Efficacy of Subcutaneous Tanezumab for the Treatment of Osteoarthritis Across Age Groups: A Subgroup Analysis of Pooled Data from Two Randomized, Placebo-Controlled Trials

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BACKGROUND

- Tanezumab is a monoclonal antibody that binds nerve growth factor (NGF) and prevents it from binding to its receptors.
- It is currently in development for relief of the signs and symptoms of moderate to severe osteoarthritis (OA) in adult patients for whom use of other analgesics is ineffective or not appropriate.
- Completed phase 3 studies in patients with OA have shown subcutaneous tanezumab to improve pain, physical function, and patient's global assessment of OA (PGA-OA).[1-4]
- Though serum NGF levels do not appear to alter with age,[5] it is important to confirm the efficacy of tanezumab in patients of different age.
- The purpose of this pooled, post hoc, subgroup analysis was to explore the efficacy of subcutaneous tanezumab in patients of different ages with OA.

METHODS

Studies

- A pooled exploratory analysis of patient-level data from 2 randomized, placebo-controlled, phase 3 trials of subcutaneous tanezumab (**Figure 1**).
- Both studies included patients aged ≥18 years with moderate to severe knee or hip OA that had not been adequately treated with acetaminophen, ≥1 oral nonsteroidal anti-inflammatory drug, and either tramadol or other opioids (or inability to tolerate/contraindication).
  - Patients with evidence of prespecified systemic or joint conditions were excluded to reduce the risk of rapidly progressive OA.
- The index joint was the most painful at baseline with a qualifying Western Ontario and McMaster Universities OA Index (WOMAC*) Pain score (≥5/10), WOMAC Physical Function score (≥5/10), PGA-OA of "fair=3," "poor=4," or "very poor=5," and Kellgren-Lawrence (KL) grade (≥2/4; increasing radiographic severity) as confirmed by the central reader.
- In study 1 (NCT02697773),[1] patients received 16 weeks of randomized subcutaneous treatment (1:1:1) and a 24-week safety follow-up:
  - Placebo (baseline and Week 8).
  - Tanezumab 2.5 mg (baseline and Week 8).
  - Tanezumab 2.5/5 mg (2.5 mg at baseline and 5 mg at Week 8). This data is pooled into the 5 mg group.
- In study 2 (NCT02709486),[2] patients received 24 weeks of randomized subcutaneous treatment (1:1:1) and a 24-week safety follow-up:
  - Placebo (baseline, Week 8, and Week 16).
  - Tanezumab 2.5 mg (baseline, Week 8, and Week 16).
  - Tanezumab 5 mg (baseline, Week 8, and Week 16).

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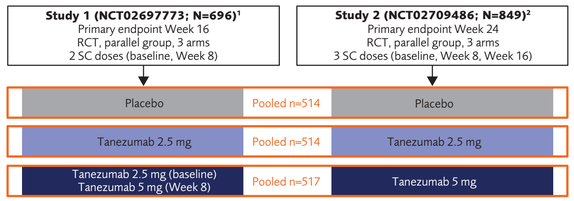
FIGURE 1: Study design for pooled analysis



RCT, randomized controlled trial; SC, subcutaneous.

Efficacy Assessments

- Co-primary endpoints in both studies were change from baseline in WOMAC Pain (0–10; increasing pain), WOMAC Physical Function (0–10; increasing difficulty), and PGA-OA (1–5; increasingly poorer assessment) scores at the end of treatment.

Statistical Analysis

- Pooled efficacy results are presented for the overall pooled population and age subgroups (<65, ≥65, <75, and ≥75 years) as least squares mean change from baseline to Week 16 vs placebo with standard error.
  - In the original studies, co-primary endpoints were planned for the overall population only, which included all patients who received treatment. Endpoints were originally planned for the end of treatment in each study (16 or 24 weeks).
- In this pooled analysis, outcomes were analyzed using an analysis of covariance model with terms for baseline score, baseline diary average pain, index joint, study number, and treatment group. Multiple imputation was used for missing values.
- This exploratory post hoc analysis was not part of the prespecified hypothesis testing plan nor included in any sample size calculations; therefore, comparisons between treatment or age subgroup should be conducted with caution.

RESULTS

Patients

- The majority of patients were female, white, and had a knee as the index joint. The average age was ~63 years and disease duration ~8–9 years (**Table 1**).
- The distributions of KL grades and WOMAC Pain, Physical Function, and PGA-OA scores were very similar between the groups at baseline (**Table 1**).
  - The majority of index joints had a KL grade of 3 or 4 (radiographs showed definite signs of OA, such as joint narrowing).
  - Mean WOMAC Pain and Physical Function scores at baseline were ~7 in all groups, suggesting moderate to severe OA-related pain and disability.
  - 1 patient in the placebo group and 1 in the tanezumab 2.5 mg group did not have baseline WOMAC Pain, Physical Function, and PGA-OA scores, so both were discounted from the efficacy analysis.

Tanezumab Efficacy in the Pooled Population

- Statistically significant mean reductions in WOMAC Pain, Physical Function, and PGA-OA were observed for the overall pooled population, as compared with placebo (**Figures 2–4**).

Tanezumab Efficacy by Age Subgroup

- Similar magnitudes of changes were observed when patients were grouped by age (**Figures 2–4**).
  - Changes observed for the 3 efficacy outcomes were statistically significant (unadjusted) compared with placebo for all age and dose combinations except 2.5 mg in the ≥75 years subgroup, possibly due to low patient numbers.

Minimally Important Change in Efficacy Measures

- Thresholds for clinically meaningful improvements in moderate to severe hip and knee OA using these efficacy measures have not been well defined for this patient population. Further study is required.
- Previously reported minimal clinically important changes in WOMAC Pain and Physical Function scores for hip and knee OA have ranged from –29.9 to –7.5 (pain) and –33.5 to –5.3 (function), on a 0–100 scale.[6-8]
- The PGA-OA is a patient-reported measure of disease status (1–5; increasingly poorer assessment), and as such, a numerical change of 1 likely denotes a clinically relevant change.
  - Previous studies have suggested the minimal clinically important difference for PGA-OA improvement is 0.4 on a Likert scale (0–4) and –15.2 (hip)/–18.3 (knee) on a visual analog scale (0–100).[7,8]

Overall Safety

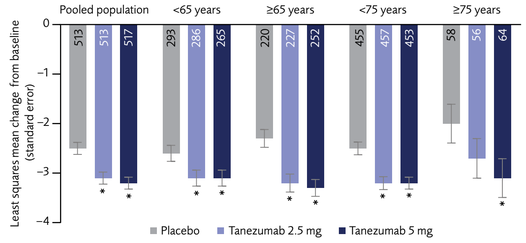
- Pooled safety analyses of subcutaneous tanezumab in 3 completed phase 3 studies have been recently reported.[9,10] Here, an additional study (NCT01089725) with 16 weeks of planned treatment was included. However, due to a clinical hold, <10% of patients received the second dose at Week 8.
  - Doses of 2.5 and 5 mg were generally well tolerated in patients with moderate to severe OA of the knee and hip.
  - Incidence of treatment-emergent adverse events and treatment/study discontinuations were similar to that observed for placebo and there was no evidence of a significant sympathetic safety signal.
  - Safety analyses showed a broadly similar safety profile for tanezumab in patients <65 and ≥65 years, with no meaningful differences.

TABLE 1: Baseline demographics and disease characteristics

	Placebo (n=514)	Tanezumab 2.5 mg (n=514)	Tanezumab 5 mg (n=517)
Female, n (%)	353 (68.7)	343 (66.7)	344 (66.5)
Age, mean years (SD)	62.5 (9.8)	63.2 (9.4)	63.4 (9.9)
Race, n (%)			
White	403 (78.4)	423 (82.3)	418 (80.9)
Black or African American	60 (11.7)	43 (8.4)	50 (9.7)
Asian	47 (9.1)	43 (8.4)	42 (8.1)
Other/unknown	4 (0.8)	5 (1.0)	7 (1.4)
Disease duration,[a] mean years (SD)	8.7 (8.1)	7.9 (7.8)	8.3 (7.2)
Index joint, n (%)			
Hip	80 (15.6)	83 (16.1)	83 (16.1)
Knee	434 (84.4)	431 (83.9)	434 (83.9)
KL grade at baseline,[b] n (%)			
2	124 (24.1)	109 (21.2)	117 (22.7)
3	221 (43.0)	232 (45.1)	226 (43.8)
4	169 (32.9)	170 (33.1)	173 (33.5)
WOMAC Pain,[c] mean score (SD)	6.9 (1.1)	6.9 (1.1)	6.9 (1.1)
WOMAC Physical Function,[c] mean score (SD)	7.0 (1.1)	7.0 (1.0)	7.0 (1.1)
PGA-OA,[c] mean score (SD)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)

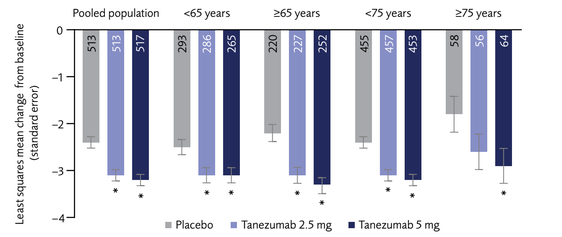
[a] Duration data missing for 2 patients in the 2.5 mg group and 2 in the 5 mg group.
[b] 3 additional patients with a KL grade of 0/1 in the index joint were included in the 2.5 mg group as protocol deviations. KL data for 1 patient missing in the 5 mg group.
[c] Data missing for 1 patient in the placebo group and 1 patient in the 2.5 mg group.
KL, Kellgren-Lawrence; OA, osteoarthritis; PGA-OA, patient's global assessment of OA; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities OA Index.

FIGURE 2: Change in WOMAC Pain from baseline to Week 16



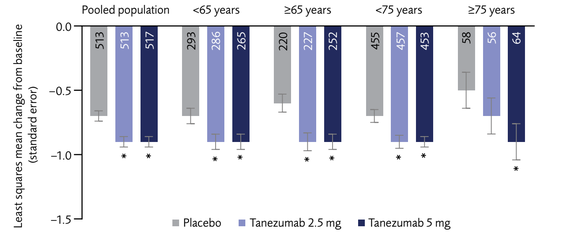
n values shown in the bars.
* P<0.05 by analysis of covariance.
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

FIGURE 3: Change in WOMAC Physical Function from baseline to Week 16



n values shown in the bars.
* P<0.05 by analysis of covariance.
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

FIGURE 4: Change in PGA-OA from baseline to Week 16



n values shown in the bars.
* P<0.05 by analysis of covariance.
PGA-OA, patient's global assessment of osteoarthritis.

CONCLUSIONS

- Subcutaneous tanezumab has efficacy in patients with moderate to severe hip and knee OA.
- Older patients appear to have similar improvements in efficacy as younger patients. When considering subcutaneous tanezumab for the treatment of OA in specific patients, age does not appear to influence improvements in pain, function, and PGA-OA.

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DISCLOSURES

YD'A receives book royalties from Springer Publishing, has been a consultant for Eli Lilly and Company and Pfizer, and has been a speaker for Salix. AK has been a consultant for AbbVie, Boehringer Ingelheim, Flexion, Gilead Sciences Inc., Janssen, Pfizer, Regeneron, Sanofi, and SUN Pharma Advanced Research, been a speaker for AbbVie, Celgene, Flexion, Genzyme, GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi, and UCB, and holds stock in Amgen, Gilead Sciences Inc., GlaxoSmithKline, Novartis, Pfizer, and Sanofi. BM has been a consultant for Eli Lilly and Company, Scilex, and Averitas and holds stock in Johnson and Johnson. JH and ZB are employees of Eli Lilly and Company and hold stock and/or stock options. SD and RY are employees of Pfizer and hold stock and/or stock options.

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