Results of Single-Arm, Phase 1b Study of Anti-C1q Treatment (ANX009) Show that the Classical Pathway is a Key Driver of Complement Activation and Consumption in Patients with Active Lupus Nephritis

SA-PO878

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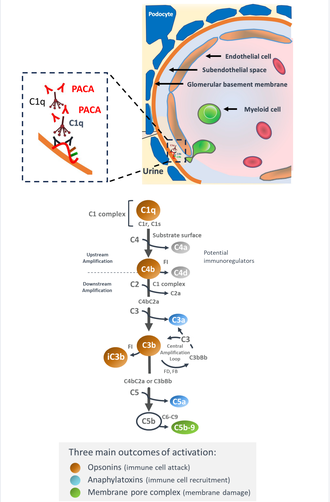
INTRODUCTION

- Lupus nephritis (LN) is an autoantibody-mediated disease involving glomerular deposition of immune complexes
- Hypocomplementemia is a hallmark of LN; however, it is unclear which pathway is the primary driver of pathology
- Circulating immune complexes (ICs) are trapped by the glomerular basement membrane (GBM) within the subendothelial space, activating C1q and the classical complement cascade
- Pathogenic anti-C1q autoantibodies (PACAs), found in >90% of LN patients, can recognize C1q within ICs, in turn recruiting and further amplifying the activation of classical complement in kidney[4]
- C4 cleavage by C1 is the first step in the "upstream" cascade that results in deposition of a covalent opsonin and activation of downstream complement components
- This initiates immune cell recruitment and direct membrane damage
- Plasma measures of classical complement activation (C4d/C4 ratio) strongly correlate with disease activity in LN patients
- We hypothesized that classical complement activity is responsible for hypocomplementemia and surmised that these patients could benefit from anti-C1q therapy (For additional information, see SA-PO931 Chang ASN 2023)[5]
- ANX009 is a subcutaneously administered antigen-binding fragment of a humanized antibody that inhibits C1q interaction with immune complexes and prevents initiation and activation of the complement cascade but leaves lectin and alternative pathway initiation and amplification in place for normal immune function[6]
- This analysis of interim results from LN-01 (NCT05780515) aims to address the hypothesis that upstream classical complement cascade inhibition prevents downstream complement activation/ amplification

Figure 1. A Classical Complement Focused View[1-3]



FD/FB, Factor D/Factor B; PACA, pathogenic anti-C1q autoantibody.

METHODS

- LN-01 is an ongoing, single-arm, phase 1b, nonrandomized open-label study evaluating the safety and tolerability of ANX009 in patients with LN
- Primary and secondary endpoints are the percentage of patients with treatment-emergent adverse events (TEAEs) and change in complement biomarkers, respectively
- Patients with LN were enrolled and underwent an 8-week screening period, an approximately 3-week intervention period, and an 11-week off-treatment follow-up period (**Figure 2**)

Figure 2. Study Schema

EOS, end of study; SC, subcutaneous.

- Patients ≥18 and ≤75 years old meeting the following criteria will be included:
  - Diagnosis of systemic lupus erythematosus (SLE) according to European Alliance of Associations for Rheumatology/ American College of Rheumatology (EULAR/ACR) 2019 Criteria
  - History of International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III or IV with or without Class V glomerulonephritis on renal biopsy within 24 months prior to screening or as performed during screening
  - Proteinuria between ≥0.5 and 3.0 g/g/day assessed via urine protein-creatinine ratio (UPCR) during screening
  - Evidence of classical complement activation at screening
- Patients could continue to receive stable background standard of care for LN and SLE, including mycophenolate mofetil, azathioprine, antimalarials, glucocorticoids, cyclosporin, voclosporin, tacrolimus, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers
- The maximum duration of participation was approximately 23 weeks

RESULTS

- As of July 31, 2023, seven patients underwent safety analysis
  - Five patients were evaluated for changes in complement biomarkers, one of whom discontinued treatment because of an unrelated serious adverse event that disrupted the dosing regimen
  - Two patients completed dosing but have not yet been evaluated for changes in complement biomarkers
- Baseline characteristics in patients evaluated for changes in complement biomarkers are reported on **Table 1**

Table 1. Baseline Characteristics

	Patient 1	Patient 2*	Patient 3	Patient 4	Patient 5
Age, years	64	20	24	32	28
Sex	Female	Male	Female	Female	Female
Body weight, kg	78	60	87	58	51
SLE duration, years	5	2.5	1.8	8.6	2.3
LN duration, years	2.5	2.3	1.8	8.6	2
LN biopsy	Class IV	Class III	Class III	Class IV	Class III
SLEDAI	20	18	8	10	16
Background therapy	MMF, steroids	MMF, CsA, steroids	MMF, steroids	HCQ, AZA, steroids	HCQ, MMF, steroids
UPCR D1 predose, g/g	1.6	1.8	2.4	2.5	1.8
eGFR, mL/min/1.73m^2	65	111	108	101	138
C4d, ng/mL	303	493	265	551	682
C4 (normal: 15-57 mg/dL), mg/dL	18	7.7	13.1	17.8	9.6
C4d/C4 ratio (screening to day 1)	1.7 - 4.4	4.8 -14.9	2.0 - 2.7	3.1 - 8.9	3.9 - 9.2
C3 (normal: 83-193 mg/dL), mg/dL	104	71	89	103	89
Anti-dsDNA (negative: <25 IU), IU	49	523	145	220	356
Anti-C1q	+	+	+	+	+

*Patient 2 discontinued treatment. AZA, azathioprine; CsA, cyclosporine; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; UPCR, urine protein-creatinine ratio.

- Four patients experienced at least one TEAE, two of whom experienced serious adverse events (**Table 2**)

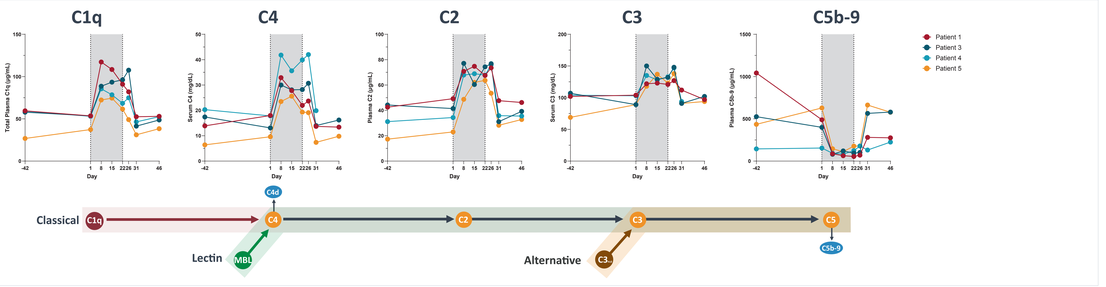
Table 2. Summary of Adverse Events and Compliance

Parameters	n (%) patients
Any TEAE	4 (57)
Drug-related TEAE	4 (57)
SAE	2 (29)
Drug-related SAE	0
Fatal TEAE	0
Injection site reactions*	4 (57)
TEAE leading to treatment discontinuation**	1 (14)
Compliance	94%

*Injection site reactions include injection site swelling, injection site erythema. **Due to non-drug-related SAE; patient completed all protocol-defined study visits. SAE, serious adverse event; TEAEs, treatment-emergent adverse event.

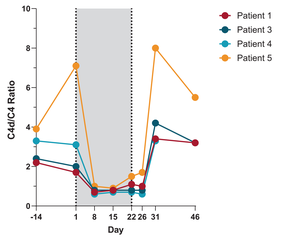
- Four patients experienced TEAEs determined by investigators to be related to ANX009
  - Injection site reactions occurred in four patients, which were erythema or swelling
  - Both patients who experienced mouth ulcers had previous episodes of mouth ulcers
  - The effect of ANX009 exposure on the skin and inhibition of subcutaneous lupus is unknown
- ANX009 resulted in normalization of downstream complement markers of activation and consumption for the entire pathway in all patients (**Figure 3** and **Figure 4**)

Figure 3. ANX009 Prevented Consumption of C1q, C4, C2, and C3 and Decreased MAC C5b-9



MAC, membrane attack complex; MBL, mannose-binding lectin.

Figure 4. ANX009 Decreases C4d/C4 Ratio by Patient

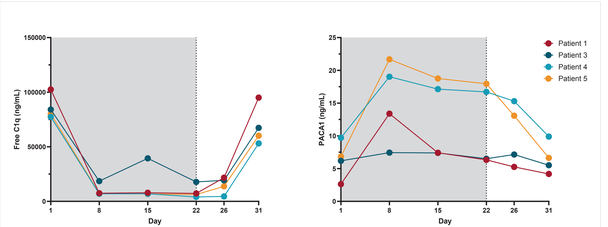


CONCLUSIONS

- **In this interim analysis, ANX009 administered subcutaneously was well tolerated and demonstrated C1q target engagement and complement inhibition in all patients**
- **Inhibition of C1q blocked all downstream markers of consumption and activation, eg, C4, C3, C5, independent of the alternative and lectin pathways. These results indicate that the classical pathway plays a major role in driving the complement-mediated disease process in LN.**
- **PACAs are autoantibodies that exacerbate C1q activity in the kidney, and the results herein suggest that ANX009 prevented kidney deposition of both C1q and PACAs**
- **As anticipated, in a short-term (3-week) study with ANX009, patients did not demonstrate consistent changes in UPCR**
- **These results support further study of anti-C1q therapy in patients with LN**

- ANX009 blocked free C1q and increased free PACA levels in circulation, suggesting inhibition of PACA binding in the kidney (**Figure 5**)

Figure 5. ANX009 Prevented PACA Binding in the Kidney



PACAs, pathogenic anti-C1q autoantibodies.

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DISCLOSURES

YAZ, EC, NY, JL, QC, AM, TY: Employment with and equity ownership in Annexon Biosciences.
JL, CA: Research funding from Annexon Biosciences.
HG: Research funding from Annexon Biosciences, Johnson & Johnson, and Merck.
MT: Research funding from Annexon Biosciences, Astra Zeneca, and Biogen; speakers bureau with Cellrion, Pfizer, and ZP Therapeutics.
YFF: Research funding from Annexon Biosciences paid to institution.
MB: Past employment with and equity ownership in Annexon Biosciences; past employment with and equity ownership in Roche/Genentech.
JO: Employment with and equity ownership in Annexon Biosciences; past employment with FibroGen.
DRA: Employment with and equity ownership in Annexon Biosciences; stock ownership in Bristol-Myers Squibb, Johnson & Johnson, and Merck.
HAK: Employment with and equity ownership in Annexon Biosciences.
MD: Consultancy/advisory role with Annexon Biosciences, AstraZeneca, Aurinia, Biogen, GlaxoSmithKline, and Pfizer; research funding from Annexon Biosciences and GlaxoSmithKline.

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