STUDYING NEONATES

WORKSHOP ON DEVELOPMENT OF ANTIBACTERIAL PRODUCTS FOR PAEDIATRIC PATIENTS

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Matthew G. Johnson, MD
Clinical Director, Infectious Diseases

Bio Biotechnology Innovation Organization

ebe european biopharmaceutical enterprises

This is a joint industry presentation on behalf of the trade associations shown

efpia European Federation of Pharmaceutical Industries and Associations

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Agenda

- Introduction
  - Definitions
  - Scope of paediatric trials

- Challenges encountered in lifecycle of paediatric programs
  1. Regulatory agency concurrence regarding design and conduct of neonatal studies
  2. Inclusiveness of neonatal indications
  3. Definition of neonatal disease states
  4. Enrollment pattern of youngest cohort(s)
  5. Adaptability of study conduct to accommodate neonates

- Key considerations

Introduction

- Definition of neonate
  - Birth to <28 days
  - Includes term and preterm (<37 weeks gestational age) infants

- Clinical research in the neonatal population has been historically neglected due to multiple ethical, logistical, and technical issues

- Recent regulatory legislation has provided impetus for studies in the paediatric population through combination of requirements and incentives
  - Must include all paediatric age groups, including neonates, in development plans

Recent, Ongoing, and Planned Paediatric Trials at MSD

Infectious Diseases

COMPOUND	PEDIATRIC TRIALS
Antibacterial	
Ceftolozane/tazobactam (ZERBAXA)	SD PK/safety, cUTI/cIAI safety/efficacy, MD PK/safety in HABP/VABP
Daptomycin (CUBICIN)	Japan cSSTI and bacteremia, acute osteomyelitis
Imipenem/relebactam	SD PK/safety, cUTI/cIAI/HABP/VABP safety/efficacy, neonatal late-onset sepsis
Tedizolid phosphate (SIVEXTRO)	ABSSSI safety/efficacy, adolescent safety/efficacy, SD PK/safety, neonatal late-onset sepsis
C. Difficile	
Bezlotuxumab (ZINPLAVA)	PK/safety/efficacy
Fidaxomicin (DIFICID)	PK/safety
Antifungal	
Caspofungin (CANCIDAS)	neonatal invasive candidiasis
Posaconazole (NOXAFIL)	PK/safety
CMV	
Letermovir (PREVYMIS)	safety/efficacy

ABSSSI=acute bacterial skin and skin structure infection; cIAI=complicated intra-abdominal infection; cSSTI=complicate skin and skin structure infection; cUTI=complicated urinary tract infection, HABP=hospital-associated bacterial pneumonia; MD=multiple dose; PK=pharmacokinetic; SD=single dose; VABP=ventilator-associated bacterial pneumonia

1. Regulatory Agency Concurrence Regarding Design and Conduct of Neonatal Studies

- Agency requests to Sponsors regarding neonatal studies are not always aligned
  - Need to conduct or not, number of neonates required, indication to be studied, comparative vs. non-comparative study

➢ Bezlotoxumab
  - EMA required separate clinical study on neonates with *C. difficile* infection which was not required by US FDA
    - Unclear significance of *C. difficile* in neonates due to high rates of asymptomatic colonization, which also is challenge to study recurrence rates of *C. difficile* infection

- Challenge to harmonize paediatric programs when different key requirements specified from the beginning

2. Inclusiveness of Neonatal Indications

- Studies in specific indications (i.e., late-onset sepsis) are often requested, despite scientific concerns that can lead to feasibility challenges

➢ Imipenem/relebactam and tedizolid
  – PDCO required PK/safety study specifically in neonates and young infants with late-onset sepsis, despite other planned PK/safety studies in neonates and young infants
    - Lack of alignment with clinical practice and epidemiology, as standard of care in neonates with suspected sepsis is empiric meningitis treatment
      – Imipenem not recommended for paediatric patients at risk of seizures
      – No data with tedizolid to support treatment of central nervous system infections

- Consider broader indications such as suspected or proven bacterial infection in lieu of or in addition to late-onset sepsis

3. Definition of Neonatal Disease States

- Certain disease states have particular criteria, defined by regulatory agencies, that are not applicable to the neonatal population
  - Also distinct subgroups unique to neonates (e.g., gestational age, birth weight, etc.)

➢ Ceftolozane/tazobactam
  - Phase 2 cIAI study includes FDA guidance regarding definition of cIAI – "…extend beyond the local viscera…" – however this criteria does not always apply to necrotizing enterocolitis
    - Necrotizing enterocolitis is one of most common causes of cIAI in neonates

- Consider looser inclusion criteria, with possible "presumed status" for some conditions, due to variable disease presentation in neonates

4. Enrollment Pattern of Youngest Cohort(s)

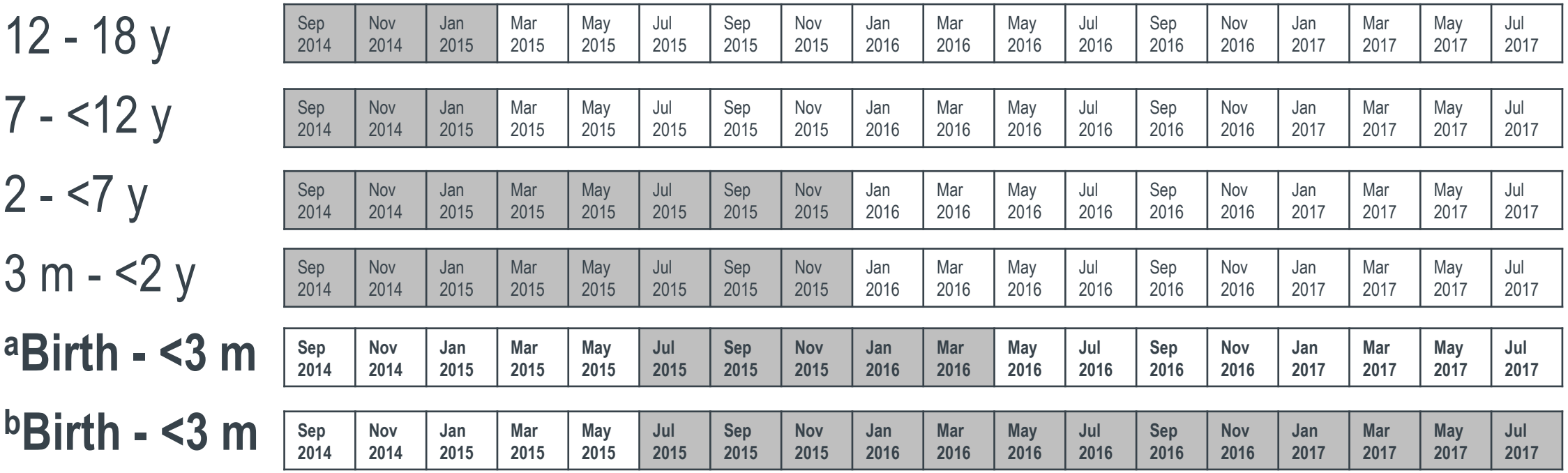
- Step-wise enrollment (i.e., older children first, then younger children) often implemented due to uncertainty with dose selection and potential safety concerns in youngest cohort(s)
  - Subsequently leads to delayed enrollment of the youngest and most challenging cohorts

➢ Ceftolozane/tazobactam
  - Phase 1 PK/safety study enrolled 3 month to <18 year cohorts prior to opening birth to <3 month cohorts
    - Longer time for study completion

- Consider thoughtful approach to staged enrollment, particularly for compounds from antibacterial classes with well defined safety record and robust PK modeling (i.e., β-lactams)

4. Enrollment Pattern of Youngest Cohort(s)

Pediatric PK/safety trial of ceftolozane/tazobactam with staged enrollment



[a] >32 w gestation

[b] ≤32 w gestation

- Long tail at end of the study may have been mitigated if enrollment of youngest cohorts began in parallel with other age groups

5. Adaptability of Study Conduct to Accommodate Neonates

- Many challenges hinder enrollment of neonates and threaten the quality of data

➢ Ceftolozane/tazobactam
  – Multiple steps taken in Phase 1 PK/safety trial to enable enrollment of neonatal cohort
    - Many protocol amendments required (i.e., revision of creatinine clearance threshold, removal of height/weight criteria)
    - Miniscule infusion volumes (i.e., 1.3 mL infusion for 1.1 kg neonate) predisposed to problems with drug administration
    - PK samples challenging to obtain – allowed flexibility in blood collection (i.e. heel/finger sticks)
    - New sites with more active NICUs and neonatal PK research experience added

- Neonatal data is a unique commodity, and every effort must be made to safely capture it

Additional Practical Challenges

The 3 Ss

Subject	• Fragile patient population	• Difficult consent process
	• Emotional family circumstances	• Too many blood draws
Site	• Long start-up times	• No weekend or after-hours coverage
	• Competing studies	• High pre-screen and screen failure rates
Study	• Rejected or limited by local regulatory authorities and/or ethics committees/IRBs	
	• Disagreements with comparator due to wide variety of standard of care in different regions	
	• Long lag time between authoring of PIP/PSP and enrollment of first patient	

Studying Neonates
Key considerations

- Regulatory agency alignment is important regarding neonatal studies
- Feasibility of neonatal studies must be emphasized
- Unique inclusion criteria often apply to neonates
- Enrollment pattern of youngest cohort(s) has significant influence on timeliness of study completion
- Flexibility in study conduct is essential for neonatal research

THANK YOU