Using a DMC for dose selection in a phase IIb/III adaptive design: the INHANCE study

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- BBS Seminar May 4th 2016

Outline

- Background and Trial Design
- Dose Selection
- Outcome
- Conclusions

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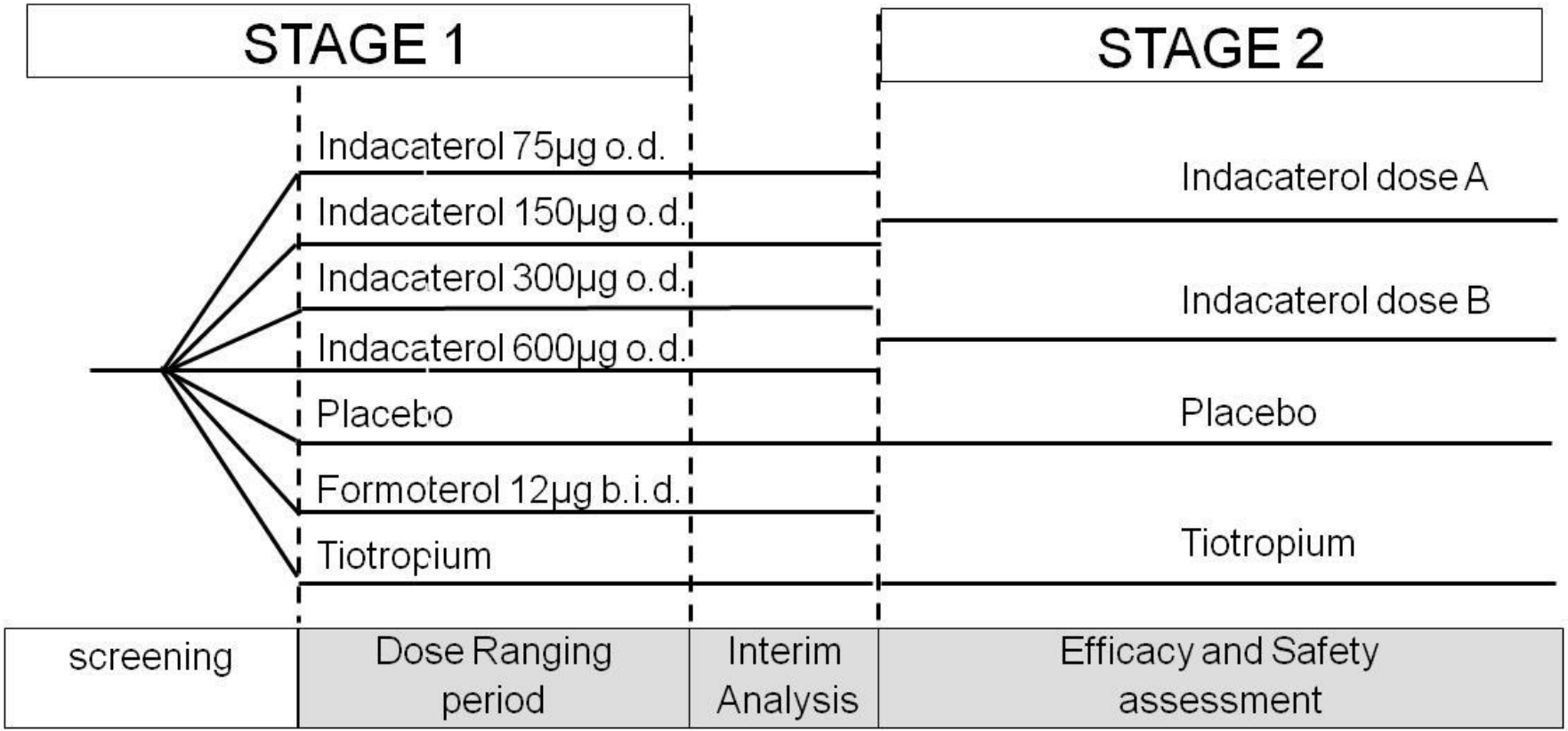
Background and Trial Design

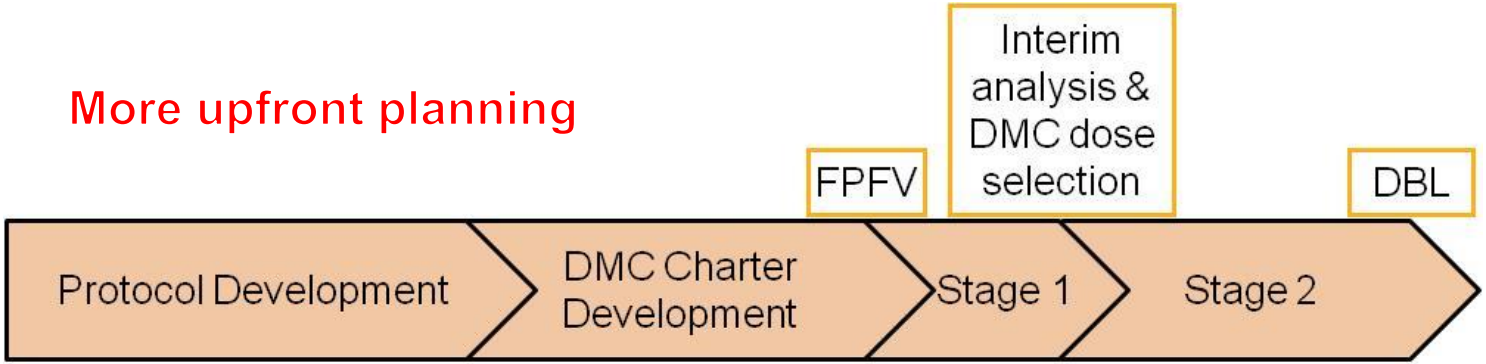
- In a chronic disease – COPD
- Adaptive seamless design (ASD) to confirm dose selection
- … and in this case, as a pivotal study
  - To support registration and label claims
  - To provide confirmation of efficacy, safety, and tolerability of the selected doses
  - To support additional studies of ‘standard’ design

Background and Trial Design



Background and Trial Design

More upfront planning



- Internal discussion
- Informal expert input
- HA interaction

- Internal discussion
- Informal expert input
- HA interaction
- DMC interaction

- Recruitment
- Detailed Interim analysis plan

- Recruitment
- Reporting

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Dose Selection

- Why was an interim analysis needed?
  - To select the most appropriate doses for full investigation in Stage 2

- Based on
  - early data read-out
  - predefined decision criteria
  - predefined data presentation

Dose Selection

- Who performs interim activities?
  - Data review
  - Decision making
- Protecting trial integrity in this trial was paramount, therefore:
  - External DMC to perform the dose selection
  - External CRO to produce the interim analysis

Dose Selection

- DMC Charter is a key document
- Input received from DMC members
- Contains description of:
  - responsibilities of all parties (sponsor, CROs, DMC)
  - timing and frequency of meetings
  - decision criteria i.e. dose selection guidelines
  - high level analysis description
  - communication plan

Dose Selection

Decision criteria

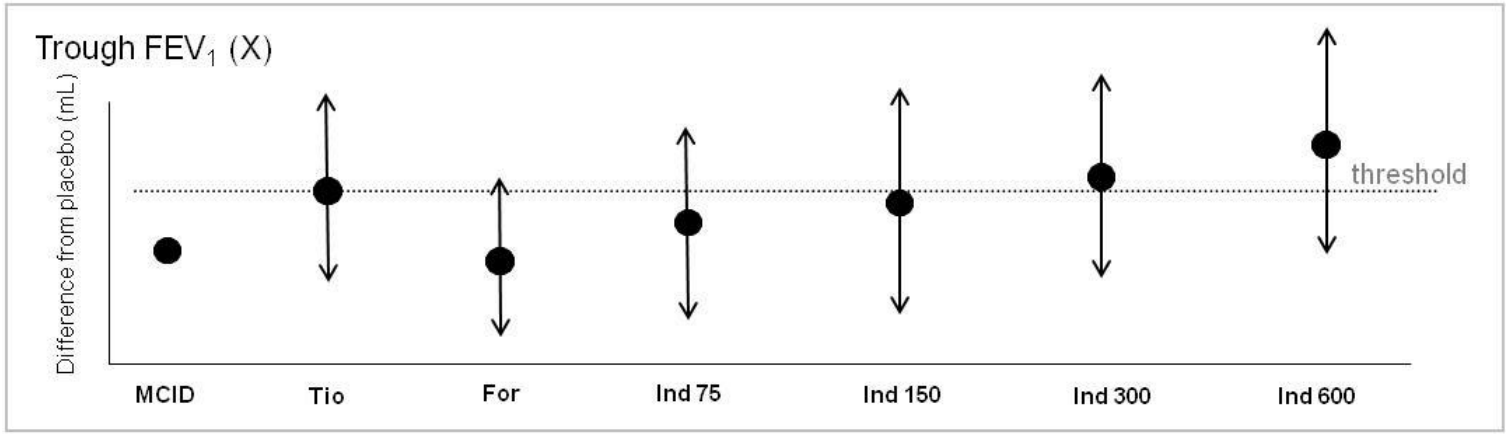
- Select 2 adjacent doses based on numerical comparison of adjusted treatment difference of each Indacaterol dose versus placebo compared to 2 thresholds – X and Y

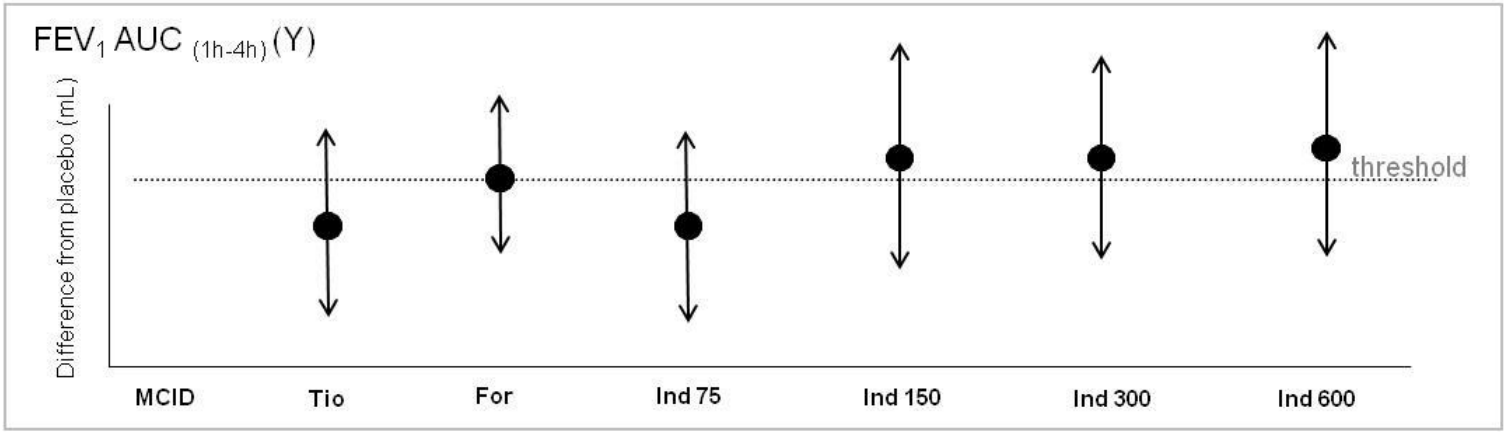
- X: based on interim primary endpoint – trough FEV_1
  - defined as the maximum of:
    - Minimum Clinically Important Difference (MCID)
    - Primary endpoint formoterol versus placebo
    - Primary endpoint tiotropium versus placebo
- Y: based on interim secondary endpoint – FEV_1 $AUC_{(1h\text{-}4h)}$
  - defined as the maximum of:
    - Primary endpoint formoterol versus placebo
    - Primary endpoint tiotropium versus placebo

Dose Selection

Outcome	Decision
If >1 dose beats X and Y	Select lowest dose that beats X and Y and the next highest OR
If 1 dose beats X and Y	Select this dose and the next highest OR
If >1 dose beats X but not Y	Select the dose that beats X and is closest to Y and the next highest OR
If 1 dose beats X but not Y	Select this dose and the next highest OR
If >1 dose beats Y but not X	Select the dose that beats Y and is closest to X and the next highest OR
If 1 dose beats Y but not X	Select this dose and the next highest OR
If 1 dose beats X but not Y and 1 dose beats Y but not X	Select the dose that beats X and the next highest OR
If 0 doses beat X or Y	Select the dose that is closest to X and the next highest

Dose Selection – hypothetical example





Dose Selection

Decision criteria

- Clear that main driver of dose selection is efficacy

BUT…

- Select two doses of indacaterol with optimal risk-benefit profile

- If a safety signal (based on AEs, parameters specific to the class of drug) is seen for any dose DMC were instructed to weigh this information against the efficacy data when selecting the doses

Dose Selection

Communication channel from DMC to sponsor defined in the DMC charter

- If there are no complexities in the data and the DMC follow the dose selection guidelines; DMC chair informs sponsor senior management reps of doses selected only

- If there are unexpected complexities that mean DMC need to deviate from guidelines then DMC may discuss unblinded results (as appropriate) with sponsor senior management representatives

Dose Selection

- Role of the sponsor
  - In the case of unexpected complexities e.g. no dose response or lack of efficacy for the active controls, the DMC has discretion to deviate appropriately from the guidelines and discuss the unblinded results with predefined sponsor representatives
  - Why?
    - Sponsor’s perspective may be relevant
    - Important sponsor’s interests may be involved
    - Adaptation decision may be complex and may lie in a domain which is traditionally sponsor’s responsibility
    - Background and Trial Design

Dose Selection

Interim analysis review meeting

- Interim analysis report sent directly to DMC members from independent statistician 1 week in advance of meeting
  - Report contained semi-blinded treatment information i.e. A, B, C etc.
  - Treatment decodes directly to DMC chair from IVRS provider
- Representatives from clinical team available to discuss trial conduct with DMC face-to-face in open meeting
- DMC discuss interim analysis with input from independent statistician in closed meeting

Dose Selection

Interim analysis review meeting

- After closed meeting:
  - Teleconference DMC with 2 senior sponsor representatives
    - If no issues DMC chair recommends 2 doses to sponsor to take forward into Stage 2
    - If issues (safety or efficacy) discuss dose selection with the same 2 senior representatives
  - DMC chair confirms dose selection in writing (fax to sponsor)
    - These doses then fed back to clinical team down a pathway pre-defined in the DMC charter
    - clinical team inform IVRS and randomisation re-starts

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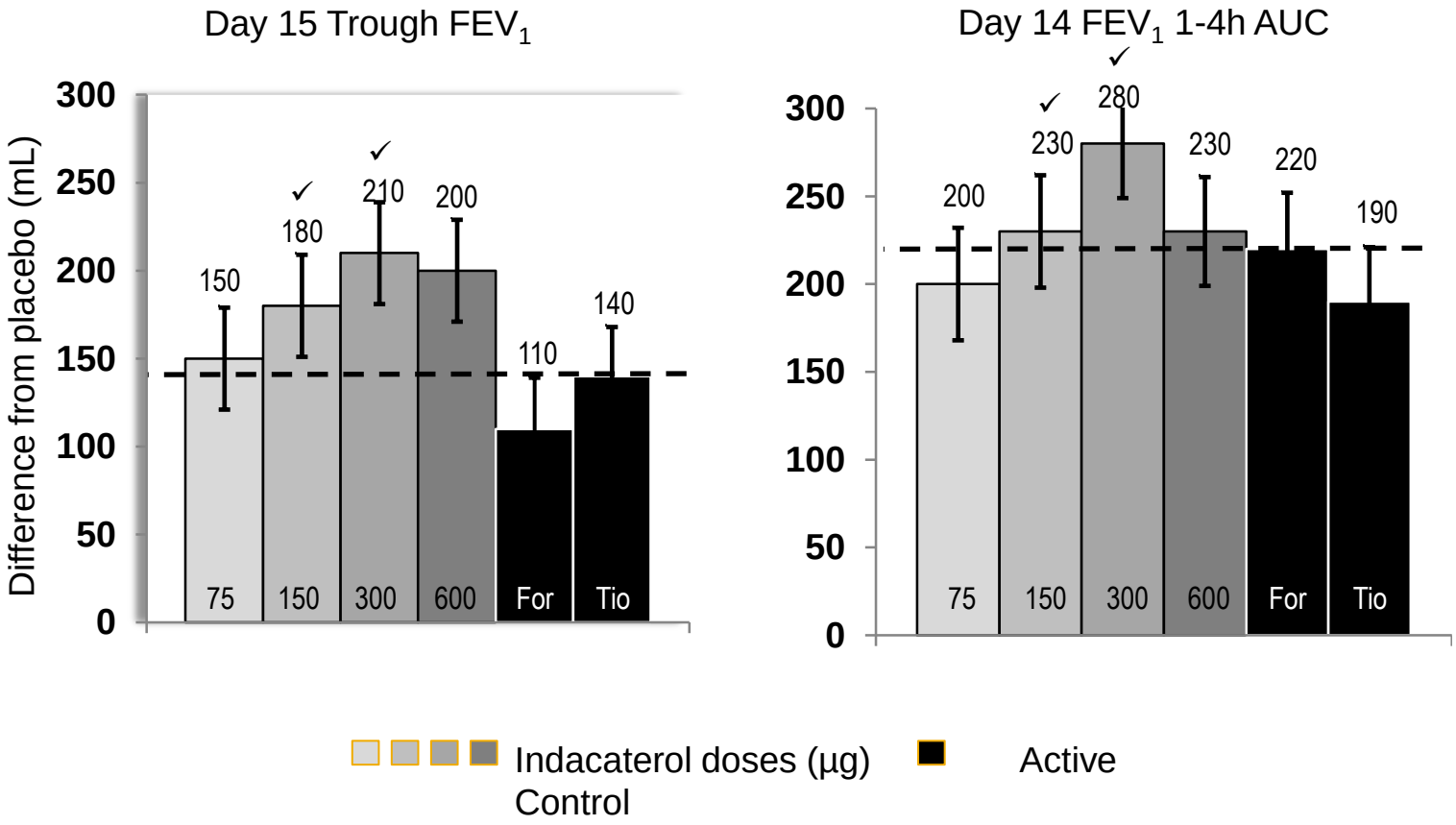

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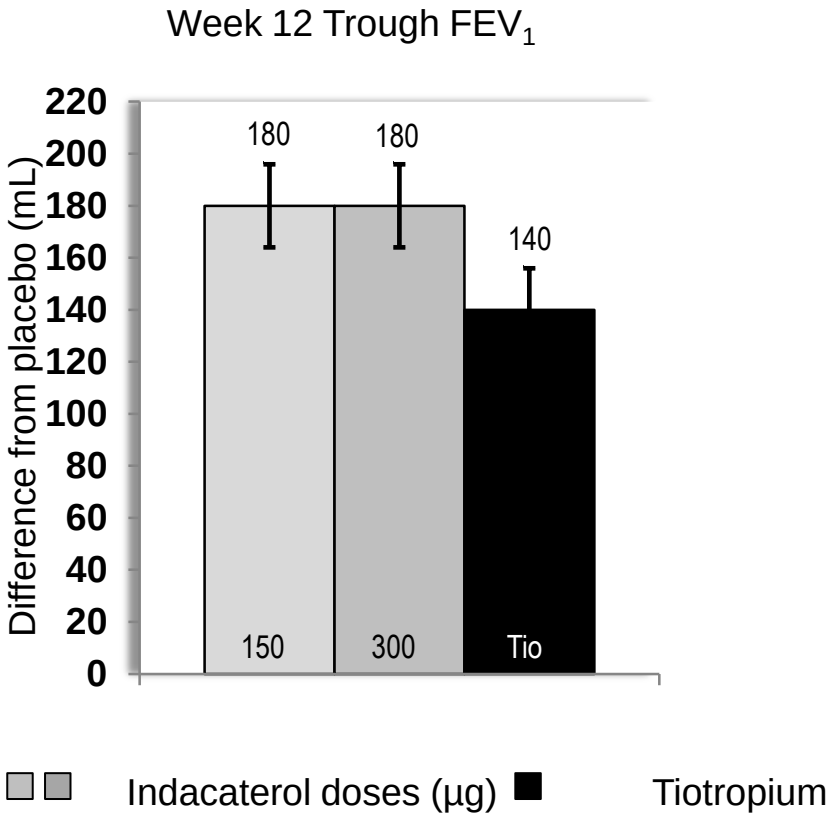
Outcome



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Conclusions

- Success requires upfront planning and discussion to promote agreement and trust between sponsor and DMC (and HAs)
- Any dose selection guidelines require thorough stress testing to limit unexpected outcomes later
  - As usual if the assumptions that go into a design are not correct then there can be unintended consequences
- Protecting trial integrity is paramount in a study reviewed to support an approval
  - ...and must be able to show integrity has been maintained
- Most important document is the DMC charter - covers detailed procedures & written specifically for the trial