A Bayesian ordinal transition model of Guillain-Barré syndrome (GBS) disability progression with anti-C1q treatment

Presenter: Glenn Morrison, MSc, PhD

Ping Lin, MS[1]; Maximilian Rohde, MS[2]; Henk-André Kroon, MD, MBA[1]; Ewout Steyerberg, MSc, PhD[3]; Glenn Morrison, MSc, PhD[1]; Kenneth C. Gorson, MD[4]; Quazi Deen Mohammad, MBBS, MD, FCPS[5]; Zhahirul Islam, PhD[6]; Khan Abul Kalam Azad, MBBS, FCPS, MD, FACP[7]; Jose Navarro, MD[8]; Peter Collins[1]; Frank E. Harrell, PhD[2]

[1]Annexon Biosciences, Brisbane, CA, USA; [2]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA; [3]Julius Center for Health Sciences and Primary Care, Utrecht, Netherlands; [4]St. Elizabeth's Medical Center, Boston, MA, USA; [5]National Institute of Neurosciences & Hospital, Dhaka, Bangladesh; [6]Gut–Brain Axis Laboratory, icddr,b, Dhaka, Bangladesh; [7]Dhaka Medical College and Hospital, Dhaka, Bangladesh; [8]José R. Reyes Memorial Medical Center, Manila, Philippines

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Conflicts of interest

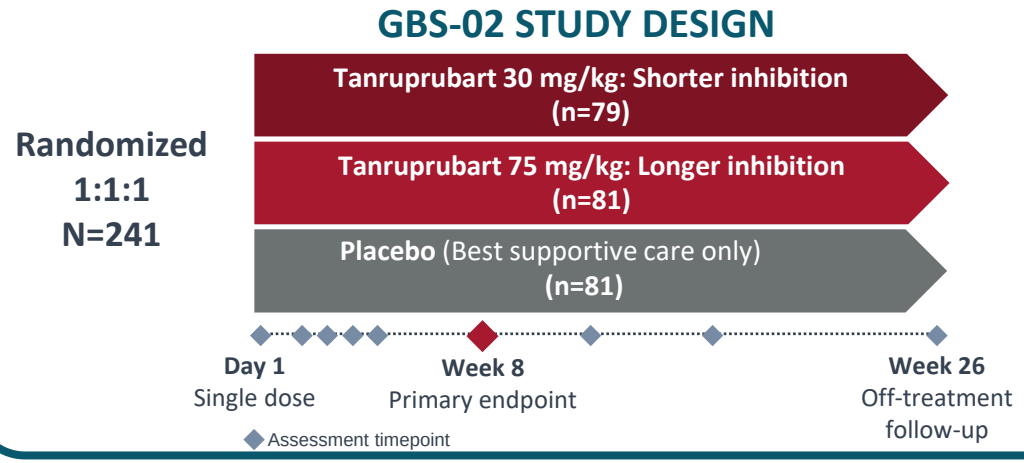
Ping Lin: Employee and shareholder of Annexon Biosciences at the time of the study; **Maximilian Rohde, Henk-André Kroon, Glenn Morrison, and Peter Collins:** Employee and shareholder of Annexon Biosciences; **Ewout Steyerberg:** Consultancy/advisory role with Annexon Biosciences; **Kenneth C. Gorson:** Consultancy/advisory role with Annexon Biosciences, argenx, Janssen, and Sanofi; **Quazi Deen Mohammad**: Consultancy/advisory role with Annexon Biosciences; **Zhahirul Islam:** Research funding from Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, USA, and Annexon Biosciences; **Khan Abul Kalam Azad:** No disclosures; **Jose Navarro:** Consultancy/advisory role with Annexon Biosciences; **Frank E. Harrell:** Consultancy/advisory role with Annexon Biosciences, Baylor Scott & White Research Institute, and Regeneron.

Tanruprubart (ANX005) is investigational and has not been approved for any indication in any jurisdiction

GBS-02: Double-blind, Phase 3 study in adults with Guillain-Barré Syndrome (NCT04701164)

- GBS, a rare, rapidly progressive and life-threatening neuromuscular emergency is a prototypical classical complement-mediated disease[1,2]

Tanruprubart (ANX005) rapidly and completely inhibits C1q, preventing classical complement pathway activation to reduce neuroinflammation and nerve damage



- **Primary endpoint met:** Participants in the tanruprubart 30 mg/kg group had **2.4 times** greater odds of being in a **better state of health** versus placebo on **GBS-DS at Week 8 (p=0.0058)**
- Tanruprubart was **well tolerated** and the majority of adverse events were **mild to moderate** in severity; most were due to GBS and not considered related to the study drug, with the exception of rash, which was the most common infusion-related reaction

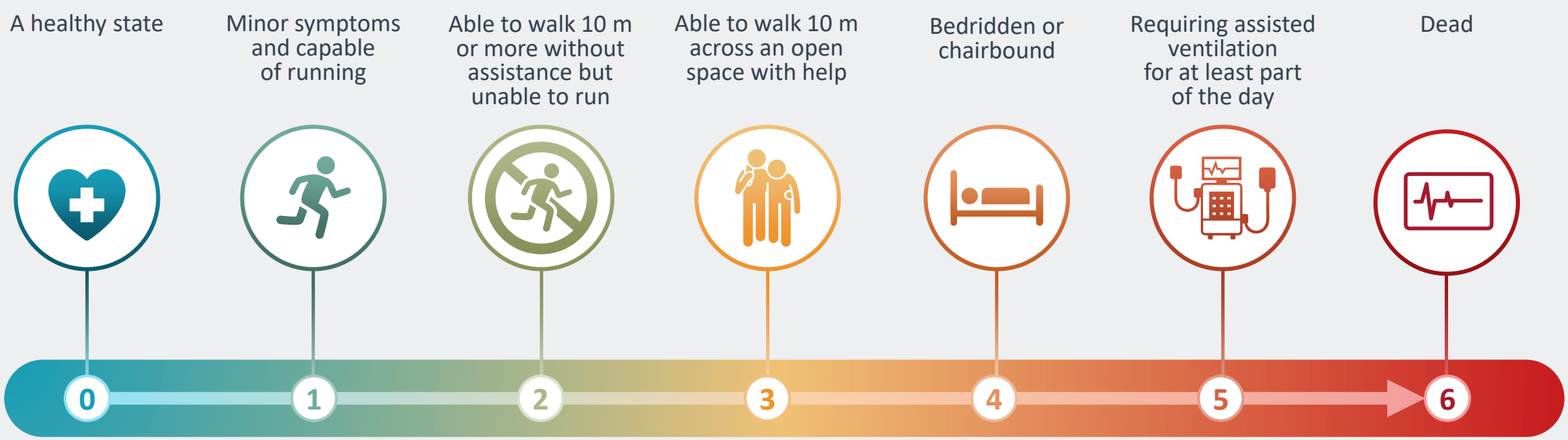
- Traditional analyses track functional impairment using GBS-DS but **do not model transitions between disability states over time and cannot handle death optimally**

Aim: To better characterize longitudinal outcomes in the GBS-DS scale in study GBS-02 using a Bayesian ordinal transition model

1. Willison HJ, et al. *Lancet*. 2016;388:717–27. 2. Willison HJ, et al. *J Neuroimmunol*. 2008;201–202:172–82.
GBS, Guillain-Barré syndrome; GBS-DS, Guillain-Barré syndrome disability score.

GBS-DS: Used to assess functional status in patients with GBS

GBS-DS GRADES[1]



1. van Koningsveld R et al. *Lancet Neurol*. 2007;6:589–94. 2. Kleyweg RP et al. *Muscle Nerve*. 1991;14):1103–9.
GBS, Guillain-Barré syndrome; GBS-DS, Guillain-Barré syndrome disability score; MRC, Medical Research Council.

Methods

- Prespecified secondary endpoint: to analyze the proportion of participants that reached a healthy state (GBS-DS=0 [normal]) calculated using logistic regression
- A Bayesian ordinal transition model with a first-order Markov transition structure was fit in a *post hoc* analysis to the longitudinal, ordinal GBS-DS data
  - Non-informative priors were used for all parameters
  - Baseline prognostic factors were used as covariates: age, days from onset of muscle weakness, and baseline MRC sumscore
  - The effect of treatment was allowed to flexibly vary over time by treatment group using natural cubic splines
  - Conditional quantities were computed using the median values for each covariate
  - Transition probabilities were used to calculate state occupancy probabilities
    - Transition probabilities: the probability of a participant moving from the state at the previous visit to the state at the current study visit
    - State occupancy probabilities: the probability of a participant being in a certain ordinal state on a given study visit

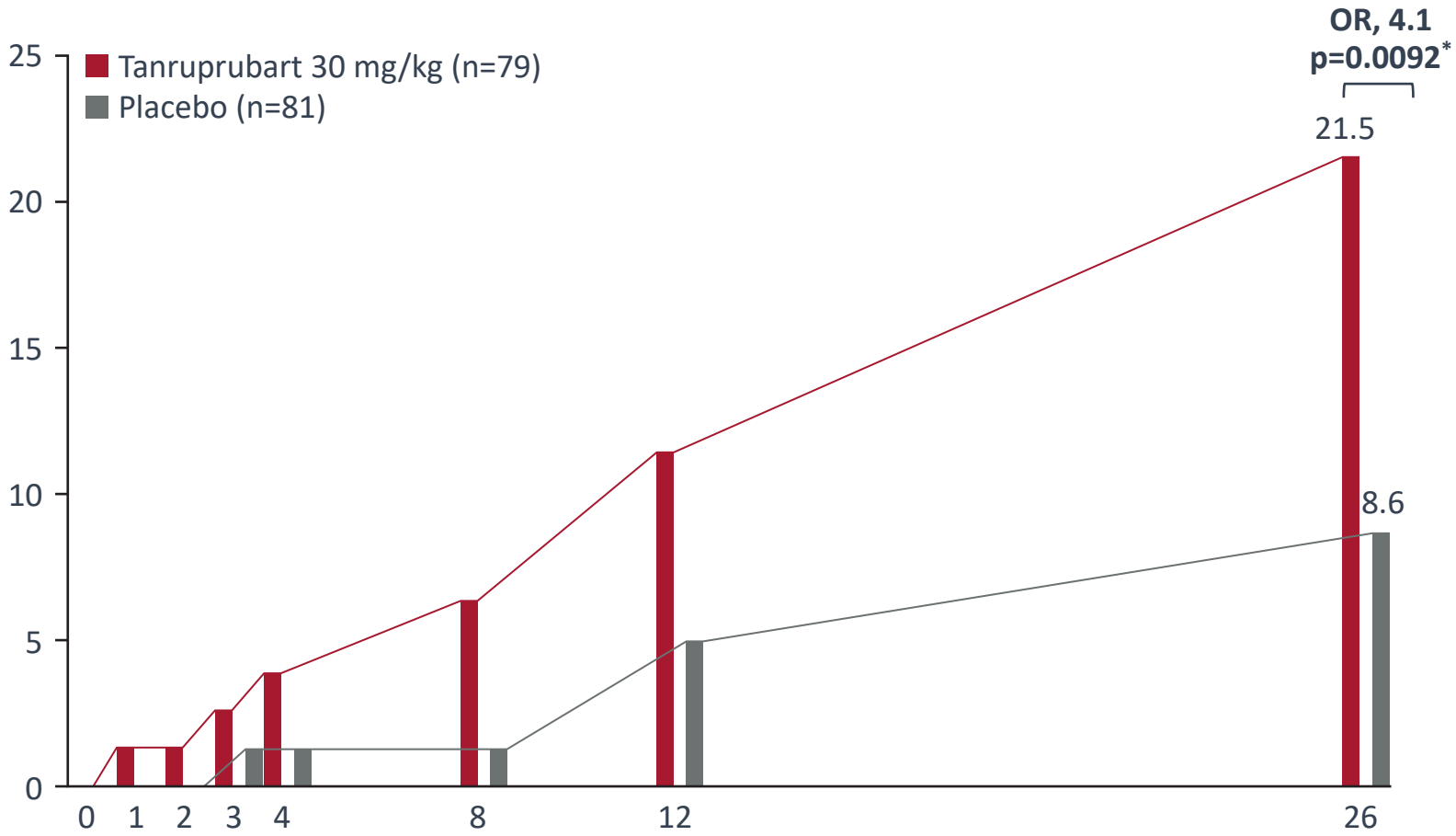
GBS-DS, Guillain-Barré syndrome disability score; MRC, Medical Research Council.

Results: Durable benefit with tanruprubart over placebo

At Week 26, participants who received tanruprubart 30 mg/kg had 4.1-fold greater odds of having fully recovered to GBS-DS=0 compared with participants who received placebo

2.5-times more tanruprubart-treated participants fully recover at Week 26 (GBS-DS=0)

Effect began early and grew throughout study

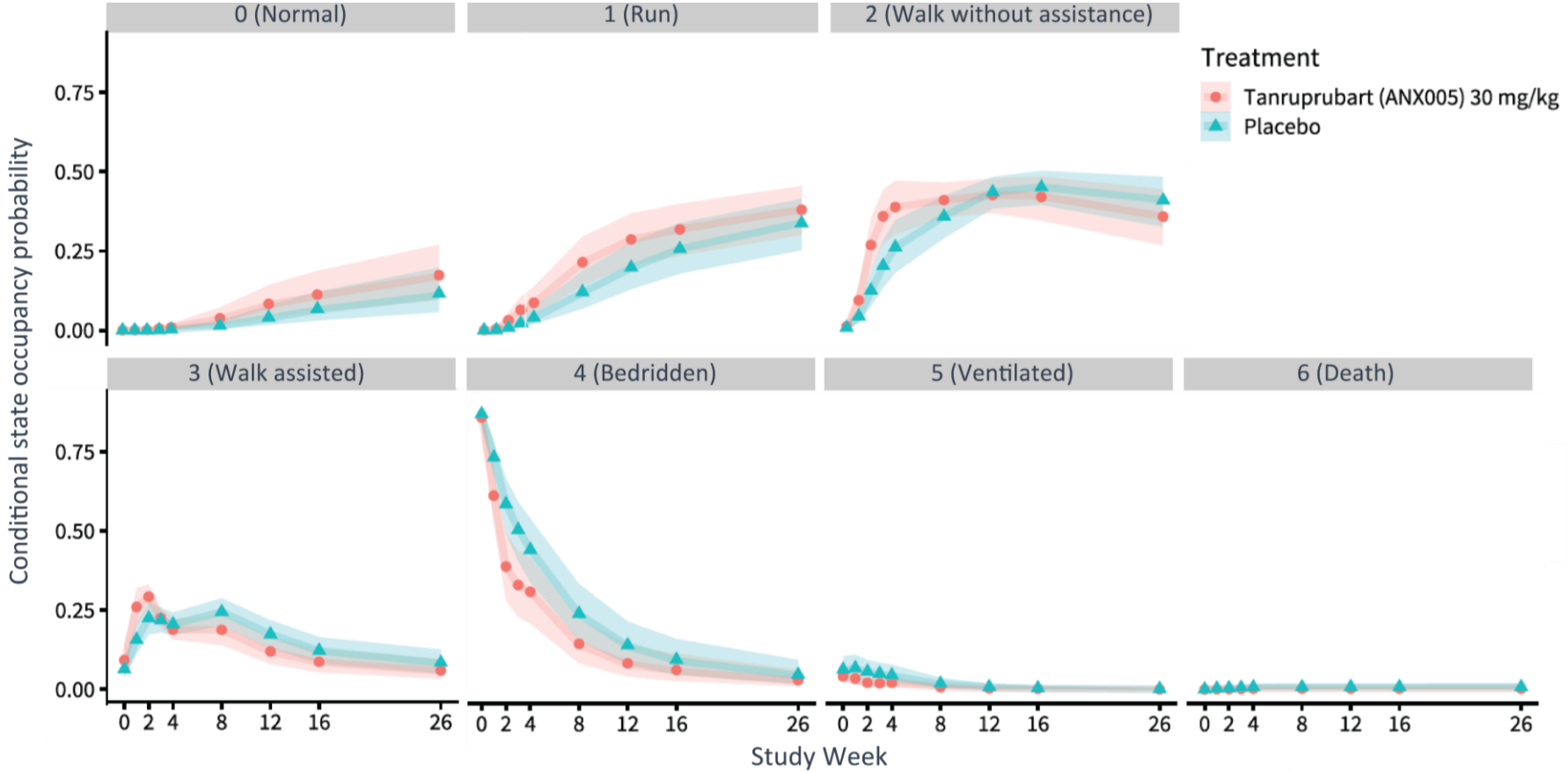


*Nominal.
OR, odds ratio.
GBS-DS, Guillain-Barré syndrome disability score.

Results: Conditional probability of health state achievement for tanruprubart 30 mg/kg vs placebo

Participants receiving tanruprubart had a higher probability of good health status at each visit through 6 months, compared with placebo, and improvements occurred rapidly within the first 3 weeks

Cumulative treatment effect across 6 months with reference baseline GBS-DS=4



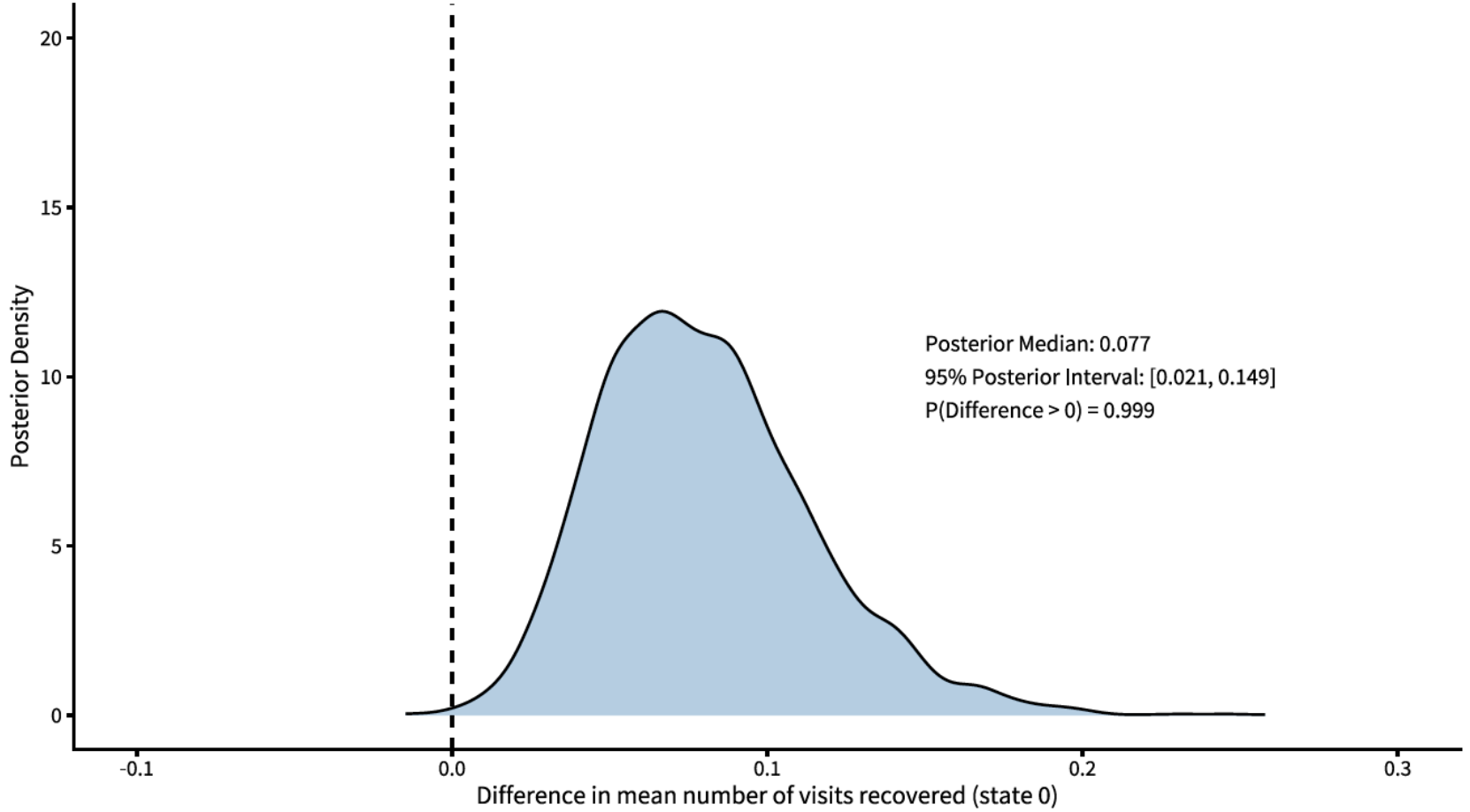
Patients in the tanruprubart group were more likely than those receiving placebo to improve their scores from the reference baseline score of 4

Patients in the tanruprubart group were less likely than those receiving placebo to have the same or worsened scores from the reference baseline score of 4

GBS-DS, Guillain-Barré syndrome disability score; SOP, state occupancy probability.

Results: Difference in mean visits recovered with tanruprubart 30 mg/kg vs placebo (covariate adjustment)

On average, participants receiving tanruprubart 30 mg/kg were more likely to have more study visits with GBS-DS=0 throughout the study versus those receiving placebo, with a high posterior probability (0.999)



GBS-DS, Guillain-Barré syndrome disability score.

Conclusion

- Tanruprubart 30 mg/kg demonstrated rapid and sustained improvement through 6 months
- Bayesian ordinal transition models can increase power and present a longitudinal view of treatment effect, compared with traditional cross-sectional methods, providing more actionable evidence about efficacy through posterior probabilities
- Across the 26-Week period of the study, participants in the tanruprubart 30 mg/kg group had a higher probability of having a good health status and making a full recovery (more days with GBS-DS=0) versus those receiving placebo
- These data highlight the potential for tanruprubart to significantly improve outcomes over time for patients with Guillain-Barré Syndrome

GBS-DS, Guillain-Barré syndrome disability score.