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Tanruprubart in GBS: Targeting Early Complement-Associated Inflammation Conserved Across the Clinical Spectrum and Regions

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Introduction: Guillain-Barré syndrome (GBS) is a rare, complement-mediated peripheral neuropathy characterized by rapidly progressive weakness with nadir at 1–2 weeks[1]

C1q classical complement drives a dual pathophysiology in GBS[1–6]

Nerve inflammation

Inflammatory edema:[2] integral part of GBS inflammatory process[2]

Affects nerve conduction leading to **functional impairment**[1]

Nerve damage

Immune cells recruitment and membrane attack complex formation[1,4]

Unopposed complement activation drives structural damage[1,5,6]**:** limiting speed and extent of recovery

C1q anchors to autoantibodies on nerve surface, activating classical complement[7]

Blocking C1q has potential for rapid recovery and large treatment effect[3]

Tanruprubart (ANX005)

- Monoclonal antibody[3,8]
- **Binds and rapidly inhibits C1q** and the classical complement cascade[3,8]
- Demonstrated early and durable improvement in muscle strength and disability in patients with GBS[9]
- Generally safe and well tolerated[9]

Aim To characterize early complement-mediated inflammatory dynamics in GBS across cohorts and evaluate the impact of tanruprubart in the GBS-02 Phase 3 trial

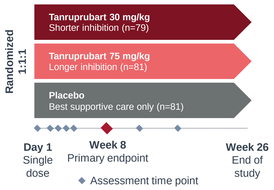
Methods: Biomarker analysis

- Serum proteome-wide longitudinal profiling using the Olink® Explore HT platform in GBS-02 patients (n=115), an IVIg/PE-treated US GBS cohort (n=11) and healthy controls (HC; n=10)
- Systemic Immune–Inflammation Index (SII)[10] on GBS-02 patients was calculated using SII = (platelet count × neutrophil count) / lymphocyte count
- Prespecified prognostic and clinical strata were defined

GBS-02 Phase 3 study

Key inclusion/exclusion criteria:

- Aged ≥16 years
- With a GBS-DS of 3, 4, or 5
- ≤10 days from onset of weakness
- Did not have access to intravenous immunoglobulin or plasma exchange



Conducted at sites in Bangladesh and the Philippines

GBS-02 biomarker study cohort

Placebo: n=33
Tanruprubart 30 mg/kg: n=41
Tanruprubart 75 mg/kg: n=41

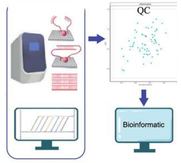
US GBS cohort IVIg: n=11

Healthy controls n=10

Longitudinal serum samples collected pre and post dose

Biomarker study design

~5400 proteins analyzed by proximity extension assay



Olink Proteomics

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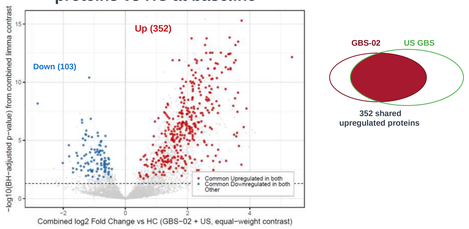
Results

Acute inflammatory signature is conserved in GBS across independent cohorts

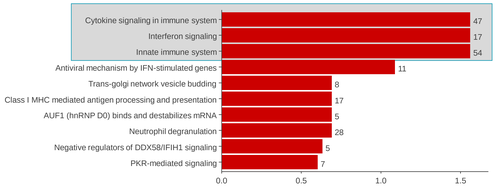
- Olink serum proteomics identified 352 shared upregulated proteins in baseline GBS-02 and US GBS cohorts vs HC (**Figure 1A**)
- A clear enrichment of inflammation-associated pathways was observed in the ten most represented Reactome pathways and protein counts (**Figure 1B**)
- Protein expression in the top three Reactome pathways was significantly upregulated at baseline (**Figure 1C**)

Figure 1A: Concordantly regulated proteins vs HC at baseline



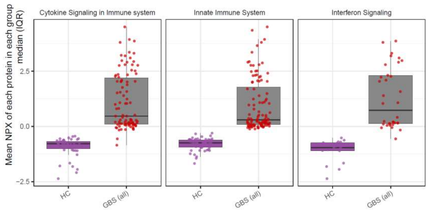
Concordantly regulated proteins (equal weight contrast) in GBS-02 (n=115) and US GBS (n=11) vs HC (n=10) at baseline. Dashed line indicates significance threshold of adjusted p=0.05.

Figure 1B: Top 10 Reactome pathways in common upregulated proteins in GBS−02 vs HC and US cohort vs HC



Reactome pathways rank ordered based on false discovery rate (FDR)-adjusted p-value. Bar labels show number of upregulated proteins per pathway. MHC, major histocompatibility complex.

Figure 1C: Expression in the top 3 Reactome pathways at baseline HC vs combined GBS cohorts



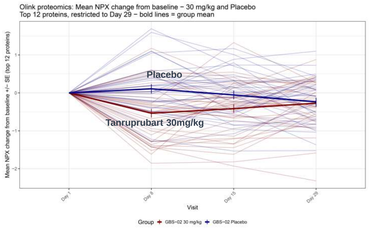
HC (n=10) **All GBS** (n=126)

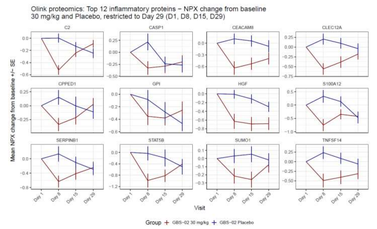
Data are mean normalized protein expression (NPX) per individual protein; box plots show median with interquartile range (IQR) and range for HC (n=10) vs all GBS (n=126).

Tanruprubart rapidly suppresses acute inflammation

Treatment-associated inflammatory proteomic changes translate to a clinically accessible SII

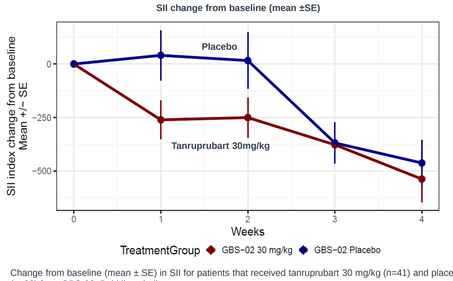
Figures 2A and B: Olink Proteomics-baseline elevated inflammatory markers suppressed by tanruprubart (top 12) relative to placebo





Olink Proteomics: (mean ± standard error [SE] NPX change from baseline) Common upregulated proteins at baseline significantly suppressed by tanruprubart at Day 8

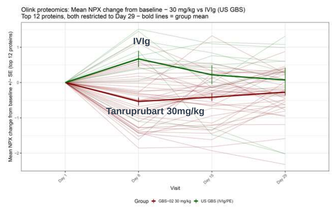
Figure 2C: Early rise in SII declines with tanruprubart 30 mg/kg treatment vs placebo

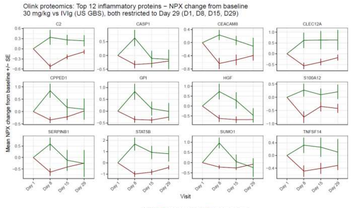


Change from baseline (mean ± SE) in SII for patients that received tanruprubart 30 mg/kg (n=41) and placebo (n=33) from GBS-02. Bold lines indicate group means

Lack of early inflammatory suppression in an independent IVIg/PE-treated US cohort

Figures 3A and B: In contrast to tanruprubart-treated GBS-02 patients, early suppression of inflammatory markers was not observed in IVIg/PE-treated US GBS patients





Data show mean ± SE NPX change from baseline in upregulated proteins significantly suppressed by tanruprubart in Olink proteomics. Bold lines indicate group means.

Conclusions

- **A consistent, complement-linked early inflammatory signature was observed across geographically and clinically diverse GBS cohorts**
- **Tanruprubart induced rapid, concordant suppression of inflammation across proteomic markers and clinically accessible SII**
- **Upstream C1q inhibition differentiates from IVIg/PE, enabling earlier, targeted intervention**

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Conflicts of interest
PP, HAK, EC, TY, RA: Employees and shareholders of Annexon Biosciences. ZI: Research funding from Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, USA, and Annexon Biosciences. DL: External contractor of Annexon Biosciences to perform data analysis. KS: Research funding from NINDS/NIH and DoD. Consultant Annexon Biosciences. YR: Former contractor of Annexon Biosciences to perform data analysis. CS: Consulting or educational talks for: Akigai, Alnylam, Annexon, argenx, CSL Behring, Grifols, Kedrion, Nevro, Novartis, Pfizer, Sanofi, Takeda, and TEVA. For additional information, please contact Preeti Paliwal ppaliwal@annexonbio.com.

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