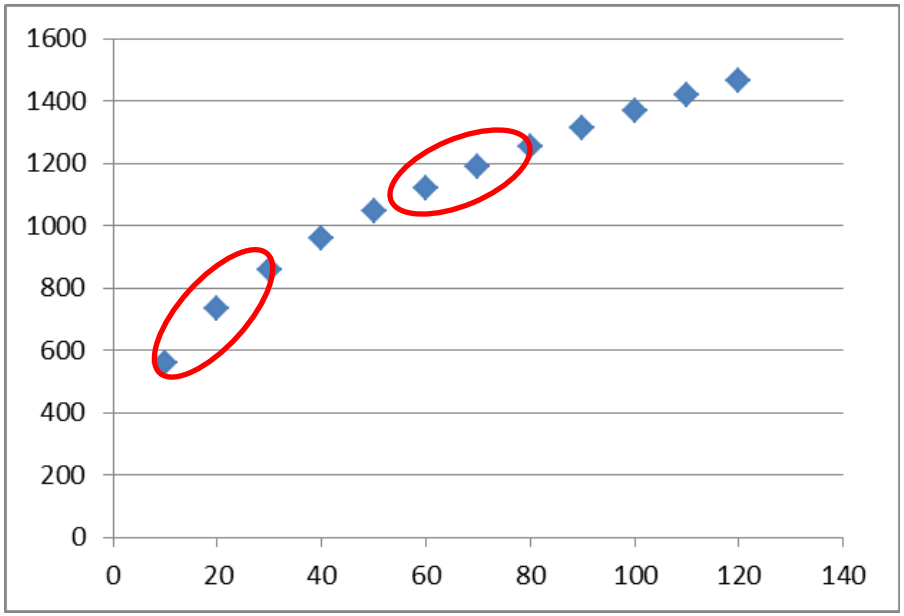
Do children need adult type trials

Individual dosing
Pharmacokinetics
Clinical scores vs endoscopy
Placebo

Infliximab AUC versus bodyweight

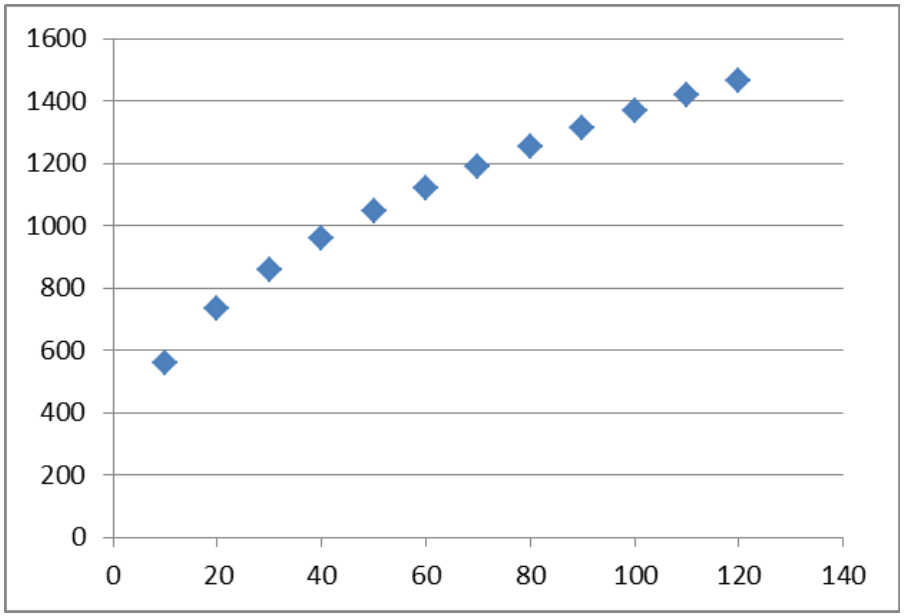
- Clearance scales allometricly with bodyweight
  - Clearance i = 0,294 * (bodyweight/70)^{0,614}
- Dose is linear with bodyweight (i.e. 5 mg / kg)
- Pediatric bodyweight range 10-70 kg



Fasanmade AA et al., Clin Ther 2011;33:946-964

Infiximab AUC versus bodyweight

- There is a potential risk of underexposure in the youngest individuals when dosing per kg while clearance scales allometricly with bodyweight
- As such it seems that a dose higher than 5 mg/kg is required for children under 40 kg with even higher doses under 20 kg.



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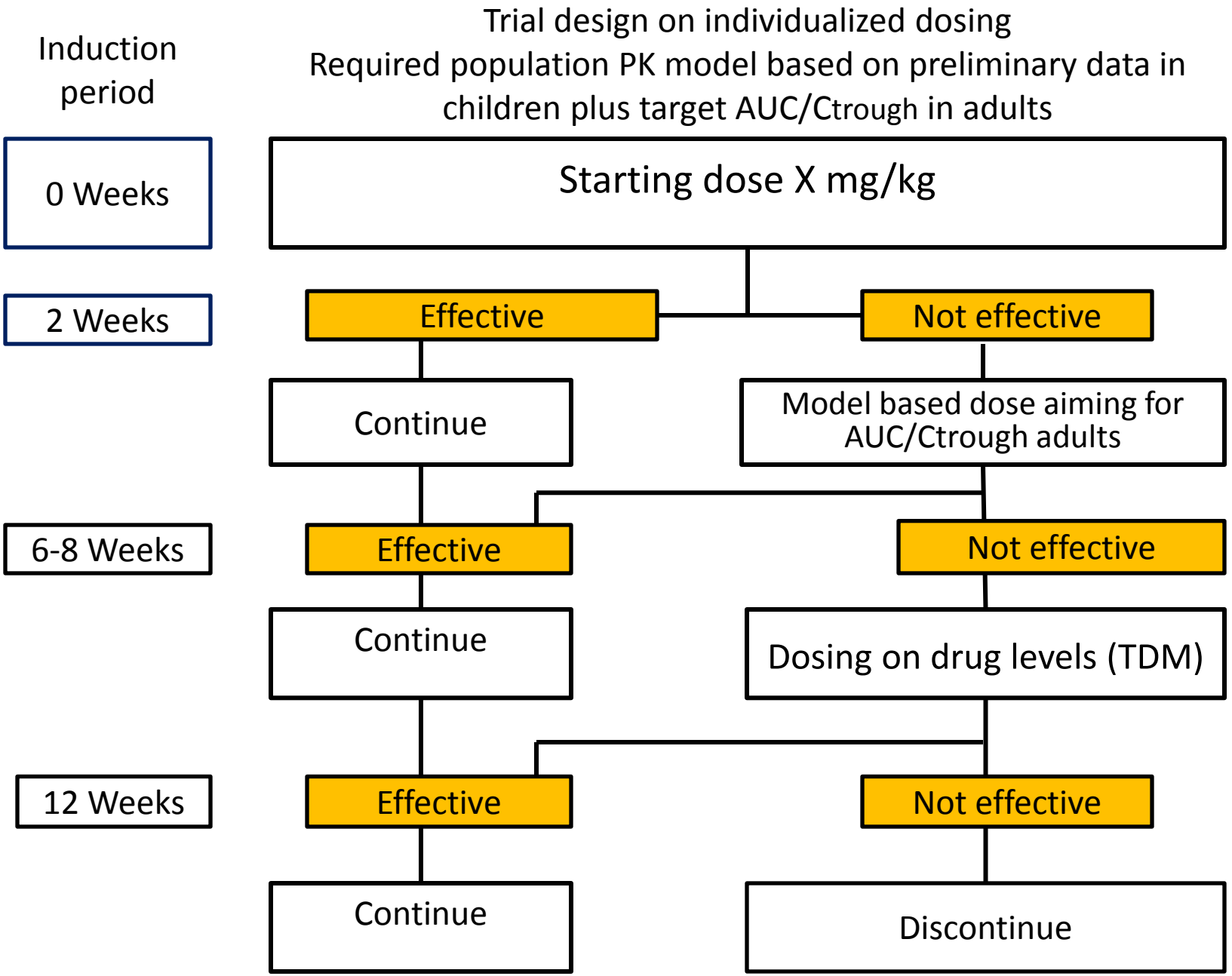

Induction period
Trial design on individualized dosing
Required population PK model based on preliminary data in children plus target AUC/Ctrough in adults
0 Weeks
Starting dose X mg/kg
2 Weeks
Effective
Not effective
Continue
Model based dose aiming for AUC/Ctrough adults
6-8 Weeks
Effective
Not effective
Continue
Dosing on drug levels (TDM)
12 Weeks
Effective
Not effective
Continue
Discontinue

Lessons

- In children: PK + efficacy studies are needed because of unknown E-R relation in peds
- Pediatric dosing should aim for similar exposure(AUC)/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)

Adalimumab

- Peds study included children < or > 40 kg
- Both high dose and low dose for each group
- Results: Cut-off for weight based dosing was suboptimal for achieving similar exposure in different weight groups
- Population PK modelling was done and only used to adjust the induction dose

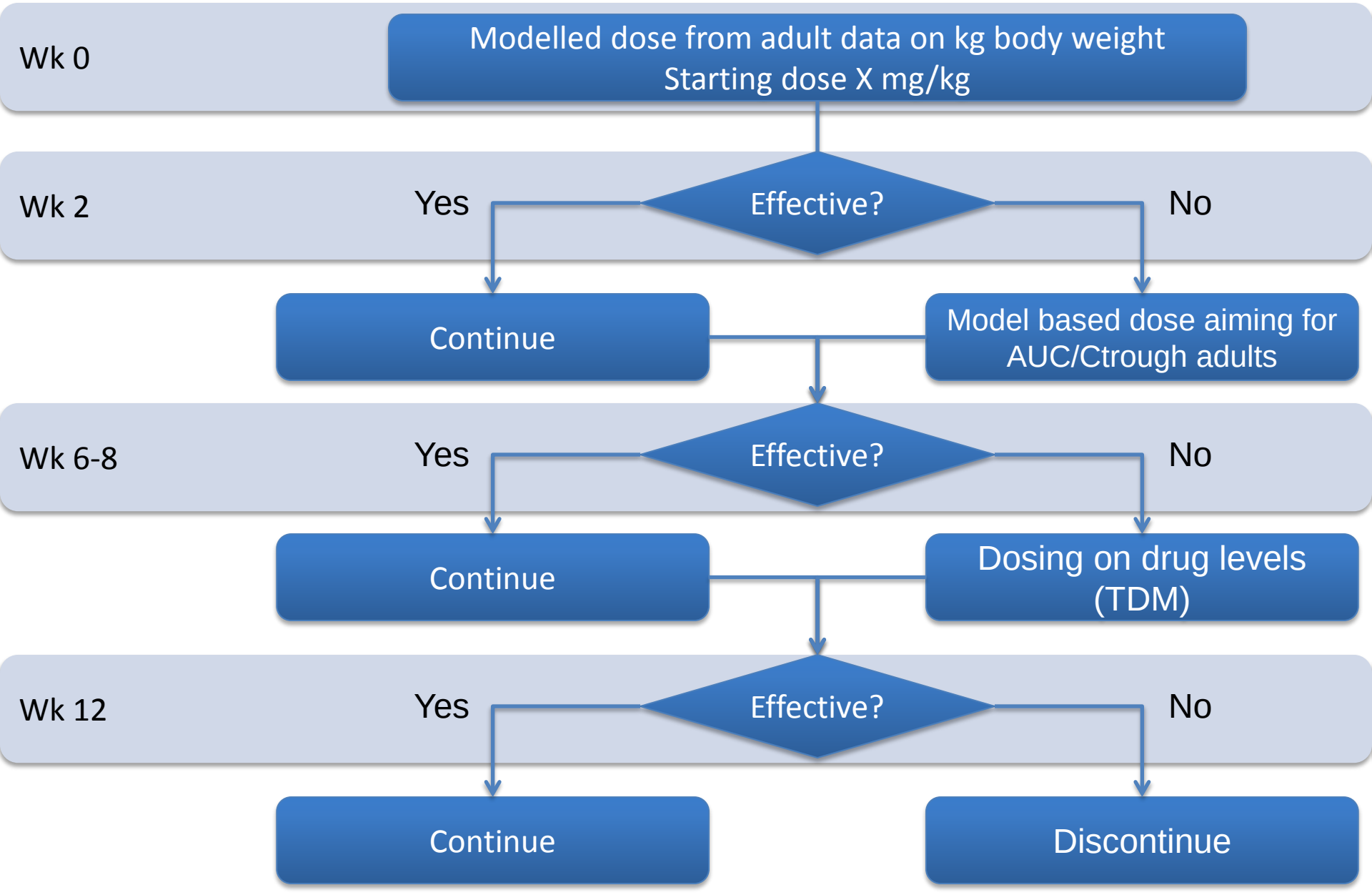
BUT: not to optimize the cut-off for weight based dosing…….

Lessons

- Population PK modelling needs to be applied to guide dosing in children
  - Can be done after completion of the studies
  - Results of all clinical studies (adults and children) should be used
  - Can still be applied despite small patient numbers
  - Covariate analysis characterises influence of weight on clearance and exposure

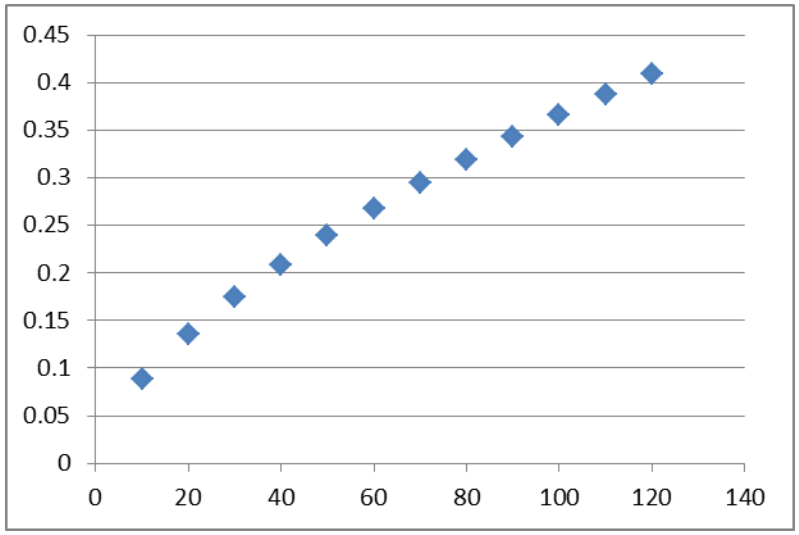
Using the final model, optimal doses per weight category can be defined

Trial design on individual dosing
Required population PK model based on preliminary data in children plus target AUC/Ctrough in adults



Formula Cli=0,294* weight/70 to the exponential 0,614 clearance vs weight Infliximab

Clearance



Body weight

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