# Negative Studies

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# Overview

- The problem of negative studies
- Examples
- Discussion of some ways FDA/DAAP interprets studies that do not meet prespecified criteria for success

# The Problem

- Negative studies happen
- Relatively frequent with analgesics
- Key question - did the study demonstrate a lack of efficacy for an ineffective drug (true negative) or did the study fail to demonstrate efficacy for an effective drug (false negative)?

# Possible contributors to a negative study

- Many possible causes for failing to demonstrate efficacy for an effective drug
  - Population
  - Tolerability
    - Adequate titration
    - Management of side effects
  - Dosing
    - Fixed dose
    - Titrate to effect
    - Flexible

# Possible contributors to a negative study -2

- Design
  - Parallel arm
  - Randomized withdrawal
  - Enriched for tolerance/efficacy
- Duration
- Rescue
- High number of early discontinuations for nonrandom reasons

# Example 1

Butrans

- Novel formulation of buprenorphine for chronic pain indication
- Initial NDA submitted with 5 efficacy studies, 3 types of study design

# Example 1

First 2 studies

- R, DB, PC, AC, parallel arm, forced titration, OA and LBP
- 60-day duration
- Pain not managed with non-opioid alone
- Primary efficacy – change from baseline, pain right now, 11-point NRS
- Missing data – LOCF

# Example 1

- Early discontinuation 40-50%, both studies
- No statistical difference compared to placebo for any active arm **including the active control**, but small numerical difference compared to placebo

# Example 1

Third study

- R, DB, parallel arm, active-controlled, titrate-to-effect
- LBP, not controlled on non-opioid alone
- Non-inferiority comparison

# Example 1

Fourth and Fifth Studies

- R, DB, PC, AC, parallel arm, titrate-to-effect, OA, LBP
- No rescue
- Efficacy – change from baseline in average pain intensity 11-point NRS, LOCF

# Example 1

Fourth and Fifth Studies

- 45-55% discontinued early
  - LOE: placebo > active
  - AE: placebo < active
- Efficacy – change in average PI
  - No statistical difference between tx groups, small numerical difference

# Example 1

Second cycle -Two new studies

- R, DB, PC, parallel arm, titrate-to-effect, LBP
- Open-label titration, randomized if able to be successfully titrated (efficacy/tolerable dose)
- One study some flexibility, one study fixed dose
- Efficacy – change from baseline to 12 weeks

# Example 1

Two new studies

- 50-57% completed open label titration
- ~30% early d/c from DB period

- Efficacy - both studies – statistically significant decrease in PI compared to placebo (BOCF)

# Example 1

What was different with second cycle?

- Enrollment much larger
- Titration reflected prior opioid experience
- Enriched
- Fewer early discontinuations

# Example 2

Cymbalta

- Indicated for DPN, FM
- Five new studies submitted in support of chronic pain indication
  - Three LBP studies – R, DB, PC, fixed dose, parallel arm, 12-13 weeks
  - Two OA studies – R, DB, PC, fixed dose, parallel arm, 13 weeks
- Primary efficacy was change from baseline in pain intensity

# Example 2

LBP studies

Two studies positive – statistically significant difference between drug and placebo, effect size ~0.5 to 0.8

One study negative

# Example 2

Advisory committee interpreted the negative OA study as evidence of a lack of efficacy in OA with additional implications for broader indication.

New indication was approved.

# Discussion

We look at the overall picture

- Our approach has evolved along with our thinking about study designs for analgesics

# Discussion

- Differences between positive and negative trials
- Negative trials
  - Was there any evidence of efficacy – numerical trends, secondary endpoints?
  - Active comparators
  - Study design features that may have contributed

# Questions?