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Safety Profile of Tanruprubart (ANX005) in Patients With Guillain-Barré Syndrome: A Randomised, Placebo-Controlled Phase 3 Study

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Introduction

- Guillain-Barré syndrome (GBS) is a rare, life-altering, neuromuscular emergency, where classical complement activation contributes to progressive muscle weakness[1]
- Tanruprubart (ANX005), a monoclonal antibody, is a targeted immunotherapy that selectively inhibits C1q, the initiating molecule of the classical complement pathway, thus providing rapid and complete inhibition of classical complement activity to halt neuroinflammation and nerve damage[2,3]
- GBS-02 (NCT04701164) was a Phase 3, multicentre, randomised, double-blind, placebo-controlled study of tanruprubart in patients with GBS in Bangladesh and the Philippines[4]
- Here, we present the safety findings from this study

Methods

- Participants aged ≥16 years with a recent GBS diagnosis without planned plasma exchange or intravenous immunoglobulins were randomised to receive a single intravenous dose of tanruprubart 30 or 75 mg/kg, or placebo
- Antihistamines, acetaminophen, and a slow ramp-up infusion protocol were used to mitigate for infusion-related reactions (IRRs)
- Vaccinations and prophylactic antibiotics were not mandated
- Safety over 6 months included:
  - Treatment-emergent adverse events (TEAEs)
  - Serious adverse events (SAEs)
  - Investigator-assessed treatment-related TEAEs
  - Events of special interest: IRRs, encapsulated bacteria infections, and systemic autoimmune disorders other than GBS

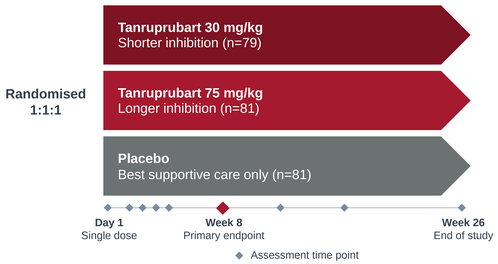
Study design

The Safety Analysis Set included all participants who received any amount of the study drug

Key inclusion/exclusion criteria:
- Aged ≥16 years
- With a GBS-Disability Score (GBS-DS) 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



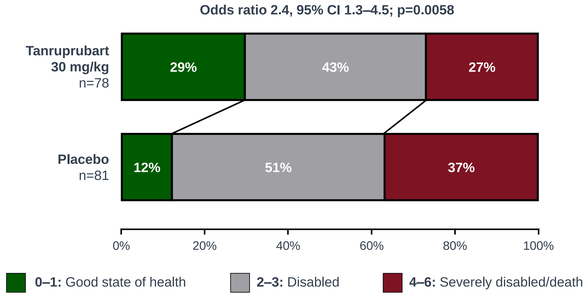
Primary endpoint:
- GBS-DS at Week 8

Key secondary endpoints:
- Overall Neuropathy Limitations Scale change from baseline at Week 8
- Medical Research Council sumscore change from baseline at Weeks 1 and 8
- Safety

Results

- The study met the primary endpoint and demonstrated that patients treated with tanruprubart 30 mg/kg had better outcomes (adjusted odds ratio 2.4, 95% CI 1.3–4.5; p=0.0058) according to the GBS-DS) relative to placebo at Week 8 (**Figure**)

Figure. GBS-02 primary endpoint: Change in GBS-DS at Week 8



Safety outcomes

- The Safety Analysis Set comprised 241 participants. Most participants (95%) did not receive prophylactic antibiotics
- Most participants (98.8%) reported ≥1 TEAE (**Table**)
- IRRs were the most common treatment-related TEAE in tanruprubart-treated participants. Most were mild to moderate and manifested as transient rashes that resolved without sequalae
- Encapsulated bacteria infection rates were similar across groups. Urinary tract infection was the most commonly reported (3.8%, 7.4%, and 4.9% in the 30 mg/kg, 75 mg/kg, and placebo groups, respectively)
- Three participants discontinued treatment, one in each tanruprubart group, who both discontinued due to an IRR, and one in the placebo group, who discontinued due to cardiogenic shock and respiratory failure
- No participants withdrew due to TEAEs
- TEAEs and SAEs were consistent with GBS morbidity
- No systemic autoimmune diseases occurred other than GBS
- Three deaths occurred per group. None were assessed by the investigator as treatment related

Table. Summary of TEAEs (Safety Analysis Set)

TEAE, n (%)	Tanruprubart 30 mg/kg (n=79)	Tanruprubart 75 mg/kg (n=81)	Placebo (n=81)
Participants with TEAEs (all grades)	79 (100.0)	80 (98.8)	79 (97.5)
Grade 1–2[a]	46 (58.2)	44 (54.3)	44 (54.3)
Grade ≥3[a]	33 (41.8)	36 (44.4)	35 (43.2)
Resolved TEAEs	78 (98.7)	79 (97.5)	78 (96.3)
TEAEs related to study drug	24 (30.4)	34 (42.0)	5 (6.2)
SAEs	15 (19.0)	9 (11.1)	15 (18.5)
SAEs related to study drug	1 (1.3)	3 (3.7)	1 (1.2)
Study drug discontinuations due to TEAEs	1 (1.3)	1 (1.2)	1 (1.2)
Discontinuations due to death[b]	3 (3.8)	3 (3.7)	4 (4.9)
TEAEs of special interest	32 (40.5)	38 (46.9)	15 (18.5)
IRRs[c]	24 (30.4)	32 (39.5)	4 (4.9)[d]
Mild-to-moderate (Grade 1–2)[a]	20 (25.3)	25 (30.9)	3 (3.7)
Severe (Grade 3)[a]	3 (3.8)	4 (4.9)	0
Life-threatening (Grade 4)[a]	1 (1.3)	3 (3.7)	1 (1.2)[d]
Fatal (Grade 5)[a]	0	0	0
Most common: Rash	18 (22.8)	22 (27.2)	2 (2.5)
Infection with encapsulated bacteria	11 (13.9)	10 (12.3)	12 (14.8)
Most common (>1 patient in any group)			
Urinary tract infection	3 (3.8)	6 (7.4)	4 (4.9)
Pneumonia	4 (5.1)	2 (2.5)	1 (1.2)
Pneumonia aspiration	3 (3.8)	0	2 (2.5)
Escherichia coli urinary tract infection	0	2 (2.5)	0
Sepsis	2 (2.5)	0	4 (4.9)
Most common TEAEs (non-IRR)			
Blood CPK increased	44 (55.7)	35 (43.2)	46 (56.8)
Musculoskeletal pain	36 (45.6)	26 (32.1)	35 (43.2)
ALT increased	21 (26.6)	23 (28.4)	23 (28.4)
Urinary tract infection	19 (24.1)	18 (22.2)	18 (22.2)
Hypokalemia	16 (20.3)	11 (13.6)	24 (29.6)

[a]Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. [b]One participant in the placebo group died before receiving treatment and was not included in the secondary endpoint analysis of all-cause mortality. [c]Most IRRs occurred during the first part of the infusion where participants in the tanruprubart 30 mg/kg and 75 mg/kg groups were receiving the same dose. [d]After unblinding of data, it was found that one patient in the placebo group had apparently received tanruprubart and had treatment-related SAEs of Grade 3 myocardial infarction and Grade 4 IRR.
ALT = alanine aminotransferase; CPK = creatine phosphokinase.

CONCLUSIONS

- In study GBS-02, single-dose tanruprubart was generally well tolerated
- Common TEAEs were associated with GBS disease course and tanruprubart did not increase risk of infections with encapsulated bacteria, despite most participants not receiving prophylactic antibiotics
- These findings support the promising potential of tanruprubart in GBS

References
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Conflicts of interest
H-AK, EP, AJ, RC: Employees and shareholders of Annexon Biosciences. EM: Employee of Nurix Therapeutics. GM: Employee of Annexon Biosciences at the time of the study.
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