Monoclonal Antibodies Targeted Against Nerve Growth Factor For the Treatment of Chronic Pain

Introduction

Ken Verburg, PhD
Medicines Development Group, Pfizer Inc.

Arthritis Advisory Committee Meeting

12 March 2012
FDA White Oak Campus
Silver Spring, MD
Background Narrative

Clinical development programs with anti-NGF mAbs and the regulatory process worked to identify a safety signal prior to marketing approval

- Signal was not predicted by 6 decades of research on NGF so a cautionary response was taken
- Concern was justified although it was later learned the initial description of the event as osteonecrosis was incorrect
  - Rapidly progressive osteoarthritis
- Careful examination of the data has allowed for identification of measures that could reduce the risk by 90%
Decision Point

- Whether to resume clinical development of anti-NGF therapies
- If so, how best to proceed
Why Is it Important to Resume Development?

- Evidence that anti-NGF therapies hold the promise of bringing a step-change improvement in pain relief
  - Need further studies to examine and demonstrate the effectiveness of this therapeutic approach
- Opportunities to advance the treatment of pain have been very limited
  - Despite decades of research, we have not seen any compounds in the clinic with similar efficacy characteristics
1 in 3 Patients Treated with Tanezumab Report Minimal to No Pain Over ≥ 4 Consecutive Months

All Patients

- placebo (N=1029)
- tanezumab (N=4273)
- active comparator (N=1266)

Baseline Scores Mean ± SD

<table>
<thead>
<tr>
<th>Baseline Scores</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>placebo</td>
<td>7.3</td>
<td>1.3</td>
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<tr>
<td>tanezumab</td>
<td>7.0</td>
<td>1.5</td>
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<tr>
<td>active comparator</td>
<td>6.8</td>
<td>1.6</td>
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WOMAC Pain Scores 0-2 at 2 or more consecutive 8-weekly visits on 0-10 NRS

*p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy
1 in 3 Patients Treated with Tanezumab Report Minimal to No Pain Over $\geq 4$ Consecutive Months$^1$

### All Patients

- **Placebo (N=1029)**: 19.1%
- **Tanezumab (N=4273)**: 36.6%
- **Active Comparator (N=1266)**: 22.5%

### Patients with Severe Pain (Baseline Score $\geq 7$)

- **Placebo (N=598)**: 15.2%
- **Tanezumab (N=2230)**: 31.3%
- **Active Comparator (N=569)**: 16.5%

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$^1$WOMAC Pain Scores 0-2 at 2 or more consecutive 8-weekly visits on 0-10 NRS

\*p ≤ 0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy
Sponsor Presentations

- To confirm with the Arthritis Advisory Committee
  - Clinical development of anti-NGF mAbs should resume
  - Proposed measures to minimize the risk, protect patient safety, and to characterize the risk further are sufficient
  - Chronic pain conditions selected and studies proposed are acceptable approaches for re-initiating the clinical programs
<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>Perspectives on Chronic Pain</td>
<td>Thomas Schnitzer, MD, PhD&lt;br&gt;Professor of Medicine, Northwestern University&lt;br&gt;Feinberg School of Medicine</td>
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<tr>
<td>Tanezumab</td>
<td>Ken Verburg, PhD&lt;br&gt;Sr. VP, Medicines Development Group, Pfizer</td>
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<tr>
<td>Fulranumab</td>
<td>David Upmalis, MD&lt;br&gt;Sr. Director, Neuroscience, Janssen R&amp;D</td>
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<tr>
<td>REGN475</td>
<td>Ned Braunstein, MD&lt;br&gt;Exec. Director, Regulatory, Regeneron</td>
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<tr>
<td>Concluding Remarks</td>
<td>Nathaniel Katz, MD, MS&lt;br&gt;President, Analgesic Solutions</td>
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## External Delegation

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<th>Name</th>
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<td>Dr. David Hungerford</td>
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<td>Dr. Michael Mont</td>
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</tr>
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<td>Dr. Edward McCarthy</td>
<td>Orthopedic Pathology</td>
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<td>Dr. Steve Abramson</td>
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<td>Dr. Tom Schnitzer</td>
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<td>Dr. Eric Vignon</td>
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<td>Dr. David Cornblath</td>
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<td>Dr. Martin Koltzenburg</td>
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<td>Dr. Bruce Kneeland</td>
<td>Radiology</td>
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<tr>
<td>Dr. Pat Mantyh</td>
<td>Pharmacology</td>
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</table>
Perspectives on Chronic Pain: Current Status and Needs

Thomas J. Schnitzer, MD, PhD
Professor
Departments of Physical Medicine and Rehabilitation and Internal Medicine/Rheumatology
Discussion Outline

• Chronic Pain is prevalent
• Chronic Pain is impactful
• Chronic Pain management paradigms fail many patients
• New therapeutics not available despite serious efforts
• NGF inhibition has shown promise and also raised concerns
Prevalence of Chronic Pain

- 2011 IOM report of the Committee on Advancing Pain Research, Care and Education
- “at least 116 million Americans burdened with chronic pain”
- Most common clinical presentations of chronic pain
  - Musculoskeletal pain\(^1\)
    - Low back pain 28% of adults
    - Osteoarthritis 26% of adults
  - Chronic headache/migraine
  - Neuropathic pain
  - Visceral pain
  - Central pain

\(^1\)CDC and NCHS, 2010
Impact of Chronic Pain

What is pain?

It is so much more than just pain intensity. Over time, many [patients] find the effects of living with chronic pain impact their ability to work, engage in recreational and social activities, and for some, perform the most basic everyday activities that people just take for granted. Not surprisingly, pain begins to chip away at their mood, often leaving them angry, frustrated, anxious, and/or depressed. Our families suffer along with us, and many relationships are forever altered.

--An advocate for people with chronic pain

Consequences of pain

- Poor health-related quality of life & poor self-rated health
- Strong link with disability
- Likely to seek medical attention

1IOM, 2011: Relieving Pain in America
Impact of Chronic Pain

Quality of Life

Effect of chronic nonmalignant pain on QOL, as indicated by SF-36 subscores, mean (SD) (n=150).\textsuperscript{1,2}

* = population norm values; PF=physical functioning; RP=role-physical; BP=bodily pain; GH=general health; VT=vitality; SF=social functioning; RE=role-emotional; MH=mental health. * p<0.001

Activities/Quality of Life Domains Impaired by Increasing Pain Severity

Boldface indicates an additional dimension that is impaired at the given level of pain.

\textsuperscript{1}Katz N, J Pain Symp Mgmt 2002;24:S38-47. \textsuperscript{2}Becker N et al, Pain 1997;73: 393-400

\textsuperscript{3}Cleland CS and Ryan KM, Ann Acad Med 1994;23:129-138
Impact of Chronic Pain Disability

Extent of Pain-Related Disability among Adults with Pain in the Last 3 months, United States, 2009

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Difficulty with Basic Activities (%)</th>
<th>Activity Limitations (%)</th>
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<tr>
<td>Low back pain</td>
<td>51.6</td>
<td>55</td>
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<tr>
<td>Neck pain</td>
<td>30.2</td>
<td>34.4</td>
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<td>Back pain</td>
<td>37.3</td>
<td>38.6</td>
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<tr>
<td>Shoulder pain</td>
<td>17.7</td>
<td>21.4</td>
</tr>
<tr>
<td>Hip pain</td>
<td>15</td>
<td>28.4</td>
</tr>
<tr>
<td>Severe headache/migraine</td>
<td>31</td>
<td>33.5</td>
</tr>
</tbody>
</table>

Defined as having difficulties in one or more of the following areas: movement, emotional, seeing, hearing or cognition.

Defined as having limitations in one or more of the following areas: self-care, social, work.

Source: CDC and NCHS, 2010

All cause mortality in OA Patients with and without disability

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1 IOM, 2011: Relieving Pain in America; Nuesch E et al. BMJ 2011; 342d1165
Impact of Chronic Pain

Economic Burden

• Annual Cost of Chronic Pain in the United States$1
  • $560-635 billion annually
    - $261-300 billion in health care costs
    - $297-336 billion in lost productivity

• Expenditures
  • Medicare: $65.3 billion or 14% of all Medicare costs in 2008
  • All federal & state programs (Medicare, Medicaid, VA, etc) $99 billion in 2008 for medical expenditures for pain

$1Conservative estimate as excludes cost of pain affecting institutionalized individuals (e.g., long-term care residents, correction inmates), military personnel; excludes lost productivity of personal caregivers, workers <24 and >65 years, and emotional costs of pain.

IOM, 2011: Relieving Pain in America
Management of Chronic Pain Fails Too Often

- Significant system and organizational barriers to adequate pain care exist.
- Education is a central part of the necessary cultural transformation of the approach to pain.
- Research to translate advances into effective therapies is a continuing need.

“Academia and industry should develop novel agents for the control of pain. This does not mean simply recycling current drugs. What is required is basic and clinical science research to discover new classes of pain therapeutics and more efficient ways of developing them.”

IOM, 2011: Relieving Pain in America
Existing Pain Medications: NSAID Limitations

**Efficacy**

<table>
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<tr>
<th></th>
<th>SMD</th>
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<tbody>
<tr>
<td>acelaminophen</td>
<td>0.2</td>
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<tr>
<td>NSAIDs</td>
<td>0.4</td>
</tr>
<tr>
<td>opioids</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Discontinuation of NSAID Use**

- **ASA, EC**
- **Ibuprofen**
- **Naproxen**
- **Piroxicam**

**NSAID Safety**

**Cardiovascular Risk**
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).
- Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS or NAPROSYN Suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

**Gastrointestinal Risk**
- NSAIDS cause an increased risk of gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

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3 www.accessdata.fda.gov/drugsatfda_docs/label/2008/017581s110,18164s60,18965s18,20067s17bl.pdf
Existing Pain Medications: Opioid Limitations

Adverse Events\textsuperscript{1,2}

- GI:
  - Constipation 40-95%;
  - Nausea 10-40%
- CNS
  - Sedation, drowsiness, cognitive impairment
  - Respiratory depression
  - Dizziness and falls
  - Addiction and dependence
- Others:
  - Hormonal
  - Immunologic
  - Dermatologic

Opioids and Fracture in Older Adults with Arthritis\textsuperscript{3}

Incidence rate highest in first 2 weeks after initiating therapy, especially for short-acting opioid group

Lack of Better Analgesics Not For Lack of Trying

- Multiple Targets Identified
  - NMDA receptor blockers
  - NK-1 receptor blockers
  - FAAH inhibitors
  - Na, Ca, K channel modulators
    - TrpV1, V3, V4
    - NaV1.7, NaV1.8
    - ASIC3
  - Cannabinoid receptor blockers: CB1, CB2
  - Delta opioid agonists
  - P2X3 inhibitors
  - P38 kinase

ClinicalTrials.gov

539 trials in chronic pain
8 with new molecular entity
2 NCE in musculoskeletal pain

New Target: NGF as a Mediator of Pain

• Key evidence
  - NGF causes pain in humans and animals
  - NGF is locally up-regulated in painful conditions
  - NGF inhibition reverses pain in many animal models

Monoclonal Antibodies Directed Against NGF

- 3 compounds under discussion: tanezumab, fulranumab, REGN475
  - fully human or humanized monoclonal antibodies
  - picomolar affinity for NGF
  - high selectivity for NGF over other members of the neurotrophin family
  - Inhibit NGF activity at both TrkA and p75 receptors
  - Plasma half-life: 22-25 days

- Evaluated after IV or SC routes of administration
  - 4, 8 & 12 wk dosing intervals
  - Doses examined: 3 to 1000 µg/kg (0.003 to 1 mg/kg)
Wide Range of Clinical Conditions Evaluated

<table>
<thead>
<tr>
<th>Chronic Pain Condition</th>
<th>Efficacy Demonstrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Chronic low back pain</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Diabetic peripheral neuropathy</td>
<td>✓</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Possible</td>
</tr>
<tr>
<td>Interstitial cystitis</td>
<td>Possible</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>Possible</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Negative</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>On-going</td>
</tr>
</tbody>
</table>

- Efficacy superior to an active comparator has been found repeatedly with tanezumab.

Safety Profile Being Defined

- Anti-NGF mAbs do not appear to have cardiovascular or gastrointestinal safety liabilities of NSAIDs
- Anti-NGF mAbs do not appear to have abuse liability or undesirable central effects of opioids
- New safety signal has appeared in clinical development: joint events
- Questions to be addressed:
  - What does this safety signal represent?
  - Under what conditions does this signal occur and at what frequency?
  - Is it advisable to undertake further research with these compounds to define better the benefit:risk?
Summary

- Anti-NGF antibodies first new pain treatment agents in years
  - Efficacy in wide spectrum of pain conditions
  - Magnitude of effect superior to existing agents
- Many people in pain with no effective treatments
- Further research is needed and possible
  - Carefully designed studies
  - Well defined populations
  - Informed consent
  - Risk mitigation strategies
Monoclonal Antibodies Targeted Against Nerve Growth Factor For the Treatment of Chronic Pain

Tanezumab

Ken Verburg, PhD
Medicines Development Group, Pfizer Inc.

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Key Points

- Relieves pain and improves function to a clinically meaningful extent across chronic pain conditions; superior to active comparator treatment

- Tanezumab monotherapy does not elevate the risk of all-cause total joint replacements – in contrast to when administered with NSAIDs

- Adjudication of total joint replacements showed:
  - Tanezumab does not elevate the risk of osteonecrosis
  - Associated with a dose-related increase in rapidly progressive OA
    - Further increased >3-fold when administered with NSAIDs

- Risk minimization should reduce the risk of rapidly progressive OA in future studies
Tanezumab Clinical Development

- Moderate to severe osteoarthritis
  - Phase 3 development
    - Monotherapy & NSAID combination therapy
    - 2.5 mg, 5 mg, and 10 mg IV/SC every 8 wks

- Moderate to severe chronic low back pain
  - Phase 2b development
    - Monotherapy
    - 5 mg, 10 mg, and 20 mg IV/SC every 8 wks

- Other chronic pain conditions
  - Early stage development
    - Cancer, neuropathic, and visceral pain
    - Monotherapy, adjunctive therapy with standard of care
    - Doses up to 20 mg IV/SC (or body-weight adjusted equivalent)
Tanezumab Clinical Program
Number of Studies and Patients

30 Studies**
N=11,079

17 OA Studies
N=8817

13 Phase 3 OA Studies*
N=8191

3 Phase 2 CLBP Studies
N=1564

8 Phase 2 Pain Studies**
N=594

10 Other Studies
N=698

2 Phase 1 studies in healthy volunteers
N=104

*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies

**Includes studies of diabetic peripheral neuropathy, post-herpetic neuralgia, interstitial cystitis, prostatitis, endometriosis, chronic pancreatitis, & bunionectomy; excludes 2 ongoing studies in metastatic bone pain

Osteoarthritis (OA); chronic low back pain (CLBP)
11,079 patients randomized and treated in completed clinical studies

- Placebo = 1649 (exposure up to 6 mo)
- Tanezumab monotherapy = 6410 (exposure up to 2 yrs)
- Tanezumab/NSAID combination therapy = 3400 (exposure up 2 yrs)
  ♦ Includes patients randomized to combination therapy and concomitant NSAID use in long-term studies
- Active comparator = 1653 (exposure up to 1 yr)
  ♦ naproxen 500 mg BID (N=1083)
  ♦ celecoxib 100 mg BID (N=256)
  ♦ diclofenac SR 75 mg BID (N=152)
  ♦ oxycodone CR 10-40 mg q12h (N=158)
Presentation Outline

- **Efficacy**
  - Osteoarthritis
  - Chronic Low Back Pain
  - Other Chronic Pain Conditions

- Joint-Related Safety

- Risk Minimization
## Tanezumab Monotherapy vs. Placebo

**Consistent Improvement with all Doses at Week 16**

<table>
<thead>
<tr>
<th>Study</th>
<th>WOMAC Pain</th>
<th>WOMAC Physical Function</th>
<th>Patient’s Global Assessment</th>
</tr>
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<tbody>
<tr>
<td>Study 1011 (Knee OA)</td>
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<td></td>
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<tr>
<td>tanezumab 2.5 mg</td>
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Baseline observation carried forward (BOCF) imputation
WOMAC Pain Response
Tanezumab Improves Response Rates vs. Placebo

Percent Improvement from Baseline

* p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs. placebo
mITT, BOCF, Study 1014
### Tanezumab Monotherapy vs. NSAIDs

**Improved Efficacy at Week 16**

<table>
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<th>Study</th>
<th>Design</th>
<th>WOMAC Pain</th>
<th>WOMAC Physical Function</th>
<th>Patient’s Global Assessment</th>
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<tr>
<td>Study 1018</td>
<td>Knee &amp; hip OA vs naproxen</td>
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Baseline observation carried forward (BOCF) imputation
WOMAC Pain Response
Tanezumab Improves Response Rates vs. Naproxen

* p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs. placebo
† p≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 vs. naproxen 500 mg BID
mITT, BOCF, Study 1015
**Efficacy Endpoints – Preliminary OA Study**

Significant Improvement vs. Oxycodone CR

- **Baseline scores**
  - placebo (N=141)
  - tanezumab 5 mg (N=161)
  - oxycodone CR 10-40 mg Q12h (N=158)

- **Mean Change (SE) from Baseline**
  - **WOMAC Pain**
    - placebo: -2.6
    - tanezumab 5 mg: -3.6
    - oxycodone CR: -3.6
  - **WOMAC Physical Function**
    - placebo: -1.9
    - tanezumab 5 mg: -3.1
    - oxycodone CR: -3.1
  - **Patient’s Global Assessment**
    - placebo: -0.5
    - tanezumab 5 mg: -0.9
    - oxycodone CR: -1.0

*† † p≤0.05; † † † p≤0.01; † † † † p≤0.001 versus placebo
†† † p≤0.05; † † † p≤0.01; † † † † p≤0.001 versus oxycodone CR; ITT, LOCF at Week 8 oxycodone CR dose = 10-40 mg Q12h
Tanezumab in Chronic Low Back Pain
Significant Improvement vs. Placebo and Naproxen

Baseline scores for Low Back Pain Intensity:
- Placebo (N=230): 6.7, 6.6, 6.7, 6.8
- Tanezumab 10 mg (N=295): 12.8, 12.2, 13.0, 12.9
- Tanezumab 5 mg (N=232): 12.8, 12.2, 13.0, 12.9
- Tanezumab 20 mg (N=295): 13.0, 13.0, 13.0, 13.0
- Placebo (N=230): 6.7, 6.6, 6.6, 6.7
- Naproxen (N=295): 3.4, 3.4, 3.3, 3.4
- Tanezumab 5 mg (N=232): 3.4, 3.4, 3.3, 3.4
- Tanezumab 20 mg (N=295): 3.4, 3.4, 3.4, 3.4

Low Back Pain Intensity assessed with a 0 to 10-point numerical rating scale. Lower scores indicate less pain.
Roland-Morris Disability Questionnaire scores range from 0 to 24 points. Lower scores indicate better function.
Patient Global Assessment assessed with a 5-point Likert scale. Lower scores indicate better evaluations.

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus placebo
†p ≤ 0.05; ‡p ≤ 0.01; §§p ≤ 0.001 versus naproxen
ITT, BOCF; naproxen dose = 500 mg BID

Low Back Pain Intensity
Roland Morris Disability Questionnaire
Patient Global Assessment
### Efficacy in Neuropathic Pain
Phase 2; Average Daily Pain at Week 8

**Diabetic Peripheral Neuropathy**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Mean (SE) Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=35, 31)</td>
<td>6.9</td>
<td>-0.9</td>
</tr>
<tr>
<td>Tanezumab 20 mg or 200 µg/kg (N=38, 32)</td>
<td>6.6</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

p = 0.009

**Post-herpetic Neuralgia**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Mean (SE) Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=35, 31)</td>
<td>6.4</td>
<td>-1.1</td>
</tr>
<tr>
<td>Tanezumab 20 mg or 200 µg/kg (N=38, 32)</td>
<td>6.4</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

p = 0.098

Studies 1031 and 1005; ITT, LOCF
Efficacy in Visceral Pain
Phase 2; Average Daily Pain at Week 6

Baseline scores:
- Interstitial Cystitis: placebo (N=28, 32) = 5.9, tanezumab 200 µg/kg (N=31, 30) = 6.4
- Prostatitis: placebo (N=28, 32) = 5.6, tanezumab 200 µg/kg (N=31, 30) = 5.5

Mean (SE) Change from Baseline:
- Interstitial Cystitis: placebo = -1.2, tanezumab = -1.6, p=0.003
- Prostatitis: placebo = -1.1, tanezumab = -1.6, p=0.265

Studies 1010 and 1019; ITT, LOCF
Efficacy Summary — Osteoarthritis

- Tanezumab monotherapy
  - Superior efficacy compared to placebo and NSAIDs
  - Favorable efficacy profile compared to oxycodone CR
  - Minimal incremental benefit of tanezumab 10 mg vs. 5 mg
  - 2.5 mg and 5 mg emerging as therapeutic doses for OA
Efficacy Summary — Chronic Pain

- Chronic low back pain
  - Superior efficacy compared to placebo and naproxen
  - Minimal incremental benefit of tanezumab 20 mg vs. 10 mg

- Neuropathic and visceral pain
  - Preliminary evidence of analgesic efficacy at doses of 20 mg
Presentation Outline

- Efficacy
  - Osteoarthritis
  - Chronic Low Back Pain
  - Other Chronic Pain Conditions

- Joint-Related Safety
  - Total Joint Replacements
  - Adjudication Outcomes

- Risk Minimization
Tanezumab Clinical Program
Number of Studies and Patients

30 Studies
N=11,079

17 OA Studies
N=8817

13 Phase 3 OA Studies*
N=8191

3 Phase 2 CLBP Studies
N=1564

*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies
Tanezumab Clinical Program
Number of Studies and Patients

17 OA Studies
N=8817

30 Studies
N=11,079

13 Phase 3 OA Studies*
N=8191

3 Phase 2 CLBP Studies
N=1564

13 total joint replacements
6 reported as osteonecrosis

373 total joint replacements
81 reported as osteonecrosis

*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies
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3 Phase 2 CLBP  
Studies  
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13 total joint replacements  
6 reported as osteonecrosis

373 total joint replacements  
81 reported as osteonecrosis

386 total joint replacements  
87 reported as osteonecrosis**

*Includes Studies 1040 and 1032 (total N=22); the Phase 3 osteoarthritis analysis set (N=8169) excludes these 2 studies

**50 patients (57.5%) underwent total joint replacement
All-Cause Total Joint Replacements
Phase 3 OA Studies

- placebo (N=1029)
- tanezumab monotherapy (N=4273)
- tanezumab + NSAID therapy (N=3028)
- active comparator (N=1266)

mean (95% CI)
tanezumab 2.5–10 mg combined
n=372 total events

*p ≤ 0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy,
All-Cause Total Joint Replacements
Phase 3 OA Studies, Event Rate by Dose

Risk Difference: *p≤0.05 vs. placebo, †p ≤ 0.05 vs. active comparator
Dose Response: p=0.553 tanezumab monotherapy, p<0.0001 tanezumab/NSAID combination therapy
All-Cause Total Joint Replacements
Phase 3 OA Studies, Event Rate by Dose

Risk Difference: *p ≤ 0.05 vs. placebo, †p ≤ 0.05 vs. active comparator
Dose Response: p = 0.553 tanezumab monotherapy, p < 0.0001 tanezumab/NSAID combination therapy
All-Cause Total Joint Replacements
Phase 3 OA & Phase 2 Non-Controlled Long-term CLBP Study

Phase 3 OA Studies

- placebo (N=1029)
- tanezumab monotherapy (N=4273)
- tanezumab + NSAID therapy (N=3028)
- active comparator (N=1266)

Events/1000 pt-yrs

- Mean (95% CI) tanezumab 2.5–10 mg combined
  - n=372 total events

Non-controlled CLBP Study

- Tanezumab monotherapy (N=484)
- Tanezumab + NSAID therapy (N=364)

Events/1000 pt-yrs

- Mean (95% CI) tanezumab 10–20 mg combined
  - n=13 total events

*p ≤ 0.05 vs. placebo, †p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab monotherapy,
Summary

- **Tanezumab monotherapy**
  - No increase in total joint replacements compared to placebo or active comparator
  - No observed dose relationship

- **Tanezumab/NSAID combination therapy**
  - At least 2-fold greater than placebo, tanezumab monotherapy, or active comparator
  - Event rate increased with escalating doses of tanezumab
Adjudication Committee

- Multidisciplinary
- Blinded to treatment assignment
- Reviewed all total joint replacements with a post-baseline radiology image available within ~9 months of the surgery
- Independently reviewed all source documentation prior to Committee meetings
  - Clinical summaries, consultation reports, operative reports, radiology & pathology reports, available images & pathology specimens
- Each patient was reviewed & discussed at Committee meetings
- Each Committee member provided their own final assessment for each patient
Adjudication Categories

1. Primary osteonecrosis
2. Worsening osteoarthritis (OA)
3. Other joint condition/diagnosis
4. Not enough information to distinguish between primary osteonecrosis & worsening OA or to specify another diagnosis
Adjudication Categories

1. Primary osteonecrosis

2. Worsening osteoarthritis (OA)
   a. Rapidly progressive OA (type 1 or type 2)
      i. type 1 – loss of joint space width ≥ 1 mm over approximately 1 year
      ii. type 2 – abnormal loss/destruction of bone uncommon for end-stage OA
   b. Normal progression of OA
   c. Not enough information to distinguish between rapidly progressive and normal progression of OA

3. Other joint condition/diagnosis

4. Not enough information to distinguish between primary osteonecrosis & worsening OA or to specify another diagnosis
Patients with total joint replacement
n = 386

Patients with events reported as osteonecrosis n = 87*

100%

249 (64.5%) patients adjudicated
OA studies n = 239
CLBP studies n = 10

Patients with total joint replacement related to OA/injury n = 299

54%

137 patients not adjudicated
OA studies n=134
CLBP studies n= 3

*50 patients (57.5%) underwent total joint replacement
## Adjudication Results
### Summarized by Category

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Total N=249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary osteonecrosis</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Worsening osteoarthritis</td>
<td>200 (80.3)</td>
</tr>
<tr>
<td>Other condition</td>
<td>29 (11.6)</td>
</tr>
<tr>
<td>Insufficient information to distinguish osteonecrosis from OA</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Lack of consensus</td>
<td>7 (2.8)</td>
</tr>
</tbody>
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### Adjudication Results
Summarized by Category

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</tr>
<tr>
<td>to distinguish osteonecrosis from OA</td>
<td></td>
</tr>
<tr>
<td>Lack of consensus</td>
<td>7 (2.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly progressive</td>
</tr>
<tr>
<td>Normal progression</td>
</tr>
<tr>
<td>Insufficient information to distinguish between rapid from normal progression</td>
</tr>
</tbody>
</table>
## Reported Osteonecrosis

### Availability of MRIs and Pathology for Committee Review

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRI image(s) available for review</strong></td>
<td>38 (43.7)</td>
</tr>
<tr>
<td><strong>Pathology specimen(s) available for review</strong></td>
<td>23 (26.4)</td>
</tr>
<tr>
<td><strong>Both MRI and pathology specimen available for review</strong></td>
<td>12 (13.8)</td>
</tr>
</tbody>
</table>
## Rapidly Progressive OA
### Availability of MRIs and Pathology for Committee Review

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Total N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI image(s) available for review</td>
<td>23 (33.8)</td>
</tr>
<tr>
<td>Pathology specimen(s) available for review</td>
<td>23 (33.8)</td>
</tr>
<tr>
<td>Both MRI and pathology specimen available for review</td>
<td>10 (14.7)</td>
</tr>
</tbody>
</table>
## Adjudication Results
### By-Patient vs. By-Joint Analyses

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Total Patients N=249</th>
<th>Total Joints N=282</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary osteonecrosis</td>
<td>2 (0.8)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Rapidly progressive OA</td>
<td>68 (27.3)</td>
<td>71 (25.2)</td>
</tr>
<tr>
<td>Normal progression OA</td>
<td>119 (47.8)</td>
<td>142 (50.4)</td>
</tr>
<tr>
<td>Other condition</td>
<td>29 (11.6)</td>
<td>33 (11.7)</td>
</tr>
<tr>
<td>Insufficient information*</td>
<td>31 (12.5)</td>
<td>34 (12.1)</td>
</tr>
</tbody>
</table>

* Total for the adjudication categories “Insufficient information to distinguish osteonecrosis from OA”, “Lack of consensus” and “Insufficient information to distinguish between rapid from normal progression”
Rapidly Progressive OA
Phase 3 OA Studies

mean (95% CI)
all tanezumab doses combined
n=67 total events

†p ≤ 0.05 vs. active comparator, #p ≤ 0.05 vs. tanezumab, comparisons to placebo (zero events) could not be made
Rapidly Progressive OA
Phase 3 OA Studies, Event Rate by Dose

Risk Difference: †p ≤ 0.05 vs. active comparator, analyses vs. placebo (zero events) could not be made
Dose Response: p=0.0124 tanezumab monotherapy, p<0.0001 tanezumab/NSAID combination therapy
Rapidly Progressive OA
Phase 3 OA Studies\(^1\) - Sensitivity Analysis

Additional adjudication outcomes analyzed as rapidly progressive OA:
- “Insufficient information to distinguish osteonecrosis from OA”
- “Lack of consensus” and
- “Insufficient information to distinguish normal vs. rapid OA progression”

Risk Difference: \( p \leq 0.05 \) vs. active comparator, analyses vs. placebo (zero events) could not be made
Dose Response: \( p=0.0164 \) tanezumab monotherapy, \( p<0.0001 \) tanezumab/NSAID combination therapy
Effect of Duration of NSAID Use
Rapidly Progressive OA – Event Rate

Mean (95% upper CI); tanezumab 2.5-10 mg combined
Non-controlled, long-term Phase 3 OA Studies 1016 & 1043
Rapidly Progressive OA

- Well recognized in orthopedic, radiology, and pathology literature by various names including:
  - Rapidly destructive OA, rapidly destructive arthrosis, or destructive arthropathy
  - Initially described in 1957 (Forestier)
  - Over 100 publications since 1970

- Predominantly occurs in the hip; less commonly in the knee or shoulder
  - Occurs in up to one-sixth of patients with hip OA

- Severe progressive joint destruction with focal joint space narrowing and extensive subchondral bone loss in femoral head, acetabulum or both

Lequesne. La Presse Med 1970; 78:1425-26
Rapidly Progressive OA
Example from Literature

Bilateral rapidly destructive arthrosis of the hip joint resulting from subchondral fracture with superimposed secondary osteonecrosis

Takuaki Yamamoto · Robert Schneider · Yukihide Iwamoto · Peter G. Bullough

• 57-year old woman
• 14-month history of bilateral hip pain
• Rapid hip destruction over 10 months
• Progressive severe pain both hips
• Bilateral total hip replacement
Rapidly Progressive OA
Pre-existing Event from Tanezumab Clinical Program

- 63-year old woman
- KL Grade 4 OA right hip at baseline
- 5-year history of generalized OA

- Increased right hip pain 7 months post-baseline
- Right hip total joint replacement
Rapidly Progressive OA
Characterization

- Evidence of OA in the affected joint prior to study = 61 patients (90%)
  - Including patient with CLBP
Rapidly Progressive OA Characterization

- Evidence of OA in the affected joint prior to study = 61 patients (90%)
  - Including patient with CLBP

- A majority of patients had rapidly progressive OA in the hip - 56%
  - 21% patients in the overall study population with hip as the index joint
Rapidly Progressive OA Characterization

- Evidence of OA in the affected joint prior to study = 61 patients (90%)
  - Including patient with CLBP

- A majority of patients had rapidly progressive OA in the hip - 56%
  - 21% patients in the overall study population with hip as the index joint

- Fewer patients with rapidly progressive OA in joints that were KL Grade 2 vs. the overall study population
  - 9% vs. 41%

![Graph showing percent of patients with rapid OA progression by KL grade](image-url)
Rapidly Progressive OA & anti-NGF mAbs
Considerations of Mechanism – Clinical Observations

- No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population
No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population

A direct link of greater pain relief to rapidly progressive OA could not be established
No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population.

A direct link of greater pain relief to rapidly progressive OA could not be established.

However, the findings do not exclude that pain relief may contribute or accelerate further damage in a susceptible joint:
  - Greater subchondral bone pathology, and/or susceptibility for subchondral insufficiency fractures or atrophic OA.
Rapidly Progressive OA & anti-NGF mAbs
Considerations of Mechanism – Clinical Observations

- No patients with loss of protective sensation; neurologic characteristics did not differ from the overall treated population

- A direct link of greater pain relief to rapidly progressive OA could not be established

- However, the findings do not exclude that pain relief may contribute or accelerate further damage in a susceptible joint
  - Greater subchondral bone pathology, and/or susceptibility for subchondral insufficiency fractures or atrophic OA

- There was no evidence that greater pain relief accounted for the greater risk of rapidly progressive OA with tanezumab/NSAID combination therapy
Summary of Adjudication Results

- Adjudication confirmed 2 patients with primary osteonecrosis

- Rapidly progressive OA
  - Observed in OA patients (and joints with moderate to severe OA)
  - Dose-related increase with tanezumab monotherapy over active comparator
  - Rate further increased >3-fold with tanezumab/NSAID combination therapy
  - NSAID use up to 90 days did not appear to elevate risk
  - Some events were pre-existing
Presentation Outline

- **Efficacy**
  - Osteoarthritis
  - Chronic Low Back Pain
  - Other Chronic Pain Conditions

- **Joint-Related Safety**
  - Total Joint Replacements and Events Reported as Osteonecrosis
  - Adjudication Outcomes

- **Risk minimization to reduce the risk of rapidly progressive OA in future studies**
The risk of rapidly progressive OA increases with chronic concomitant NSAID use

In OA, tanezumab 10 mg did not provide additional benefit over tanezumab 5 mg

Preliminary review of the data suggest most patients who respond to tanezumab do so after 1-2 doses

Expert review of baseline radiographs indicate that some patients had rapidly progressive OA at study entry

This evidence was used to define the risk minimization plan
### Application of Risk Minimization Measures

**Rapidly Progressive OA – Phase 3 OA Studies**

<table>
<thead>
<tr>
<th>N=66 patients</th>
<th>Patients with Rapidly Progressive OA Impacted by the Risk Minimization Measure (n)</th>
<th>Cumulative Reduction in Rapidly Progressive OA events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding chronic concomitant NSAID use with anti-NGF therapy</td>
<td>47 patients; 71% reduction</td>
<td>![Graph showing 71% reduction]</td>
</tr>
<tr>
<td>Careful selection of anti-NGF doses for further clinical investigation - Discontinue further study of tanezumab 10 mg in OA</td>
<td>12 patients; 89% reduction</td>
<td>![Graph showing 89% reduction]</td>
</tr>
<tr>
<td>Discontinuing patients who do not respond adequately to initial dose(s) of anti-NGF therapy</td>
<td>3 patients; 94% reduction</td>
<td>![Graph showing 94% reduction]</td>
</tr>
<tr>
<td>Excluding patients with pre-existing rapidly progressive OA from study participation</td>
<td>1 patient; 95% reduction</td>
<td>![Graph showing 95% reduction]</td>
</tr>
</tbody>
</table>
Application of Risk Minimization Measures
Rapidly Progressive OA – Phase 3 OA Studies

Rapidly Progressive OA: Observed Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent (n) of Patients</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanezumab overall (N=6701)</td>
<td>1.0% (66)</td>
<td>110</td>
</tr>
<tr>
<td>Tanezumab 2.5–10 mg monotherapy (N=4273)</td>
<td>0.4% (19)</td>
<td>273</td>
</tr>
<tr>
<td>Tanezumab + NSAID 2.5–10 mg (N=3028)</td>
<td>1.6% (47)</td>
<td>68</td>
</tr>
<tr>
<td>Active comparator (N=1266)</td>
<td>0.1% (1)</td>
<td></td>
</tr>
</tbody>
</table>

Rapidly Progressive OA: Results with Risk Minimization Measures

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent (n) of Patients</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanezumab 2.5–10 mg monotherapy (N=4273)</td>
<td>0.2% (3)</td>
<td>2447 **</td>
</tr>
<tr>
<td>Tanezumab 2.5-5 mg (N=1578)</td>
<td>0.0% (0)</td>
<td>956</td>
</tr>
<tr>
<td>Tanezumab 2.5 mg (N=396)</td>
<td>0.3% (3)</td>
<td></td>
</tr>
<tr>
<td>Tanezumab 5 mg (N=1182)</td>
<td>0.2% (1)</td>
<td></td>
</tr>
<tr>
<td>Active comparator (N=670)</td>
<td>0.2% (1)</td>
<td></td>
</tr>
</tbody>
</table>

** Indicates that a negative number is needed to harm, lower risk with tanezumab than active comparator.

NNH = Number of patients treated with tanezumab instead of active comparator to observe 1 additional event.
Application of Risk Minimization Measures
Composite Endpoint – Phase 3 OA Studies

1 Includes all-cause total joint replacement, adjudicated osteonecrosis or RPOA and 10 patients with subchondral insufficiency fracture
**Indicates that a negative number is needed to harm, lower risk with tanezumab than active comparator

NNH = Number of patients treated with tanezumab instead of active comparator to observe 1 additional event

Composite Endpoint:\nObserved Results

- tanezumab overall (N=6701): 1.1% (76)
- tanezumab 2.5–10 mg monotherapy (N=4273): 0.5% (23)
- tanezumab + NSAID 2.5–10 mg (N=3028): 1.8% (53)
- active comparator (N=1266): 0.2% (2)

Composite Endpoint:\nResults with Risk Minimization Measures

- tanezumab 2.5–10 mg (N=396): 0.3% (4)
- tanezumab 2.5–10 mg monotherapy (N=3028): 0% (0)
- tanezumab 2.5 mg (N=1578): 0.3% (4)
- tanezumab 5 mg (N=1182): 0.3% (2)
- active comparator (N=670): 0.3% (2)

Percent (n) of Patients

percent (95% CI)

NNH=102  NNH=263  NNH=63

**  **  NNH=2506
Conclusions

- Relieves pain and improves function to a clinically meaningful extent across chronic pain conditions; superior to active comparator treatment

- Tanezumab monotherapy does not elevate the risk of all-cause total joint replacements – in contrast to when administered with NSAIDs

- Adjudication of total joint replacements showed:
  - Tanezumab does not elevate the risk of osteonecrosis
  - Associated with a dose-related increase in rapidly progressive OA
    - Further increased >3-fold when administered with NSAIDs

- Risk minimization should reduce the risk of rapidly progressive OA in future studies
All-Cause Total Joint Replacements
Controlled Phase 3 OA Studies\(^1\): Event Rate by Dose

![Bar chart showing event rates by dose and treatment group.](chart.png)

**Legend:**
- Placebo (N=1029)
- Tanezumab 2.5 mg (N=401)
- Tanezumab 5 mg (N=1581)
- Tanezumab 10 mg (N=1684)
- Tanezumab 2.5 mg + NSAID (N=157)
- Tanezumab 5 mg + NSAID (N=686)
- Tanezumab 10 mg + NSAID (N=687)
- Active comparator (N=1266)\(^3\)

**Mean (95% CI):**
- Placebo: 32 events/1000 pt-yr
- Tanezumab 2.5 mg: 38 events/1000 pt-yr
- Tanezumab 5 mg: 37 events/1000 pt-yr
- Tanezumab 10 mg: 30 events/1000 pt-yr
- Tanezumab 2.5 mg + NSAID: 35 events/1000 pt-yr
- Tanezumab 5 mg + NSAID: 86 events/1000 pt-yr
- Tanezumab 10 mg + NSAID: 95 events/1000 pt-yr
- Active comparator: 42 events/1000 pt-yr

**Risk Difference:**
- \(*p \leq 0.05\) vs. placebo
- \(†p \leq 0.05\) vs. active comparator

**Dose Response:**
- \(p=0.655\) for tanezumab monotherapy
- \(p=0.0004\) for tanezumab/NSAID combination therapy

\(^1\) Includes Studies 1011, 1014, 1015, 1017, 1025, 1026, 1027, & 1030

\(^2\) Includes all reported osteonecrosis adverse events with or without total joint replacement

\(^3\) Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID

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B 19
All-Cause Total Joint Replacements
Phase 3 OA Study 1025, Event Rate by Treatment

- NSAIDs = naproxen 500 mg BID, celecoxib 100 mg BID
- Includes all reported osteonecrosis adverse events with or without total joint replacement
- Risk difference: *p≤0.05 vs. tanezumab 5 or 10 mg, †p≤0.05 vs. NSAID

1 NSAIDs (N=539; 416 pt-yrs)
2 Includes all reported osteonecrosis adverse events with or without total joint replacement

n=150 total events

Mean (95% CI)

- tanezumab 5 mg (N=541; 426 pt-yrs)
- tanezumab 10 mg (N=542; 415 pt-yrs)
- tanezumab 5 mg + NSAID (N=536; 423 pt-yrs)
- tanezumab 10 mg + NSAID (N=542; 416 pt-yrs)
- NSAIDs (N=539; 416 pt-yrs)
# Adjudicated vs. Non-Adjudicated Patients

<table>
<thead>
<tr>
<th>Treatment Assignments</th>
<th>Adjudicated Patients</th>
<th>Non-Adjudicated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>4 (1.6)</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>tanezumab (2.5 – 10 mg)</td>
<td>161 (64.7)</td>
<td>94 (68.6)</td>
</tr>
<tr>
<td>tanezumab (2.5 - 10 mg) + NSAID</td>
<td>65 (26.1)</td>
<td>28 (20.4)</td>
</tr>
<tr>
<td>active comparator</td>
<td>19 (7.6)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>tanezumab treatment duration</td>
<td>4 / 4.7</td>
<td>5 / 4.6</td>
</tr>
<tr>
<td>median / mean (no. of injections)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Time to reported osteonecrosis or total joint replacement (days)

<table>
<thead>
<tr>
<th>From 1st administration of study medication (median / mean)</th>
<th>286 / 297.4</th>
<th>291 / 286.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>From last administration of study medication (median / mean)</td>
<td>83 / 87.4</td>
<td>76 / 77.9</td>
</tr>
</tbody>
</table>
Rapidly Progressive OA
Incidence by Number of Doses – Phase 3 OA Studies\(^1\)

- **tanezumab monotherapy (N=4273)**
- **tanezumab + NSAID (N=3028)**\(^2\)
- **active comparator (N=1266)**\(^3\)

Percent (95% CI)  
N=67 total events

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>tanezumab + NSAID</th>
<th>Active Comparator</th>
<th>Tanezumab Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dose</td>
<td>0.3 (3)</td>
<td>0.7 (2)</td>
<td>0.3 (3)</td>
</tr>
<tr>
<td>2 Doses</td>
<td>1.5 (8)</td>
<td>0.3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3 Doses</td>
<td>1.3 (10)</td>
<td>1.3 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4 Doses</td>
<td>2.1 (9)</td>
<td>0 (0)</td>
<td>0.2 (1)</td>
</tr>
<tr>
<td>5 Doses</td>
<td>1.8 (8)</td>
<td>1.0 (5)</td>
<td>1.0 (5)</td>
</tr>
<tr>
<td>≥6 Doses</td>
<td>1.9 (10)</td>
<td>0.5 (4)</td>
<td>0.5 (4)</td>
</tr>
</tbody>
</table>

\(^1\) Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030 & 1043. The placebo treatment group is not shown.

\(^2\) Patients receiving concomitant NSAID treatment with tanezumab in long-term studies are included in the tanezumab + NSAID treatment groups.

\(^3\) Active comparator = naproxen 500 mg BID, celecoxib 100 mg BID, diclofenac SR 75 mg BID or oxycodone CR 10-40 mg BID.
Distribution of Hip JSW Changes
Tanezumab 1025 Study

Hip cohort = 458
Analyzed = 331
KL2 = 142 (42.9%), KL3 = 113 (34.1%), KL4 = 75 (22.7%)
Mean (SD) Baseline JSW = 2.42 (1.46) mm
Mean (SD) JSW Change = -0.12 (0.55) mm
Median exposure = 337 days
Patients with Hip JSW Change Exceeding the Experimental Measurement Threshold

Tanezumab Study 1025

Hip cohort = 458
Analyzed = 331
KL2 = 142 (42.9%), KL3 = 113 (34.1%), KL4 = 75 (22.7%)
Mean (SD) Baseline JSW = 2.42 (1.46) mm
Mean (SD) JSW Change = -0.12 (0.55) mm
Median exposure = 337 days

<table>
<thead>
<tr>
<th>N</th>
<th>Mean Change</th>
<th>SD Change</th>
<th>1.96 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>331</td>
<td>-0.12 mm</td>
<td>0.55 mm</td>
<td>1.08 mm</td>
</tr>
</tbody>
</table>

Threshold above which a change in JSW can be considered relevant based on the evaluation of the measurement error; Ornetti et al. OARSI-OMERACT Definition of Relevant Radiological Progression in Hip/Knee Osteoarthritis. Osteoarthritis and Cartilage. 2009; 17:856-863. Bland-Altman technique was used.
## Patients with Hip JSW Change Exceeding Experimental Measurement Threshold

<table>
<thead>
<tr>
<th></th>
<th>tanezumab 5 mg (N = 92)</th>
<th>tanezumab 10 mg (N = 93)</th>
<th>tanezumab + NSAID 5 mg (N = 446)</th>
<th>tanezumab + NSAID 10 mg (N = 452)</th>
<th>NSAID (N = 446)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients Analyzed, N</strong></td>
<td>69</td>
<td>67</td>
<td>65</td>
<td>59</td>
<td>71</td>
</tr>
<tr>
<td><strong>Patients with JSN ( \geq -1.08 ) mm n (%)</strong></td>
<td>2 (2.9%)</td>
<td>5 (7.5%)</td>
<td>6 (9.2%)</td>
<td>3 (5.1%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td><strong>Risk Difference vs NSAID [95% CI]</strong></td>
<td>0.1% [-13.0, 17.2]</td>
<td>4.7% [-8.7, 21.6]</td>
<td>6.4% [-7.5, 24.0]</td>
<td>2.3% [-11.4, 20.3]</td>
<td>-</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>1.00</td>
<td>0.51</td>
<td>0.41</td>
<td>0.77</td>
<td>-</td>
</tr>
</tbody>
</table>

### Notes

1. Threshold above which a change in JSW can be considered relevant based on the evaluation of the measurement error; Ornetti et al. OARSI-OMERACT Definition of Relevant Radiological Progression in Hip/Knee Osteoarthritis. Osteoarthritis and Cartilage. 2009; 17:856-863. Bland-Altman technique was used.

### Table: Mean Change and Standard Deviation

<table>
<thead>
<tr>
<th>N</th>
<th>Mean Change</th>
<th>SD Change</th>
<th>1.96 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>331</td>
<td>-0.12 mm</td>
<td>0.55 mm</td>
<td>1.08 mm</td>
</tr>
</tbody>
</table>
Distribution of Hip JSW Changes
Tanezumab Study 1025

Percent of Patients

<table>
<thead>
<tr>
<th>Distribution</th>
<th>N (Patients)</th>
<th>Mean Change (mm)</th>
<th>SD Change (mm)</th>
<th>1.96 SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tanezumab 5 mg</td>
<td>331</td>
<td>-0.12</td>
<td>0.55</td>
<td>1.08</td>
</tr>
<tr>
<td>tanezumab 10 mg</td>
<td>350</td>
<td>-0.12</td>
<td>0.55</td>
<td>1.08</td>
</tr>
<tr>
<td>tanezumab 5 mg + NSAID</td>
<td>347</td>
<td>-0.12</td>
<td>0.55</td>
<td>1.08</td>
</tr>
<tr>
<td>tanezumab 10 mg + NSAID</td>
<td>370</td>
<td>-0.12</td>
<td>0.55</td>
<td>1.08</td>
</tr>
<tr>
<td>NSAID</td>
<td>369</td>
<td>-0.12</td>
<td>0.55</td>
<td>1.08</td>
</tr>
</tbody>
</table>
Distribution of Hip JSW Changes
Dougados et al. Echodiah Study

N = 463
0-1 yr = 423; 0-2 yr = 378
KL 2 = 284 (61.3%), KL 3 = 164 (35.4%), KL 4 = 2 (0.4%)
Mean (SD) Baseline JSW = 2.22 (0.76) mm
Mean (SD) JSW Change = -0.49 (0.67) mm
Mean (SD) JSW Change, 1 yr = -0.33 (0.55) mm

*Rate of change between the first and last available radiograph during the two-year study period.
Dougados et al. Radiographic features predictive of radiographic progression of hip osteoarthritis.
# Change in Hip Joint Space Width
## Tanezumab Study 1025

<table>
<thead>
<tr>
<th>Patients Analyzed, n (%)</th>
<th>5 mg N = 92</th>
<th>10 mg N = 93</th>
<th>5 mg N = 90</th>
<th>10 mg N = 90</th>
<th>NSAID N = 93</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69 (75.0)</td>
<td>67 (72.0)</td>
<td>65 (72.2)</td>
<td>59 (65.6)</td>
<td>71 (76.3)</td>
</tr>
<tr>
<td>Baseline Mean (SD) JSW(mm)</td>
<td>2.45 (1.36)</td>
<td>2.37 (1.43)</td>
<td>2.35 (1.42)</td>
<td>2.20 (1.56)</td>
<td>2.72 (1.53)</td>
</tr>
<tr>
<td>Mean (SE) JSW Change (mm)</td>
<td>-0.08 (0.07)</td>
<td>-0.14 (0.07)</td>
<td>-0.24 (0.07)</td>
<td>-0.14 (0.07)</td>
<td>-0.02 (0.07)</td>
</tr>
<tr>
<td>Comparison vs NSAID Mean JSW Change [95% CI]</td>
<td>-0.06 [-0.24, 0.13]</td>
<td>-0.12 [-0.30, 0.07]</td>
<td>-0.22 [-0.40, -0.03]</td>
<td>-0.12 [-0.31, 0.07]</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.54</td>
<td>0.20</td>
<td>0.02</td>
<td>0.21</td>
<td>-</td>
</tr>
</tbody>
</table>
WOMAC Pain
Tanezumab Provides Consistent Pain Relief vs. Placebo

Effect size (95% CI); LS mean difference/SD of difference vs. placebo at Week 16; WOMAC Pain Subscale (0-10 NRS)

1Studies 1011, 1014, 1015, and 1018 combined; ITT, BOCF; naproxen dose = 500 mg BID
WOMAC Pain: Long-Term Efficacy
Double-Blind Parent Study → Study 1016 (5 mg)

Baseline scores
placebo = 7.2
tanezumab 5 mg = 7.2
naproxen = 7.1

Mean Change from Baseline

placebo/tanezumab 5 mg (N=182)
tanezumab 5 mg/tanezumab 5 mg (N=556)
naproxen/tanezumab 5 mg (N=93)
## Sensory Examinations in Lower Extremities for RPOA vs Non-RPOA: Phase 3 Controlled and Long-term OA Studies* (Combined Doses)

<table>
<thead>
<tr>
<th></th>
<th>All Tanezumab Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With RPOA</td>
</tr>
<tr>
<td></td>
<td>N=66</td>
</tr>
<tr>
<td><strong>NIS Sensory Score in Great Toes</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>0.24</td>
</tr>
<tr>
<td>p-value for Baseline means</td>
<td>0.530</td>
</tr>
<tr>
<td>LS Mean Change from Baseline</td>
<td>-0.02</td>
</tr>
<tr>
<td>LS Mean Difference (SE)</td>
<td>0.07 (0.11)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.522</td>
</tr>
</tbody>
</table>

RPOA= rapidly progressive osteoarthritis

*Studies 1011, 1014, 1015, 1016, 1017, 1018, 1025, 1026, 1027, 1030, & 1043;  
**NIS= Neuropathy Impairment Score; Patient score can range from 0 (normal sensory exam) to 12 (absent joint position, vibration and pinprick in both great toes).
For patients with a joint safety adjudication and a neurological consultation, (N=54) an expert external neurologist reviewed patients’ neurological consultation data.

- Neurological consultations were reviewed without knowledge of study treatment assignment or adjudication outcome.
- Neurologist provided a diagnosis for each case where possible.
# Neurological Diagnoses in Patients with both Joint Safety Adjudication and Neurological Consult

249 Patients with Joint Safety Adjudication

195 (78%) - Adjudication but No Neurological Consultation Required

54 (22%) - Both Adjudication and Neurological Consultation

<table>
<thead>
<tr>
<th>Adjudication Outcomes</th>
<th>Neurological Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Osteonecrosis n= 1</td>
<td>1</td>
</tr>
<tr>
<td>Rapidly Progressive Osteoarthritis n=17</td>
<td>7</td>
</tr>
<tr>
<td>Osteoarthritis – Normal Progression n=25</td>
<td>13</td>
</tr>
<tr>
<td>All Other Adjudication Outcomes n=11</td>
<td>4</td>
</tr>
<tr>
<td>Total N=54</td>
<td>25</td>
</tr>
</tbody>
</table>

Only one RPOA or ON patient had polyneuropathy and carpal tunnel reported by nerve conduction study
# Meta-Analysis – All-Cause Total Joint Replacements
Tanezumab 5 mg vs. Placebo

<table>
<thead>
<tr>
<th>Study (weight)</th>
<th>Number of Patients with Event [Treatment Group N/Treatment Exposure (pt-yrs)]</th>
<th>OR (95% CI) (^2) Eliminating Studies with 0 events</th>
<th>OR (95% CI) (^2) With Correction for Studies with 0 events (^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comparison Group 1 Tanezumab 5 mg</td>
<td>Comparison Group 2 Placebo</td>
<td></td>
</tr>
<tr>
<td>1011 (32.7)</td>
<td>1 [172/70]</td>
<td>0 [172/61]</td>
<td>7.4 [0.2, 372.4]</td>
</tr>
<tr>
<td>1014 (27.2)</td>
<td>2 [154/64]</td>
<td>3 [155/48]</td>
<td>0.7 [0.1, 3.9]</td>
</tr>
<tr>
<td>1015 (29.2)</td>
<td>1 [206/62]</td>
<td>2 [208/55]</td>
<td>0.5 [0.05, 5.0]</td>
</tr>
<tr>
<td>1018 (29.0)</td>
<td>0 [211/64]</td>
<td>2 [209/53]</td>
<td>0.1 [0.01, 2.1]</td>
</tr>
<tr>
<td>1026 (14.9)</td>
<td>0 [73/29]</td>
<td>0 [72/30]</td>
<td>NA</td>
</tr>
<tr>
<td>1027 (10.2)</td>
<td>0 [63/19]</td>
<td>2 [72/22]</td>
<td>0.2 [0.01, 2.5]</td>
</tr>
<tr>
<td>1030 (23.7)</td>
<td>1 [161/52]</td>
<td>1 [141/44]</td>
<td>0.9 [0.05, 14.1]</td>
</tr>
<tr>
<td>Combined Studies</td>
<td>-</td>
<td>-</td>
<td>0.7 [0.2, 2.5]</td>
</tr>
</tbody>
</table>

1 Study weight is calculated as \(1/\text{[Comparison Group 1 exposure]} + 1/\text{[Comparison Group 2 exposure]}\)\(^1\)  
2 Odds ratios and 95% confidence intervals calculated using the Peto odds ratio method.  
3 Correction for studies with 0 events is the addition of \(n_i/N\) in each group so that 1 patient in total is added and the OR is 1.0 for that study.  
(ITT, All Placebo-Controlled Studies)
Perspectives on Chronic Pain: Current Status and Needs

Thomas J. Schnitzer, MD, PhD
Professor
Departments of Physical Medicine and Rehabilitation and Internal Medicine/Rheumatology
Discussion Outline

- Chronic Pain is prevalent
- Chronic Pain is impactful
- Chronic Pain management paradigms fail many patients
- New therapeutics not available despite serious efforts
- NGF inhibition has shown promise and also raised concerns
Prevalence of Chronic Pain

• 2011 IOM report of the Committee on Advancing Pain Research, Care and Education
• “at least 116 million Americans burdened with chronic pain”
• Most common clinical presentations of chronic pain
  - Musculoskeletal pain\(^1\)
    • Low back pain 28% of adults
    • Osteoarthritis 26% of adults
  - Chronic headache/migraine
  - Neuropathic pain
  - Visceral pain
  - Central pain

\(^1\)CDC and NCHS, 2010
Impact of Chronic Pain

What is pain?

It is so much more than just pain intensity. Over time, many [patients] find the effects of living with chronic pain impact their ability to work, engage in recreational and social activities, and for some, [perform] the most basic everyday activities that people just take for granted. Not surprisingly, pain begins to chip away at their mood, often leaving them angry, frustrated, anxious, and/or depressed. Our families suffer along with us, and many relationships are forever altered.

--An advocate for people with chronic pain

Consequences of pain

- Poor health-related quality of life & poor self-rated health
- Strong link with disability
- Likely to seek medical attention

IOM, 2011: Relieving Pain in America
Impact of Chronic Pain
Quality of Life

Effect of chronic nonmalignant pain on QOL, as indicated by SF-36 subscores, mean (SD) (n=150).\textsuperscript{1,2}

* = population norm values; PF=physical functioning; RP=role-physical; BP=bodily pain; GH=general health; VT=vitality; SF=social functioning; RE=role-emotional; MH=mental health. * p<0.001

Activities/Quality of Life Domains Impaired by Increasing Pain Severity

<table>
<thead>
<tr>
<th>Enjoy</th>
<th>Work</th>
<th>Sleep</th>
<th>Active</th>
<th>Mood</th>
<th>Walk</th>
<th>Relate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>Sleep</td>
<td>Active</td>
<td>Mood</td>
<td>Work</td>
<td>Enjoy</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Mood</td>
<td>Mood</td>
<td>Mood</td>
<td>Work</td>
<td>Enjoy</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Work</td>
<td>Work</td>
<td>Work</td>
<td>Work</td>
<td>Enjoy</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>Enjoy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Boldface indicates an additional dimension that is impaired at the given level of pain.

\textsuperscript{1} Katz N, J Pain Symp Mgmt 2002;24:S38-47. \textsuperscript{2} Becker N et al, Pain 1997; 73: 393-400
\textsuperscript{3} Cleland CS and Ryan KM, Ann Acad Med 1994; 23: 129-138
Impact of Chronic Pain Disability

Extent of Pain-Related Disability among Adults with Pain in the Last 3 months, United States, 2009

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Difficulty with Basic Activities (%)</th>
<th>Activity Limitations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low back pain</td>
<td>51.6</td>
<td>55</td>
</tr>
<tr>
<td>Neck pain</td>
<td>30.2</td>
<td>34.4</td>
</tr>
<tr>
<td>Back pain</td>
<td>37.3</td>
<td>38.6</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>17.7</td>
<td>21.4</td>
</tr>
<tr>
<td>Hip pain</td>
<td>15</td>
<td>28.4</td>
</tr>
<tr>
<td>Severe headache/migraine</td>
<td>31</td>
<td>33.5</td>
</tr>
</tbody>
</table>

Defined as having difficulties in one or more of the following areas: movement, emotional, seeing, hearing or cognition

Defined as having limitations in one or more of the following areas: self-care, social, work

Source: CDC and NCHS, 2010

All cause mortality in OA Patients with and without disability

---

IOM, 2011: Relieving Pain in America; Nuesch E et al. BMJ 2011; 342d1165
Impact of Chronic Pain
Economic Burden

• Annual Cost of Chronic Pain in the United States\(^1\)
  • $560-635 billion annually
    - $261-300 billion in health care costs
    - $297-336 billion in lost productivity

• Expenditures
  • Medicare: $65.3 billion or 14% of all Medicare costs in 2008
  • All federal & state programs (Medicare, Medicaid, VA, etc) $99 billion in 2008 for medical expenditures for pain

\(^1\)Conservative estimate as excludes cost of pain affecting institutionalized individuals (e.g., long-term care residents, correction inmates), military personnel; excludes lost productivity of personal caregivers, workers <24 and >65 years, and emotional costs of pain.

IOM, 2011: Relieving Pain in America
Management of Chronic Pain Fails Too Often

- Significant system and organizational barriers to adequate pain care exist.
- Education is a central part of the necessary cultural transformation of the approach to pain.
- Research to translate advances into effective therapies is a continuing need.

“Academia and industry should develop novel agents for the control of pain. This does not mean simply recycling current drugs. What is required is basic and clinical science research to discover new classes of pain therapeutics and more efficient ways of developing them.”

IOM, 2011: Relieving Pain in America
Existing Pain Medications: NSAID Limitations

**Efficacy**

![Graph showing efficacy of different medications]

- Aspirin (ASA)
- Ibuprofen
- Naproxen
- Piroxicam

**Discontinuation of NSAID Use**

Proportion Remaining on NSAID over Months

- ASA EC
- Ibuprofen
- Naproxen
- Piroxicam

**NSAID Safety**

**Cardiovascular Risk**
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).
- Naproxen as NAPROSIN, EC-NAPROSIN, ANAPROX, ANAPROX DS or NAPROSYN Suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

**Gastrointestinal Risk**
- NSAIDs cause an increased risk of gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

---

3. www.accessdata.fda.gov/drugsatfda_docs/label/2008/017581s110,18164s60,18965s18,20067s17lbl.pdf
Adverse Events\textsuperscript{1,2}

- **GI:**
  - Constipation 40-95%;
  - Nausea 10-40%

- **CNS**
  - Sedation, drowsiness, cognitive impairment
  - Respiratory depression
  - Dizziness and falls
  - Addiction and dependence

- **Others:**
  - Hormonal
  - Immunologic
  - Dermatologic

---

Opioids and Fracture in Older Adults with Arthritis\textsuperscript{3}

<table>
<thead>
<tr>
<th></th>
<th>Incidence Rate/1000 pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>120 (111-130)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>25 (17-34)</td>
</tr>
</tbody>
</table>

HR = 2.6 (1.5–4.4) (Long-acting opioids)

HR = 5.1 (3.7–7.1) (Short-acting opioids)

Incidence rate highest in first 2 weeks after initiating therapy, especially for short-acting opioid group

---

Lack of Better Analgesics Not For Lack of Trying

- Multiple Targets Identified
  - NMDA receptor blockers
  - NK-1 receptor blockers
  - FAAH inhibitors
  - Na, Ca, K channel modulators
    - TrpV1, V3, V4
    - NaV1.7, NaV1.8
    - ASIC3
  - Cannabinoid receptor blockers: CB1, CB2
  - Delta opioid agonists
  - P2X3 inhibitors
  - P38 kinase

ClinicalTrials.gov

539 trials in chronic pain
8 with new molecular entity
2 NCE in musculoskeletal pain

New Target: NGF as a Mediator of Pain

• Key evidence
  - NGF causes pain in humans and animals
  - NGF is locally up-regulated in painful conditions
  - NGF inhibition reverses pain in many animal models

Monoclonal Antibodies Directed Against NGF

- 3 compounds under discussion: tanezumab, fulranumab, REGN475
  - fully human or humanized monoclonal antibodies
  - picomolar affinity for NGF
  - high selectivity for NGF over other members of the neurotrophin family
  - Inhibit NGF activity at both TrkA and p75 receptors
  - Plasma half-life: 22-25 days

- Evaluated after IV or SC routes of administration
  - 4, 8 & 12 wk dosing intervals
  - Doses examined: 3 to 1000 µg/kg (0.003 to 1 mg/kg)
Wide Range of Clinical Conditions Evaluated

<table>
<thead>
<tr>
<th>Chronic Pain Condition</th>
<th>Efficacy Demonstrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>√ √</td>
</tr>
<tr>
<td>Chronic low back pain</td>
<td>√ √</td>
</tr>
<tr>
<td>Diabetic peripheral neuropathy</td>
<td>√</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Possible</td>
</tr>
<tr>
<td>Interstitial cystitis</td>
<td>Possible</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>Possible</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Negative</td>
</tr>
<tr>
<td>Cancer pain</td>
<td>On-going</td>
</tr>
</tbody>
</table>

- Efficacy superior to an active comparator has been found repeatedly with tanezumab.

Safety Profile Being Defined

• Anti-NGF mAbs do not appear to have cardiovascular or gastrointestinal safety liabilities of NSAIDs
• Anti-NGF mAbs do not appear to have abuse liability or undesirable central effects of opioids
• New safety signal has appeared in clinical development: joint events
• Questions to be addressed:
  - What does this safety signal represent?
  - Under what conditions does this signal occur and at what frequency?
  - Is it advisable to undertake further research with these compounds to define better the benefit:risk?
Summary

- Anti-NGF antibodies first new pain treatment agents in years
  - Efficacy in wide spectrum of pain conditions
  - Magnitude of effect superior to existing agents
- Many people in pain with no effective treatments
- Further research is needed and possible
  - Carefully designed studies
  - Well defined populations
  - Informed consent
  - Risk mitigation strategies
Anti-NGF Antibody Clinical Development
Contextual Factors and Policy Implications

Nathaniel Katz, MD, MS
Analgesic Solutions, Inc.
Tufts University School of Medicine
March 12, 2012
Chronic Pain in America

- National survey of 500,000 US households
- 9% of adult U.S. population estimated to have chronic moderate-to-severe pain (17,482,410)
- 64% of these have either arthritis or back pain
- Most have had it for over 5 years
- 64% of patients with “arthritis” rate their pain as “severe” or “very severe” despite treatment

Roadblocks to Pain Relief, Roper Starch, 1998
US Annual Analgesic Use

- **Opioids:**
  - 180 million scripts/yr
  - >4 million chronic users (about 1/3 for “arthritis”)

- **NSAIDs:**
  - 90 million scripts/yr
  - 14 million chronic users

- **Adjuvants**
  - 63 million scripts/yr

- **OTC products:**
  - 430 million dose packs sold per yr

ACPM, 2011; IMS, 2005; Laine 2002; Parsells Kelly 2008
Risks of opioids

- **Patients** on long-term opioid therapy have a 0.2-1.8% risk of overdose per year.
- About 12,000 deaths in the US per year from prescription opioids (2/day in MA)
- About 5% of primary care patients prescribed hydrocodone will develop abuse or addiction
- 1.7 million prescription opioid addicts in the US
- The majority of patients on long-term opioid therapy develop clinically significant endocrinopathy

Dunn KM 2010; CDC 2011; Adams E 2006; NSDUH 2009
Risks of NSAIDs

- Thousands of deaths per year from NSAID-associated GI bleeds
- Approximately 1-2% of regular NSAID users will develop serious GI adverse events
- Over 80% have no warning
- NSAIDs double the risk of CHF admissions and increase risk of recurrent MI and death in patients with prior MI
- NSAIDs double risk of hospitalization for ARF

Cryer 2005; Wolfe 1999; Moore 2007; Schjerning Olsen 2011; Evans 1995
Can we do better?
A personal career in analgesic drug development

- NMDA antagonists
- Glycine antagonists
- Opioid-NMDA combinations
- Ultra-low-dose antagonists
- Vanilloid-receptor antagonists
- NK-1 antagonists
- N-Ca Channel Blockers
- GABA agonists
Figure 21. WOMAC Pain and Physical Function Subscales and Patient’s Global Assessment of Osteoarthritis: Change from Baseline to Week 16 in Study 1025 – Naproxen Cohort

Mean (SE) Change from Baseline

- WOMAC Pain
- WOMAC Physical Function
- Patient’s Global Assessment

Baseline scores = 6.4 6.5 6.5 6.3 6.3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WOMAC Pain</th>
<th>WOMAC Physical Function</th>
<th>Patient’s Global Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>tanezumab 5 mg (N=285)</td>
<td>-1.9 (***p ≤ 0.001)</td>
<td>-1.4 (***p ≤ 0.001)</td>
<td>0.0 (***p ≤ 0.001)</td>
</tr>
<tr>
<td>tanezumab 10 mg (N=288)</td>
<td>-2.0 (**p ≤ 0.01)</td>
<td>-2.1 (***p ≤ 0.001)</td>
<td>0.0 (***p ≤ 0.001)</td>
</tr>
<tr>
<td>tanezumab 5 mg + naproxen (N=280)</td>
<td>-1.9 (***p ≤ 0.001)</td>
<td>-2.2 (***p ≤ 0.001)</td>
<td>0.0 (***p ≤ 0.001)</td>
</tr>
<tr>
<td>tanezumab 10 mg + naproxen (N=288)</td>
<td>-2.4 (***p ≤ 0.001)</td>
<td>-2.3 (***p ≤ 0.001)</td>
<td>0.0 (***p ≤ 0.001)</td>
</tr>
<tr>
<td>naproxen (N=283)</td>
<td>-0.5 (p ≤ 0.05)</td>
<td>-0.6 (p ≤ 0.05)</td>
<td>-0.7 (**p ≤ 0.01)</td>
</tr>
</tbody>
</table>

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001 versus naproxen

Study 1025; Week 16; ITT, BOCF; naproxen dose = 500 mg BID
## Risks of tanezumab monotherapy vs. comparators (NSAIDs/opioids)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Comparators</th>
<th>Tanezumab monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE dropout (%)</td>
<td>2.8</td>
<td>7.9</td>
<td>7.0</td>
</tr>
<tr>
<td>SAE/1000 pt-yrs</td>
<td>80</td>
<td>107</td>
<td>110</td>
</tr>
<tr>
<td>All TJR/1000 pt-yrs</td>
<td>32</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>RPOA/1000 pt-yrs</td>
<td>0</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Expected RPOA after mitigation (%)</td>
<td>0</td>
<td>.2</td>
<td>.2</td>
</tr>
</tbody>
</table>
Options

- Continue with cautious development
- Study only risk-free medications
- Only accept risks for “serious diseases”
- Accept our current treatment options
- Wait for something better to come along
PrIMUM non nocere

Beneficence