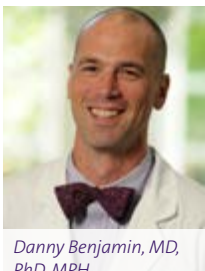




# Post

THE ANNUAL REVIEW

## A Message from the Lead Principal Investigator



Danny Benjamin, MD, PhD, MPH

In the last issue of the *PTN Post*, we noted that one of our studies resulted in a label change for the widely used drug, lisinopril. The change could affect hundreds of children who are prescribed lisinopril after kidney transplants each year. Label changes, like lisinopril, mark important milestones and underscore the continuing significance of the work we do. With that in mind, I'd like to review the progress we have made to date in other therapeutic areas as well.

Thanks to the hard work and dedication of PTN investigators and sites, the list of accomplishments is long. However, there is much more work to be done to determine the safest and most effective use of medications and devices in the pediatric population. This issue of the *PTN Post* celebrates the progress we've made and the work that lies ahead.

### As of September 15, 2016...

*The following Food and Drug Administration (FDA) labels have been updated under Best Pharmaceutical Children's Act (BPCA) programs:*

**Propylthiouracil** for hyperthyroidism: label changed for safety and dosing

**Pralidoxime** relabeled for use in organophosphate poisoning

**Sodium nitroprusside** for hypertension: label changed for efficacy, safety, and dosing

**Meropenem** for complicated abdominal infections: label changed for safety and dosing; efficacy extrapolated

**2D and 3D Mercy TAPE devices** to assess weight without electricity in children 2 months through 16 years of age

**Lisinopril** for hypertension: label changed for treatment of hypertension in pediatric renal transplant patients

**Lorazepam** for seizures: label changed for efficacy, safety, and dosing

*BPCA legacy (prior to PTN) and PTN-led studies submitted the following clinical study reports (CSRs) to the FDA*

### Final CSR Submitted

**Ampicillin** for treatment of complicated infections in pre-term neonates to determine safety and dosing (PTN)—this CSR is on the FDA docket for label change

**Clindamycin** for treatment of complicated infections

to determine PK and safety for obese children (PTN)—this CSR is on the FDA docket for label change

**Hydroxyurea** for treatment of sickle cell disease to determine PK and bioavailability of a liquid formulation (this is a PTN partnership submission with NHLBI)

**Fluconazole** for prevention of candidiasis in neonates and infants to determine efficacy, safety, and dosing, prevention of candida infections for infants and children on ECMO, and treatment of invasive candidiasis for infants <12 months of age (PTN)


**Acyclovir** for treatment of neonatal HSV infection/encephalitis to determine dosing and safety (PTN)

**Lithium** for treatment of bipolar disorder to determine efficacy, safety, and dosing (BPCA legacy)

**Metronidazole** for treatment of abdominal infections to determine dosing and provide additional safety data (PTN)

**Vincristine and actinomycin** for treatment of cancer to determine safety and dosing (BPCA legacy)

After CSRs of off-patent products are approved by the FDA to move forward, per section 409i of the BPCA, study data must be posted to the **FDA docket**, the official repository for the administrative proceedings of drug label change negotiations between the FDA and the application holder. Once the data are posted to the docket, the FDA has 180 days to complete their review, and determine the suitability of a label change.



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## Draft CSR Submitted

**Isotretinoin** for treatment of neuroblastoma to determine efficacy, safety, and dosing (BPCA legacy)

**Methadone** for treatment of pain and opiate withdrawal to determine safety and dosing (PTN)

**Rifampin** for treatment of complicated infections in neonates to determine safety and dosing (PTN)

*With an eye toward the future, we anticipate submitting data for the following trials by July 2017.*

**Diazepam** for seizure control to determine improved dosing (BPCA legacy and PTN)

**Lorazepam** for sedation to determine efficacy, safety, and dosing (BPCA legacy and PTN)

**Clindamycin** for treatment of tissue infection to determine efficacy, safety, and dosing (PTN in partnership with NIAID); and another for treatment of complicated infections in neonates to determine safety and dosing (PTN)

15  
active  
INDs

72  
enrolling  
sites

>6,000  
total enrolled  
subjects

7  
label  
changes

17 active  
studies



**Sulfamethoxazole and trimethoprim** for treatment of soft tissue infection to determine efficacy, safety, and dosing (PTN in partnership with NIAID)

**Caffeine citrate** for treatment of apnea of prematurity to determine efficacy, safety, and dosing (PTN in partnership with NHLBI)

31  
total projects:  
20 prospective clinical  
trials;  
11 retrospective  
studies or meta-  
analyses

5  
countries:  
US, Canada,  
Singapore,  
Israel, UK

74  
molecules  
investigated

**Ondansetron** for treatment of nausea and vomiting after chemotherapy or surgery in normal weight and obese children and adolescents

**Pantoprazole** for treatment of gastroesophageal reflux disease (GERD), in obese children and adolescents

**Doxycycline** for treatment of common severe infections including tick born illnesses in children and adolescents

35  
manuscripts  
published using  
data generated  
by PTN

*Since September of 2015, PTN faculty members have published eleven manuscripts in professional journals.*

1. Lee JA, Sauer B, Tuminski W, Cheong J, Fitz-Henley J 2nd, Mayers M, Ezuma-Igwe C, Arnold C, Hornik CP, Clark RH, Benjamin DK Jr, Smith PB, Ericson JE; Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee. [Effectiveness of Granulocyte Colony-Stimulating Factor in Hospitalized Infants with Neutropenia](#). *American Journal of Perinatology* • September 2016 [Epub ahead of print]
2. Ericson JE, Kaufman DA, Kicklighter SD, Bhatia J, Testoni D, Gao J, Smith PB, Prather KO, Benjamin DK Jr; Fluconazole Prophylaxis Study Team on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee; [Fluconazole Prophylaxis Study Team. Fluconazole Prophylaxis for the Prevention of Candidiasis in Premature Infants: A Meta-analysis Using Patient-level Data](#). *Clinical Infectious Diseases* • September 2016, issue 63, volume 5, pages 604-10.
3. Hornik CP, Benjamin DK Jr, Smith PB, Pencina MJ, Tremoulet AH, Capparelli EV, Ericson JE, Clark RH, Cohen-Wolkowicz M; Best Pharmaceuticals for Children Act—Pediatric Trials Network. [Electronic Health Records and Pharmacokinetic Modeling to Assess the Relationship between Ampicillin Exposure and Seizure Risk in Neonates](#). *Journal of Pediatrics* • August 2016, issue 3476, volume 16, pages 30546-7.
4. Romaine A, Ye D, Ao Z, Fang F, Johnson O, Riggs B, Benjamin DK, Cotton CM, Testoni D, Clark RH, Chu V, Smith PB, Hornik CP, Best Pharmaceuticals for Children Act—Pediatric Trials Network. [Safety of histamine-2 receptor blockers in hospitalized VLBW infants](#). *Early Human Development* • August 2016, volume 99, pages 27-30.
5. Wang LA, Gonzalez D, Leeder JS, Tyndale RF, Pearce RE, Benjamin DK Jr, Kearns GL, Cohen-Wolkowicz M; Best Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee. [Metronidazole Metabolism in Neonates and the Interplay between Ontogeny and Genetic Variation](#). *Journal of Clinical Pharmacology* • July 2016. [Epub ahead of print]
6. England A, Wade K, Smith PB, Berezny K, Laughon M, on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network Administrative Core Committee. [Optimizing Operational Efficiencies in Early Phase Trials: The Pediatric Trials Network Experience](#). *Contemporary Clinical Trials* • March 2016, volume 47, pages 376-82.
7. Estepp JH, Melloni C, Thornburg CD, Wiczling P, Rogers Z, Rothman JA, Green NS, Liem R, Brandow AM, Cray SE, Howard TH, Morris MH, Lewandowski A, Garg U, Jusko WJ, Neville KA; Best Pharmaceuticals for Children Act-Pediatric Trials Network Administrative Core Committee. [Pharmacokinetics and bioequivalence of a liquid formulation of hydroxyurea in children with sickle cell anemia](#). *Journal of Clinical Pharmacology* • March 2016, volume 56, issue 3, pages 298-306.
8. Gonzalez D, Delmore P, Bloom BT, Cotten CM, Poindexter BB, McGowan E, Shattuck K, Bradford KK, Smith PB, Cohen-Wolkowicz M, Morris M, Yin W, Benjamin DK, Laughon MM, on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee. [Clindamycin Pharmacokinetics and Safety in Preterm and Term Infants](#). *Antimicrobial Agents and Chemotherapy* • April 2016, volume 60, issue 5, pages 2888-94.
9. Samiee-Zafarghandy S, Van den Anker JN, Laughon MM, Clark RH, Smith PB, and Hornik CP, Sildenafil and Retinopathy of Prematurity Risk in Very Low Birth Weight Infants, on behalf of the Best Pharmaceuticals for Children's Act- Pediatric Trials Network Administrative Core Committee. [Sildenafil and Retinopathy of Prematurity Risk in Very Low Birth Weight Infants](#). *American Journal of Perinatology* • February 1, 2016, volume 36, issue 2, pages 137-140.
10. Rowe S, Siegel D, Benjamin DK Jr; Best Pharmaceuticals for Children Act-Pediatric Trials Network Administrative Core Committee. [Gaps in Drug Dosing for Obese Children: A Systematic Review of Commonly Prescribed Emergency Care Medications](#). *Clinical Therapy* • September 1, 2015, volume 39, issue 9, pages 1924-1932.
11. Arnold CJ, Ericson JE, Cho N, Tian J, Wilson S, Chu VH, Hornik CP, Clark RH, Benjamin Jr. DK, and Smith PB, on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network Administrative Core Committee. [Cefepime and Ceftazidime Safety in Hospitalized Infants](#). *Pediatric Infectious Disease Journal* • September 2015, volume 34, issue 9, pages 964-968.

The Pediatric Trials Network (PTN) is made possible by the Best Pharmaceuticals for Children Act (BPCA). The BPCA, first enacted in 2002, provides mechanisms for studying on- and off-patent drugs in children. Visit us on the web at [www.pediatrictrials.org](http://www.pediatrictrials.org).

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News Bite

For a full listing of PTN publications, click [here](#).