General Safety and Tolerability of Subcutaneous Tanezumab for the Treatment of Osteoarthritis: A Pooled Analysis of Randomized, Placebo-Controlled Trials

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BACKGROUND

- Tanezumab, a monoclonal antibody against nerve growth factor (NGF), is in clinical development for the treatment of the signs and symptoms of osteoarthritis (OA).[1]
- Clinical trials conducted pre-2015 demonstrated that intravenous (IV) tanezumab provides efficacy in patients with OA of the knee or hip, but joint safety events and abnormal peripheral sensation were observed in some patients.[2-4] In addition, possible changes in sympathetic neuronal morphology were reported in preclinical studies.[5]
- Tanezumab OA trials conducted post-2015 used subcutaneous (SC) administration, excluded the tanezumab 10 mg dose, limited enrollment to patients with inadequate response to other OA treatments, restricted concomitant nonsteroidal anti-inflammatory drug (NSAID) use, and incorporated comprehensive sympathetic neurological and joint safety screening and monitoring approaches.
- Here we present a pooled analysis of patient-level data from 3 randomized, placebo-controlled, phase 3 trials of SC tanezumab in patients with moderate to severe OA and a history of inadequate response to other OA treatments (eg, acetaminophen, NSAIDs, opioids).
- The aim of the analysis was to summarize the general safety and tolerability of tanezumab with a focus on joint safety, events of abnormal peripheral sensation, and events of possibly decreased sympathetic function.

METHODS

Data Sources

- In study A4091027 (NCT01089725; conducted pre-2015), patients received IV and SC placebo, SC tanezumab 2.5 mg, SC tanezumab 5 mg, and IV or SC tanezumab 10 mg every 8 weeks for 16 weeks, with an 8-week safety follow-up period.[6] The IV tanezumab 10 mg arm is not included in the current presentation of SC data.
  - As a result of a 2010 clinical hold, most treated patients (90.5%) received only 1 dose of study medication. Of these, a majority (70.7%) remained in the study for more than 16 weeks.
- In study A4091056 (NCT02697773; conducted post-2015), patients received SC placebo (at baseline and Week 8), SC tanezumab 2.5 mg (at baseline and Week 8), or SC tanezumab 2.5/5 mg (2.5 mg at baseline and 5 mg at Week 8) for 16 weeks, with a 24-week safety follow-up period.[7]
- In study A4091057 (NCT02709486; conducted post-2015), patients received SC placebo, SC tanezumab 2.5 mg, or SC tanezumab 5 mg every 8 weeks for 24 weeks, with a 24-week safety follow-up period.[8]

Safety Assessments

- Data for overall treatment-emergent adverse events (TEAEs) were derived from all 3 studies.
- Data for the composite joint safety endpoint (events of rapidly progressive OA [RPOA] type 1 or 2, subchondral insufficiency fracture, primary osteonecrosis, or pathological fracture) and total joint replacements (TJRs) were derived from the 2 post-2015 studies, which incorporated comprehensive joint safety screening and monitoring procedures.
  - Radiographs of both knees, hips, and shoulders were obtained from all patients at screening and at various points during the trial. All radiographs were reviewed by a central reader for inclusion/exclusion criteria and possible joint safety events. All cases of TJRs and possible or probable joint safety events (reported as TEAEs or as determined by the central reader on post-baseline images) were reviewed by a blinded adjudication committee of external experts for a final decision on outcome/diagnosis.
- Data for TEAEs of abnormal peripheral sensation (eg, paresthesia, hypoesthesia, burning sensation) were derived from all 3 studies.
- Data for key TEAEs of possible decreased sympathetic function (syncope, bradycardia, orthostatic hypotension, anhidrosis, and hypohidrosis) were derived from the 2 post-2015 studies, which incorporated comprehensive sympathetic function safety screening and monitoring procedures.
- Data for overall TEAEs, TEAEs of abnormal peripheral sensation, and TEAEs of possible decreased sympathetic function were presented for the pooled treatment periods. However, because an imbalance in joint safety events typically persisted during the safety follow-up period (not seen for other safety endpoints), joint safety data were presented for the pooled full study (treatment + follow-up) periods.

RESULTS

Patients

- The pooled patient population (N=1840; placebo=586, tanezumab 2.5 mg=602, tanezumab 2.5/5 mg=219, tanezumab 5 mg=347, tanezumab 10 mg=86) was predominantly white (80.9%) and female (66.6%).
- The approximate mean (range) age and disease duration of the population was 62 (21–89) and 9 (0–52) years, respectively. A majority of patients (79.3%) had at least 2 joints with a Kellgren-Lawrence (KL) grade ≥2 (based on radiographs of both hips and both knees). A knee was designated as the index joint in 86.6% of patients.
- The mean (standard deviation [SD]) number of SC doses received was 2.2 (0.7), 2.3 (0.7), 2.0 (0.0), 2.6 (0.8), and 1.1 (0.3) in the placebo, tanezumab 2.5 mg, tanezumab 2.5/5 mg, tanezumab 5 mg, and tanezumab 10 mg arms, respectively.

Overall TEAEs

- TEAE rates were 51.7% for placebo, 52.3% for tanezumab 2.5 mg, 47.0% for tanezumab 2.5/5 mg, 54.8% for tanezumab 5 mg, and 39.5% for tanezumab 10 mg. A majority of events were mild or moderate in severity and few were considered severe or serious (**Table 1**).
- Among common TEAEs (occurring in ≥2% of patients in any group), injection site reaction (10 mg), edema peripheral (2.5/5 mg and 5 mg), joint stiffness (2.5/5 mg), synovial cyst (10 mg), hypoesthesia (10 mg), and paresthesia (5 mg and 10 mg) had a higher incidence (95% confidence interval [CI] excluded 0) in a tanezumab group relative to placebo.
- The proportion of patients discontinuing treatment due to TEAEs was 2.0%, 1.3%, 0.5%, 1.2%, and 0% for placebo, tanezumab 2.5 mg, tanezumab 2.5/5 mg, tanezumab 5 mg, and tanezumab 10 mg, respectively.
- The only TEAEs that led to treatment and/or study discontinuation in >1 patient in any group were arthralgia (placebo n=7, tanezumab 2.5 mg n=2, and tanezumab 2.5/5 mg n=1) and osteoarthritis (tanezumab 2.5 mg n=3).

Joint Safety Events

- No patients in the placebo group had an event included in the composite joint safety endpoint, while the proportion of patients who had an event included in the endpoint was 1.9% for tanezumab 2.5 mg, 0.5% for tanezumab 2.5/5 mg, and 3.2% for tanezumab 5 mg (**Table 2**).
  - The risk difference (95% CI) vs placebo was significantly greater for tanezumab 5 mg (3.17 [0.56 to 7.18]; *P*=0.037), but not for tanezumab 2.5 mg (1.89 [–0.05 to 4.71]; *P*=0.084) or tanezumab 2.5/5 mg (0.46 [–1.63 to 4.47]; *P*=0.696).
- The most common event was RPOA type 1 (see **Table 2** footnote for definition).
- The proportion of patients who had a TJR was 4.5% for placebo, 5.9% for tanezumab 2.5 mg, 6.8% for tanezumab 2.5/5 mg, and 7.0% for tanezumab 5 mg. These rates observed for tanezumab were not significantly different from placebo.
  - The risk difference (95% CI) vs placebo was 1.40 (–2.17 to 5.73) for tanezumab 2.5 mg (*P*=0.443), 2.37 (–2.24 to 8.60) for tanezumab 2.5/5 mg (*P*=0.333), and 2.57 (–1.72 to 8.10) for tanezumab 5 mg (*P*=0.253).

TEAEs of Abnormal Peripheral Sensation

- Rates of TEAEs of abnormal peripheral sensation were 2.2% (n=13) for placebo, 5.1% (n=31) for tanezumab 2.5 mg, 3.2% (n=7) for tanezumab 2.5/5 mg, 6.1% (n=21) for tanezumab 5 mg, and 12.8% (n=11) for tanezumab 10 mg. Paresthesia and hypoesthesia were the most common adverse events (**Table 3**).
- Most tanezumab-treated patients with a TEAE of abnormal peripheral sensation had only a mild event (77.1%), none had an event considered severe or serious, and only 1 patient discontinued treatment as a result (hypoesthesia in tanezumab 5 mg group). These adverse events typically resolved (75.7%).

Key TEAEs of Possibly Decreased Sympathetic Function

- Rates of key TEAEs of possibly decreased sympathetic function were 0.8% (n=4) for placebo, 1.5% (n=8) for tanezumab 2.5 mg, 0.5% (n=1) for tanezumab 2.5/5 mg, and 2.8% (n=8) for tanezumab 5 mg. Bradycardia and orthostatic hypotension were the most common adverse events (**Table 4**).
  - Exposure-adjusted incidence rates (events/1000 patient years) for any key TEAEs of possibly decreased sympathetic function were 21.4 for placebo, 40.4 for tanezumab 2.5 mg, 14.7 for tanezumab 2.5/5 mg, and 63.2 for tanezumab 5 mg.
    - The risk difference (95% CI) vs placebo was 19 (–15.9 to 54.0) for tanezumab 2.5 mg (*P*=0.286), –6.6 (–42.3 to 29.1) for tanezumab 2.5/5 mg (*P*=0.716), and 41.8 (–6.7 to 90.4) for tanezumab 5 mg (*P*=0.091).
- Most tanezumab-treated patients with a key TEAE of possibly decreased sympathetic function had an event that was mild (88.2%), none had an event considered severe or serious, none discontinued treatment due to these adverse events, and all events resolved.
- Overall, the number of patients who had a neurologic consultation due to a key TEAE of possibly decreased sympathetic function was 11 (2.1%) for placebo, 7 (1.3%) for tanezumab 2.5 mg, 5 (2.3%) for tanezumab 2.5/5 mg, and 5 (1.8%) for tanezumab 5 mg. No patient was diagnosed with a sympathetic neuropathy.

TABLE 1: Summary of overall TEAEs up to end of the pooled treatment periods[a]

Patients, n (%)	Placebo (n=586)	Tanezumab 2.5 mg (n=602)	Tanezumab 2.5/5 mg (n=219)	Tanezumab 5 mg (n=347)	Tanezumab 10 mg (n=86)
Number of TEAEs	647	684	209	482	78
Any TEAE	303 (51.7)	315 (52.3)	103 (47.0)	190 (54.8)	34 (39.5)
Serious TEAE	9 (1.5)	13 (2.2)	3 (1.4)	9 (2.6)	0
Severe TEAE	10 (1.7)	13 (2.2)	6 (2.7)	13 (3.7)	0
Discontinued treatment due to a TEAE	12 (2.0)	8 (1.3)	1 (0.5)	4 (1.2)	0
Common TEAEs[b]					
Arthralgia	67 (11.4)	52 (8.6)	19 (8.7)	30 (8.6)	4 (4.7)
Nasopharyngitis	33 (5.6)	44 (7.3)	11 (5.0)	23 (6.6)	0
Back pain	22 (3.8)	28 (4.7)	6 (2.7)	18 (5.2)	0
Headache	27 (4.6)	26 (4.3)	7 (3.2)	14 (4.0)	5 (5.8)
Paresthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)
Osteoarthritis	10 (1.7)	13 (2.2)	1 (0.5)	13 (3.7)	0
Joint swelling	10 (1.7)	15 (2.5)	4 (1.8)	10 (2.9)	2 (2.3)
Influenza	7 (1.2)	7 (1.2)	0	9 (2.6)	1 (1.2)
Fall	14 (2.4)	26 (4.3)	4 (1.8)	8 (2.3)	0
Musculoskeletal pain	15 (2.6)	14 (2.3)	2 (0.9)	8 (2.3)	1 (1.2)
Hypoesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)
Pain in extremity	10 (1.7)	14 (2.3)	7 (3.2)	7 (2.0)	3 (3.5)
Upper respiratory tract infection	9 (1.5)	14 (2.3)	3 (1.4)	7 (2.0)	0
Edema peripheral	1 (0.2)	6 (1.0)	6 (2.7)	6 (1.7)	0
Peripheral swelling	5 (0.9)	4 (0.7)	2 (0.9)	5 (1.4)	2 (2.3)
Diarrhea	7 (1.2)	9 (1.5)	5 (2.3)	4 (1.2)	0
Bronchitis	8 (1.4)	7 (1.2)	0	3 (0.9)	2 (2.3)
Synovial cyst	2 (0.3)	3 (0.5)	1 (0.5)	3 (0.9)	2 (2.3)
Joint stiffness	1 (0.2)	4 (0.7)	5 (2.3)	2 (0.6)	0
Urinary tract infection	4 (0.7)	10 (1.7)	3 (1.4)	2 (0.6)	2 (2.3)
Injection site reaction	3 (0.5)	2 (0.3)	0	1 (0.3)	4 (4.7)

[a] Treatment period was 16, 16, and 24 weeks for studies A4091027, A4091056, and A4091057, respectively.
[b] Occurring in ≥2% of patients in any treatment group.
TEAE, treatment-emergent adverse event.

TABLE 2: Summary of joint safety up to the end of the pooled full study periods[a]

Patients, n (%)	Placebo (n=514)	Tanezumab 2.5 mg (n=528)	Tanezumab 2.5/5 mg (n=219)	Tanezumab 5 mg (n=284)
Analyzed by the adjudication committee	**24 (4.7)**	**41 (7.8)**	**17 (7.8)**	**33 (11.6)**
Included in the composite joint safety endpoint	**0**	**10 (1.9)**	**1 (0.5)**	**9 (3.2)**
RPOA type 1[b]	0	6 (1.1)	1 (0.5)	5 (1.8)
RPOA type 2[c]	0	3 (0.6)	0	3 (1.1)
Primary osteonecrosis	0	0	0	1 (0.4)
Subchondral insufficiency fracture	0	1 (0.2)	0	0
Normal progression of OA	**22 (4.3)**	**30 (5.7)**	**16 (7.3)**	**19 (6.7)**
Other joint outcome[d]	**2 (0.4)**	**1 (0.2)**	**0**	**5 (1.8)**
With ≥1 TJR	23 (4.5)	31 (5.9)	15 (6.8)	20 (7.0)

[a] Full study comprised both the treatment + safety follow-up periods. This was 16 + 24 and 24 + 24 weeks for studies A4091056 and A4091057, respectively.
[b] RPOA type 1 was defined as a significant loss of joint space width ≥2 mm within approximately 1 year, without gross structural failure.
[c] RPOA type 2 was defined as abnormal bone loss or destruction, including limited or total collapse of at least 1 subchondral surface, which is not normally present in conventional end-stage OA.
[d] Other joint outcomes included 2 instances of preexisting conditions in the placebo group; 1 instance of preexisting conditions in the tanezumab 2.5 mg group; and 2 instances of preexisting conditions, 2 instances of no change in joint, and 1 instance of posttraumatic condition in the tanezumab 5 mg group.
OA, osteoarthritis; RPOA, rapidly progressive osteoarthritis; TJR, total joint replacement.

TABLE 3: Summary of TEAEs of abnormal peripheral sensation up to the end of the pooled treatment periods[a]

Patients, n (%)	Placebo (n=586)	Tanezumab 2.5 mg (n=602)	Tanezumab 2.5/5 mg (n=219)	Tanezumab 5 mg (n=347)	Tanezumab 10 mg (n=86)
Any TEAE	13 (2.2)	31 (5.1)	7 (3.2)	21 (6.1)	11 (12.8)
Serious TEAE	0	0	0	0	0
Severe TEAE	0	0	0	0	0
Discontinued treatment due to a TEAE	0	0	0	1 (0.3)	0
Specific TEAEs					
Paresthesia	6 (1.0)	14 (2.3)	3 (1.4)	14 (4.0)	6 (7.0)
Hypoesthesia	5 (0.9)	11 (1.8)	3 (1.4)	8 (2.3)	5 (5.8)
Burning sensation	1 (0.2)	1 (0.2)	0	2 (0.6)	0
Carpal tunnel syndrome	0	3 (0.5)	0	1 (0.3)	0
Sciatica	1 (0.2)	3 (0.5)	0	1 (0.3)	0
Decreased vibratory sense	3 (0.5)	1 (0.2)	1 (0.5)	1 (0.3)	1 (1.2)
Neuralgia	0	1 (0.2)	0	1 (0.3)	0
Neuropathy peripheral	0	0	0	1 (0.3)	1 (1.2)
Paresthesia oral	0	0	0	1 (0.3)	0
Hypoesthesia oral	1 (0.2)	0	0	0	0
Sensory disturbance	0	0	0	0	1 (1.2)

[a] Treatment period was 16, 16, and 24 weeks for studies A4091027, A4091056, and A4091057, respectively.
TEAE, treatment-emergent adverse event.

TABLE 4: Summary of key TEAEs of possibly decreased sympathetic function up to the end of the pooled treatment periods[a]

Patients, n (%)	Placebo (n=514)	Tanezumab 2.5 mg (n=528)	Tanezumab 2.5/5 mg (n=219)	Tanezumab 5 mg (n=284)
Any TEAE	4 (0.8)	8 (1.5)	1 (0.5)	8 (2.8)
Serious TEAE	0	0	0	0
Severe TEAE	0	0	0	0
Discontinued treatment due to a TEAE	0	0	0	0
Specific TEAEs				
Bradycardia	3 (0.6)	4 (0.8)	0	4 (1.4)
Orthostatic hypotension	1 (0.2)	3 (0.6)	1 (0.5)	3 (1.1)
Hypohidrosis	0	1 (0.2)	0	0
Syncope	0	0	0	1 (0.4)
Anhidrosis	0	0	0	0

[a] Treatment period was 16 and 24 weeks for studies A4091056 and A4091057, respectively.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Treatment with SC tanezumab up to 24 weeks (3 doses) was generally well tolerated in most patients with moderate to severe OA of the knee and hip, based on rates of overall TEAEs, serious TEAEs, and treatment/study discontinuations that were similar to those observed for placebo and no evidence of a sympathetic safety signal.
- Joint safety events, most commonly RPOA, were infrequent overall but more common with tanezumab than placebo. TJRs were not significantly increased with tanezumab in these placebo-controlled studies.
- TEAEs of abnormal peripheral sensation, most commonly paresthesia and hypoesthesia, were infrequent overall but more common with tanezumab than placebo.
- Joint safety events and TEAEs of abnormal peripheral sensation were less frequent with tanezumab 2.5 mg than with higher doses.
- It should be noted that studies included in these analyses were relatively short-term (16–24 weeks, 2–3 SC doses), placebo-controlled trials and longer-term comparator studies will provide additional information regarding long-term safety of tanezumab.

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DISCLOSURES

FB has served as a consultant and speaker to Pfizer Inc and Eli Lilly and Company. TS has served as a consultant to Pfizer Inc and Eli Lilly and Company. AK has served as an advisor, speaker, and consultant to Pfizer Inc and Eli Lilly and Company. LV is an employee of Eli Lilly and Company. AH, GP, MB, ID, and CW are employees of, and own stock/options in, Pfizer Inc.

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