Safety, Tolerability, and Clinical Pharmacology of ANX009, an Inhibitory Antibody Fab Fragment Against C1q, Administered Subcutaneously to Healthy Volunteers

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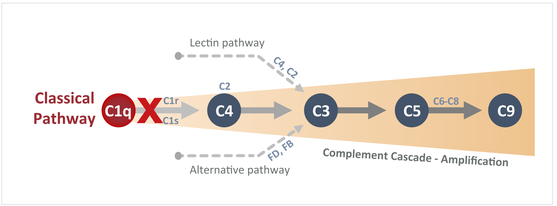
INTRODUCTION

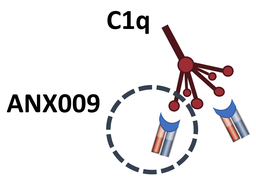
- The complement system is essential for immune response and homeostasis, but aberrant activation of the complement system can drive pathogenesis of several autoimmune, inflammatory, and neurodegenerative diseases[1-4]
- Certain autoantibodies that bind to tissue antigens or that deposit in tissues as a component of immune complexes can activate the classical complement cascade, leading to inflammation and tissue damage[5]

- As the initiating molecule of the classical complement cascade, C1q is an attractive target for preventing complement activation and its multiple tissue-damaging effects
  - Inhibition of C1q blocks initiation of the classical complement cascade
  - Blocking C1q prevents activation of all downstream components of the classical pathway that drive a localized immune response and tissue destruction
- By selectively targeting C1q and only blocking the classical complement pathway, the alternative and lectin pathways are left intact, which is potentially important for maintaining pathogen surveillance



ANX009 was designed to inhibit C1q, the initiating molecule of the classical complement cascade

- ANX009 is a high-affinity antigen binding fragment (Fab) of a humanized antibody against C1q that inhibits C1q substrate interactions and fully blocks activation of all downstream classical complement components
  - While inhibiting the classical cascade, ANX009 leaves the lectin and alternative complement pathways intact for their normal immune functions
- ANX009 is formulated for subcutaneous administration and is designed for treatment of blood-based and vascular antibody-mediated autoimmune diseases, such as autoimmune hemolytic anemia (AIHA), where complement activation is a key component of disease pathology

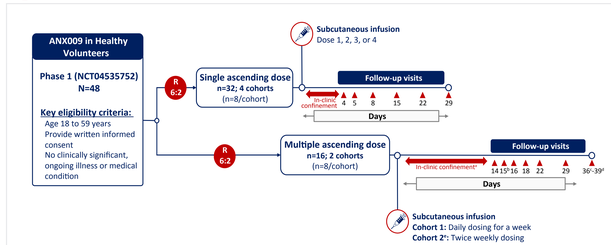


OBJECTIVE

- To demonstrate the safety, tolerability, and clinical pharmacology of ANX009 administered subcutaneously to healthy volunteers

METHODS

Figure 1. Study Schema



[a]In-clinic confinement through day 9 for Cohort 1. [b]Day 15 follow-up only for MAD Cohort 2 participants. [c]Day 36 end of study for MAD Cohort 1. [d]Day 39 end of study for MAD Cohort 2. [e]Subcutaneous infusion sites will be rotated for participants in Cohort 2.
MAD, multiple ascending dose; R, randomization.

- The primary objective is to evaluate the safety and tolerability of ANX009 administered as subcutaneous infusions in normal healthy volunteers
- The secondary objective is to evaluate the pharmacodynamic effect of ANX009 on classical complement pathway inhibition and to determine the pharmacokinetic profile of ANX009

Evaluations

Safety and tolerability
- AEs, SAEs
- Discontinuation due to AE
- Clinically significant laboratory or physical findings
- Clinically significant ECG findings

Pharmacodynamics
- Serum unbound C1q target
- CH_{50} hemolysis of antibody-sensitized sheep red blood cells

Pharmacokinetics
- Serum unbound ANX009

AE, adverse event; CH_{50}, 50% hemolytic complement assay; ECG, electrocardiogram.

Results

Baseline demographics

- Total of 48 participants were randomized to receive ANX009 or placebo on study (**Table 1**)
- In the single ascending dose (SAD) study:
  - 32 participants received ANX009 or placebo (n=8 per cohort)
  - 4 doses of ANX009 tested
- In the multiple ascending dose (MAD) study:
  - 16 participants received ANX009 or placebo (n=8 per cohort)
  - 2 doses and frequencies of ANX009 tested

Table 1. Baseline demographics

	Single ascending dose (n=32)	Multiple ascending dose (n=16)
Median age, y (range)	25.5 (18–56)	25.0 (19–52)
Male sex, n (%)	22 (68.8)	9 (56.3)
Race, n (%)		
Asian	10 (31.3)	9 (56.3)
White	20 (62.5)	6 (37.5)

Safety

- Overall, no drug-related safety signals, dose-limiting toxicities, serious adverse events, or adverse events leading to discontinuations were observed with ANX009 administered subcutaneously as single or multiple doses
  - All dose levels were well tolerated in both the SAD and MAD cohorts (**Table 2**)
  - Treatment-emergent adverse events (TEAEs) occurring in ≥1 patient were observed as follows:
    - SAD: 14/24 (58%) ANX009, 6/8 (75%) placebo
    - MAD: 12/12 (100%) ANX009, 3/4 (75%) placebo
  - No serious TEAEs were observed
  - No participant had a TEAE that resulted in study drug infusion interruption or permanent discontinuation in study treatment
- Most TEAEs were grade 1 in severity and only 1 grade ≥3 TEAE occurred but was deemed to be unrelated hypoglycemia
- Administrative site reactions were the most common TEAE, were generally mild in severity and transient in nature, and were observed at a similar frequency in participants receiving ANX009 or placebo
  - Administration site reactions were observed as follows:
    - SAD: 6/24 (25%) ANX009, 3/8 (38%) placebo
    - MAD: 6/12 (50%) ANX009, 2/4 (50%) placebo

Table 2. Summary of safety events in single and multiple ascending dose cohorts

	ANX009					Placebo
Single ascending dose	**Dose 1 (n=6)**	**Dose 2 (n=6)**	**Dose 3 (n=6)**	**Dose 4 (n=6)**	**All doses (n=24)**	**(n=8)**
Number of TEAEs	15	5	4	8	32	7
Number (%) of participants with ≥1 TEAE	4 (67)	3 (50)	4 (67)	3 (50)	14 (58)	6 (75)
Number of treatment-related TEAEs	0	2	2	4	8	4
Number (%) of participants with ≥1 treatment-related TEAE	0	2 (33)	2 (33)	3 (50)	7 (29)	3 (38)
Number of SAE	0	0	0	0	0	0
Number of AE leading to discontinuation	0	0	0	0	0	0

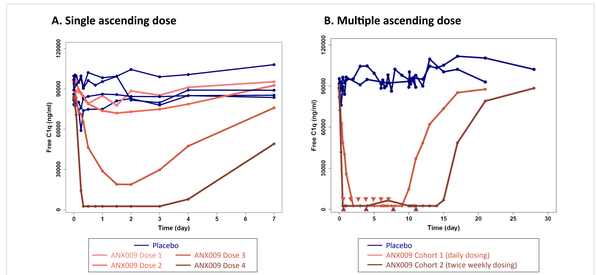
	ANX009			Placebo
Multiple ascending dose	**Cohort 1 (n=6)**	**Cohort 2 (n=6)**	**All doses (n=12)**	**(n=4)**
Number of TEAEs	16	16	32	9
Number (%) of participants with ≥1 TEAE	6 (100)	6 (100)	12 (100)	3 (75)
Number of treatment-related TEAEs	5	5	10	5
Number (%) of participants with ≥1 treatment-related TEAE	2 (33)	5 (83)	7 (58)	2 (50)
Number of SAE	0	0	0	0
Number of AE leading to discontinuation	0	0	0	0

AE, adverse event; SAE, serious adverse event; TEAE, treatment emergent adverse event.

Pharmacodynamics

- In SAD cohorts:
  - A clear dose-response relationship was observed in SAD cohorts with escalating doses (**Figure 2A**)
  - Negligible reduction in free C1q in serum was observed in the two lowest dose cohorts
  - An 80% maximum mean reduction in free C1q in serum was observed at 48 hours post-dose at the third dose level, and full reduction in free C1q in serum through 72 hours was observed at the highest dose level
  - At the highest dose level, full reduction in free C1q in serum was observed within 6-8 hours post-dose, consistent with absorption from the subcutaneous space
- Similar reduction of free C1q in serum was observed throughout the dosing interval in the MAD cohort 1 with daily dosing, as well as in the MAD cohort 2 with twice weekly dosing
- Full reduction of C1q in serum was maintained for at least 4 days following the last dose in the MAD cohort 2 (**Figure 2B**)

Figure 2. Mean inhibition of serum C1q with A) single dosing or B) multiple dosing of ANX009 by subcutaneous infusion



- Ex vivo functional activity of C1q in serum, as measured by CH_{50} in sensitized red blood cell hemolysis assays, was inhibited in close correspondence with free C1q levels

Pharmacokinetics

- No exposure of free ANX009 was detected in the serum, as expected for an Fab fragment with rapid clearance of unbound drug

CONCLUSIONS

- **Subcutaneous administration of ANX009, a high-affinity Fab targeting the substrate-binding domains of C1q, results in robust and complete inhibition of the classical complement pathway in serum**
- **Combined safety, tolerability, and clinical pharmacology results from this phase 1 study support advancement of ANX009 to studies in patients with complement-mediated autoimmune disorders**

References

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Disclosures

AG, JT, ER, H-AK, TY, SK, SR: Employee, Annexon Biosciences; Equity, Annexon Biosciences

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