Current Approaches and Accepted Endpoints: Drugs and Biologics

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FDA Priorities

(1) foster the development of novel analgesic drugs

(2) decrease opioid analgesic exposure and prevent new addiction

https://www.fda.gov/about-fda/office-clinical-policy-and-programs/opioid-policy-steering-committee

Duration of Pain

- Acute pain is defined as pain, lasting up to 30 days, typically in response to some type of underlying injury, such as trauma or surgery.

vs

- Chronic pain is defined as pain that persists longer than 3 months or pain that lasts beyond normal healing time.

Pain Indications

- General: Is the drug expected to treat all/most types of pain?
- Specific: Is the drug expected to only treat one type of pain? Does the company want to pursue a specific type of pain for other reasons?
- “Broad”: something in the middle

Clinical Scenarios (Acute and Chronic)

Specific Indications

- Pain due to osteoarthritis of the knee
- Pain following a fracture
- Pain following hip arthroplasty
- Pain from diabetic peripheral neuropathy

Broad Indications

- Musculoskeletal pain
- Neuropathic pain
- Post-surgical pain

Clinical Trial Considerations

- Why does the classification matter?
  - Primary efficacy endpoint/timepoint
  - Importance of onset
  - Other requirements
- Requires at least two adequate and well-controlled trials
- Number of trials may depend on a number of factors
  - Established class vs New Molecular Entity (NME)
  - Is there a related approved indication?

Acute Pain: Primary Endpoint Considerations

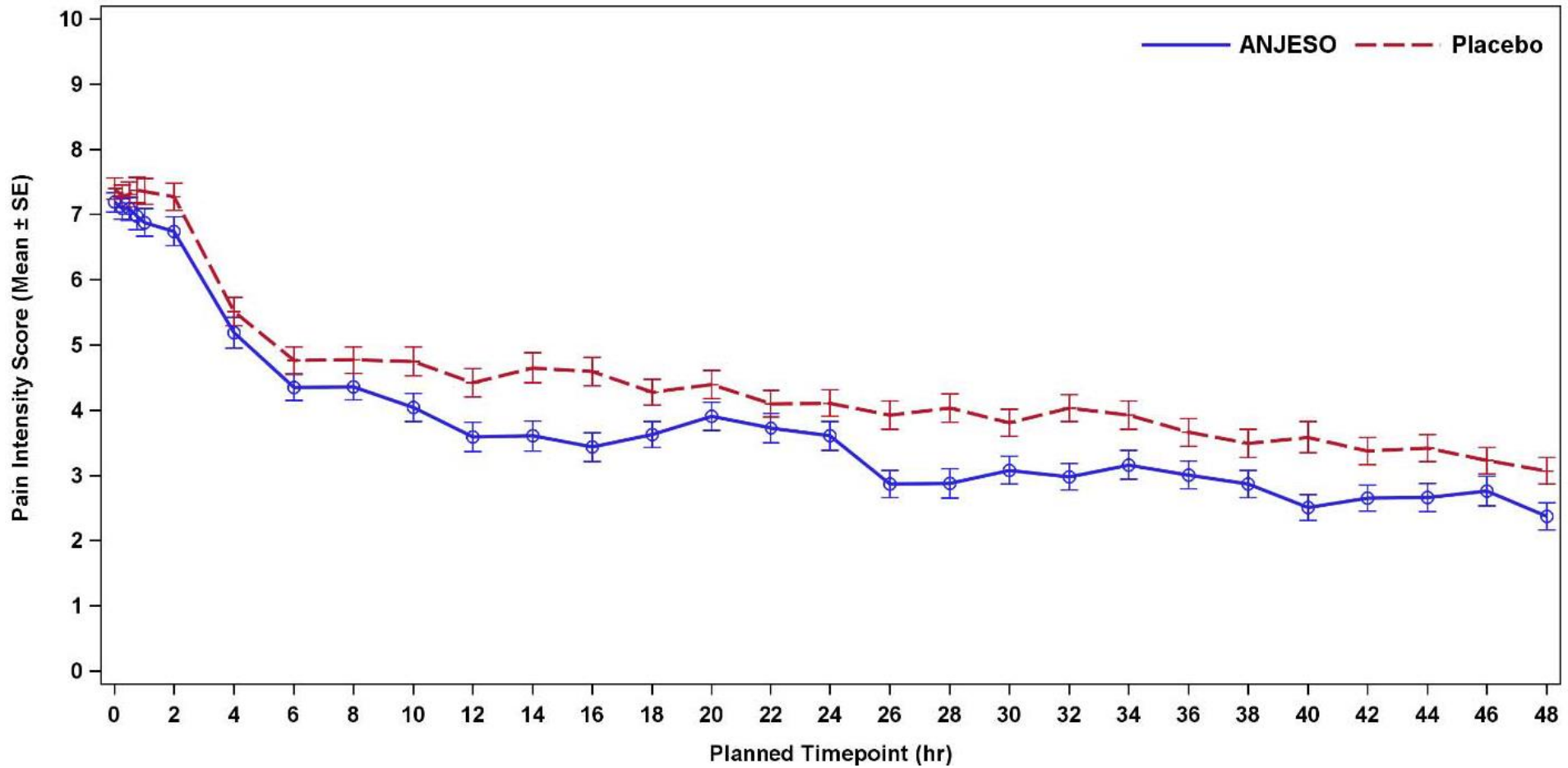
- Primary endpoint should assess the change in pain using a period of time that is appropriate for the pain model that is used in the trial.
- Critical to consider expected duration of need for analgesia
- Post-surgical vs post-fracture

Acute Pain: Primary Endpoint

- Summed Pain Intensity Difference (SPID)
  - SPID-24
  - SPID-48
  - Consideration of other time points, as appropriate

- Is it enough to show a statistically significant difference?
- Does the effect size need to be clinically meaningful?
  - Benefit-risk

Summed Pain Intensity Difference



Time to Onset of Analgesia

- Perceptible Pain Relief
- Meaningful Pain Relief
- What is the best way to measure?

- It’s not a primary endpoint but the data are critical
  - Example: It is a prescriber’s expectation that an intravenous opioid will work with a quick onset. If it takes 2 hours to work, it may win on the primary endpoint but would have an unclear role in the management of patients. A delayed onset may also lead to safety issues (rescue, stacking).

Secondary Endpoints: Considerations

- The primary efficacy endpoint alone does not paint the full picture.
- Secondary endpoints can help characterize the drug
  - Critical to inform labeling to help prescribers most appropriately and safely use an analgesic
- Time to onset of pain relief
  - Critical for acute pain drugs
  - Needs to support the primary endpoint
  - Needs to support the expected use of the drug

Secondary Endpoints (2)

- Other secondary outcome measures: time to rescue, assessment of use of rescue medications, physical function, patient global impression of change of pain.
- Consider efficacy assessment at different time points
  - Depends on duration of study

Chronic Pain: Primary Endpoint Considerations

- The primary endpoint is most often based on the change in pain from baseline to the end of the study period
- Twelve weeks has been an accepted primary efficacy timepoint
- Caution to early efficacy that is not sustained ------> summed pain intensity over time not ideal
- Daily pain scores ------> Average of first week and 12^{th} week
- Time to onset and time to first rescue are not very informative.
- Pain curves provide critical information.

Chronic Pain: Primary Endpoint

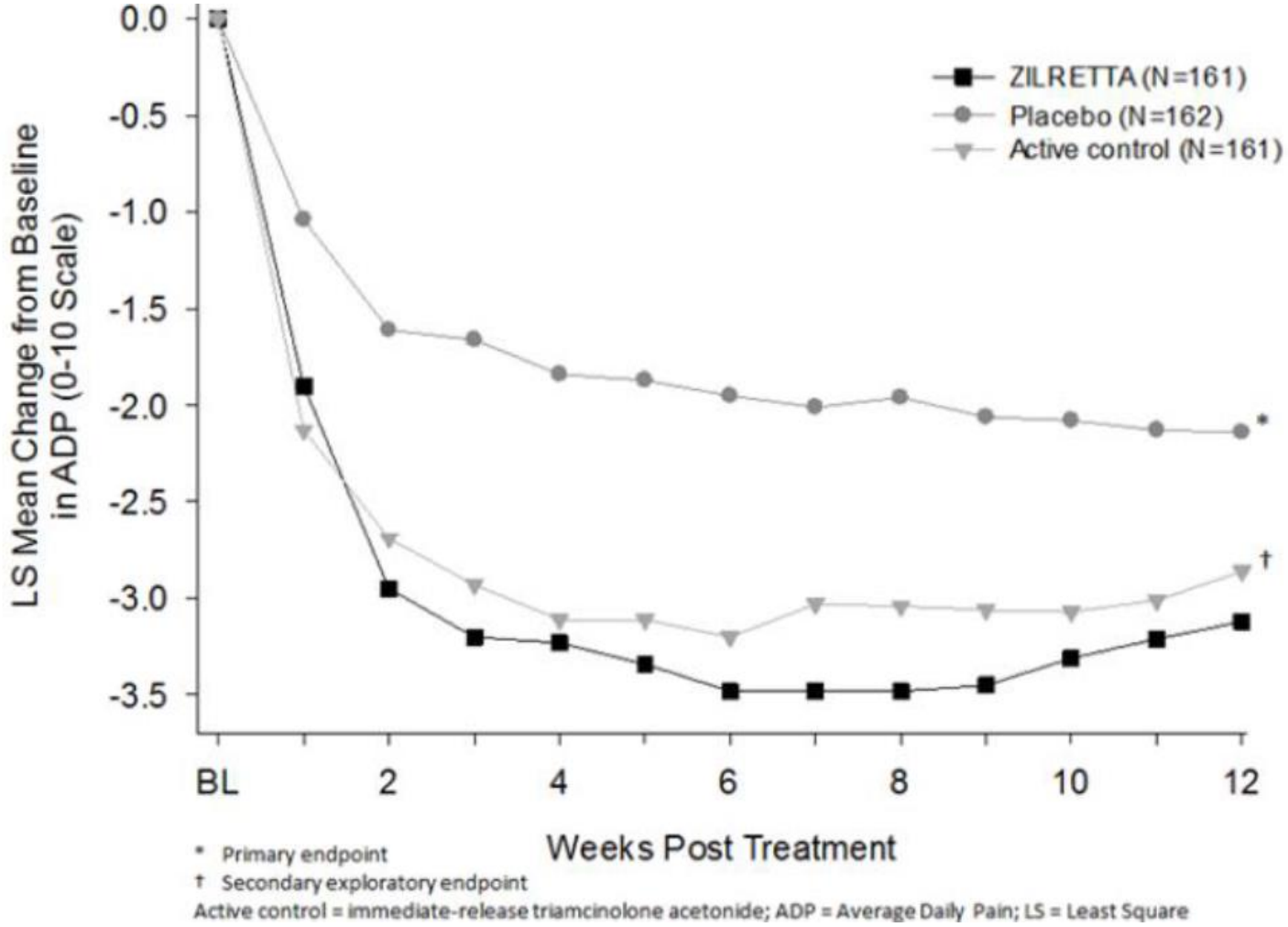
For most chronic pain conditions:

- Numeric Pain Rating Scale (NPRS)
- Visual Analog Scale (VAS)

Pain of osteoarthritis (not “signs and symptoms”):

- The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale
- Secondary: WOMAC function, Patient Global Assessment

Pain Curve: Change from baseline to Week 12 for average daily pain



Trial designs: General Considerations

- Repeat-dose, randomized, double-blind, superiority
- Non-inferiority historically not accepted
- Pain intensity can be influenced by study design factors, such as the use of rescue medication and placebo effect.
- A noninferiority trial showing no difference between analgesic treatments could mean that neither product worked in that study.

Trial designs: General Considerations (2)

- Suitable comparators for a superiority study could include placebo or another analgesic if the new product is expected to be more effective than the analgesic.
- Even if using an active comparator, a placebo is important for assay sensitivity.
- If using a placebo, an active control arm (standard of care) can inform the overall risk-benefit.

“Opioid-Sparing”: General Thoughts

- What is clinically meaningful?
- Is <u>any</u> reduction in opioid use considered clinically meaningful?
  - Is there a specific cut-off (percentage, MME) that represents a meaningful reduction?
  - Is a reduction in opioid use linked to a clinical benefit?
- What about elimination of opioid use?
- Important to include labeling that describes the actual benefit
- Not a catch-all term

Pediatric Considerations

- The Pediatric Research Equity Act (PREA) gives FDA the authority to require pediatric studies in certain drugs and biological products. The goal of the studies is to obtain pediatric labeling for the product.
- Pain clinical trials in the very young continue to present a host of challenges.
  - Ethics: no child should be subject to pain
  - Assessments: how is pain best rated in a child that can’t provide their own rating

Pediatric Considerations (2)

- For drugs with an established mechanism of action, we have: (Berde 2012):
  - Accepted extrapolation of efficacy for ages 2 to 16 years age with required safety data
  - Required efficacy data required from birth to age 2
- For new molecular entities,
  - Required efficacy data from birth to 16 years

Pediatric Considerations (3)

- When attempting to extrapolate, how do we determine comparable exposures?
- What is appropriate for labeling?
- Does pure extrapolation without any efficacy data the best approach?
- How should we assess pain in the youngest patients?

Final Thoughts

- Analgesic drug development, particularly non-opioid development, is important yet challenging.
- Acceptance of certain approaches does not mean we are not open to new and alternative ones.
- Answers to difficult questions will require time, collaboration and innovation.

Thank you