Literature Model for FEV1 in COPD Trials

Separating the Dynamic Components of Placebo Effect, Disease Progression and Interacting Drug Effects

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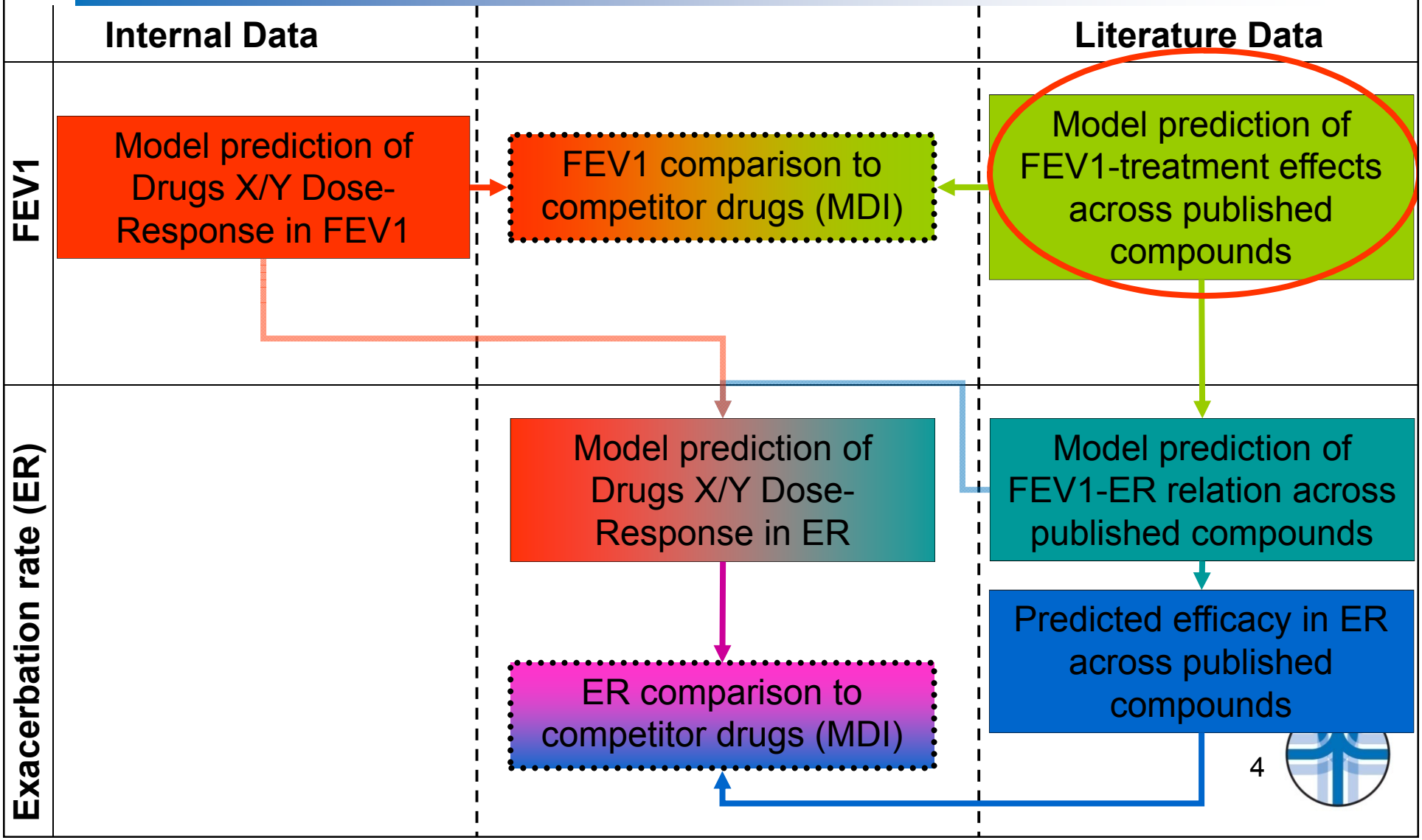
The FEV1 biomarker in COPD

- Chronic obstructive pulmonary disease (COPD)
  - Third leading cause of death in US and projected to increase world-wide due to smoking
- Forced expiratory volume in one second (FEV1)
  - Important endpoint for diagnosis and the primary biomarker for dose selection in ph2b
  - Ph3 need to show reduced exacerbations

Example of how literature analysis aids internal development at Pfizer

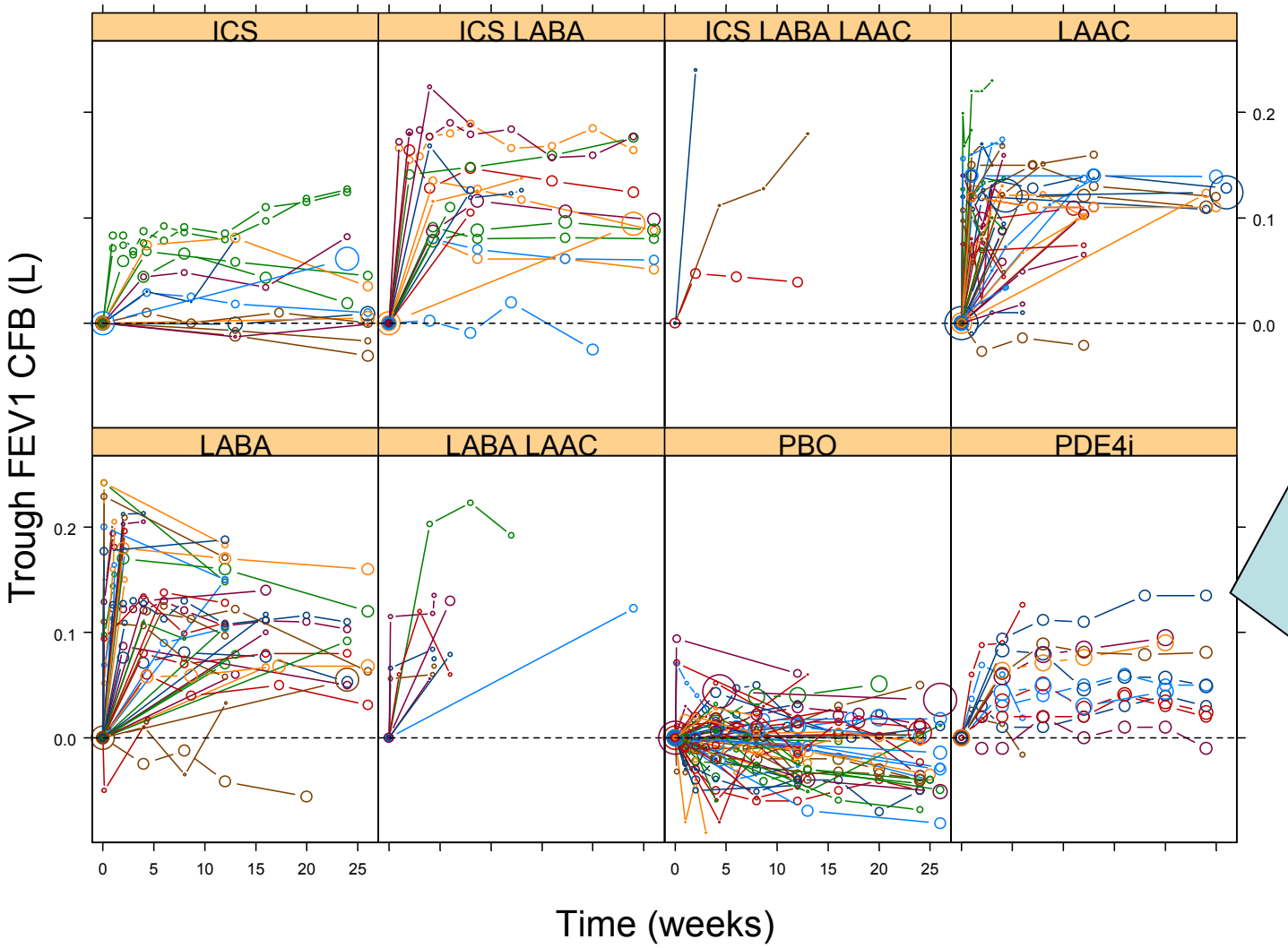


Drug Class of interest in COPD

- Long-acting bronchodilators (inhaled)
  - Long-acting β_2 agonists (**LABA**)
  - Long-acting anticholinergics (**LAAC**)
- Anti-inflammatory therapy
  - Inhaled corticosteroids (**ICS**)
  - PDE4-inhibitors (**PDE4i**)

Literature FEV1 in COPD

Change from baseline trough FEV1 (up to wk 26) by treatment class



Absolute FEV1 is analysed, but displayed as change from baseline, due to dominating variability in baseline!

Linear disease progression
Disease modifying effects?

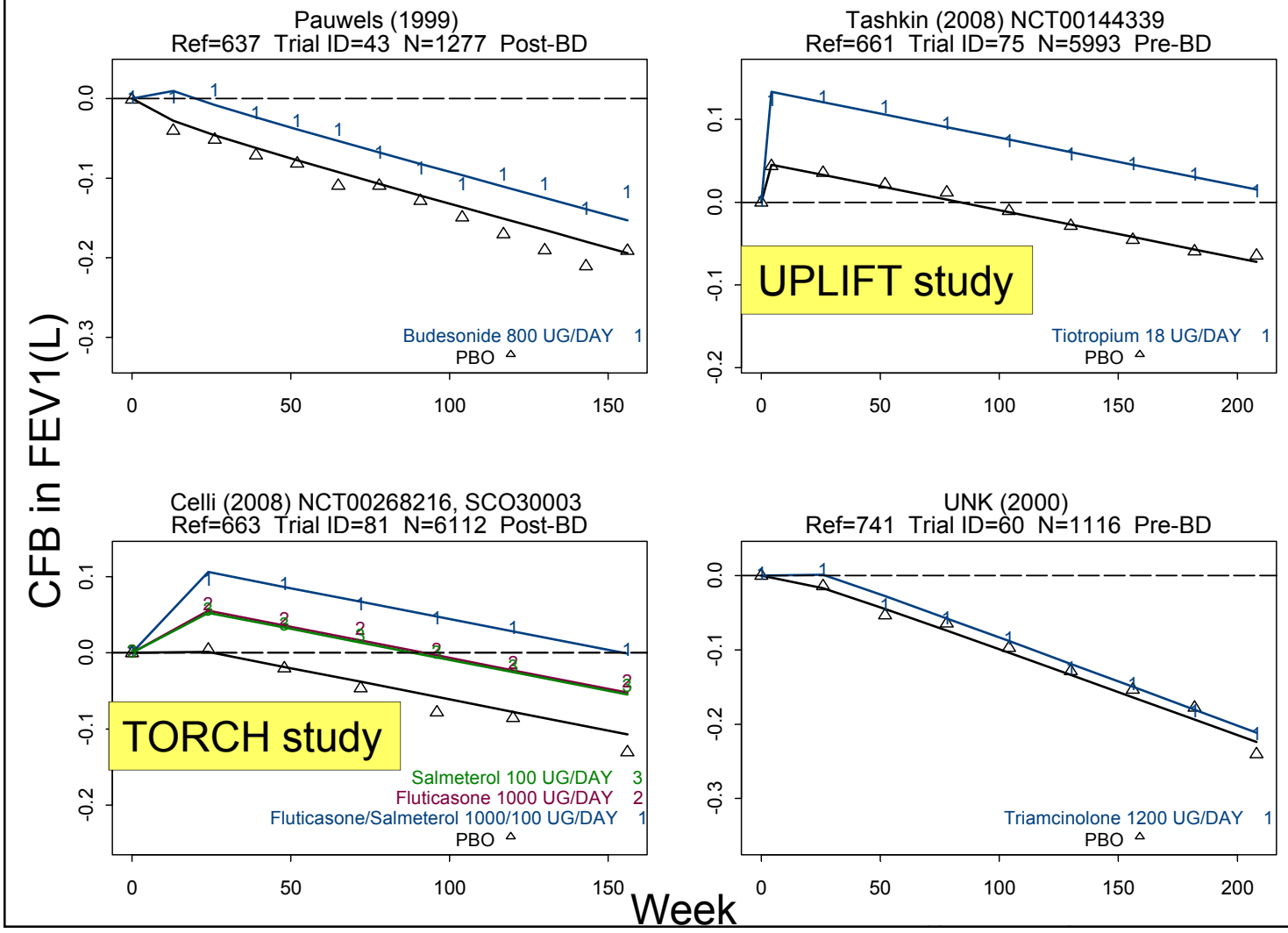
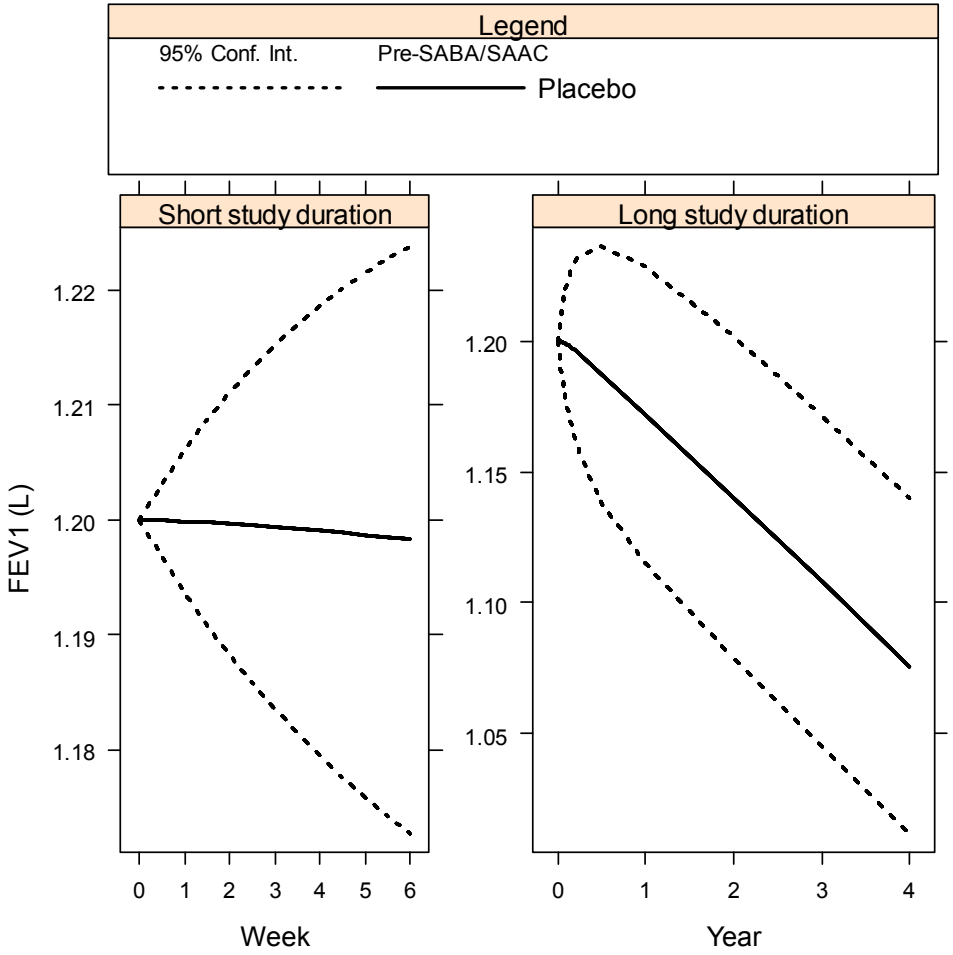


Illustration of ISV in placebo effect at typical disease progression

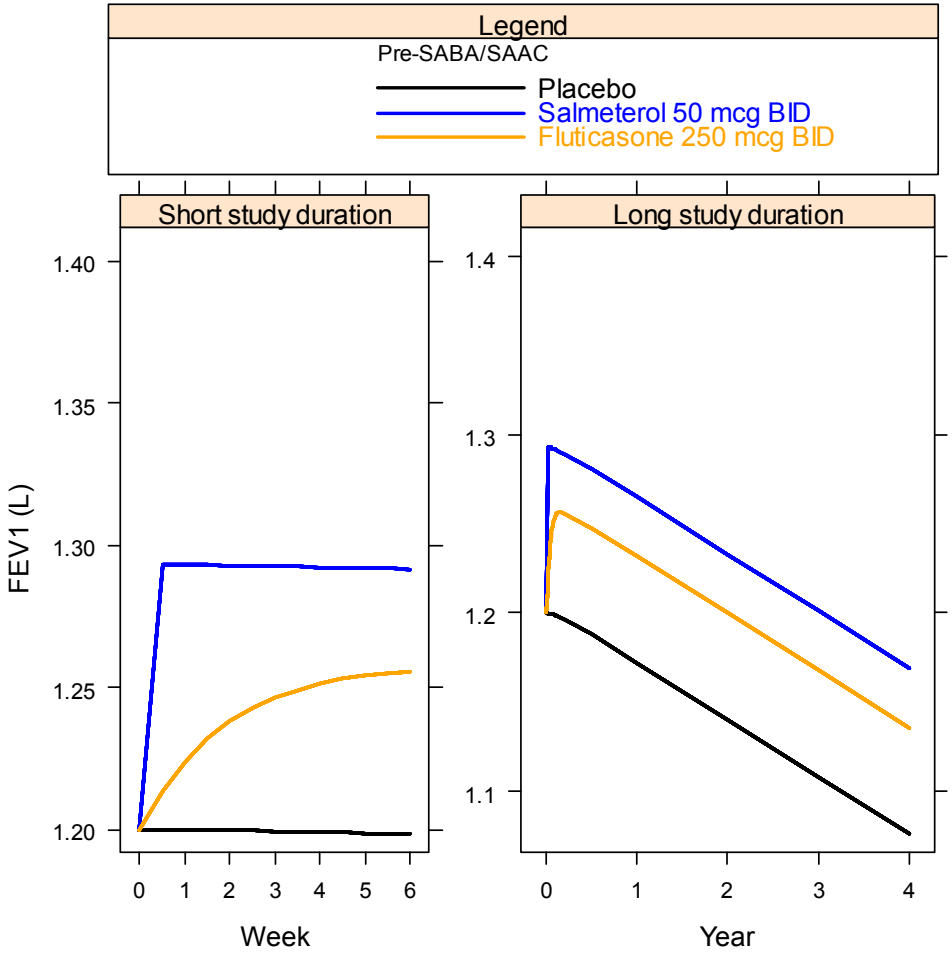
$FEV1_{active} = Baseline + Eff_{placebo} + Progression_{disease}$



Graph illustrates gradual placebo response, but mixture component allowed immediate placebo response as well

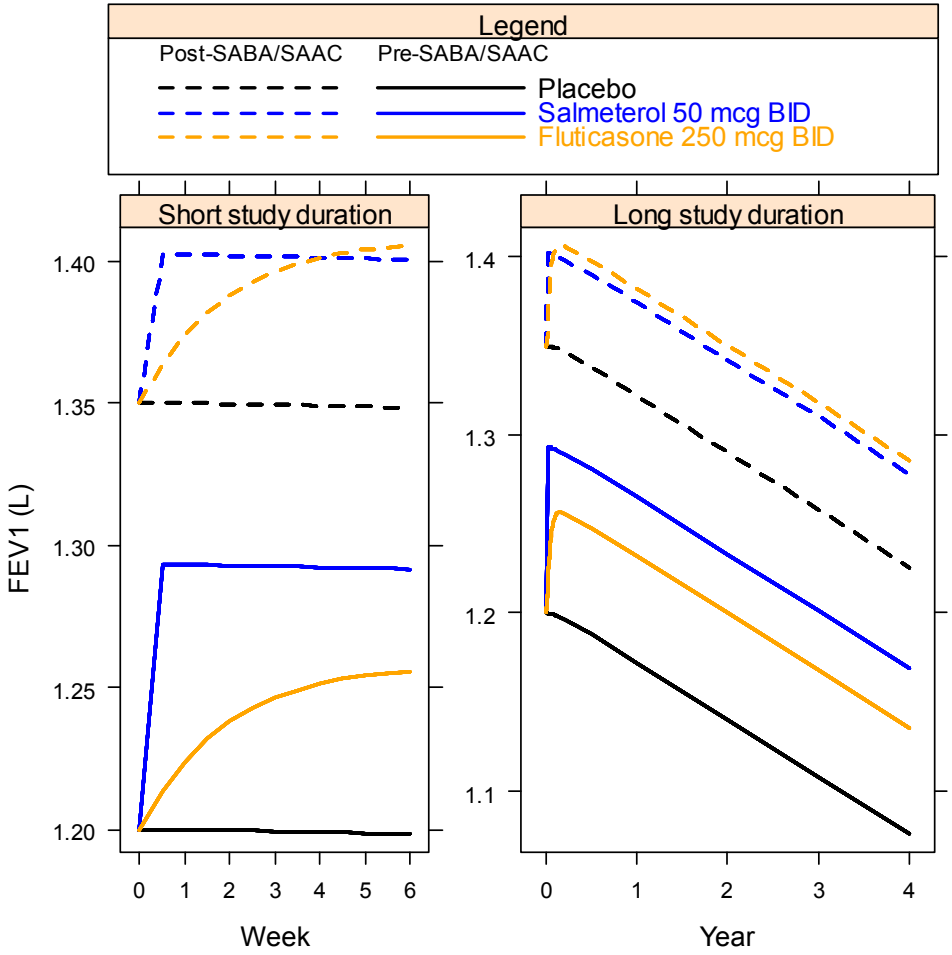
Placebo, Salmeterol (LABA) and Fluticasone (ICS)

$FEV1_{active} = Baseline + Eff_{placebo} + Progression_{disease} + \mathbf{Eff_{drug}}$



Salmeterol interaction with FEV1 post-SABA/SAAC

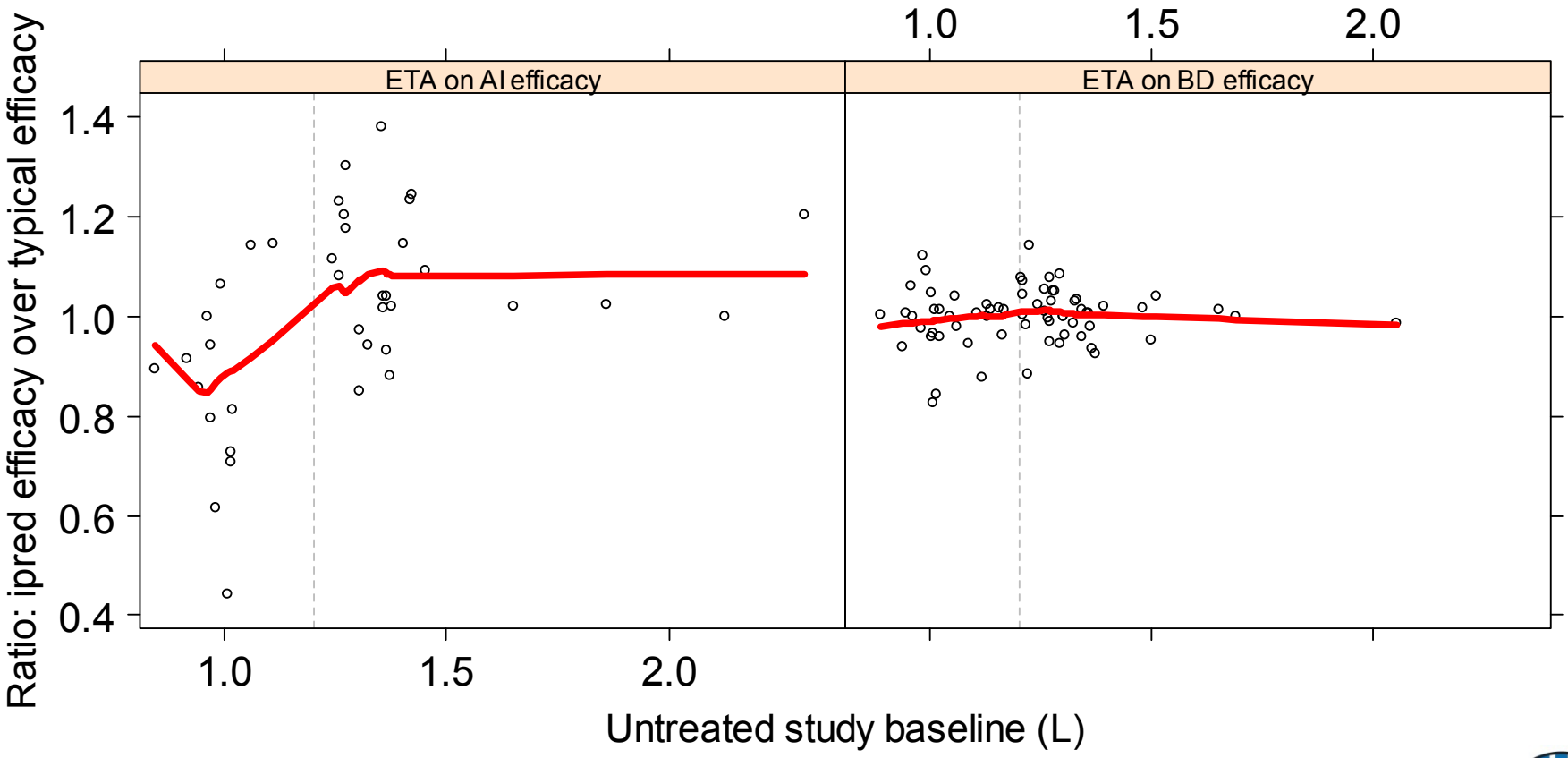
$$FEV1_{active} = Baseline + Eff_{placebo} + Progression_{disease} + \mathbf{Eff_{drug}}$$



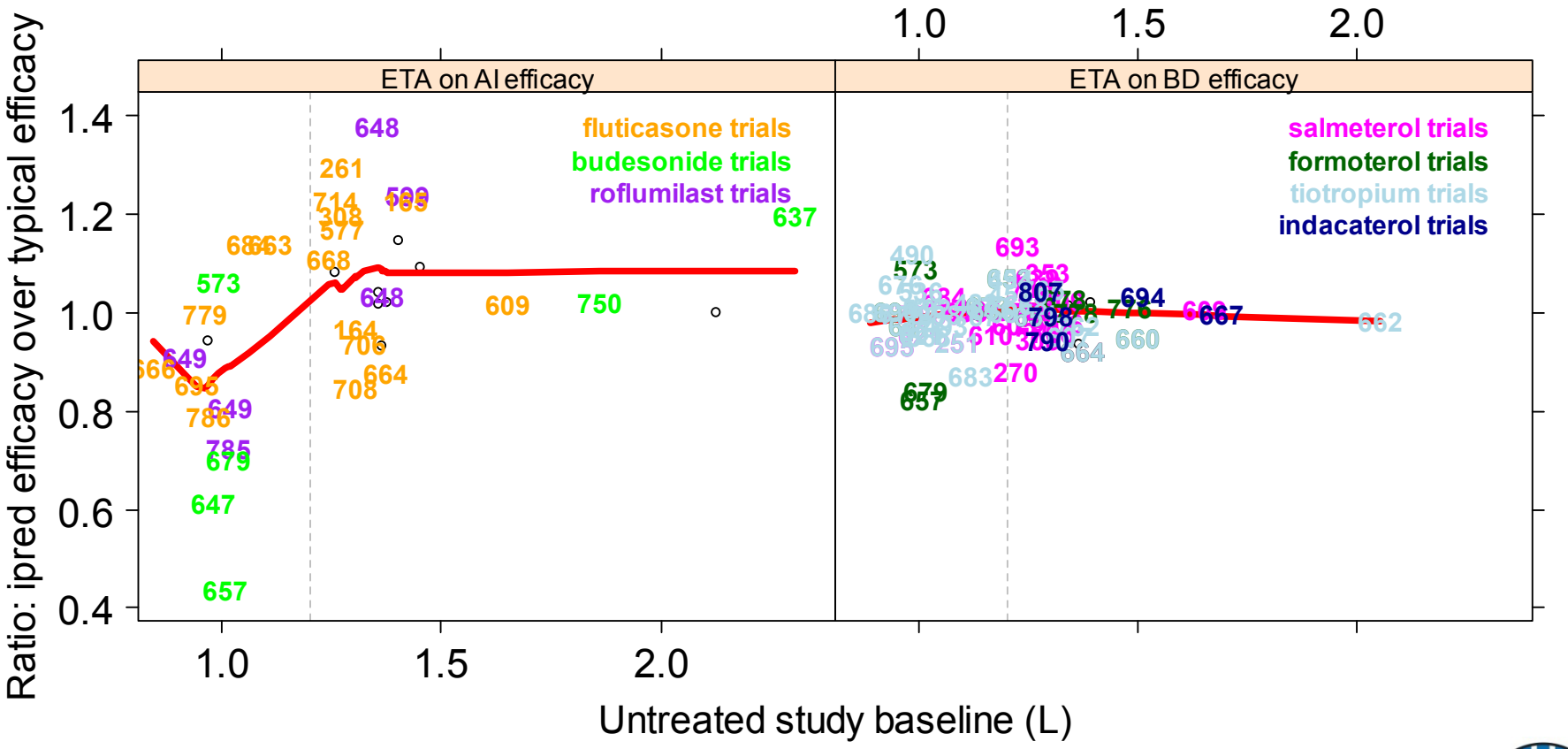
Covariates

- Pre-specified
  - baseline parameter, based on inclusion criteria:
    - Min/max disease severity:mild/moderate/severe/v. severe
    - Restricted medical history limits more severe patients
    - min/max #exacerbations in previous year (no, any#, ≥1, ≥2)
  - Disease prog. proportional to (ipred) $baseline_{untreated}$
- Selected at p<0.001:
  - Baseline decline with Age
  - Baseline < 1.2 L: Linear decline in anti-inflammatory efficacy

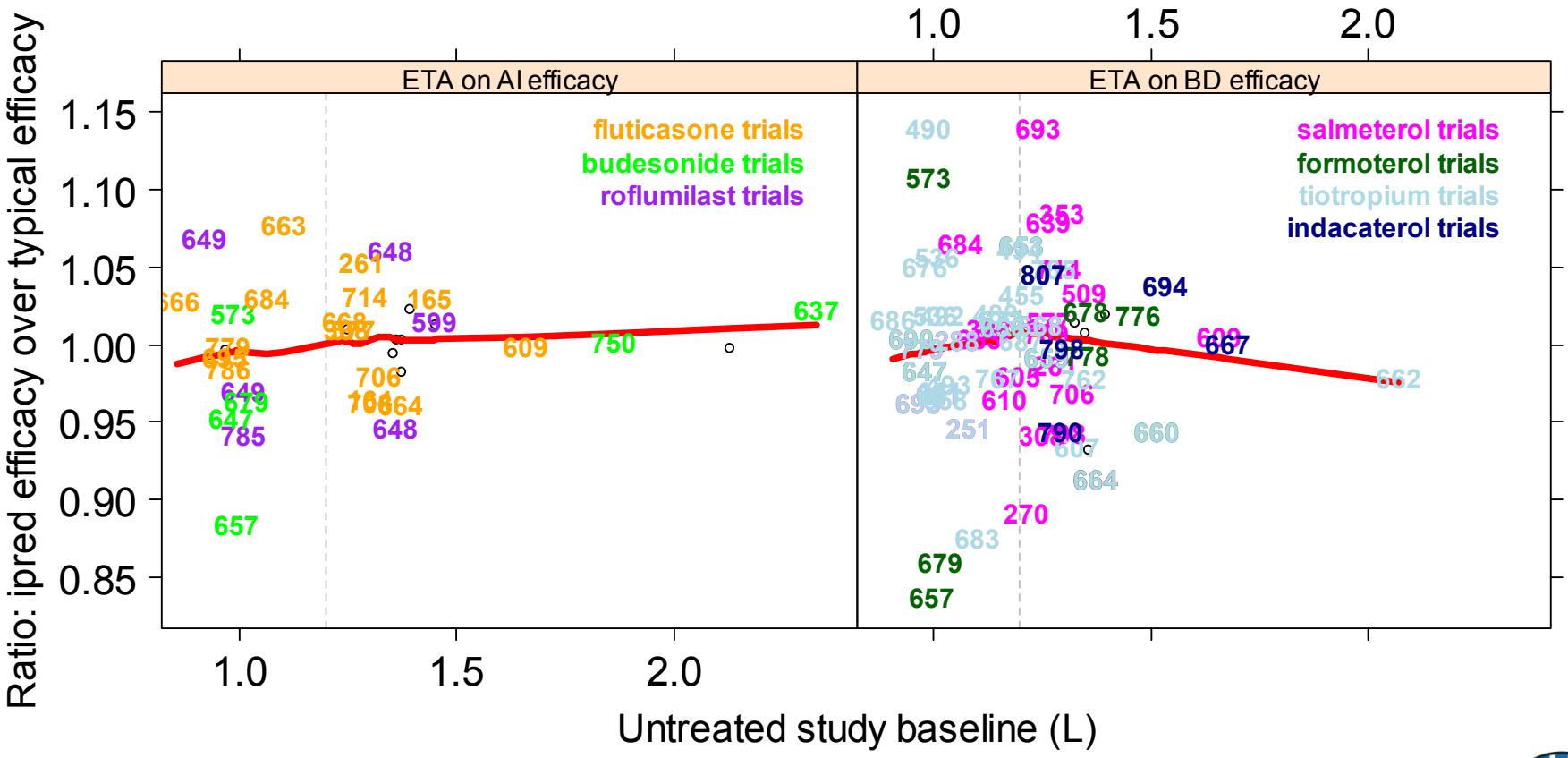
η-diagnostics: Base model Baseline affects drug response



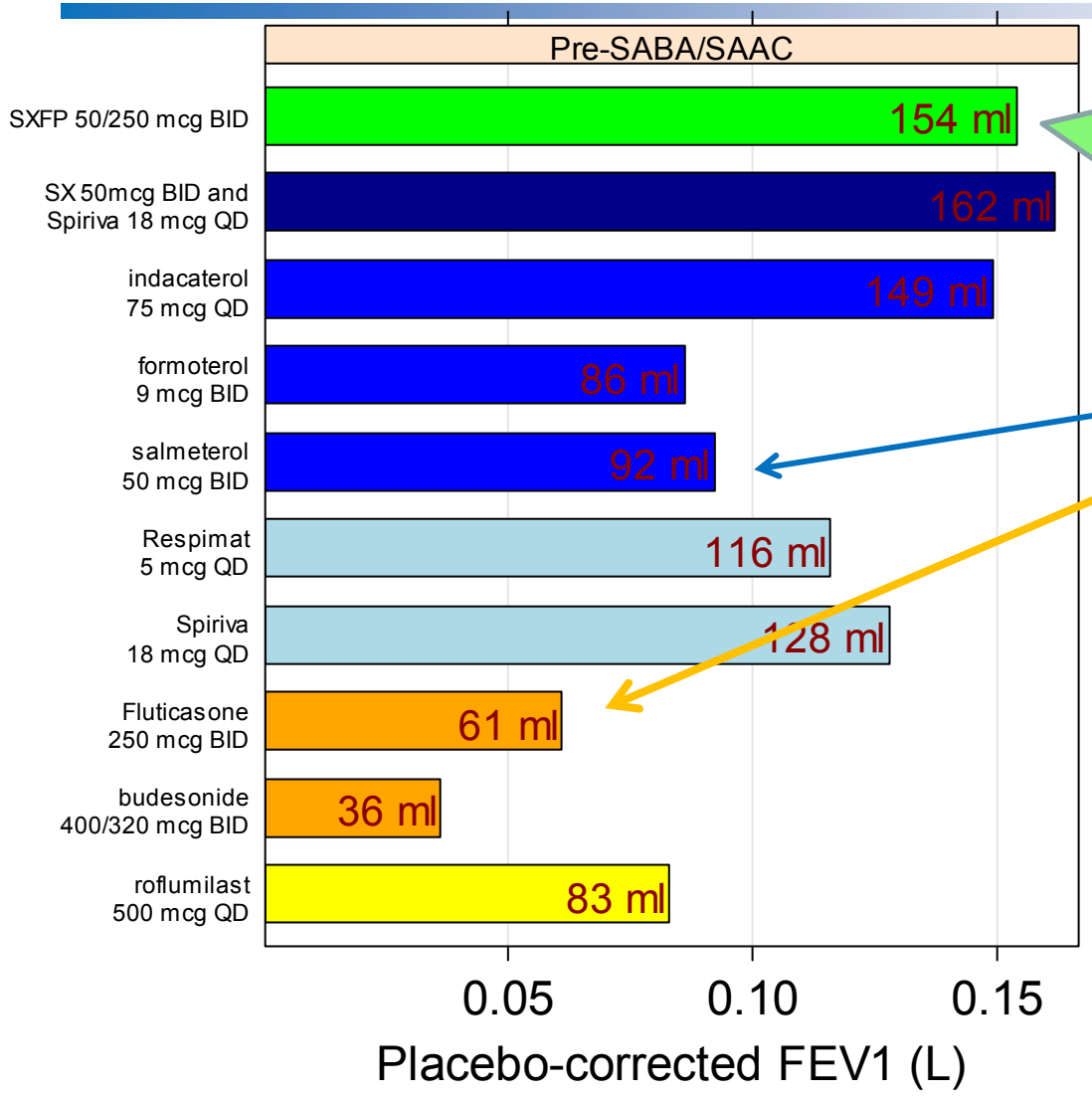
η-diagnostics: Base model Baseline affects drug response



ETA diagnostics: Final model

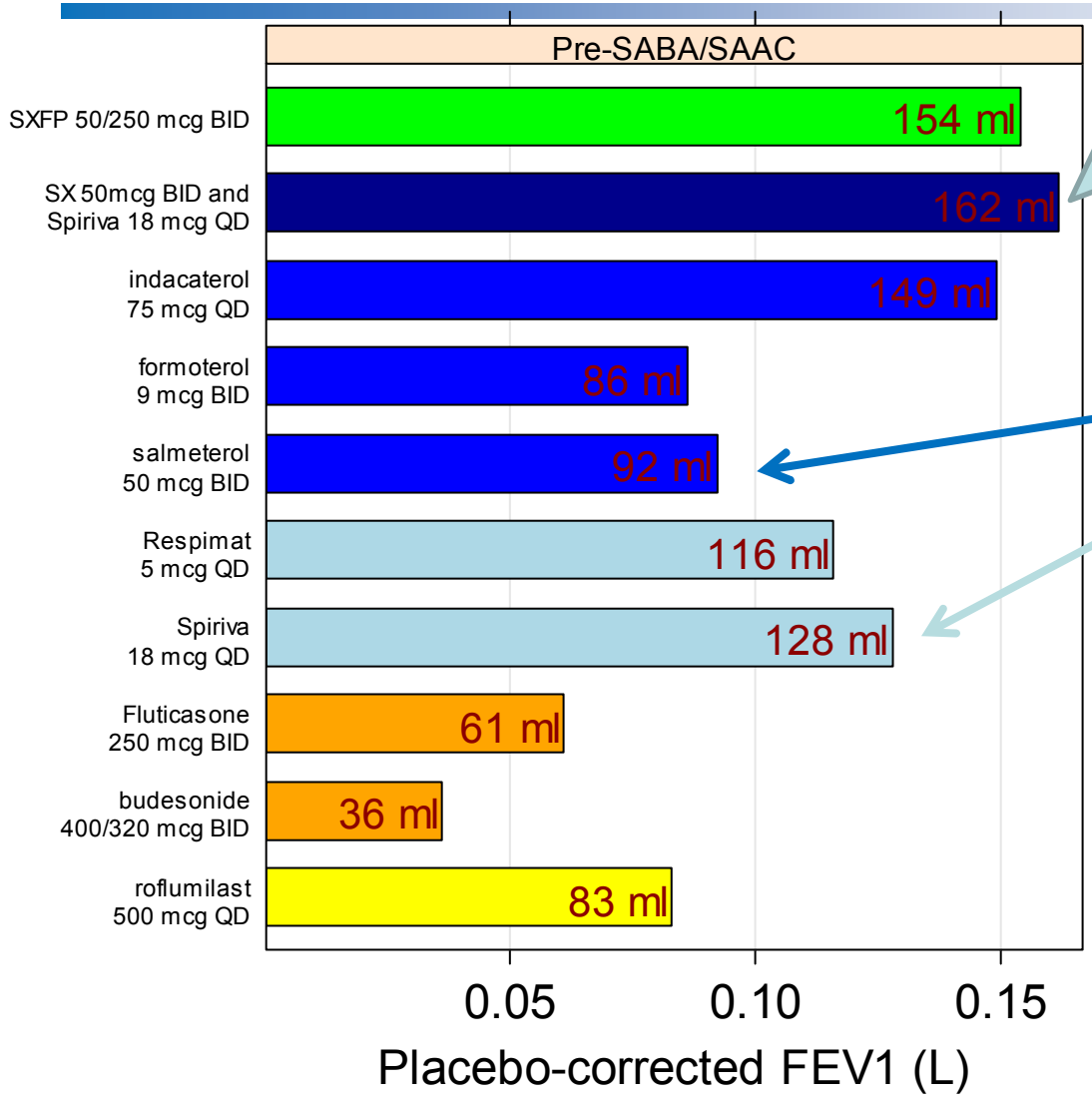


Efficacy in moderate COPD



LABA + ICS same efficacy as the sum of the two mono components

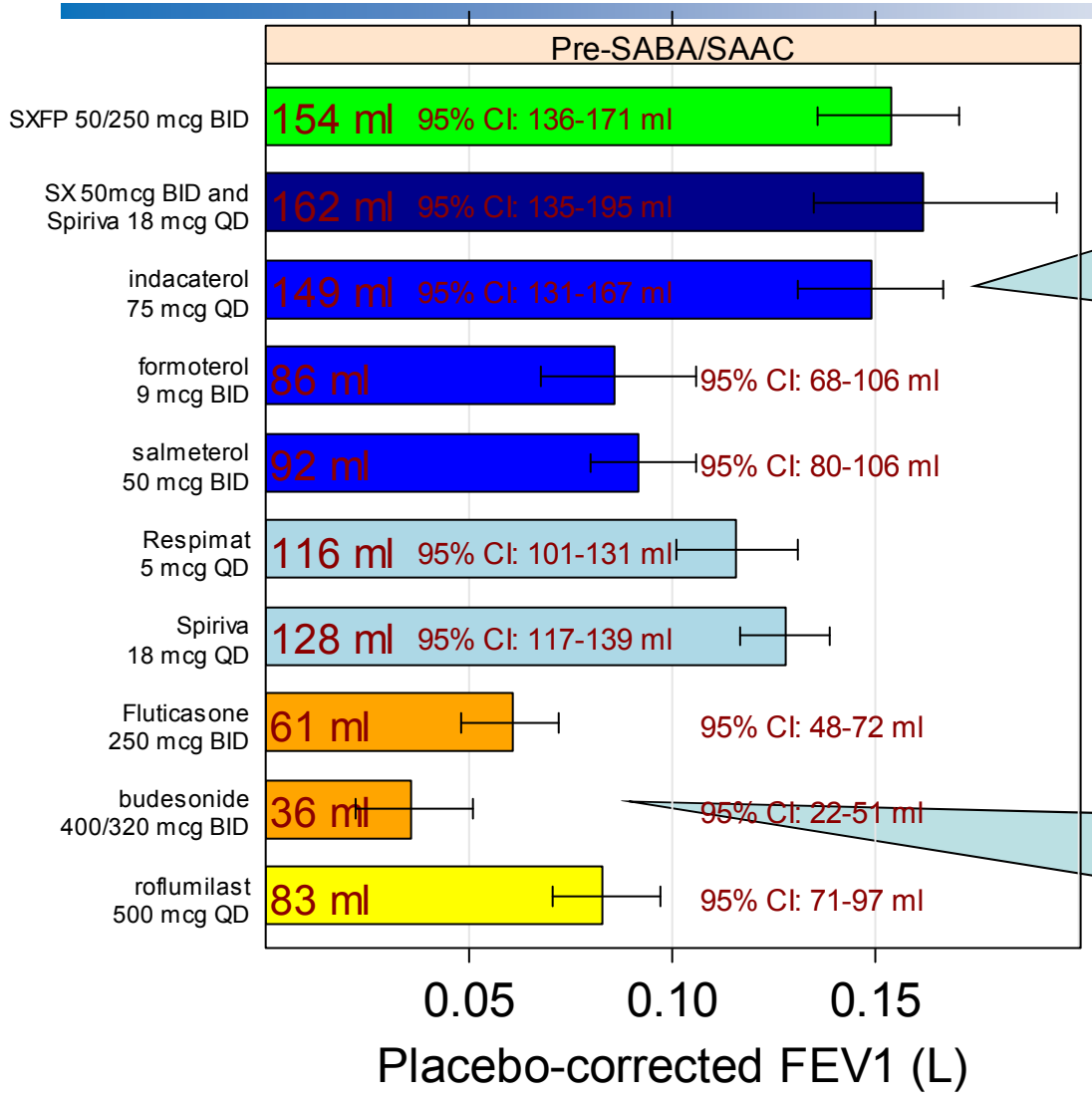
Efficacy in moderate COPD



LABA+LAAC interaction estimated as a relative reduction in LABA effect

Efficacy in moderate COPD

95% CI **excluding** treatment heterogeneity

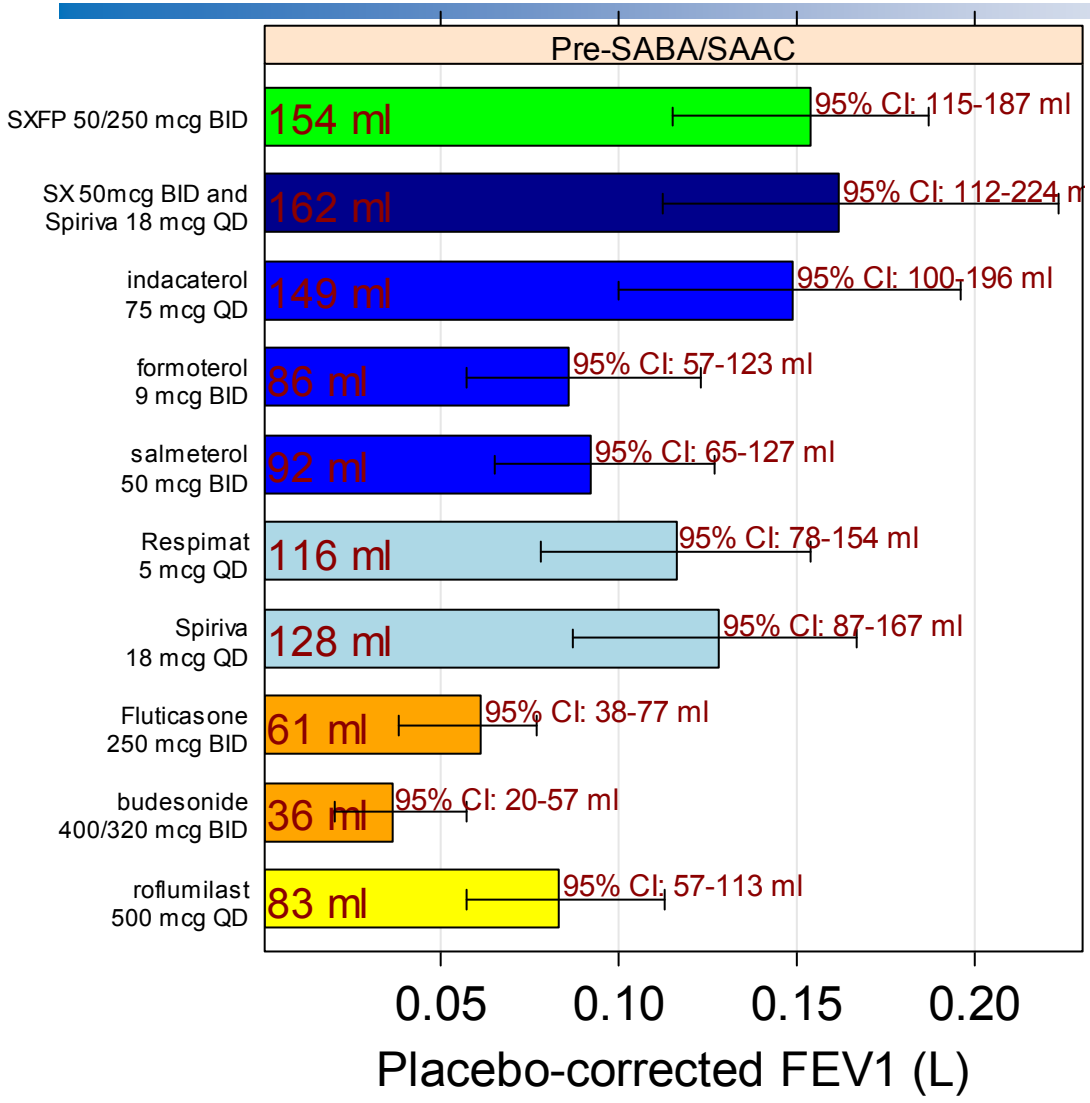


Indacaterol (QD) has superior trough efficacy in comparison to the two BID LABAs.

Several large studies indicating poor efficacy for budesonide. Due to protocol/study conduct or compound?

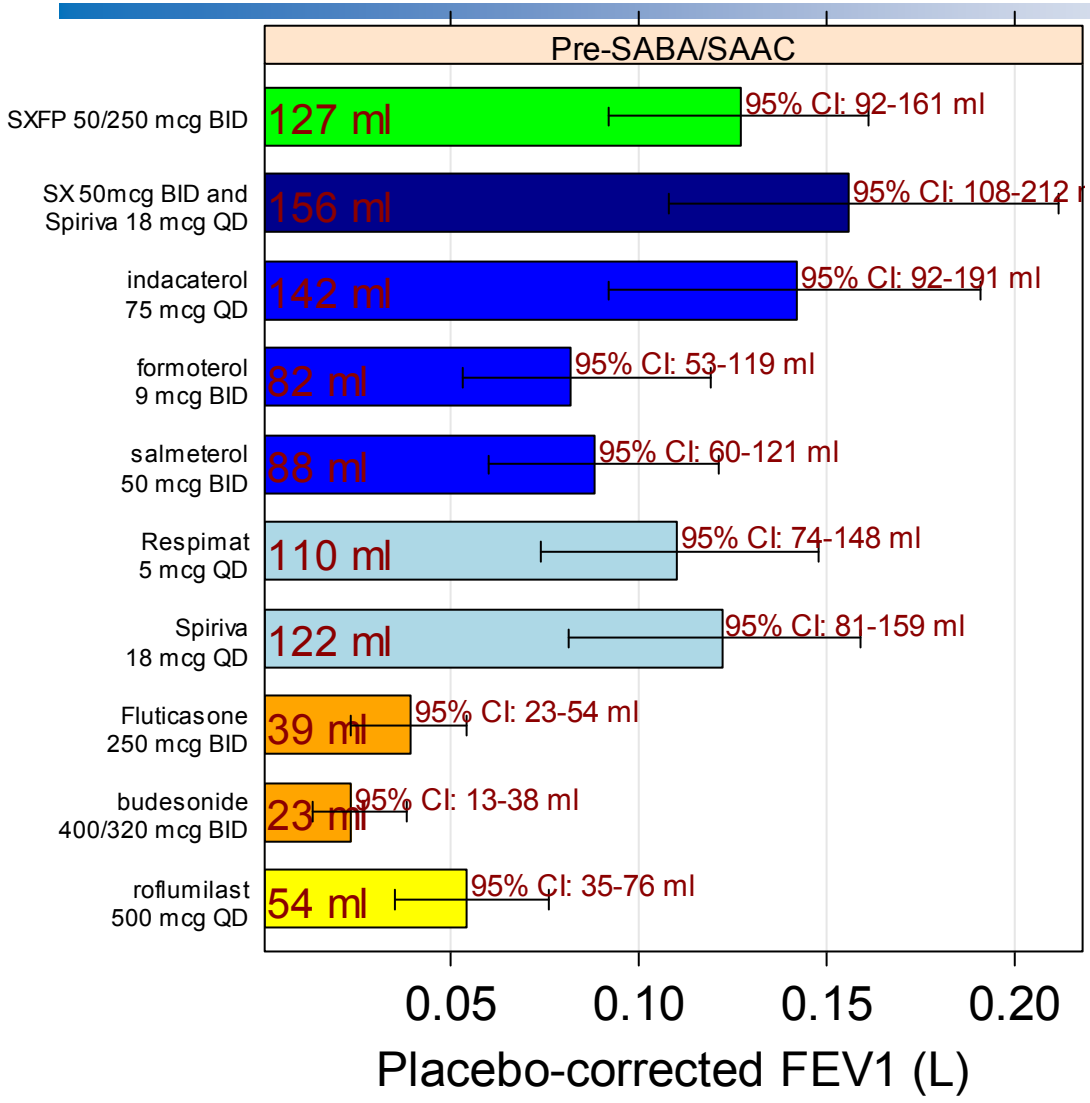
Efficacy in moderate COPD

95% CI **including** treatment heterogeneity (ISV Emax)

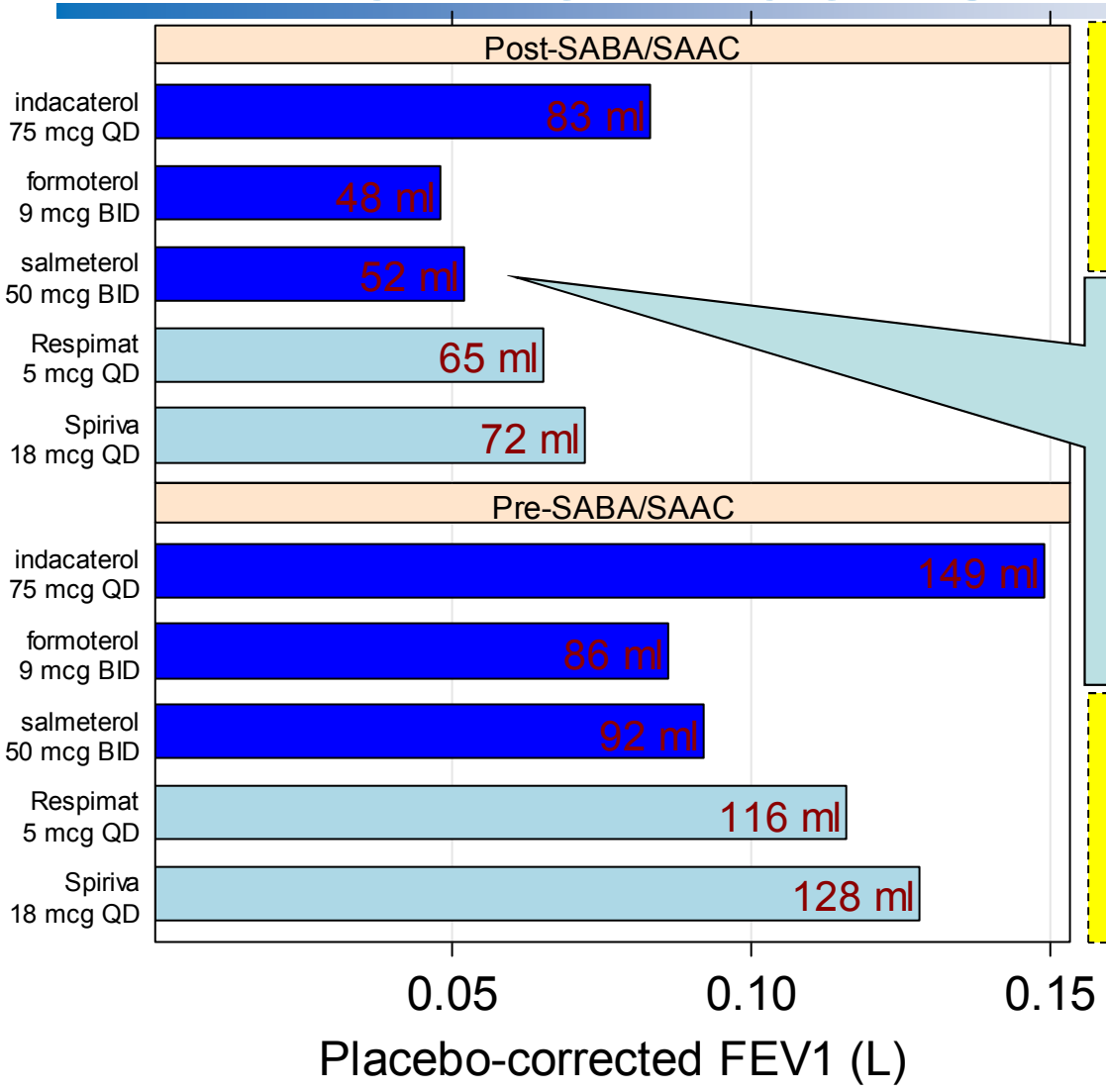


Efficacy with untreated baseline 1 L

95% CI **including** treatment heterogeneity



Predicted efficacy: Morning trough Pre- vs. Post-SABA/SAAC



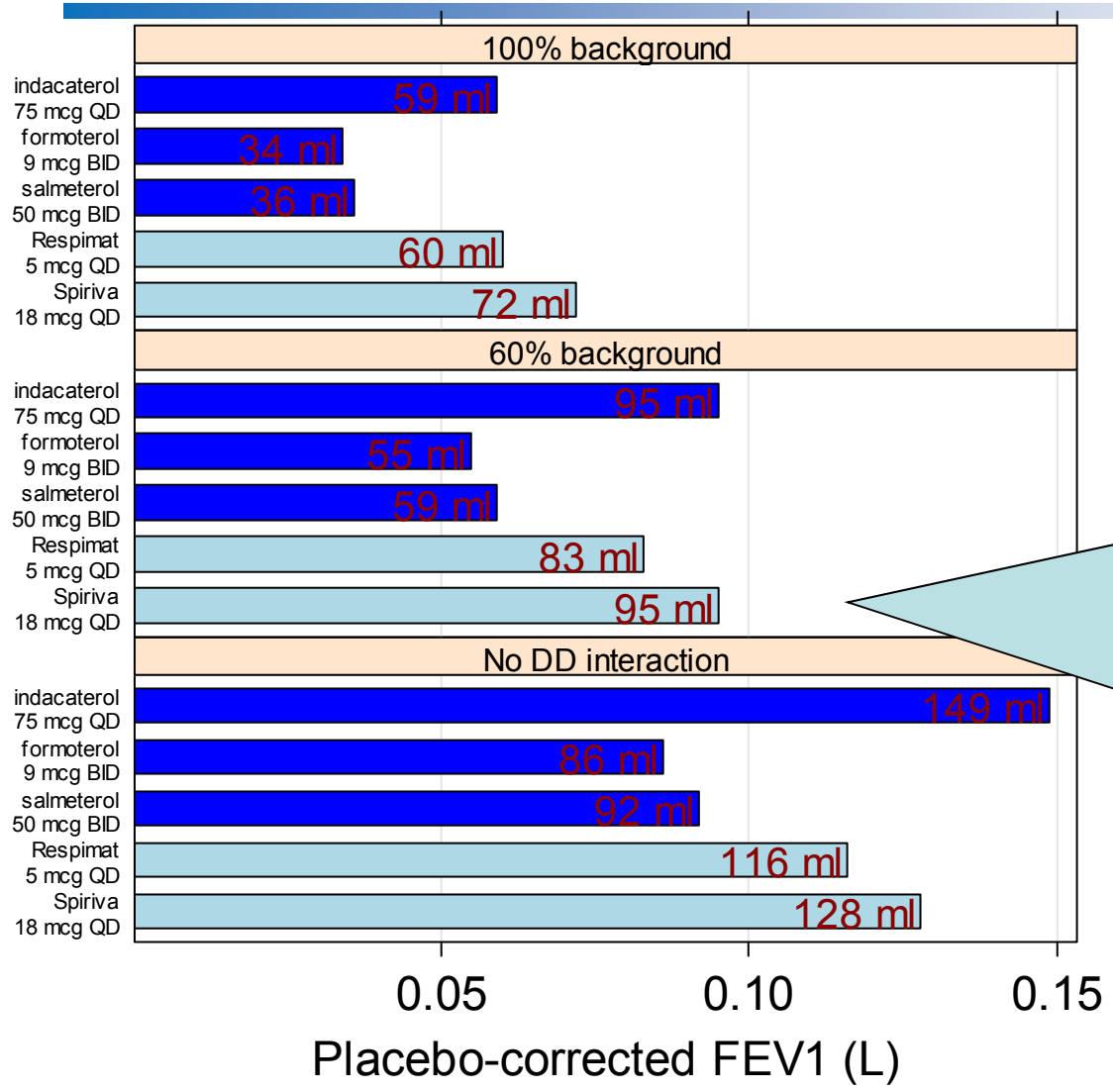
LABA and LAAC efficacy when FEV1 is measured post-SABA/SAAC

In TORCH (ref 650) reports a disappointing 40 ml efficacy for salmeterol. Low efficacy due to measuring post SABA

LABA and LAAC efficacy when FEV1 is measured pre-SABA/SAAC

Model Predicts LABA/LAAC Interaction

LABA with LAAC background and vice versa



UPLIFT (661) reports 87-103 ml efficacy for Spiriva. Canadian study (686) reports 80-120 ml. 60% and 54% LABA background, respectively.

Discussion

- Placebo effect has no typical direction
  - Still important to account for: individual studies have marked placebo effect
- Dropout due to lack of efficacy
  - Masks any disease progression
  - Reduce signs of disease modifying effects
- Low study baseline
  - ➢lower efficacy of anti-inflammatory drugs
  - ➢Weak trend towards lower efficacy in bronchodilators (LABA or LAAC)
    - Mixed message in literature on individual data

Conclusion

- DD-interactions and covariates account for the sometimes disappointing results on FEV1 in late-stage trials
  - TORCH, UPLIFT & rolumilast exacerbation trials
  - Except LABA/LAAC interaction (UPLIFT) these do not necessarily translate into lower effect on exacerbations!
- Model provides efficacy bench mark for published compounds, accounting for treatment heterogeneity (ISV E_{max})