Enpr-EMA PAEDIATRIC ANTIBIOTIC WORKING GROUP

Rationale and outlook

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RATIONALE

- The work plan for the **Committee for Medicinal Products for Human Use** (CHMP) **Infectious Diseases Working Party** (IDWP) for 2016 included the production of a **Paediatric Addendum** to the **guideline on the evaluation of medicinal products** indicated **for treatment of bacterial infections**

- A draft **Concept Paper** was released for public consultation in April 2016 (EMA/CHMP/213862/2016)

- The **first draft of the Paediatric Addendum** is planned to be **released for consultation 1Q 2017**

- The board of the **European networks for paediatric research at the EMA** (EnprEMA) has on parallel agreed to set up a new **Working Group (WG) on paediatric antibiotic clinical trial (CT) design**, involving **academic**, **regulatory** and **industry** representatives

- **AIM**: to **facilitate the harmonisation** of **neonatal** and **paediatric AB CTs** considering specific aspects of design and conduct. **Complimentary to the Paediatric Addendum** potentially adding value based on **experience from the networks** and **members** involved in the WG.

Draft Concept paper on an addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) to address paediatric-specific clinical data requirements

TERMS of REFERENCE

- The WG considered **trial design** for **neonates**, **infants**, **children** and **adolescents**
- The WG **focused only on antibiotics** (AB), but considered available guidance on all antimicrobial CT design
- The **role** of the WG is **advisory to elicit and summarise views from a range of key stakeholders**
- The WG has representation from the **Paediatric Committee** (**PDCO**), **CHMP IDWP**, relevant **academic groups/networks**, and **industry**
- The WG has **close liaison with other current European and/or global initiatives** focusing on **paediatric antibiotic CT design**, including the **CTTI Paediatric AB Trials group**
- The WG **liaised closely with the planned Paediatric Addendum** to the EMA Guidance on PK/PD core components in antibiotic design
- The WG **considered** the following **major CIS**:
  - Bloodstream infections (BSI/sepsis)
  - Neonatal sepsis
  - Community-acquired pneumonia (CAP)
  - Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
  - Complicated urinary tract infections (cUTI)
  - Complicated intra-abdominal infections (cIAI)
  - Acute bacterial skin and soft tissue-infections (cSSTI)

Draft concept paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99) and conversion to a CHMP guideline

DELIVERABLES

1. Review the current international **regulatory** and **non-regulatory guidance** in **design** and **conduct** of **paed CTs**
2. Review the literature of **conducted** and **planned paediatric antibiotic CTs**
3. Produce a **summary document** of the **key components of design for paediatric AB CTs*** on **efficacy**
4. The **core components** of **PK design across all age groups**
    - The specific aspects of **modelling** and **extrapolation** relevant to paediatric CTs*
5. The **key components** of **safety** in **paediatric AB CTs***
    - The feasibility of **standardizing sample sizes** for **safety** regulatory paediatric AB CTs
6. The conduct of paediatric AB CTs within **populations infected** with **MDR pathogens**
7. Suggestions on **enhancement of CT reporting** according to CONSORT guidance
8. Specific factors with AB trials to **enhance patient and public engagement** and **trial recruitment**
9. To discuss options for **improving the pharmacovigilance** of neonatal and paediatric AB post marketing approval

**Draft Reflection paper on extrapolation of efficacy and safety in paediatric medicine development (EMA/199678/2016)*

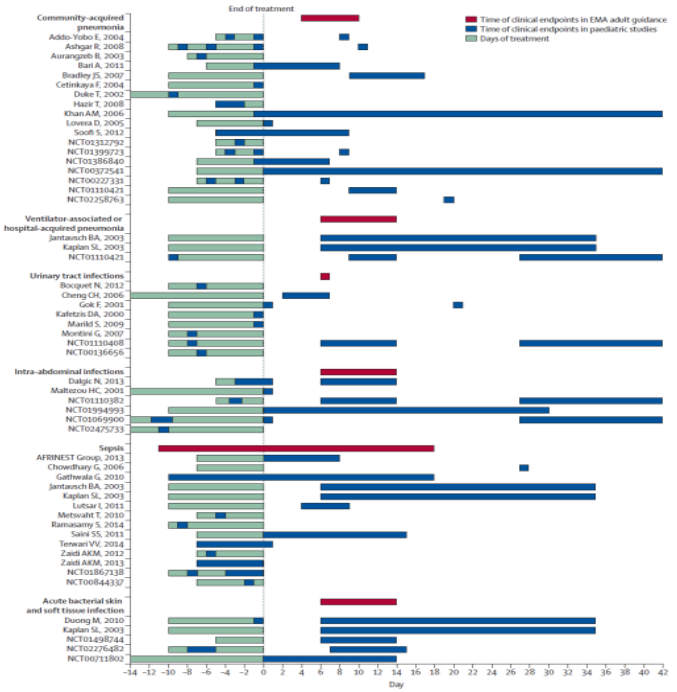
INCLUSION/EXCLUSION CRITERIA and ENDPOINTS for INFECTIOUS CIS in PAEDIATRIC AB CTs

- Currently there is **too much heterogeneity** for the inclusion and exclusion criteria used **in paediatric studies**
- It is important that there is a **consensus guideline to use for each CIS** to avoid every study having different criteria
- The **Paediatric addendum will not be addressing inclusion and exclusion criteria**

SUMMARY DOCUMENT for each CIS:

- inclusion/exclusion criteria
- endpoints

by adapting the EMA ***Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*** for adults **according to the results of the systematic review of paediatric AB CTs on efficacy**



Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review

Laura Folgori, Julia Bielicki, Beatriz Ruiz, Mark A Turner, John S Bradley, Daniel K Benjamin Jr, Theoklis E Zaoutis, Irja Lutsar, Carlo Giaquinto, Paolo Rossi, Mike Sharland

Lancet Infect Dis 2016; 16: e178–89

INCLUSION/EXCLUSION CRITERIA and ENDPOINTS for INFECTIOUS CIS in PAEDIATRIC AB CTs

cUTI (including pyelonephritis, renal abscess, catheter-related UTI, bacteraemia from urinary tract without specification)		
Inclusion criteria	**Exclusion criteria**	**Endpoints**
<u>Infant and children ≤ 2 years:</u> - Abnormal urinary dipstick test (leucocyte esterase >1+, or nitrite positive) **OR** - urinalysis (pyuria with at least 10 WBC per high power field in centrifuged urine, and bacteriuria with any bacteria per high power field on an unstained specimen of urinary sediment) **AND** at least two of the following clinical or biological signs: (1) fever with rectal or oral temperature of ≥38°C (2) general, non-specific signs such as irritability, vomiting, diarrhoea, or feeding problems in infants (3) CRP > 1.5 mg/dl OR procalcitonin > 2 ng/ml **AND** - positive urine culture with no more than two species of microorganisms: ▪ spontaneously voided urine with ≥ 10^5 microorganisms per ml of urine **OR** ▪ suprapubic aspirate/urinary catheter with ≥ 10^4 microorganisms per ml of urine **OR** - positive blood culture **AND** no other recognized cause **<u>Children >2 years:</u>** ….	- Chronic/underlying conditions (e.g. impaired renal function) - Urinary tract abnormalities - Recurrent UTIs: at least 3 episodes in 6 months or 4 episodes in 12 months - Allergy to study drugs - Recent infection/AB course in the last 7 days - Renal or hepatic failure	**Treatment failure:** - Persistence of bacterial growth in the follow-up urine culture (EOT and TOC visits) - Recurrence of clinical symptoms, such as fever, and flank pain during the treatment course - Development of complications/sequelae: renal scarring (defined as cortical defect or heterogeneous parenchymal uptake, with or without renal shape modification) documented at the 6-month DMSA scintigraphy - Serious Adverse Events (SAEs) **Timing for evaluation:** - End of Treatment (EOT) - Test of Cure (TOC) 7-10 days after the EOT - Follow up DMSA after 6 months

Example of criteria & endpoints for cUTI

PK STUDIES of a NEW AB for the PAEDIATRIC POPULATION

- **When to conduct PK:**

- in children where there is a **clear clinical unmet need** (unless known or suspected toxicity issues)

- if there is an **urgent unmet medical need in paediatrics**, studies should **start earlier** (e.g. after phase I and limited data in adults. Usually when data on safety and efficacy in phase 2 studies in adults are available)

- **When to partially extrapolate PK:**

- **extrapolation** of **dosing** and **PK accepted in rare circumstances** (new combinations when PK data already available for single components)

  - PK studies will be very limited: i.e. one population and then extrapolation to others

- classical PK studies no need to performed for **non-absorbable or topical AB**

- in **adolescents** or whether the **data from children and adults can be bridged**

ICH E11(R1) guideline on clinical investigation of 4 medicinal products in the pediatric population. EMA/CHMP 2016
Guideline on the role of PK in the development of medicinal products in the paediatric population. EMA 2004

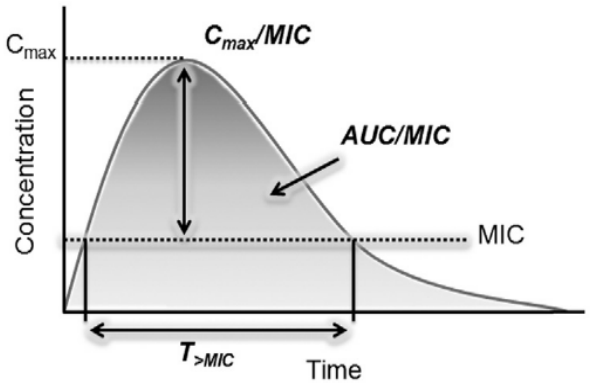
- **Populations to cover and age groups:**
  a. 12-18 years
  b. 2-11 years (could be divided into 2-5 years and 6-11 years)
  c. PMA >44 weeks to 2 years
  d. PMA <44 weeks (important to include VLBW and ELBW)

*Can be **studied in parallel** for agents from the **same class** with **similar PK** to agents with **existing data** in all age groups*

⇨ studies from **2-18 years** could be **conducted in parallel** if **allometric size scaling**

⇨ modelling a **starting dose for those <2 yr need to be defined**

- **Study design:**
  - **Sample size** should be justified **according to expected variability in PK** using **adult** and or **PBPK extrapolation**
    a. **7-9 evaluable patients per age cohort** is usually the **minimum requirement**
    b. **50 time-points at differents times** are needed in sparse sampling studies
  - **Food effect**, drug-drug interactions (*only in neonates*) and **palatability**



- **Data analysis:**
  - **Population PK models** should be developed first **from adult data to support extrapolation**, and then **updated to cover all studied paediatric age groups**
  - **Probability of target attainment** (**PTA**) should be **simulated for all age groups**
  - **Immaturity of organ system** should not prevent the conduct of PK studies and maturation should be **studied as a covariate**

KEY COMPONENTS of SAFETY in PAEDIATRIC AB CTs

- The concept of **extrapolation for safety** has been proposed recently to **minimise unnecessary studies in children** and to **maximise** the amount of **information extracted from adults**
- **Safety** information **from the source population** may be used to **predict events in the target population** if mode of **action of the drug and appropriate dose can be extrapolated**
- Considering the **different stages of growth and maturation among different ages**, the collection of safety data to identify **unexpected** (**age-specific**) **adverse events** (AEs) may be **required in the target population**

To **build the evidence to support extrapolation**, and considering the challenges of conducting large-scale RCTs in children, a **systematic review** and **meta-analysis** of **"safety"** AND **"antibiotics"** in **children** was conducted

WIDER AIM:

To determine the **extent to which safety data on ABs for children** can be actually **extrapolated from adults**

SPECIFIC OBJECTIVES:

- To evaluate if the **overall quality of safety studies** conducted **in children** allows to **gather a sufficiently robust evidence**
- To determine if **age-specific AEs** could be **identified per different AB classes**

Reflection paper on extrapolation of efficacy and safety in paediatric medicine development. EMA 2016

- 62 RCTs for a total of **15,716 patients** were **included in the quantitative analysis**
- **AEs** in paediatric AB CTs **class-specific** and **broadly predictable** compared to adults
- **No children-specific** or **unexpected toxicity** have been pointed out
- Rate of **specific AEs generally low** – Median **SAEs 0.3%**
- **Not possible to stratify safety data by different paediatric age groups**

Drug class	N patients	Overall AEs	Discontinuation due to AEs	Nephro-toxicity	Oto-toxicity	Gastro intestinal	Systemic**	Neurological	Respiratory	Dermatologic	Muscolo-skeletal	Infusional	Lab tot	Overall specific AEs
Penicillins	3,019	12.8 (9.4 – 29.7)	1.1 (0 – 2.7)	0.6*	nr	4.2 (2.3 – 8.3)	0 (0 – 0.8)	0 (0 – 0)	nr	0.7 (0 – 5.3)	nr	0 (0 – 0)	17.7*	9.1 (3.1 – 29.7)
Aminoglycosides	1,308	3.3 (1.1 – 15.8)	0*	1.8 (1.1 – 20)	1 (0 – 1.1)	nr	nr	0 (0 – 0)	nr	nr	nr	nr	nr	2.3 (0.6 – 15.8)
Cephalosporins	2,462	16.5 (4.5 – 42.1)	0.3 (0 – 3)	nr	nr	12.1 (3.6 – 20.5)	0 (0 - 0)	0 (0 – 0)	0 (0 - 0)	0 (0 – 4.2)	nr	nr	0 (0 – 5.2)	14.8 (4.5 – 42.1)
Macrolides	2,931	21.8 (7.7 – 35.9)	0 (0 – 3.3)	nr	nr	8.6 (3.4 – 23.3)	0 (0 – 0)	nr	0 (0 – 0)	0 (0 – 2.2)	nr	nr	9.8*	18.8 (6 – 31.6)
Penicillins+BLI	2,566	46.3 (32.7 – 67.8)	1 (0 – 2.8)	nr	nr	33.9 (23.4 – 43)	0 (0 – 2.3)	nr	0 (0 – 0.3)	7.2 (3.4 – 12.9)	0 (0 – 0)	nr	0 (0 – 0)	43.0 (19.6 – 63.0)
Fluoroquinolones	1,920	35.7 (24.2 – 66.7)	0.8 (0 – 2.2)	nr	nr	17.1 (2.4 – 23.7)	1.1 (0 – 7.5)	nr	0 (0 – 11.4)	0 (0 – 6.25)	3.1 (1.2 – 3.2)	nr	12.5 (3.3 – 19.9)	31.2 (23.4 – 61.1)
Carbapenems	385	32.7*	1.9*	nr	nr	5.8*	nr	nr	nr	nr	nr	10.5*	9.6*	25.9*
Linezolid	683	60.7 (44.5 – 70.4)	2 (0.9 – 7)	nr	nr	9.8 (7.6 – 12.6)	0.5 (0 – 1.3)	0 (0 – 0)	0 (0 – 2.3)	1.3 (0 – 1.4)	nr	0 (0 – 0)	45.6 (5.7 – 52.6)	58.2 (43.7 – 64.3)
Glycopeptides	265	75.4 (37.5 – 90.9)	4.3 (1.7 – 5.7)	8.4*	nr	9.3 (0 – 12.5)	18.6 (5.3 – 27.5)	nr	nr	6.4 (5.3 – 9.1)	nr	nr	41.0 (15.8 – 72.0)	75.4 (27.6 – 87.9)
Sulfonamides + trimethoprim	152	4.6*	2.6*	nr	nr	2.6*	1.3*	nr	nr	0.7*	nr	nr	nr	4.6*
Amphenicols	25	4*	0*	nr	nr	4*	nr	nr	nr	nr	nr	nr	nr	4*
Total	**15,716**	**22.5 (7.7 – 44.6)**	**0.9 (0 – 3)**	**1.8 (0.8 – 15.8)**	**1 (0.2 – 1.1)**	**7.7 (0 – 20.5)**	**0 (0 – 0.5)**	**0 (0 – 0)**	**0 (0 – 0)**	**0 (0 – 4.0)**	**0 (0 – 0)**	**0 (0 – 0)**	**6.8 (0.4 – 21.0)**	**19.2 (4.6 – 42.6)**

Data are expressed as median proportion and IQR range. *Expressed as mean because reported in < 3 studies; **including fever, anaphylaxis and Red Man Syndrome; nr: not reported.

1. **Extrapolation** of safety data **from adults** **feasible for some AB classes** but specific **age-groups data still necessary**
2. **Low quality** and **high heterogeneity** (*study design, population, data reporting*) **reduce the strength of conclusions**

STANDARDISING SAMPLE SIZES for REGULATORY PAEDIATRIC AB CTs

- Sample size for **single-arm interventional paediatric AB CTs** having **safety** as a **primary endpoint**, according to the **rates of AEs per single drug class**
- To ensure **sufficient children receive a new antibiotic** to enable :
  - *A high probability of determining that the overall AE/SAE rate is estimated reasonably precisely*
  - *A reasonable probability of observing an adverse event which occurs in 1/20 children*

Drug class	Overall percentage experiencing AEs*	Sample size to provide >0.95 probability that final 95% CI around estimated AE rate is no more than 10% above this	Upper 97.5% confidence limit around an observation of 0/N	Sample size to provide >0.95 probability that final 95% CI around estimated AE rate is no more than 15% above this	Upper 97.5% confidence limit around an observation of 0/N
Penicillins	13	172	2.1%	83	4.3%
Aminoglycosides	3	79	4.6%	49	7.3%
Cephalosporins	16	190	1.9%	93	3.9%
Macrolides	22	229	1.6%	108	3.4%
Penicillins+BLI	46	283	1.3%	128	2.8%
Fluoroquinolones	36	277	1.3%	125	2.9%
Carbapenems	33	270	1.4%	125	2.9%
Linezolid	61	258	1.4%	110	3.3%
Glycopeptides	75	185	2.0%	74	4.9%
Sulfonamides + trimethoprim	5	102	3.6%	57	6.3%
Amphenicols	4	91	4.0%	53	6.7%

Flahault A et al. J Clin Epidemiol 2005

CONCLUSION

- The WG has **highlighted** a number of **specific areas** where there is **potential for harmonisation** in the **design** and **conduct** of paediatric AB CTs
- **Standardisation of key inclusion/exclusion criteria** for specific CIS would allow **improved comparison between studies** using **meta-analytical approaches**
- An improved used of **bridging of safety** could allow potentially more **simplified design** of CTs, **improving** their **conduct** and **efficiency**
- **Summary document** based on the **available evidence** and **expert opinion** of the **key components of CT design for paediatric AB studies**
- **Not a regulatory guideline** but the aim is that **it will align with the Paediatric Addendum**
- **First draft** of the summary document **currently in circulation between WG members**

QUESTIONS ??

EnprEMA
European network of paediatric research at the European Medicines Agency

St George's University of London

THANKS FOR YOUR ATTENTION

PIDRG
Paediatric Infectious Diseases Research Group