Erratum to the FDA Briefing Document
Joint Meeting of the Arthritis Advisory Committee and the
Drug Safety and Risk Management Advisory Committee
March 24 & 25, 2021

This erratum contains corrections to FDA's briefing information for the March 24-25, 2021 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee. At this meeting, the committees will discuss biologics license application (BLA) 761130, tanezumab subcutaneous injection, submitted by Pfizer Inc., for the proposed indication of relief of signs and symptoms of moderate to severe osteoarthritis in adult patients for whom use of other analgesics is ineffective or not appropriate.

Page vi (p 6 of pdf): Should read, "…The ETASU were amended by the Applicant to include prescriber certification, healthcare setting certification, pharmacy certification, patient enrollment, patient monitoring that includes bilateral X-rays of the knees and hips at baseline and then yearly thereafter, as well as monitoring each patient for signs and symptoms of RPOA."

Page 16 (p 29 of pdf): Table 2. Summary of Clinical Pharmacology Findings, "Bioanalysis" row strikeout and correction (*italics*) as follows:
The ~~Angiotensin-converting enzyme~~ *Affinity Capture Elution* (ACE) technique along with the ADA was used in the assay sensitivity and drug tolerance to minimize Nerve Growth Factor (NGF) interference.

Page 29 (p 42 of pdf): Should read, "There are no relevant trials that compare tanezumab to opioids."

Page 30, Section 3.3.2. (p 43 of pdf): FDA briefing document states:
The Applicant did not conduct subgroup analyses for efficacy. Responder analyses (based on percentage decrease in pain from baseline or OMERACT-OARSI [improvement ≥50% and ≥2 points on the WOMAC pain or function OR the patient experienced ≥20% improvement and ≥1 point on two of the three outcome measures {WOMAC pain, WOMAC function, patient global}]) did not suggest that a substantial proportion of patients treated with tanezumab were "super-responders ." However, because a continuous responder analysis was not conducted, the numbers of patients who experience large reductions in pain (e.g., 80 or 90%) are not known.

Correction: Pfizer conducted a categorical analysis for all the key efficacy parameters noted above, including 90% responders for WOMAC Pain. WOMAC Function 90% responder analyses and WOMAC Pain and Function. Continuous responder curves were presented in the CSRs for Studies 1056, 1057, and 1058. The percent of subjects with 90% improvement in WOMAC Pain or WOMAC Function was small, and similar for all treatment arms within each study.

Page 33 (p 46 of pdf): Tables 8 & 9 – Duration of Treatment
Replace with:

Table 8. Duration of Exposure, Safety Population, Placebo-Controlled Studies 1027, 1056, 1057

Variable	Placebo N=586 n (%)	Tanezumab 2.5 mg N=602 n (%)	Tanezumab 2.5/5 mg N=219 n (%)	Tanezumab 5 mg N=347 n (%)	Tanezumab 10 mg N=170 n (%)
Duration of treatment (days)					
Mean (SD)	126.4 (43.4)	130.5 (40.3)	113.3 (11.3)	149.4 (41.5)	80.7 (21.1)
Median (min, max)	115 (1, 183)	120 (2, 252)	113 (52, 169)	169 (8, 233)	85 (8, 114)
Subjects treated, by duration, n (%)					
<60 days	54 (9.2)	37 (6.1)	3 (1.4)	15 (4.3)	30 (17.6)
>=60 to <120 days	261 (44.5)	259 (43.0)	175 (79.9)	64 (18.4)	140 (82.4)
>=120 to <180 days	263 (44.9)	294 (48.8)	41 (18.7)	252 (72.6)	0
>=180 to <224 days	8 (1.4)	11 (1.8)	0	15 (4.3)	0
>=224 to <365 days	0	1 (0.2)	0	1 (0.3)	0
>=365 days	0	0	0	0	0

Source: adsl.xpt; Software: Python
14 subjects who were randomized to tanezumab 2.5/5 in Trial 1056 but only received the first dose of tanezumab 2.5 were summarized and analyzed as tanezumab 2.5.
The observation period was defined as the period from the Treatment Start Date in Period 1 (TR01SDT) up to the End of Treatment 1 Date (EOT1DCDT).
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

and

Table 9. Duration of Exposure, Safety Population, Trial 1058

Variable	NSAID N=996 n (%)	Tanezumab 2.5 mg N=1002 n (%)	Tanezumab 5 mg N=998 n (%)
Duration of treatment (days)			
Mean (SD)	251.2 (144.5)	256.2 (143)	254.2 (140.4)
Median (min, max)	262 (1, 490)	288 (1, 477)	280 (1, 530)
Subjects treated, by duration, n (%)			
<180 days	451 (45.3)	442 (44.1)	437 (43.8)
>=180 to <392 days	175 (17.6)	186 (18.6)	197 (19.7)
>=392 to <560 days	370 (37.1)	374 (37.3)	364 (36.5)
>=560 to <800 days	0	0	0
>=800 days	0	0	0

Source: adsl.xpt; Software: R
The observation period was defined as the period from the Treatment Start Date in Period 1 (TR01SDT) up to the End of Treatment Date (EOTDCDT).
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

Page 37 (p 50 of pdf): Table 12 – Deaths
Replace with:

Table 1. Deaths Up to End of Study and Post Study: OA + CLBP Controlled Pre- and Post-2015 Studies

Parameter	Tan Only N=8527 PY=5778‡	Tan+NSAID N=1530 PY=1083‡	Placebo N=2181 PY=927‡	NSAIDs N=2399 PY=1712‡	Oxy N=158 PY=46‡	Tramadol N=602 PY=531‡
Number (%) of subjects	24 (0.3)	5 (0.3)	3 (0.1)	1 (0.04)	0	1 (0.2)
Incidence rate*	4.2	4.6	3.2	0.6	0	1.9
Cause of death						
Cardiovascular	11	1	1	1		
Malignancy	3	2	1			
Infection	2					1
Overdose/toxicity	3					
Other	5	2	1			

Source: Medical reviewer Anjelina Pokrovnichka based on analyses provided by the FDA safety statistical review team
Studies included: 14 pre- and post- 2015 randomized, controlled OA and CLBP clinical studies: 1011, 1014, 1015, 1017, 1018, 1025, 1026, 1027, 1030, 1056, 1057, 1058, 1012, 1059 (for study description, refer to Section IV.6.1)
* Incidence rate per 1,000 PY.
‡ Total observation time. Observation time was defined as:
a) If subject experienced the event: Time from first IV/SC dose to the date of death.
b) If the subject did not experience the event: Time from first IV/SC dose to the end of study.
Abbreviations: OA, osteoarthritis; CLBP, Chronic Low Back Pain; N, number of subjects in treatment arm; PY, patient-years; Oxy, oxycodone

Page 41 (p 54 of pdf): Tables 16 and 17 Treatment-emergent Adverse Events
Replace with:

Table 16. Adverse Events Where the Incidence in Tanezumab is Greater Than the Comparator, Safety Population, Occurring in at Least 1.0% of Subjects in Treatment Arm, Placebo-Controlled Studies 1027, 1056, 1057

Preferred Term	Placebo N=586 n (%)	Tanezumab 2.5 mg N=602 n (%)	Tanezumab 2.5/5 mg N=219 n (%)	Tanezumab 5 mg N=347 n (%)	Tanezumab 10 mg N=170 n (%)
Any AE	357 (60.9)	378 (62.8)	130 (59.4)	221 (63.7)	80 (47.1)
Nasopharyngitis	49 (8.4)	61 (10.1)	16 (7.3)	31 (8.9)	0
Back pain	32 (5.5)	42 (7.0)	8 (3.7)	26 (7.5)	1 (0.6)
Musculoskeletal pain	23 (3.9)	31 (5.1)	7 (3.2)	13 (3.7)	4 (2.4)
Fall	21 (3.6)	35 (5.8)	9 (4.1)	10 (2.9)	2 (1.2)
Osteoarthritis	19 (3.2)	22 (3.7)	2 (0.9)	22 (6.3)	1 (0.6)
Pain in extremity	16 (2.7)	26 (4.3)	9 (4.1)	12 (3.5)	7 (4.1)
Upper respiratory tract infection	13 (2.2)	18 (3.0)	10 (4.6)	9 (2.6)	2 (1.2)
Joint swelling	13 (2.2)	17 (2.8)	6 (2.7)	12 (3.5)	4 (2.4)
Bronchitis	13 (2.2)	16 (2.7)	0	4 (1.2)	3 (1.8)
Influenza	10 (1.7)	14 (2.3)	1 (0.5)	11 (3.2)	1 (0.6)
Diarrhea	9 (1.5)	10 (1.7)	8 (3.7)	5 (1.4)	1 (0.6)
Hypoaesthesia	8 (1.4)	15 (2.5)	5 (2.3)	8 (2.3)	7 (4.1)
Urinary tract infection	8 (1.4)	15 (2.5)	4 (1.8)	4 (1.2)	2 (1.2)
Dizziness	8 (1.4)	11 (1.8)	4 (1.8)	6 (1.7)	3 (1.8)
Nausea	8 (1.4)	11 (1.8)	1 (0.5)	0	0
Paresthesia	7 (1.2)	15 (2.5)	3 (1.4)	14 (4.0)	12 (7.1)
Muscle spasms	6 (1.0)	8 (1.3)	5 (2.3)	3 (0.9)	3 (1.8)
Sinusitis	6 (1.0)	8 (1.3)	3 (1.4)	2 (0.6)	1 (0.6)

Source: adae.xpt; Software: Python

Treatment-emergent adverse events defined as the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period) or the event was seen prior to the start of treatment but increased in severity during treatment.
The observation period was defined as the period from treatment start date up to the end of the follow-up date of the study.
14 subjects who were randomized to tanezumab 2.5/5 in Trial 1056 but only received the first dose of tanezumab 2.5 were summarized and analyzed as tanezumab 2.5.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

and

Table 17. Adverse Events Where the Incidence in Tanezumab is Greater Than the Comparator, Occurring in at Least 1.0% of Subjects in Treatment Arm, Safety Population, Study 1058

Preferred Term	NSAID N=996 n (%)	Tanezumab 2.5 mg N=1002 n (%)	Tanezumab 5 mg N=998 n (%)
Any AE	663 (66.6)	679 (67.8)	742 (74.3)
Arthralgia	155 (15.6)	173 (17.3)	215 (21.5)
Fall	63 (6.3)	84 (8.4)	74 (7.4)
Nasopharyngitis	56 (5.6)	67 (6.7)	75 (7.5)
Musculoskeletal pain	46 (4.6)	58 (5.8)	63 (6.3)
Osteoarthritis	32 (3.2)	57 (5.7)	97 (9.7)
Headache	31 (3.1)	58 (5.8)	51 (5.1)
Hypoesthesia	19 (1.9)	30 (3.0)	29 (2.9)
Edema peripheral	19 (1.9)	21 (2.1)	45 (4.5)
Bronchitis	17 (1.7)	24 (2.4)	34 (3.4)
Contusion	16 (1.6)	22 (2.2)	21 (2.1)
Joint swelling	15 (1.5)	44 (4.4)	53 (5.3)
Paresthesia	14 (1.4)	18 (1.8)	32 (3.2)
Muscle strain	11 (1.1)	12 (1.2)	15 (1.5)
Rapidly progressive osteoarthritis	10 (1.0)	33 (3.3)	61 (6.1)
Cough	10 (1.0)	13 (1.3)	30 (3.0)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period) or the event was seen prior to the start of treatment but increased in severity during treatment.
The observation period was defined as the period from treatment start date up to the end of the follow-up date of the study.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

Page 59 (p 72 of pdf): Table 26 CJSE in Joints with Baseline KLB 0/1 (Study 1058)
Replace with:

Table 26. CJSE in Joints With Baseline KLG 0/1 (Study 1058)

	NSAIDs N=996 n (%)	Tanezumab 2.5 mg N=1002 n (%)	Tanezumab 5 mg N=998 n (%)
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: Created by clinical reviewer Anjelina Pokrovnichka using data provided in response to information request submitted on May 13, 2020
Abbreviations: CJSE, Composite Joint Safety Endpoint; KLG, Kellgren-Lawrence grade; NSAIDs (nonsteroidal anti-inflammatory drugs; RPOA, rapidly progressing osteoarthritis; SIF, subchondral insufficiency fracture; ON, osteonecrosis

Page 64 (p 77 of pdf): Table 29 title should read, "Incidence of All-Cause TJR and Adjudicated Joint Events in Study 1025"

Page 65 (p 78 of pdf): Unanswered questions
The first question about treatment failure is resolved and this bullet should be deleted.

Page 85-86 (p 98-99 of pdf): REMS Proposed by Applicant
In February, the proposed REMS was amended by the Applicant to include Prescriber Certification. Their revised goals and objectives are:

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

1. Ensuring healthcare providers are educated about the increased risk of rapidly progressive OA associated with the use of tanezumab.
2. Ensuring that healthcare providers are educated on and adhere to the following:
    a. Document that baseline and annual X-rays are completed to identify rapidly progressive OA and risk factors for rapidly progressive OA by submitting the Patient Enrollment Form and Patient Continuation Form.
    b. 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.
3. Ensuring safe use of tanezumab by:
    a. Ensuring that tanezumab is only administered to enrolled patients in certified healthcare settings after verification of baseline and annual X-rays, and counseling patients on the importance of avoiding NSAIDs.
4. Ensuring that patients are informed about:
    a. The increased risk of rapidly progressive OA associated with the use of tanezumab.
    b. The requirement for X-rays at baseline and annually thereafter if continuing treatment.
    c. The importance of avoiding NSAIDs while being treated with tanezumab and for 16 weeks after the last dose of tanezumab.

Under this proposal, the prescriber would be required to take training about the risk of RPOA. They would have to enroll into the REMS program and also enroll their patients. They would be responsible for assessing and monitoring the patient for RPOA for the duration of treatment. This includes obtaining x-rays at baseline and at yearly intervals. They would also counsel patients on avoiding NSAIDs and reporting symptoms of RPOA. The Applicant developed materials for these processes.

Page 90 (p 103 of pdf): Table 36 – Summary of Regulatory History

Add row below October 2, 2017 to document a January 12, 2018 Advice Letter that indicated that, at that time, the Division believed that the REMS with ETASU will be necessary to ensure that the benefits of the drug outweigh the risks of rapidly progressive osteoarthritis.

Pages 136-138 (p 149-151 of pdf): Figures 20, 21, and 22
The corresponding studies are 1056, 1057, and 1058, respectively. The source for all three figures is "statistical reviewer." The abbreviations are: LS= least square; TRT = treatment, and CTL = control.