Case Example: Ofirmev® (IV acetaminophen)

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Disclaimer

- The views expressed in this presentation are mine and do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
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Overview

- Recommended study design for neonatal pain trials
- Example: Ofirmev® (IV acetaminophen)
  - Regulatory History
  - Protocol Summary
  - Study Results
  - Failed study – why?

Recommended Study Design for Efficacy Evaluation in Neonatal Pain Trials

- Add-on with immediate rescue paradigm
- Randomized, DB, PC study design
- Standard of care (opioid) provided to all enrolled
  - One arm receives study drug, and one arm receives placebo in addition to SOC
- Primary endpoint is a measure of opioid use.
- Secondary endpoint is pain score.
- Post-operative pain is managed using nurse-controlled analgesia.

Ofirmev® (IV Acetaminophen) Regulatory History

11/2010	Ofirmev® NDA approved for use in adults and pediatric patients ≥ 2 years old with the following indication: – Management of mild to moderate pain – Management of moderate to severe pain with adjunctive opioid analgesics – Reduction of fever
11/2010	Under the Pediatric Research Equity Act (PREA), Applicant required to conduct an efficacy, PK/PD, and safety study of IV APAP for the treatment of acute pain in pediatric patients ages birth to 2 years.

Ofirmev® (IV Acetaminophen) Regulatory History

8/2012 – 8/2015	Applicant conducted the Ofirmev® pediatric pain trial at 18 sites in the US.
4/2016	The final study report (included in NDA 022450 Supplement 10) was submitted to the FDA for review.
1/2017	FDA approved NDA 022450 Supplement 10 with the following labeling changes to the indication: – Reduction of fever in adult and pediatric patients

Ofirmev® Pediatric Pain Trial – Protocol Summary

Study Design:

R, DB, PC, parallel-group, multiple-dose, multiple-center study

Objectives:

To study the efficacy and safety of IV acetaminophen

To characterize the concentration-effect (PK/PD) relationship of IV acetaminophen

To determine the PK profile of IV acetaminophen

Study Population:

Hospitalized pediatric patients who were ≥ 28 weeks to ≤ 40 weeks gestational age at birth and < 2 years old at randomization

Acute post-surgical or post-traumatic injury pain

Expected to have moderate to severe pain requiring IV analgesia for 24 hours

PI score ≥ 4 on Leuven Neonatal Pain Scale (LNPS) for ages < 6 months

PI score ≥ 4 on Face, Legs, Activity, Cry, and Consolability (FLACC) for ages 6 to < 24 months

Needed at least one dose of IV opioid within 6 hours prior to randomization

Anticipated to require at least one dose of rescue IV opioid during the 24-hr treatment period

Have reliable vascular access for study drug infusion and PK sampling

Ofirmev® Pediatric Pain Trial – Protocol Summary

Treatment:

- IV APAP groups – received Ofirmev IV every 6 hours x 4 doses plus SOC
- Control groups – received normal saline placebo IV plus SOC

Opioid use:

- Types of opioid – morphine, fentanyl, or hydromorphone
- PRN before randomization and during the 24-hour treatment period
- Loading dose 30 minutes before study drug infusion
- Dosing and frequency at investigator's discretion; goal pain score ≤ 3
- Opioid rescue medication mandatory for pain score ≥ 6

Efficacy Data:

- Frequent pain intensity (PI) scores using LNPS and FLACC
- Frequent sedation scores using University of Michigan Sedation Scale
- Global Evaluation of Satisfaction with study treatment

Safety Data:

- AEs; Vital signs/PE; Clinical laboratory tests

Ofirmev® Pediatric Pain Trial – Endpoints

Primary Endpoint:

- Total amount of rescue opioid over 24 hours (µg/kg IV morphine or morphine equivalent)

Secondary and Other Endpoints:

- PD/PK correlation between APAP concentration and pain scores at 1 hour
- PD/PK correlation between APAP concentration and total rescue opioid use in first 12 hours
- Standard PK parameters (using sparse blood sampling and pop PK analyses)
- Weighted SPID3
- Total amount of rescue opioid over first 12 hours and over the 6 hours for each dosing interval
- Time to first rescue medication
- Percentage of patients requiring rescue opioids at 12 and 24 hours
- Mean PI scores adjusted for corresponding quantity of rescue opioids
- Sedation score in first 12 hours
- Global evaluation by assessor and caregiver

Ofirmev® Pediatric Pain Trial – Results

Demographics

198 pediatric patients received at least one dose of study drug

128 received IV APAP and 70 received normal saline placebo

38 neonates (ages < 29 days)

54 younger infants (ages 29 days to < 6 months)

55 intermediate infants (ages 6 months to < 12 months)

51 older infants/children (ages 12 months to < 24 months)

2/3 male and 1/3 female

69% Caucasian, 15% African-American, 7% Asian, 7% other races, <1% American Indian or Alaska Native

Disposition

80% of 198 patients completed the study

Exposure

85% of IV APAP group received all four doses

79% of placebo group received all four doses

Ofirmev® Pediatric Pain Trial – Results

<u>Primary Efficacy Endpoint Results</u>

- No statistically significant differences in 24-hour total rescue opioid use between the IV APAP groups and the combined placebo groups.
- Average amount of 24-hour rescue opioid use for each treatment group was relatively small and similar between the IV APAP groups and the placebo groups.

Ofirmev® Pediatric Pain Trial – Results

Secondary and Other Efficacy Endpoint Results

- Very small treatment differences for amount of rescue opioid used over different time intervals, number of rescue opioid doses, percentage of patients requiring rescue opioids at different timepoints, and time to first rescue medication.
- Treatment differences in sedation score and global evaluation were minimal.
- Pain scores were much reduced in response to the opioid loading dose and were in the range of 0.6 to 2.2 at baseline before first dose of study drug.
- Pain scores after study drug infusion showed no clear trend to suggest a treatment effect from IV APAP.

Ofirmev® Pediatric Pain Trial – Results

Safety

- No deaths
- 3 nonfatal SAEs (1 in IV APAP group: opioid-related respiratory depression)
- 10 AEs leading to discontinuation (2 in IV APAP group: opioid-related respiratory depression and infection)
- Common AEs – vomiting, hypokalemia, pyrexia, constipation, pleural effusion, hypertension, anemia

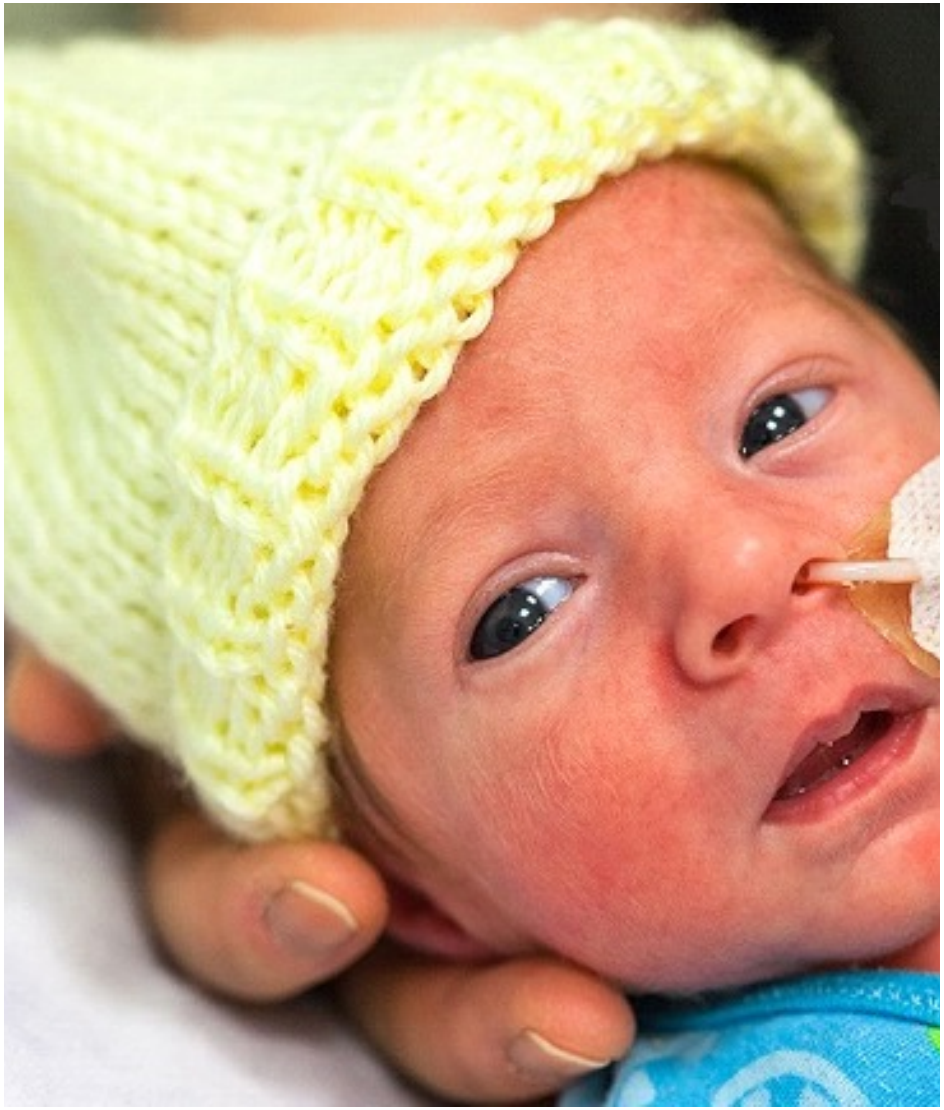
Why did the Ofirmev® Pediatric Pain Trial Fail?

Possible reasons include:

- Use of pain scales that are unable to adequately differentiate pain from other states that may look like pain
- Opioids are used to treat more than just pain in neonates and infants
- Analgesic properties of IV APAP may not be strong enough to demonstrate a treatment effect when used in conjunction with SOC opioids

Summary

- FDA recommends an add-on with immediate rescue study design:
  - Subjects randomized to receive either study drug or placebo in addition to SOC
  - Primary endpoint is measure of opioid use
  - Secondary endpoint is pain score
- To date, no analgesic drug products have been approved in the birth to 2 years age group using this approach
- FDA is open to discussing alternative study designs and endpoints with industry



Thank you!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