A Phase 2 study evaluating the efficacy and safety of ALXN2050, a complement factor D inhibitor, in patients with immunoglobulin A (IgA) nephropathy or proliferative lupus nephritis (LN)

Abhijit Bapat[1], Katherine Garlo[1], Kara Rice[1], Nader Najafian[1]
[1]Alexion, AstraZeneca Rare Disease, Boston, MA, USA

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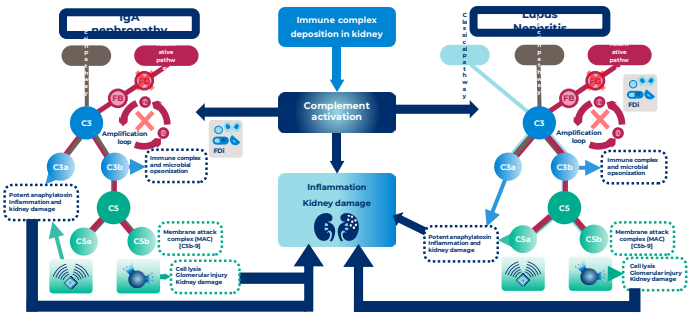
BACKGROUND

- IgA nephropathy and LN are kidney disorders characterized by deposition of immune complexes leading to activation of the complement system.[1–3]
- Complement activation triggers inflammation, and kidney damage **(Figure 1)**.[4–7]

Figure 1: Role of complement in the pathophysiology of IgA nephropathy[a] and LN and hypothesized mechanism of action of vemircopan (ALXN2050) in these disease states



[a]The involvement of classical pathway in pathogenesis of IgA nephropathy is still under investigation and remains to be established.

- Despite treatment, approximately 25–35% of patients with IgA nephropathy, and 10–30% of patients with LN, progress to end-stage kidney disease, and both diseases are associated with significant morbidity and mortality.[1,2,8–11]
- Vemircopan (ALXN2050) is an oral, small molecule complement factor D inhibitor (FDi). Factor D inhibition acts upstream in the complement cascade providing proximal complement inhibition that blocks formation of both C3 and C5 with potentially rapid-onset of anti-inflammatory effects that may halt kidney damage **(Figure 1)**.[6,8]

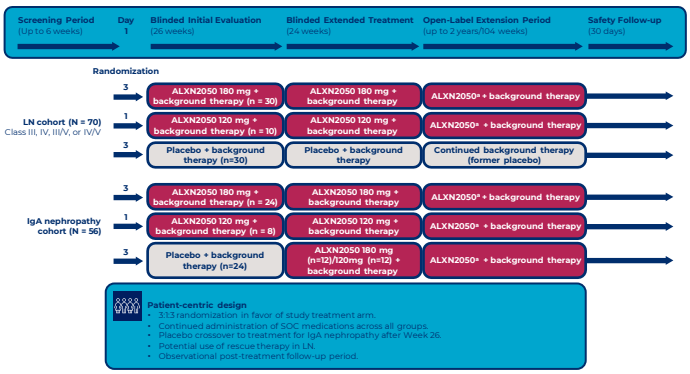
OBJECTIVE

- This global, multicenter, Phase 2 study (NCT05097989) will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of ALXN2050 in adults with IgA nephropathy and LN, and demonstrate proof-of-concept for the efficacy of Factor D inhibition in IgA nephropathy and LN.

STUDY DESIGN

- This is a Phase 2, dose-finding, double-blind, placebo-controlled, multicenter study of ALXN2050 administered orally, in addition to background therapy consistent with SOC, compared to placebo in 126 adult participants (18–75 years of age) with IgA nephropathy or LN.
- This study is **actively recruiting**.
- Key study design elements are shown in **Figure 2**.

Figure 2: Study design



[a]Randomization will be stratified by whether corticosteroid treatment was initiated prior to screening vs. during screening (LN) or by mean proteinuria (1–2 g/day vs. >2 g/day) based on two valid 24-hour urine collections during screening (IgA nephropathy); [b]**Background therapy consists of corticosteroids and mycophenolate mofetil (LN) or stable, maximally tolerated dose of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (IgA nephropathy);** [c]Optimal dose will depend on the results of the Week 26 primary analysis.

KEY ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

Both cohorts

- Aged 18–75 years.

LN cohort

- Diagnosis of 2018 Revised ISN/RPS classification of active focal or diffuse proliferative LN Class III/IV confirmed by kidney biopsy within 6 months prior to screening/during screening period. Participants may co-exhibit Class V disease.
- Clinical diagnosis of SLE by 2019 ACR/EULAR criteria.
- Clinically active LN, requiring/receiving immunosuppression induction treatment.
- Proteinuria with UPCR ≥1 g/g based on one 24-hour urine collection during the screening period.

IgA nephropathy cohort

- Diagnosis of IgA nephropathy based on kidney biopsy at any time or during screening.
- Presence of hematuria as defined by 1+ blood based on urine dipstick or ≥10 red blood cells/HPF microscopy on urine sediment during screening period (only applicable if diagnostic biopsy is >2 years prior to screening).
- On stable, optimal dose of RAS inhibitor treatment for ≥3 months prior to screening.
- Controlled and stable blood pressure for past 3 months (<140/90 mmHg).
- Mean proteinuria ≥1 g/day on two complete and valid 24-hour urine collections during the screening period.

KEY EXCLUSION CRITERIA

Both cohorts

- eGFR <30 mL/min/1.73 m^2.
- 50% interstitial fibrosis, tubular atrophy, glomerular sclerosis, or crescent formation in glomeruli on most recent kidney biopsy.
- BM insufficiency (ANC <1.3 x 10^3/L; platelets <50,000/mm^3).

IgA nephropathy cohort

- Secondary etiologies of IgA nephropathy.

STUDY ENDPOINTS

PRIMARY ENDPOINT

- Percentage change in proteinuria from baseline to Week 26 based on 24-hour urine collections.

SECONDARY ENDPOINTS (BOTH COHORTS)

- Percentage change in proteinuria from baseline to Week 50 based on 24-hour urine collections.
- Change in eGFR from baseline at Weeks 26 and 50.
- Percentage of participants with >30% and >50% reduction in proteinuria at Weeks 26 and 50.

SECONDARY ENDPOINTS (LN COHORT)

- Percentage of patients meeting the criteria for complete and/or partial renal response.[a,b]
- Percentage of patients achieving corticosteroid taper to 7.5 mg/d.
- Percentage of patients with renal flare and extrarenal flare.

SECONDARY ENDPOINT (IGA NEPHROPATHY COHORT)

- Percentage of patients meeting criteria for partial remission, defined as mean proteinuria <1g/ 24 hours based on two valid 24-hour urine collections obtained within 2 weeks of study visit (Weeks 26 or 50).

EXPLORATORY BIOMARKER ENDPOINTS

- Complement split products in the blood, urine, and kidney biopsy histology at Weeks 26 and 50.

[a]CRR (LN cohort) was defined as meeting all three of the following criteria: 1) a decrease in mean UPCR to ≤0.5 g/g based on two valid 24-hour urine collections obtained within 2 weeks prior to study visit (Weeks 26 or 50); 2) eGFR >60 mL/min/1.73m^2 or no decrease of ≥20% from baseline based on the mean of two values, the first value must be obtained within 2 weeks prior to study visit (Weeks 26 or 50); 3) no treatment failure, defined as receipt of rescue therapy at anytime during the study for protocol defined renal flare or severe extrarenal SLE flare; [b]PRR (LN cohort) was defined as participants who did not achieve CRR and met the following criteria: 1) a decrease in mean UPCR ≥ 50% compared with baseline based on two valid 24-hour urine collections collected within 2 weeks prior to study visit (Weeks 26 or 50); 2) eGFR >60 mL/min/1.73m^2 or no reduction ≥20% from baseline based on the mean of two values, the first value must be obtained within 2 weeks prior to study visit (Weeks 26 or 50); 3) no treatment failure.

CONCLUSIONS

- **This trial is actively recruiting.**
- **Complement activation plays an important role in the pathophysiology of IgA nephropathy and LN.**
- **Data from this Phase 2 study will inform the potential of alternative pathway inhibition, and Factor D inhibition in particular, to treat IgA nephropathy and LN and guide the design of future studies.**

For additional information please contact Dr. Abhijit Bapat, Senior Medical Director at Abhijit.Bapat@alexion.com

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ACR, American College of Rheumatology; CRR, complete renal response; eGFR, estimated glomerular filtration rate; EULAR, European League Against Rheumatism; HPF, high power field; IgA nephropathy, immunoglobulin A nephropathy; ISN, International Society of Nephrology; LN, lupus nephritis; SOC, standard of care; RAS, renin-angiotensin-system; RPS, Renal Pathology Society; UPCR, urine protein-to-creatinine

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Corresponding author email address: Abhijit.Bapat@alexion.com