EMA EFPIA workshop
Break-out session no. 3

Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to <10 years of age

MAIN ISSUES

To bridge the data gap of limited or no information using M&S

- data integration
- evidence "synthesis"

Background & Rationale

Topiramate

2 yrs

6 yrs

10 yrs

Adjunct therapy

Approved

Data

Mono therapy

Approved

Data

Available Data

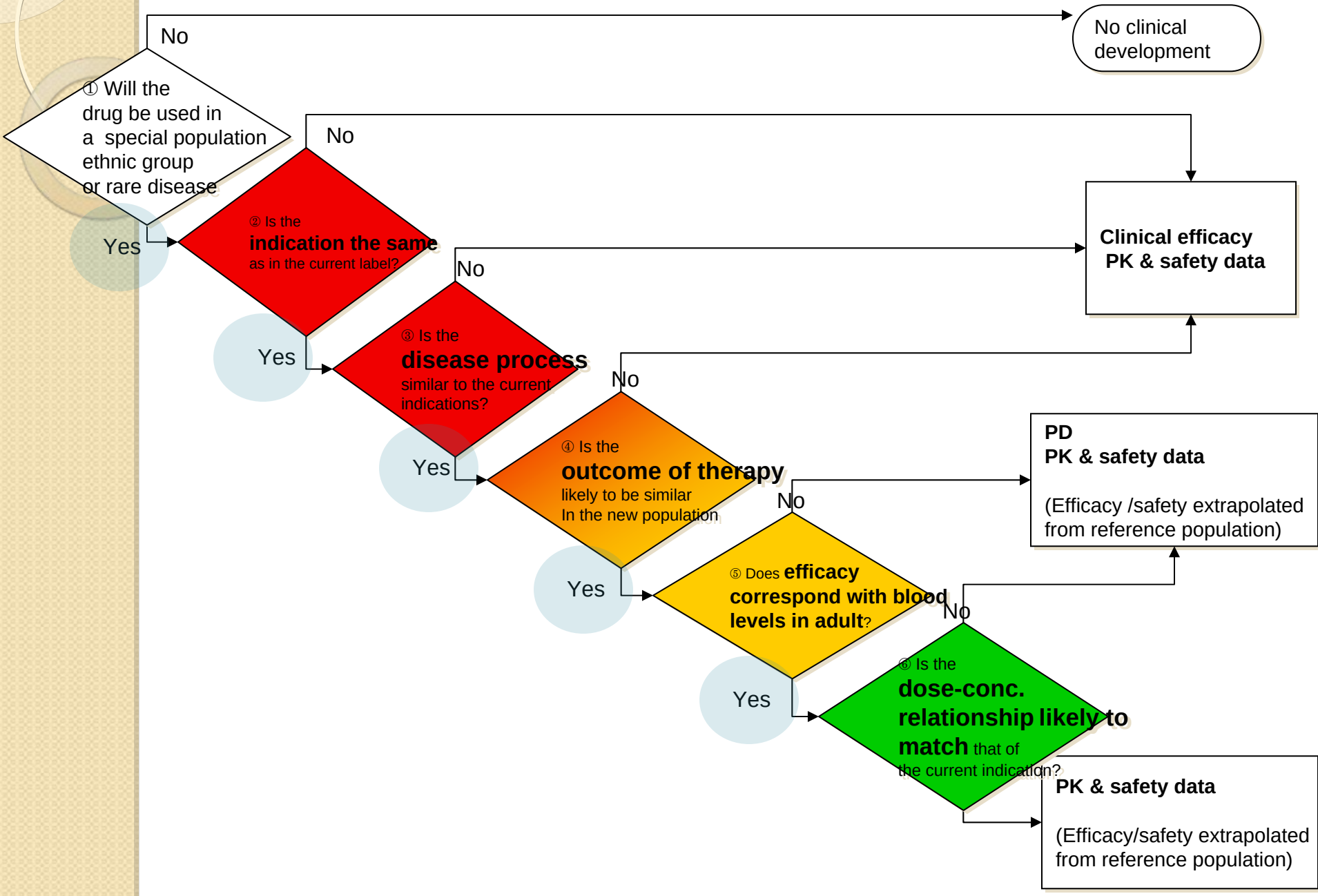
- 11 studies
  - 8 adjunct: 2-68 years (12 patients < 6 years)
  - 3 monotherapy: 6-85 years
- PK
  - 1217 patients, 4640 observations
- PD Efficacy endpoint
  - Adjunct therapy
    - % reduction in seizure frequency
    - Responder rate
  - Monotherapy:
    - time to first seizure

M&S Assumptions

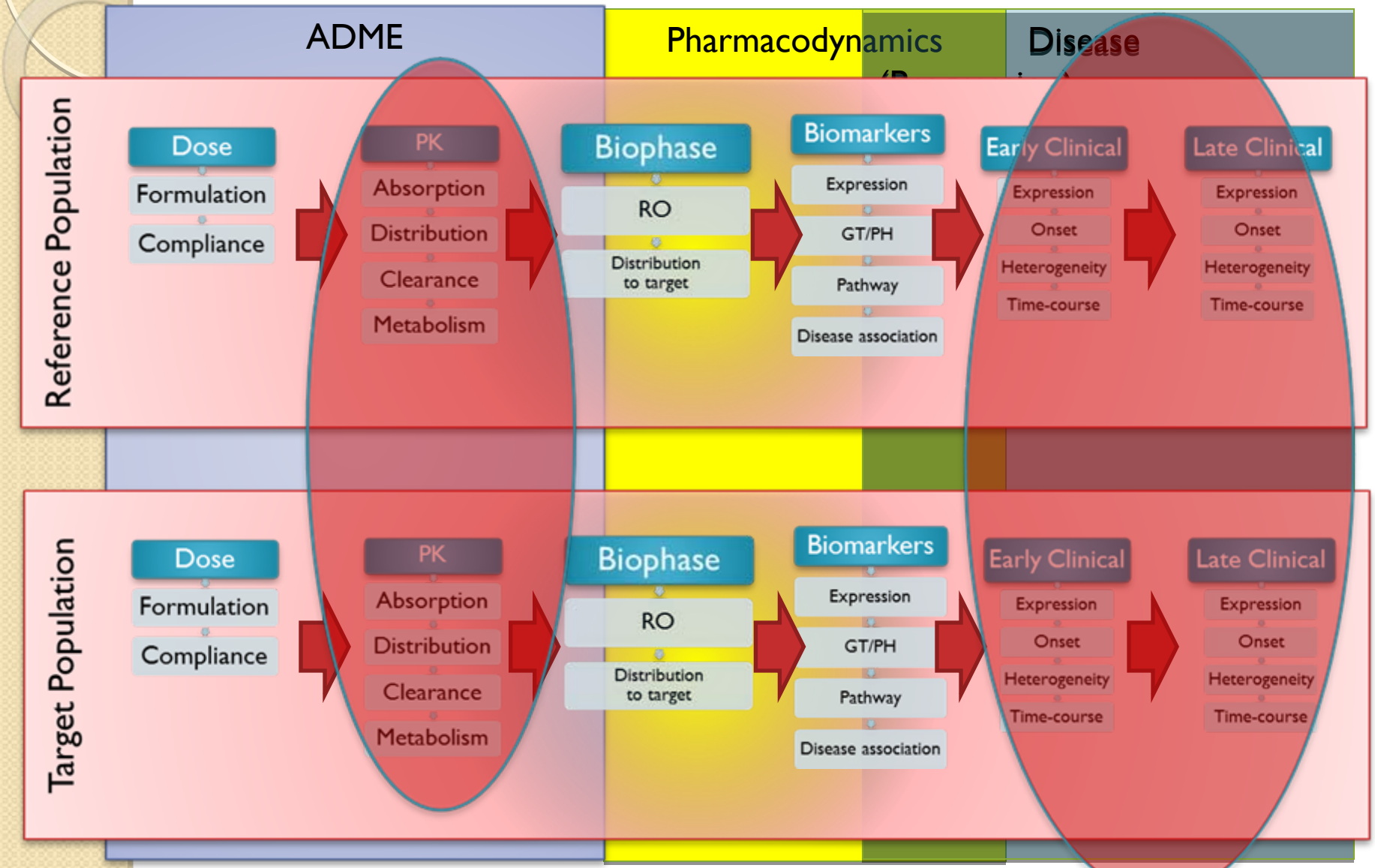
Pediatrics vs Adults

- **Epilepsies in children:**
  - **Partial onset seizures (POS) and Lennox-Gastaud syndrome**
    - **treatment effect can be extrapolated from adults to children**
  - **Infantile epilepsies are specific to children: most relevant issue +++**
    - **no possible extrapolation for treatment effect from adults to children**
    - **no possible extrapolation for PK/PD**
      - **epilepsy is often refractory and may even be worsened**
    - **no possible extrapolation for adverse events**
    - **possible model-based extrapolation for PK**

Where are we?


No
No clinical development
① Will the drug be used in a special population ethnic group or rare disease
No
Yes
② Is the indication the same as in the current label?
No
Clinical efficacy PK & safety data
Yes
③ Is the disease process similar to the current indications?
No
Yes
④ Is the outcome of therapy likely to be similar In the new population
PD PK & safety data
(Efficacy /safety extrapolated from reference population)
No
Yes
⑤ Does efficacy correspond with blood levels in adult?
No
Yes
⑥ Is the dose-conc. relationship likely to match that of the current indication?
PK & safety data
(Efficacy/safety extrapolated from reference population)

Factors Determining Treatment Response...



M&S Results (PK)

- Two-compartment with 1st –order absorption

Parameter	Typical value (%SE)	Interindividual variability (%SE)
Clearance (L/h)		
CLSTM (baseline clearance monotherapy) (θ_1)	1.21 (1.2)	27.28 (10.2)
CLSTA (effect of adjuvant) (θ_2)	0.479 (25.3)	
FCWT (effect of weight) (θ_3)	0.453 (9.0)	
FCAGE (effect of age) (θ_4)	-0.00306 (30.9)	
FCIN (effect of INMD) (θ_5)	1.94 (7.8)	
FCVP (effect of valproate) (θ_6)	0.686 (7.8)	
FCNE (effect of NEMD) (θ_7)	0.635 (6.2)	
Central volume of distribution (L)		
VST (θ_8)	4.61 (33.2)	116.2 (35.0)
FVWT (effect of weight) (θ_9)	1.14 (19.1)	
Ka (h-1) (θ_{10})	0.105 (27.0)	22.34 (88.2)
K23 (h-1) (θ_{11})	0.577 (16.7)	NE
K32 (h-1) (θ_{12})	0.0586 (23.6)	NE
CCV residual error (%CV)		25.46 (7.8)
Additive residual error (mg/L)		0.1797 (39.9)

%SE – percent standard error, NE, not evaluated.

M&S Results (PK/PD, adjunct-therapy)

- % change in seizure frequency

$$Y_{obs,i} = \beta_o + \beta_1 C_{MIN,i} + \beta_2[\log(B_i) - \log(B)] + \beta_3 C_{MIN,i}[\log(B_i) - \log(B)] + \varepsilon_{y,I}$$

where, $$Y = \log\left(\frac{100(S - B)}{B} + 110\right)$$

- responder rate

$$P_{RESP} = g\left\{p_0 + \frac{E_{MAX} \cdot C_{MIN}}{EC_{50} + C_{MIN}} + p_{PED} \cdot PED\right\}$$

where,

$$g\{x\} = \frac{e^x}{1 + e^x}$$

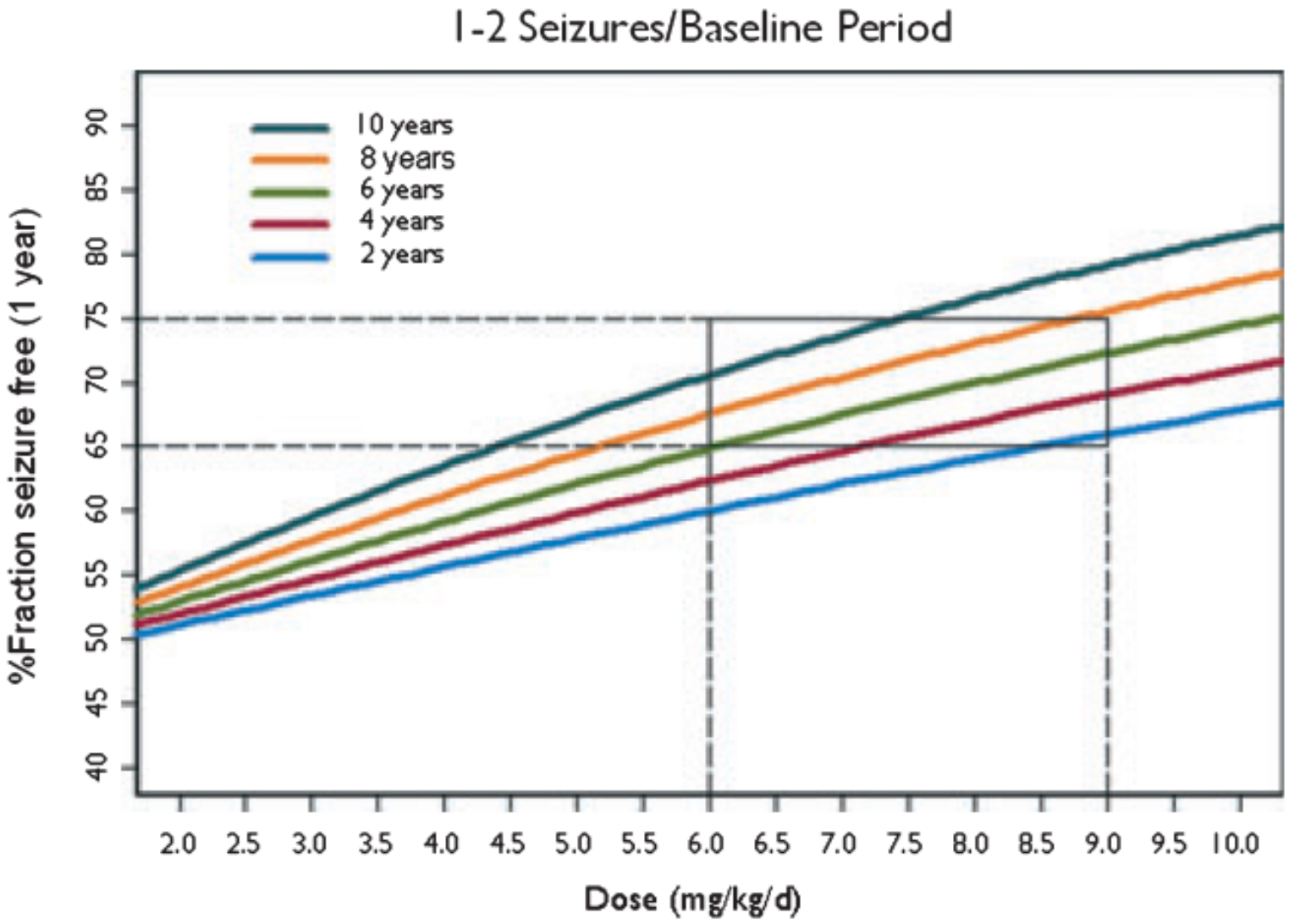
M&S Results (PK/PD, monotherapy)

$$\log(\lambda_i) = \lambda_0 + \lambda_t \cdot t + \lambda_{C_{MIN}} \cdot C_{MIN,i} + \lambda_{BS3-10} \cdot BS_{3-10,i} + \lambda_{BS10} \cdot BS_{10,i}$$

Parameter	Estimate ± SE	p-value
λ_0	−3.130 ± 0.0919	–
λ_t	−0.051 ± 0.0036	<0.0001
λ_{CMIN}	−0.112 ± 0.0151	<0.0001
λ_{BS3-10}	1.048 ± 0.1046	<0.0001
$\lambda_{BS>10}$	2.411 ± 0.1356	<0.0001

SE, standard error; λ_0, hazard (the instantaneous risk of a first seizure after randomization to occur); λ_t, parameter describing the relationship between log (hazard) and t; λ_{CMIN}, parameter describing the relationship between log (hazard) and C_{MIN}; λ_{BS3-10}, parameter describing the relationship between log (hazard) and $BS_{3-10,i}$; $\lambda_{BS>10}$, parameter describing the relationship between log (hazard) and $BS_{>10,i}$.

M&S Results (Dose-Response, monotherapy)



Conclusions

- **Absence of evidence of an effect of age is ONLY VALID for POS and Lennox-Gastaud syndrome**

- **Otherwise MAJOR EFFECT OF AGE**
  - **other types of epilepsies … the most relevant to consider specifically**
    - **symptoms are different (epilepsy syndromes) and are severe**
    - **refractory epilepsies**
    - **poor cognitive prognosis**

  - **need for a specific approach to infantile and juvenile epilepsies resistant to usual first and second line anti-epileptic treatment: 2 step approach:**
    - **add-on observational approach: identification of candidate syndrome (s)**
    - **add-on comparative trial vs placebo in the identified syndromes**

freedom in different age groups.

- **Avoid oversimplification in extrapolation for PK while ignoring the maturational differences in younger age-groups (below 2 years of age): model-based modelling approach rather than allometric approach**

freedom rate after 1 year for pediatric patients aged 2–

- FDA decision tree is not fully adequate in the most specific aspects of paediatric drug development due to oversimplification