NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Sparsentan for treating primary IgA nephropathy

Company/Developer	Vifor Pharma UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26933	NICE ID: 11866	UKPS ID: 668865

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Sparsentan is in development for the treatment of immunoglobin A nephropathy (IgAN). IgAN is a chronic kidney disease which mainly affects young adults. In IgAN a protein called immunoglobulin A (IgA) becomes trapped in the very fine filters of the kidney (glomeruli), causing damage and scarring to the whole kidney. The cause of IgAN is not known, but it is thought that it may be due to over-activity of the immune system. In the early stages, IgA often has no symptoms. The first sign that the patient may notice is blood in the urine. There are currently no approved non-immunosuppressive medicines indicated for IgAN. There is therefore an unmet need to develop new well-tolerated, effective treatment options for IgAN.

Sparsentan is a substance that blocks the receptors (targets) for two hormones called endothelin and angiotensin II that are involved in the regulation of blood pressure and kidney function. Blocking the action of angiotensin II allows blood vessels to widen, reducing blood pressure, and helps to reduce the amount of water re-absorbed by the kidneys, improving urine production. Endothelin is thought to be involved in the progression of primary IgAN; blocking its action is expected to reduce damage to the kidney. By blocking the effects of both hormones, the medicinal product is expected to help slow down the progression of symptoms and prevent or delay kidney failure and associated complications in patients with the condition. Sparsentan is administered orally. If licenced, sparsentan would be the first non-immunosuppressive treatment option for patients with IgAN.

Proposed Indication

The treatment of primary immunoglobulin A nephropathy (IgAN) in adults.[1]

Technology

Description

Sparsentan (RE-021) is a first-in-class, orally active, single molecule that functions as a high affinity dual-acting antagonist of both endothelin type A (ETA) and angiotensin II subtype 1 (AT1) receptors which are associated with kidney disease progression.[1,2] The endothelin-1 (ET-1) and angiotensin II (Ang II) signalling pathways play fundamental roles in disease pathophysiology and progression in several kidney diseases, including IgAN.[2]

Sparsentan is currently in clinical development for the treatment of primary IgAN. In the phase III clinical trial (PROTECT, NCT03762850) patients are given sparsentan 200mg oral tablet daily for the first 2 weeks of the study, followed by 400mg daily until week 110 for patients who tolerate the initial dose.[1]

Key Innovation

There are currently no approved non-immunosuppressive medicinal products indicated for IgAN.[3] There is therefore an unmet need for well-tolerated, effective treatments for IgAN. Pre-clinical data have shown that blockade of both ETA and AT1 pathways in forms of rare chronic kidney disease reduces proteinuria, protects podocytes and prevents glomerulosclerosis and mesangial cell proliferation.[2]

The phase III PROTECT study (NCT03762850) met its pre-specified interim primary efficacy endpoint with statistical significance. After 36 weeks of treatment, patients receiving sparsentan achieved a mean reduction in proteinuria from baseline of 49.8%, compared to a mean reduction in proteinuria from baseline of 15.1% for comparator group patients ($p<0.0001$).[4] There are currently no National Institute for Health and Care Excellence (NICE) recommended or approved pharmacological treatment options. If licenced, sparsentan would offer an additional treatment option for patients with IgAN who currently have limited options.

Regulatory & Development Status

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

Sparsentan is also in phase II and III clinical development for anti-neutrophil cytoplasmic antibody - associated vasculitis and focal segmental glomerulosclerosis respectively.[5]

Sparsentan has been awarded an orphan drug designation in the EU in 2020 for the treatment of primary IgAN.[6]

Patient Group

Disease Area and Clinical Need

IgAN is a chronic kidney disease which mainly affects young adults. IgAN is a type of glomerulonephritis (inflammation of the glomerulus; the filtering part of the kidney).[7] In IgAN a protein called immunoglobulin A (IgA) becomes trapped in the very fine filters of the kidney (glomeruli), causing damage and scarring to the whole kidney. IgA is normally present in the bloodstream and its main role is to fight infections throughout the body, however, in IgAN patients the body's immune cells produce abnormally formed IgA. It is not yet known why this happens. Around 30% of IgAN patients will go on to lose kidney function and

will require a transplant or life on dialysis. IgAN may be undetected for several years as it commonly does not cause any obvious symptoms, however, some common finding are; blood in urine (haematuria), protein in urine (proteinuria), high blood pressure and high levels of creatine in blood.[8]

IgAN is the most common glomerulonephritis worldwide, but its true prevalence is hard to estimate and is confounded by differing biopsy practice across the world.[9] A systematic review of biopsy-based studies spanning multiple countries suggests an overall incidence of at least 2.5 per 100,000.[10] The exact prevalence of primary IgA nephropathy in England is uncertain, however, it is estimated that around 4 in 10,000 people have the condition in Europe.[11]

Recommended Treatment Options

There are currently no non-immunosuppressive pharmaceutical options approved for the treatment of IgAN. There is no cure for IgAN and no published NICE guidance for the management of the condition. The aim of current treatment is to treat proteinuria and prevent or delay kidney failure and associated complications.[12]

Modified release budesonide has been approved by the MHRA for the treatment of primary IgAN in adults at risk of rapid disease progression with a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/gram.[13]

Clinical Trial Information

Trial	**PROTECT,** NCT03762850, EudraCT 2017-004605-41; A Randomized, Multicenter, Double-blind, Parallel-group, Active-control Study of the Efficacy and Safety of Sparsentan for the Treatment of Immunoglobulin A Nephropathy **Phase III** – Active, not recruiting **Locations:** 11 EU countries, UK, USA and other countries. **Primary completion date:** August 2023
Trial Design	Randomised, parallel assignment, double-blinded, quadruple-masked
Population	N=308 (estimated); biopsy-proven primary IgAN; aged 18 years and older with an estimated glomerular filtration rate (eGFR) of at least 30 mL/min per 1·73m² and proteinuria of 1 g/day or higher
Intervention(s)	Sparsentan 400mg daily (oral)
Comparator(s)	Irbesartan 300mg daily (oral)
Outcome(s)	Primary outcome measure: • Urine protein/creatinine ratio (UP/C) at week 36 [Time frame: after the last patient randomised has undergone the week 36 visit] See trial record for full list of other outcomes
Results (efficacy)	At week 36, the geometric least squares mean percent change from baseline in urine protein–creatinine ratio was statistically significantly greater in the sparsentan group (–49·8%) than the irbesartan group (–15·1%), resulting in a between-group relative reduction of 41% (least squares mean ratio=0·59; 95% CI 0·51–0·69; p<0·0001).[14]
Results (safety)	Treatment-emergent adverse events with sparsentan were similar to irbesartan. There were no cases of severe oedema, heart failure, hepatotoxicity, or

	oedema-related discontinuations. Bodyweight changes from baseline were not different between the sparsentan and irbesartan groups.[14]

Estimated Cost

The cost of sparsentan was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Targeted-release budesonide for treating IgA nephropathy (GID-TA11028). Expected January 2024.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. 2021.[15]

Additional Information

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