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

Francis Berenbaum[1], Bill McCarberg[2], Iris Zink[3], Claudia Rivera-Salas[3], Jerry Hall[4], Mojgan Sadrarhami[5], Ruoyong Yang[5]

[1]Sorbonne Université, INSERM, AP-HP Hospital Saint Antoine, Paris, France; [2]University of California, San Diego, CA, USA; [3]Lansing Rheumatology, East Lansing, MI, USA; [4]Eli Lilly and Company, Indianapolis, IN, USA; [5]Pfizer Inc, New York, NY, USA

BACKGROUND

- Tanezumab is a monoclonal antibody against nerve growth factor. 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.
- Previously completed phase 3 studies in patients with moderate to severe hip or knee OA have shown subcutaneous tanezumab to improve pain, physical function, and patient's global assessment of OA (PGA-OA).[1-4]
- Obesity is a known risk factor for both hip and knee OA.[5-7] Furthermore, obesity can alter the pharmacokinetics, and therefore the effectiveness, of some drugs.
- The purpose of this pooled, post hoc, subgroup analysis was to explore the efficacy of subcutaneous tanezumab in patients of differing body mass index (BMI) 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 were randomized to receive subcutaneous treatment (1:1:1) during a 16-week period with 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.

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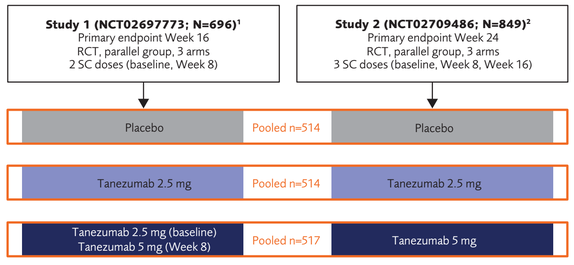
FIGURE 1: Study design for pooled analysis



RCT, randomized controlled trial; SC, subcutaneous.

- In study 2 (NCT02709486),[2] patients were randomized to receive subcutaneous treatment (1:1:1) during a 24-week period with 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).

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 BMI subgroups (<25, 25–<30, 30–<35, and ≥35 kg/m^2) 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 treatments or BMI subgroups should be conducted with caution.

RESULTS

Patients

- Overall, 67% of patients were female, 81% white, and 84% had a knee as the index joint. The average age was ~63 years and disease duration ~8–9 years (**Table 1**).
- The distribution 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 baseline 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.

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 BMI Subgroup

- Similar magnitudes of changes were observed when patients were grouped by BMI (**Figures 2–4**).
  - Changes in WOMAC Pain and Physical Function were statistically significant (unadjusted) compared with placebo in the majority of comparisons. Changes in PGA-OA were not generally statistically significant, likely due to the smaller range of the scale and the relatively low patient numbers in each group, as compared with the overall pooled population.

Minimally Important Change in Efficacy Measures

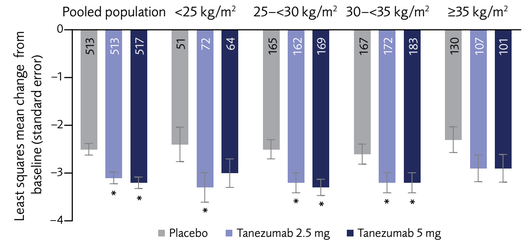
- Thresholds for clinically meaningful improvements in moderate to severe hip and knee OA using these efficacy measures have not been well defined for this patient population. Further study is required.
- Previously reported minimal clinically important changes in WOMAC Pain and Physical Function scores 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.[8-10]
- 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).[9,10]

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)
Body mass index, n (%)			
<25 kg/m^2	51 (9.9)	72 (14.0)	64 (12.4)
25–<30 kg/m^2	165 (32.1)	162 (31.5)	169 (32.7)
30–<35 kg/m^2	168 (32.7)	172 (33.5)	183 (35.4)
≥35 kg/m^2	130 (25.3)	108 (21.0)	101 (19.5)
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)

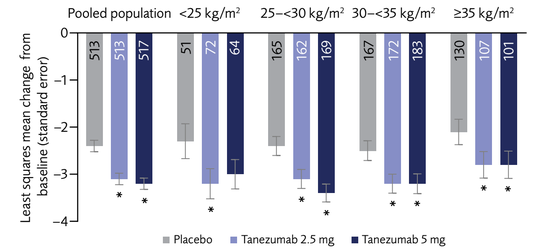
[a] Duration data missing for 2 patients in the 2.5 mg group and 2 in the 5 mg group.
[b] 3 additional patients with a KL grade of 0/1 in the index joint were included in the 2.5 mg group as protocol deviations. KL data for 1 patient missing in the 5 mg group.
[c] Data missing for 1 patient in the placebo 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



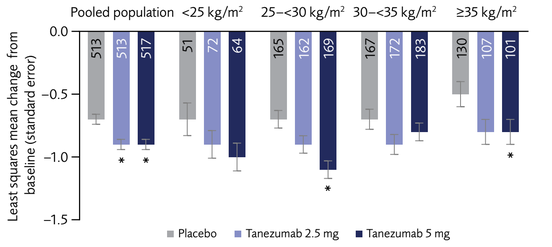
n values shown in the bars.
* P<0.05 by analysis of covariance.
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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.
BMI, body mass index; 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.
BMI, body mass index; PGA-OA, patient's global assessment of osteoarthritis.

CONCLUSIONS

- Subcutaneous tanezumab has demonstrated efficacy in patients with moderate to severe hip and knee OA.
- This exploratory analysis indicates that patient BMI does not influence the improvements in pain, physical function, and PGA-OA associated with short-term tanezumab use.

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DISCLOSURES

FB has received consulting fees or other remuneration from 4P Pharma, AbbVie, Boehringer Ingelheim, Bone Therapeutics, Eli Lilly and Company, Expanscience, Flexion, Galapagos, Gilead, GSK, Janssen, Medivir, Merck, Merck Serono, Nordic Pharma, Novartis, Peptinov, Pfizer, Regeneron, Regulaxis, Roche, Sandoz, Sanofi, Servier, TRB Chemedica, and UCB. BM has been a consultant for Eli Lilly and Company, Scilex, and Averitas and has stock in Johnson and Johnson. IZ has been a speaker for AbbVie, BMS, and Horizon. CRS has no disclosures. JH is an employee of Eli Lilly and Company and holds stock and/or stock options. MS and RY are employees of Pfizer and hold stock and/or stock options.

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