Methods

Statistical analysis

For the co-primary endpoints, the number of COPD exacerbations (HCRU exacerbation events), will be analysed using Poisson regression. The model will include treatment, country and smoking status as factors. Log-time on study will be used as an offset and standard errors will be estimated allowing for extra-Poisson variation. The change in pre-dose morning FEV_1 will be submitted to a mixed model for repeated measures including the following fixed effects: treatment, country, smoking status, visit, baseline, treatment x visit interaction and baseline x visit interaction. An unstructured covariance will be assumed.

For the secondary endpoints, the variables measured repeatedly over time during the treatment period will be analysed using a mixed model for repeated measures similar to the one used for the primary analysis. The change from baseline to the average pre-dose FEV_1 over the treatment period, the change from pre-dose to 2-hour post-dose FEV_1 and FVC at all clinic visits, the change from baseline to the end of treatment in the SGRQ scores and the change from baseline to the entire treatment period in the percentage of rescue use-free days and in the average use of rescue medication will be analysed using an ANCOVA model with treatment, country and smoking status as factors and baseline as a covariate. A Kaplan-Meier plot for time to first COPD exacerbation will be provided, with time to first COPD exacerbation further analysed using a Cox proportional hazards regression model including effects for treatment, country and smoking status.