## 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 to Determine the Efficacy, Safety, and Tolerability of AMG 785 in Adults with a Fresh Unilateral Hip Fracture, Status Post Surgical Fixation

Study To Assess FRacTure Healing with SclerosTin Antibody - Hip (STARTT-Hip)

**Investigators and Study Centers:** This study was conducted at 63 centers in 22 countries. Centers and principal investigators are listed in Section 16.1.4.

**Publication:** None

**Study Period:** 20 June 2010 (first subject enrolled) to 31 January 2013 (last subject completed end-of-study visit)

**Development Phase:** 2

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**Objectives:** The primary objective was to investigate the effect of romosozumab compared to placebo on functional healing as measured by the timed-up-and-go test (TUG) over weeks 6 through 20 in subjects with fresh unilateral low energy hip fractures

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

- Timed-up-and-go value by visit
- Time to radiographic healing defined as effacement of the fracture lines by newly formed bone along the cortices and within the trabecular bone on anteroposterior (AP) and lateral (or oblique) radiographs
- Radiographic Union Scale for Hip (RUSH) score by visit
- Harris Hip Score
- Pain as a result of the hip fracture as assessed by the Visual Analog Scale (VAS)

Exploratory, safety, pharmacokinetic (PK), and pharmacodynamic (PD) objectives are listed in the protocol Section 1, included in Section 16.1.1 of this document.

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**Methodology**: This was an international, multi-center, randomized, double-blind, placebo-controlled study of romosozumab in adults with fresh unilateral low energy hip fracture treated with internal fixation with a sliding hip screw, an intermedullary (IM) nail or with at least 3 cancellous screws.

Subjects were randomized in a 2:3:3:3 ratio to 1 of 3 romosozumab treatment groups (70-mg, 140-mg, 210-mg) or placebo. Subjects received 3 subcutaneous (SC) injections per visit of romosozumab or placebo treatment on Day 1, week 2, 6 and 12.

All subjects were required to take at least 1000 mg of elemental calcium and 800 International unit of vitamin D daily from screening to week 36.

Subjects undergoing fracture fixation were screened during hospitalization. Fracture fixation had to have been completed no later than 7 days after injury for intertrochanteric or undisplaced femoral neck fractures and no later than 2 days after injury for displaced femoral neck fractures. Randomization followed operative fracture repair and was

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stratified by type of fracture, type of fixation device and age at entry. There were 7 strata:

- intertrochanteric, sliding hip screw, 55-75 years
- intertrochanteric, sliding hip screw, ≥ 76 years
- intertrochanteric, IM nail, 55-75 years
- intertrochanteric, IM nail, ≥ 76 years
- displaced femoral neck, sliding hip screw
- displaced femoral neck, cancellous screws
- undisplaced femoral neck

The primary analysis of the primary endpoint was performed on unblinded data after all subjects had completed the scheduled week 24 assessments or were early terminated before that time. The analysis was repeated at end-of-study (week 52) after all subjects had completed the scheduled week 52 assessments or are early terminated before that time. The results were similar for week 24 and week 52 assessments. Final results from end-of-study are presented in this document.

**Number of Subjects Planned:** approximately 330 subjects

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

- adult male or female, age ≥ 55 to ≤ 95 years
- fresh unilateral low energy intertrochanteric or femoral neck fracture as the primary injury, confirmed by X-ray and in the opinion of the treating surgeonamenable to repair by internal fixation
- internal fixation of the fracture with devices approved by local regulatory agency,performed no later than 7 days after injury for intertrochanteric or undisplaced femoral neck fractures and no later than 2 days after injury for displaced femoralneck fractures
  - intertrochanteric fracture: sliding hip screw or IM nail
  - femoral neck fracture: sliding hip screw or at least three cancellous screws

Key exclusion criteria were as follows:

- severe symptomatic osteoarthritis of the lower extremity
- inability to independently rise from armchair or walk 200 meters before the hip fracture
- presence of concomitant injuries such as rib fractures, wrist fractures, or acute symptomatic vertebral fractures which severely impaired the ability to rise from achair
- associated extremity injuries including ipsilateral or contralateral fractures of the foot, tibia or fibula, wrist, humerus, femoral shaft, femoral head or hip dislocation,that may have delayed weight-bearing beyond one week after surgery
- head-injury, as defined by the Glasgow Coma Scale < 13 prior to randomization
- use of bone grafts or bone substitutes at the time of fracture fixation
- major polytrauma or significant axial trauma, with Injury Severity Score of > 16

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- pathological fracture or history of metabolic or bone disease (exceptosteoporosis) that may have interfered with the interpretation of the results, such as Paget's disease, rheumatoid arthritis, osteomalacia, osteopetrosis, ankylosingspondylitis, Cushing's disease, and hyperprolactinemia
- history of symptomatic spinal stenosis that had not been surgically corrected. 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 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)
- Bone Morphogenetic Protein (BMP)-2 or BMP-7 at the time of definitive fracture fixation

Full inclusion and exclusion criteria are listed in the protocol Section 4, included as Section 16.1.1.

**Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:** Romosozumab was administered SC at doses of 70, 140, or 210-mg on day 1 and at weeks 2, 6 and 12. No dosing adjustments for investigational product were permitted. Manufacturing batch numbers are provided in Section 16.1.6.

**Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:** Matched placebo was administered SC. Manufacturing batch numbers are provided in Section 16.1.6.

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

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**Study Endpoints:** The primary endpoint was the difference in mean TUG over weeks 6 through 20 for the romosozumab and placebo groups.

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

- timed-up-and-go value by visit
- time to radiographic healing, defined as effacement of the fracture lines by newly formed bone along the cortices and within the trabecular bone on AP and lateral (or oblique) radiographs. Radiographic fracture healing was determined by a panel of independent reviewers blinded to treatment
- radiographic Union Scale for Hip score by visit
- Harris Hip score by visit
- pain score as measured by VAS by visit

Exploratory, safety, PK, and PD endpoints are listed in the statistical analysis plan (SAP) Section 4, included as Section 16.1.9.

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**Statistical Methods:** A first planned interim analysis was performed on blinded data after approximately 50 subjects had completed the scheduled week 20 assessments. The primary analysis was performed after all the subjects had completed the scheduled week 24 assessments. The end of study analyses was performed after all subjects had completed the scheduled week 52 assessments or were early terminated before that time.

The analyses of efficacy and safety endpoints were based on the analysis sets defined in Section 7 of the SAP (Section 16.1.9).

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

The primary analysis for the primary endpoint was a test for dose response over weeks 6 through 20 using contrasts on dose level. For time to event variables with competing risk, the cumulative incidence function (CIF) method was used to estimate the quartiles (median, 25$^{th}$ and 75$^{th}$ percentiles) of the variable for each treatment group, along with 95% confidence intervals (CIs) (Kalbfleisch and Prentice, 2002; Gray, 1988). The 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 (Cox, 1972; Prentice et al, 1978).

Additional details are provided in Section 10 of the protocol (Section 16.1.1) and Section 10 of the SAP (Section 16.1.9).

**Summary of Results:**

**Subject Disposition:** A total of 332 subjects were randomized to study: 89 subjects to placebo and 243 subjects to romosozumab (60 in the romosozumab 70-mg; 93 in the romosozumab 140-mg; and 90 in the romosozumab 210-mg groups). A total of 229 (69.0%) subjects completed the study: 62 (69.7%) subjects in the placebo group and 167 (68.7%) subjects in the romosozumab groups (44 [73.3%] in the 70-mg, 62 [66.7%] in the 140-mg, 61 [67.8%] in the 210-mg groups).

A total of 103 (31.0%) subjects discontinued the study: 27 (30.3%) subjects in the placebo group and 76 (31.3%) subjects in the romosozumab groups (16 [26.7%] in the 70-mg, 31 [33.3%] in the 140-mg, 29 [32.2%] in the 210-mg groups). The most common reasons for study discontinuation were full consent withdrawn (15.6% romosozumab, 16.9% placebo), death (4.1% romosozumab, 2.2% placebo), lost to follow up (3.3% romosozumab, 4.5% placebo), and noncompliance (4.5% romosozumab, 3.4% placebo); other reasons for study discontinuation were reported for $\leq$ 4.0% of subjects overall.

Of the randomized subjects, 261 (78.6%) subjects completed all the scheduled doses of investigational product: 70 (78.7%) subjects in the placebo group and 191 (78.6%) subjects in the romosozumab group (51 [85.0%] subjects in the 70-mg, 71 [76.3%] subjects in the 140-mg and 69 [76.7%] subjects in the 210-mg groups). Overall, 7 (2.1%) subjects never received investigational product; 2 (2.2%) subjects assigned placebo and 5 (2.1%) subjects assigned romosozumab group (4 [4.3%] subjects in the 140-mg and 1 [1.1%] subject in the 210-mg groups).

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**Baseline Demographics:**

**Sex:** 228 (68.7%) women; 104 (31.3%) men

**Age:** mean (SD) = 76.3 (9.5) years old

**Ethnicity/Race:** 280 (84.3%) white; 49 (14.8%) Asian; 2 (0.6%) Hispanic; 1 (0.3%) black

**Efficacy Results:** The primary endpoint of the study is the difference in mean TUG over Weeks 6 through 20 between the placebo and the romosozumab dose groups. The TUG scores improved over time for all the romosozumab groups and the placebo group. These differences between treatment groups in TUG score over week 6 to 20 were not statistically significant (p-value=0.1983).

The estimated median time to radiographic healing was 16.9 weeks (95% CI: 12.9, 20.3) in the 70-mg, 16.6 weeks (95% CI: 13.3, 17.1) in the 140-mg, and 16.9 weeks (13.3, 20.9) in the 210-mg romosozumab group compared to 16.4 weeks (95% CI: 15.3, 20.1) in the placebo group. The hazard ratio relative to placebo was 1.1 (95% CI: 0.7, 1.6) in the 70-mg, 1.1 (95% CI: 0.8, 1.6) in the 140-mg and 1.1 (95% CI: 0.7, 1.6) in the 210-mg romosozumab group with no apparent dose related trends, (a hazard ratio of $>$ 1 favors romosozumab).

The Harris hip score improved over time for all the romosozumab groups and the placebo group. The values were similar between the placebo group and all the romosuzumab groups up to week 24. For the week 36 and week 52 Harris Hip scores, the repeated measures model indicated a significant difference for the 140-mg romosozumab group favoring romosozumab, compared with placebo.

The RUSH score, and pain score generally improved over time for subjects in the placebo and romo dose groups. No relationship was apparent between these scores and romosozumab dose group or treatment group. For Harris hip score, there was a significant difference in the mean value between the placebo group and the romosozumab 140-mg group at week 36 (placebo: 80.3; romosozumab 140-mg: 86.8; p-value=0.0062) and at week 52 (placebo: 84.3; romosozumab 140-mg: 89.0; p-value=0.0365), favoring romosozumab. There was no substantial difference in the distribution of RUSH scores and mean pain VAS scores between the placebo arm and each romo dose arm at any time point.

Overall, 14 subjects had unplanned revision surgery; 3 (3.4%) in the placebo group compared to 2 (3.3%) in the 70-mg, 3 (3.4%) in the 140-mg and 6 (6.7%) in the 210-mg romosozumab groups. No relationship was apparent between unplanned revision surgery and romosozumab dose group or treatment group. Through 52 weeks, there was no consistent difference in the primary and secondary endpoints between treatment groups.

**Pharmacokinetic Results**: Systemic exposure measured by maximum observed drug concentration($C_{max}$) and area under curve (AUC) during a dosing interval (tau) ($AUC_{tau}$) (day 1 to week 2), showed approximate dose proportionality. For a subset of subjects, intensive PK samples were collected every other day after the first dose on day 1 for 2 weeks, allowing AUC to be calculated. Pharmacokinetic data were available at trough time points ($C_{trough}$) at weeks 2, 6, 12 and 16. After the first dose, exposure, as measured by the $C_{max}$ and the $AUC_{tau}$, increased approximately dose proportionally. $C_{max}$ increased approximately 2.3 and 2.7-fold for the 2-fold (70-mg to 140-mg) and 3-fold (70-mg to 210-mg) increase in dose, and $AUC_{tau}$ exhibited a 2.4 and 2.7-fold increase after a 2-fold (70-mg to 140-mg) and 3-fold (70-mg to 210-mg) increase in dose. The

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median time to maximum concentration ($t_{max}$) ranged from 4.6 to 5.8 days following a single SC dose on day 1.

Mean trough serum romosozumab concentrations ($C_{trough}$) at week 2 prior to the second dose increased approximately 3.8-fold for the 3-fold increase in dose. After two doses of romosozumab, mean $C_{trough}$ concentrations at week 6 increased approximately 4.3-fold for the 3-fold increase in dose. Following three doses at week 12 and all the four doses at week 16, mean $C_{trough}$ concentrations increased approximately 6.8-fold and 6.4-fold, respectively, for the 3-fold increase in dose, suggesting accumulation at higher doses.

**Safety Results**: A total of 325 subjects received ≥ 1 dose of investigational product; 87 in the placebo group and 238 in the romosozumab groups (60 in the 70-mg, and 89 in each the 140-mg and 210-mg groups) and were included in the safety subset. A total of 69 (79.3%) subjects in the placebo group and 157 (66.0%) subjects in the romosozumab group (39 [65.0%] in the 70-mg, 54 [60.7%] in the 140-mg, and 64 [71.9%] in the 210-mg groups) reported at least 1 treatment-emergent adverse event.

No trends were apparent in pattern or types of adverse events across treatment groups. However, the numerical differences were observed between placebo and romosozumab groups for certain adverse events occurred in both directions showing that these are random findings due to small sample sizes of the groups and multiple comparisons of variables.

Higher percentage of subjects reported back pain (placebo [0%] and romosozumab 6.7% [11.7% in the 70-mg, 5.6% in the 140-mg, 4.5% in the 210-mg] ) and arthralgia (placebo [2.3%] and romosozumab 5.9% [5.0% in the 70-mg, 6.7% in the 140-mg, 5.6% in the 210-mg] ) in the romosozumab group compared to placebo group. However, higher percentage of subjects reported constipation (placebo [12.6%] and romosozumab 8.8% [10.0% in the 70-mg, 10.1% in the 140-mg, 6.7% in the 210-mg] ), diarrhoea (placebo [9.2%] and romosozumab 3.8% [3.3% in the 70-mg, 2.2% in the 140-mg, 5.6% in the 210-mg] ), and pain in extremity (placebo [5.7%] and romosozumab 0.8% [0.0% in the 70-mg, 0.0% in the 140-mg, 2.2 % in the 210-mg] ) in the placebo group compared to romosozumab group. Overall, the adverse events were mild to moderate in severity and consistent with expected events in an elderly population following hip fracture.

Fifty (21.0%) subjects across all the romosozumab groups (9 [15.0%] in the 70-mg, 15 [16.9%] in the 140-mg, and 26 [29.2%] in the 210-mg groups) and 25 (28.7%) subjects in the placebo group reported serious adverse events. No serious adverse event preferred term was reported for > 3 subjects per group. Ten (4.2%) subjects across all the romosozumab groups (2 [3.3%] in the 70-mg, 2 [2.2%] in the 140-mg, and 6 [6.7%] in the 210-mg) and 2 (2.3%) subjects in the placebo group had fatal adverse events. None of these deaths were considered related to investigational product. Ten (4.2%) subjects across all the romosozumab groups (2 [3.3%] in the 70-mg, 5 [5.6%] in the 140-mg, and 3 [3.4%] in the 210-mg groups) and 4 (4.6%) subjects in the placebo group reported adverse events leading to investigational product discontinuation.

The overall incidences of adverse events and clinical significant adverse events are comparable between the placebo and romosozumab groups. One subject ([redacted]) in the romosozumab 210-mg group had serious adverse event of acute generalized exanthematous pustulosis 2 days after the first dose, which was considered related to investigational product by the investigator. One subject ([redacted]) in the romosozumab 140-mg group reported a moderate adverse event of hypocalcaemia 10 days after the first dose. The investigator considered the event as not related to the investigational product. One (1.1%) subject ([redacted]) in the placebo group had an

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adverse event of mild injection site pruritus that led to withdrawal of investigational product after the first injection of investigational product. One (1.7%) subject in the romosozumab 70-mg reported mild injection site haematomoa and one (1.1%) subject in the romosozumab 210-mg reported mild injection site erythema. One (1.1%) subject in the placebo group reported an adverse event of extraskeletal ossification. One subject ([redacted]) in the romosozumab 210-mg group had a serious adverse event of acute myeloid leukemia that led to withdrawal from study after the last injection of investigational product. Two subjects in the placebo group reported serious adverse event of worsening of osteoarthiritis.

Binding antibodies developed in 20 (9.4%) subjects who received romosozumab and were transient (negative result at last timepoint tested) in 8 (3.8%) of these subjects. Five subjects (2.3%) who received romosozumab developed transient neutralizing antibodies to romosozumab. No subjects in the placebo group developed binding or neutralizing antibodies.

No patterns in physical findings, vital sigs, laboratory values and electrocardigram suggestive of a treatment-related effect were observed. Use of concomitant medications was generally balanced across treatment groups, and no safety signals were apparent that could be detected through concomitant medication use.

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**Conclusions:** There was no statistically significant dose response trend and no consistent difference between the placebo group and any of the romosozumab dose groups for the primary and secondary efficacy endpoints for functional, radiographic, and quality of life measures of acceleration of fracture healing. Antiromosozumab antibodies, did not appear to affect the safety profile of romosozumab. The safety profile of romosozumab was comparable to placebo in the incidences of all advere events, serious adverse events, fatal adverse events, discontinuation adverse events and clinically significant adverse events; no dose-related trends were apparent for adverse events or laboratory values.

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## 2. SYNOPSIS

This was a phase 2, multi-center, randomized, double-blind, placebo-controlled study to determine the efficacy, safety, and tolerability of romosozumab in adults with a fresh unilateral hip fracture, status post surgical fixation. The Study 20080394 main clinical study report (CSR) that provided analysis of results of the week-24 and end-of-study visit (week-52) data (data cut-off at 20 March 2013) was dated 12 September 2013. Subjects who completed the 52 week treatment and observation period were scheduled to participate in the long-term radiographic assessment at week 104. Based on recent regulatory guidance and on the efficacy results from the acceleration of fracture healing endpoints, but not on safety, the decision was made to discontinue the study without the completion of the week-104 radiographic follow-up visit.

The main objective of the radiographic assessment at week 104 was to assess the long-term effect of romosozumab on radiographic healing and callus size at week 104. The endpoints of this assessment were: radiographic healing, defined as obliteration of fracture lines by newly formed bone along the cortices and within the trabecular bone on anteroposterior and lateral (or oblique) radiographs, and callus size at the fracture site at week 104.

At the end of 52 weeks, 229 subjects completed the study. At the week-104 visit, 72 subjects completed the long-term radiographic assessment. More women (61.1 %) than men (38.9%) completed the radiographic assessment at week 104. Most subjects were white (84.7 %) and 15.3 % were Asian. The mean (SD) age was 72.2 (9.0) years.

At week 104, the cumulative incidence of radiographic healing was 78.3% in the romosozumab 70-mg dose group, 78.7% in the romosozumab 140-mg dose group, 71.9% in the romosozumab 210-mg dose group, and was 75.9% in the placebo group. At week 52, the cumulative incidence of radiographic healing was 76.7% in the romosozumab 70-mg dose group, 77.5% in the romosozumab 140-mg dose group, 67.4% in the romosozumab 210-mg dose group, and was 75.9% in the placebo group.

Moderate or exuberant callus formation was reported as the predominant findings across all treatment groups at both weeks 52 and 104. At week 104, moderate or exuberant callus formation was seen in 5 (50.0%), 12 (80.0%), and 14 (66.7%) subjects in the romosozumab 70-mg dose group, 140-mg dose group, and 210-mg dose group, respectively, and in 10 (66.7%) subjects in the placebo group. At week 52, moderate or exuberant callus formation was seen in 22 (64.7%), 30 (58.8%), and 29 (60.4%) subjects in the romosozumab 70-mg dose group, 140-mg dose group and 210-mg dose group, respectively, and in 28 (58.4%) subjects in the placebo group.

At week 104, the mean (standard deviation [SD]) maximum callus diameter in the romosozumab 70-mg dose group, 140-mg dose group and 210-mg dose group was 24.0 (6.7) mm, 28.3 (10.0) mm, and 34.3 (12.4) mm, respectively, and was 27.1 (8.7) mm in the placebo group. At week 52, the mean (SD) maximum callus diameter in the romosozumab 70-mg dose group, 140-mg dose group and 210-mg dose group was 26.2 (6.6) mm, 29.9 (11.4) mm, and 29.3 (9.4) mm, respectively, and was 30.9 (8.6) mm in the placebo group.

No additional adverse event data was collected during the week-52 to week-104 interval. All serious adverse events that occurred between the week-52 and week-104 visit were reported in the Study 20080394 main CSR.

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In conclusion, there was no dose response trend and no consistent difference between the placebo group and any of the romosozumab dose groups for cumulative incidence of radiographic healing and callus formation at week 104. Results of the week-104 follow-up analysis were consistent with the end-of-study analysis (week 52).

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