Pediatric Regulation 2007

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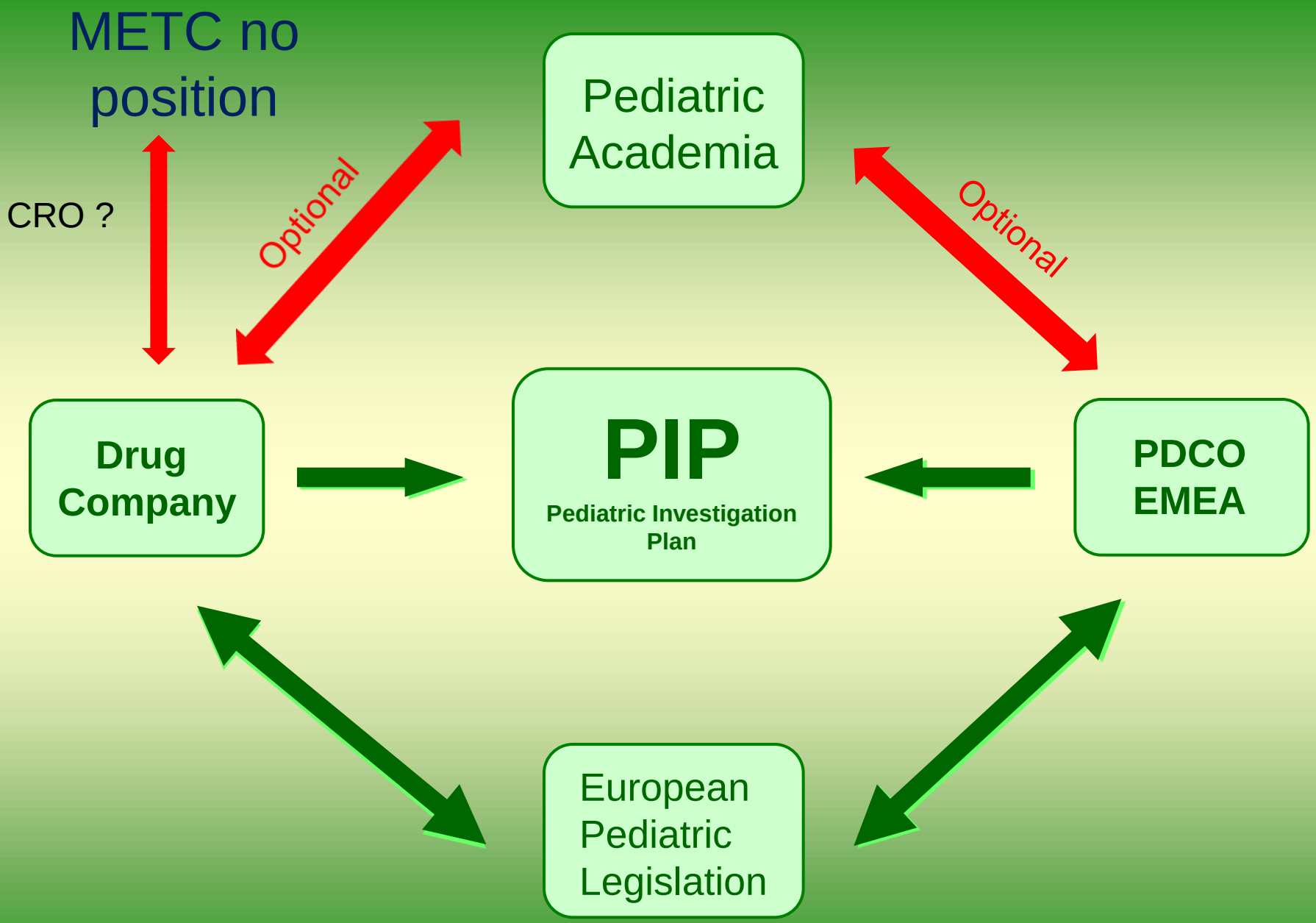
Presented are personal opinions, not of Committees mentioned


METC no position
CRO ?
Optional
Pediatric Academia
Optional
Drug Company
PIP
Pediatric Investigation Plan
PDCO EMEA
European Pediatric Legislation

Example of development of a PIP

Inflammatory Diseases
Crohn and Ulcerative Colitis in children

Anti-Inflammatory Antibodies (AIA)

Higher clearance at younger age from 12 years downwards

Lower trough levels at younger age

Unexplained no response after induction with low trough levels

Children are eliminated from maintenance studies

Less response in severe disease at younger age

Different immune defects at younger age

Clinical endpoints

- Mucosal healing different results from clinical scores: Endoscopy
- Clinical scores less responsive than mucosal healing
- PROs to be developed
- Endoscopy is not possible at every dose change
- At some point endoscopy needed for individual E/R evaluation

Lessons

Placebo not needed similar pathophysiology

In children: PK + efficacy studies are needed because of unknown E-R relation in pediatrics

Pediatric dosing should aim for similar exposure/Ctrough across all weight ranges

1. Adjust the dose a priori taking into account non linear change in clearance with weight
2. Adjust the dose in case of low trough levels (TDM-therapeutic drug monitoring)

Proposal

1. Always pop-PK
2. Individual reporting for all co-variates
3. Dose escalation allowed at all randomization points
3. Variation in endpoint performance
5. Comparators
6. Rapid AIA tests are becoming available (< 2 hours)
7. Numbers adequate for all ages

Part of current EMA Crohn and Ulcerative Colitis Clinical Guidelines

METC

To discuss in case of children

Trough PK needed

Endoscopy needed

Extrapolation

- No placebo in induction phase
- Placebo withdrawal
- Small numbers
- Young age very small numbers
- Small numbers, no placebo, different endpoints (scores instead of endoscopy) generates always inferior data

Considerations for trials in children

- Placebo is not needed *per se*
- Dose adjustment per weight category should be improved aiming for similar exposure across all weight ranges
- Population PK modeling should be applied after all studies to guide dosing (despite small patient numbers and in appropriate age distribution)
- Novel trial designs aiming for individualized dosing (including TDM) should be evaluated
- Remission on clinical scores, endoscopy at 52 weeks for safety issues as well
- With optimal high dose, adjustment for all co-variates, appropriate dosing interval (trough level with some drug concentration), efficacy over longer periods observed than now in real life loss of response data

Area	Number of measures	Description
Quality-related studies	2	**Study 1:** Development of a chewable tablet **Study 2:** Development of an age-appropriate oral liquid dosage form
Non-clinical studies	1	**Study 3:** Definitive juvenile toxicity study in Rats

Clinical studies	8	**Study 4** Randomised, double-blind, parallel-group, placebo-controlled study over 52 weeks to assess the efficacy and safety of fevipiprant when added to existing asthma therapy in adolescents (and adults) with uncontrolled severe asthma. (CQAW0039A2307/CQAW039A2314) **Study 5** Bioequivalence/comparative bioavailability to determine the bioavailability study of two different paediatric fevipiprant oral formulations relative to film-coated tablets as well as the relative bioavailability of the two paediatric formulations (CQAW039A2114) **Study 6** Open-label, pharmacokinetic, safety and tolerability study of fevipiprant in paediatric patients aged 6 to <12 years. (CQAW039B2201) **Study 7** Open-label, pharmacokinetic, safety and tolerability study of fevipiprant in paediatric patients aged 1 to <6 years. (CQAW039B2102) **Study 8** Randomised, double-blind, parallel-group, placebo-controlled study to determine efficacy and safety of once daily fevipiprant, compared with placebo in children 6 to <12 years with uncontrolled moderate to severe persistent asthma. (CQAW039B2302) **Study 9** Randomised, double-blind, parallel-group, placebo-controlled study to determine efficacy and safety of once daily fevipiprant, compared with placebo in children 1 to <6 years with uncontrolled moderate to severe persistent asthma. (CQAW039B2301) **Study 10** Randomised, double-blind double-dummy, parallel group study to demonstrate the non-inferiority of once-daily fevipiprant compared with low-dose inhaled corticosteroids (ICS) in children 1 to <6 years with uncontrolled mild persistent asthma. (CQAW039B2304) **Study 11** Randomised, double-blind double-dummy, parallel group study to demonstrate the non-inferiority of once-daily fevipiprant compared with low-dose inhaled corticosteroids (ICS) in children and adolescents 6 to <18 years with uncontrolled mild persistent asthma. (CQAW039B2305)

Take home messages

- Studie maakt deel uit van een geheel ontwikkelingsplan
- Ratio van elk deel moet door firma / CRO gecommuniceerd worden naar de METC
  - Dit ontbreekt veelal