Calliditas Therapeutics
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Breaking new ground with a late-phase rare-disease pipeline

With its lead phase 3 candidate Nefecon in development for the treatment of primary immunoglobulin A nephropathy and a late-stage orphan focused NOX program, Calliditas Therapeutics is pioneering new rare-disease therapies.

Calliditas Therapeutics has broken new ground throughout its history. Having been the first company to deliver positive phase 3 data in the rare disease immunoglobulin A nephropathy (IgAN), Calliditas is awaiting regulatory approval decisions in the US and European Union (EU) on its novel therapeutic, which has the potential of being disease-modifying, addressing a significant unmet medical need in this indication. Calliditas is advancing its lead program while continuing to innovate with a second late-stage program in another orphan indication.

Lead candidate Nefecon (a targeted-release budesonide formulation) is positioned, if approved, to transform the treatment of IgAN. Today, the 130,000–150,000 people estimated to suffer from this kidney disease in the US lack any approved therapies. Over time, these patients' kidneys lose their ability to remove waste products from the blood, putting up to 50% of them at risk of developing end-stage renal disease (ESRD) and thus requiring hemodialysis or kidney transplantation within 20 years.

With its ground-breaking work on the early development of the framework supporting proteinuria as a surrogate endpoint for accelerated/conditional approval, Calliditas has assisted in advancing the entire field of IgAN research. The link between reduction in urine protein levels and the subsequent impact on estimated glomerular filtration rate (eGFR) provided a promising framework that could help support accelerated approval in IgAN, to address a pressing need perceived in a nephrology community where few therapeutics have been approved over the last 15 years.

Targeting the disease origin

Although other therapeutic avenues are being explored, Nefecon continues to lead the way with a unique and differentiated proposed mechanism of action, which targets what the predominant theory identifies as the origin of the disease. While IgAN manifests through problems in the kidneys, the disease is believed to originate in the small intestine. Specialized lymphoid tissue in the ileum, called Peyer's patches, act as sites of B lymphocyte differentiation which leads to the production of pathogenic secretory IgA1 antibodies. In IgAN patients, these IgA antibodies enter systemic circulation where their presence triggers an autoimmune response and leads to the formation of immune complexes that deposit in the kidneys.

Nefecon is designed to deliver budesonide, a potent immunosuppressant, to the Peyer's patches to prevent the formation of pathogenic IgA1 and stop the disease at its source, setting the drug apart from other candidates that try to treat patients systemically (Fig. 1).

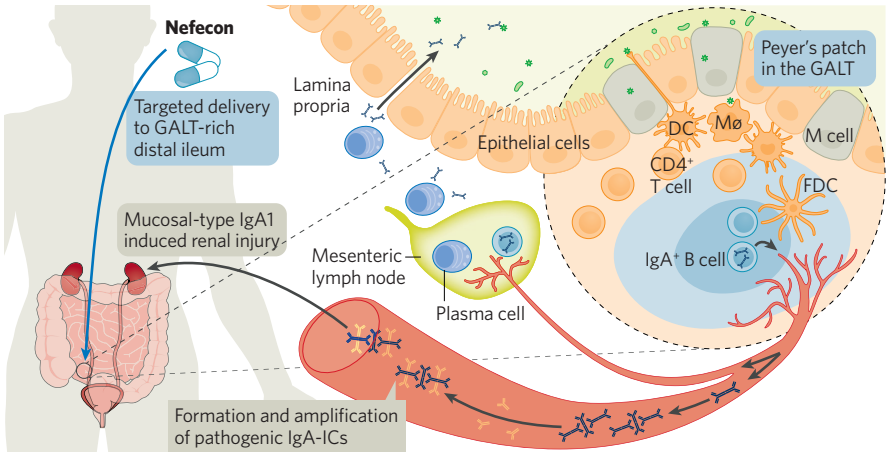

Fig. 1 | Treating patients with IgAN with Nefecon. Nefecon is designed to deliver budesonide to the Peyer's patches to prevent the formation of immunogenic IgA1 antibodies that, in patients with IgAN, lead to disfunction in the kidney. DC, dendritic cell; FDC, follicular dendritic cell; GALT, galactose-1-phosphate uridyl transferase; IgA, immunoglobulin A; IC, immune complex; M cell, microfold cell.

Calliditas has generated substantial clinical data supporting its novel approach. Calliditas became the first company to meet primary and key secondary endpoints in a controlled, large IgAN phase 2b trial, providing evidence that treatment with Nefecon led to a significant reduction in proteinuria levels and a stabilization of kidney function after nine months of treatment. Then, Calliditas delivered the first phase 3 trial in the indication to meet primary and key secondary endpoints, again providing evidence of Nefecon's potential to significantly reduce proteinuria and to stabilize kidney function during treatment in 199 adult patients who received the drug candidate for nine months.

Having generated these positive data, Calliditas filed for accelerated approval in the US and conditional marketing authorization in the EU. Subject to approval, Calliditas will launch Nefecon in the US early in 2022 and targets an entry into the EU market through partner STADA around the middle of the year.

Expanding the pipeline

In the second half of 2020, Calliditas positioned itself to deliver breakthrough drugs in other orphan indications by acquiring a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) inhibition platform. The acquisition sets Calliditas up to continue to innovate, as it is about to become the first company to run a pivotal trial with this new drug class.

Calliditas' lead NOX inhibitor, setanaxib, targets key drivers of fibrogenesis in multiple organs and has already generated promising clinical data in a phase 2 trial in primary biliary cholangitis (PBC). Building on these early data, Calliditas is starting a phase 2b/3 study in patients with PBC. The clinical trial will assess the ability of setanaxib, which has recently received US Food and Drug Administration fast track designation in PBC, to reduce biomarker parameters associated with the disease and its effect on fatigue—the symptom that has one of the biggest negative impacts on patients' quality of life.

The pivotal PBC clinical trial is targeting a Q4 start. Calliditas also plans to run a phase 2 trial in head and neck cancer with setanaxib while exploring various kidney indications. NOX enzymes have been implicated in multiple pathophysiological processes, and the wide breadth of indications in which NOX inhibitor therapies are being explored speaks to the potential of this new class of drugs.

The name 'Nefecon' refers to Calliditas' investigational, delayed release formulation of budesonide. Nefecon is an investigational product and is not approved for use by any regulatory authority.

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