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Development of a Framework to Compare Treatment Outcomes Between Guillain Barré Syndrome Populations

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INTRODUCTION

- Guillain-Barré syndrome (GBS) is a rapidly progressing immune-mediated peripheral nerve disease, with most cases resulting from an aberrant autoimmune response following respiratory or gastrointestinal infection[1,2]
  - Approximately 20-30% of patients will progress to respiratory failure requiring mechanical ventilation
- Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are accepted therapies for patients with GBS
  - However, even with IVIg/PE, approximately 20% of patients remain unable to walk after 6 months, demonstrating a need for improved treatments[1,3]
- Activation of the classical complement cascade has been implicated in the pathogenesis of GBS[4]
- ANX005 is an inhibitory recombinant humanized monoclonal antibody against C1q, the initiating molecule of the classical complement cascade,[5] which completely blocks activation of the classical cascade
  - In a controlled Phase 1b study in patients with GBS, ANX005 treatment demonstrated improvement in GBS Disability Scale (GBS-DS) score and muscle strength compared with placebo, with trends in shorter intensive care unit stay and duration of mechanical ventilation[6]
  - A recently completed Phase 3 study further evaluated ANX005 treatment in participants with GBS in Bangladesh and the Philippines[7] (ANX005-GBS-02 [GBS-02])
- We have developed a study protocol to establish comparability and compare clinical outcomes of participants treated with ANX005 in GBS-02 with those of a propensity score-matched cohort of patients treated with IVIg or PE in other geographic locations from the real-world International GBS Outcome Study (IGOS)[8] (**Figure**)

METHODS

Datasets

- GBS-02 was a randomized, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of ANX005 in participants with GBS in Bangladesh and the Philippines[7]
- IGOS is a prospective observational cohort study containing data from approximately 2000 patients with GBS in 21 countries across 6 continents[8]

Establishment of External Comparator Cohort

- Key GBS-02 inclusion and exclusion criteria will be applied to the IGOS population (**Table 1**)
  - In order to evaluate comparability of GBS-02 participants with patients in IGOS, IGOS patients from Bangladesh will be excluded
  - In collaboration with the IGOS consortium, comparability of the IGOS and GBS-02 cohorts will be assessed using baseline data of IGOS patients (approximate n=2000) to determine the ability of known GBS prognostic factors[9,10] to predict clinical outcomes

Table 1. Key ANX005 GBS-02 inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
Aged ≥16 years	Clinically significant findings that may interfere with the conduct of the study or the interpretation of the data or increase the participant's risk[1]
Confirmed diagnosis of GBS[2]	Body weight <30 kg or >150 kg at screening
Onset of GBS-related weakness ≤10 days prior to start of treatment	Previous or intended treatment with IVIg or PE for GBS
GBS-DS score of 3, 4, or 5 at study entry	Diagnosis of a variant of GBS (eg, Miller Fisher syndrome, Bickerstaff's encephalitis, or Miller Fisher overlap)
	History of a prior episode of GBS

Additional exclusion factors applied to IGOS patients include Bangladesh country of origin and previous participation in a clinical trial for GBS.
[1]Includes electrocardiogram results, laboratory test results, or physical examination that are not specific to GBS. [2]Confirmed diagnosis according to the National Institute of Neurological Disorders and Stroke Diagnostic Criteria for Guillain-Barré Syndrome.
GBS, Guillain-Barre syndrome; GBS-DS, GBS Disability Scale; IVIg, intravenous immunoglobulin; PE, plasma exchange.

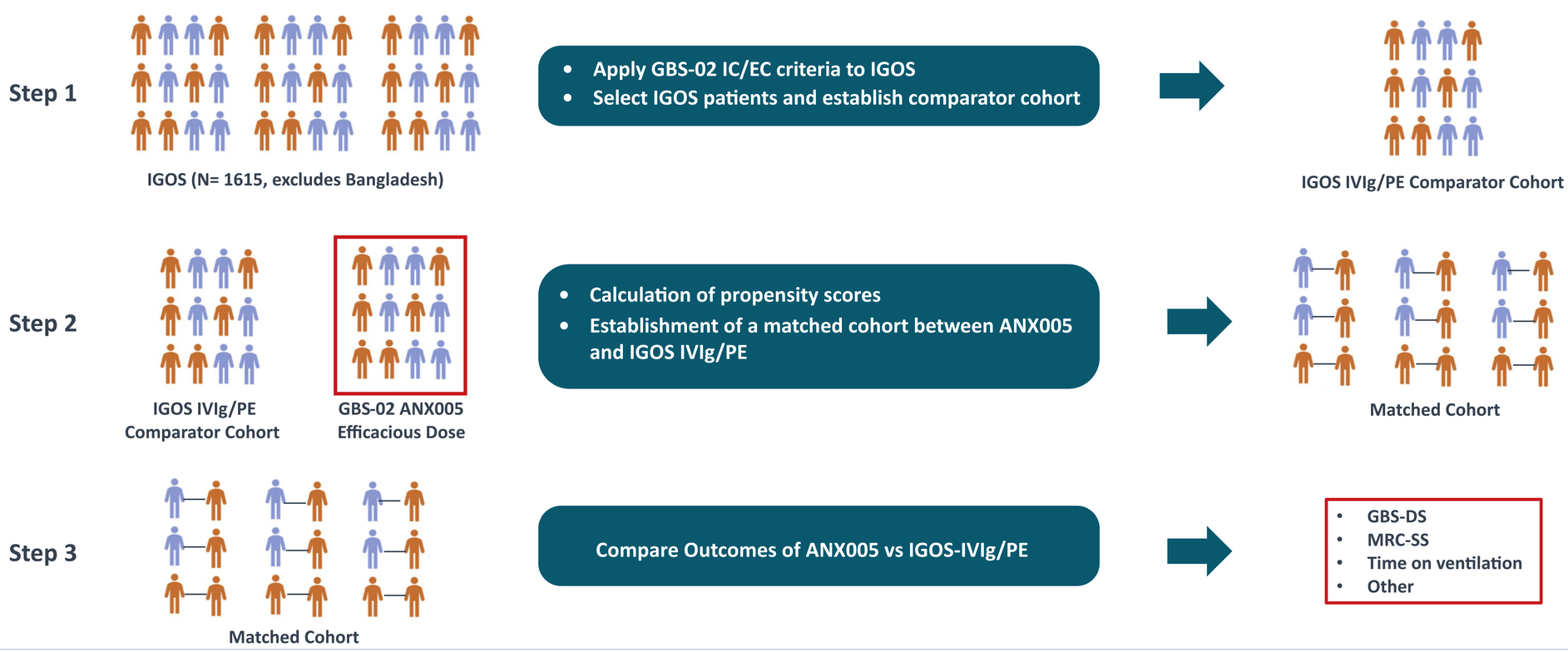
Establishment of Matched Cohorts

- The IGOS IVIg/PE comparator cohort will then be matched to GBS-02 participants by propensity score matching[11] using a tiered factor approach based on prognostic factors for GBS
  - Considerations for tiering of prognostic factors will include clinical importance based on publications and the results of the assessment for prediction of outcomes using IGOS data

Outcomes Analysis

- Endpoint analysis will be performed in the propensity score-matched populations using patients treated with the efficacious dose of ANX005 in GBS-02
  - The primary efficacy endpoint is GBS-DS score
  - Secondary endpoints include change from baseline in Medical Research Council sum score (MRC-SS) and duration of ventilator support over multiple time points
- For the endpoint analyses, the regression models including specified covariates will be the same as those used in GBS-02
  - Other covariates and propensity scores may also be used in the regression models as appropriate
- Analysis results will be published in collaboration with the IGOS Consortium

Figure. Study design concept



IC, inclusion criteria; EC, exclusion criteria; GBS-DS, Guillain Barré Syndrome Disability Scale; IVIg, intravenous immunoglobulin; MRC-SS, Medical Research Council sum score; PE, plasma exchange.

CONCLUSION

- This study presents a design and analysis strategy for robust real-world evidence generation, offering promising potential for comparative studies of novel treatments for GBS

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DISCLOSURES

EW: nothing to disclose. **ES:** consultancy for Annexon Biosciences. **DRC:** consultancy for Annexon Biosciences, AstralBio, Avilar Therapeutics, Boehringer Ingelheim, Dianthus Therapeutics, Grifols S.A., Immunovant, Johnson & Johnson, Longboard Pharmaceuticals, Novartis, Nuvig Pharma, Octapharma AG, Pfizer, Seattle Genetics; Data Safety Monitoring Boards for Avidity Bio, PledPharma AB, Hansa Medical AB, Mitsubishi Tanabe Pharma Corporation, Passage Bio, Sanofi, Vertex; Scientific Advisory Boards for Algotherapeutics, Nervosave; technology licensing from Beijing 3E-Regenacy Pharmaceuticals, CMIC Group, Fundacion GELTAMO, MedImmune, Passage Bio, RWS Life Sciences, Worldwide Clinical Trials. **PAvD: KK, HAK, PP, EH, BH, AJA:** employment with and equity ownership in Annexon Biosciences. **BCJ:** support for research in IGOS and consultancy from Annexon Biosciences.

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