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HEALTH TECHNOLOGY BRIEFING
APRIL 2021

Sparsentan for treating Focal Segmental Glomerulosclerosis

NIHRIO ID	9516	**NICE ID**	10482
Developer/Company	Travere Therapeutics Inc.	**UKPS ID**	657889

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Sparsentan is in clinical development for the treatment of patients with primary and genetic focal segmental glomerulosclerosis (FSGS). FSGS is a rare kidney disease characterised by dysfunction in the part of the kidney that filters blood (the glomeruli) and causes serious scarring that leads to permanent kidney damage and even kidney failure. When glomeruli become damaged or scarred (sclerosis), proteins begin leaking into the urine (proteinuria). FSGS can be "primary" meaning it is of unknown cause; "secondary" which is caused by another disease or a drug; or "genetic" caused by an abnormal version in a gene.

Sparsentan is developed as an oral treatment that sustainably reduces proteinuria. It has an innovative dual mechanism of action, with a potentially greater protective effect to the kidneys, compared to existing treatments. If licensed, sparsentan would increase the treatment options for FSGS.

PROPOSED INDICATION

Treatment of patients with focal segmental glomerulosclerosis (FSGS).[a]

TECHNOLOGY

DESCRIPTION

Sparsentan (RE-021, PS433540) is a first-in-class, orally active, single molecule that functions as a high affinity dual-acting antagonist of both endothelin type A and angiotensin II type 1 which are associated with kidney disease progression.[1,2] Endothelin type A and angiotensin II have a role in kidney function decline by contributing to inflammation and fibrosis in the kidney; changes to the shape of podocytes; podocyte loss, and increased permeability of the glomerular filtration barrier. Endothelin type A and angiotensin II are also vasoconstrictive, meaning they cause a narrowing of blood vessels and an increase in pressure in the glomeruli. [2]

Sparsentan is in clinical development for the treatment of primary and genetic FSGS. In the phase III clinical trial (DUPLEX; NCT03493685), sparsentan is administered as a single oral morning dose; an initial dose of 400 mg daily titrating up to a target dose of 800 mg, daily.[3]

INNOVATION AND/OR ADVANTAGES

Sparsentan is developed to provide a well-tolerated, safe and effective treatment that sustainably reduces proteinuria and protects the long-term health of kidneys in people living with FSGS.[2]

Sparsentan offers an innovative dual mechanism of action approach to the treatment of FSGS with a potentially greater nephroprotective effect, compared to renin-angiotensin-aldosterone system (RAAS) or endothelin inhibition alone.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Sparsentan does not currently have Marketing Authorisation in the EU/UK for any indication.

Sparsentan was granted orphan drug designation in the EU in 2015 for the treatment of FSGS.[5]

Sparsentan is currently in phase II and III trials for immunoglobulin A nephropathy (IgAN).[6,7]

PATIENT GROUP

DISEASE BACKGROUND

Focal segmental glomerulosclerosis (FSGS) is a rare disease in which scar tissue develops on the parts of the kidneys that filter waste from the blood (glomeruli).[8] When the glomeruli become damaged or scarred (sclerosis), proteins begin leaking into the urine (proteinuria). Only some glomeruli are

[a] Information provided by company on UK PharmaScan

affected, but continued damage can lead to permanent kidney damage and even kidney failure.[9] Proteinuria is a standard measure of disease activity, and a predictor of and contributor to disease progression in FSGS.[2]

The types of FSGS include: Primary FSGS, which is of unknown cause, is also called idiopathic FSGS. Secondary FSGS is caused by several factors such as infection, drug toxicity, diseases such as diabetes or sickle cell disease, obesity, and even other kidney diseases. Genetic (or familial) FSGS is a rare form of FSGS caused by genetic mutations and is suspected when several members of a family show signs of FSGS. It can also occur when neither parent has the disease, but each carries one copy of an abnormal gene that can be passed on to the next generation.[8]

FSGS affects both children and adults, with males being affected slightly more often than females.[10] Early stages of FSGS may not cause any symptoms. However, the signs and symptoms of FSGS include: swelling in body parts like legs, ankles and around the eyes (called edema); weight gain; foamy urine caused by high protein levels in the urine (proteinuria); high fat levels in the blood (high cholesterol); and low levels of protein in the blood.[10] FSGS is one of the causes of a serious condition known as Nephrotic Syndrome which refers to a group of symptoms associated with kidney damage including, proteinuria of $\geqslant$3.5 g/d, low levels of blood albumin ($\leqslant$3.5 g/dL), with or without edema.[9,11]

CLINICAL NEED AND BURDEN OF DISEASE

Race, ethnicity, and gender all have a significant effect on the incidence of FSGS.[11] It is more common in people of African ancestry, both children and adults, and affects men slightly more often than women. FSGS occurs most often in adults about 45 years or older.[11,12]

FSGS is estimated to affect about 7 people per million in the general population, although specific incidence rates vary in different populations. It accounts for about 40% of adults with nephrotic syndrome and about 20% of children with nephrotic syndrome.[12] Clinical surveys from North America and the UK have reported the incidence of nephrotic syndrome to be between two and four new cases per 100,000 children per year, with biopsy-confirmed FSGS comprising 15–20% of the total. FSGS becomes less common with advancing age, but it is still a significant problem in the elderly. In a series of 1368 renal biopsies from patients over 60 years of age, FSGS was present in 5.4% of those patients with nephrotic syndrome.[13]

The rate of occurrence of FSGS in patients with nephrotic syndrome is approximately 10% in children under age 6 years, 20% in adolescents, and 20% to 25% in adults. Over 50% of patients will reach end-stage renal disease (ESRD) within 8 years, requiring dialysis or kidney transplant.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of FSGS is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Specific therapeutic procedures and interventions may vary, depending upon numerous factors, such as the underlying cause of FSGS; how far kidney function has declined; the presence or absence of certain symptoms; and an individual's age and general health.[12] Treatment aims to reduce proteinuria to induce a complete or partial remission which is important for long-term preservation of kidney function.[11]

There are several supportive therapies that are given to help manage the various symptoms associated with FSGS including diuretics and a low sodium diet to relieve edema; blood thinning medications that help prevent blood clots (anticoagulants); statins to lower cholesterol levels; and

angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), which can help to control blood pressure and lower the amount of protein in the urine.[12] When medications fail, dialysis and kidney transplant become the next treatment options.[14]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the following options for the treatment of FSGS:[15]

- Treatment with a corticosteroid such as prednisolone is recommended for the initial episode of FSGS.
- For adults with FSGS, calcineurin inhibitors can be considered as alternatives for those with relative contraindications or intolerance to corticosteroids.
- Ciclosporin is recommended for steroid-resistant FSGS.
- Combination treatment with mycophenolate mofetil and high-dose dexamethasone is recommended for people with steroid-resistant FSGS who are intolerant to ciclosporin.

PLACE OF TECHNOLOGY

If licensed, sparsentan will offer an additional treatment option for patients with FSGS.

CLINICAL TRIAL INFORMATION

Trial	**DUET,** NCT01613118**, RET-D-001;** Efficacy and Safety of RE-021, a Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients With Focal Segmental Glomerulosclerosis (FSGS): a Randomized, Double-Blind, Active-Control, Dose-Escalation Study. **Phase II** – ongoing **Primary completion date:** June 2016
Trial design	Randomised, double-blind, parallel assignment
Population	N=100; aged 8 years to 75 years; all sexes; with biopsy-proven primary FSGS (Primary FSGS confirmed by renal biopsy report) or documentation of a genetic mutation in a podocyte protein associated with the disease.
Intervention(s)	Oral sparsentan as a single morning dose for 8 weeks: • Arm 1: 200mg • Arm 2: 400mg • Arm 3: 800mg
Comparator(s)	Oral irbesantan as a single dose of 150mg for the first week before escalating to 300mg for the remaining 7 weeks.
Outcome(s)	Primary Outcome Measure: Evaluate change in urine protein/creatinine (Up/C). [Time Frame: 8 weeks] Primary efficacy objective is to determine the change in Up/C in FSGS patients receiving RE-021 (Sparsentan) over a range of dose levels compared to treatment with irbesartan as active control.
Results (efficacy)	Of 109 patients randomized, 96 received study drugs and had baseline and week 8 UP/C measurements. Sparsentan-treated patients had greater reductions in UP/C than irbesartan-treated patients did when all doses (45% versus 19%; P=0.006) or the 400 and 800 mg doses (47% versus 19%; P=0.01) were pooled for

	analysis. The FSGS partial remission end point was achieved in 28% of sparsentan-treated and 9% of irbesartan-treated patients (P=0.04). After 8 weeks of treatment, BP was reduced with sparsentan but not irbesartan, and eGFR was stable with both treatments.[16]
Results (safety)	The incidence of adverse events was similar between groups. Hypotension and edema were more common among sparsentan-treated patients but did not result in study withdrawals.[16]

Trial	**DUPLEX,** NCT03493685**, 021FSGS16010;** A Randomized, Multicenter, Double-blind, Parallel, Active-control Study of the Effects of Sparsentan, a Dual Endothelin Receptor and Angiotensin Receptor Blocker, on Renal Outcomes in Patients With Primary FSGS. **Phase III** – ongoing **Location(s):** EU (incl UK), Canada, United States and other countries **Primary completion date:** June 2022
Trial design	Randomised, multicenter, parallel assignment, double-blind, active-controlled
Population	N=300; aged 8 years to 75 years; all sexes; with biopsy-proven FSGS lesion(s) or documentation of a genetic mutation in a podocyte protein associated with FSGS.
Intervention(s)	Oral sparsentan as a single morning dose; an initial dose of 400 mg daily titrating up to a target dose of 800 mg, daily
Comparator(s)	Oral irbesartan as a single morning dose; an initial dose of 150 mg daily titrating up to a target dose of 300 mg, daily
Outcome(s)	Primary Outcome Measures: • Slope of estimated glomerular filtration rate (eGFR) [Time Frame: Week 6 to Week 108]. The slope of estimated glomerular filtration rate (eGFR) from Week 6 to Week 108. • Proportion of patients achieving a UP/C ⩽1.5 g/g and a >40% reduction [Time Frame: Week 36]. Proportion of patients achieving a UP/C ⩽1.5 g/g and a >40% reduction from baseline in UP/C at Week 36
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of sparsentan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Evidence summary [ES1]: Minimal change disease and focal segmental glomerulosclerosis in adults: rituximab. November 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy Statement: Rituximab for the treatment of refractory Focal Segmental Glomerulosclerosis in the native kidney in adults (1818). July 2019.

OTHER GUIDANCE

- NHS University Hospitals of Leicester: Nephrotic Syndrome Children's Guideline. 2021.[17]
- International Society of Nephrology (ISN). KDIGO Clinical Practice Guideline for Glomerulonephritis. June 2012.[18]

ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.