained.

Lab results should be attached whenever possible. If lab results cannot be attached, please type (DO NOT handwrite) the results in the space below.

Laboratory Test	Baseline Values (Prior to the event of interest)		Values (At the time of the event of interest)		Values (After cessation of treatment)		Reference Range (include units)	Maternal or infant test results	Pending?
	Date (dd/mmm/yyyy)	Value (include units)	Date (dd/mmm/yyyy)	Value (include units)	Date (dd/mmm/yyyy)	Value (include units)			
									☐ Yes
									☐ Yes
									☐ Yes

8. Reporter Details			
Name of Reporter:		**Profession of Reporter:**	
Name & Address of the Institution:		**Country:**	
		Telephone:	
		Fax:	
		e-mail:	
Handwritten Signature of Reporting Person: Date: _____ (dd/mmm/yyyy)			
Privacy Notification: The personal data that you provide, such as your name and contact details, will be handled and stored by CSL Vifor. You can read in detail what information we save and how the information will be handled in our Privacy Notices on the CSL Vifor website (www.viforpharma.com/dataprivacy) where you also find contact details if you have questions. NOTE: The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to use and disclose health information without authorization in order to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA. Please submit only that health information which is reasonably necessary to achieve the purpose of the report.			

Annex 6 Details of Proposed Additional Risk Minimisation Activities

Draft key messages of the additional risk minimisation measures

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) as ordered by your doctor
- Signs or symptoms of drug-induced liver injury and when to seek attention from a healthcare professional

Annex 7 Other Supporting Data (Including Referenced Material)

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