Model based longitudinal meta-analysis of FEV1 in COPD trials
A tool for efficacy benchmarking

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The Concept

Why analysing literature data?
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
The Concept

Why analysing literature data?

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

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Existing treatments have often already been studied multiple times

⇒ Use the information available in literature!
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
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
Our Work
FEV1 literature model in COPD
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:

<table>
<thead>
<tr>
<th>Direct bronchodilators (BD)</th>
<th>Anti-inflammatory (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting $\beta_2$-agonists (LABA)</td>
<td>Inhaled corticosteroids (ICS)</td>
</tr>
<tr>
<td>Long-acting anticholinergics (LAAC)</td>
<td>Phosphodiesterase4 inhibitors (PDE4i)</td>
</tr>
<tr>
<td>Neutrophil elastase inhibitors (NEi)</td>
<td>P38 MAP kinase inhibitors (P38i)</td>
</tr>
</tbody>
</table>
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

FEV1 literature model in COPD

Longitudinal FEV1 literature data

Absolute morning trough FEV1 response:

<table>
<thead>
<tr>
<th>Database</th>
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<tbody>
<tr>
<td>until July 2013</td>
</tr>
<tr>
<td>references</td>
</tr>
<tr>
<td>studies</td>
</tr>
<tr>
<td>arms</td>
</tr>
<tr>
<td>compounds</td>
</tr>
<tr>
<td>combinations</td>
</tr>
<tr>
<td>obs.</td>
</tr>
<tr>
<td>subjects</td>
</tr>
</tbody>
</table>

Randomised, controlled trials (exception Spiriva®)
FEV1 literature model in COPD

Longitudinal FEV1 literature data

Change from baseline morning trough FEV1:

Database

- until July 2013
- references: 133
- studies: 141
- arms: 419
- compounds: 19
- combinations: 105
- obs.: 1982
- subjects: 106,422

Randomised, controlled trials (exception Spiriva®)
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
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:

(DIR) 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
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
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:

**UPLIFT**

- ID 75, Tashkin (2008), Ref 661, N 5993, PreBD
- Study Treatment:
  - 1 Tiotropium 18 UG/DAY QD

**TORCH**

- ID 81, Celli (2008), Ref 663, N 6112, PostBD
- Study Treatment:
  - 1 Fluticasone/Salmeterol 1000/100 UG/DAY BiD
  - 2 Fluticasone 1000 UG/DAY BiD
  - 3 Salmeterol 100 UG/DAY BiD
Treatment effect in moderate COPD with 1.2L baseline:

Point estimates and predictions for treatment combinations at steady state.
Treatment effect in moderate COPD with 1.2L baseline:

- LABA + ICS: Additive effect
  - e.g. salmeterol + fluticasone: 84 ml + 52 ml = 136 ml
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 $\beta_2$-agonists
  - Superior efficacy compared to older BID $\beta_2$-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:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABD</td>
<td>– 4.7%</td>
</tr>
<tr>
<td>AI</td>
<td>– 27.8%</td>
</tr>
</tbody>
</table>

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**: 
\[ΔΔFEV1 \text{ at 24 weeks } 50 \text{ ml} \]
for salmeterol arm measured post salbutamol
LABA - LAAC interaction:

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

**e.g. UPLIFT:**

\[ \Delta \Delta FEV1 \ 87 - 103 \text{ ml} \]

in tiotropium group with 60% LABA background
Wrapping it up...
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
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)
Conclusion

A model based, longitudinal meta-analysis of literature data is a powerful tool for decision making in clinical drug development.
Questions ?
Comments ?
BACK-UP SLIDES
The Concept

Integrated analysis approach

Internal Data

FEV1
- Model prediction of dose-response in FEV1 for drug X
- Comparison to competitor drugs

Exacerbation Rate (ER)
- Model prediction of dose-response in ER for drug X
- Comparison to competitor drugs

Literature Data

FEV1
- Model prediction of treatment effects across published compounds

Exacerbation Rate (ER)
- Model prediction of biomarker relation across published compounds
- Predicted efficacy in ER across published compounds

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

Integrated analysis approach

**Internal Data**

- Model prediction of dose-response in FEV1 for drug X

**Exacerbation Rate (ER)**

- Model prediction of dose-response in ER for drug X

**Literature Data**

- Model prediction of treatment effects across published compounds
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Comparison to competitor drugs

Based on Ribbing J, PAGE 21 (2012) Abstr 2530
The Concept
Integrated analysis approach

Exacerbation Rate (ER)

Model prediction of dose-response in ER for drug X

Comparison to competitor drugs

Model prediction of treatment effects across published compounds

FEV1

Model prediction of dose-response in FEV1 for drug

Model prediction of biomarker relation across published compounds

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:

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>%FEV1_{pred}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≥80</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;50 - 80</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;30 - 50</td>
</tr>
<tr>
<td>Very Severe</td>
<td>≤30</td>
</tr>
</tbody>
</table>

In addition to ratio FEV1 / FVC < 70%

FEV1 literature model in COPD

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:
FEV1 literature model in COPD

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
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
FEV1 literature model in COPD

Longitudinal FEV1 literature data

Change from baseline – over 26 weeks:

<table>
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<td>subjects 106,422</td>
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Randomised, controlled trials (exception Spiriva®)
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:

\[
\text{FEV1}_{\text{obs}} = \text{FEV1}_{\text{adj}} - B_{\text{mean}} + B_{\text{obs}}
\]
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:
    \[
    E_{max} = E_{ref} \times \frac{D_{ref} + ED_{50}}{D_{ref}}
    \]
  - 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 $\beta_2$-agonists:

- Indacaterol QD
  - 75 ug/day
  - 64.22 ug/day

- Formoterol BID
  - 18 ug/day
  - 10.84 ug/day

- Vilanterol QD
  - 25 ug/day
  - 2.06 ug/day

- Arformoterol BID
  - 50 ug/day
  - 6.42 ug/day
FEV1 literature model in COPD

Results & Predictions

Dose - response for long-acting anticholinergics:

- **Spiriva QD**
  - DOSE (ug/day): 4.23 ug/day
  - FEV1 (L): 0.18

- **Acldinium BID**
  - DOSE (ug/day): 234.42 ug/day
  - FEV1 (L): 0.18

- **Resprimat QD**
  - DOSE (ug/day): 5 ug/day
  - FEV1 (L): 0.15

- **Acldinium QD**
  - DOSE (ug/day): 200 ug/day
  - FEV1 (L): 0.15

- **Respimat QD**
  - DOSE (ug/day): 0.99 ug/day
  - FEV1 (L): 0.098

- **Acldinium QD**
  - DOSE (ug/day): 61.27 ug/day
  - FEV1 (L): 0.083
FEV1 literature model in COPD

Results & Predictions

Dose - response for other compounds:
FEV1 literature model in COPD

Results & Predictions

LABA - LAAC interaction:
FEV1 literature model in COPD

Results & Predictions

LABA - LAAC interaction:

BA and AC effect are both modified by the interaction:

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

\[ \theta_{INT} = 1.42 \]
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):

<table>
<thead>
<tr>
<th>Dose</th>
<th>FEV1 (L)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 ml</td>
<td></td>
<td>127-149 ml</td>
</tr>
<tr>
<td>178 ml</td>
<td></td>
<td>166-197 ml</td>
</tr>
<tr>
<td>131 ml</td>
<td></td>
<td>124-140 ml</td>
</tr>
<tr>
<td>136 ml</td>
<td></td>
<td>127-148 ml</td>
</tr>
<tr>
<td>120 ml</td>
<td></td>
<td>115-126 ml</td>
</tr>
<tr>
<td>94 ml</td>
<td></td>
<td>76-95 ml</td>
</tr>
<tr>
<td>130 ml</td>
<td></td>
<td>126-143 ml</td>
</tr>
<tr>
<td>140 ml</td>
<td></td>
<td>126-157 ml</td>
</tr>
<tr>
<td>50 ml</td>
<td></td>
<td>30-61 ml</td>
</tr>
<tr>
<td>54 ml</td>
<td></td>
<td>44-63 ml</td>
</tr>
<tr>
<td>84 ml</td>
<td></td>
<td>49-78 ml</td>
</tr>
<tr>
<td>79 ml</td>
<td></td>
<td>65-92 ml</td>
</tr>
<tr>
<td>PH797804</td>
<td></td>
<td>57-94 ml</td>
</tr>
<tr>
<td>75 ml</td>
<td></td>
<td>57-94 ml</td>
</tr>
<tr>
<td>21 ml</td>
<td></td>
<td>18-25 ml</td>
</tr>
</tbody>
</table>

**PH797804**

New P38 inhibitor

Similar efficacy as roflumilast.
FEV1 literature model in COPD

Results & Predictions

Efficacies – 95% CI without ISV (heterogeneity):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-SABA/SAAC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 1500 mg BID</td>
<td>140 ml</td>
<td>127-149 ml</td>
</tr>
<tr>
<td>Azithromycin 500 mg BID</td>
<td>178 ml</td>
<td>166-197 ml</td>
</tr>
<tr>
<td>Ciprofloxacin 500 mg BID</td>
<td>131 ml</td>
<td>124-140 ml</td>
</tr>
<tr>
<td>Ciprofloxacin 250 mg BID</td>
<td>136 ml</td>
<td>127-148 ml</td>
</tr>
<tr>
<td>Doxycycline 100 mg BID</td>
<td>120 ml</td>
<td>115-126 ml</td>
</tr>
<tr>
<td>Doxycycline 50 mg BID</td>
<td>94 ml</td>
<td>79-85 ml</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg BID</td>
<td>130 ml</td>
<td>120-143 ml</td>
</tr>
<tr>
<td>Moxifloxacin 200 mg BID</td>
<td>140 ml</td>
<td>126-157 ml</td>
</tr>
<tr>
<td>Tetracycline 500 mg BID</td>
<td>50 ml</td>
<td>30-61 ml</td>
</tr>
<tr>
<td>Tetracycline 250 mg BID</td>
<td>54 ml</td>
<td>44-63 ml</td>
</tr>
<tr>
<td>Amoxicillin 1000 mg BID</td>
<td>84 ml</td>
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<td>75 ml</td>
<td>57-94 ml</td>
</tr>
<tr>
<td>Azithromycin 250 mg BID</td>
<td>21 ml</td>
<td>18-25 ml</td>
</tr>
</tbody>
</table>

AZD9668
New NE inhibitor

Very poor efficacy with 100% background of ICS & LABA
### FEV1 literature model in COPD

#### Results & Predictions

Comparative effectiveness for bronchodilator treatments:

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Formoterol</td>
<td>1</td>
<td>1.19</td>
<td>1.82</td>
<td>1.96</td>
<td>1.83</td>
<td>1.91</td>
<td>1.79</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.00 – 1.45</td>
<td>1.50 – 2.24</td>
<td>1.60 – 2.42</td>
<td>1.55 – 2.17</td>
<td>1.52 – 2.44</td>
<td>1.33 – 2.46</td>
<td>1.25 – 2.27</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>0.84</td>
<td>0.69 – 1.00</td>
<td>1.53</td>
<td>1.65</td>
<td>1.53</td>
<td>1.60</td>
<td>1.43</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.69 – 1.00</td>
<td>1.30 – 1.79</td>
<td>1.38 – 1.94</td>
<td>1.36 – 1.73</td>
<td>1.31 – 1.98</td>
<td>1.07 – 1.87</td>
<td>1.13 – 2.03</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>0.55</td>
<td>0.55 – 0.77</td>
<td>0.65</td>
<td>0.93</td>
<td>1.00</td>
<td>1.05</td>
<td>0.93</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.44 – 0.67</td>
<td>0.65</td>
<td>0.89 – 1.31</td>
<td>0.87 – 1.16</td>
<td>0.85 – 1.31</td>
<td>0.69 – 1.24</td>
<td>0.74 – 1.34</td>
</tr>
<tr>
<td>Vilanterol</td>
<td>0.61</td>
<td>0.51 – 0.73</td>
<td>0.56</td>
<td>0.93</td>
<td>1.00</td>
<td>0.97</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.51 – 0.63</td>
<td>0.76 – 1.13</td>
<td>0.89 – 1.31</td>
<td>0.87 – 1.16</td>
<td>0.85 – 1.31</td>
<td>0.64 – 1.15</td>
<td>0.68 – 1.25</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>0.55</td>
<td>0.65</td>
<td>1.00</td>
<td>1.07</td>
<td>1.05</td>
<td>1.05</td>
<td>0.93</td>
<td>0.98</td>
</tr>
<tr>
<td>Spiriva</td>
<td></td>
<td>0.46 – 0.65</td>
<td>0.86 – 1.15</td>
<td>0.90 – 1.26</td>
<td>0.87 – 1.28</td>
<td>0.87 – 1.28</td>
<td>0.70 – 1.21</td>
<td>0.75 – 1.32</td>
</tr>
<tr>
<td>Glycopyrronium</td>
<td>0.53</td>
<td>0.62</td>
<td>0.95</td>
<td>1.03</td>
<td>0.96</td>
<td>1</td>
<td>0.89</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.61 – 0.66</td>
<td>0.76 – 1.17</td>
<td>0.81 – 1.29</td>
<td>0.78 – 1.15</td>
<td>0.64 – 1.20</td>
<td>0.68 – 1.30</td>
<td>0.68 – 1.30</td>
</tr>
<tr>
<td>Aclidinium BID</td>
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<td>0.81 – 1.44</td>
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FEV1 literature model in COPD

Results & Predictions

Comparative effectiveness for anti-inflammatory treatments:

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Note: Values are comparative effectiveness ratios with confidence intervals.
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