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PAGANZ
Population Approach Group of Australia & New Zealand

Model based longitudinal meta-analysis of FEV1 in COPD trials

A tool for efficacy benchmarking

Julia Korell (1), Steven W. Martin (2),
Mats O. Karlsson (1), Jakob Ribbing (1,3)

(1) Uppsala University, Sweden
(2) Pfizer Inc, Cambridge, MA, USA
(3) Pfizer AB, Sollentuna, Sweden

Pharmacometrics Research Group
Department of Pharmaceutical Biosciences
Uppsala University, Sweden

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The Concept

Why analysing literature data?

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Why analysing literature data?

Efficacy benchmarking is a major component in decision making during clinical drug development

- How does a new compound compare with the existing treatment options?

Clinical trials are expensive and time-consuming

- Conducting head-to-head trials with all available competitors is most often unfeasible

Existing treatments have often already been studied multiple times

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The Concept

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Existing treatments have often already been studied multiple times

⇨ ***Use the information available in literature!***

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Methodology

Model based meta-analysis

Methodology

Model based meta-analysis

Characteristics:

- Longitudinal, parametric analysis of aggregate data found in literature
- Analysis of **mean response** across individuals in each study arm at **all available time points**:
  - At least baseline & end of treatment
  - Often intermediate time points available
- Study = individual:
  - ⇨ Equivalent to population approach / mixed effects analysis

Methodology

Model based meta-analysis

3 levels of variability:

1) Inter-study variability (ISV)

= Inter-individual variability in population analysis

= **Heterogeneity** in random effects meta-analysis

- Broader inclusion criteria for studies in model based meta-analysis results in better ability to estimate treatment heterogeneity
- Should also be included on other components in the model, not just treatment effects
- Allows investigation of covariate effects

Methodology

Model based meta-analysis

3 levels of variability:

2) Inter-arm variability (IAV)

= Between-occasion variability in pop. analysis

- Different subjects allocated to different study arms results in slightly different observed baseline values
- *Not equivalent to residual error, as all subjects come from the same population ⇨ correlation!*
- Particularly important for small studies

  ⇨Weighted by sqrt(n)

Methodology

Model based meta-analysis

3 levels of variability:

3) Residual unexplained variability (RUV)

- Random variability due to sampling & measurement error
- Smaller studies have larger random error
  - ⇨Weighted by sqrt(n)

Methodology

Model based meta-analysis

Benefits of a longitudinal meta-analysis:

- Data obtained at intermediate time points contain additional information
- Allows investigation of:
  - Time course of on- & offset of effect
  - Tolerance development / loss of effect
  - Covariate effects
    - Often confounded in large & long, later-phase trials on more severe patients
    - Signal is augmented by inclusion of smaller, shorter dose-ranging studies on less severe patients

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Our Work

FEV1 literature model in COPD

Clinical background

COPD = Chronic obstructive pulmonary disease:

- 3rd leading cause of death in US & 4th worldwide
- Slow developing, but progressive disease
- Airway obstruction & inflammation
- Maintenance treatment classes:

Direct bronchodilators (BD)	Anti-inflammatory (AI)
Long-acting β_2-agonists (**LABA**)	Inhaled corticosteroids (**ICS**)
Long-acting anticholinergics (**LAAC**)	Phosphodiesterase4 inhibitors (**PDE4i**)
	Neutrophil elastase inhibitors (**NEi**)
	P38 MAP kinase inhibitors (**P38i**)

FEV1 literature model in COPD

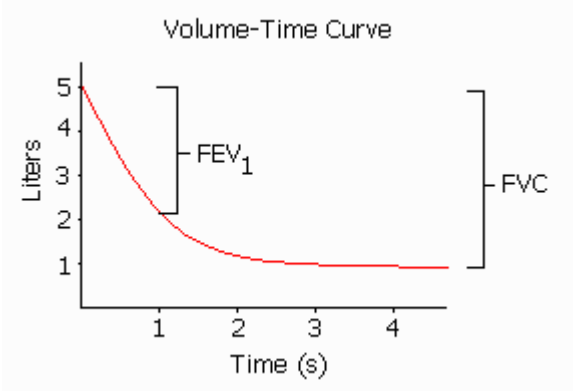
Clinical background

Forced expiratory volume in 1 sec (FEV1):

⇨ Measure for airway obstruction

- Diagnosis & assessment of COPD
- Biomarker for dose selection in Phase 2b studies

= greatest volume that can be exhaled in 1 sec after a deep breath



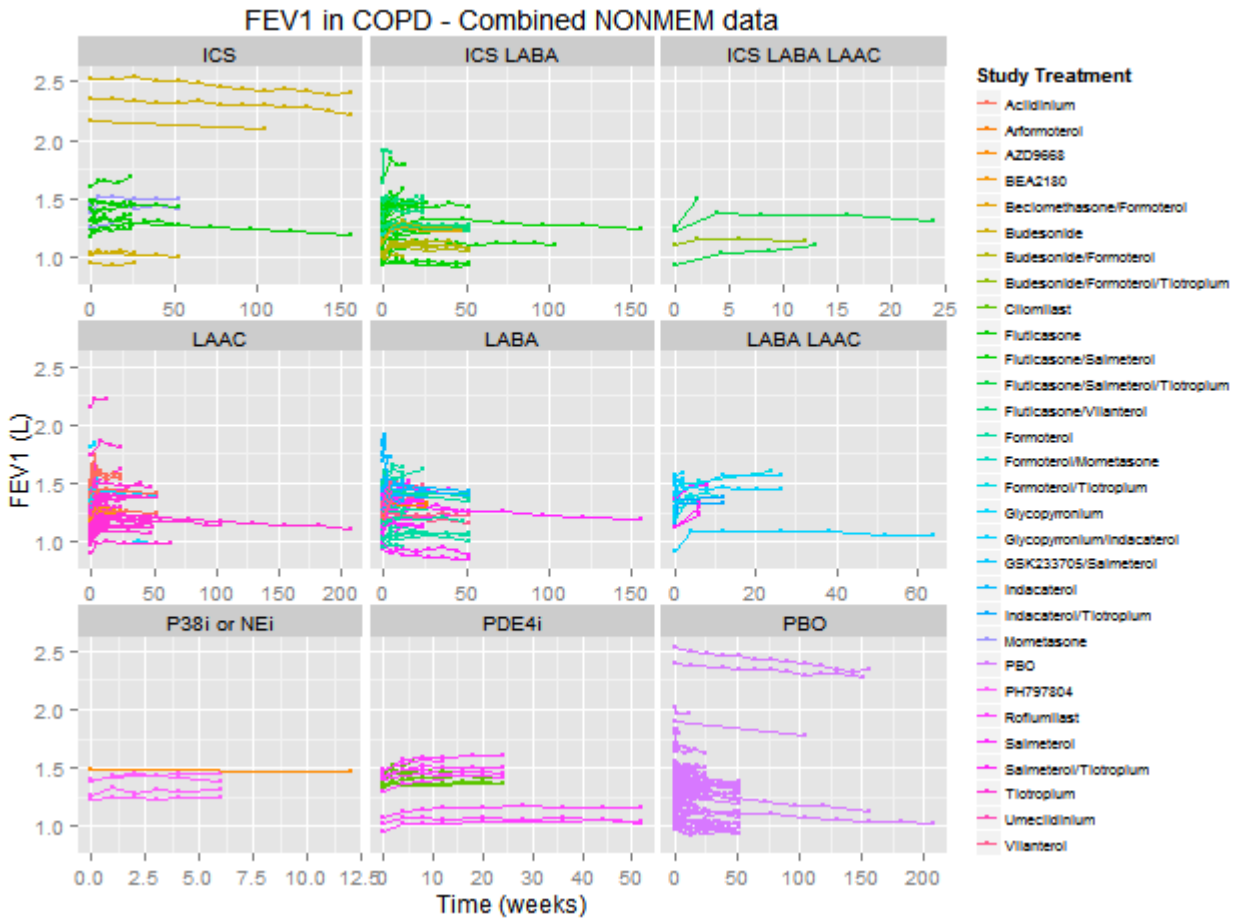
http://meded.ucsd.edu/isp/1998/asthma/html/spirexp.html

FEV1 literature model in COPD

Longitudinal FEV1 literature data

Absolute morning trough FEV1 response:

Database	
until July 2013	
references	133
studies	141
arms	419
compounds	19
combinations	105
obs.	1982
subjects	106,422
Randomised, controlled trials (exception Spiriva®)	



Longitudinal FEV1 literature data

Change from baseline morning trough FEV1:

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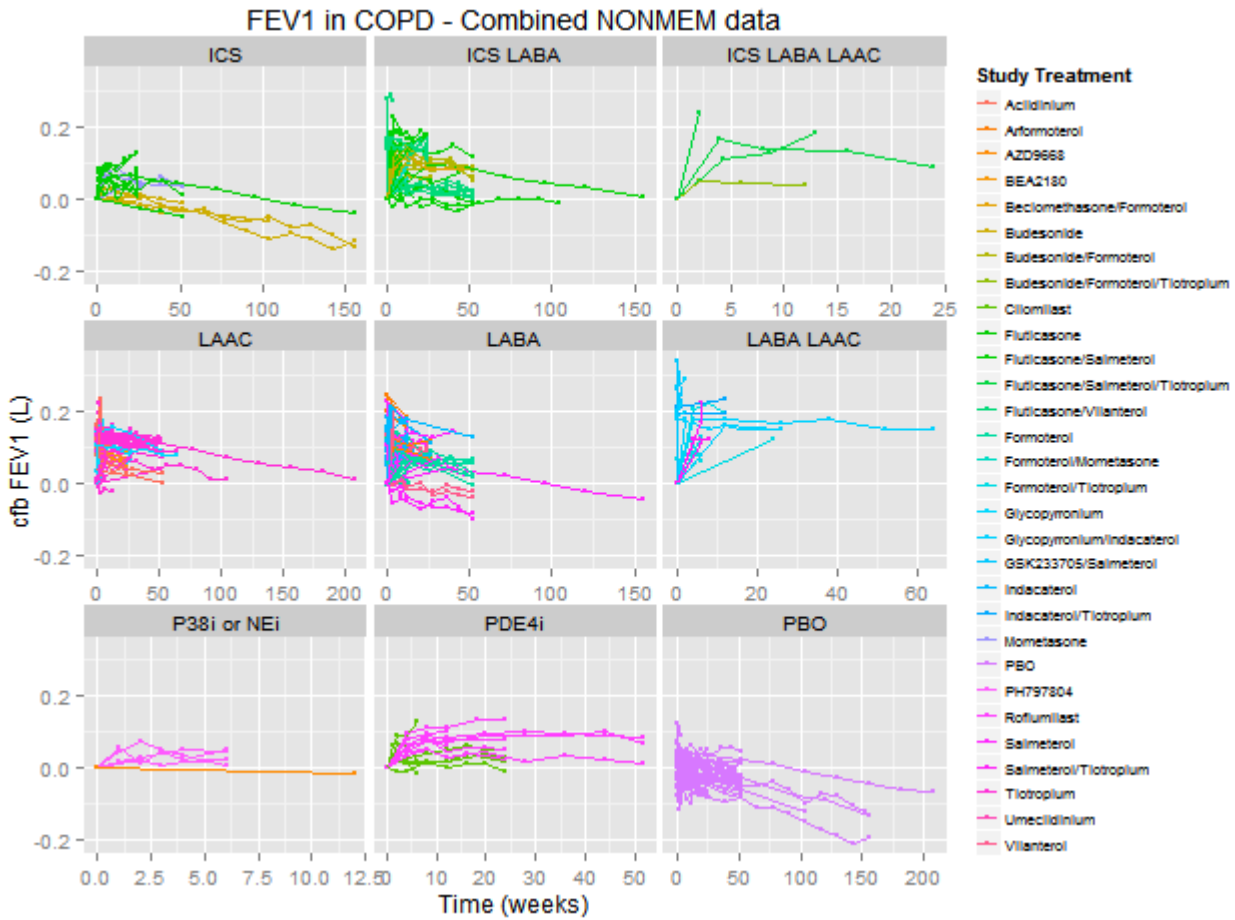


FEV1 literature model in COPD

Model characteristics

Components in the model:

- Baseline (B) with disease severity as covariate, ISV & IAV
- Disease progression (DP) with ISV
- Placebo effect (E_{PBO}) with ISV on max. effect
- Effect of background treatment (E_{back}) with ISV
- Effect of study drug treatment (E_{drug}) with ISV

$$FEV1 = B - DP + E_{PBO} + E_{back} + E_{drug}$$

⇨ Not entirely additive due to:

- Baseline is correlated with DP, E_{back} & E_{drug}
- Drug - drug interactions

FEV1 literature model in COPD

Model characteristics

Drug effects:

- Dose - response relationship (Emax model) identifiable for 10 compounds
- For the other 9 compounds efficacy was assumed to be equal at all dose levels
- ISV included on all drug effects

FEV1 literature model in COPD

Model characteristics

Covariates:

⇨ Mainly **pre-specified covariates** available at study begin included to **ensure *a priori* predictive performance** of the model:

- On baseline:
  - Mean age at study begin
  - Study inclusion criteria regarding:
    - Disease severity
    - History of exacerbation frequency

FEV1 literature model in COPD

Model characteristics

Correlation with individually predicted baseline:

- Drug effects (ind. pred. baseline < 1.2 L)
- Disease progression

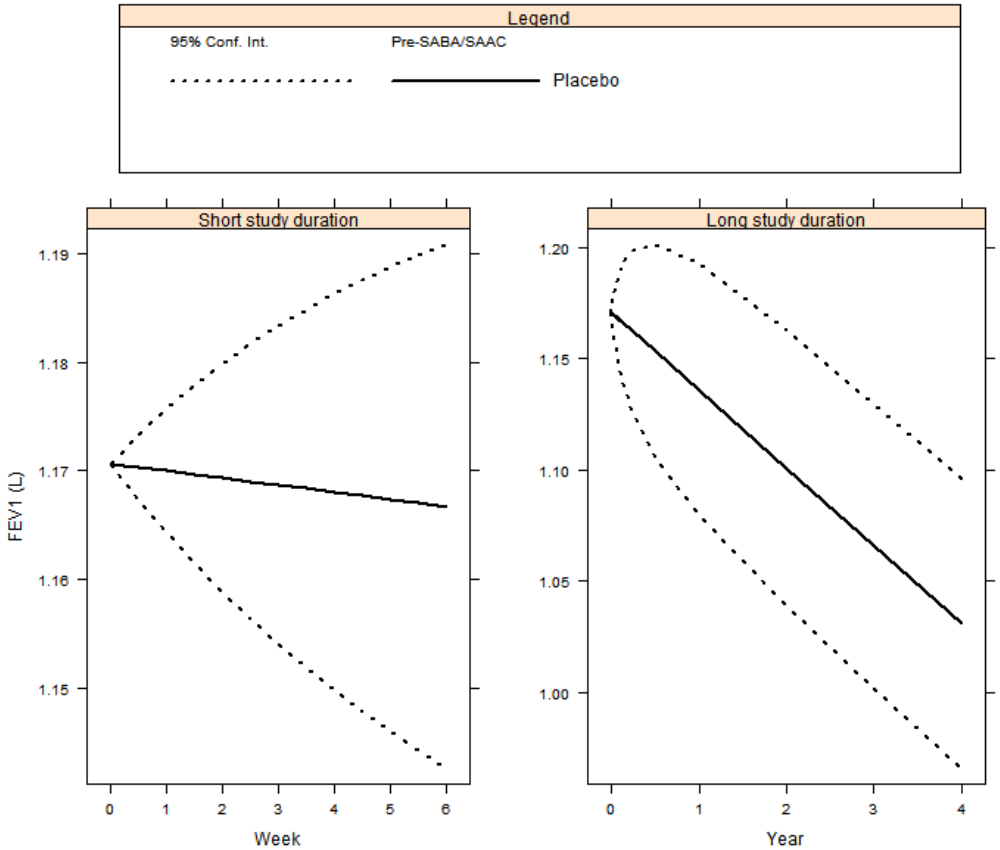
Time course of effect onset included for:

- Placebo effect
  - Gradual or immediate onset possible
  - Mixture model
- Drug effects
  - Anti-inflammatory treatments
  - Once-daily administered bronchodilators

FEV1 literature model in COPD

Results & Predictions

Placebo effect & linear disease progression:



Disease progression:

Mean 35.9 ml / year

$ISV_{CV\%}$ 37.9%

for a baseline of 1.2 L

Placebo effect:

Mean ~0 ml

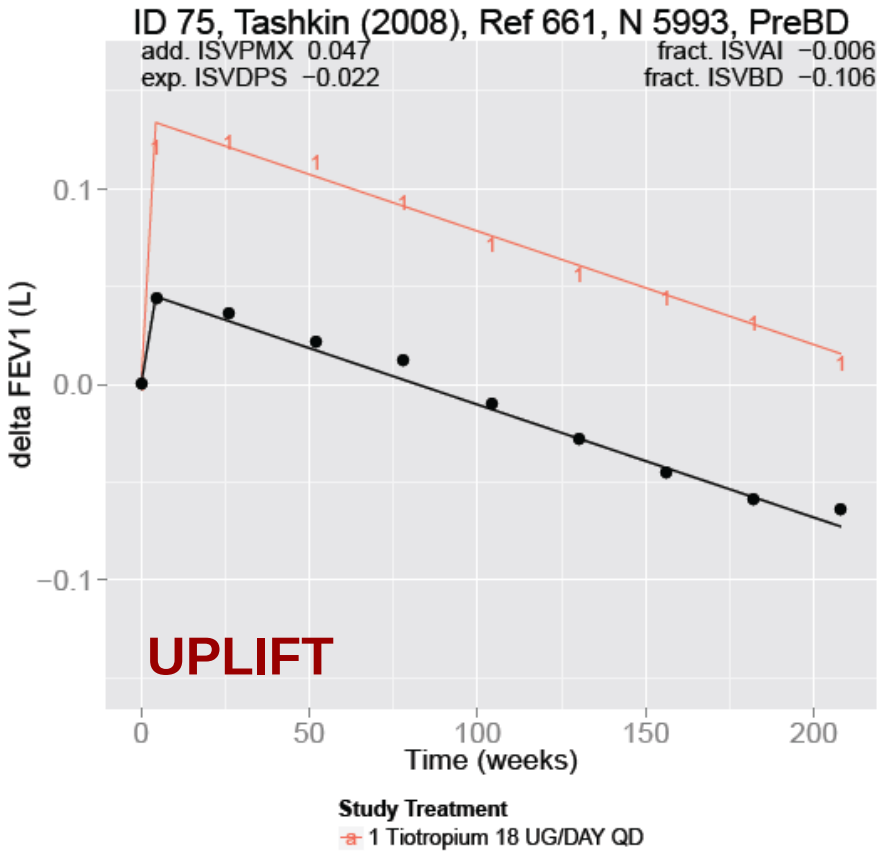
ISV_{SD} ±34.6 ml

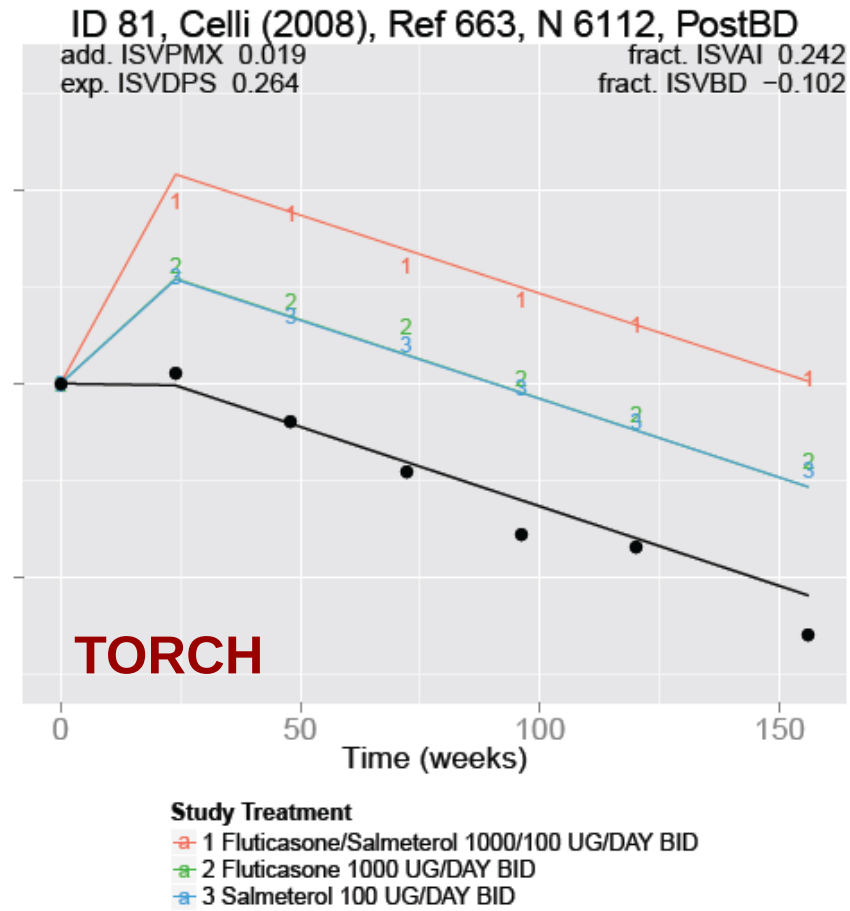
Model also allows for an early onset of placebo response

FEV1 literature model in COPD

Results & Predictions

Model fits for two selected studies:

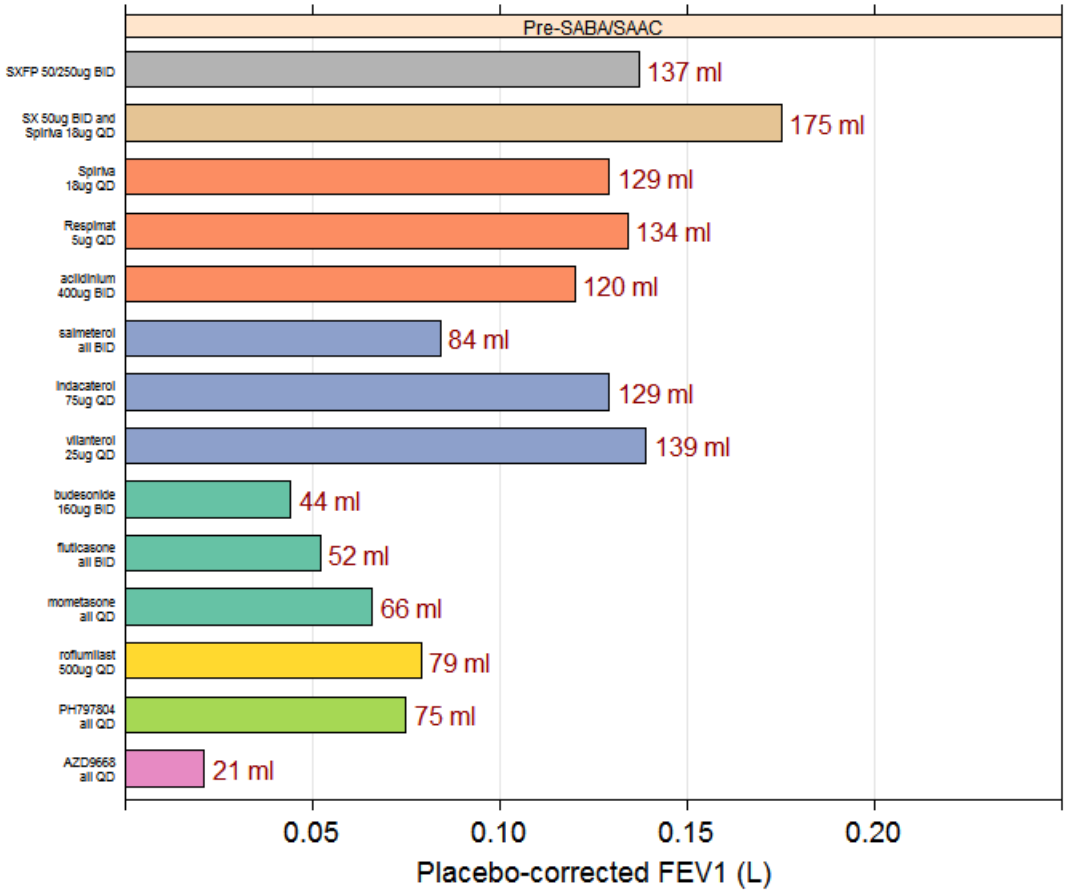




FEV1 literature model in COPD

Results & Predictions

Treatment effect in moderate COPD with 1.2L baseline:

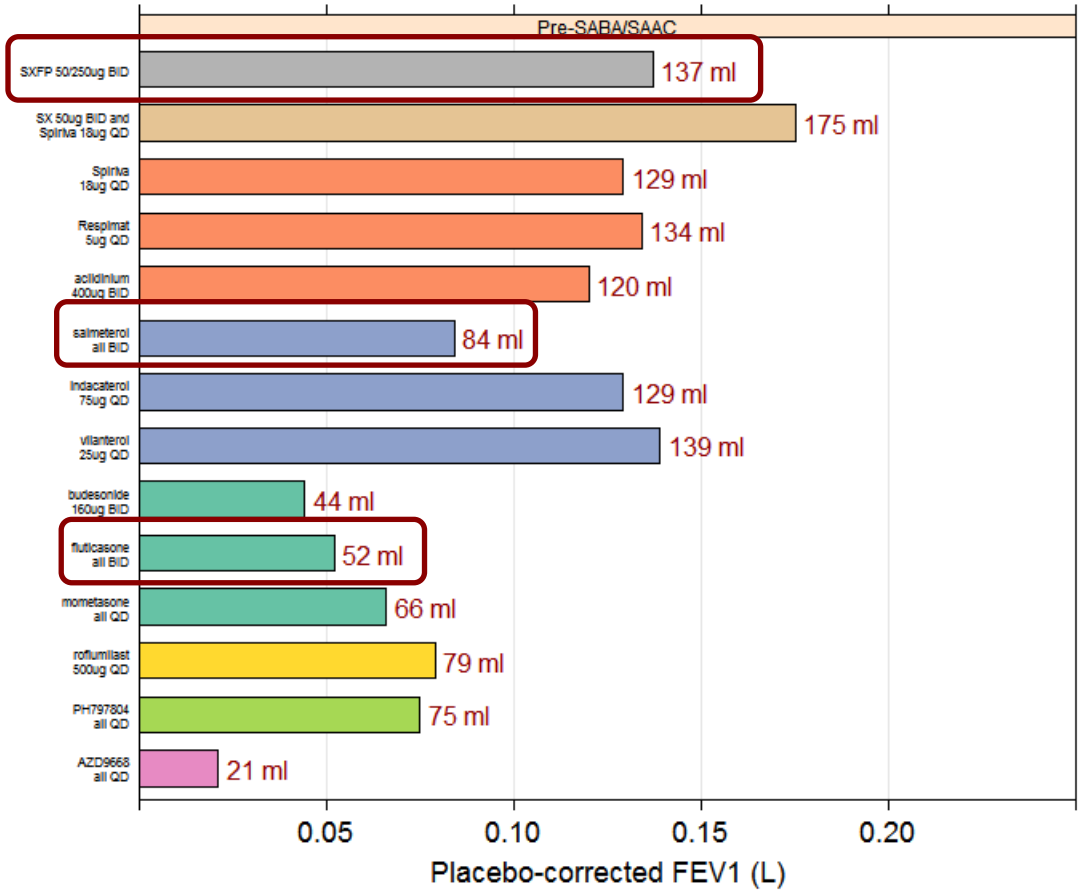


Point estimates and predictions for treatment combinations at steady state.

FEV1 literature model in COPD

Results & Predictions

Treatment effect in moderate COPD with 1.2L baseline:



LABA + ICS:

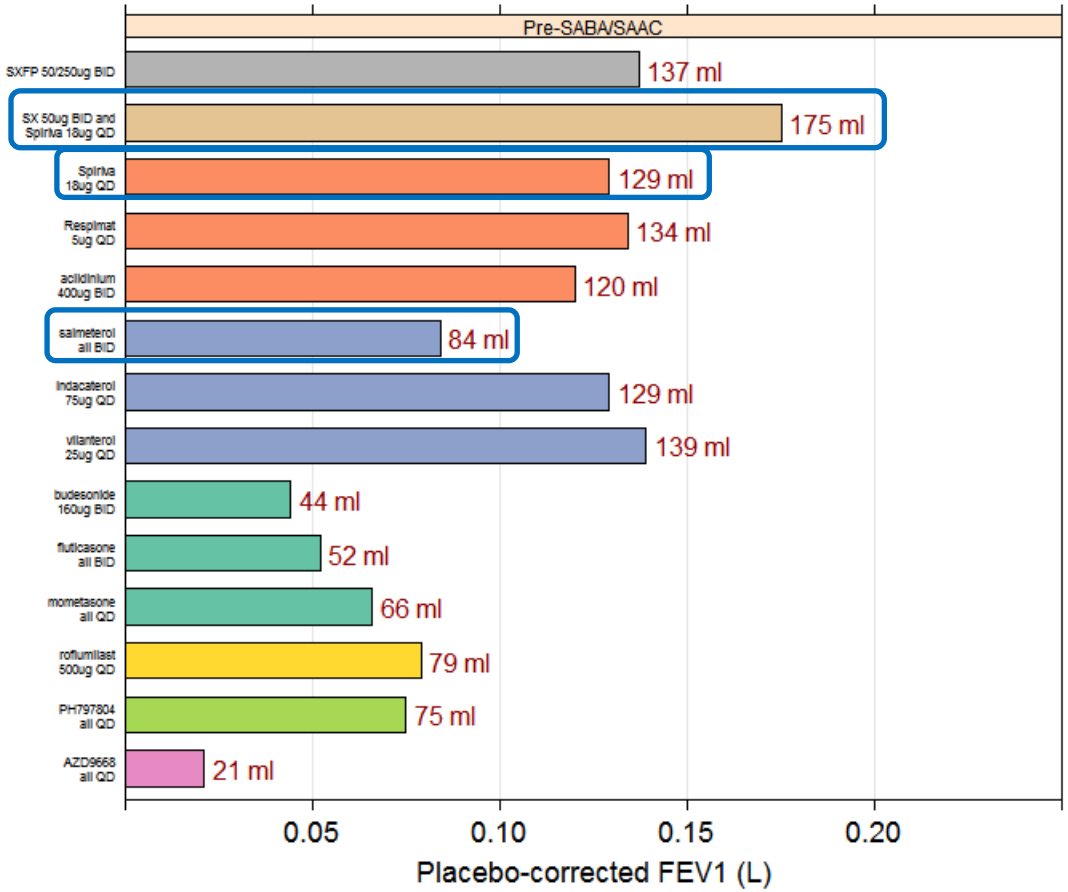
Additive effect

e.g. salmeterol + fluticasone:
84 ml + 52 ml = 136 ml

FEV1 literature model in COPD

Results & Predictions

Treatment effect in moderate COPD with 1.2L baseline:



LABA + ICS:

Additive effect

e.g. salmeterol + fluticasone:
84 ml + 54 ml = 138 ml

LABA + LAAC:

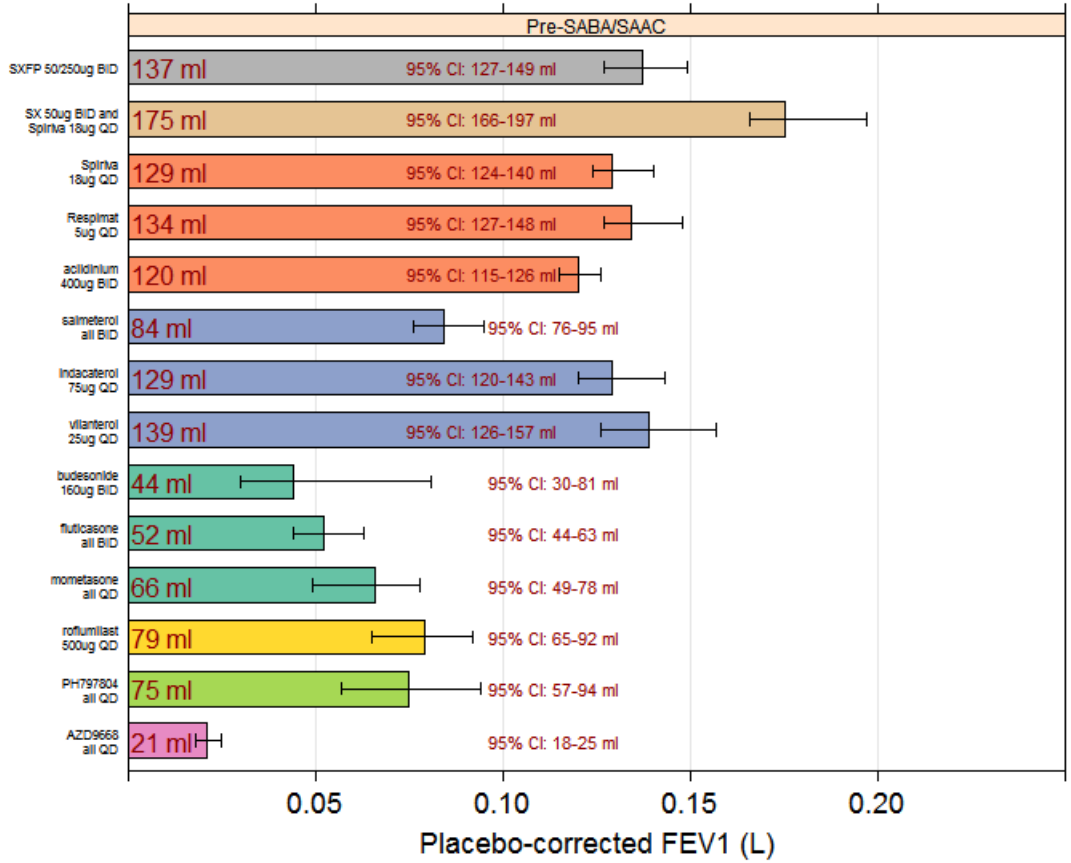
Infra-additive effect

e.g. salmeterol + tiotropium:
84 ml + 129 ml = 213 ml
⇨ ~18% reduction in total effect

FEV1 literature model in COPD

Results & Predictions

Treatment effect – 95% CI **without** ISV (heterogeneity):



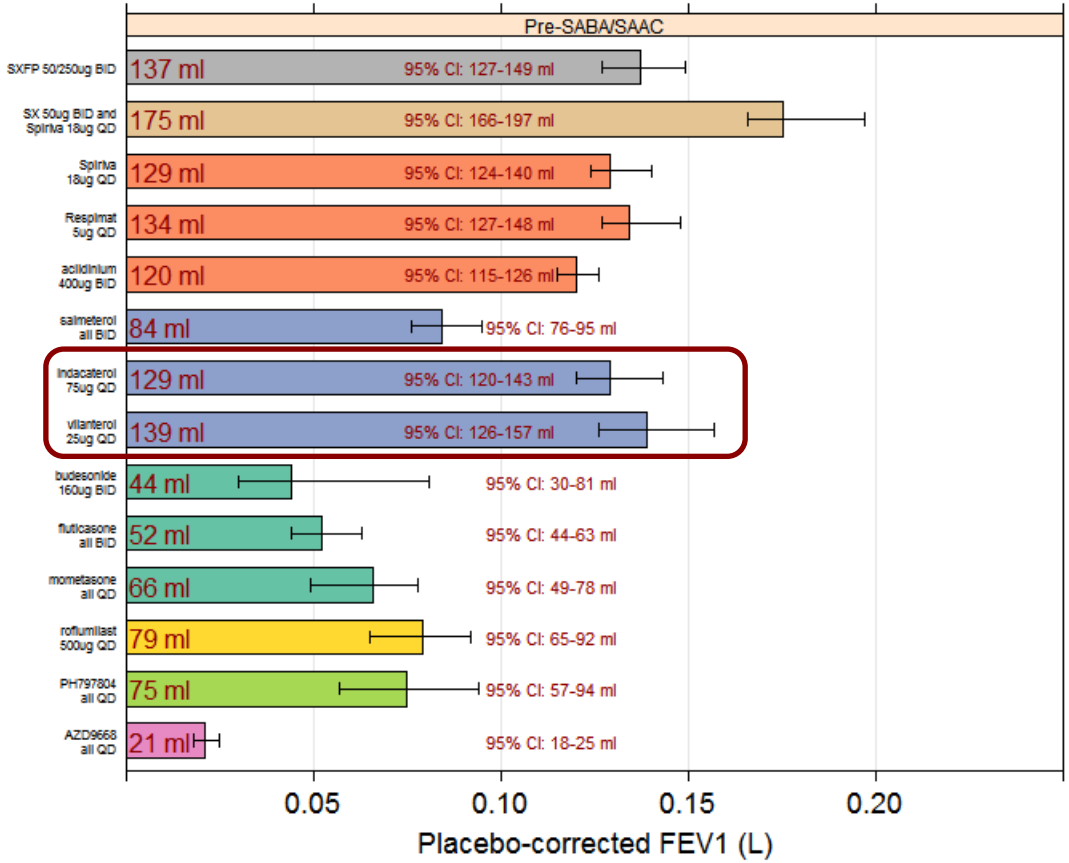
Magnitude of **uncertainty** in treatment effects when results of **several big studies** for a given compound are analysed together.

Can be used for efficacy benchmarking!

FEV1 literature model in COPD

Results & Predictions

Treatment effect – 95% CI **without** ISV (heterogeneity):



Indacaterol & Vilanterol

New ultra long acting QD β_2-agonists

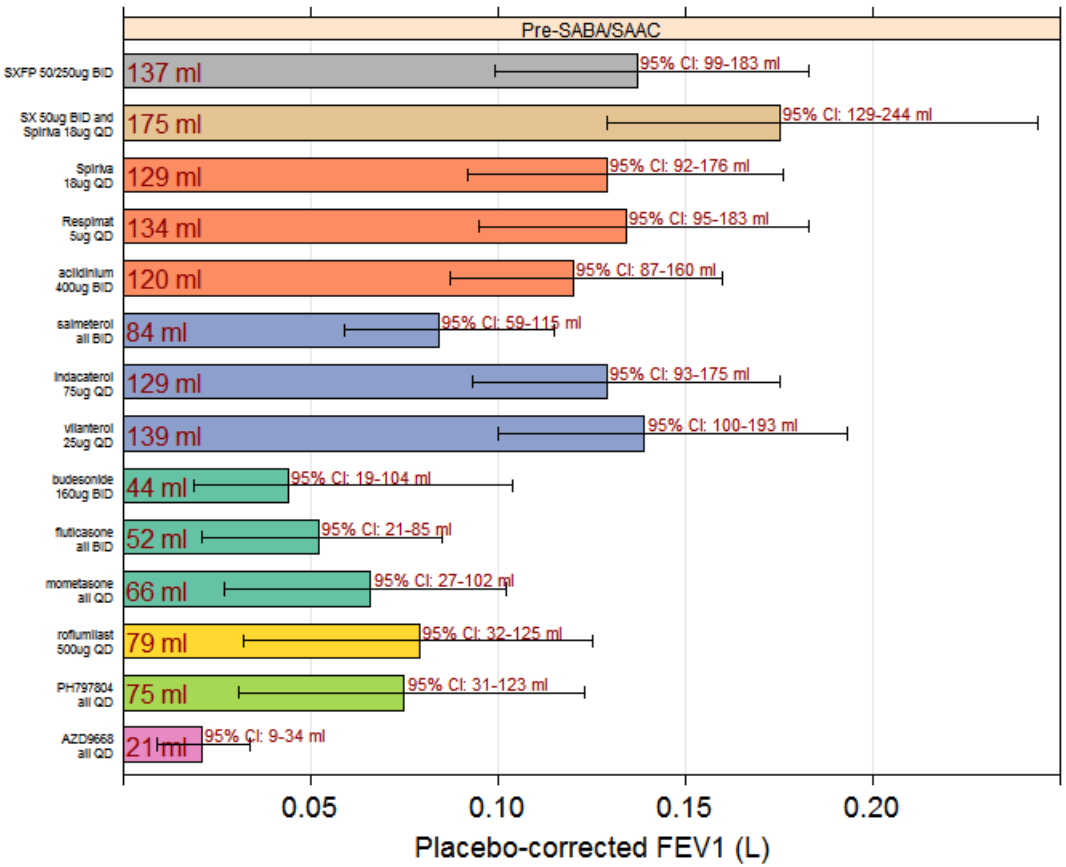
Superior efficacy compared to older BID β_2-agonists

Formoterol efficacy similar to salmeterol

FEV1 literature model in COPD

Results & Predictions

Treatment effect – 95% CI **with** ISV (heterogeneity):

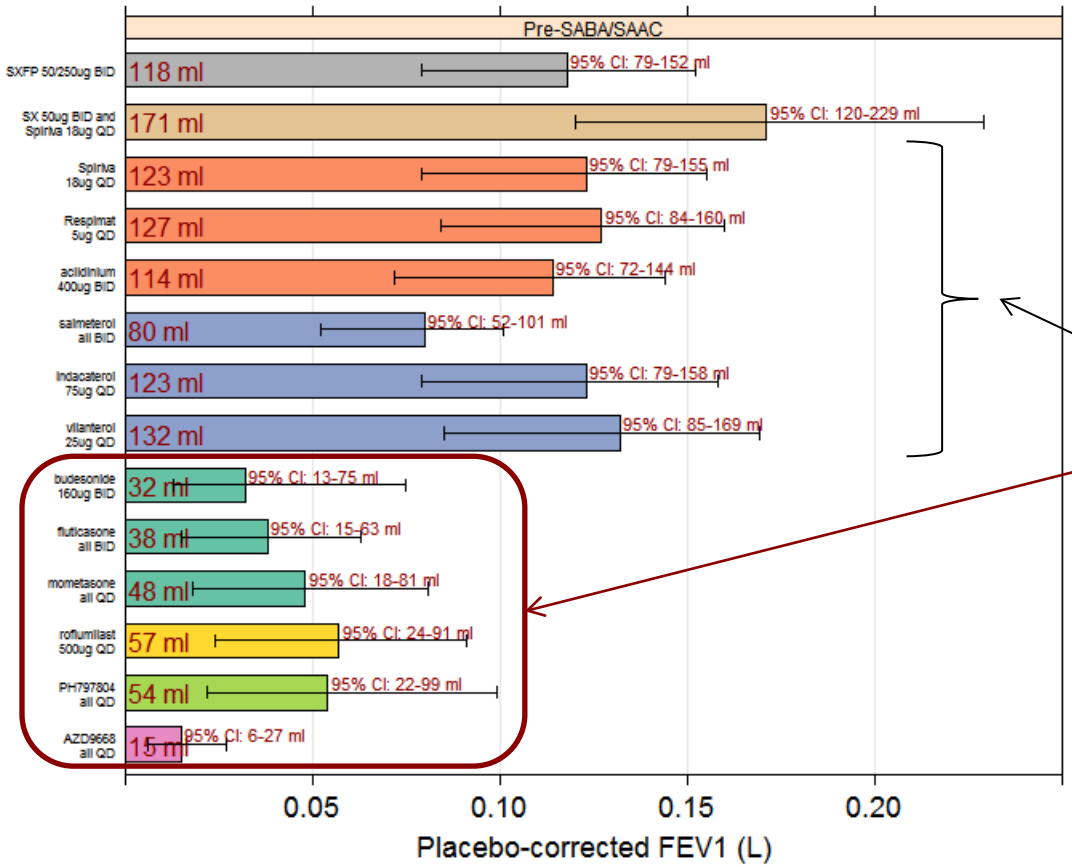


Magnitude of **variability** that could be observed in a **single study** for a given compound.

FEV1 literature model in COPD

Results & Predictions

Treatment effect in severe COPD with **1L** baseline:



Effect of baseline <1.2L on treatment effects:

Treatment	Reduction
LABD	– 4.7%
AI	– 27.8%

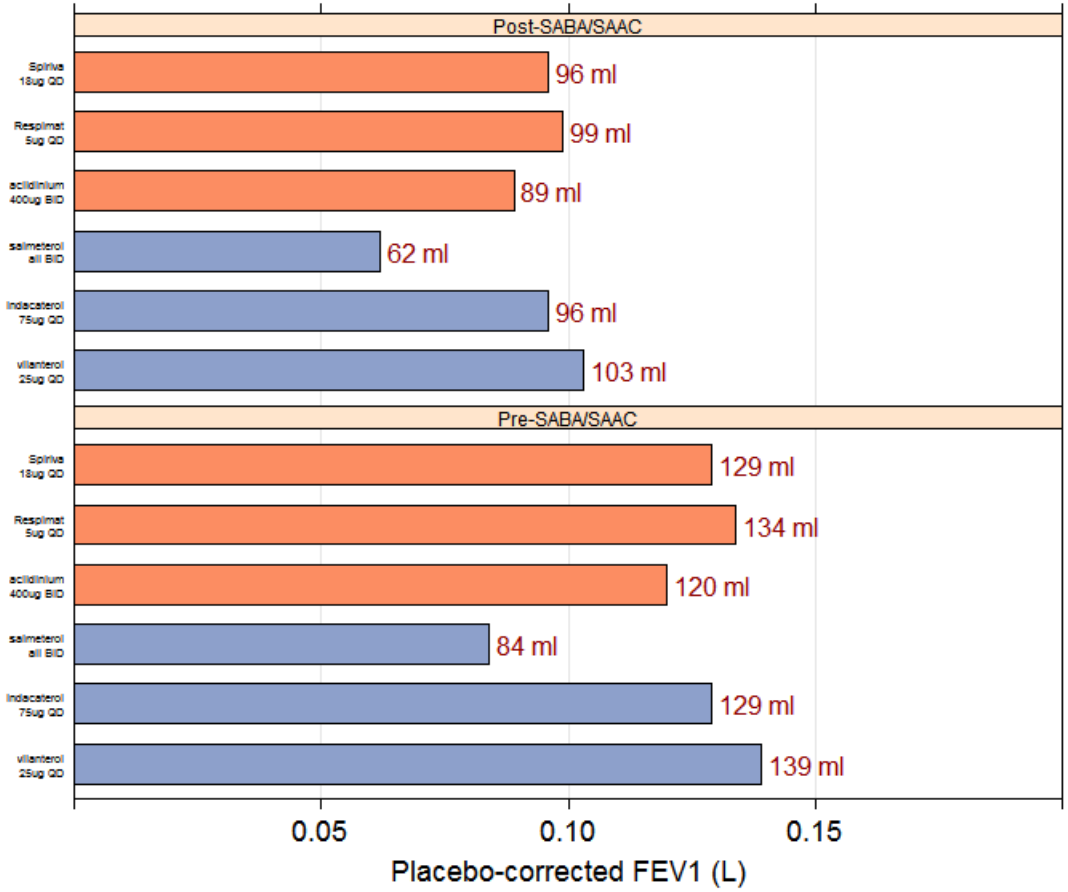
Accounts for disappointing results in published studies on roflumilast!

Reported efficacy ~50 ml

FEV1 literature model in COPD

Results & Predictions

Pre- *versus* post short-acting BD response:



Relative efficacy of LABD when FEV1 is measured post SABD:

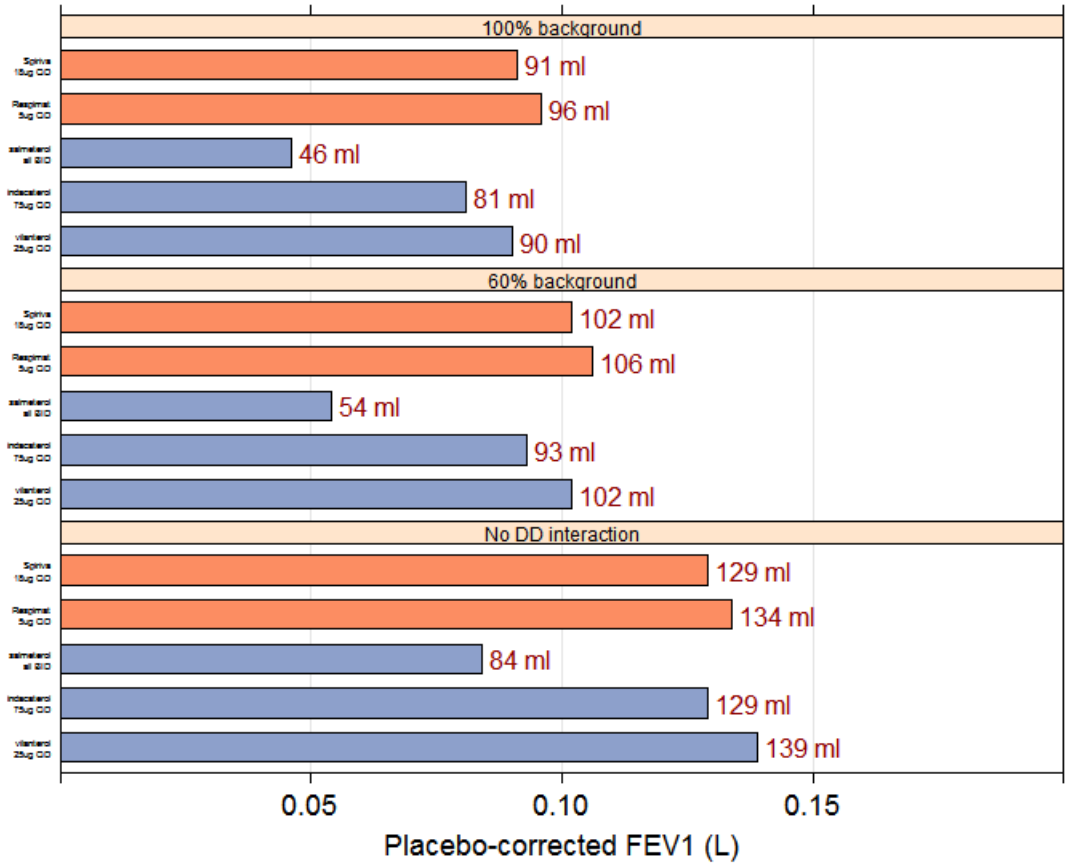
74.2%
of its preSABD efficacy

e.g. *TORCH*:
ΔΔFEV1 at 24 weeks **50 ml** for salmeterol arm measured post salbutamol

FEV1 literature model in COPD

Results & Predictions

LABA - LAAC interaction:



Infra-additive interaction results in **reduced observed efficacy** of study treatment in the presence of background.

e.g. *UPLIFT*:
ΔΔFEV1 **87 – 103 ml**
in tiotropium group with 60% LABA background

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Wrapping it up…

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Discussion

A model based, longitudinal meta-analysis …

- Provides predictions for efficacy across compounds and treatment combinations
  - ⇨ Taking into account:
    - Uncertainty and ISV (heterogeneity)
    - Covariates, e.g. disease severity
    - Dose - response relationships
    - Drug - drug interactions
- Can also account for:
  - Placebo effects
  - Disease progression
  - Time course of effects

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Discussion

Application of the FEV1 literature model:

- Efficacy benchmarking across different compounds and study setups
- Improve design of future studies taking covariate effects into account
- Predictions of FEV1 response at specific time points serve as input in a population model that links FEV1 with exacerbation rate in COPD (primary endpoint in phase 3 studies)

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Conclusion

A model based, longitudinal meta-analysis of literature data is a powerful tool for decision making in clinical drug development.

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THANK YOU!

Questions ?

Comments ?

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BACK-UP SLIDES

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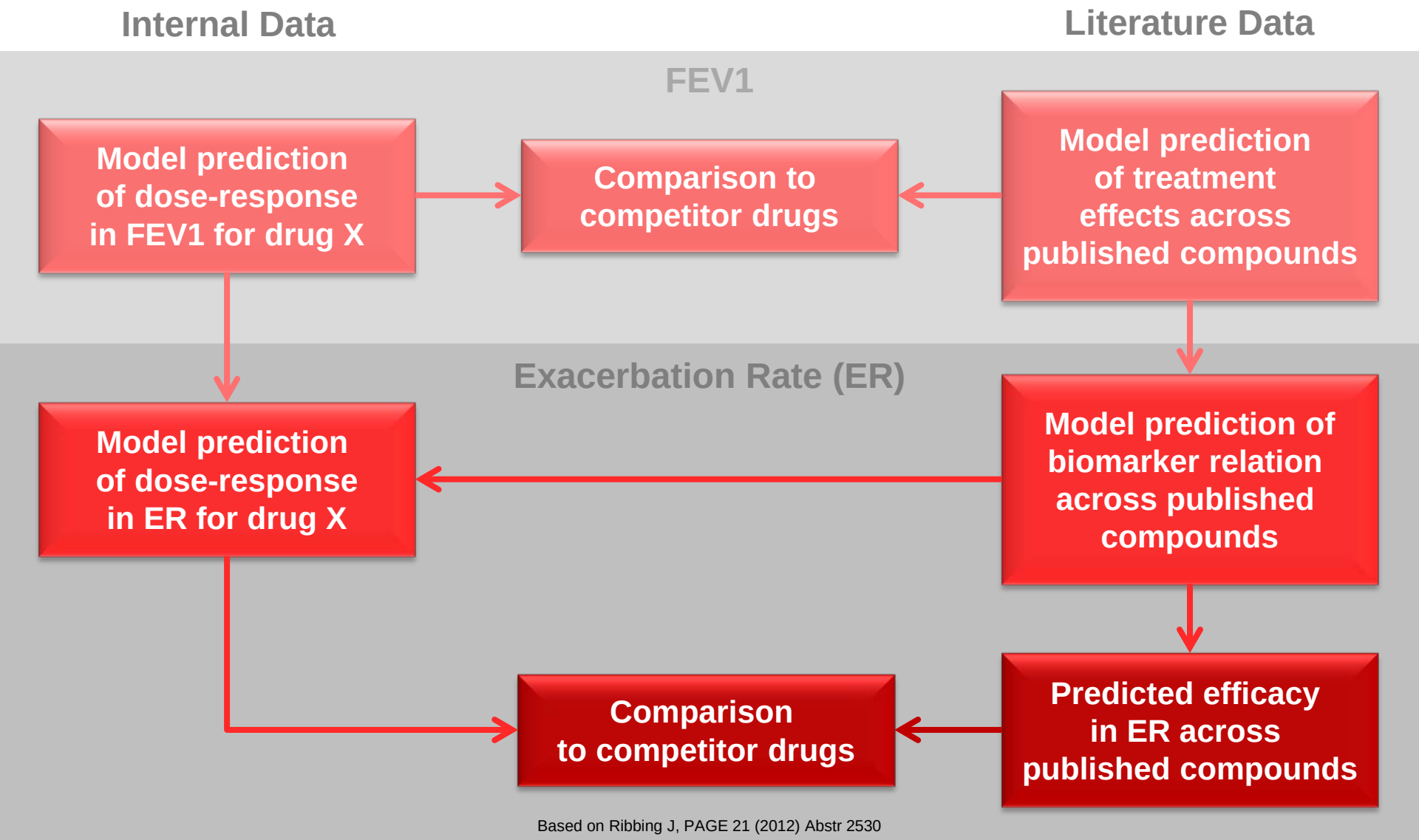
The Concept

Integrated analysis approach



Based on Ribbing J, PAGE 21 (2012) Abstr 2530

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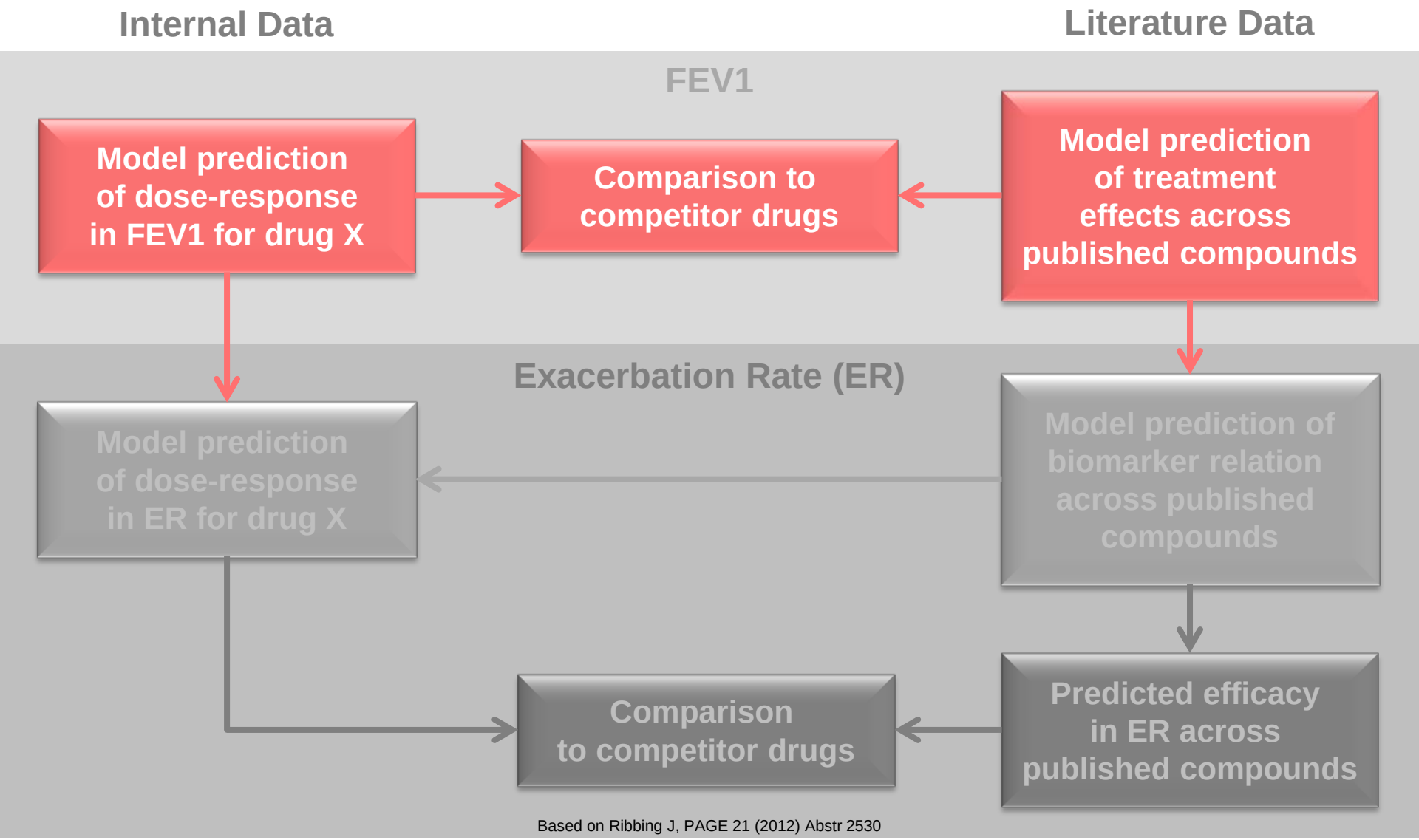
The Concept

Integrated analysis approach



Based on Ribbing J, PAGE 21 (2012) Abstr 2530

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The Concept

Integrated analysis approach

Internal Data | **Literature Data**

FEV1

Model prediction of dose-response in FEV1 for drug X

Comparison to competitor drugs

Model prediction of treatment effects across published compounds

Off limits

Exacerbation Rate (ER)

Model prediction of dose-response in ER for drug X

Model prediction of biomarker relation across published compounds

Comparison to competitor drugs

Predicted efficacy in ER across published compounds

Based on Ribbing J, PAGE 21 (2012) Abstr 2530

FEV1 literature model in COPD

Clinical background

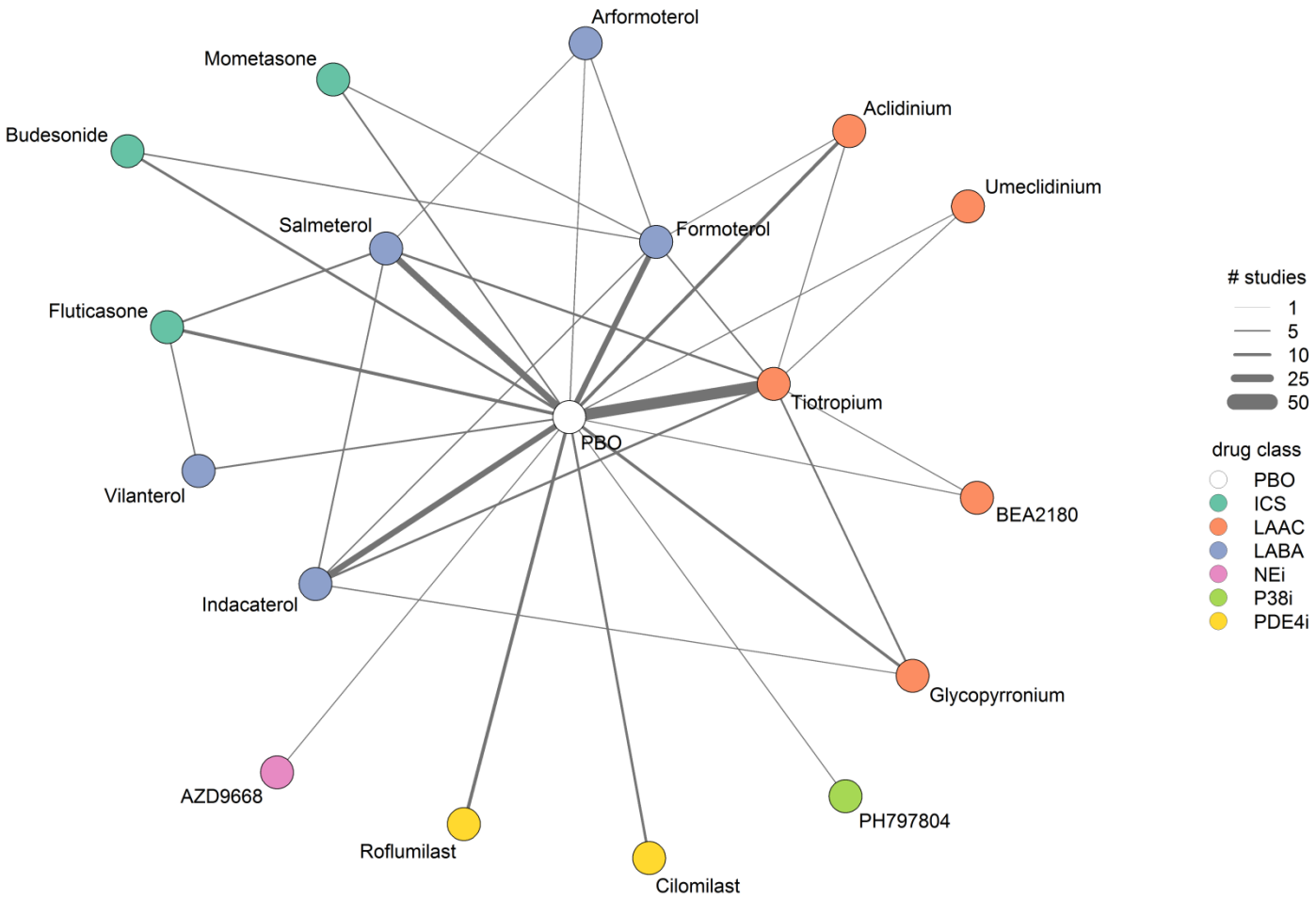
GOLD classification of airway obstruction:

Disease severity	$\%FEV1_{pred}$
Mild	≥80
Moderate	>50 - 80
Severe	>30 - 50
Very Severe	≤30
In addition to ratio FEV1 / FVC < 70%	

http://www.goldcopd.org/guidelines-pocket-guide-to-copd-diagnosis.html

Longitudinal FEV1 literature data

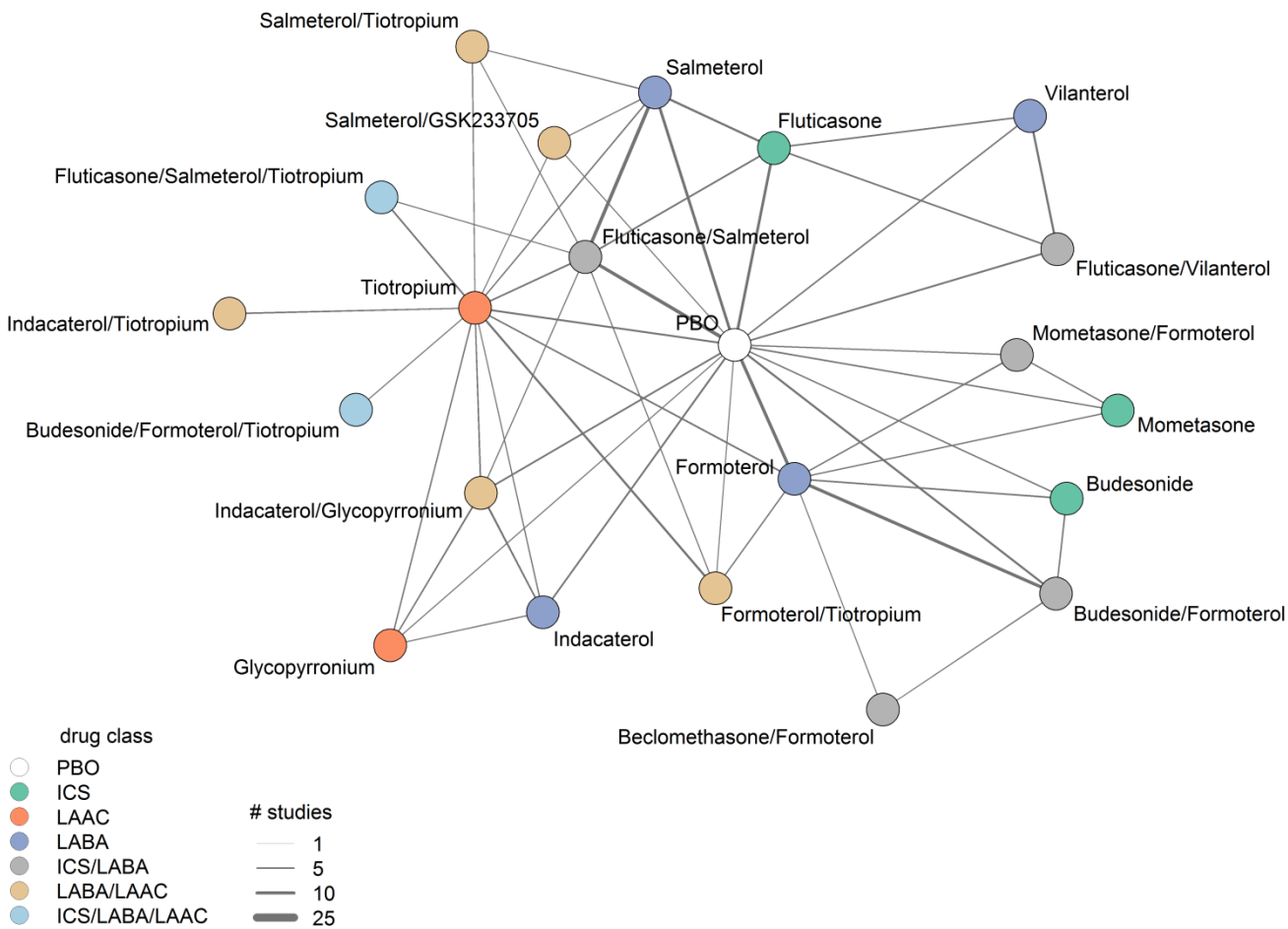
Head-to-head comparisons in literature data:



FEV1 literature model in COPD

Longitudinal FEV1 literature data

Head-to-head comparisons in literature data:



Longitudinal FEV1 literature data

The database:

- Based on literature review until July 2013
- Randomised, controlled, blinded trials
  - Exception for open label Spiriva® (tiotropium)
- 142 studies on 19 compounds:
  - 11 long-acting bronchodilators
  - 8 anti-inflammatory drugs
- 106,422 subjects in total

⇨ 1982 morning trough FEV1 observations

Longitudinal FEV1 literature data

The database:

- 105 different treatment combinations:
  - Up to 3 study drugs given simultaneously:
    - e.g. ICS & LABA & LAAC
  - Differences in dose level & dosing frequency
- Additional open label background treatments:
  - % of patients on background of all treatment classes in each study arm captured

Longitudinal FEV1 literature data

Change from baseline – over 26 weeks :

Database	
until July 2013	
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studies	142
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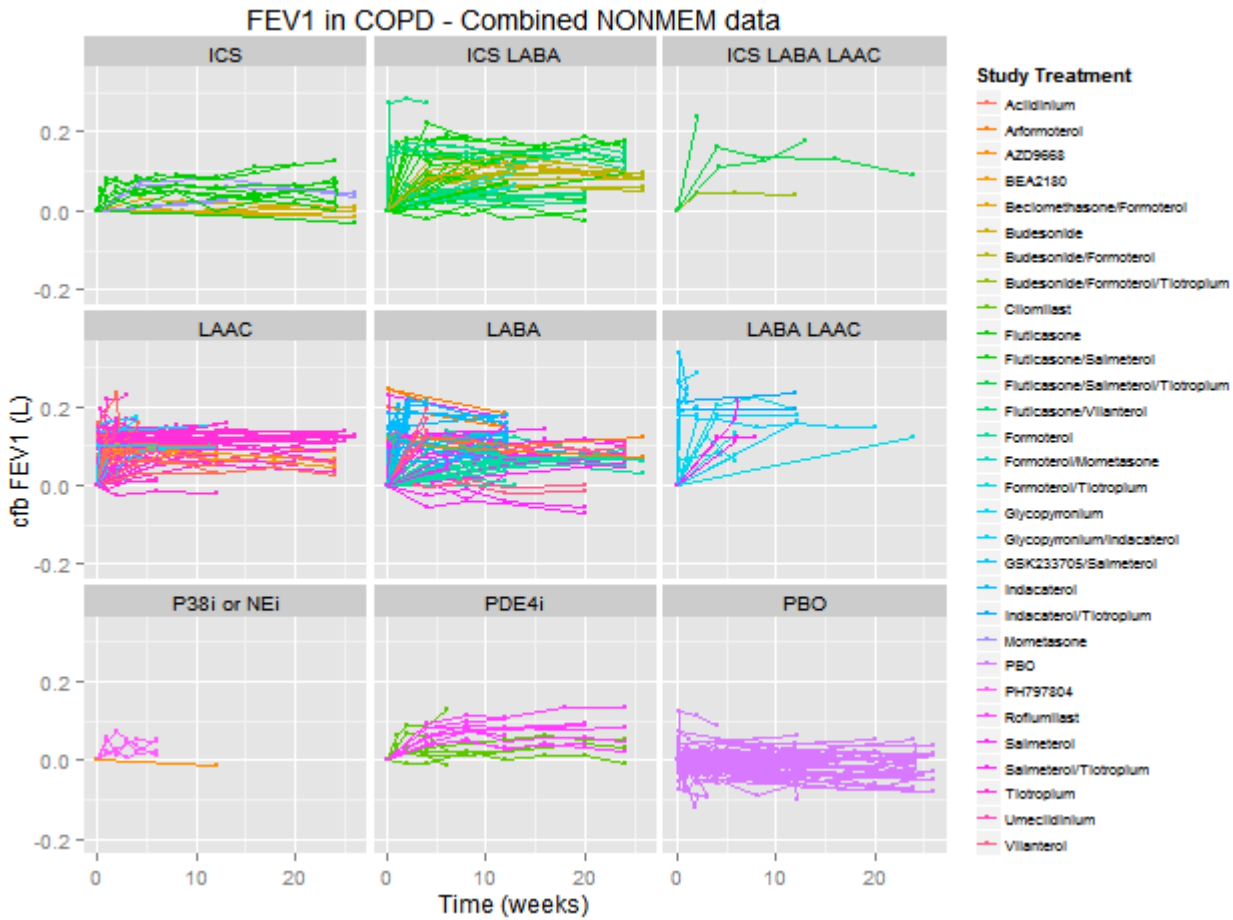
Randomised, controlled trials (exception Spiriva®)	



FEV1 literature model in COPD

Model characteristics

Absolute response is modelled, not change from baseline:

- Observed baseline depends on:
  - Inclusion criteria for disease severity
  - Background treatment
  - ⇨Accounted for in the model

- Baseline adjusted FEV1 response data were back-calculated to observed response:

$$FEV1_{obs} = FEV1_{adj} - B_{mean} + B_{obs}$$

FEV1 literature model in COPD

Model characteristics

Drug effects:

- Dose - response relationship identifiable for 10 compounds based on the available data:
  - ED_{50} estimated together with efficacy (E_{ref}) of reference dose (D_{ref})
  - ⇨ E_{max} derived to calculate effect of other doses:

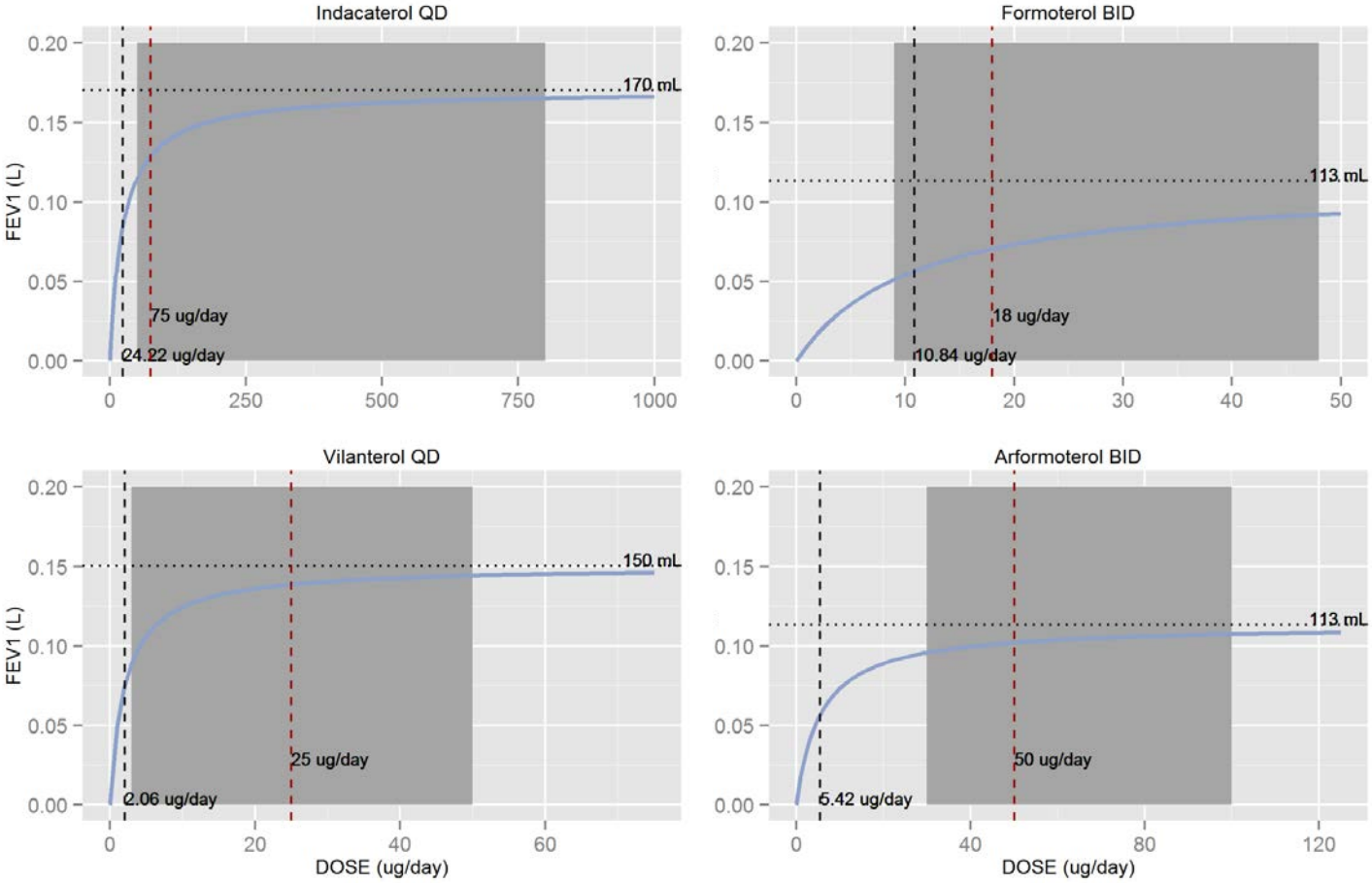
$$E_{max} = E_{ref} * (D_{ref} + ED_{50}) / D_{ref}$$

- For the other compounds efficacy was assumed to be equal at all dose levels
- ISV included on all drug effects

FEV1 literature model in COPD

Results & Predictions

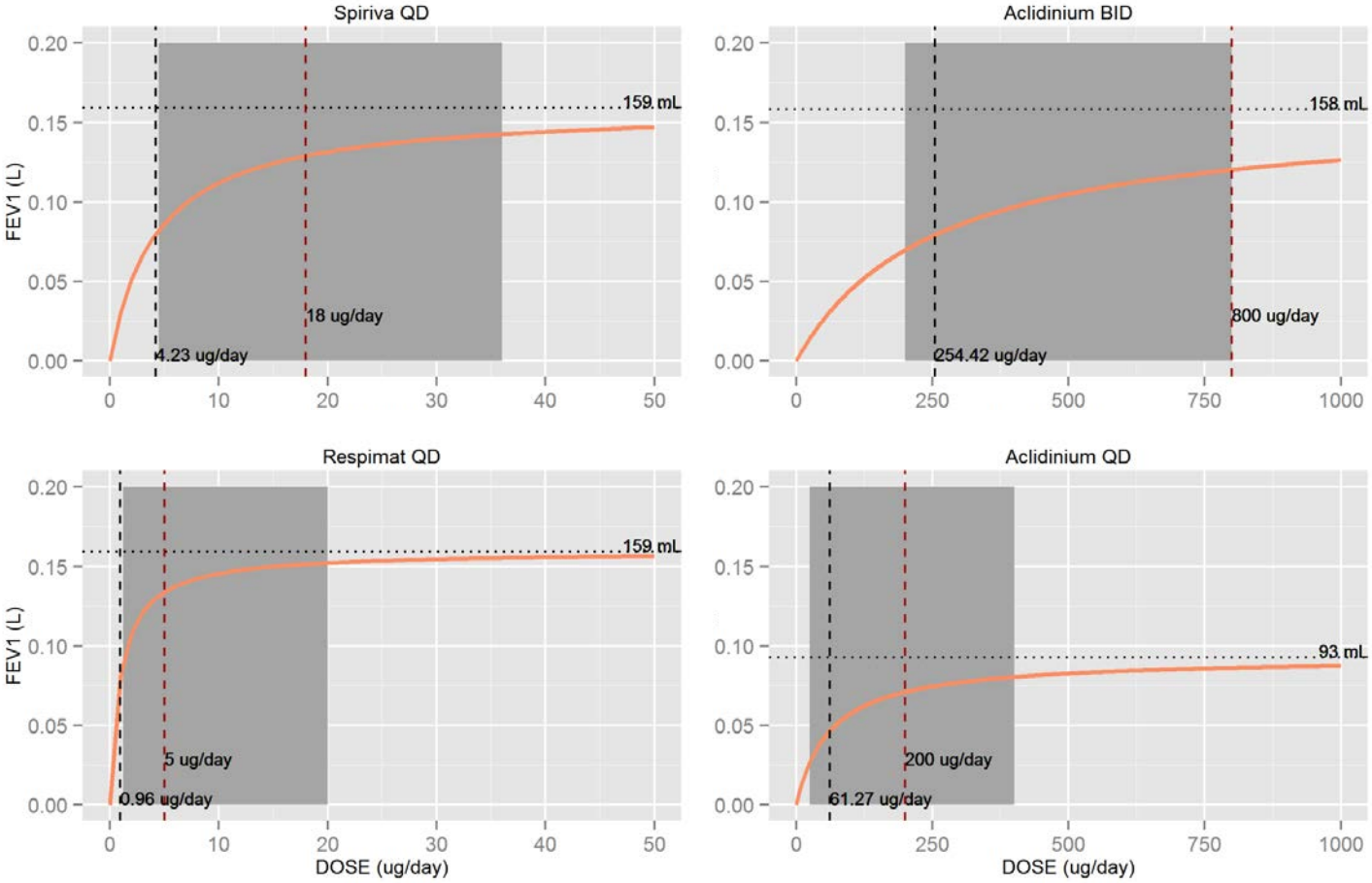
Dose - response for long-acting β_2-agonists :



FEV1 literature model in COPD

Results & Predictions

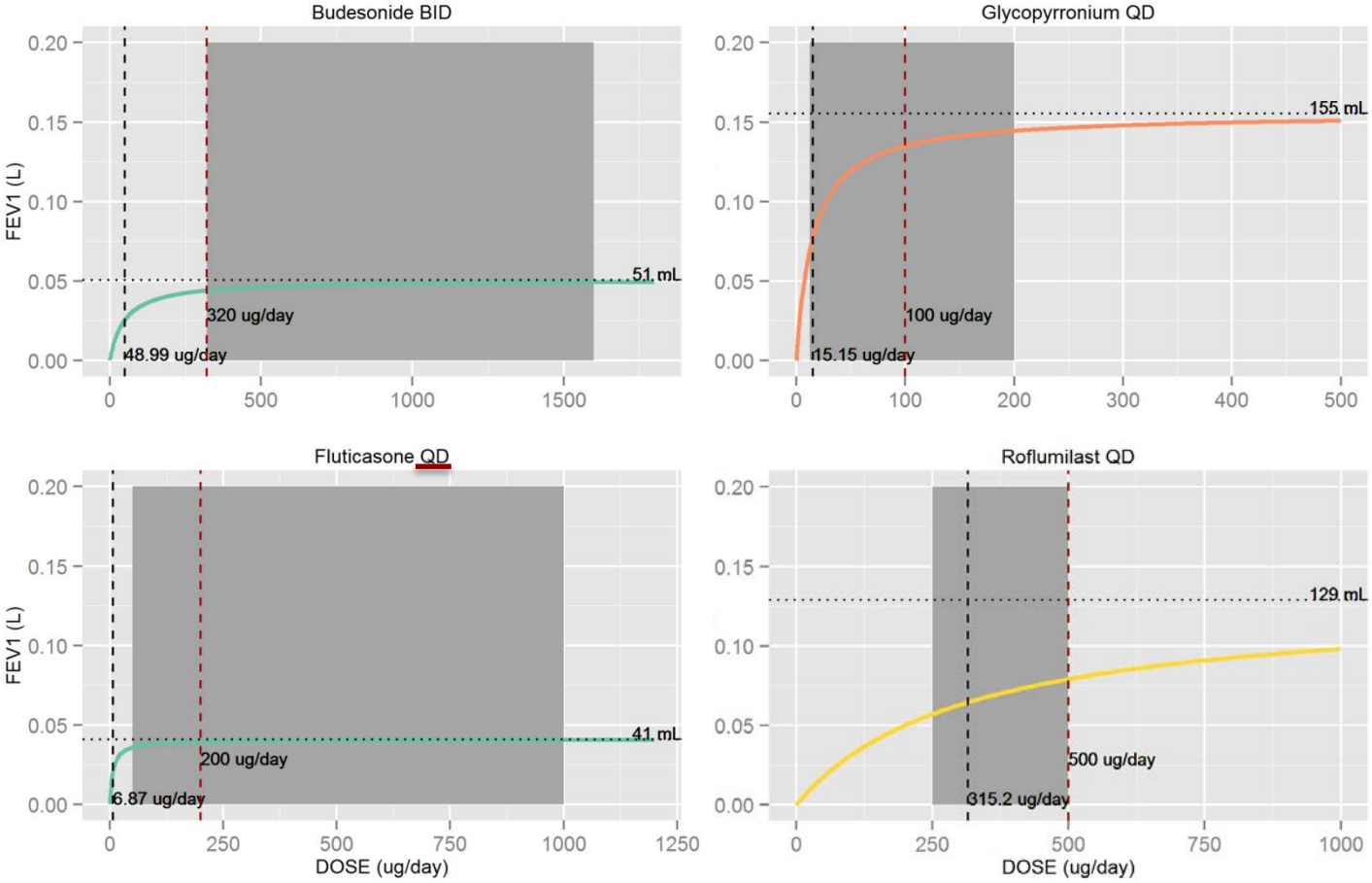
Dose - response for long-acting anticholinergics :



FEV1 literature model in COPD

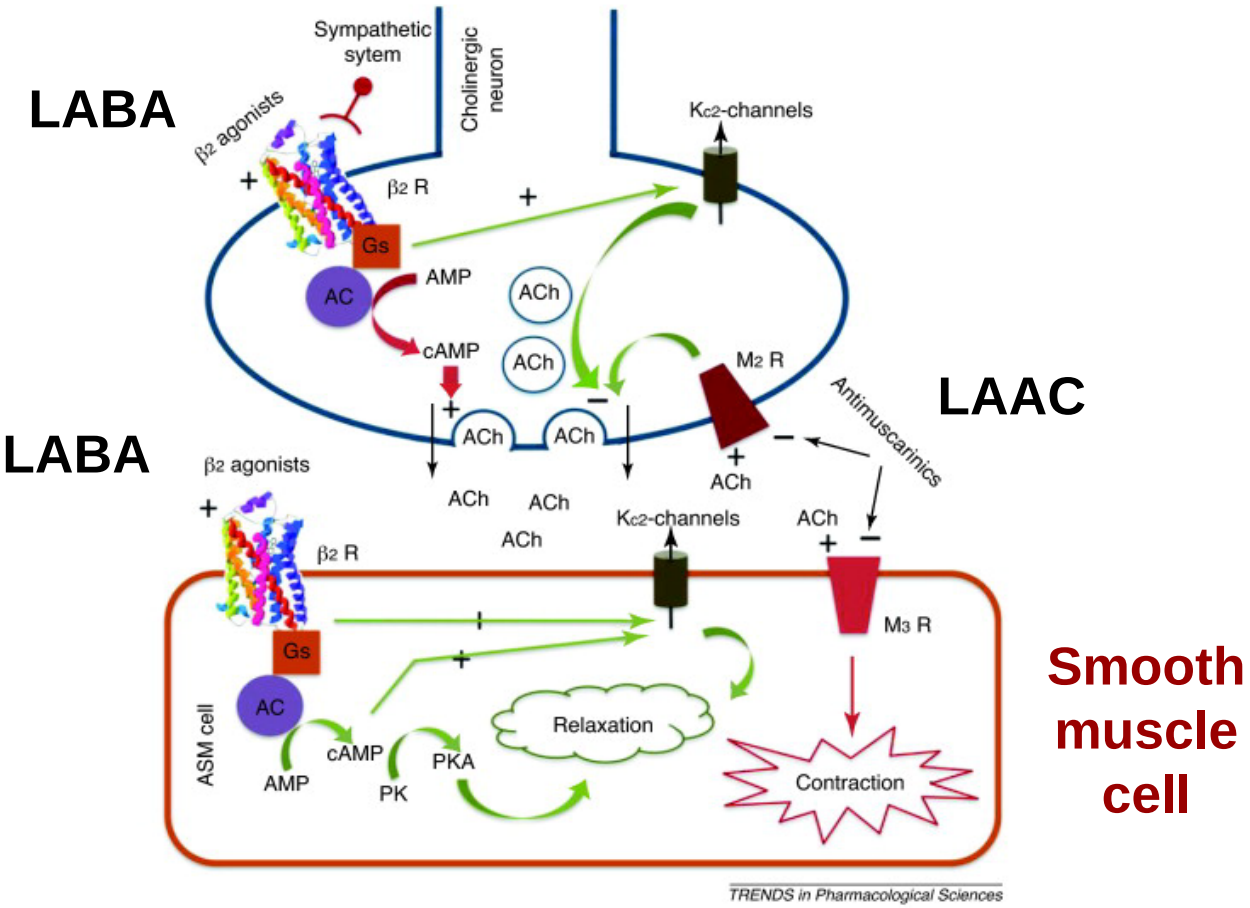
Results & Predictions

Dose - response for other compounds:



Results & Predictions

LABA - LAAC interaction:



Results & Predictions

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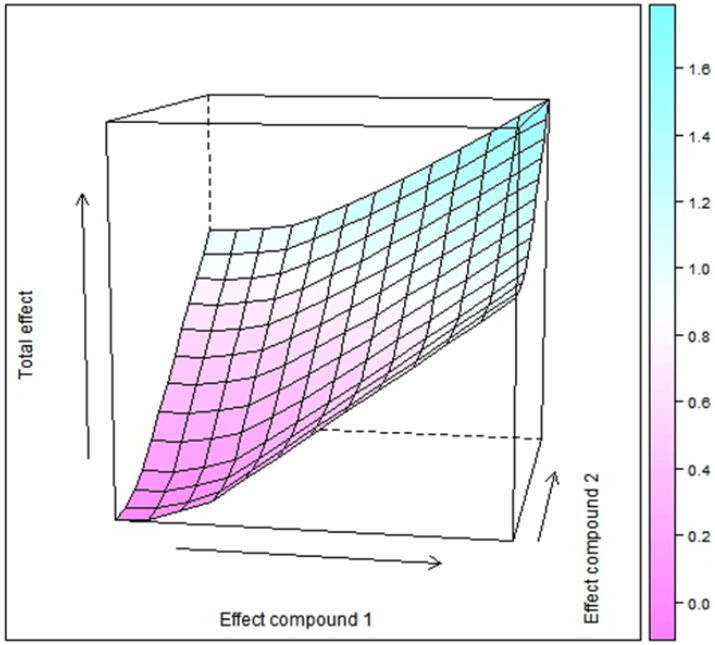

BA and AC effect are both modified by the interaction:

$$E_{tot} = \left({E_{BA}}^{\theta_{INT}} + {E_{AC}}^{\theta_{INT}}\right)^{1/\theta_{INT}}$$

$$\theta_{INT} = 1.42$$

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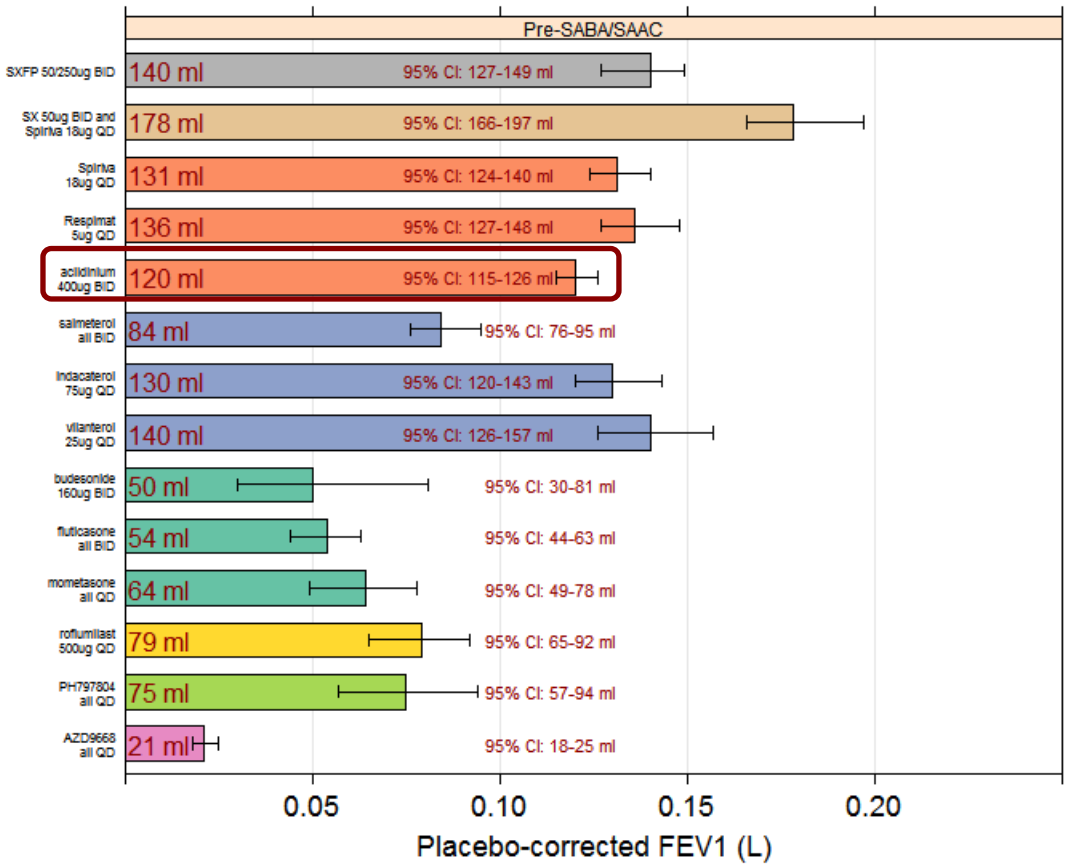
FEV1 literature model in COPD

Results & Predictions

Efficacies – 95% CI **without** ISV (heterogeneity):



Aclidinium

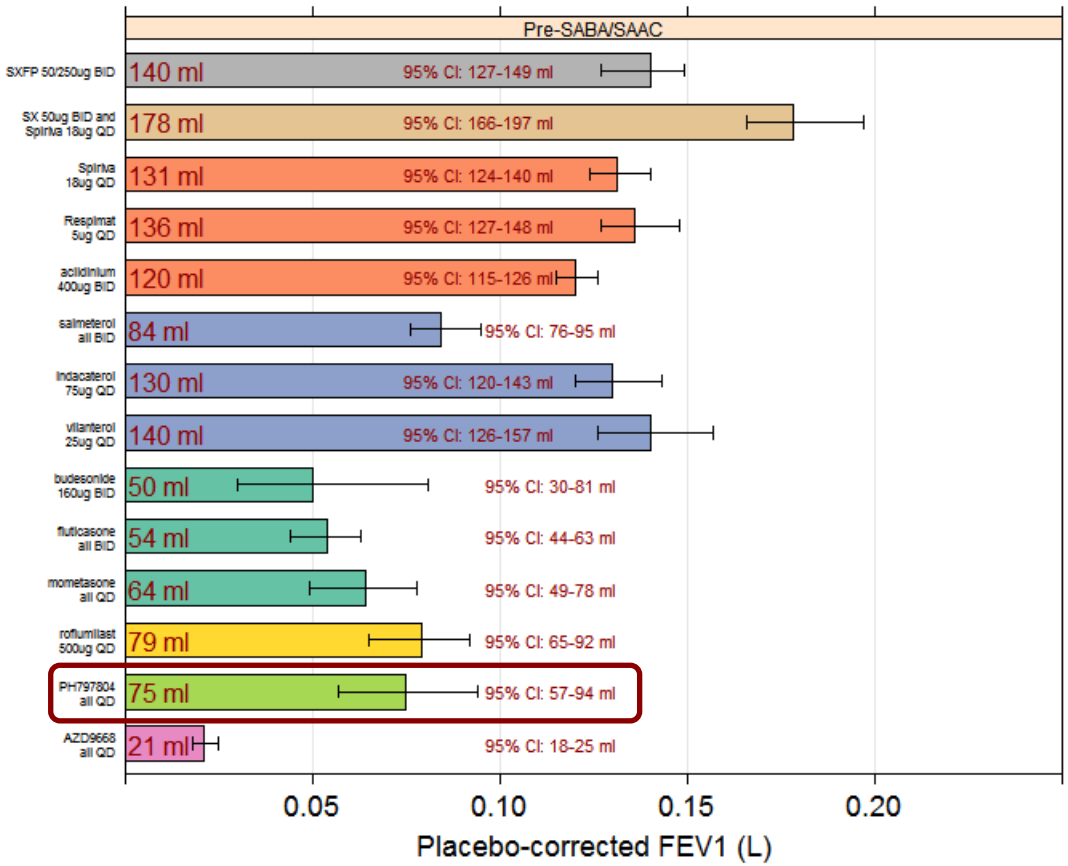
New long acting BID anticholinergic

Similar efficacy as QD tiotropium (Spiriva® & Respimat ®)

FEV1 literature model in COPD

Results & Predictions

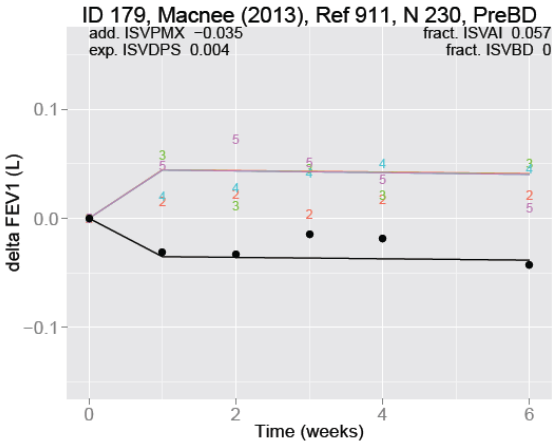
Efficacies – 95% CI **without** ISV (heterogeneity):



PH797804

New P38 inhibitor

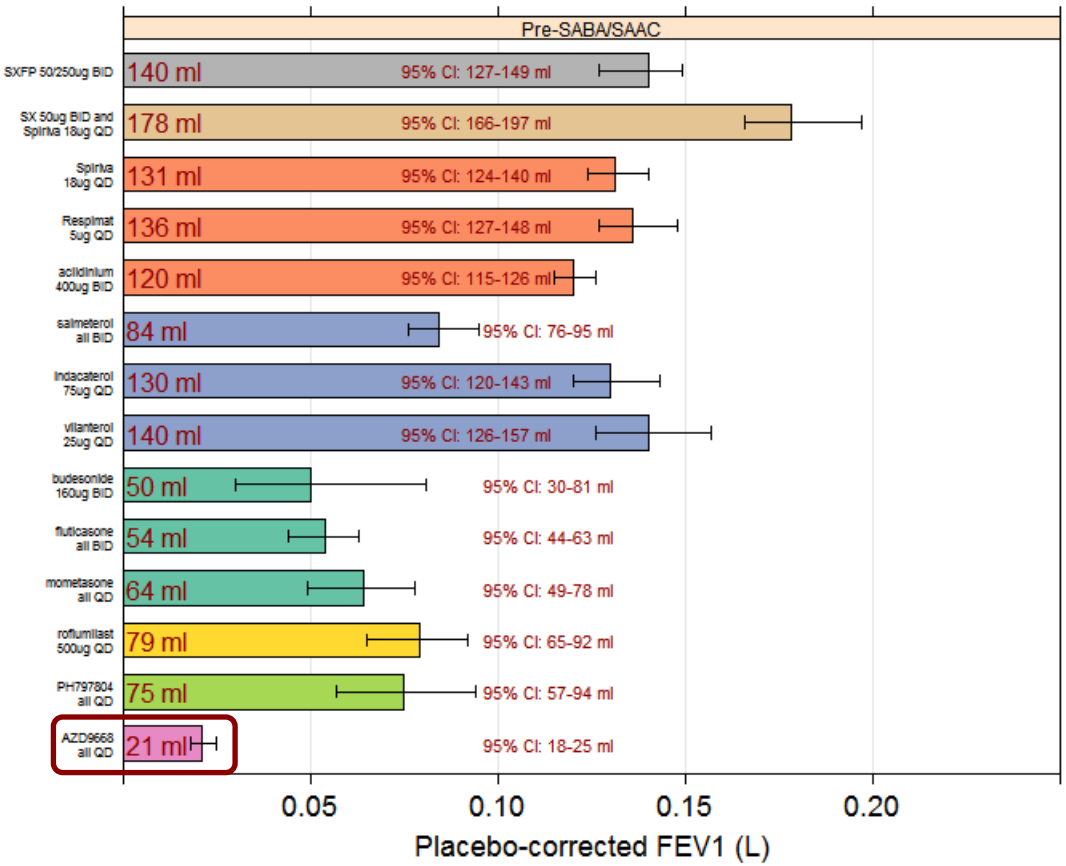
Similar efficacy as roflumilast.



FEV1 literature model in COPD

Results & Predictions

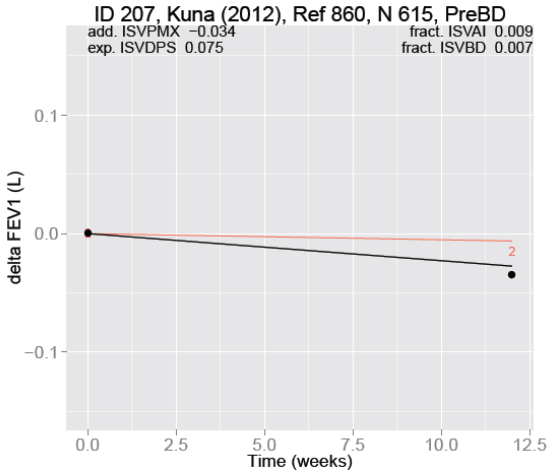
Efficacies – 95% CI **without** ISV (heterogeneity):



AZD9668

New NE inhibitor

Very poor efficacy with 100% background of ICS & LABA



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FEV1 literature model in COPD

Results & Predictions

Comparative effectiveness for bronchodilator treatments:

Drug 1 / Drug 2	Form.	Salm.	Ind.	Vil.	Tio. Sp.	Glyco.	Acli. BID	Ume.
Formoterol	1	1.19 1.00 – 1.45	1.82 1.50 – 2.24	1.96 1.60 – 2.42	1.83 1.55 – 2.17	1.91 1.52 – 2.44	1.79 1.33 – 2.46	1.70 1.25 – 2.27
Salmeterol	0.84 0.69 – 1.00	1	1.53 1.30 – 1.79	1.65 1.38 – 1.94	1.53 1.36 – 1.73	1.60 1.31 – 1.98	1.43 1.07 – 1.87	1.50 1.13 – 2.03
Indacaterol	0.55 0.44 – 0.67	0.65 0.55 – 0.77	1	1.08 0.89 – 1.31	1.00 0.87 – 1.16	1.05 0.85 – 1.31	0.93 0.69 – 1.24	0.98 0.74 – 1.34
Vilanterol	0.51 0.41 – 0.63	0.61 0.51 – 0.73	0.93 0.76 – 1.13	1	0.93 0.79 – 1.10	0.97 0.78 – 1.23	0.87 0.64 – 1.15	0.91 0.68 – 1.25
Tiotropium Spiriva	0.55 0.46 – 0.65	0.65 0.58 – 0.74	1.00 0.86 – 1.15	1.07 0.90 – 1.26	1	1.05 0.87 – 1.28	0.93 0.70 – 1.21	0.98 0.75 – 1.32
Glycopyrronium	0.53 0.41 – 0.66	0.62 0.50 – 0.76	0.95 0.76 – 1.17	1.03 0.81 – 1.29	0.96 0.78 – 1.15	1	0.89 0.64 – 1.20	0.94 0.68 – 1.30
Aclidinium BID	0.59 0.44 – 0.80	0.70 0.53 – 0.93	1.07 0.81 – 1.44	1.15 0.87 – 1.56	1.07 0.83 – 1.41	1.12 0.83- 1.55	1	1.05 0.74 – 1.54
Umeclidinium	0.56 0.40 – 0.76	0.67 0.49 – 0.88	1.02 0.75 – 1.35	1.10 0.80 – 1.47	1.02 0.76 – 1.34	1.07 0.77 – 1.46	0.95 0.64 – 1.36	1

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FEV1 literature model in COPD

Results & Predictions

Comparative effectiveness for anti-inflammatory treatments:

Drug 1 / Drug 2	Beclo.	Bude.	Fluti. BID	Mome BID	Cilo.	Roflu.
Beclomethasone	1	1.45 0.51 – **Inf**	1.73 0.72 – **Inf**	1.81 0.67 – **Inf**	1.52 0.58 – Inf	2.61 1.09 – **Inf**
Budesonide	0.69 **0** – 1.95	1	1.19 0.78 – 2.42	1.24 0.66 – 2.65	1.04 0.58 – 2.15	1.80 1.17 – 3.48
Fluticasone BID	0.58 **0** – 1.38	0.84 0.43 – 1.27	1	1.05 0.62 – 1.72	0.87 0.55 – 1.33	1.51 1.14 – 2.03
Mometasone BID	0.55 **0** – 1.49	0.80 0.37 – 1.52	0.96 0.58 – 1.62	1	0.83 0.46 – 1.53	1.44 0.86 – 2.47
Cilomilast	0.66 0 – 1 .71	0.96 0.46 – 1.71	0.15 0.75 – 1.80	1.20 0.65 – 2.18	1	1.73 1.12 – 2.75
Roflumilast	0.38 **0** – 0.92	0.56 0.28 – 0.86	0.66 0.49 – 0.88	0.69 0.40 – 1.16	0.58 0.36 – 0.90	1

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Discussion

In the FEV1 literature model …

- Placebo effect highly dependent on study
  - No clear direction of effect
  - Insufficient washout ?
  - Early onset in some studies
- Disease progression appears linear
  - But masked by dropout
- Low study baseline reduces AI efficacy and to a much lower extent also BD efficacy
- Drug - drug interactions (LABA - LAAC, SABD - LABD) can explain unsatisfactory study results