2. SYNOPSIS

Name of Sponsor: Amgen, Inc.

Name of Finished Product: Romosozumab

Name of Active Ingredient: Romosozumab (AMG 785)

Title of Study: A Multi-center, Randomized, Double-blind, Placebo-controlled Study of AMG 785 in Skeletally Mature Adults with a Fresh Unilateral Tibial Diaphyseal Fracture Status Post Definitive Fracture Fixation with an Intramedullary Nail
Study To Assess Healing of Repaired Tibias with SclerosTin Antibody (STARTT)

Investigator(s) and Study Center(s): This study was conducted at 66 centers in Europe, India, North America, Australia, New Zealand, Hong Kong, and Mexico. Centers and principal investigators are listed in Appendix 4.

Publications: none

Study Period: 02 September 2009 (first subject enrolled) to 14 September 2012 (last subject completed end-of-study visit)

Development Phase: 2a

Objectives: The primary objective was to investigate the effect of romosozumab compared to placebo on time to radiographic healing of fresh tibial diaphyseal fractures.

Secondary objectives were to evaluate the effect of romosozumab compared to placebo on the following:

- physical functioning as measured by Short Form (36) Health Survey Physical Functioning subscale (SF-36 PF),
- incidence of unplanned revision surgery, and
- time to clinical healing as determined by the ability to bear weight on the fractured limb and the absence of pain at the fracture site (Functional Index in Trauma [FIX-IT]).

Exploratory, safety, pharmacokinetic, and pharmacodynamic objectives are listed in the protocol, included as Appendix 1.

Methodology: This was an international, multi-center, randomized, double-blind, placebo-controlled study of romosozumab in skeletally mature adults with a fresh unilateral tibial diaphyseal fracture status post a definitive fracture fixation with an intramedullary (IM) nail.

Subjects were randomized 1:1:1:1:1:1:1:1:1:3 to 1 of 9 romosozumab treatment groups (2, 3, or 4 doses each of 70, 140, or 210 mg) or placebo. All subjects were required to take at least 1000 mg of elemental calcium and 800 IU of vitamin D daily from screening to week 36.

Subjects undergoing definitive fracture fixation were screened during hospitalization. Fracture fixation must have been completed no later than 14 days after a closed fracture or no later than 24 hours after an open fracture. Randomization followed surgery and was stratified by type of fracture and definitive fracture fixation (closed with reamed IM nail, Gustilo type I/II open with reamed IM nail, Gustilo type I/II open with unreamed IM nail).

The primary analysis of the primary endpoint was performed after all subjects had the opportunity to complete the scheduled week 24 assessments. At the same time, an interim analysis of the secondary and exploratory endpoints was completed. The end-of-study analysis was performed after all subjects had the opportunity to complete the scheduled week 52 assessments.

Number of Subjects Planned: approximately 400

Number of Subjects Enrolled: 402

Diagnosis and Main Criteria for Eligibility: Key inclusion criteria were as follows:

- skeletally mature adults, age ≥18 to ≤ 85 years at randomization, with radiographically closed growth plates
- fresh unilateral closed or Gustilo type I or type II open tibial diaphyseal fracture (fracture line must not have extended into the ankle or knee joint) as the primary injury

Key exclusion criteria were as follows:

- major polytrauma or significant axial trauma, with injury severity score > 16
- head injury, as defined by Glasgow Coma Scale < 13 at time of randomization
- associated fracture of the lower extremity or any other condition that, in the opinion of the surgeon, would delay the subject's ability to bear weight beyond the normal time expected for a tibial shaft fracture
- use of bone grafts at the time of definitive fracture fixation
- history of pathological fracture or metabolic or bone disease that could interfere with the interpretation of the results, such as Paget's disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, Cushing's disease, or hyperprolactinemia
- history of symptomatic spinal stenosis that had not been corrected surgically (If surgically corrected, the subject must have been asymptomatic to be eligible for the study.)
- history of facial nerve paralysis
- malignancy (except fully resected cutaneous basal cell or squamous cell carcinoma, cervical carcinoma in situ) within the last 5 years
- history of solid organ or bone marrow transplants
- evidence (currently or within the past 5 years) of elevated transaminases (≥ 2.0 x upper limits of normal) or significantly impaired renal function (creatinine clearance of ≤ 30 mL/min)
- evidence of current hypercalcemia or hypocalcemia (outside of 1.1 x the normal range)

Full inclusion and exclusion criteria are listed in the protocol, included as Appendix 1.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Romosozumab was administered subcutaneously (SC) at doses of 70, 140, or 210 mg. Manufacturing batch numbers of romosozumab were [redacted].

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Matched placebo was administered SC. Manufacturing batch numbers of placebo were [redacted].

Duration of Treatment: After randomization, subjects were followed for a 52-week treatment and observation period.

Study Endpoints: The primary endpoint was time to radiographic healing of tibial fracture for the romosozumab and placebo groups, defined as bridging of 3 out of 4 cortices. Radiographic fracture healing was determined by a panel of independent reviewers (orthopedic/trauma surgeons and radiologists) blinded to treatment.

Secondary endpoints evaluated for the romosozumab and placebo groups were as follows:

- physical functioning as measured by change from baseline at weeks 12, 16, 20, 24, 36, and 52 in the SF-36 PF subscale
- subject incidence of unplanned revision surgery by week 52
- time to clinical healing as determined by the ability to bear weight on the fractured limb (FIX-IT score of 6) and the absence of pain at the fracture site (FIX-IT score of 6).

Exploratory, safety, pharmacokinetic, and pharmacodynamic endpoints are listed in the statistical analysis plan, included as Appendix 2.

Statistical Methods: The primary analysis for the primary endpoint was a test for dose response using linear contrasts on dose schedule and dose level. If the test of dose-response was significant at 0.05, pairwise comparison of each romosozumab schedule versus placebo and

each of the 3 romosozumab dose levels with placebo was carried out. To control the overall type I error at a significant level of 0.05, testing of multiple comparisons was done simultaneously using Hochberg procedure (Westfall et al, 1999; Hochberg, 1988).

The analyses of efficacy and safety endpoints were based on the analysis sets defined in Section 7 of the Statistical Analysis Plan (Appendix 2). The primary and final (end of study) analyses were conducted after all subjects had the opportunity to complete week 24 and week 52 assessments, respectively. A final safety analysis will be conducted after all subjects have had the opportunity to complete the long term follow-up week 104 assessment.

Continuous variables were summarized using descriptive statistics, which includes n (number of non-missing observations), mean, median, 25th and 75th percentiles, standard deviation, minimum, and maximum. The minimum and maximum were reported using the same precision as the original measurement. The mean, median, other selected percentiles, and standard deviation were reported in 1 decimal place more than the precision of the original measurement. For categorical variables, descriptive statistics include frequency and percentage.

For time to event variables with competing risk, the cumulative incidence function (CIF) method was used to estimate the quartiles (median, 25th and 75th percentiles) of the variable for each treatment group, along with 95% confidence intervals (CI) (Kalbfleisch and Prentice, 2002; Gray, 1988). CIF estimates are presented graphically for each treatment group. The hazard ratio and its 2-sided 95% CI were estimated using a proportional hazards model (Prentice et al, 1978; Cox, 1972). The proportional hazard model was utilized for the primary analysis of primary endpoint (ie, time to radiographic healing) and the analysis of time to clinical healing as a secondary endpoint.

Additional details are provided in the protocol (Appendix 1) and Statistical Analysis Plan (Appendix 2).

Summary of Results:

Subject Disposition: A total of 458 subjects were screened, and 402 subjects were randomized (299 total romosozumab, 103 placebo). Of the randomized subjects, 331 (82.3%) completed all scheduled doses of investigational product (249 subjects [83.3%] romosozumab, 82 subjects [79.6%] placebo). Nine subjects (2.2%) never received investigational product (6 subjects [2.0%] romosozumab, 3 subjects [2.9%] placebo).

Baseline Demographics:

Sex: 288 (71.6%) male, 114 (28.4%) female

Age: mean [standard deviation (SD)] = 40.9 (14.4) years old

Ethnicity/Race: 299 (74.4%) white, 86 (21.4%) Asian, 8 (2.0%) black, 8 (2.0%) Hispanic, and 1 (0.2%) other

Efficacy Results: At week 24, radiographic healing ranged from 63.2% (95% CI: 46.5%, 79.8%) to 84.7% (95% CI: 68.9%, 95.1%) across romosozumab dose groups versus 76.1% (95% CI: 67.1%, 84.2%) in the placebo group. The estimated median time to radiographic healing ranged from 14.4 (95% CI: 12.6, 17.0) to 18.6 (95% CI: 14.0, 24.4) weeks in the romosozumab dose groups and was 16.4 (95% CI: 14.6, 18.0) weeks in the placebo group. The hazard ratios across romosozumab groups relative to placebo ranged from 0.82 (95% CI: 0.53, 1.26) to 1.18 (95% CI: 0.75, 1.84) (hazard ratio > 1 favors romosozumab. There was no significant linear trend in overall dose response (p = 0.7549).

At week 24, clinical healing ranged from 59.4% (95% CI: 43.2, 76.2) to 82.8% (95% CI: 67.3, 93.7) of subjects in romosozumab dose groups versus 68.6% (95% CI: 59.1, 77.6) in the placebo group. The estimated median time to clinical healing ranged from 14.6 (95% CI: 12.9, 18.6) to 22.3 (95% CI: 15.0, 24.3) weeks in the romosozumab dose groups and was 18.4 (95% CI: 16.6, 20.4) weeks in the placebo group. The hazard ratios ranged from 0.68 (95% CI: 0.44, 1.05) to 1.34 (95% CI: 0.87, 2.07) across romosozumab groups. There was no consistent trend of treatment benefit across the romosozumab dose groups.

In general, SF-36 PF scores improved over time for all groups. However, there was no consistent trend of treatment benefit across the romosozumab dose groups. Eighteen subjects had unplanned revision surgery (3.4% across all romosozumab dose groups [range: 0% to 9.4%] and

8.0% in the placebo group). No relationship was apparent between unplanned revision surgery and romosozumab dose or frequency.

Pharmacokinetics Results: Following dosing with 70 mg, 140 mg, or 210 mg romosozumab given on 2 (day 0 and week 2), 3 (day 0, week 2, and week 6), or 4 (day 0, week 2, week 6, and week 12) occasions, pharmacokinetic samples were collected at the typical visit schedule following definitive fracture fixation. More frequent sampling was performed at time points following the third and fourth doses, which allowed area under the concentration-time curve (AUC) to be estimated.

Serum romosozumab concentrations on week 2 were greatest for groups receiving 210 mg, followed by the 140-mg groups, then the 70-mg groups and increased approximately 6-fold for the 3-fold increase in dose.

For groups receiving 3 or 4 doses, trough serum romosozumab concentrations were greatest on week 2, followed by week 6, and then week 12, which corresponds to 2 weeks, 4 weeks, and 6 weeks after the previous dose. The maximum concentration at week 6 values increased approximately 3.6- and 1.9-fold, and AUC from week 6 to 12 weeks post dose values increased approximately 4.3- and 1.9-fold for the 2-fold (70 mg to 140 mg) and 1.5-fold (140 mg to 210 mg) increases in dose, respectively.

For groups receiving 4 doses, systemic exposure after the fourth dose (week 12) were determined. The observed maximum concentration values after the week 12 dose increased approximately 2.9- and 2.2-fold, and AUC from week 12 to infinity values increased approximately 2.6- and 2.5-fold for the 2-fold (70 mg to 140 mg) and 1.5-fold (140 mg to 210 mg) increases in dose, respectively.

Safety Results: A total of 393 subjects received ≥ 1 dose of investigational product (293 romosozumab, 100 placebo) and were included in the Safety Subset. One hundred forty-nine subjects (51%) across all romosozumab groups and 50 subjects (50%) in the placebo group reported at least 1 treatment-emergent adverse event. The most frequent adverse events (reported in > 5% of subjects across all romosozumab groups or the placebo group) were arthralgia (8% romosozumab, 6% placebo), edema peripheral (7%, 6%), pain in extremity (3%, 6%), and pain (2%, 7%). No trends were apparent between the incidence of adverse events and romosozumab dose or frequency.

Twenty-four subjects (8%) across all romosozumab groups and 10 subjects (10%) in the placebo group reported serious adverse events. No serious adverse event preferred term was reported for > 2 subjects. No fatal adverse events were reported. Adverse events leading to study or investigational product discontinuation were reported for 2 subjects across all romosozumab groups and 2 subjects in the placebo group.

No patterns in laboratory values, vital signs, or electrocardiograms suggestive of a treatment-related effect were observed.

The incidence of subjects developing antiromosozumab antibodies after treatment was 16.6% (47 out of 283). Of the 47 subjects who had a positive binding antibody result on study, 12 subjects tested negative for binding antibodies at their last timepoint tested (transient antibodies). Twenty subjects (7.1%) tested positive for neutralizing antiromosozumab antibodies while on study. Of these, 17 subjects tested negative for neutralizing antibodies at their last timepoint tested (transient neutralizing antibodies). Antiromosozumab antibodies did not appear to affect the safety profile of romosozumab.

Conclusions:

There was no statistically significant dose response trend and no substantial difference between the placebo group and any of the romosozumab dose groups for the primary or secondary efficacy endpoints. The safety profile of romosozumab was comparable to placebo; no dose-related trends were apparent for adverse events or laboratory values.