NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
June 2024

Targeted-release budesonide for treating primary IgA nephropathy

Company/Developer	STADA Arzneimittel AG

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 38775	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Targeted-release budesonide is in clinical development for the treatment of primary immunoglobulin A (IgA) nephropathy (IgAN). IgAN is one of the most common causes of chronic kidney disease and kidney failure and is caused by the immune system (the body's natural defences) producing a faulty version of an antibody, which is a protein, called IgA. This causes IgA to build up in small blood vessels in the kidney, called glomeruli, that filter the blood. This damages the glomeruli and makes them leak blood and protein into the urine. Primary IgAN is a long-term debilitating and life-threatening disease with no obvious underlying cause which causes the kidneys to gradually stop working properly and can eventually fail. Current treatment options are focused on management as there is no cure, therefore there remains a need for effective treatment options for patients with IgAN.

Targeted-release budesonide is administered by oral capsules and is a well-known type of medicine called a corticosteroid. Corticosteroids have a wide range of effects that suppress the immune system. This medicine is designed to travel through the digestive system without being absorbed, reducing systemic side effects, until it reaches the end of the lower small intestine, where it is released and expected to reduce the production of faulty IgA antibodies from immune tissue in the intestine. This is expected to decrease their build-up in the kidneys, reducing damage to the kidneys and slowing disease progression. If recommended, budesonide would be available to a wider patient population with primary IgAN than it is currently licensed for, relieving some of the burdens and side effects that accompany standard care/management.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

For the treatment of adults aged 18 years and older with primary immunoglobulin A (IgA) nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio (UPCR) ≥0.8 g/g).[1,2]

Technology

Description

Targeted-release budesonide (Nefecon, Kinpeygo) is a type of corticosteroid designed to deliver the drug to the Peyer's patch region of the lower small intestine (in the final section of the small intestine), where the disease originates, as per the predominant pathogenesis models.[3,4] Targeted-release budesonide is derived from the TARGIT technology, which allows for the substance to pass through the stomach and intestine without being absorbed, and to be released in a pulse like fashion only when it reaches the lower small intestine.[4] The intended action of targeted-release budesonide is the suppression of mucosal B-cells, located in the Peyer's patches, and inhibition of their proliferation and differentiation into plasma cells that produce mucosal galactose-deficient IgA1 antibodies (Gd-IgA1). Consequently, it is expected that the occurrence of Gd-IgA1 antibodies and formation of immune complexes in the systemic circulation will be suppressed, therefore preventing the downstream effects of glomerular mesangial deposition of immune complexes containing Gd-IgA1, manifesting as glomerulonephritis and loss of renal function.[5]

Targeted-release budesonide is in clinical development for the treatment of primary IgAN. In the phase III clinical trial (NefIgArd, NCT03643965) patients were administered 16mg targeted-release budesonide oral capsules daily for 9 months.[1]

Key Innovation

Currently, there is no available cure for IgAN and there are limited pharmacological options to delay disease progression.[3] If recommended, targeted-release budesonide has the potential to treat primary IgAN and delay disease progression in this patient population, expanding the population eligible to receive treatment for this disease and relieving some of the burdens and side effects that accompany standard care/management. For example, targeted-release budesonide is mainly released in the terminal ileum, reducing IgA production at this site and it is not absorbed systemically to the same extent as prednisolone. It is therefore expected that patients receiving budesonide will experience the side effects associated with prednisolone at a lower frequency and intensity. Indirect estimates suggest that the amount of targeted-release budesonide that is absorbed systemically is equivalent to 5 to 7mg of prednisolone, whereas prednisolone would usually be given at a dose of 40 to 60mg for IgAN. For this reason, clinical experts suggest that the serious side effects of prednisolone such as loss of bone mineral density are not expected with targeted-release budesonide.[3] Another advantage of using this active substance is that it has very low bioavailability, i.e. around 90% of it is inactivated in the liver before it reaches the systemic circulation. This means that a high concentration can be applied locally where needed but with only very limited systemic exposure and side effects.[4] The findings from the phase III NefIgArd trial (NCT03643965) indicated that targeted-release budesonide has the potential to be the first disease-modifying therapy for primary IgAN to preserve kidney function and slow disease progression.[6]

Regulatory & Development Status

Targeted-release budesonide currently has Marketing Authorisation in the EU/UK for the treatment of primary IgAN in adults at risk of rapid disease progression with a UPCR ≥1.5 g/gram.[7]

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Budesonide has the following regulatory designations/awards:[4,8]

- Orphan drug designation in the EU in 2016 for the treatment of primary IgAN
- Accelerated Assessment Procedure in the EU in 2021 for the treatment of IgAN

Targeted-release budesonide is not currently in phase II/III trials for any other indications.[9]

Patient Group

Disease Area and Clinical Need

IgAN is a progressive chronic kidney disease (CKD) which mostly affects young adults.[3,10] It is caused by IgA antibodies building up in the kidney causing inflammation and scarring, which can lead to kidney failure (end-stage renal disease). In primary IgAN there is no obvious underlying cause, but genetic and environmental factors such as exposure to toxins are thought to be contributing factors in some cases. Disease progression is defined by estimated glomerular filtration rate (eGFR)-based CKD stages. The eGFR shows how well the kidneys are filtering waste products from the body. eGFR is categorised from stage 1 (eGFR of more than 90 ml/min/1.73 m^2), defined as no reduction in kidney function, to stage 5 (eGFR of less than 15 ml/min/1.73 m^2), defined as kidney failure. Progression to kidney failure typically happens at a substantially earlier age with IgAN than other types of CKD, although the disease can be highly variable. In most people, IgAN progresses to kidney failure within 10 to 15 years after diagnosis, with higher proteinuria (high levels of protein in urine) being a key risk factor for faster progression.[3]

IgAN can have a broad range of symptoms such as bone and joint pain, fatigue, muscle weakness, blood and/or protein in urine, high blood pressure and swelling in different parts of the body.[3,10] As the condition progresses, CKD and associated infections can lead to hospitalisation or emergency department visits. A high risk of certain comorbidities has also been reported for people with IgAN, including an increased risk of future ischaemic heart disease. People with IgAN can spend a significant amount of time in hospital, especially when having dialysis. This can substantially limit the person's capacity to stay in work, maintain relationships and fulfil day-to-day responsibilities without support. IgAN is a significant burden for people and can substantially affect both physical and psychological aspects of quality of life.[3] IgAN affects around 1 in 50,000 people in the UK and is one of the most common causes of CKD and kidney failure.[11] The population likely to be eligible to receive targeted-release budesonide could not be estimated from available published sources.

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommend targeted-release budesonide as an option for treating primary IgAN when there is a risk of rapid disease progression in adults with a UPCR of 1.5 g/g or more. It 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.[12]

Standard treatment for IgAN is not focused on cure, but management by controlling blood pressure and reducing proteinuria to slow the rate of kidney function decline.[3] Initially, lifestyle modifications such as diet control, weight control and smoking cessation are implemented to slow disease progression.[13] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), which are both types of renin-angiotensin-system inhibitors (RASi), are standard care for patients with IgAN who are at risk of kidney failure, and can slow the rate of disease progression.[3,8] Systemic corticosteroids, such as

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prednisolone, can also be used to treat IgAN, however these are infrequently used in the UK because they have an unfavourable risk to benefit profile.[3]

Clinical Trial Information

Trial	**NefIgArd; NCT03643965, EudraCT 2017-004902-16;** A Randomized, Double-blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy at Risk of Progressing to End-stage Renal Disease (NefIgArd) **Phase III** – Completed **Location(s):** 10 EU countries, UK, USA, Canada, and other countries **Primary completion date:** July 2023
Trial Design	Randomised, double-blind, parallel assignment
Population	N=365 (actual); patients aged 18 years and older with primary IgAN
Intervention(s)	Budesonide 16mg oral capsules administered daily for 9 months
Comparator(s)	Placebo
Outcome(s)	**Primary outcome measures:** • Change in Proteinuria, measured as Urine Protein to creatinine ratio (UPCR) [time frame: 9 months]. The primary outcome measure is UPCR (based on 24-hour urine collections) at 9 months following the first dose of study drug compared to baseline. • Renal function measured as eGFR [time frame: Up to 2 years]. Based on eGFR measure compared to baseline calculated using the CKD-EPI formula. See trial record for full list of other outcomes.
Results (efficacy)	The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with budesonide versus placebo (difference 5·05 mL/min per 1·73 m2 [95% CI 3·24 to 7·38], p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m2 (95% CI −3·88 to −1·02) reported with budesonide and −7·52 mL/min per 1·73 m2 (−8·83 to −6·18) reported with placebo.[6]
Results (safety)	The most commonly reported treatment-emergent adverse events during treatment with budesonide were peripheral oedema (31 [17%] patients, vs placebo, seven [4%] patients), hypertension (22 [12%] vs six [3%]), muscle spasms (22 [12%] vs seven [4%]), acne (20 [11%] vs two [1%]), and headache (19 [10%] vs 14 [8%]). No treatment-related deaths were reported.[6]

Estimated Cost

The NHS indicative price of budesonide is £4,681.24 for a 120-pack of 4-mg modified-release capsules (hospital only).[14]

Relevant Guidance

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NICE Guidance
• NICE technology appraisal in development. Sparsentan for treating primary IgA nephropathy (GID-TA11359). Expected December 2024. • NICE technology appraisal. 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.[13]

Additional Information

STADA Arzneimittel AG did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *A Randomized, Double-blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients With Primary IgA (Immunoglobulin A) Nephropathy at Risk of Progressing to End-stage Renal Disease (NefIgArd). Trial ID: NCT03643965*. 2018. Status: Completed. Available from: https://clinicaltrials.gov/study/NCT03643965 [Accessed 13 May 2024].

2 European Medicines Agency. *Kinpeygo - opinion on variation to marketing authorisation*. 2024. Available from: https://www.ema.europa.eu/en/medicines/human/variation/kinpeygo [Accessed 18th June 2024].

3 National Institute for Health and Care Excellence (NICE). *Targeted-release budesonide for treating primary IgA nephropathy - 3 Committee discussion (TA937)*. Available from: https://www.nice.org.uk/guidance/ta937/chapter/3-Committee-discussion [Accessed 13 May 2024].

4 Calliditas Therapeutics. EMA Grants Accelerated Assessment Procedure for Nefecon for the Treatment of IgA Nephropathy. Calliditas Therapeutics; 2021. Available from: https://www.calliditas.se/en/ema-grants-accelerated-assessment-procedure-for-nefecon-for-the-treatment-of-iga-nephropathy/ [Accessed 13 May 2024].

5 Electronic Medicines Compendium (eMC). *Kinpeygo 4 mg modified release hard capsules*. 2024. Available from: https://www.medicines.org.uk/emc/product/15393/smpc [Accessed 13 May 2024].

6 Lafayette R, Kristensen J, Stone A, Floege J, Tesař V, Trimarchi H, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA

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nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *The Lancet*. 2023;402(10405):859-70. Available from: https://doi.org/10.1016/S0140-6736(23)01554-4.

7 National Institute for Health and Care Excellence (NICE). *Targeted-release budesonide for treating primary IgA nephropathy - 2 Information about targeted-release budesonide (TA937)*. Available from: https://www.nice.org.uk/guidance/ta937/chapter/2-Information-about-targeted-release-budesonide [Accessed 13 May 2024].

8 European Medicines Agency (EMA). *EU/3/16/1778 - orphan designation for treatment of primary IgA nephropathy - Budesonide*. 2016. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-16-1778 [Accessed 13 May 2024].

9 ClinicalTrials.gov. *Showing results for: Other terms: nefecon OR Kinpeygo OR PL-56 | Phase: 2, 3*. Available from: https://clinicaltrials.gov/search?term=nefecon%20OR%20Kinpeygo%20OR%20PL-56&aggFilters=phase:2%203 [Accessed 13 May 2024].

10 Kidney Research UK. *IgA nephropathy (IgAN)*. Available from: https://www.kidneyresearchuk.org/conditions-symptoms/iga-nephropathy/ [Accessed 14 May 2024].

11 Kidney Care UK. *IgA nephropathy*. 2023. Available from: https://kidneycareuk.org/kidney-disease-information/kidney-conditions/iga-nephropathy/ [Accessed 14 May 2024].

12 National Institute for Health and Care Excellence (NICE). *Targeted-release budesonide for treating primary IgA nephropathy - 1 Recommendations (TA937)*. Available from: https://www.nice.org.uk/guidance/ta937/chapter/1-Recommendations [Accessed 17 May 2024].

13 Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney International*. 2021;100(4):S1-S276. Available from: https://doi.org/10.1016/j.kint.2021.05.021.

14 British National Formulary. *Budesonide - Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/budesonide/medicinal-forms/ [Accessed 20 June 2024].

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