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HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Voclosporin for lupus nephritis

NIHRIO ID	11906	**NICE ID**	9972
Developer/Company	Aurinia Pharmaceuticals	**UKPS ID**	659969

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Voclosporin is in clinical development for the treatment of lupus nephritis (LN). LN is a complication of systemic lupus erythematosus (SLE) which is a chronic autoimmune disease. LN is related with an increased risk of premature death and sufferers can experience symptoms such as high blood pressure, bloody urine, proteinuria and inflammation/scarring of the kidneys as confirmed through a kidney biopsy. If untreated, LN causes permanent renal damage which may lead to end-stage renal disease (ESRD) and subsequent dialysis or kidney transplant. Current therapies have low effectiveness in preventing ESRD and have non-favourable side-effects so additional therapies are required.

Voclosporin, administered orally, is a novel protein inhibitor that prevents the binding of calcineurin which is a protein involved in the immune response. By binding, immune cells cannot be activated which reduces the immune response and stabilises cells in the kidney. If licensed, voclosporin in combination with immunosuppressants will offer an additional treatment aimed to improve the outcomes of LN patients.

PROPOSED INDICATION

Adult patients with active lupus nephritis (LN).[1]

TECHNOLOGY

DESCRIPTION

Voclosporin (ISA247, Lukpynis) is a novel calcineurin inhibitor. It is structurally similar to cyclosporin-A (CsA) except for a modification of a functional group on amino acid–1 of the molecule. Voclosporin is an immunosuppressant, with a synergistic and dual mechanism of action. By inhibiting calcineurin, voclosporin blocks IL-2 expression and T-cell mediated immune responses and stabilizes the podocyte in the kidney.[2]

In the phase III clinical trial (AURORA, NCT03021499), voclosporin was administered orally in 23.7mg doses, twice daily.[1]

INNOVATION AND/OR ADVANTAGES

In phase III trials, patients treated with voclosporin in combination with mycophenolate mofetil (MMF) and rapidly tapered low dose steroids had a significantly higher complete renal response rate, compared with placebo (73 [41%] of 179 patients *vs* 40 [23%] of 178 patients; OR 2·65; 95% CI 1·64–4·27; p<0·0001). More patients in the voclosporin group than in the placebo group achieved an Urine protein / creatinine ratio (UPCR) of 0.5mg/mg or less (116 [65%] of 179 patients vs 78 [44%] of 178 patients) and the time to reach this threshold was significantly shorter for the voclosporin group (p<0.001). (UPCR is a standard measurement used to monitor proteinuria).[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Voclosporin has been studied in phase II/III clinical trials for dry eye disease, psoriasis and in kidney transplantation.[3]

PATIENT GROUP

DISEASE BACKGROUND

Lupus nephritis (LN) is a frequent renal complication of systemic lupus erythematosus (SLE) which occurs in approximately 33% of SLE patients.[4] SLE is a chronic, multifaceted, autoimmune disease which is characterised by loss of self-tolerance to nuclear autoantigens leading to lymphoproliferation, autoantibody production, immune complex disease and multi-organ tissue inflammation.[5] LN occurs when there is renal involvement in the SLE disease course, which can range from low levels of proteinuria (protein in urine) to acute glomerulonephritis (inflammation of the glomeruli in the kidney)and renal failure.[6]

LN is associated with high blood pressure, haematuria (blood in urine), proteinuria and inflammation / scarring of the kidneys as confirmed through a kidney biopsy and is associated with increased risk of premature death. The usual disease course of LN involves a number of flares of disease and subsequent periods of quiescence.[7] Patients can experience symptoms

such as oedema (swelling) mainly in the extremities or the eyes, foamy urine, increased urination and high blood pressure. If untreated, LN causes permanent renal damage which may lead to end-stage renal disease (ESRD). If a patient develops ESRD or kidney failure, they would require regular dialysis or a kidney transplant.[8]

While the specific mechanisms of pathogenesis are still being elucidated, studies have shown that immune complex deposition, complement pathway activation and local inflammatory responses from renal cells play a role in LN development.[7] Immune complex deposits in glomerular areas consisting of immunoglobulins are a diagnostic hallmark of LN and activate local proinflammatory effects in renal cells. This inflammation damages the kidney and can lead to glomerulonephritis and nephrotic syndrome. Additionally, immune complex deposition activates the complement system which directly causes renal inflammation and immunopathology.[5]

Patients with LN have poorer quality of life than those with SLE but without LN, with disease symptoms, medication, emotional health, body image and life goals being specific areas of concern amongst this patient group.[9]

CLINICAL NEED AND BURDEN OF DISEASE

Gender is considered one of the strongest risk factors for the development of SLE. Around 90% of studies containing SLE patients contain all-female populations and the incidence of SLE in females is approximately 5.8 times higher than that of males (8.34 per 100,000 per year for females compared to 1.44 per 100,000 per year for males). In a retrospective cohort study that included data from 1999 to 2012, the incidence of SLE peaked in females aged 40-49 years, whereas the peak age in males was 60-69 years..[10,11]

In 2012, the prevalence of SLE was 97 per 100,000 people in the UK.[11] Of these people, approximately one third will develop LN throughout the disease period.[4] Based on the population estimates for the UK (mid-2019), the number of expected adult patients with diagnosed LN is 16,548.[12]

Using 2019/20 hospital episode statistics, SLE (ICD-M32) accounted for 6,644 finished consultant episodes (FCE), 5,982 admissions and 7,584 FCE bed days.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main goal for managing and treating LN is to reduce proteinuria in order to preserve long-term renal function, prevent flare of disease, avoid treatment-related side effects and improve patient quality of life. It is recommended that LN patients are treated in specialist healthcare centres by a nephrologist or experienced rheumatologist.[14]

CURRENT TREATMENT OPTIONS

There is no current licensed standard of care in the UK for LN. Patients are treated with products off label such as corticosteroids, calcineurin inhibitor drugs (cyclosporine, tacrolimus), cyclophosphamide, mycophenolate mofetil (MMF), rituximab or belimumab.

In patients that do not respond to treatment and develop ESRD, it is possible to ameliorate symptoms with dialysis and/or renal transplantation.[4,14]

PLACE OF TECHNOLOGY

If licensed, voclosporin will offer an additional treatment to the current standard of care for adult patients LN.

CLINICAL TRIAL INFORMATION

Trial	**AURORA 1; NCT03021499;** A randomized, controlled double-blind study comparing the efficacy and safety of voclosporin (23.7 mg twice daily) with placebo in achieving renal response in subjects with active Lupus Nephritis **Phase III** - completed **Location(s):** 4 EU countries, USA, Canada and other countries **Study completion date:** October 2019
Trial design	Randomized, parallel assignment, quadruple-blinded, placebo-controlled
Population	N= 357; 18-75 years old; evidence of active nephritis
Intervention(s)	Voclosporin 23.7mg twice daily (BID), orally + Mycophenolate Mofetil and oral steroids
Comparator(s)	Matched placebo
Outcome(s)	The number of subjects achieving renal response [Time frame: 52 weeks] See trial record for full list of other outcomes
Results (efficacy)	• The primary endpoint of complete renal response at week 52 was achieved in significantly more patients in the voclosporin group than in the placebo group (73 [41%] of 179 patients vs 40 [23%] of 178 patients; odds ratio 2·65; 95% CI 1.64-4.27; p<0·0001).[15] • Secondary endpoints were achieved in significantly more patients in the voclosporin group than in the placebo group; these included renal response at 24 weeks, partial renal response at 24 weeks, partial renal response at 52 weeks, time to Urine Protein Creatinine Ratio (UPCR) to decrease to 0.5,g/mg or less and time to 50% reduction of UPCR.[1]
Results (safety)	• The adverse event profile was balanced between the two groups; serious adverse events occurred in 37 (21%) of 178 in the voclosporin group and 38 (21%) of 178 patients in the placebo group. • The most frequent serious adverse event involving infection was pneumonia, occurring in 7 (4%) patients in the voclosporin group and in 8 (4%) patients in the placebo group. • A total of six patients died during the study or study follow-up period (one [<1%] patient in the voclosporin group and five [3%] patients in the placebo group).

	None of the events leading to death were considered by the investigators to be related to the study treatments.[15]

Trial	**AURORA 2**; NCT03597464; Aurinia Renal Response in Lupus With Voclosporin. **Phase III** – Active, not recruiting **Location(s):** USA **Primary Completion Date:** August 2021
Trial design	Randomized, parallel assignment, double-blinded, placebo-controlled
Population	N= 216; 18-75 years old; evidence of active nephritis; subjects who have completed 52 weeks of treatment with study drug in the AURORA 1 study
Intervention(s)	Voclosporin 23.7mg twice daily, orally + MMF (1g, BID) + oral steroids
Comparator(s)	Matched placebo
Outcome(s)	• Adverse events (AE) profile and routine biochemical and haematological assessments. [Time frame: 36 months] See trial record for full list of other outcomes
Results (efficacy)	• Mean UPCR at pre-treatment (AURORA 1) baseline was 3.94 mg/mg in the voclosporin arm (n=116) and 3.87 mg/mg in the control arm (n=100). The least squares (LS) mean change in UPCR from pre-treatment baseline to year two was -3.1 mg/mg for the voclosporin arm (n=73) and -2.1 mg/mg for control arm (n=51) • Mean estimated Glomerular Filtration Rate (eGFR) at pre-treatment (AURORA 1) baseline was 79.6 ml/min for the voclosporin arm (n=116) and 78.9 ml/min for the control arm (n=100) and at year two, was 79.0 ml/min for the voclosporin arm (n=73) and 82.9 ml/min for the control arm (n=51). There was a small early decrease in mean eGFR in the first four weeks of treatment (in AURORA 1) after which eGFR remained stable throughout year one and year two.[16]
Results (safety)	There were no unexpected new AEs observed in patients who continued voclosporin treatment compared to control-treated patients for more than one year.[16]

Trial	**AURA-LV; NCT02141672; A randomized, controlled double-blind study comparing the efficacy and safety of voclosporin**

	(23.7 mg BID, or 39.5 mg BID) with placebo in achieving remission in patients with active Lupus Nephritis **Phase II** - completed **Location(s):** 3 EU countries, USA and other countries **Study completion date:** January 2017
Trial design	Randomized, parallel assignment, quadruple-blinded, placebo-controlled
Population	N=265; 18-75 years old; Diagnosis of LN
Intervention(s)	• Voclosporin 23.7 mg BID (low dose) +MMF (1g BID) + oral corticosteroids • Voclosporin 39.5 mg BID (high dose) +MMF (1g BID) + oral corticosteroids
Comparator(s)	Matched placebo
Outcome(s)	• Number of subjects achieving complete renal remission (CRR) at 24 weeks. CRR is defined as confirmed protein/creatinine ratio of ⩽0.5 mg/mg and eGFR ⩾ 60 mL/min/1.73m2 or no confirmed decrease from baseline in eGFR of ⩾20%. Subjects who receive rescue medication for lupus or ⩾10 mg prednisone for >3 consecutive days or >7 days total from weeks 16-26 will not be considered as achieving complete remission. See trial record for full list of other outcomes
Results (efficacy)	• CRR at week 24 was achieved by 29 (32.6%) subjects in the low-dose voclosporin group, 24 (27.3%) subjects in the high-dose voclosporin group, and 17 (19.3%) subjects in the placebo group (OR=2.03 for low-dose voclosporin versus placebo). • The significantly greater CRR rate in the low-dose voclosporin group persisted at 48 weeks, and CRRs were also significantly more common in the high-dose voclosporin group compared to placebo at 48 weeks. See trial record for full results.
Results (safety)	There were more serious adverse events in both voclosporin groups, and more deaths in the low-dose group compared to placebo and high-dose voclosporin groups (11.2%, 1.1%, and 2.3%, respectively). See trial record for full results.

ESTIMATED COST

The cost of voclosporin is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Anifrolumab for treating active autoantibody-positive systemic lupus erythematosus. [GID-TA10676]. Expected April 2022.
- NICE technology appraisal guidance in development. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (review of TA397). Expected July 2021.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

NHS England. Clinical Commissioning Policy: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. A13/PS/a. August 2013.

OTHER GUIDANCE

Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. 2020.[14]

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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.