Tanezumab: FDA Efficacy Review

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Outline

- Focus on “Post-2015” studies
- Uncontroverted issues
  - Two adequate and well-controlled (AWC) studies demonstrate efficacy for the tanezumab 2.5 mg subcutaneous (SQ) dose vs placebo (PBO) in patients with osteoarthritis (OA) of the hip or knee
  - One randomized, double-blind, controlled study failed to demonstrate superiority of tanezumab 2.5 mg compared to prescription (Rx) strength NSAIDs
- Controverted issues
  - Treatment effect size
  - Strengths and weaknesses of the Health Technology Assessment Report vs. the FDA review process

Focus on “Post-2015” Studies

- Preponderance of the data for the dose and route proposed for marketing
- Selection criteria most consistent with proposed indication
- All studies were completed as planned

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- Controverted issues
  - Treatment effect size
  - Strengths and weaknesses of the Health Technology Assessment Report vs. the FDA review process

Study 1056: Primary Efficacy Results

Outcome Measure	Change From Baseline to Week 16	Placebo (N=232)	Tanezumab 2.5 mg (N=231)	Tanezumab 2.5/5 mg (N=233)
WOMAC pain subscale (0-10 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-2.6 (0.23)	-3.2 (0.23) -0.6 (-1.1, -0.1) 0.013	-3.4 (0.22) -0.7 (-1.2, -0.3) 0.002
WOMAC function subscale (0-10 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-2.6 (0.22)	-3.2 (0.22) -0.7 (-1.1, -0.2) 0.007	-3.5 (0.22) -0.9 (-1.4, -0.1) <0.001
Patient Global Assessment (1-5 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-0.65 (0.08)	-0.87 (0.08) -0.22 (-0.4, -0.1) 0.011	-0.90 (0.08) -0.25 (-0.4, -0.1) 0.004

Source: Generated by the statistical team based on BLA 761130 CSR 1056 Table 29 p.121
Abbreviations: CI, confidence interval; LS, least square; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PBO, placebo

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Source: Generated by the statistical team based on BLA 761130 CSR 1056, Table 29, p.121
Abbreviations: CI, confidence interval; LS, least square; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PBO, placebo

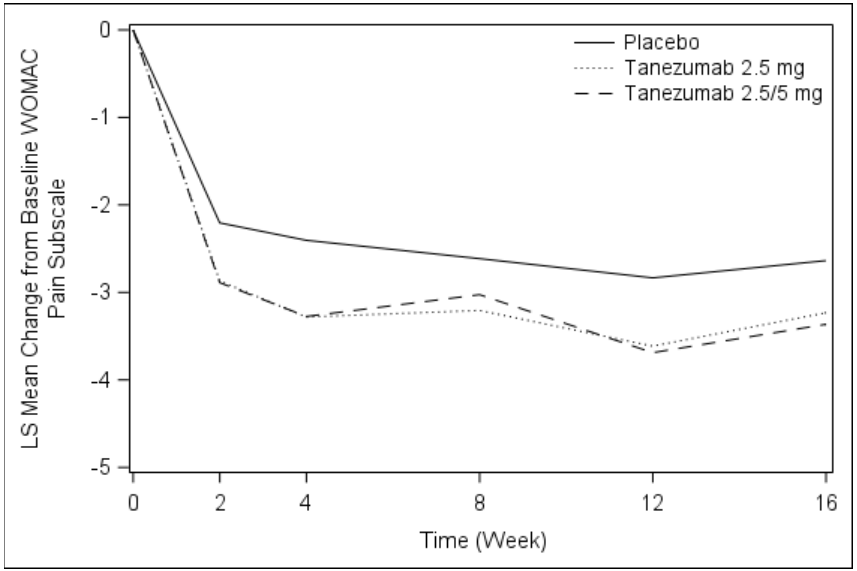
Study 1057: Primary Efficacy Results

Outcome Measure	Change From Baseline to Week 24	Placebo (N=282)	Tanezumab 2.5 mg (N=283)	Tanezumab 5 mg (N=284)
WOMAC pain subscale (0-10 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-2.2 (0.17)	-2.7 (0.17) -0.5 (-0.8, -0.1) 0.009	-2.9 (0.17) -0.6 (-1.0, -0.3) <0.001
WOMAC function subscale (0-10 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-2.1 (0.17)	-2.7 (0.17) -0.6 (-0.9, -0.2) <0.001	-2.8 (0.17) -0.7 (-1.1, -0.4) <0.001
Patient Global Assessment (1-5 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-0.72 (0.06)	-0.82 (0.06) -0.11 (-0.24, +0.02) 0.11	-0.90 (0.06) -0.19 (-0.32, -0.06) 0.005

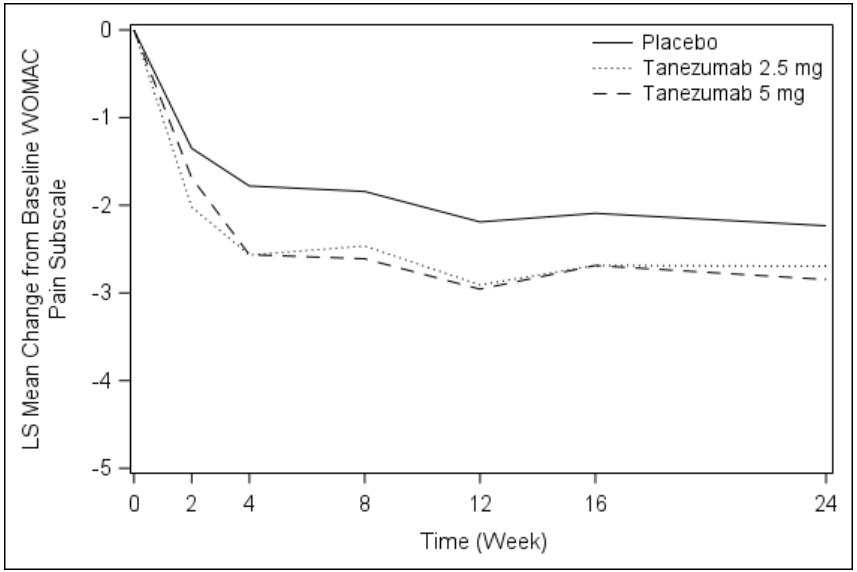
Source: Generated by the statistical team based on BLA 761130 CSR 1057, table 28, p. 128
Abbreviations: CI, confidence interval; LS, least square; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PBO, placebo

Plot of Change From Baseline for WOMAC Pain

Study 1056



Study 1057



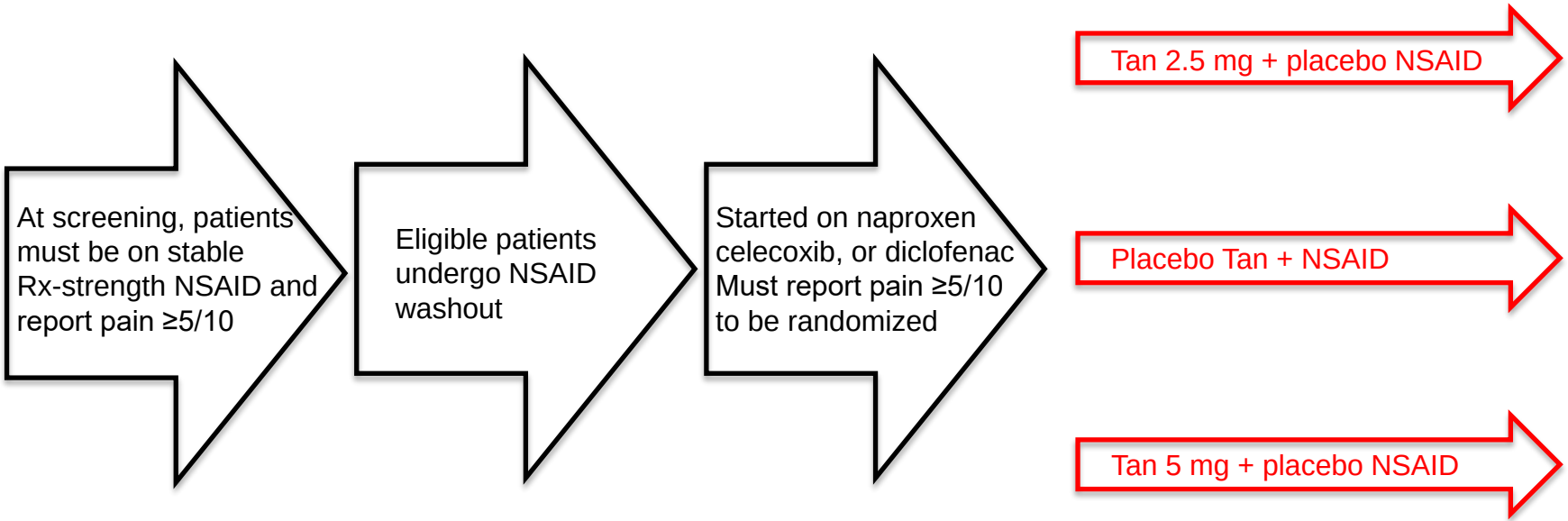
Source: Generated by the statistical team based on BLA 761130 CSR 1056 Figure 3, page 123 and CSR 1057 Figure 4, page 131
Abbreviations: LS, least square; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Study 1058: Primary Efficacy Results

Outcome Measure	Change From Baseline to Week 16	NSAIDs (N=996)	Tanezumab 2.5 mg (N=1002)	Tanezumab 5 mg (N=998)
WOMAC pain subscale (0-10 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-3.1 (0.11)	-3.3 (0.11) -0.2 (-0.4, +0.1) 0.16	-3.3 (0.11) -0.3 (-0.5, -0.1) 0.015
WOMAC function subscale (0-10 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-3.1 (0.11)	-3.3 (0.11) -0.2 (-0.4, +0.2) 0.07	-3.4 (0.11) -0.3 (-0.5, -0.1) 0.003
Patient Global Assessment (1-5 scale)	LS mean (SE) Difference from PBO 95% CI on difference p-value	-0.94 (0.04)	-0.96 (0.04) -0.02 (-0.1, +0.1) 0.63	-0.97 (0.04) -0.19 (-0.1, +0.04) 0.34

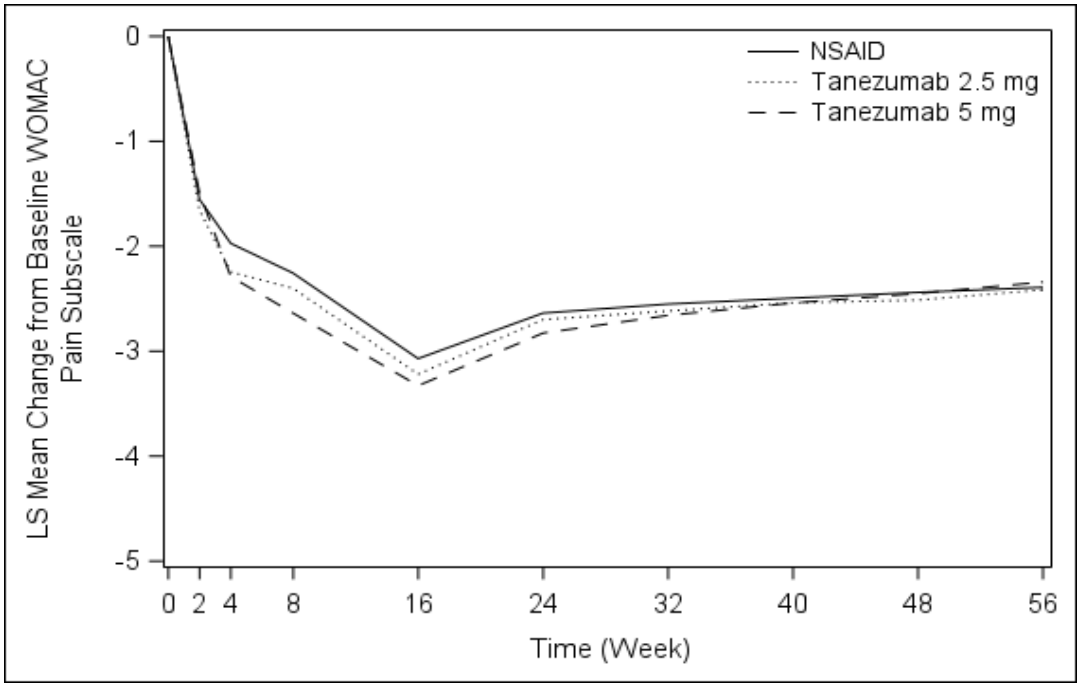
Source: Generated by the statistical team based on BLA 761130 CSR 1058, Table 25, p.138
Abbreviations: CI, confidence interval; LS, least square; NSAIDs, nonsteroidal anti-inflammatory drugs; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PBO, placebo

Study 1058: NSAID Dosing



Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; Rx, prescription; Tan, tanezumab

Study 1058: Plot of Change From Baseline WOMAC Pain to Week 56



Source: Generated by the statistical team based on BLA 761130 CSR 1058 figure 14.2.1.1.3 page 375
Abbreviations: LS, least square; NSAID, nonsteroidal anti-inflammatory drug; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

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  - One randomized, double-blind, controlled study failed to demonstrate superiority of tanezumab 2.5 mg SQ compared to Rx strength NSAIDs
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Treatment Effect Size of Approved OA Products

Product	Drug Class	Active	Placebo	Difference
Tanezumab 1056	α-NGF	-3.23	-2.64	0.59 (0-10 scale)
Tanezumab 1057	α-NGF	-2.70	-2.24	0.46 (0-10 scale)
Tanezumab 1058**	α-NGF	-3.22	-3.07	0.15 (0-10 scale)
Zilretta	Intra-articular steroid	-3.12	-2.14	0.98 (0-10 scale)
Vivlodex	Meloxicam capsules	-34 to -36	-25.68	8-10 (100-point scale)
Zorvolex	Diclofenac capsules	-42 to -47	-33.9	11.6 (100-point scale)
Pennsaid*	Topical diclofenac	-4.5	-3.6	0.9 (0-10 scale)

Source: Tanezumab CSRs, package inserts, FDA reviews available publicly
4-week study
**NSAID -controlled
Abbreviations: OA. Osteoarthritis; NGF, nerve growth factor; NSAID, nonsteroidal anti-inflammatory drug

Health Technology Assessment (HTA) Report

- The Center for Treatment Comparisons and Integrative Analysis at Tufts Medical Center prepared an HTA to assess the short and long term efficacy and safety of tanezumab for knee and hip OA compared to opioids and NSAIDs.
- 95 randomized controlled studies (RCT) were included in the review: 72 RCTs for NSAIDs, 18 for opioids and 5 for tanezumab (studies 1056, 1057, 1058 and the pre-2015 studies 1011 and 1014)

- Conclusions:
  - Tanezumab, NSAIDs, and opioids result in small to moderate improvements in pain and function in the short-term in patients with moderate to severe OA
  - Drug-specific adverse events can lead to withdrawal from treatment in some patients and can include cardiovascular (CV) or gastrointestinal (GI) effects with NSAIDs
  - Long-term use of tanezumab resulted in moderate improvements in pain and function and demonstrated a safety profile comparable to NSAIDs and opioids

Comparison of Tufts HTA and FDA Review

Parameter	Tufts	FDA
Methodology	Current meta-analysis technique in studies of patients with OA	Standard review practices for established regulatory decision-making
Data available	Study-level	Patient-level
High-level confounds	Heterogeneous study populations and treatment duration	Trials were reviewed individually
Quantity of data available	As many as 72 trials to pool for certain comparisons (NSAID vs placebo). For tanezumab only 5 studies were available, 2 pre-2015 and 3 post-2015	Primary analysis of 3 individual studies (post-2015) with pooling of other studies for certain analyses
Key efficacy metrics	Average (several studies) change from BL in pain score	Comparison of concurrent control for change from BL in WOMAC pain score
Key safety events	Risk Difference unadjusted for follow-up time	Incidence rate differences and hazard ratios on patient-level data. Subgroup and post-hoc analyses

Source: HTA submitted August 14, 2020
Abbreviations: HTA, health technology assessment; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; BL, baseline

Efficacy Conclusions

1. Tanezumab 2.5 mg is superior to placebo for pain and function
2. Tanezumab 2.5 mg is not superior to Rx NSAIDS for pain.
    a. In Study 1058, patients who remained on NSAIDs appeared to respond to placebo tanezumab similarly to the active arms.
3. The treatment effect size for tanezumab 2.5 mg is modest

Tanezumab: FDA Safety Review

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Outline

- Points of emphasis in FDA safety review
- Uncontroverted issues
- Controverted issues
  - Certain issues related to joint safety
  - Effectiveness of risk mitigation measures
- Conclusions and unanswered questions

Emphases in Review

- Focus on post-2015 studies
  - Pertinent patient population, dosing, and joint safety monitoring
- Assessment of what critical safety questions the Applicant has adequately addressed and what is still not known

Advisory Committee and Post-2015

- 2012 Advisory Committee opined that further development of anti-NGF agents was acceptable with a contingency and two goals
  - Future studies should include comprehensive joint safety surveillance and risk mitigation measures
  - Studies should elucidate which patients benefit and which patients are at risk to develop joint destruction
  - Studies should elucidate the pathophysiology behind the joint destruction adverse events

Risk Mitigation Measures Post-2015

Measure	Details	Comment
Restrict patient population	• Inadequate response for APAP, +unable for NSAIDs, + unwilling for opioids • OA patients excluded from CLBP studies	• Instituted for safety reasons • Data on joint safety in non-OA patients
Limit dose	• OA – max of 5 mg • CLBP – max of 10 mg	• 2.5 mg SC mainly in post-2015 • Higher and IV doses in pre-2015
Limit NSAID use	• 10 days in 8 weeks, 30 days in 6 months, 60 days in 1 year; may resume 4 months after last dose	• Data on TAN+NSAID s from pre-2015 studies
Stop treatment	• Safety: persistent, severe joint pain or CJSE • Efficacy: If ≤ 30% ↓ in pain after 2 doses	• Interpretation of safety and efficacy
Serial imaging, Central Reader	• Baseline and serial f/u X-rays at app. 24 wks • MRI 'for cause' and in 1058 for K/H at baseline and f/u for KLG3/4	• Essential as CJSE are radiological Dx • Not designed to c/o X-ray vs MRI
Extend safety (f/u)	• From 8 to 24 weeks	• Important for detection of delayed joint events

Source: FDA

Abbreviations: APAP, acetaminophen; CJSE, composite joint safety endpoint; CLBP, chronic low back pain; f/u, follow-up; IV, intravenous; KLG, Kellgren-Lawrence Grade; K/H, knee/hip; MRI, magnetic resonance imaging; NSAIDS, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; SC, subcutaneous; TAN, tanezumab

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Uncontroverted Issues

- The general safety analysis show two key risks:
  - Joint destruction
  - Peripheral sensory adverse events

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- Controverted issues
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Controverted Issues

- Joint Safety
  - Time-to-event curves do not clearly plateau
  - One risk factor was identified (concomitant nonsteroidal anti-inflammatory drug [NSAID] use)
- Risk Management
  - The value of the risk mitigations employed is uncertain
    - Key unknown is whether stopping drug after radiographic evidence of accelerated joint damage slows, stops, or reverses the process
    - Best imaging modality undetermined

Adjudicated Joint Safety Events

- Clinical significance of rapidly progressive osteoarthritis Type 1 (RPOA1)
- Risk of joint event vs. placebo and NSAIDs
- Time-to-event curves
- Joints affected
- Joint outcomes following composite joint safety endpoint (CJSE)
- Prediction and risk mitigation
  - No animal model. No accepted pathogenesis.
  - One risk factor identified
  - Most cases are clinically silent and depend on imaging for signal detection

RPOA1 - Definition and Significance

- Criteria are purely radiographic:
  - Joint space width (JSW) loss ≥2 mm within 1 year without gross structural changes
  - If baseline JSW < 2 mm, could not meet criteria and remained undetected
  - MRI required to confirm Dx (Aug 2016)
- Literature supports that the loss of 2 mm of JSW in one year is rapid:
  - Meta-analysis (patients with evidence of knee OA): range of narrowing between -0.1 to 0.7 mm/year [1]
  - Large randomized controlled trial (RCT) (patients with symptomatic knee OA Kellgren-Lawrence Grade [KLG] 2/3): mean JSW change from baseline - 0.13 mm (± 0.36) at Week 48 and -0.22 mm (± 0.45) at Week 96 [2]

1 Emrani PS, et al.,Osteoarthritis Cartilage. 2008 August
2 Hellio Le Graverand MP, et al., Semin Arthritis Rheum. 2013 August

CJSE in Placebo-Controlled Studies (1056 and 1057)

Parameter	Placebo	Tan 2.5	Tan 2.5/5	Tan 5
N	514	528	219	284
Observed PY	396.1	414.8	162.4	240.0
# of Subjects with CJSE (IR*/100 PY)	0 (0)	10 (2.4)	1 (0.6)	11 (4.6)
RD / 100 PY [95% CI]	-	2.4 [1.0, 4.4]	0.6 [-0.5, 3.4]	4.6 [2.4, 8.0]
NNH / year [95% CI]	-	41 [23, 105]	162 [29, -213]	22 [12, 42]

Source: FDA analysis
Study 1056: 16 wks (treatment) + 24 wks (post-treatment f/u); Study 1057: 24 wks (treatment) + 24 wks (post-treatment f/u)
CJSE includes: RPOA1, RPOA2, SIF, ON, pathologic fracture events
Abbreviations: CI, confidence interval; CJSE, composite joint safety endpoint; IR, incidence rate; NNH, number needed to harm; PY, patient years; RD, risk difference; Tan, tanezumab

CJSE in NSAID-Controlled Study (1058)

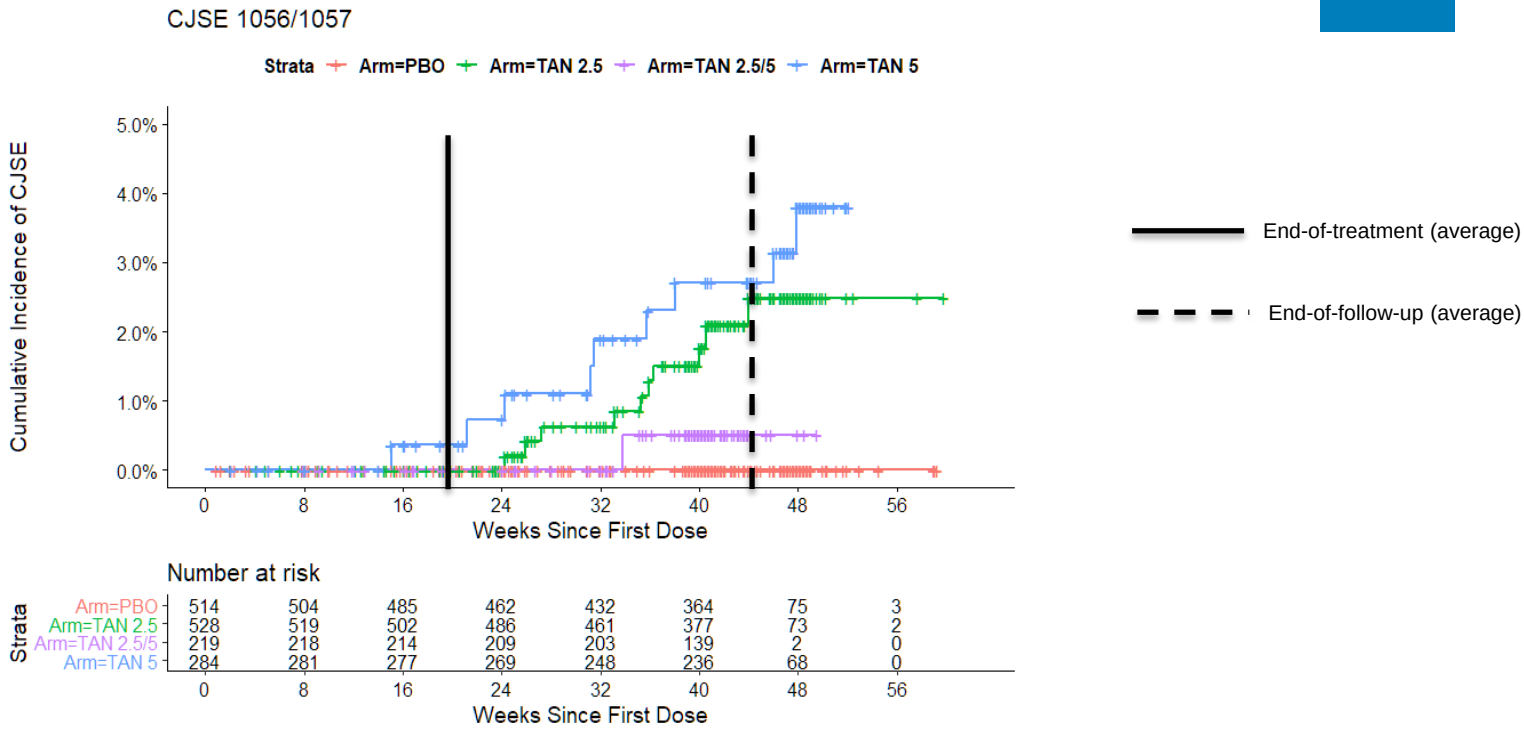
Parameter	NSAID	Tan 2.5	Tan 5
N	996	1002	998
Observed PY	1010.9	1017.1	993.0
# of Subjects with CJSE (IR*/100 PY)	15 (1.5)	39 (3.8)	72 (7.3)
RD/100 PY [95% CI]†	-	2.4 [1.0, 3.8]	5.8 [4.0, 7.6]
NNH/year [95% CI]	-	43 [26, 104]	17 [13, 25]
HR [95% CI]^	-	2.6 [1.4, 4.7]	5.0 [2.9, 8.8]

Source: FDA analysis
Study 1058: 56 wks (treatment, 7 doses) + 24 wks (post-treatment f/u)
Abbreviations: CJSE, composite joint safety endpoint; CI, confidence interval; HR, hazard ratio; NNH, number needed to harm; NSAID, nonsteroidal anti-inflammatory drug; PY, patient years; RD, risk difference; TAN, tanezumab

Long-Term Safety Data

- Post-2015 data are limited to 56 weeks of treatment
- Follow-up off study drug was 24 weeks
- Time-to-event, Kaplan-Meier (KM), curves were generated

CJSE KM Curves (1056 and 1057)

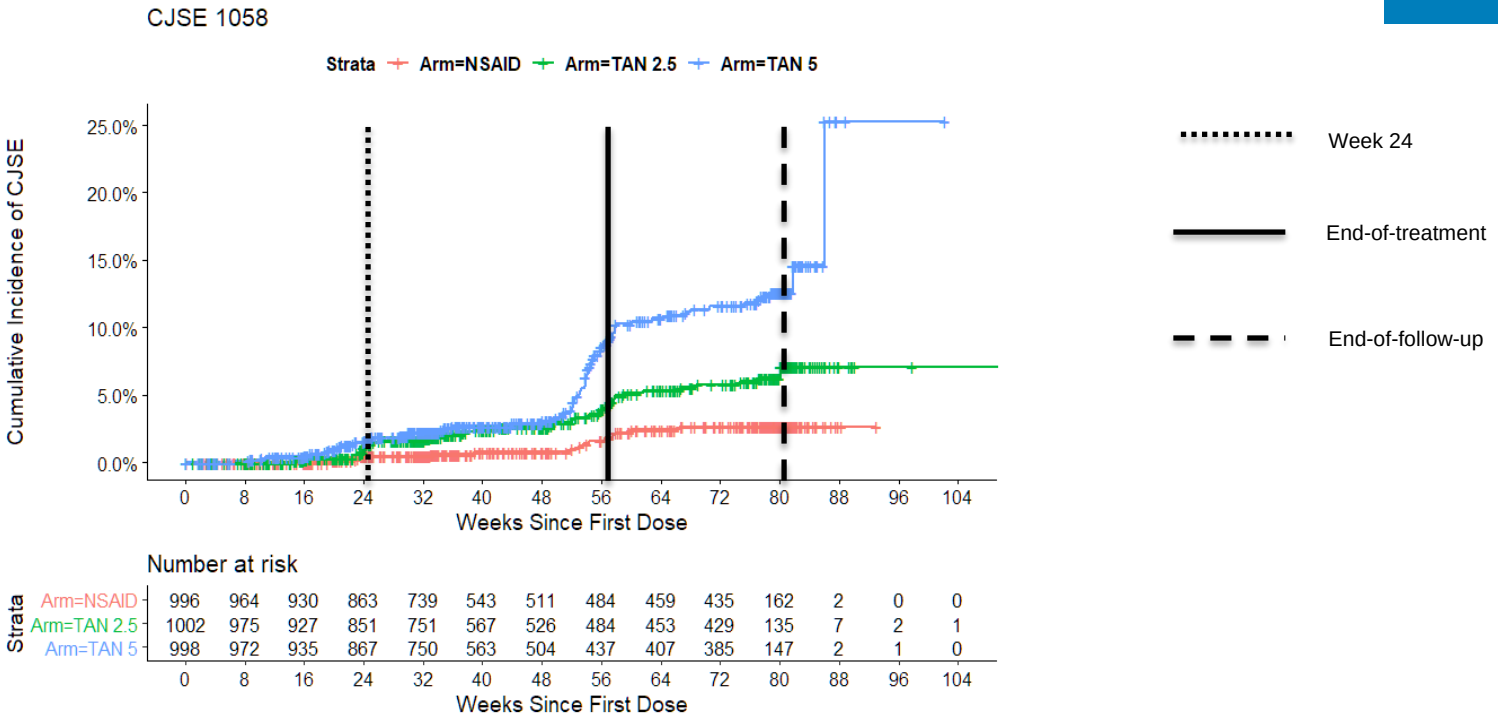


Source: FDA analysis

* Due to the small number of subjects remaining at risk towards the tail, this plot excluded 2 CJSE events that occurred in the tanezumab 5 mg arm of Trial 1057, which occurred at Weeks 53.2 and 52.4, respectively

Abbreviations: CJSE, composite joint safety endpoint; PBO, placebo; TAN, tanezumab

CJSE KM Curves (1058)



Source: FDA analysis

* Due to the small number subjects remaining at risk towards the tail, this plot excluded 2 CJSE events in the tanezumab 5 mg arm, which occurred at Weeks 81.9 and 86.0, respectively.

Abbreviations: CJSE, composite joint safety endpoint; NSAID, nonsteroidal anti-inflammatory drug; TAN, tanezumab

CJSE is Not Limited to Arthritic Joints

Study 1058			
Parameter	**NSAID (N=996)**	**Tan 2.5 mg (n=1002)**	**Tan 5 mg (998)**
CJSE in any joint, n (%)	15 (1.5)	39 (3.9)	72 (7.2)
CJSE in KLG 0/1 joint, n (%)	2 (0.2)	8 (0.8)	19 (1.9)
RPOA1	1	7	13
RPOA2	0	0	3
SIF	1	0	2
ON	0	1	1

Source: Table created using data provided in response to information on May 13, 2020
Study 1056: No CJSE in KLG 0/1 joints.
Study 1057: Four CJSE in KLG 0/1 joints, two in Tan 2.5 mg (both RPOA1) and two in Tan 5 mg (one RPOA1 and one ON).
Abbreviations: CJSE, composite joint safety endpoint; KLG, Kellgren-Lawrence Grade; NSAID, nonsteroidal anti-inflammatory drug; ON, osteonecrosis; RPOA1(2), rapidly progressive osteoarthritis Type 1 (2); SIF, subchondral insufficiency fracture; Tan, tanezumab

Follow-Up Data - Patients With RPOA1

- Worst Adjudication Committee classification was reported
- Following RPOA1, limited long-term follow-up imaging available (N=101*):
    - N=67, at any time point
    - N=48, ≥ 4 months after diagnosis
    - N=13, ≥ 6 months after diagnosis

* Numbers reflect data provided in response to information request submitted on March 13, 2020

Risk Factors for CJSE

- Study 1025 (pre-2015) demonstrated that concomitant use of NSAIDs increases the risk 2-fold
- Post-2015 studies were not designed to assess the risk of concomitant NSAIDs
- Tanezumab was associated with increased risk of CJSE regardless of maximum KL Grade at screening

Study 1025 – Concomitant Use of NSAIDs

- Provides head-to-head comparison of TAN mono and TAN+NSAIDs

Parameter	NSAIDs	Tan mono		Tan+NSAIDs	
		5 mg	10 mg	5 mg+NSAID	10 mg+NSAID
N	539	541	542	536	542
Total exposure (PY)	416	426	415	423	416
RPOA 1 and 2, n (%)	1 (0.2)	4 (0.7)	7 (1.3)	9 (1.7)	13 (2.4)
RPOA 1 and 2, events/1000 pt-yrs	2.4	9.4	16.9	21.3	31.2

Source: Adapted from Applicant's tables provided in 1025 study report
Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PY, patient years; RPOA1 and 2, rapidly progressive osteoarthritis Type 1 and 2; Tan, tanezumab

All-Cause Total Joint Replacement (TJR)

- Risk of TJR vs placebo (Study 1056 vs 1057)
- Risk of TJR vs NSAIDs (Study 1058)
- TJR outcome study (Study 1064)

Risk of TJR vs Placebo (1056)

Parameter	Placebo	Tan 2.5	Tan 2.5/5
N	232	245	219
Observed PY	161.2	170.7	161.4
# of Subjects with TJR (IR*/100 PY)	4 (2.3)	9 (5.3)	15 (9.3)
RD / 100 PY [95% CI] †	-	2.8 [-1.3, 6.9]	6.8 [1.7, 11.9]
NNH / year [95% CI]	-	35 [14, -74]	15 [8, 57]
HR [95% CI]^	-	2.1 [0.6, 6.7]	3.6 [1.2, 10.9]

Source: FDA analysis
Study 1056: 16 wks (treatment) + 24 wks (post-treatment f/u)
Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; NNH, number needed to harm; PY, patient years; RD, risk difference; Tan, tanezumab; TJR, total joint replacement

Risk of TJR vs Placebo (1057)

Parameter	Placebo	Tan 2.5	Tan 5
N	282	283	284
Observed PY	233.4	244.4	240.0
# of Subjects with TJR (IR*/100 PY)	21 (9.0)	25 (10.2)	20 (8.3)
RD / 100 PY [95% CI] †	-	1.2 [-4.1, 6.5]	-0.7 [-5.8, 4.4]
NNH / year [95% CI]	-	81 [15, -25]	-147 [23, -17]
HR [95% CI]^	-	1.1 [0.6, 2.0]	1.0 [0.5, 1.8]

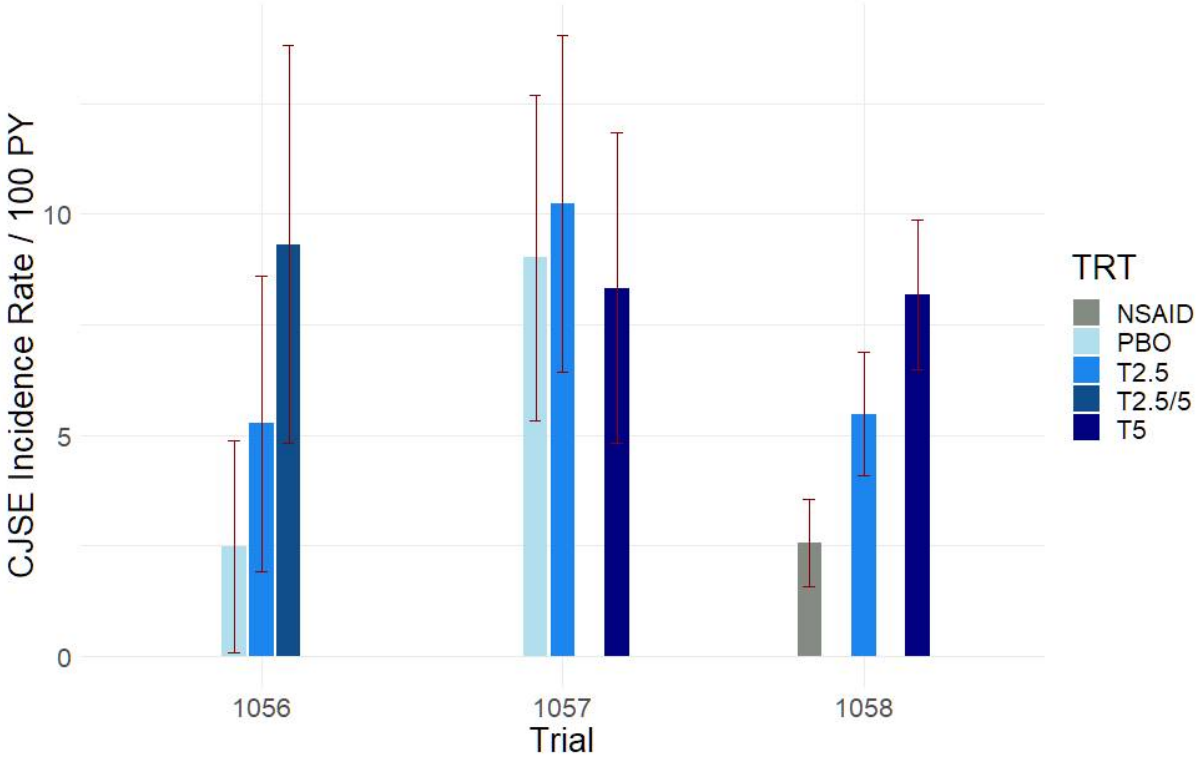
Source: FDA analysis
Study 1057: 24 wks (treatment) + 24 wks (post-treatment f/u)
Abbreviations: CI, confidence interval; HR, hazard ratio; NNH, number needed to harm; PY, patient years; RD, risk difference; Tan, tanezumab; TJR, total joint replacement

Risk of TJR vs NSAIDs (1058)

Parameter	NSAID	Tan 2.5	Tan 5
N	996	1002	998
Observed PY	1011.9	1022.8	1004.1
# of Subjects with TJR (IR*/100 PY)	26 (2.6)	56 (5.5)	82 (8.2)
RD/100 PY [95% CI]†	-	2.9 [1.2, 4.6]	5.6 [3.6, 7.6]
NNH/year [95% CI]	-	34 [22, 83]	18 [13, 27]
HR [95% CI]^	-	2.1 [1.3, 3.3]	3.2 [2.1, 5.0]

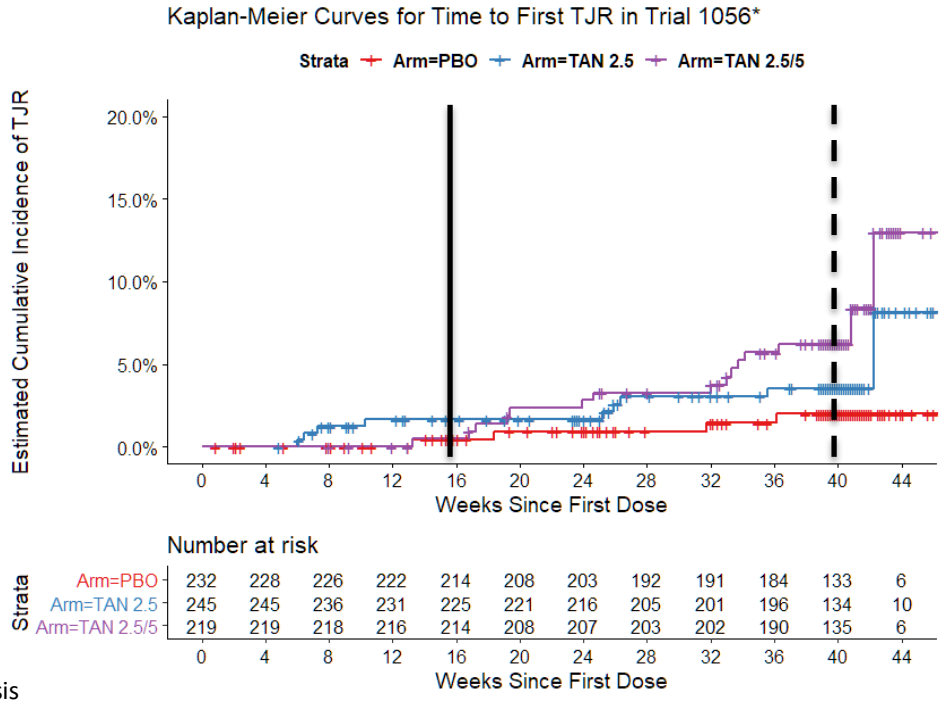
Source: FDA analysis
Study 1058: 56 wks (treatment) + 24 wks (post-treatment f/u)
For reference, the estimated IR of total knee replacement in the progression cohort (symptomatic OA with KLG ≥ 2) in the OAI study was 2.4 per 100 PY (Yura Kim at al., Arthritis Care Res (Hoboken), 2020 December)
Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; NNH, number needed to harm; NSAID, nonsteroidal anti-inflammatory drug; PY, patient years; RD, risk difference; Tan, tanezumab; TJR, total joint replacement

TJR - Between Study Comparison



Source: FDA analysis; Abbreviations: CJSE, composite joint safety endpoint; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; PY, patient years; T, Tanezumab; TJR, total joint replacement

TJR KM Curves (1056)



End-of-treatment

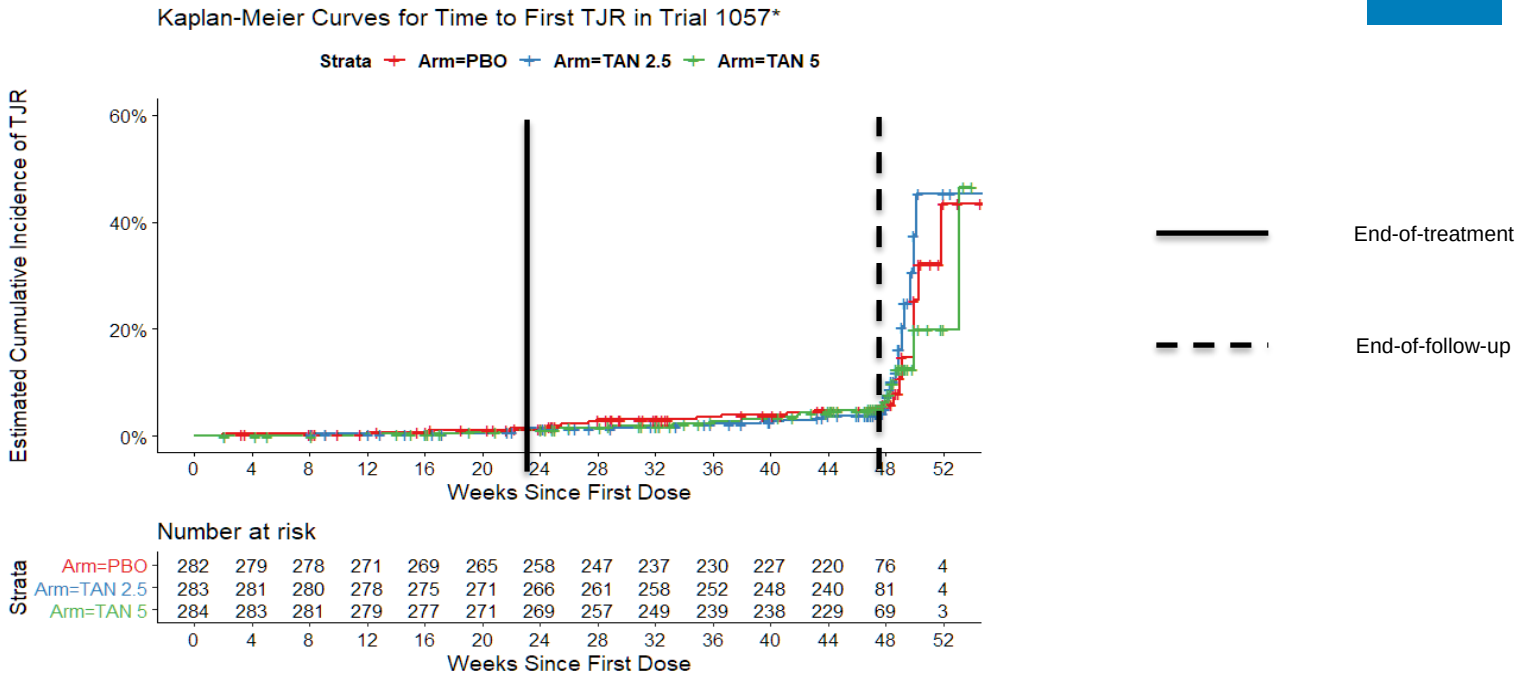
End-of-follow-up

Source: FDA analysis

* Data after 0.848 year (~44 weeks) are not shown in the K-M plot. At Year 0.848 (~Week 44), there were 22 subjects remaining in the risk set (6 for placebo, 10 for tanezumab 2.5 mg and 6 for tanezumab 2.5/5 mg), and 0 additional TJR events were observed after Year 0.85. Trial 1056 was designed to have a 16-week treatment period followed by a 24-week safety follow-up period (for a total of 40-week, or 0.77-year study duration).

Abbreviations: PBO, placebo; TAN, tanezumab; TJR, total joint replacement

TJR KM Curves (1057)

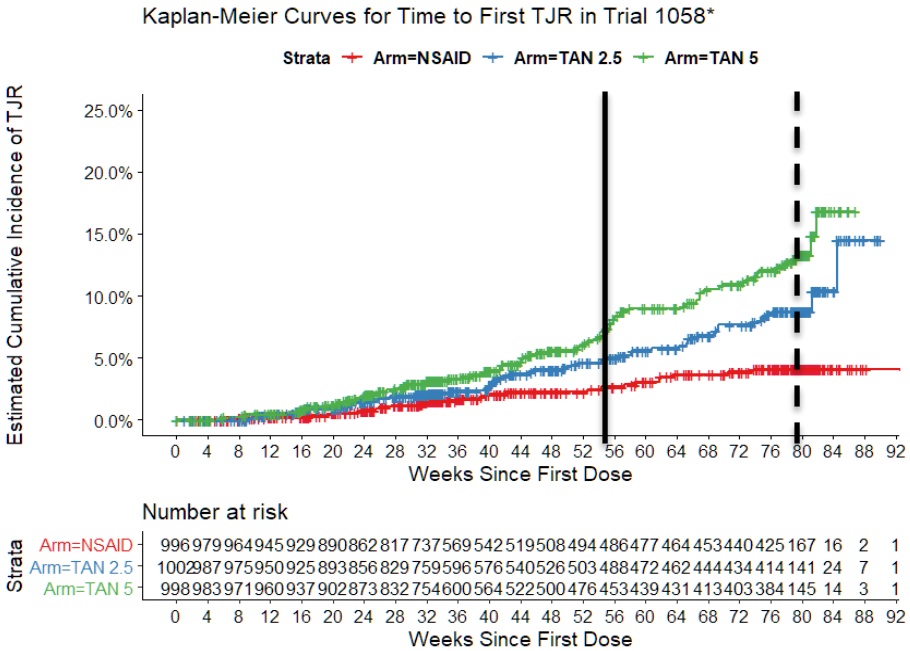


Source: FDA analysis

* Data after 1 year (52 weeks) are not shown in the K-M plot. At 1 year, there were 11 subjects remaining in the risk set (4 for placebo, 4 for tanezumab 2.5 mg and 3 for tanezumab 5 mg), and 2 additional TJR events were observed (1 for tanezumab 2.5 mg and 1 for tanezumab 5 mg) after 1 year. Trial 1057 was designed to have a 24-week treatment period followed by a 24-week safety follow-up period (for a total of 48-week, or 0.92-year study duration).

Abbreviations: PBO, placebo; TAN, tanezumab; TJR, total joint replacement

KM Curves for TJR (1058)



End-of-treatment

End-of-follow-up

Source: FDA analysis

* Data after 1.69 year (~88 weeks) are not shown in the K-M plot. At Year 1.69, there were 12 subjects remaining in the risk set (2 for NSAID, 7 for tanezumab 2.5 mg and 3 for tanezumab 5 mg), and 2 additional TJR events were observed (1 for tanezumab 2.5 mg and 1 for tanezumab 5 mg) after Year 1.69. Trial 1058 was designed to have a 56-week treatment period followed by a 24-week safety follow-up period (for a total of 80-week, or 1.54-year study duration). The zoomed-in version of the TJR K-M plot for Trial 1058 shows only 0%-25% on the y-axis since confidence bands become very wide towards the tails of the K-M plot with a small number of subjects remaining at risk.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; TAN, tanezumab; TJR, total joint replacement

Study 1064 - Prospective TJR Surgical Outcomes Study

- Background: Literature suggests marked bone resorption in setting of RPOA may compromise the success of TJR surgery
- Inadequate to draw conclusions
  - 150/258 enrolled, only 12 with CJSE
  - Surgical difficulties/complications/corrective procedures
    - Small number of patients (<10), but all received TAN

Controverted Issues

- Joint Safety
  - Time-to-event curves do not clearly plateau
  - One risk factor was identified (concomitant NSAID use)
- Risk Management
  - The value of the risk mitigation measures employed is uncertain
    - Key unknown is whether stopping drug after radiographic evidence of accelerated joint damage slows, stops, or reverses the process
    - Best imaging modality undetermined

Prediction and Risk Mitigation Measures

- Detection of tanezumab-associated joint destruction is critical and complicated by:
  - No animal model
  - No accepted pathogenetic mechanism
  - One risk factor has been identified
  - Cases are clinically silent and may affect “healthy” joints
  - Signal detection has been limited to medical imaging
- Effectiveness of risk mitigation scheme is undermined

Imaging for Detection of CJSE

- Imaging protocol in all Phase 3 studies utilized plain radiographs of large joints at baseline and at later visits. In Study 1058 only, MRIs conducted in patients with baseline KLG 3 and 4
- Plain radiography is dependent on technique, positioning, and consistent interpretation
- Despite a trained central radiologist and a dedicated adjudication committee, the number of CJSE differed substantially: Adjudication Committee (AC) 145 vs. Central Reader (CR) 241
- MRI was used to confirm diagnosis and some data suggest better sensitivity for MRI

Once CJSE is Detected, Options are Limited

- Event onset does not coincide with event detection
- Joint destruction process already underway and seemingly irreversible once detected
- Insufficient data to characterize the evolution of the destructive process:
  - While on treatment
  - After tanezumab is discontinuation

Were the Risk Mitigation Measures Effective?

- Pre-2015 studies: designed and conducted prior to identification of joint safety signal
  - Standard clinical study risk mitigation measures
- Post-2015 studies: substantial risk mitigation measures focused on joint safety were added
  - Limit dose, NSAIDs use, discontinue for lack of efficacy after 2nd dose, extend follow-up period, frequent imaging/central reader

Data Pre- and Post-2015 Not Comparable

Parameter	Comments
Pre-2015 studies used higher doses and the IV route.	• Resulted in higher tanezumab exposures. • Tend to bias the assessment towards concluding that the risk mitigation measure are effective.
Targeted surveillance for joint events implemented in post-2015 studies. Blinded CR and AC introduced.	• Favors detection of more events.
The definition of RPOA1 changed post-2015.	• Threshold decrease in JSW (increased from 1mm to 2mm), biases against detecting RPOA1 event.
There is latency to joint events and they can occur long after drug discontinuation. The follow-up pre-2015 was only 8 weeks compared to 24 weeks in the post-2015 studies.	• Increases the likelihood of detecting a joint event.

Key Safety Conclusions and Remaining Questions

Key Conclusions	Unanswered Questions
Tanezumab carries a risk of accelerated joint destruction that is clinically silent and can affect radiographically healthy joints.	1. What is the pathogenesis of the joint destruction process? 2. What is the risk if patients are treated >1 year? 3. Does stopping drug after RPOA1 halt the destructive process? 4. Assuming yes for #3, are the proposed risk mitigation measures adequate? 5. Does tanezumab treatment portend higher incidence or more severe surgical complications with TJR surgery?
Tanezumab is associated with abnormal peripheral sensation that is typically mild and self-limited.	None

Tanezumab: FDA Patient Preference Study Review

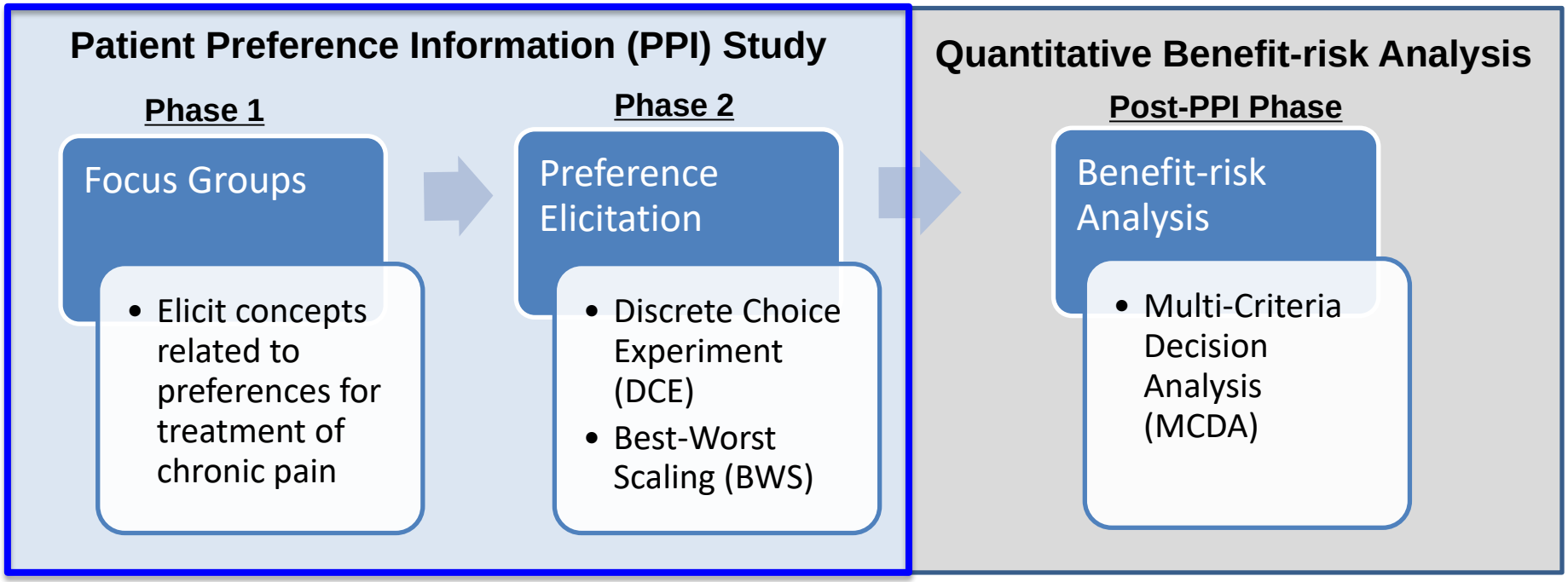
Martin Ho, MS

Associate Director, Office of Biostatistics and Epidemiology

Center for Biologics Evaluation and Research, FDA

on behalf of Center for Drug Evaluation & Research

Overall Schematic



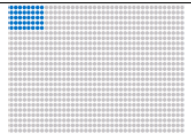
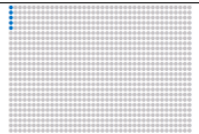
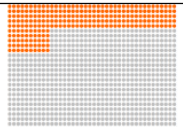
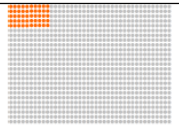
PPI Study Objectives

1. To quantify patients' preferences for attributes of pharmaceutical treatments for chronic moderate-to-severe musculoskeletal pain associated with osteoarthritis (OA) and/or chronic lower back pain (CLBP) that:
   - are relevant to patients and
   - differentiate tanezumab from alternative analgesics
2. To quantify:
   - the relative importance of each treatment attribute and
   - the tradeoffs patients are willing to make among these attributes

Study Data Subset of Review Focus

1. U.S. study results from PPI study
2. Data from respondents who self-reported presence of OA only, or OA and CLBP (i.e. excluding respondents who reported CLBP only)
   - Sample of 400 respondents = 201 (OA only) + 199 (OA and CLBP)
3. Marginal rates of substitutions between benefit, risks, and administration mode and frequency
   - Excluding analysis related to costs

Study Design (DCE)

Medicine Feature	Medicine A	Medicine B
Symptom control: Symptom control while you are taking the medicine	**GOOD** mild symptoms; no limitations on normal activities	**VERY GOOD** no symptoms; no limitations on normal activities
Additional risk of severe joint problems: Additional risk each year of having joint problems that are severe enough that you would need a total joint replacement while you are taking the medicine or within 6 months of stopping the medicine	 40 people out of 1,000 (4%)	 5 people out of 1,000 (0.5%)
Additional risk of heart attack: Additional risk each year of having a heart attack while you are taking the medicine	 5 people out of 1,000 (0.5%)	 No additional risk (0%)
Risk of physical dependence: Risk each year of becoming physically dependent on the medicine	 250 out of 1,000 people (25%)	 50 people out of 1,000 (5%)
How you take the medicine	 Oral pills once a day	 Injection every 8 weeks (about every 2 months)
Cost: Personal cost of the medicine to you every month	$0 every month	$30 every month
Which medicine would you choose if these were the only two medicines available?	☐	☐

- 400 respondents with OA only or OA + CLBP self-administered the online survey
- DCE consisted of 8 choice questions where respondents choose one of the 2 presented options
- 5 treatment-related attributes:

  Benefit

  1. Symptom control

  Risk

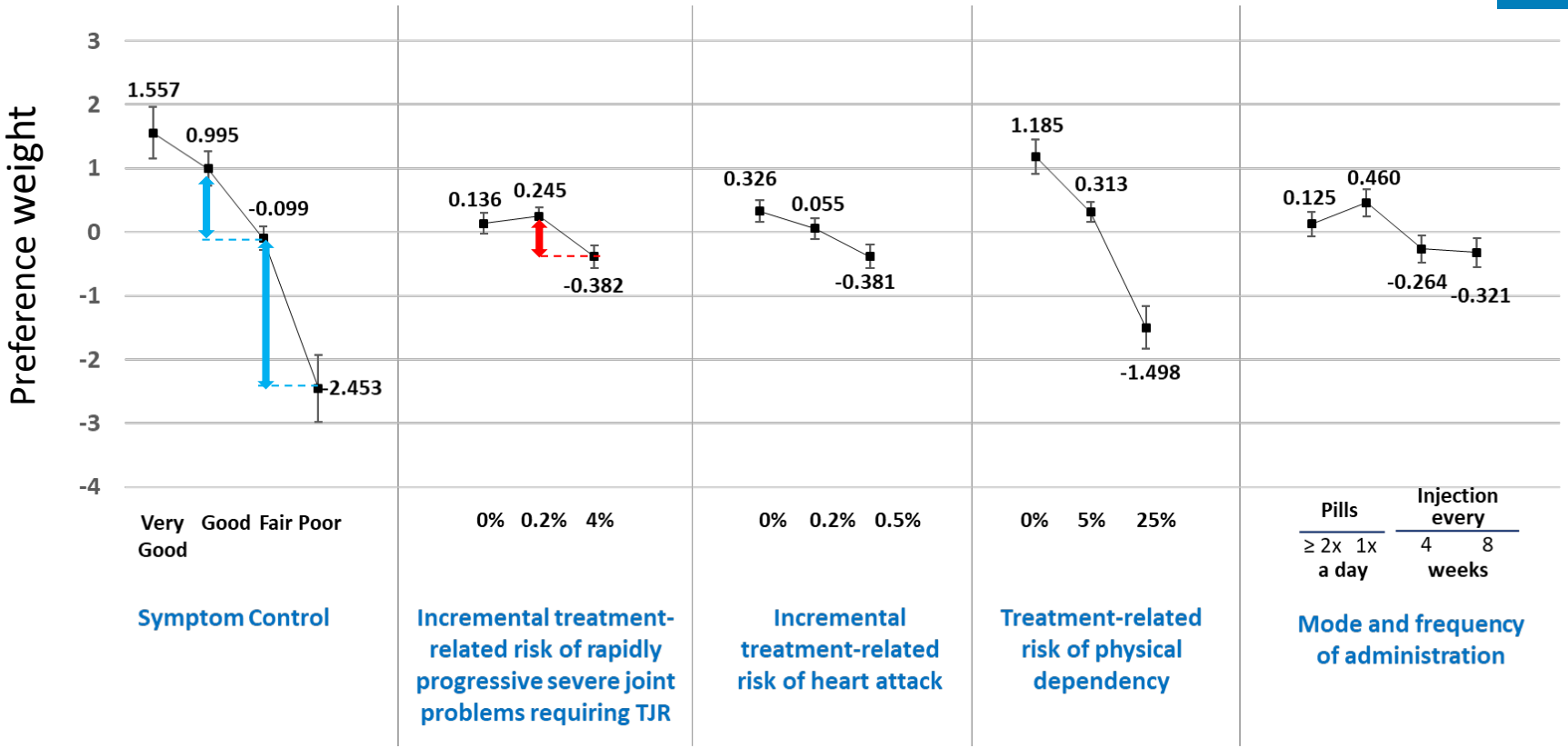
  2. Additional risk of severe joint problems that require total joint replacement
  3. Additional risk of heart attack
  4. Risk of physical dependence

  Administration

  5. Mode and frequency of administration

Source: 5.3.5.4 A9001505 Non-Interventional Final Study Report Appendix 10 Survey Instrument Figure A4-1

Main Study Results (DCE)



Source: Adapted from IR Response: Additional Discrete Choice Analysis Excluding Respondents with CLPB Only §3.3 Figure 5

Main Study Results (DCE)

The Applicant concluded that:

1. ***"On average, respondents strongly preferred better symptom control & avoiding the treatment-related risk of physical dependence. Avoiding incremental annual treatment-related risks of heart attack & severe rapidly progressive joint problems requiring total joint replacement were much less important, both statistically and qualitatively, than either improving symptom control or avoiding the risk of physical dependence."***
2. Respondents with moderate to severe OA were willing to accept a more than 4% additional risk of severe joint problems requiring total joint replacement (TJR) for most levels of symptom improvement, i.e., poor → fair, or poor → good, or fair → good.

Insufficient Evidence

We conclude that the evidence submitted is insufficient to support the Applicant's interpretation of the PPI study result that respondents were willing to accept a more than 4% incremental annual risk of severe rapidly progressive joint problems requiring total joint replacement for an incremental improvement in symptom control (e.g., from poor to fair).

Key Review Concerns

1. Missing pain and function as individual attributes in preference study, leading to ambiguous interpretation of benefit in symptom control
2. Inadequate description of severe joint problems and TJR on patients' daily lives was under-explained in the survey descriptions
3. Forced choice format of the DCE differed from relevant clinical setting where patients would have been able to decline both presented medicine options.

1. Missing Essential Attributes

- Main benefit attribute was symptom control in the survey. The levels were defined following the PGA-OA in the clinical trials (poor, fair, good, very good)
- In the survey, symptom control consisted of the following components:
  1. Pain, tenderness, and stiffness in the affected joint(s)
  2. Loss of flexibility or limitations in the range of motion of the affected joint(s)
  3. A grating sensation when you use the affected joint(s)
  4. Bone spurs that may form around the affected joint(s) & feel like hard lumps
- Ambiguity: How much did the respondents attribute an incremental benefit (an improvement in symptom control) to each of these 4 components

1. Missing Essential Attributes (cont.)

- Missing 2 out of 3 co-primary endpoints from the clinical trials: WOMAC pain and functional domain scores
  - Thus, it is impossible to discern respondents' relative attribution of improvement in overall symptom to pain and functional improvement.
- FDA has provided key attributes to the Applicant in response to a pre-BLA meeting, when the PPI study design was presented to FDA but after the PPI study was completed.

Benefits	Risks
1. Pain relief	1. Joint destruction
2. Function improvement	2. Neurosensory disturbance
3. Patient Global Assessment	3. Cardiovascular (CV) risks
	4. GI bleeding
	5. Addiction and dependence
	6. Overdose

2. Inadequate Description of Severe Joint Problems Requiring TJR

- Description of severe joint problems requiring TJR is inadequate to convey the impact of TJR, such as the pain associated with the surgical procedure, the pain and reduction in joint function pre and post the rehabilitation period, and the uncertain level of function after rehabilitation

"These joint problems are painful and get bad so quickly that, if they occur, you would need to have a total joint replacement.
This type of severe joint problem can occur in any of the major joints in your body while you are taking the medicine or within 6 months of stopping the medicine, even if you don't have pain or stiffness in that joint when you start taking the medicine."

Source: The PPI Study 9001505, Survey Instrument p.23

2. Inadequate Description of Severe Joint Problems Requiring TJR (cont.)

- Applicant's focus group interview guide did not include the TJR risk and was not discussed with patients.
- Focus group participants, spontaneously mentioned joint replacement, however moderator did not follow up with participants on this topic when mentioned.

Attribute Important to Focus Groups Participants
1. Efficacy 2. Side effects 3. Risk of addiction/dependence 4. Mode of administration 5. Frequency of administration 6. Out of pocket cost

2. Inadequate Description of Severe Joint Problems Requiring TJR (cont.)

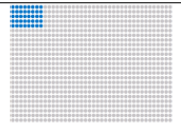
- Lack of discussion and probing about how participants view TJR, especially the potential systematic risk of Tanezumab to the nearly healthy joints, as a possible safety event in the focus group transcripts
- Understanding the potential complete impact of TJR is directly related to how respondents weigh the importance of this risk

We believe that the inadequate description of the impact of the additional risk of severe joint problems requiring TJR may have led to an under-weighing of this risk attribute, leading to a high estimated maximum acceptable risk

3. Forced Choice Format of Survey Design

- Respondents had to choose one of two of the presented options and cannot "opt-out" or choose to stick with status quo
- Preference weights and maximum acceptable risk estimand elicited under forced choice and unforced choice formats can be different

In daily clinical encounters, patients can decline offered options if they prefer their status quo. Therefore, we find the PPI elicited with the unforced choice format more informative because reflects standard of care outside of the trial setting.

Medicine Feature	Medicine A	Medicine B
Symptom control: Symptom control while you are taking the medicine	**GOOD** mild symptoms; no limitations on normal activities	**VERY GOOD** no symptoms; no limitations on normal activities
Additional risk of severe joint problems: Additional risk each year of having joint problems that are severe enough that you would need a total joint replacement while you are taking the medicine or within 6 months of stopping the medicine	 40 people out of 1,000 (4%)	 5 people out of 1,000 (0.5%)
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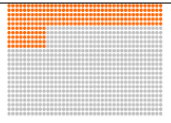
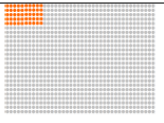
Risk of physical dependence: Risk each year of becoming physically dependent on the medicine	 250 out of 1,000 people (25%)	 50 people out of 1,000 (5%)
How you take the medicine	 Oral pills once a day	 Injection every 8 weeks (about every 2 months)
Cost: Personal cost of the medicine to you every month	$0 every month	$30 every month
Which medicine would you choose if these were the only two medicines available?	☐	☐

Source: 5.3.5.4 A9001505 Non-Interventional Final Study Report Appendix 10 Survey Instrument Figure A4-1

Other Issues: Study Sample

- Members of internet survey panels with self-reported moderate-to-severe OA pain
- Screening tool included questions on the worst possible pain in the past week, and current/ever use of pain treatments in the past 2 years
    - Pain score of 5 or greater
    - Taken or tried ≥3 classes of pain treatment; or 2 prior classes of pain treatment, either excluding nonsteroidal anti-inflammatory drugs (NSAIDs) due to contraindication or excluding opioids due to unwillingness to take opioids; or 1 prior class of pain treatment excluding NSAIDs due to contraindication and excluding opioids due to unwillingness to take opioids

Other Issues: Study Sample (cont.)

- Lack of data or evidence to support the performance of these screening questions
- Recall period (past 2 years) for which the study sample had to recall their past analgesic use may not been appropriate for the study sample to reflect on.

Compared to OA patients with physician-confirmed diagnosis, a study sample with self-reported OA from internet panels may be suboptimal in terms of representativeness of the proposed indicated population.

Limitations of web panels are discussed in FDA Patient-Focused Drug Development Guidance Document on Collecting Comprehensive and Representative Input https://www.fda.gov/media/139088/download

Conclusions

The submitted PPI results were not fit-for-purpose to inform our benefit-risk assessment in this application for three main reasons:

1. Insufficient explanation of the impact of severe joint problems requiring TJR to respondents might have biased the estimates
2. Missing pain and function as individual attributes in preference study, leading to ambiguous interpretation of benefit in symptom control
3. Survey instrument's forced choice format might have yielded the wrong type of PPI data for regulatory consideration

Risk Management

Somya Dunn, MD
CDR, U.S. Public Health Service
Risk Management Analyst
Division of Risk Management
Office of Medication Error Prevention and Risk
Office of Surveillance and Epidemiology
CDER, FDA

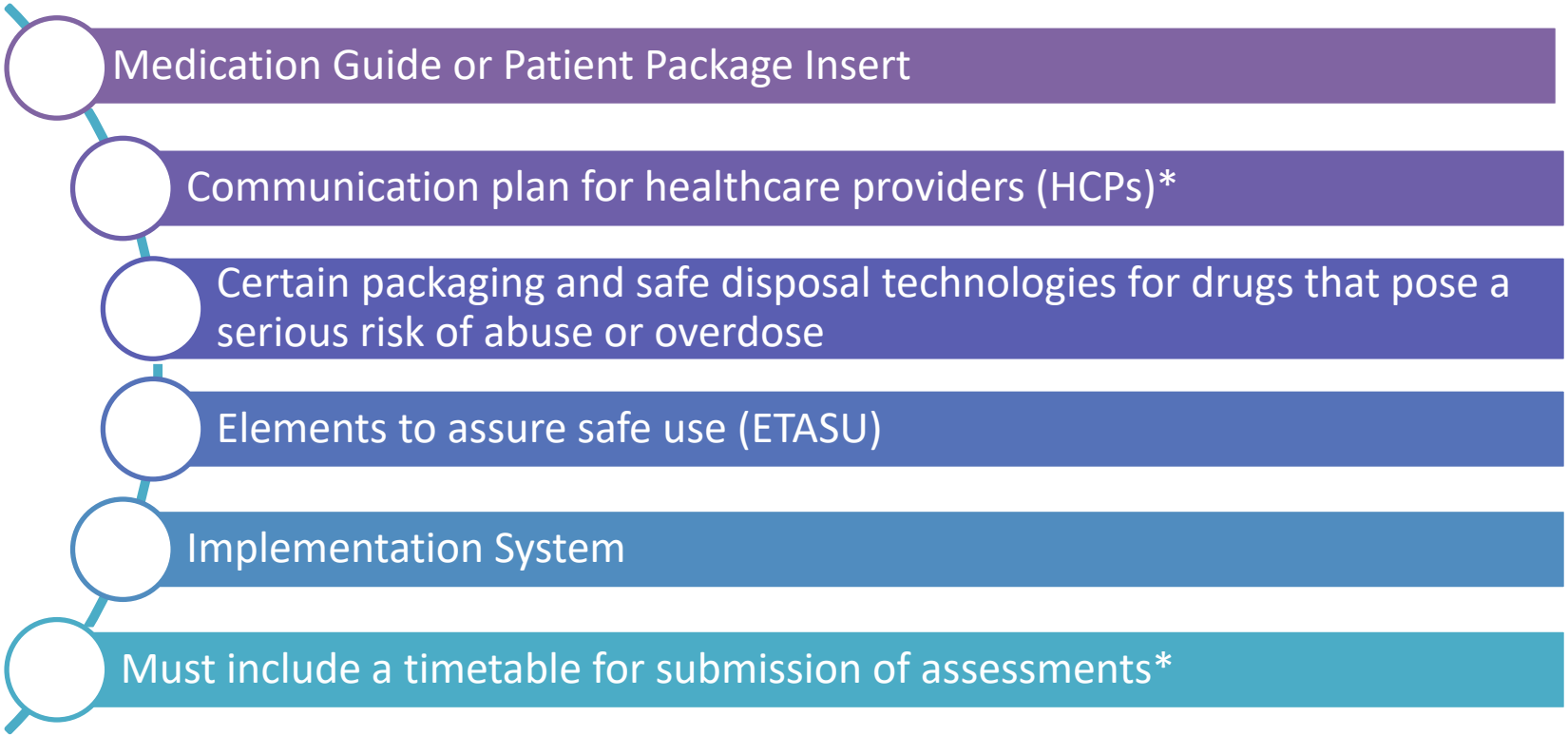
Presentation Overview

- Background on Risk Evaluation and Mitigation Strategies (REMS)
- Applicant's proposed REMS
- Agency's review of the proposed REMS

A REMS is a Drug Safety Program That FDA Can Require For Certain Drugs

- The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require Applicants or Application holders to develop and comply with REMS programs if determined necessary to ensure the benefits of a drug outweigh the risks.
- REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.
- FDA has authority to require a REMS pre-approval or post-approval.

A REMS Can Include a Number of Components



** This requirement applies to NDAs and BLAs only. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS.*

A REMS Can Include Any of the Following ETASUs

- Certification and/or specialized training of the healthcare providers who prescribe the drug
- Certification of pharmacies, practitioners, or healthcare settings that dispense the drug
- Limited settings for dispensing or administration of the drug, such as a hospital setting
- Monitoring of each patient using the drug
- Dispensing/administration of drug only with evidence of safe-use conditions (e.g. pregnancy test)
- Enrollment of treated patients in a registry

Applicant Proposed REMS—Goal

The goal of the tanezumab REMS is to mitigate the increased risk of rapidly progressive osteoarthritis (OA) with tanezumab by:

- Ensuring healthcare providers are educated about the increased risk of rapidly progressive OA associated with the use of tanezumab.

- Ensuring that healthcare providers are educated on and adhere to the following:
  - Document that baseline and annual X-rays are completed to identify rapidly progressive OA and its risk factors by submitting the Patient Enrollment Form and Patient Continuation Form.
  - Counsel patients on the increased risk of rapidly progressive OA and the importance of avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.

Applicant Proposed REMS—Goal Cont.

- Ensuring safe use of tanezumab by:
  - Ensuring that tanezumab is only administered to enrolled patients in certified healthcare settings after verification of baseline and annual X-rays.
  - Counseling patients on the importance of avoiding NSAIDs.

- Ensuring that patients are informed about:
  - The increased risk of rapidly progressive OA associated with the use of tanezumab.
  - The requirement for X-rays at baseline and annually thereafter if continuing treatment.
  - The importance of avoiding NSAIDs while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.

Applicant Proposed REMS—ETASU

The key components of the proposed REMS include the following ETASU

- Prescriber Certification
- Healthcare Setting Certification
- Pharmacy Certification
- Patients are enrolled in the REMS and informed of the risk of rapidly progressive osteoarthritis (RPOA)
- Patients must be monitored for signs (e.g., x-rays) and symptoms of RPOA (such as increased pain and/or swelling)
- Documentation of bilateral x-rays of the knees and hips at baseline and then yearly thereafter

Patient Selection & Pre-treatment Screening

Mitigation in Post-2015 Trials	Proposed REMS Mitigation

• Baseline x-rays of knees, hips, shoulders read by specially trained radiologists
• Exclusion criteria of other types of pre-existing joint disease
• Inclusion of patients with more severe OA unresponsive to or intolerant of multiple standard of care analgesics
	• Limit dose to 2.5 mg (labeled dose)
	• Baseline x-rays of both knees and hips
	• Educate prescribers about appropriate patient selection
	  • exclude patients with other types of pre-existing joint disease
	  • reserve for patients with more severe OA or unresponsive to other analgesics

Agency Concerns:

- Tanezumab is associated with RPOA development in healthy joints
- Use of specially trained radiologists through the REMS is not feasible and raises concerns about the ability to detect RPOA in a real world setting
- Substantial disagreements of x-ray interpretation between experts during clinical trials

During Tanezumab Treatment

Mitigation in Post-2015 Trials	Proposed REMS Mitigation
• X-rays of knees, hips, shoulders read by specially trained radiologists • NSAID use was limited • Patients were evaluated for new symptom onset • Patients were stopped if they were not responding to tanezumab	• Yearly x-rays of knees and hips • Counsel patient not to use NSAIDs and to report new symptom onset • Educate prescribers to discontinue tanezumab after 2 doses in patients not responding

Agency Concerns:

- The Applicant's proposed REMS can support that X-rays are obtained at defined intervals; however:
  - Radiologists will not be specially trained
  - RPOA is not easily identified and followed with x-rays
  - Joint changes may be subtle, findings are affected by patient positioning and comparison to previous X-rays
- Patients will be counseled not to use NSAIDs and to report symptoms; however, patients may be asymptomatic and NSAID use may still occur.

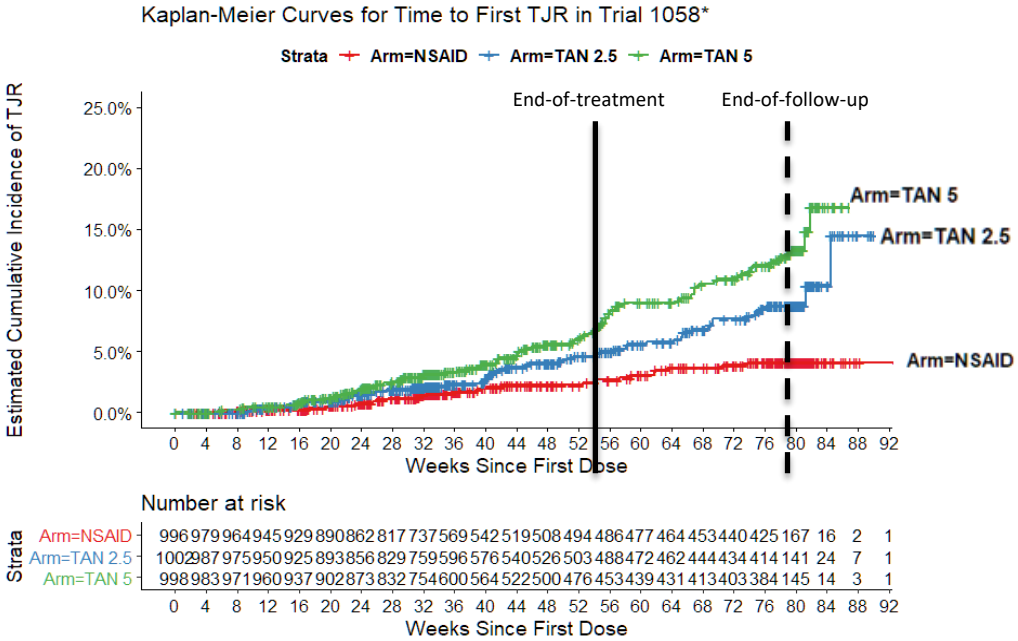
If RPOA is Identified During Treatment

Mitigation in Post-2015 Trials	Proposed REMS Mitigation
• Stop treatment	• Stop treatment

Agency Concerns:

- Joint destruction is already underway and irreversible once detected
- We don't know if stopping tanezumab will halt further destruction to the joint
- Long term progression of joint destruction is unknown

KM Curves for TJR (1058)



Source: FDA analysis

* Data after 1.69 year (~88 weeks) are not shown in the K-M plot. At Year 1.69, there were 12 subjects remaining in the risk set (2 for NSAID, 7 for tanezumab 2.5 mg and 3 for tanezumab 5 mg), and 2 additional TJR events were observed (1 for tanezumab 2.5 mg and 1 for tanezumab 5 mg) after Year 1.69. Trial 1058 was designed to have a 56-week treatment period followed by a 24-week safety follow-up period (for a total of 80-week, or 1.54-year study duration). The zoomed-in version of the TJR K-M plot for Trial 1058 shows only 0%-25% on the y-axis since confidence bands become very wide towards the tails of the K-M plot with a small number of subjects remaining at risk.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; TAN, tanezumab; TJR, total joint replacement

Agency's Conclusions

What a REMS Can Accomplish	What a REMS Cannot Accomplish
A restricted distribution program Education about the risk and need for monitoring through and certification of: • Prescribers • Pharmacies • Healthcare settings Enrollment and counseling of patients to help ensure: • Patients are counseled about the risk and avoiding NSAID use • Serial x-rays are performed	• Concerns - REMS will not be able to reproduce the risk mitigation strategies applied to the post-2015 clinical trials • RPOA difficult to identify and follow in x-rays • Uncertainty that the proposed measures impact the progression of RPOA • REMS cannot prevent RPOA • Concerns - REMS would not be able ensure that the clinical benefit of tanezumab outweighs the risk of RPOA

Tanezumab: FDA Summary

Robert Shibuya, MD
Medical Officer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine

Key Agency Findings and Concerns

1. Tanezumab 2.5 mg shows modest efficacy vs. placebo in treatment-resistant OA patients.
2. Tanezumab is associated with a risk of joint destruction with manifestations ranging from rapid loss of joint space width (JSW) to destructive lesions that may culminate in total joint replacement.
    a. The trajectory of risk with treatment longer than 1 year is unknown.
    b. This adverse reaction has been identified in once radiographically normal joints.
3. The risk of joint destruction does not appear to be mitigable.
    a. Excepting concomitant NSAID use and tanezumab dose, no predictive risk factors have been identified.
    b. Most cases were clinically silent and there are no early premonitory signs or symptoms.
    c. The pathogenetic mechanism for joint destruction is unknown.
4. Regarding the REMS:
    a. Even under optimal conditions, there was substantial discordance between experts in assessing JSW which is the trigger to discontinue drug.
    b. There is little evidence that stopping treatment after RPOA1 improves outcome.
5. The PPI Study did not use appropriate attributes and choice format to inform the benefit-risk relationship.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Back-up Slides Shown

Select Baseline Characteristics (1057)

Parameter	Placebo (N=282)	Tan 2.5 (N=283)	Tan 5 (N=284)
Age (years)			
Mean	64	65	65
≥65	144 (51%)	145 (51%)	169 (60%)
≥75	39 (14%)	36 (13%)	47 (17%)
KLG index joint			
0	0	2 (0.7%)	0
1	0	0	0
2	59 (21%)	49 (17%)	58 (20%)
3	123 (44%)	131 (46%)	121 (43%)
4	100 (36%)	101 (36%)	105 (37%)
Max KLG any joint			
0	0	0	0
1	0	0	1
2	42 (15%)	40 (14%)	44 (16%)
3	127 (45%)	125 (44%)	123 (43%)
4	113 (40%)	118 (42%)	117 (41%)

Source: Adapted from Applicant's demographic and baseline characteristics tables in 1057 study report
Abbreviations: KLG, Kellgren-Lawrence Grade; OA, Osteoarthritis, ITT, intent-to-treat; Tan, tanezumab

Incidence Rate of TJR – Yura Kim

- Kim Y, Levin G, Nikolov NP, Abugov R, Rothwell R, *Concept Endpoints Informing Design Considerations for Confirmatory Clinical Trials in Osteoarthritis*, Arthritis Care Res (Hoboken). 2020 Dec 20. doi: 10.1002/acr.24549. Online ahead of print.
- Goal: Define appropriate measures in clinical trials for therapies that target the underlying pathophysiology of OA
- OAI study progression cohort, N=1390, 80% followed for 5 years
  - Symptomatic knee OA with radiographic evidence of KLG ≥ 2
- N=1332 with post-baseline observation, N=138 had TKR surgery
- **Estimated incidence rate of TKR surgeries: 2.4 cases per 100 person-years**