ID #1200

C1q Blockade With Tanruprubart Rapidly Attenuates Complement-Driven Acute Neuroinflammation and Accelerates Early Muscle Strength Recovery in Guillain–Barré Syndrome

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INTRODUCTION

- Guillain-Barré syndrome (GBS) is a rare, complement-mediated, peripheral neuropathy characterized by rapidly progressive muscle weakness and a monophasic course, with a disease nadir typically occurring within 1–2 weeks of onset[1]
- Following exposure to an infectious agent, antibodies that cross-react with nerve components activate C1q and the classical complement pathway, generating anaphylatoxins (C3a, C4a, C5a) that trigger an acute inflammatory response, including immune cell recruitment, neutrophil activation, and degranulation[2]
- The resulting neuroinflammatory edema amplifies structural nerve damage or destruction, leading to motor nerve conduction block. The resulting severe acute paralysis can be fatal in some cases, and recovery is often incomplete, with the extent of nerve damage largely determining the degree of long-term disability[1,3-5]
- Tanruprubart (ANX005), a monoclonal antibody, is a targeted immunotherapy that selectively binds to C1q, providing rapid inhibition of complement-mediated neuroinflammation and nerve damage[6,7]
- GBS-02 (NCT04701164), a Phase 3, multicenter, double-blind, placebo-controlled trial in patients with GBS achieved its primary endpoint: tanruprubart 30 mg/kg rapidly improved patient disability and was generally well tolerated[8]

OBJECTIVE

- To evaluate the impact of tanruprubart on complement-driven inflammatory activity in the GBS-02 Phase 3 trial

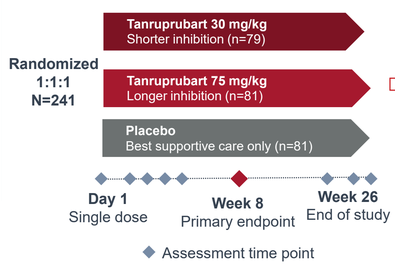
METHODS

GBS-02 study design

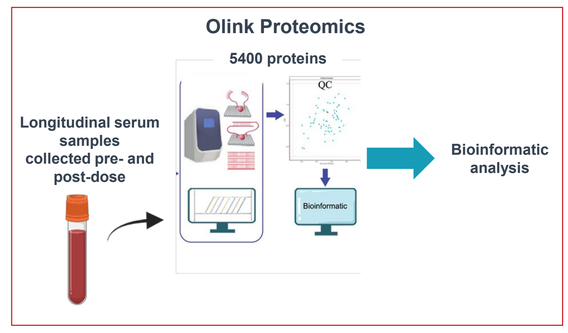
Key inclusion/exclusion criteria:
- Aged ≥16 years
- With a GBS disability score of 3, 4, or 5
- ≤10 days from onset of weakness
- Did not have access to intravenous immunoglobulin or plasma exchange

Stratified by baseline prognostic factors: muscle strength and time from onset of weakness

Conducted at sites in Bangladesh and the Philippines



Biomarker study



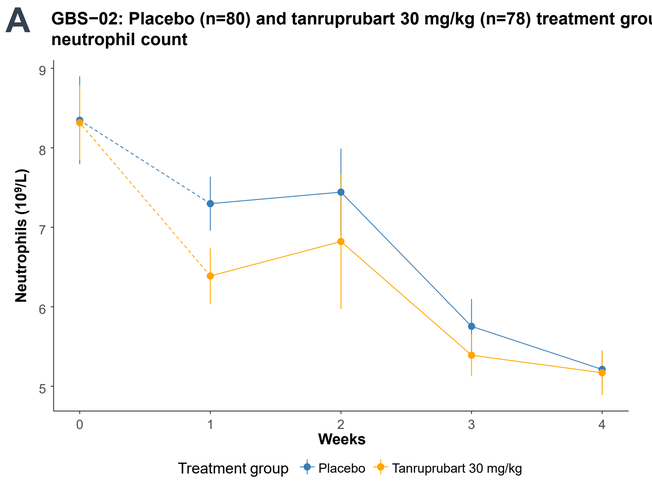
Assessments

- Serum C1q levels and serum absolute neutrophil count (ANC) were assessed over 26 weeks in the overall GBS-02 study population
- An unbiased Olink serum proteomics workflow identified tanruprubart treatment effects in a GBS-02 subset (n=74) with baseline characteristics representing the commonly observed GBS phenotype
  - 41 participants from the tanruprubart 30 mg/kg cohort
  - 33 participants from the placebo cohort
  - 10 healthy serum controls from BioIVT
- Efficacy measures included Medical Research Council sumscore (MRCss), which assesses muscle strength[9]

RESULTS

- A single administration of tanruprubart 30 mg/kg led to rapid reduction of serum free C1q to undetectable levels for ~1 week, while mean serum levels of free C1q in the placebo group remained near baseline values until the end of the study
- Absolute neutrophil counts (ANC) were elevated at baseline in the overall study population and mean ANC was above the upper limit of normal (**Figure 1A**), consistent with an inflammatory state
  - Baseline mean (standard deviation) ANC was 8.32×10^9/L (4.19) and 8.35×10^9/L (4.97) in the tanruprubart and placebo groups, respectively
- In placebo-treated participants, neutrophil levels remained elevated during the first 1–2 weeks, coinciding with the clinical nadir of GBS (**Figure 1A**). ANC normalized by Week 4 in all patients, in parallel with spontaneous recovery of muscle strength
- In contrast, tanruprubart-treated participants exhibited rapid reductions in ANC within 1 week after administration which were maintained through Week 4 (**Figure 1A**)
- In the overall study population, declines in ANC paralleled rapid gains in muscle strength by Week 1 (**Figure 1B**). The same pattern was seen in the biomarker subset (n=74)
- At baseline, biomarker analysis identified neutrophil degranulation and inflammatory markers among the top three enriched pathways in GBS-02 participants vs healthy donor sera (**Figure 2A**)
  - A select panel of 17 biomarkers known to be associated with neutrophil activation and degranulation were found to be elevated at baseline in GBS-02 participants vs healthy controls (**Figure 2B**)
- Tanruprubart reduced neutrophil activation/degranulation markers and other inflammatory proteins at Week 1 vs placebo ($p<0.0001$; **Figure 3A**), consistent with the reduced neutrophil count shown in **Figure 1A**
- The longitudinal trajectory of neutrophil and other inflammatory biomarkers with placebo treatment supports the involvement of acute inflammation in GBS, peaking at Week 1, which is consistent with the clinical nadir of GBS approximately 1 week after hospitalization (**Figure 3B**). Tanruprubart 30 mg/kg rapidly reduces acute inflammation at the peak of the disease

Figure 1. (A) Mean (± standard error [SE]) ANC over time to Week 4 (N=241); (B) MRCss mean (±SE) change from baseline over time to Week 4 (N=241)



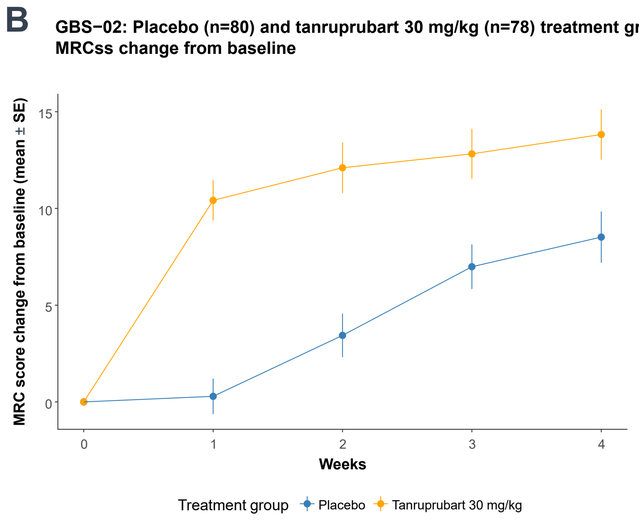
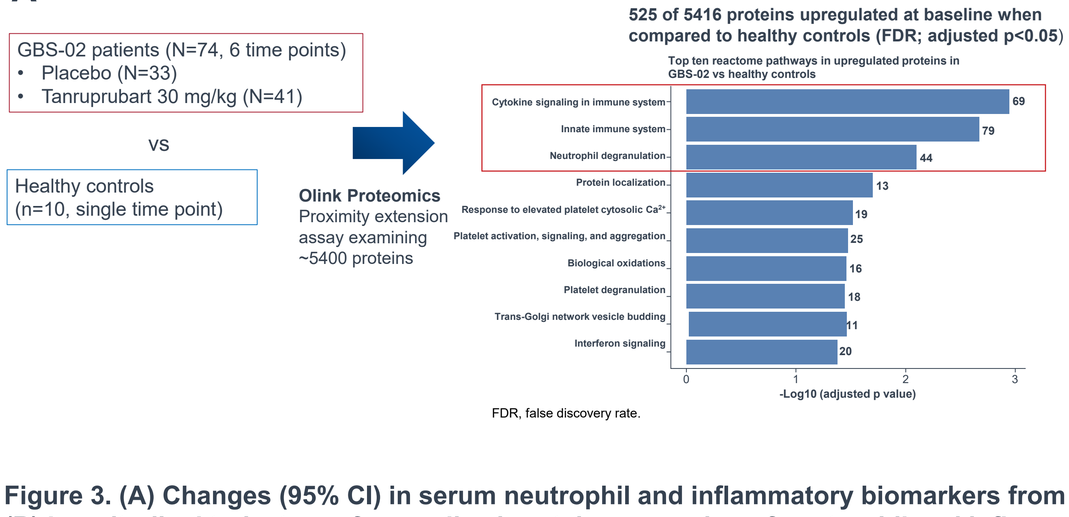


Figure 2. (A) Top ten protein pathways enriched in GBS-02 participants vs healthy controls; (B) Mean changes (95% confidence intervals [CIs]) in serum neutrophil and inflammatory biomarkers at baseline in GBS-02 participants vs healthy controls



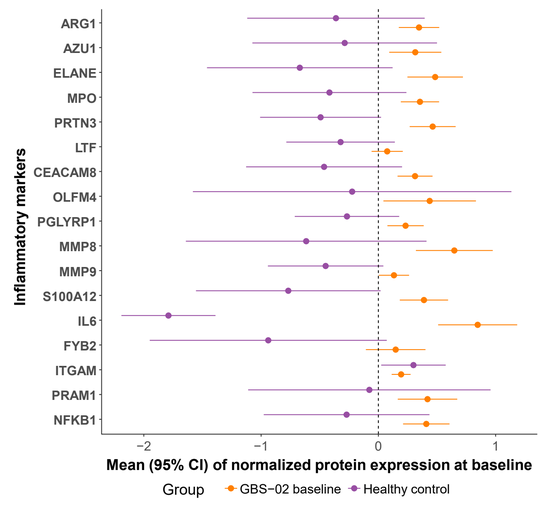
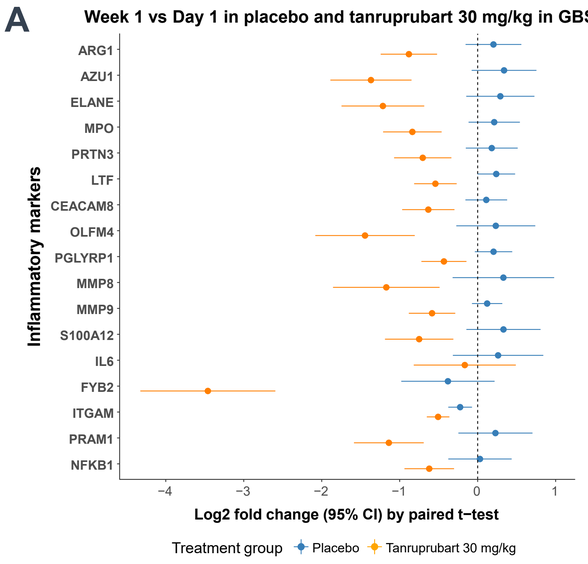
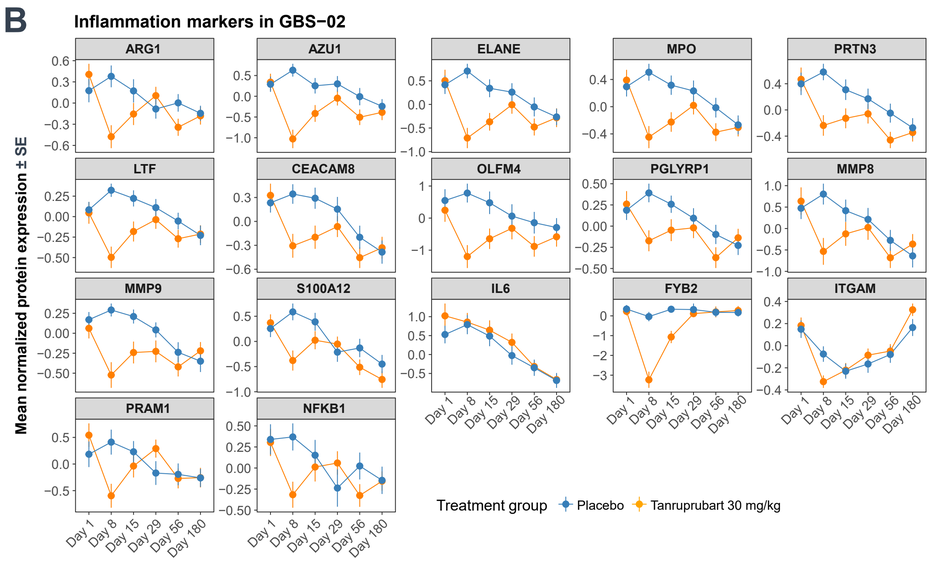


Figure 3. (A) Changes (95% CI) in serum neutrophil and inflammatory biomarkers from baseline (Day 1) to Week 1 (Day 8); (B) Longitudinal trajectory of normalized protein expression of neutrophil and inflammatory biomarkers up to Week 26





CONCLUSIONS

- **C1q inhibition by tanruprubart was associated with rapid, substantial reductions in neutrophil counts and inflammatory markers, consistent with immediate dampening of complement-driven neuroinflammation**
- **The rapid anti-inflammatory effects observed with tanruprubart 30 mg/kg align with the rapid improvements observed in GBS disability and are consistent with reduction in edema, restoration of nerve conduction and blockade of nerve injury during the acute progressive phase of GBS**

References

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Disclosures

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