EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Alternative Study Designs and their Suitability for Paediatric Development

Frank Pétavy
Biostatistics and Methodology Support, Medicines Evaluation Division

Workshop on the development of new medicinal products for the treatment of Ulcerative Colitis and Crohn's disease

Presented by Frank Pétavy on 29 June 2015
Biostatistics and Methodology Support, Medicines Evaluation Division

An agency of the European Union

Disclaimer

The views expressed are those of the presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency (EMA) or its scientific committees or reflecting the position of the EMA.

Agenda

- What is specific to paediatric clinical trials in UC/CD?
- Current designs, including randomised withdrawal design
- ‘Alternative’ designs

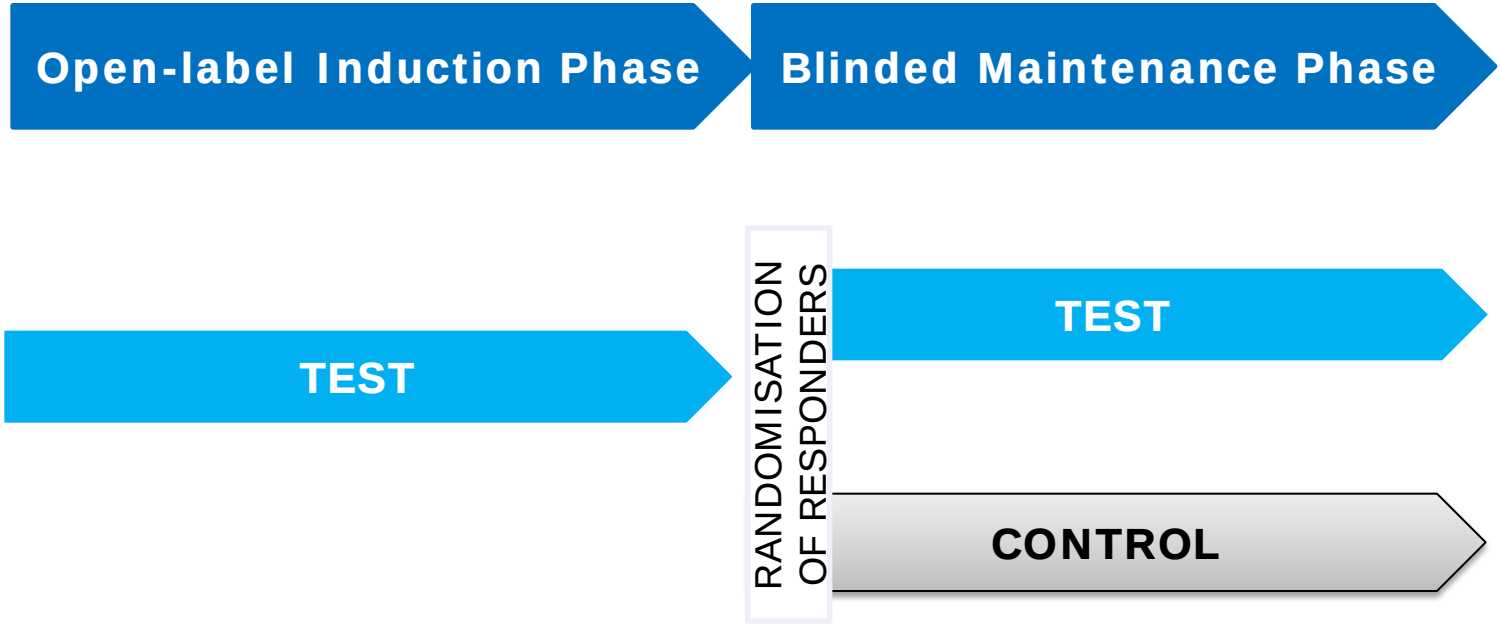
What is specific to paediatric clinical trials? … and impact on design

- **Ethics**: limit exposure to placebo
  - Are add-on designs not enough? (not pure placebo, but with standard of care)
  - No placebo arm in all cases?
  - Is shorter exposure to placebo acceptable?
  - It is also unethical to run studies that have no realistic chance of credibly showing efficacy
- **Logistics**: avoid repetitive visits
- **Outcome**: avoid invasive endpoints
  - Mucosal healing is objective but invasive; but subjective measures have limitations too
- Is the **weight of evidence** changed if the drug works in adults?
  - Is it strong enough not to need a control arm? Or not to conduct any clinical trial in children?

Current designs for paediatric clinical trials in UC/CD

- Approved drugs in the EU: no ‘real’ control arm, open-label, lack of consistency in outcome measures
  - Humira: standard dose (induction) and randomisation to two doses (maintenance)
  - Remicade: standard dose (induction) and randomisation of responders to two regimens (maintenance, open-label)
- Agreed PIPs: in general, randomised withdrawal design
  - Primary endpoint mainly at end of maintenance phase

Randomised withdrawal design



Randomised withdrawal design

ICH E10 (Choice of control group)

- Advantages
  - Study long-term efficacy when long-term placebo treatment is not acceptable
  - Period of placebo exposure with poor response is short
  - Useful for dose finding (placebo and several doses in second phase)
  - For relapse-prevention studies
  - To determine how long a therapy should be continued

- Limitations
  - Lack of control arm in induction phase (no internal validity)
  - No benefit accrued, but withdrawal leading to disease exacerbation -> erroneous conclusion of persisting efficacy
  - Population enriched with responders -> treatment effects larger vs. in an unselected population

Options

- **Extrapolation**
  - Is it possible? Are all conditions in place to rely on extrapolation?
- No Extrapolation
  - Or some extrapolation…
  - But **some level of evidence is needed**
  - What are the clinical questions? What level of evidence is needed?

- **Alternative** designs… alternative to what? Typical RCT or current designs in UC/CD?

‘Alternative’ designs (1)

- **Internal control** in the induction phase: randomised placebo-controlled trial
  - Depends on population
  - Active control too? In that case, no placebo arm or fewer patients on placebo?
  - Or low dose as control?
- “Early escape”
  - To address ineffective therapy, worsening of clinical status
  - Study withdrawal or rescue treatment
  - Need to change treatment can become an endpoint
- Limit number of patients exposed to placebo
  - Unbalanced randomisation with more patients on test drug arm, e.g. 2:1, 3:1
- Limited placebo period: important to establish assay sensitivity for short-term effects

‘Alternative’ designs (2)

- **Adaptations** in design: improve efficiency of the trial
  - Strong requirements in planning and pre-specification
  - See CHMP Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design (2007)
- Sample size re-assessment
  - Although rarely used to reduce number of patients
- Dropping arms
  - If patients randomised to different doses/regimens, ineffective dose/regimen could be dropped
- Changing the randomisation allocation
  - Forcing patients to be randomised to a more promising dose

‘Alternative’ designs (3)

- If no control arm in induction phase, what about an **external control**?
- Is there relevant historical data for UC/CD in paediatrics?
- If there is, there are still challenges
  - Lack of randomisation and blinding -> bias likely and unmeasurable
  - Unknown/unmeasured confounding factors
- Requirements for a more robust comparison using historical controls
  - strong belief of the superiority of the test therapy compared to treatment alternatives
  - disease well documented and with predictable course
  - Objective endpoint and impact of covariates well characterised
  - similar patient characteristics (inclusion criteria, confounders)

Acknowledgements

- EMA: Chrissi Pallidis, Dorota Distlerova, Joachim Musaus, Richard Veselý, Andrew Thomson
- Health Canada: Catherine Njue

- Paper in preparation on Clinical Trial Design Issues and Methodology for Pediatric IBD Trials

Thank you for your attention

Further information

[Insert relevant information sources or contact details as applicable.]

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**