Use of preART-Adjusted Endpoints in the Analysis of an HIV Therapeutic Vaccine Trial

Yunda Huang1, Lilly Zhang1, Darren Jolliffe1, Arnt-Ove Hovden1, Mats Okvist1, Giuseppe Pantaleo1, Maja A. Sommerfelt2

1Vaccine & Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington U.S.A., 2S-cubed Biometrics Ltd., Oxfordshire, United Kingdom, Bionor Pharma ASA, Oslo, Norway, 3Lausanne University Hospital, Lausanne, Switzerland

Introduction

- Vacc-4x is a peptide-based therapeutic vaccine targeting conserved domains on the HIV protein p24.
- In a recent randomized, double-blind, placebo-controlled phase 2 clinical trial of Vacc-4x, 136 HIV-infected patients virologically suppressed on combination antiretroviral therapy (cART) were randomized in a 2:1 ratio to receive six Vacc-4x or placebo immunizations at weeks 1, 2, 3, 4, 16, and 18.
- 126 participants (Vacc-4x:Placebo = 88:38) received all six immunizations and underwent an analytical treatment interruption (ATI) at 10 weeks after the last immunization (protocol cohort).
- 103 participants (Vacc-4x:Placebo = 71:32) at week 40, 83 participants (Vacc-4x:Placebo = 58:25) at week 48, and 50 participants (Vacc-4x:Placebo = 56:24) at week 52 stayed in the study and remained off-cART with available data.

Objectives and Endpoints

- Objective: To evaluate the effect of Vacc-4x on cART-free VL and CD4 count as compared to placebo.
- cART-free VL and CD4 count are measured or estimated while off-cART.
- Endpoints:
  - Week 40 VL and CD4 count
  - "Set-point" viral load and CD4 count: geometric mean of Weeks 48 and 52 values
- Longitudinal VL and CD4 count between weeks 32 – 52

Analysis cohort: Participants with available preART VL and preART CD4 count values in the protocol cohort.

Methods

- Multiple imputation models were used to fill in missing VL or CD4 count data within 6 months before ART initiation.
- 500 sets of plausible values from model-based predictive distribution were used to baseline imputation predictors: treatment assignment, gender, age, country, time on cART, time since HIV diagnosis, reasons for resuming cART, CD4 count nadir, and preART VL or preART CD4 count.
- Two types of univariate and multivariate linear regression models were performed and compared to account for preART values in the evaluation of vaccine effect.
- Covariate-adjusted models: included baseline preART VL or preART CD4 count as a covariate in the regression models.
- Fold-change models: evaluated the fold-change of cART-free VL or CD4 count over participants baseline preART values.
- The Rubin's rule was used to calculate the final estimates and standard errors of vaccine effect based on each imputed dataset (Little et al., Wiley, 2002).
- Simulation studies were performed to compare the statistical power of assessing vaccine effect based on the two models.

Results

- Estimates of Vaccine Effect per log10 Increase of Endpoint

Conclusions

- After accounting for missing data and differences in participants' baseline values between treatment groups, the Vacc-4x group was confirmed for the achieved better cART VL control. Furthermore, an improved maintenance of CD4 count during ATI.
- Based on the Vacc-4x trial data, the fold-change model more effectively accounted for the imbalance in baseline preART VL values between treatment groups, as compared to the covariate-adjusted model.
- Additional simulation studies confirmed that the fold-change model can render a significantly greater power when baseline values differ between treatment groups.
- Future HIV therapeutic vaccine studies may adopt similar fold-change endpoints to account for important prognostic factors of trial outcomes, especially in subgroup (including PP cohort) analysis.