PRECURSORS TO PEDIATRIC MASTER PROTOCOLS: PROOF OF CONCEPT

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A project of the Best Pharmaceuticals for Children Act

Disclosures

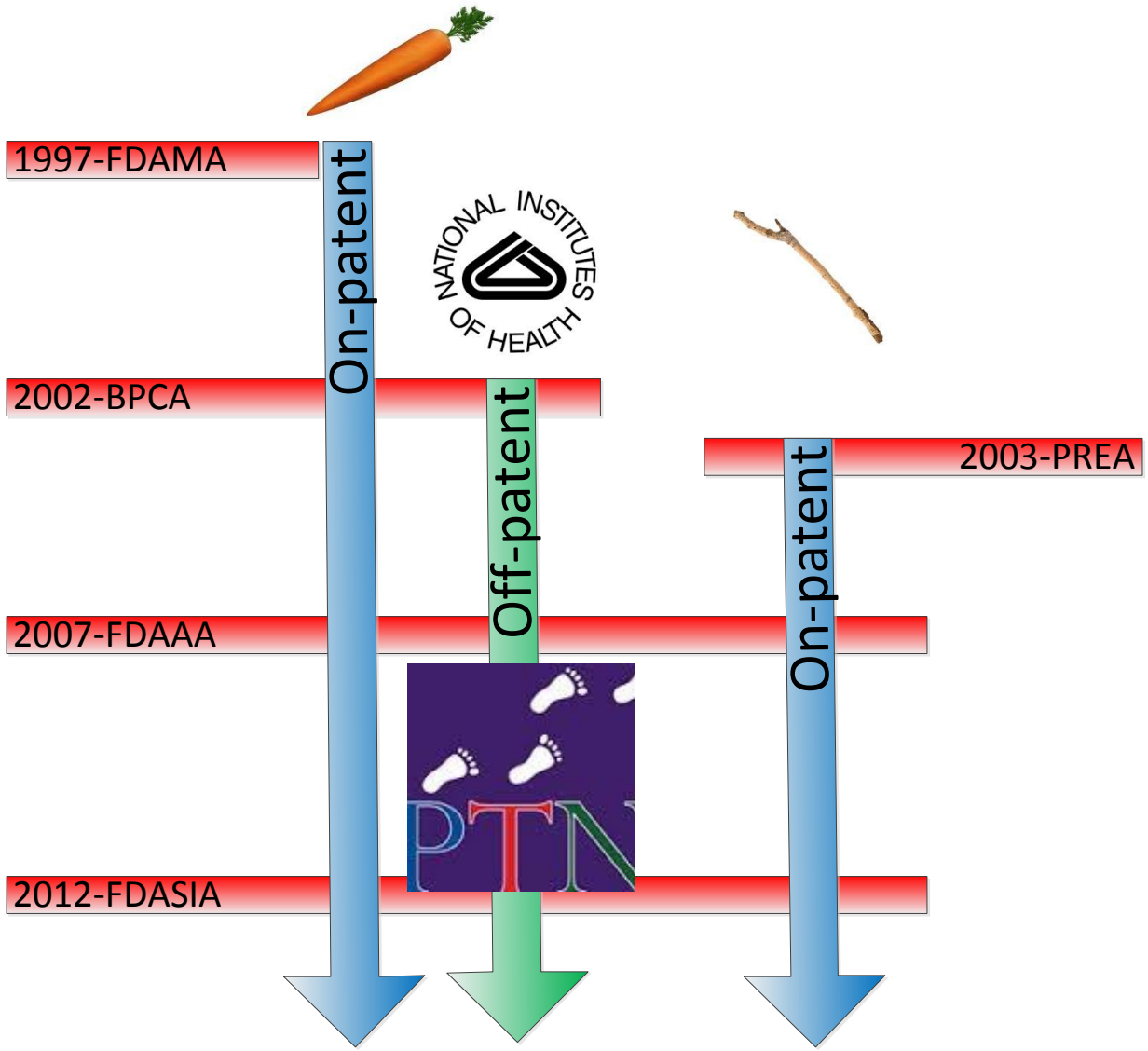
- None

What is the Pediatric Trials Network?

“Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health.”

- Sponsored by NIH - $95,000,000
- Study age-appropriate drug dosing, efficacy, safety, and device validation
- Success - improve dosing, safety information, labeling, and ultimately child health
- PI – Danny Benjamin, MD PhD MPH – Duke Clinical Research Institute (DCRI)

Pediatric Trials Network (PTN)



How PTN works

1. NIH develops a priority list of off-patent therapeutics
   - http://bpca.nichd.nih.gov/prioritization/status/documents/priority_list_10-26-2012.pdf
2. Investigators submit study concept sheet to PTN
3. PTN Administrative Core reviews science and feasibility
4. If approved, PTN forms protocol development team
   - protocol chair, thought leaders, pharmacologists, operations experts
5. NIH provides small amount of funding for protocol development
6. PTN sends protocol and budget to NIH
7. PTN selects sites from rapid start network based on site study interest & availability, previous history of enrollment
8. PTN executes trial

Innovative study protocols key to network success

Pediatric Trials Network – Progress Since 2010

Contract Scope of Work

- Projects
  - 16 clinical trials
  - Phase I-II studies
- Enrollment
  - ~100 children enrolled per project
  - 1600 total enrolled
- Therapeutic areas
  - Primary contract included hypertension; but had flexibility with respect to number and type of areas
- Flexibility with respect to data submitted to FDA but reasonable goal of ~4 product submissions (by 2015)

Accomplished

- Projects
  - 30 total projects; 18 clinical trials
  - 74 molecules studied
  - Phase I-IV studies
- Enrollment
  - Over 100 sites enrolling
  - > 5000 children enrolled
- Across therapeutic areas
  - Hypertension, Neonatology, ID, Obesity, Neurology, Psychiatry, Critical Care, GI, Pulmonary, Hematology, Oncology
- Data for 15 products submitted to FDA and >25 products with planned submission by 2017

Overview

Single Drug Studies

Meropenem
Metronidazole

Master Protocol Precursors

Staph Trio
SCAMP
LAPS

Master Protocols

POPS
Anesthetics and Analgesics

Meropenem

- Legacy trial conducted prior to PTN
- Single drug PK & safety in neonates with complicated intraabdominal infection
- 200 subjects at 25 sites
- Status: meropenem label changed by FDA based on study findings
- Enhanced operational efficiency in PTN following meropenem trial:

Legacy Trials: example Meropenem	PTN Trials: example Metronidazole
RFP release to signature 24 months	RFP release to signature 6 months
IND 31 months	IND 7 months
First patient 34 months	First patient 9 months
Last patient 48 months	Last patient 18 months
Clinical Study Report 60 months from RFP release	Clinical study report 21 months

Smith PB Pediatr Infect Dis J. 2011; Cohen-Wolkowiez M Clin Infect Dis. 2012

Staph Trio Design

- Multidrug protocol of 3 anti-staphylococcal agents: clindamycin, rifampin, and ticarcillin-clavulante
- Multicenter (N=10), open-label, multiple-dose PK study
- Participants: 16-32 infants for each drug
- Study Intervention: study drug over 2-4 days
- Duration of Participation:
  - 2-4 days of study drug
  - Up to 30 days of safety monitoring
- Outcomes: Pharmacokinetic and Safety

Staph Trio Results

- Rifampin: 27 subjects enrolled - CSR submitted to FDA for label change
- Clindamycin: 21 subjects enrolled – data analysis complete, final combined CSR pending completion of separate clindamycin safety study (SCAMP)
- Ticarcillin-calvulanate: 15 subjects enrolled - CSR in preparation

Gonzalez D. Antimicrob Agents Chemother. 2016

SCAMP Design

- Phase 2/3 – safety, prospective, open-label, randomized, multi-center
- 210 premature infants (≤33 weeks gestation at birth) randomized 1:1:1 to:
  - Group 1 (N=70): ampicillin, gentamicin, and metronidazole
  - Group 2 (N=70): ampicillin, gentamicin, and clindamycin
  - Group 3 (N=70): piperacillin-tazobactam and gentamicin
- 2 additional subgroups:
  - Group 4 (N=50): metronidazole in addition to the antibiotic regimens prescribed per SOC
  - Group 5: 24 infants (any gestational age) with suspected or confirmed infection for which the study drug may provide therapeutic benefit and CSF is to be collected per SOC
- Primary Endpoint: Safety of drug regimens used in infants with complicated intra-abdominal infections
- Secondary Endpoints: Efficacy, PK, biomarkers, CYP450 polymorphisms, CSF PK

SCAMP Results

- 46 sites
- 215 infants, enrollment ongoing:

Group1	Group 2	Group 3	Group 4	Group 5
53	44	59	49	20

- Eligible participants: 1.2 participants/site/month
- Enrollment: 0.2 participants/site/month = 17% of eligible participants

LAPS Design

- Two drug (aripiprazole, risperidone) standard of care, prospective, long-term safety
- 850 subjects, 60 sites, 3 year follow up
  - 350 aripiprazole
  - 350 risperidone
  - 100 sibling controls
- Primary endpoint: long term weight gain
- Secondary endpoints: elicited adverse events, benefits, pharmacokinetics in obese and 3-9 year old children

POPS Design

- Study type: Open-label, opportunistic, PK of understudied drugs in children given as part of standard of care
- >2000 children enrolled to date, ongoing
- Sites: Up to 40 (U.S./Singapore/Israel/U.K./Canada)
- Drugs of interest (DOI): 40 total to date
- Blood, urine, and CSF sampling
- Dried blood and plasma spots
- DNA samples (opt-in)
- Opportunistic and study/DOI specific sampling schemes (opt-in)

POPS Results (examples)

- Ampicillin
  - 142 plasma samples from 73 infants to develop a population PK model in infants ≤28 days
  - Model based simulations to optimize dosing regimen based on gestational & postnatal age
  - Retrospective safety review of electronic medical records and data collected in prior PPRU study
  - Status: combined PK & safety data submitted to FDA for labeling changes –on docket

- Methadone
  - 65 participants across 12 sites
  - Data combined with 26 participants enrolled in separate dedicated PK study of methadone
  - Status: combined CSR submitted to FDA
  - Request for additional information following FDA meeting resulting in additional retrospective efficacy and safety data collection for 65 POPS participants

Tremoulet A. et al, Antimicrob Agents Chemother. 2014

Future directions and challenges

- PTN demonstrated proof of concept for master protocols
  - Focused initially on antimicrobials but expanding to other therapeutic areas
  - Included historically difficult populations (e.g., premature neonates)
  - Combine data from multiple studies
  - Federal funding for off patent therapeutics

- Can this approach be applied in Industry
  - Competition
    - Pediatrics/Exclusivity
  - Solving regulatory hurdles
    - Meeting PREA requirements
    - Harmonizing with EMA