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Disease Trajectory modeling of SLE clinical endpoints using a Latent Variable Model: Analysis of Pooled Patient-Level Placebo (Standard-of-Care) Data

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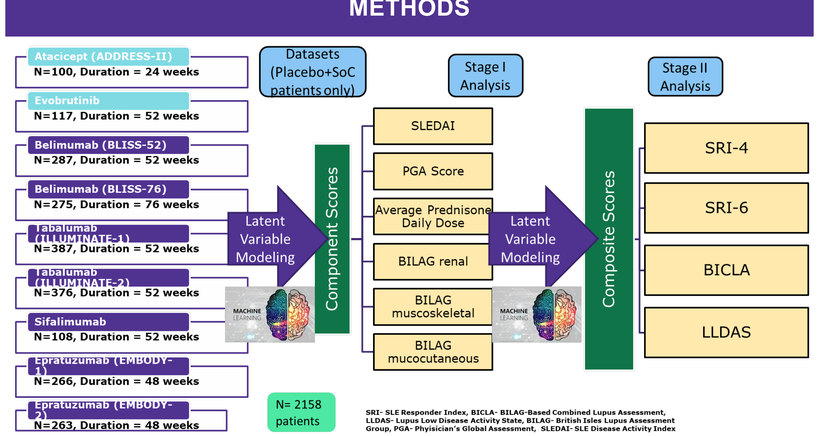
INTRODUCTION

- Systemic lupus erythematosus (SLE) is a multifactorial disease in a heterogeneous population
- Response rates for current SOC are high (40%–50%) in an unselected patient population.
- High placebo+SoC (placebo added on to standard-of-care therapy) response is likely one reason for many failed clinical trials in SLE and complicates the assessment of the actual treatment effect of a new investigational agent.
- Therefore, identification of patient characteristics predictive of poor response to current SOC is desirable to define enrichment strategies for
  - Efficient POC studies
  - Precision medicine strategies
  - Increased probability of success
- Objective: To understand the time course of clinical endpoints and identify clinically important covariates, we developed a mathematical framework to describe the SLE disease trajectory with placebo+SoC data using a latent variable modeling approach.
- Simulations from such models are envisioned to enable optimal clinical trial designs for model-informed drug development in SLE
- A cross-functional team was formed for this effort to enable multi-disciplinary integration of disease area knowledge, pharmacometrics and statistical expertise.

METHODS



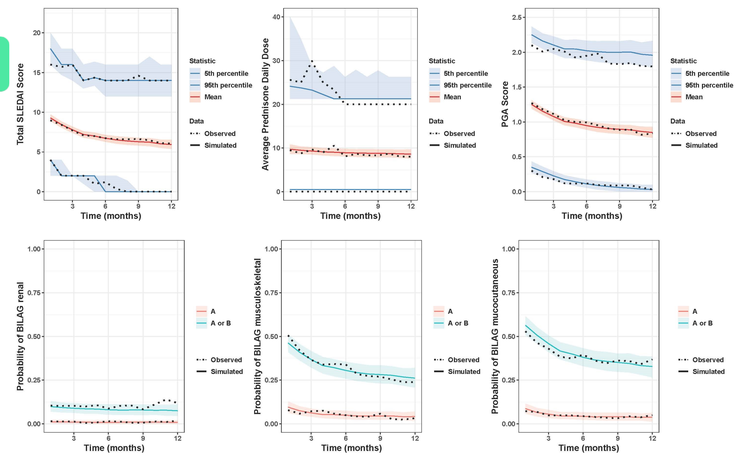
- Individual patient-level placebo+SoC data from 9 different SLE Phase II or Phase III trials were pooled to form the analysis set (N= 2158 patients).
- The analysis set was divided into 60% of the dataset for model development, 20% for model validation and 20% for testing.
- Following graphical evaluations of the data, Stage I of the analysis developed a longitudinal latent variable (LV) model that was developed to jointly describe the clinical endpoints of British Isles Lupus Assessment Group (Renal, mucocutaneous, musculoskeletal organ system scores), SLE disease activity index total score, average prednisone-equivalent daily dose and Physician's Global Assessment.
- In Stage II, learnings from modeling of components in Stage I were applied to jointly describe the composite endpoints (SLE Responder Index, British Isles Lupus Assessment Group-based Composite Lupus Assessment, Lupus low disease activity state) and the drop-out rate.

METHODS

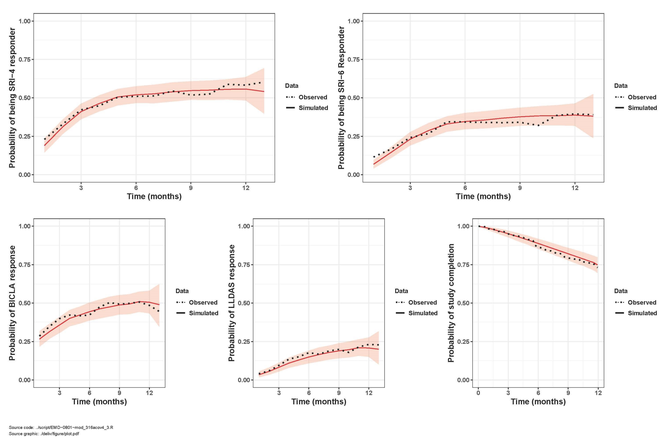
- Several latent variable models, including linear, mono-exponential and Emax, were explored to define the SLE disease burden over time. Covariate screening was performed through LASSO and Random Forest (RF) models of the posterior median random effects; variable importance was assessed using multiple algorithms (Boruta, Permutation, Random-split, Shapley methods).
- A full covariate model was fit, integrating the learnings from the covariate screening step.
- All modeling activities were performed in the Bayesian framework using R and Stan.

RESULTS

Component Scores



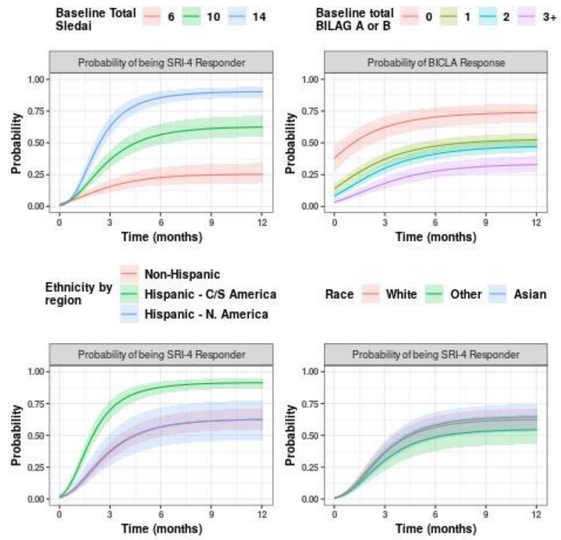
Composite Scores



Visual predictive checks showed that latent Variable Model predicted both the Component & Composite Scores well for the median, 5th and 95th percentiles of the observed data

RESULTS

- The mono-exponential model best described the disease burden of the latent process over time.
- Machine Learning algorithms identified similar covariates in Stage II as in Stage I.
- Some of the baseline covariates that were identified to be important via LASSO and RF and confirmed through the LV model were SLEDAI total score, number of organ systems with a BILAG score of A or B, and low complement levels.
- The model developed using the 60% data set predicted both the 20% validation and 20% test datasets well for both the component and composite clinical endpoints.



Simulations showed that:
- Increasing probability of SRI-4 response with increasing baseline total SLEDAI
- while baseline total BILAG A or B organ scores influenced the probability of BICLA responders
- Ethnicity by Region to be important on disease activity over time

CONCLUSION

- Simulations suggested increasing probability of SRI-4 response with increasing baseline total SLEDAI while baseline total BILAG A or B organ scores influenced the probability of BICLA responders.
- Asian race was not a meaningful contributor to heterogeneity in disease trajectory, supporting the conduct of Asia-inclusive multi-regional clinical trials (MRCT) in SLE.
- However, differences in disease trajectory between Hispanic patients from the Central/South American region and the remainder of the population may suggest the value of considering appropriate stratifications to control heterogeneity in the design of pivotal MRCTs in SLE.
- Covariate selections results did not identify any differences between the classes of SoC medications, whether prior to study enrollment or concomitant, in influencing trajectory of latent SLE disease.
- This example illustrates the value of latent variable models in understanding the trajectories of complex composite endpoints in chronic diseases.