Pediatric Master Protocols

Overall Assessment and Pathway Forward

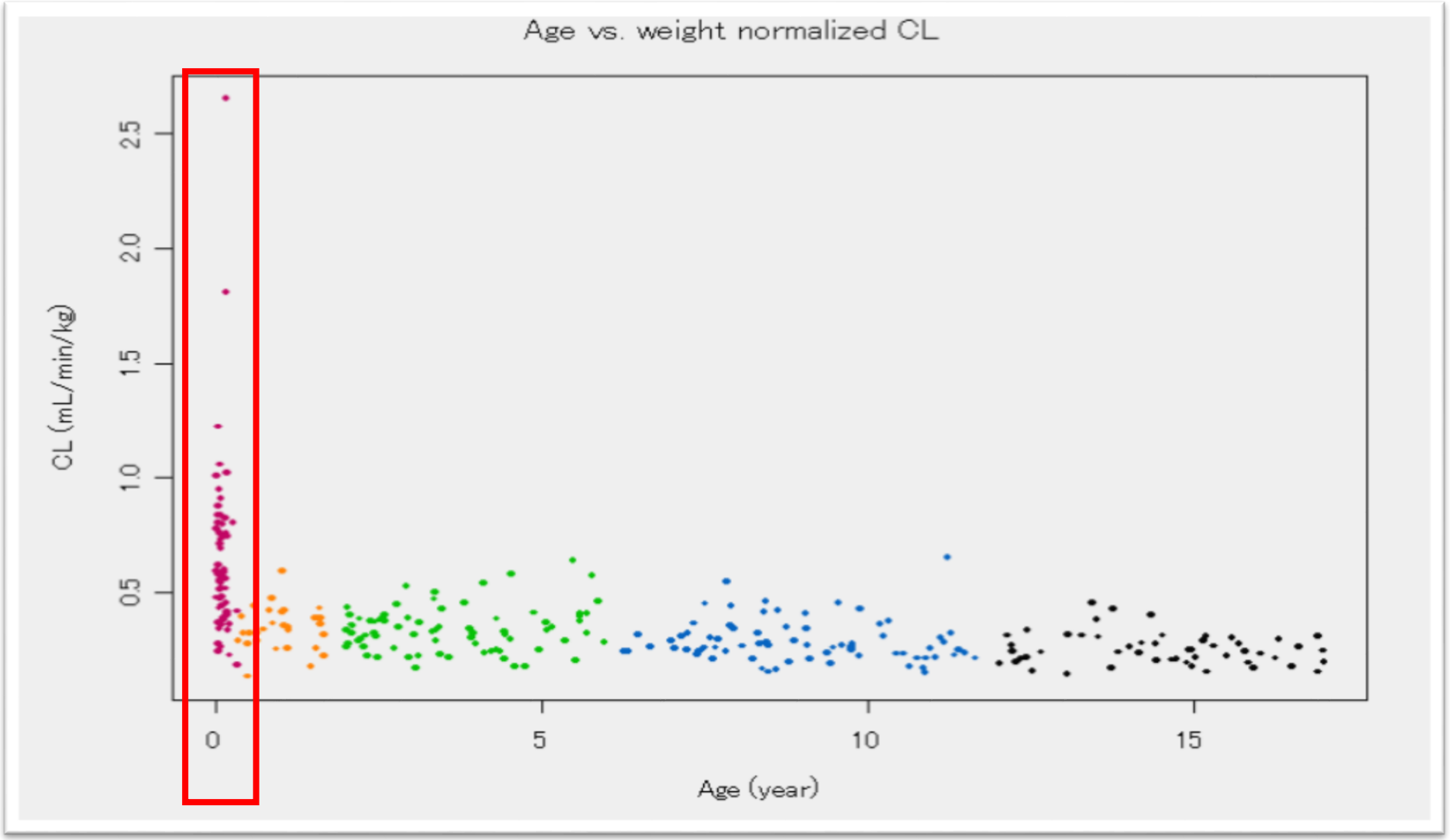
Friday, September 23, 2016

Mycamine®(micafungin sodium)

- Member of the echinocandin class of antifungals

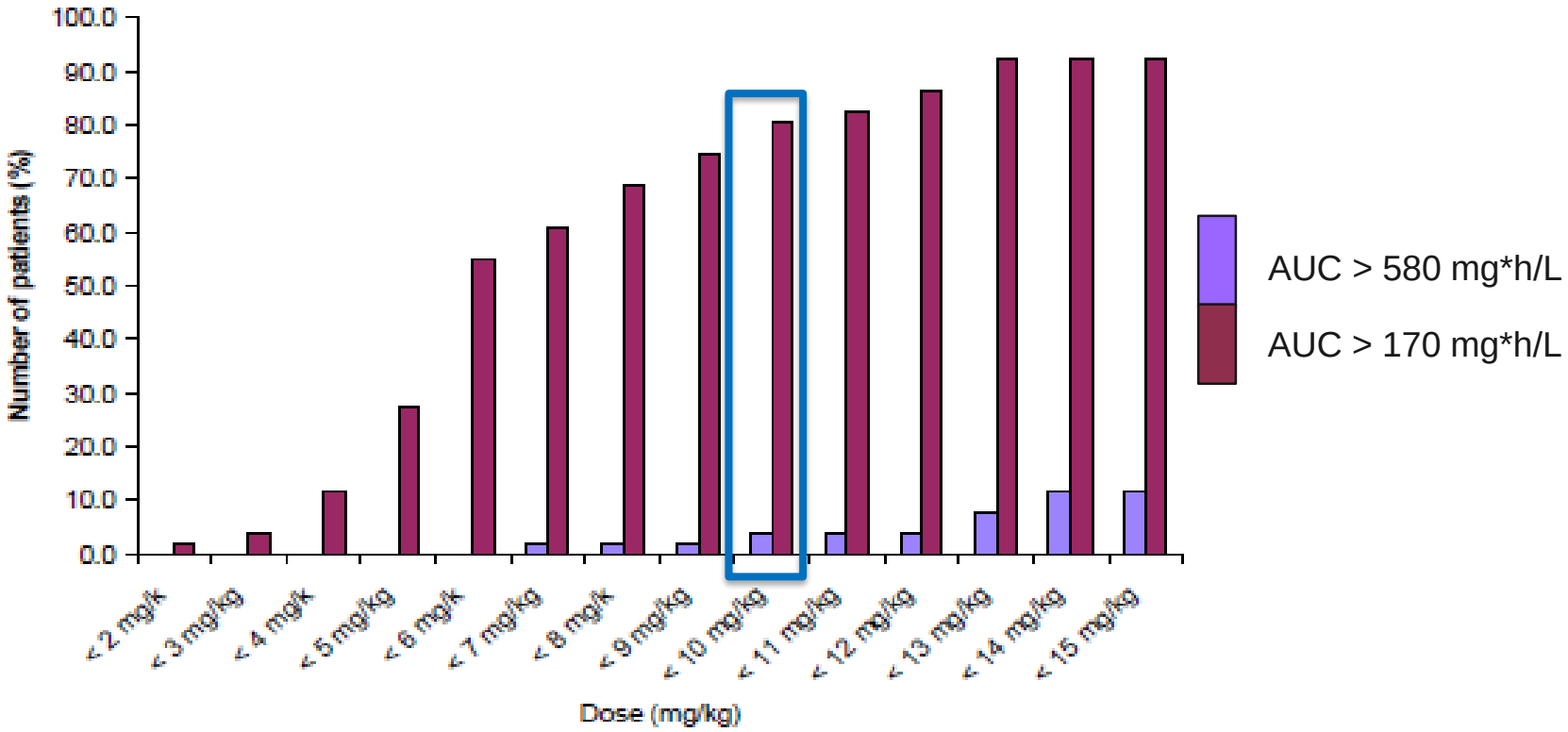
- Approved in the U.S. for adults and pediatric patients > 4 months of age for:
  - Treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis, and abscesses;
  - Treatment of esophageal candidiasis;
  - Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplant

Mycamine: Increased Weight-normalized Clearance in Infants < 4 Months of Age



Benjamin Clin Pharmacol Ther, 2010;87(1):93-9; Hope AAC, 2007

Population PK Bridging Study Demonstrates Dose of 10 mg/kg is Most Appropriate



- Monte Carlo simulations demonstrated that a Mycamine dose of 10 mg/kg achieves the target exposure in >85% of the population with <10% of the population at risk of reaching the range where non-clinical toxicities were seen, notably liver enzyme changes

Further Investigation in Young Infants May Be Necessary

- Unique drug disposition compared to older children and adults
- Prominent CNS disease in this population
  - CNS involvement requires higher target exposures for treatment
- There was limited safety and efficacy of this dose and exposure

Phase 3 Study Overview

Phase 3, randomized (2:1), multi-center, double-blind, non-inferiority study comparing micafungin to conventional amphotericin B

Primary Endpoint: Fungal free survival - 1 week following the last dose of study drug

Population: 225 infants, 2-120 days of life with culture proven candidiasis

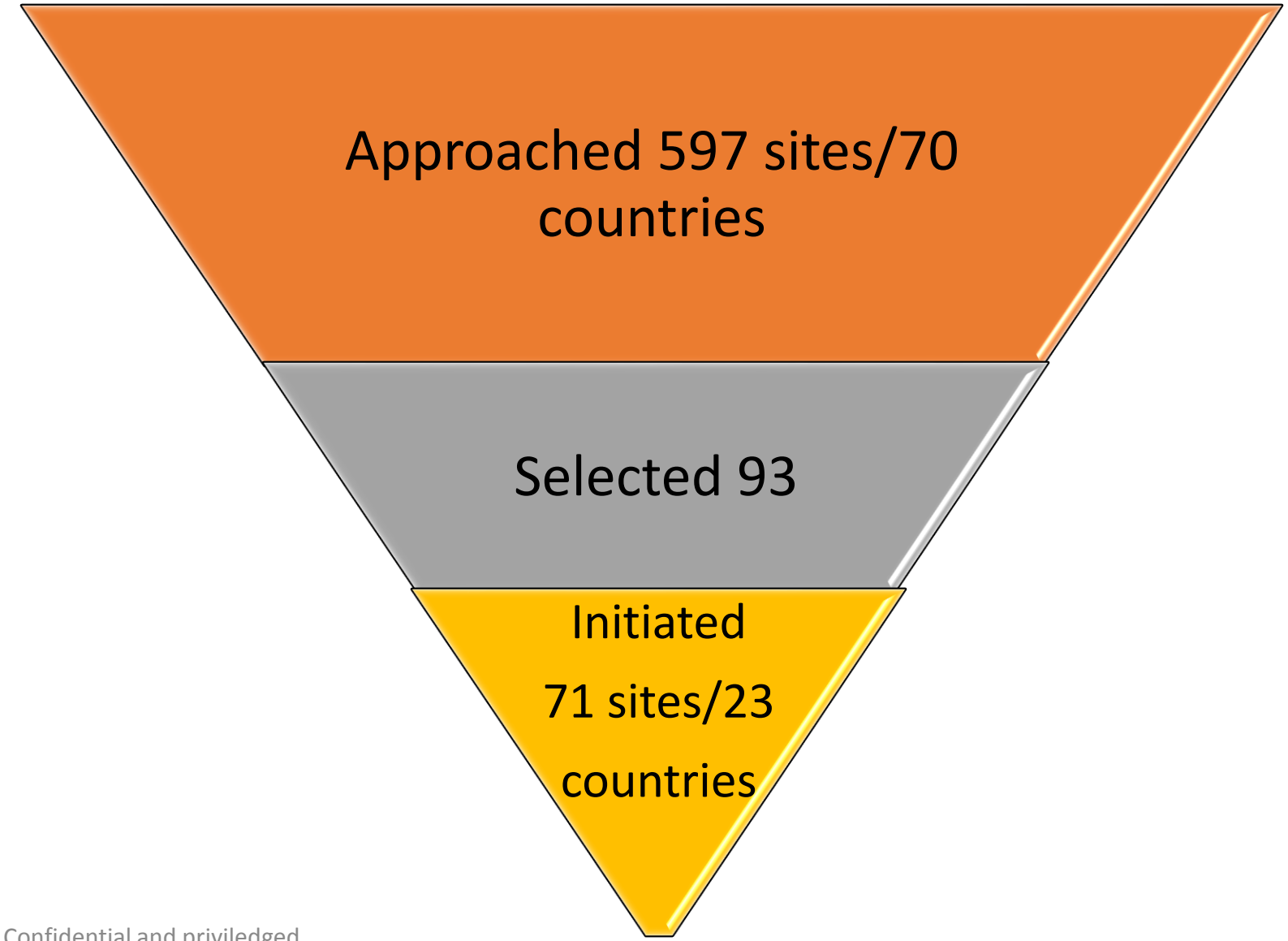
Randomization stratification: gestational age and region

Study Conduct: Getting Started

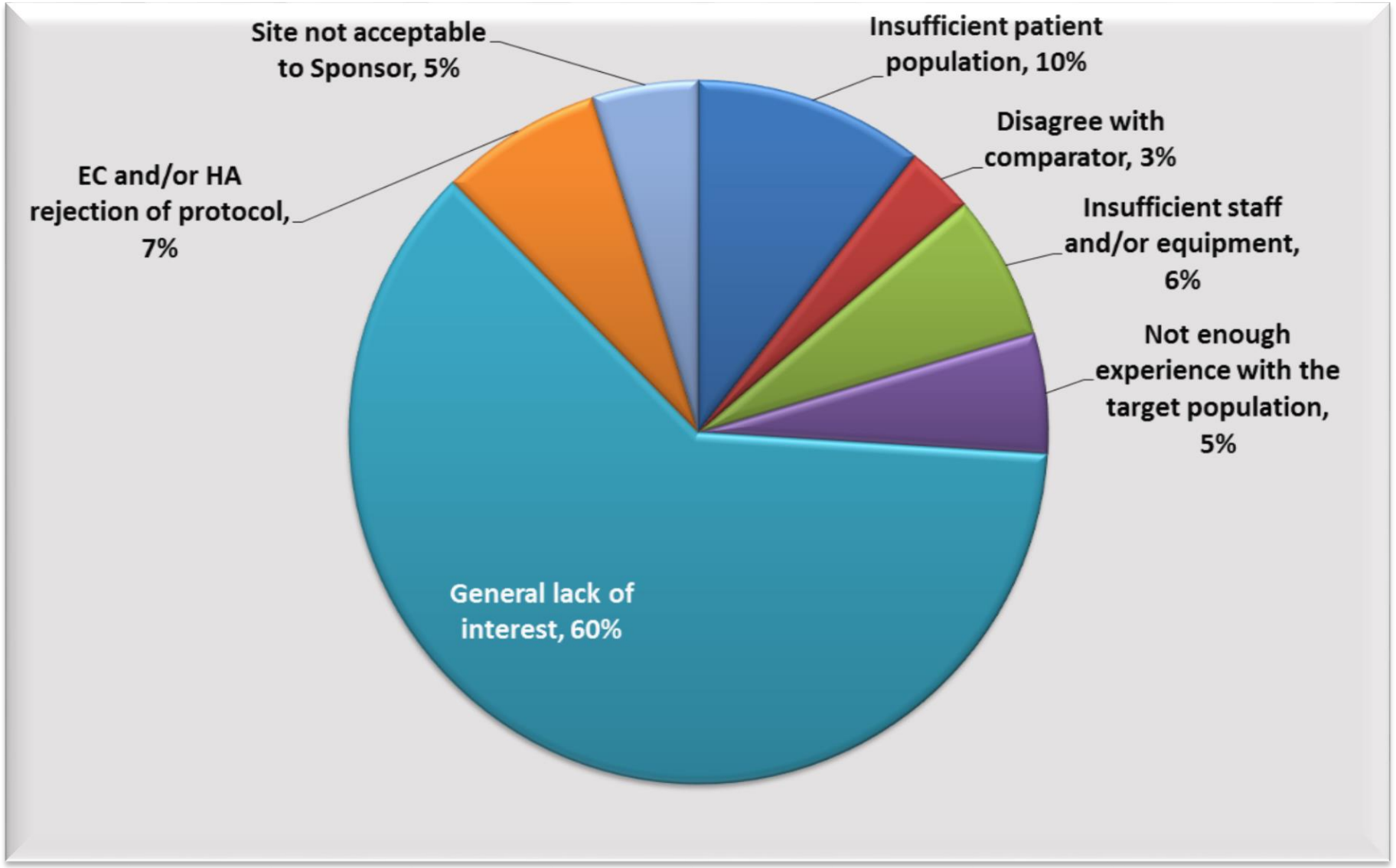
- Contacted pediatric clinical trial networks globally experienced with disease state, including:
  - Pediatric Trials Network, Pediatric Fungal Network, Pediatrix, Children's Research Network (UK), International Conference of Clinical Neonatology (ICCN), Treat Infections in Neonates (TINN) (EU)

- Established a Scientific Committee to advise on study
  - Daniel Benjamin, MD, PhD (Protocol Chair); Duke, North Carolina, USA
  - William Hope, MD; University of Liverpool Liverpool, UK
  - P. Brian Smith, MD; Duke, Durham, North Carolina, USA
  - David Kaufman, MD; University of Virginia Charlottesville, Virginia, USA
  - Thomas J. Walsh, MD; Weill Cornell Medical Center New York, New York, USA
  - Antonio Arrieta, MD; Children's Hospital of Orange County, Orange, California, USA

Site Selection Challenges

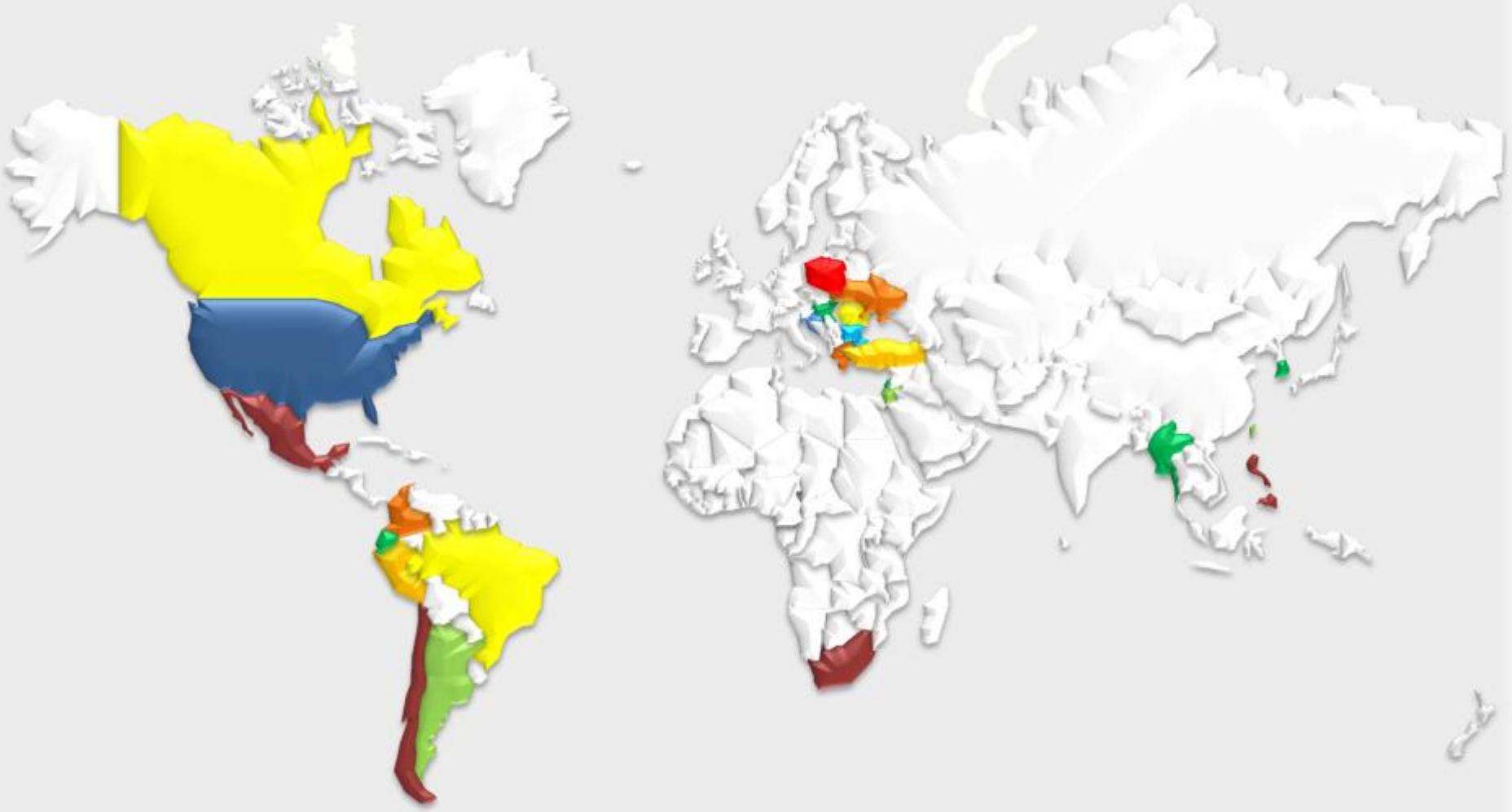


Reasons for Not Participating

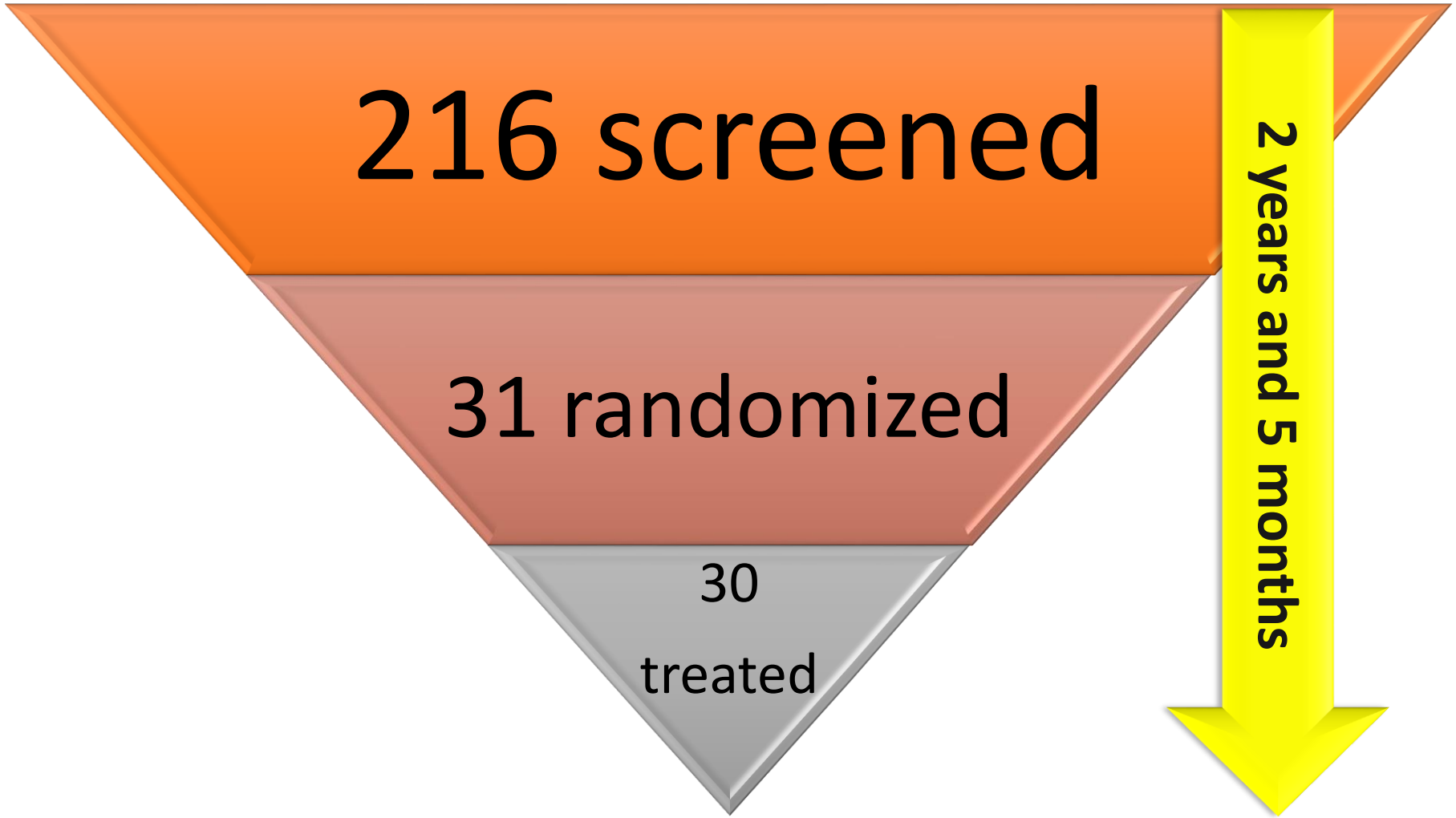


Global Study

71 sites participating from 23 countries



Enrollment Challenges



Pharmacokinetic Sampling

- Plasma PK
  - 17 participants (57%)
- CSF PK
  - 2 participants (7%)

Pediatric Trials Network Time to Site Activation

Average – 10 months

Site	Time From Selection to Activation (months)	Status
1	17	Selected
2	16	Selected
3	13	Active
4	13	Active
5	13	Selected
6	13	Selected
7	12	Selected
8	11	Active
9	10	Active
10	10	Active
11	8	Active
12	8	Active
13	7	Active
14	7	Active
15	6	Active
16	5	Active
17	5	Active
18	4	Active
19	4	Active

Add-on PK Therapy Studies - Infants

Drug	N	Citation
Micafungin	12	PIDJ 2009
Micafungin	12	CPT 2010
Fluconazole loading dose	13	PIDJ 2011
Fluconazole ECMO	20	PIDJ 2012
Daptomycin	20	PIDJ 2012
Meropenem	200	PIDJ 2013
Acyclovir	32	PIDJ 2014
Metronidazole	24	AAC 2012
Anidulafungin	15	CPT 2011
Cefazolin	10	pending
Piperacillin-tazobactam	32	AAC 2014

Hurdles - Pediatric Trials

- No “healthy children volunteer”
- Low rates of parental informed consent
- Limited blood volume
- Lack of clinical pharmacology expertise
- Timing of consent
- Contamination
- Sick population – increases variability
- Variability in site enrollment
- Clinician concerns/beliefs about therapies and trials
- Variability in site outcomes
- Competing research priorities
- Contracting
- IRBs
- Study documents - CRF, protocol, MOP, SAP, ICF
- Data management
- Site training
- Cost
- Limited number of patients with the disease

Efficiencies in master protocols

Conclusions

- It’s doable
- Pediatrics is perfect location
- NICHD’s Pediatric Trials Network has done this
- Industry should do it for PREA and exclusivity
- EMA/FDA should deleverage risk by putting some thoughts in writing when they provide comments to PIP or WR