**Appendix Text 1.** Patients enrolled in Study CL001 were 35 to 65 years of age with a body mass index (BMI) of 18 to 39 kg/m2, and in general good health except for diagnosis of OA of the knee, present for at least 6 months, using the American College of Rheumatology criteria [[1](#_ENREF_1)]. To be eligible for the study, patients had to indicate a minimum joint pain intensity score of ≥40 points on an electronically validated Visual Analog Scale (VAS; scale 0−100 points, with higher scores denoting greater pain), or require medication for the control of OA pain for more than 75% of days during the 3 months prior to Screening. Patients then had to have a mean daily VAS pain score ≥25 in an electronic diary on at least 4 of the 7 days immediately prior to the day of randomization and have proper electronic diary compliance over this time, (defined as at least 75% on 3 consecutive days with 4 diary entries per day).

Key exclusion criteria included the diagnosis or history of rheumatoid arthritis, inflammatory arthritis of any kind, gout, Paget’s disease, or any disease that would interfere with assessment of pain and other symptoms of OA; fibromyalgia; peripheral neuropathy requiring medication for pain control or interfering with performance of activities of daily living; arthroscopy or surgery on the index knee within the past 6 months or intra-articular viscosupplementation in the index knee joint within the past 4 months; pregnancy or lactation; history or symptoms of autoimmune disorders; cancer within the past 5 years, other than cutaneous basal cell or squamous cell cancer removed by excision; diabetes mellitus requiring oral hypoglycemic agents or insulin; significant head trauma in the past year; hospital admission for asthma, chronic obstructive pulmonary disease, or other chronic respiratory disease within the past 2 years; history of alcohol or drug abuse; tobacco consumption (>0.5 pack cigarettes per day); hepatitis B or C; human immunodeficiency virus (HIV) infection; previous exposure to NGF or an anti-NGF antibody; allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody or IgG-fusion protein; clinically significant cardiovascular or neurological disease or psychiatric disorders; or other significant medical conditions.

**Reference**

[1] Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum 2000;43(9):1905-1915.

**Appendix Text 2.** The following treatments were required to be discontinued at least 60 days before study drug administration and throughout the study: topical capsaicin preparations, intra-articular corticosteroids in the index knee. Hyaluronic acid or viscosupplementation in the index knee was to be discontinued 120 days prior to study drug and throughout the study. Patients could use one type of rescue medication except for the 2 days prior to and after administration of study drug. Allowed rescue medications were acetaminophen (500 mg to a maximum of 4000 mg/day) or ibuprofen (200 mg to a maximum of 1600 mg/day). Rescue medication use (allowed only for pain in the index knee) was recorded daily. Patients were admitted to a Phase 1 unit for assessments on study Days –1, 1, and 2, and observed for 24 hours after study drug administration prior to discharge. Eligible patients were randomized to tanezumab or placebo treatment.

**Appendix Text 3.** The safety population included all patients who received ≥1 administration of study drug, while the modified intent-to-treat (mITT) population included all patients who received ≥1 administration of study drug and had ≥1 post-dosing pain assessment for efficacy. The sample size of 4 to 6 tanezumab-treated patients in each cohort in Part 1 was sufficient to provide adequate safety data for evaluation. For Part 2, a sample size of 33 patients per arm (total sample size of 99 patients) was required to detect statistical significance at 81% power with a type I error rate of 5% and effect size of 0.617. The primary comparison was the combined tanezumab groups versus placebo. The study sponsor stopped enrollment when 79 patients had been treated because they were made aware of 2 serious adverse events (pseudoseizure and seizure) in patients receiving tanezumab 300 µg/kg in Study CL002 that were considered by the investigator to be treatment-related. This sample size provided power of 72% at a type I error rate of 5% and effect size of 0.617.

The primary efficacy measure, SPID for VAS in current knee pain for Days 2 to 14, for the combined tanezumab treatment groups compared with placebo was assessed using analysis of covariance (ANCOVA) with adjustment for baseline pain scores. Changes in current knee pain (SPID) for other time points, comparisons between each dose and placebo, changes in WOMAC scores and subscales, and walking pain (SPID) also were analyzed by ANCOVA. Rescue medication usage (as a sum of the number of pills used) for each tanezumab dose compared with placebo was analyzed via analysis of variance (ANOVA). Analyses of pharmacodynamic (PD) endpoints (defined as efficacy assessments in Part 1 of the study) employed the same statistical analyses, although exploratory analyses to determine treatment effect over time also were performed. Statistical significance was α = 0.05 (2-sided) for all analyses. Unless otherwise noted, results are presented as the least squares (LS) mean versus placebo.

**Appendix Text 4.** Healthy men or women aged 18 to 65 years with a BMI of 18 to 39 kg/m2 and requisite memory function (defined as HVLT-R total recall score of ≥22) [[2](file:///C:\Users\JENNIE~1.KIN\AppData\Local\Temp\Appendix%20Text%204.docx#_ENREF_2)] who underwent primary unilateral first metatarsal bunionectomy and met criteria for American Society of Anesthesiologists Classes I and II were enrolled [[1](file:///C:\Users\JENNIE~1.KIN\AppData\Local\Temp\Appendix%20Text%204.docx#_ENREF_1)].

Key exclusion criteria were diagnosis of any concurrent condition that would interfere with assessment of postoperative pain: loss of sensation affecting the foot; neurological or painful conditions affecting the foot or ankle of the operative foot; and chronic pain conditions such as fibromyalgia, osteoarthritis, or rheumatoid arthritis requiring medication for pain control. In addition, patients were excluded if they had peripheral vascular disease affecting the operative foot. Other key exclusion criteria relating to general health were similar to those described for Study CL001.

**References**

1. American Society of Anesthesiologists (ASA). ASA Physical Status Classification System

2. Brandt J, Benedict RHB. Hopkins Verbal Learning Test-Revised Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc., 2001.

**Appendix Text 5.** The first dose of postoperative rescue medication was acetaminophen/codeine (300 mg/30 mg). Allowed rescue medications at all other times were ibuprofen (400 mg to a maximum of 8 tablets or 3200 mg/day), acetaminophen/codeine (300 mg/30 mg; up to a maximum of 12 tablets/day), or ketorolac (30 mg IV to a maximum of 120 mg/day during the research unit admission portion of the study only). Less potent medication was to be considered first, when possible, and patients were instructed to use rescue medication only when truly necessary for pain. Individual patients could receive additional analgesic medications on a case-by-case basis if judged clinically appropriate by the investigator.

**Appendix Text 6.** The safety population included all patients who received ≥1 administration of study drug, and the mITT population included all patients who received ≥1 administration of study drug and had ≥1 post-dosing pain assessment for efficacy. The study was not fully powered to detect statistically significant differences in efficacy and sample size was based on accurate characterization of PK parameters. It was deemed that 8 subjects per tanezumab arm was adequate for this purpose. To enable a preliminary evaluation of tanezumab efficacy, a sample size using a 4:1 ratio of tanezumab:placebo within each dose cohort was used, resulting in a total sample size of 40:10 for tanezumab- and placebo-treated patients, respectively. Intermittent missing data were imputed by linear interpolation. Last observation carried forward (LOCF) imputation was used for ≥3 consecutive missing data scores.

Analysis of PD parameters used an ANOVA model for comparisons of each tanezumab dose with placebo. *P*-values were reported adjusted using Dunnett’s correction for multiple treatment comparisons and unadjusted for multiple comparisons as appropriate for studies with exploratory analyses for efficacy. The number of patients requiring rescue medication and patients who stopped using rescue medication were analyzed using a 2-sided Fisher’s exact test. The time to first use of rescue medication was analyzed using the log-rank test. Analysis of number of days without rescue medication was carried out using ANOVA with unadjusted *P*-values. PGE was analyzed using Fisher’s exact test for categorical response, and a mixed-model, repeated-measures analysis with model terms for treatment group, study day, and treatment-by-day interaction.

**Appendix Text 7.** The patient who was reported to have pseudoseizures was a 24-year-old female with a history of pseudoseizure and head injury who exhibited 2 serious adverse events of seizure-like activity reported on study Days 113 and 127. On both occasions, the patient was hospitalized after presenting with seizure-like activity which persisted despite treatment with anticonvulsants in the emergency room. Inpatient work-up included computed tomography and magnetic resonance imaging scans following the first event, which were normal, and laboratory tests that were generally normal. An electroencephalogram (EEG) revealed a normal, mostly asleep, EEG and no epileptiform activity was seen. During the hospitalization, the patient was evaluated by psychiatric and neurologic staff. Continuous video EEG monitoring, which is the gold standard for diagnosis of pseudoseizure, was not performed. However, following review of the information in the case, the investigator considered the patient to have pseudoseizures rather than a seizure disorder.

There were no deaths. No clinically significant changes in vital signs or ECG parameters were noted between tanezumab and placebo-treated patients in either study. HVLT-R showed no notable mean changes from baseline in any treatment group and no notable differences between the tanezumab and placebo.

**Appendix Text 8.** Occurrence of adverse events of abnormal peripheral sensation appeared to be dose-dependent since none of these adverse events were reported by any patients receiving the lowest tanezumab doses (≤30 µg/kg) and were more frequently seen with the 2 highest doses (≥300 µg/kg). Most adverse events of abnormal peripheral sensation were initially reported within the first 2 weeks of the IV infusion, resolved by 4 weeks, and generally were mild or moderate in severity. None of the patients who reported adverse events of abnormal peripheral sensation had objective evidence of sensory loss on neurological examination. In Study CL001, 3 patients in the tanezumab 300-μg/kg group and 1 patient in the placebo group reported peripheral neuropathy; only 1 patient (from the tanezumab 300-μg/kg group) was documented as experiencing an adverse event of peripheral neuropathy (**Appendix Table 2**). At study day 91, the investigator noted that this patient had “decreased pinprick discrimination in L-4/L-5 distribution, missed approximately 40% of sharp/dull discriminant, decreased pinprick to left hand missed approximately 50% of sharp/dull discriminants”; this abnormality was noted to be Grade 1 according to the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE). This case was documented as a mild-intensity adverse event, which was considered related to the study drug, and from which the patient recovered. Subsequent neurological examinations noted no abnormalities. The 2 other patients from the tanezumab 300-μg/kg group had “decreased sensation of right lateral foot, grade 1 and mild weakness of right peroneal muscles” (in 1 patient) and “right foot sensation (sharp/dull) below baseline.” The investigator reported “vibratory and sharp/dull sensation below baseline” in the placebo patient. The abnormalities in these 3 patients were noted to be NCI CTCAE Grade 1 and all subsequent neurological examinations were normal.

In Study CL002, 4 patients in the tanezumab 30-μg/kg, 100-μg/kg, and 1000-μg/kg groups had abnormal findings in their neurological examinations conducted at study visits. However, only 1 patient in the tanezumab 1000-μg/kg group developed persistent symptoms suggestive of peripheral neuropathy; no case was documented as an adverse event (**Appendix Table 3**).

Among patients who received tanezumab 1000 µg/kg, 2 of 6 patients in Study CL001 and 5 of 8 patients in Study CL002 reported a dysesthesia-like adverse event. In addition, 1 patient receiving tanezumab 100 µg/kg in Study CL001 reported dysesthesia. All cases were judged related to study drug by the investigators, and no patients receiving placebo reported any dysesthesia-like adverse event at that time. No patients in Study CL001 had objective evidence of sensory loss on neurological examination, and the investigators stated that peripheral neuropathy had not been present in these or any other patients. However, it was considered that these subjective sensations could have been interpreted as neuropathic in quality. Therefore, a decision was made to halt the dose escalation at 1000 µg/kg and remove a planned tanezumab 2000-µg/kg tanezumab cohort in CL001.

In Study CL002, wound healing following bunionectomy surgery was evaluated by a podiatrist using a wound-healing scale on Day 12 and a postoperative radiograph of the affected foot on Day 49 ± 7 days; all patients healed normally. Two patients treated with tanezumab (1 who received tanezumab 30 μg/kg and 1 in the tanezumab 300-μg/kg group) had serosanguinous discharge at Day 12. Although the sample size is small, these results suggest that tanezumab did not affect wound healing after surgery.

**Supplementary Table 1.** Treatment-emergent adverse events in Study CL001, Part 1, following administration of a single dose of tanezumab.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Tanezumab  3 µg/kg  (*n* = 4) | Tanezumab  10 µg/kg  (*n* = 4) | Tanezumab  30 µg/kg  (*n* = 4) | Tanezumab  100 µg/kg  (*n* = 6) | Tanezumab  300 µg/kg  (*n* = 6) | Tanezumab  1000 µg/kg  (*n* = 6) | Placebo  (*n* = 12) |
| Patients reporting: |  |  |  |  |  |  |  |
| Any adverse events, *n* | 3 | 2 | 4 | 6 | 4 | 5 | 10 |
| Serious adverse events, *n* | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Discontinued due to adverse events, *n* | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse events reported by ≥2 tanezumab- or placebo-treated patients | | | | | | | |
| Areflexia, *n* | 0 | 0 | 1 | 1 | 1 | 0 | 3 |
| Chest pain, *n* | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Cough, *n* | 0 | 0 | 1 | 0 | 1 | 1 | 2 |
| Diarrhea, *n* | 0 | 0 | 1 | 2 | 0 | 1 | 0 |
| Dizziness, *n* | 1 | 0 | 0 | 0 | 0 | 1 | 2 |
| Dysethesia, *n* | 0 | 0 | 0 | 1 | 0 | 2 | 3 |
| Headache, *n* | 1 | 2a | 1 | 2a | 1 | 1a | 2 |
| Adverse events of abnormal peripheral sensation | | | | | | | |
| Burning sensation, *n* | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Dysethesia, *n* | 0 | 0 | 0 | 1a | 0 | 2a | 0 |
| Hyperesthesia, *n* | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Hypoesthesia, *n* | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Paresthesia, *n* | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

a Judged by the investigator as treatment-related.

**Supplementary Table 2.** Treatment-emergent adverse events in Study CL001, Part 2, following administration of a single dose of tanezumab.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Tanezumab  100 µg/kg  (*n* = 27) | Tanezumab  300 µg/kg  (*n* = 26) | Placebo  (*n* = 26) |
| Patients reporting: |  |  |  |
| Any adverse events, *n* (%) | 25 (92.6) | 23 (88.5) | 18 (69.2) |
| Serious adverse events, *n* (%) | 0 | 0 | 0 |
| Discontinued due to adverse events, *n* (%) | 0 | 0 | 0 |
| Adverse events reported by ≥5% of tanezumab-treated patients | | | |
| Abdominal distension | 2 (7.4) | 0 | 0 |
| Arthralgia | 4 (14.8) | 4 (15.4) | 3 (11.5) |
| Back pain | 1 (3.7) | 2 (7.7) | 1 (3.8) |
| Cough | 2 (7.4) | 1 (3.8) | 1 (3.8) |
| Diarrhea | 4 (14.8) | 7 (26.9) | 2 (7.7) |
| Dizziness | 3 (11.1) | 0 | 2 (7.7) |
| Dysesthesia | 2 (7.4) | 2 (7.4) | 0 |
| Dyspepsia | 2 (7.4) | 0 | 2 (7.7) |
| Gamma-glutamyltransferase increased | 2 (7.4) | 0 | 0 |
| Headache | 7 (25.9) | 8 (30.8) | 7 (26.9) |
| Joint swelling | 0 | 3 (11.5) | 0 |
| Muscle tightness | 2 (7.4) | 0 | 0 |
| Musculoskeletal pain | 2 (7.4) | 0 | 0 |
| Nasopharyngitis | 0 | 1 (3.8) | 2 (7.7) |
| Nausea | 1 (3.7) | 1 (3.8) | 3 (11.5) |
| Pain in extremity | 3 (11.1) | 6 (23.1) | 2 (7.7) |
| Peripheral edema | 3 (11.1) | 2 (7.7) | 2 (7.7) |
| Rhinitis | 2 (7.4) | 1 (3.8) | 0 |
| Wheezing | 0 | 2 (7.7) | 0 |
| Adverse events of abnormal peripheral sensation | | | |
| Allodynia, *n* (%) | 0 | 1 (3.8) | 0 |
| Dysethesia, *n* (%) | 2 (7.4) | 2 (7.7) | 0 |
| Hyperesthesia, *n* (%) | 2 (7.4) | 0 | 0 |
| Hypoesthesia, *n* (%) | 2 (7.4) | 1 (3.8) | 1 (3.8) |
| `Paresthesia, *n* (%) | 4 (14.8) | 6 (23.1) | 0 |
| Hyperpathia, *n* (%) | 0 | 1 (3.8) | 0 |
| Neuralgia, *n* (%) | 0 | 1 (3.8) | 0 |
| Peripheral sensory neuropathy, *n* (%) | 0 | 1 (3.8) | 0 |

**Supplementary Table 3.** Treatment-emergent adverse events in Study CL002 following administration of a single dose of tanezumab.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Tanezumab  10 µg/kg  (*n* = 8) | Tanezumab  30 µg/kg  (*n* = 8) | Tanezumab  100 µg/kg  (*n* = 8) | Tanezumab  300 µg/kg  (*n* = 8) | Tanezumab  1000 µg/kg  (*n* = 8) | Placebo  (*n* = 10) |
| Patients reporting: |  |  |  |  |  |  |  |
| Any adverse events, *n* (%) |  | 7 (87.5) | 8 (100.0) | 6 (75.0) | 8 (100.0) | 8 (100.0) | 8 (80.0) |
| Serious adverse events, *n* (%) |  | 0 | 0 | 0 | 2 (25.0)a | 1 (12.5)a | 0 |
| Discontinued due to adverse events, *n* (%) | | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse events reported by ≥2 of tanezumab- or placebo-treated patients, or combined | | | | | | | |
| Allodynia, *n (%)* |  | 0 | 0 | 0 | 0 | 4 (50) | 0 |
| Arthralgia, *n* (%) |  | 0 | 0 | 0 | 0 | 2 (25.0) | 0 |
| Convulsion, *n* (%) |  | 0 | 0 | 0 | 2 (25.0) | 0 | 0 |
| Cough, *n* (%) |  | 0 | 1 (12.5) | 1 (12.5) | 1 (12.5) | 0 | 0 |
| Diarrhea, *n* (%) |  | 0 | 1 (12.5) | 0 | 1 (12.5) | 2 (25.0) | 0 |
| Dizziness, *n* (%) |  | 1 (12.5) | 4 (50.0) | 3 (37.5) | 3 (37.5) | 0 | 3 (30.0) |
| Dysethesia, *n* (%) |  | 0 | 0 | 0 | 0 | 1 (12.5) | 0 |
| Headache, *n* (%) |  | 2 (25.0) | 2 (25.0) | 1 (12.5) | 5 (62.5) | 0 | 0 |
| Hematuria, *n* (%) |  | 0 | 0 | 1 (12.5) | 0 | 1 (12.5) | 0 |
| Menorrhagia, *n* (%) |  | 0 | 0 | 1 (12.5) | 0 | 1 (12.5) | 0 |
| Muscle spasms*, n* (%) |  | 0 | 0 | 0 | 0 | 2 (25.0) | 0 |
| Muscle twitching, *n* (%) |  | 0 | 0 | 1 (12.5) | 1 (12.5) | 0 | 0 |
| Musculoskeletal chest pain, *n* (%) |  | 1 (12.5) | 1 (12.5) | 0 | 0 | 0 | 0 |
| Myalgia, *n* (%) |  | 1 (12.5) | 1 (12.5) | 0 | 0 | 1 (12.5) | 1 (10.0) |
| Nausea, *n* (%) |  | 2 (25.0) | 5 (62.5) | 1 (12.5) | 3 (37.5) | 1 (12.5) | 5 (50.0) |
| Nasopharyngitis, *n* (%) |  | 0 | 2 (25.0) | 0 | 1 (12.5) | 2 (25.0) | 4 (40.0) |
| Pain (General disorder / admin site) |  | 0 | 1 (12.5) | 0 | 0 | 1 (12.5) | 0 |
| Pain in extremity, *n* (%) |  | 0 | 0 | 1 (12.5) | 0 | 1 (12.5) | 0 |
| Pharyngitis streptococcal, *n* (%) |  | 0 | 0 | 1 (12.5) | 2 (25.0) | 0 | 0 |
| Somnolence, *n* (%) |  | 0 | 0 | 1 (12.5) | 0 | 1 (12.5) | 0 |
| Upper abdominal pain, *n (%)* |  | 1 (12.5) | 1 (12.5) | 0 | 0 | 0 | 2 (20.0) |
| Vomiting, *n* (%) |  | 1 (12.5) | 1 (12.5) | 1 (12.5) | 1 (12.5) | 2 (25.0) | 3 (30.0) |
| Adverse events of abnormal peripheral sensation | | | | | | | |
| Allodynia, *n* (%) |  | 0 | 0 | 0 | 0 | 4 (50.0) | 0 |
| Dysethesia, *n* (%) |  | 0 | 0 | 0 | 0 | 1 (12.5) | 0 |

a Judged by the investigator as treatment-related.