Health Technology Briefing
September 2024

Sibeprenlimab for treating Immunoglobulin A Nephropathy

Company/Developer	Otsuka Pharmaceutical Co Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29860	NICE ID: NA	UKPS ID: 674082

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Sibeprenlimab is in clinical development for the treatment of adults with Immunoglobulin A Nephropathy (IgAN). IgAN is a chronic kidney disease with a mean age of diagnosis of 42 years in adult patients. 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 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. At present, there are no approved treatments for IgAN that do not involve immunosuppression. There is therefore an unmet need to develop new well-tolerated, effective treatment options for IgAN.

Sibeprenlimab is a specially designed protein that can target and bind to specific molecules in the body. In this case, sibeprenlimab binds to and blocks a specific signalling molecule called APRIL (A Proliferation-Inducing Ligand). By stopping APRIL, sibeprenlimab reduces the build-up of the protein IgA in the kidneys, which can help prevent further damage. By stopping the effects of APRIL, sibeprenlimab is expected to help in reducing the presence of an abnormal amount of protein in the urine, which prevents the complications in patients with the condition. Sibeprenlimab is administered under the skin. If approved, Sibeprenlimab would be the first monoclonal antibody treatment for IgAN that offers lasting benefits and a good safety record for patients.

Proposed Indication

Treatment of Immunoglobulin A Nephropathy (IgAN) in adult patients[1]

Technology

Description

Sibeprenlimab (VIS649)[1] is an investigational drug designed to treat IgAN, also known as Berger's disease. It is administered through subcutaneous routes. This humanised immunoglobulin G2 (IgG2) monoclonal antibody, developed using hierotope technology, targets the cytokine A Proliferation Inducing Ligand (APRIL).[2] APRIL acts through the following two receptors: the transmembrane activator and calcium-modulator and cytophilin ligand interactor and the B cell maturation antigen.[3] APRIL induces B cell class switching to IgA production by the transmembrane activator and calcium-modulator and cytophilin ligand interactor signalling and promotes mature plasma cell survival by B cell maturation antigen signalling. APRIL may also enhance T-cell–independent immune responses, modulate IgA production in the mucosa, and play a direct role in Gd-IgA1 production by reprogramming the glycosylation machinery in autoantigen-reactive B cells. Thus, APRIL is a valid potential target for IgAN therapy.[4] By blocking APRIL, sibeprenlimab helps regulate IgA production, including the harmful galactose-deficient IgA1 (Gd-IgA1).[5] Sibeprenlimab significantly reduces proteinuria in patients with high-risk IgAN.[6]

Sibeprenlimab is currently in clinical development for the treatment of IgAN. In the phase III clinical trial (NCT05248646), adult patients with IgAN who are already on maximally tolerated standard-of-care therapy receive sibeprenlimab. The treatment involves administering a 400 mg subcutaneous dose of sibeprenlimab to adults every four weeks.[1]

Key Innovation

Sibeprenlimab differs from other treatments for IgAN because of its specific mechanism of action and targeted approach. Unlike traditional therapies that primarily focus on managing symptoms or reducing inflammation, sibeprenlimab directly targets the underlying cause of the disease. The key innovation of sibeprenlimab is its ability to inhibit the cytokine, a proliferation-inducing ligand (APRIL; also known as TNFSF13) which is thought to play a key role in the pathogenesis of IgAN.[7] Treatment with sibeprenlimab not only addresses a root cause of IgAN but also offers the potential for more effective and sustained disease management compared to existing treatments.[8] Sibeprenlimab selectively inhibits APRIL and does not affect the level of B-cell activating factor of the tumour necrosis factor α family (BAFF), thus avoiding lymphocyte depletion and its potential consequences. The specificity of sibeprenlimab in targeting APRIL sets it apart, making it a promising option for patients seeking a more precise and potentially more effective treatment for IgAN.[9]

If licenced, sibeprenlimab would offer an additional treatment option for patients with IgAN who currently have limited options.

Regulatory & Development Status

Sibeprenlimab does not currently have marketing authorisation in the EU/UK for any indication.
Sibeprenlimab is not in phase II/III for any other indications.
Sibeprenlimab has the following regulatory designations/awards:

- an EMA Orphan drug designation in 2021 for the treatment of primary IgAN.[10]
- a Breakthrough Therapy by the US FDA for the same condition in February 2024. [11]

Patient Group

Disease Area and Clinical Need

IgAN is a progressive autoimmune kidney disease and a leading cause of glomerular disease that can result in kidney failure (KF). The median age at diagnosis is 35 to 37 years and approximately 50% of patients will progress to KF within 20 years.[12] 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 findings are; blood in urine (haematuria), protein in urine (proteinuria), high blood pressure and high levels of creatine in blood.[13]

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.[14] A systematic review of biopsy-based studies spanning multiple countries suggests an overall incidence of at least 2.5 per 100,000.[15] Based on high-quality data from European national registries, IgAN point prevalence was estimated at 2.53 per 10,000 in patients of all ages. Prevalence was considerably lower in paediatric and elderly populations.[16] In the UK, IgAN affects around 1 in 50,000 people. It is one of the most common causes of chronic kidney disease and kidney failure. Men are more likely to be affected than women.[17]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following regimen for treating the adult patients with IgAN:[18]

- Targeted-release budesonide is recommended as an option for treating IgAN when there is a risk of rapid disease progression in adults with a urine protein-to-creatinine ratio of 1.5 g/g or more.
- Targeted-release budesonide is recommended only if:
  • it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) unless these are contraindicated.
- the company provides it according to the commercial arrangement.

Clinical Trial Information

Trial	NCT04287985, 2019-002531-29; A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in Participants With Immunoglobulin A (IgA) Nephropathy **Phase II -** Completed **Location(s):** Spain, UK, USA, Canada, and other countries **Study completion date:** June 2023
Trial Design	Randomised, parallel assignment, quadruple blinded (participant, care provider, investigator, outcomes assessor).
Population	N=155; Participants (male/female) aged 18 years and older, with biopsy-confirmed IgAN, who have medical records showing they have been on stable and maximally tolerated doses of either ACEI (Angiotensin-Converting Enzyme

	Inhibitor) or ARB (Angiotensin Receptor Blocker), as per local SOC (Standard of Care) and applicable guidelines, for at least 3 months preceding screening.
Intervention(s)	○ Low Dose-VIS649 (dose level = low (2mg/kg) ○ Medium Dose-VIS649 (dose level = medium (4mg/kg) ○ High Dose-VIS649 (dose level = high (8mg/kg)
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Safety assessment [Time frame: 12 months] Incidence of adverse events graded by severity • Efficacy Objective--effect on Proteinuria of repeated doses of VIS649 added to SOC (ACEI/ARB therapy) vs. SOC [Time Frame: 12 months] Change from baseline in uPCR (Urine protein/creatinine ratio) measured on natural log scale from 24-hour urine collection. See trial record for full list of other outcomes.
Results (efficacy)	In patients with IgAN, 12 months of treatment with sibeprenlimab resulted in a significantly greater decrease in proteinuria than placebo. At 12 months, the geometric mean ratio reduction (±SE) from baseline in the 24-hour urinary protein-to-creatinine ratio was 47.2±8.2%, 58.8±6.1%, 62.0±5.7%, and 20.0±12.6% in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups and the placebo group, respectively.[5]
Results (safety)	The incidence of adverse events that occurred after the start of administration of sibeprenlimab or placebo was similar in both groups. The most common adverse events were Covid-19, pyrexia, nasopharyngitis, upper respiratory tract infection, headache, hypertension, diarrhoea, and muscle spasm. No increased risk of infection was observed.[5]

Trial	NCT05248646; A Phase 3, Multicentre, Randomised, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy **Phase III** - Active, not recruiting **Location(s): Two EU countries,** USA, UK, Canada, and other countries. **Primary Completion date:** December 2026
Trial Design	Randomised, parallel assignment, double blinded (participant, investigator)
Population	N = 530; Participants (male/female) aged 18 years and older, with biopsy-confirmed IgAN
Intervention(s)	○ Sibeprenlimab 400 mg (subcutaneously, every 4 weeks)
Comparator(s)	• Matched placebo
Outcome(s)	Primary outcome measure: • Urinary protein to creatinine ratio (uPCR) in a 24-hour collection [Time Frame: At 9 months]

	See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT05248659, 2021-005526-17; A Phase 2/3, Multicentre, Open-label Extension Trial to Evaluate the Long-term Safety, Tolerability, and Efficacy of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy **Phase II/III** - Enrolling by invitation **Location(s):** USA and other countries **Primary Completion date:** Dec 2028
Trial Design	Single group assignment, open label
Population	N = 600; Participants (male/female) aged 18 years and older, who completed Trial 417-201-00007 or VIS649-201 without safety concerns and who, in the opinion of the investigator, could potentially benefit from treatment with sibeprenlimab.
Intervention(s)	• Sibeprenlimab 400 mg administered subcutaneously. (Q4weeks)
Comparator(s)	-
Outcome(s)	Primary outcome measure: • Adverse Events [Time Frame: From baseline to the end-of-trial visit in Week 112.] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of sibeprenlimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Sparsentan for treating primary IgA nephropathy [GID-TA11359]. Expected April 2025
- NICE Technology appraisal guidance. Targeted-release budesonide for treating primary IgA nephropathy [TA937]. December 2023.

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[19]

Additional Information

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