http://dx.doi.org/10.2106/JBJS.19.01008

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APPENDIX

Eligibility criteria

Inclusion Criteria

- Skeletally mature adults, aged ≥ 18 to ≤ 85 years at randomization, with radiographically closed growth plates
- Fresh unilateral closed or Gustilo type I/II open tibial diaphyseal fracture (fracture line must not extend into the ankle or knee joint) as the primary injury
- For closed fractures: definitive fracture fixation with reamed IM nailing (modern, statically interlocking nail) performed no later than 14 days after injury
- For Gustilo type I/II open fractures: definitive fracture fixation with reamed or unreamed IM nailing (modern, statically interlocking nail) performed no later than 24 hours after injury

Exclusion Criteria

- Major polytrauma or significant axial trauma, with injury severity score > 6
- Head injury, as defined by Glasgow Coma Scale < 13 at the time of randomization
- Associated fracture of the lower extremity or any other condition that, in the opinion of the surgeon, would delay the patient'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 may have interfered with the interpretation of the results, such as Paget's disease, rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, Cushing's disease, hyperprolactinemia
- History of symptomatic spinal stenosis that had not been surgically corrected. If surgically corrected, the patient 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 any of the following per patient report, chart review, or local laboratory result (currently or within the past 5 years):
  - Elevated transaminases (a) serum aspartate aminotransferase (AST; serum glutamate-oxaloacetic transaminase ≥ 2.0 x upper limits of normal); (b) serum alanine aminotransferase (ALT; serum glutamate-pyruvate transaminase ≥ 2.0 x upper limits of normal)
  - Significantly impaired renal function as determined by a derived creatinine clearance of ≤ 30 mL/min using the Modification of Diet in Renal Disease equation
- Per patient report, chart review, or local laboratory result, evidence of current hypercalcemia or hypocalcemia, outside of 1.1 x the normal range set by the local laboratory
- Known to have tested positive for human immunodeficiency virus, hepatitis C virus, or hepatitis B surface antigen
- Use of the following agents affecting bone metabolism:

  - Intravenous bisphosphonates at any time
  - Denosumab at any time
  - Fluoride (for osteoporosis) within the past 24 months
  - Oral bisphosphonates, parathyroid hormone, or strontium within the past 12 months
  - Calcitonin, selective estrogen receptor modulators, or systemic oral or transdermal estrogen within the past 3 months (estrogen-containing contraceptive therapy was permitted)
  - Systemic glucocorticosteroids (≥ 5 mg prednisone equivalent per day for more than 10 days) within the past 3 months
  - Tibolone within the past 3 months
  - Bone morphogenetic protein (BMP)-2 or BMP-7 at the time of definitive fracture fixation

- Current use of anticoagulants (doses for deep vein thrombosis prophylaxis were permitted)
- Patient was currently enrolled in or had not completed at least 30 days since ending other investigational device or drug study(s), or patient was receiving other investigational agent(s)
- Previous enrollment in a romosozumab clinical study
- Patient of childbearing potential who was pregnant (eg, positive human chorionic gonadotropin test) or breast feeding
- Females of childbearing potential: patient refuses to use an effective contraception (or true abstinence) to achieve a highly effective contraception result during treatment with study drug and for an additional 3 months after the end of treatment with study drug (ie, 3 months after the week 12 study visit)
- Known intolerance to calcium supplements or vitamin D products
- Known sensitivity to mammalian cell-derived drug products
- Any kind of disorder that, in the opinion of the investigator,
  - compromised the ability of the patient (or legally acceptable representative) to give written informed consent
  - prevented the patient from complying with study procedures
  - prevented the patient from completing the study
  - interfered with the interpretation of the study results

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TABLE E-I Randomized Patients by Country

Country	Number of Trial Sites N=66	Enrollment N=402 n (%)
Australia	1	1 (0.2)
Bulgaria	2	20 (5)
Canada	5	21 (5.2)
Denmark	2	19 (4.7)
France	1	1 (0.2)
Germany	1	5 (1.2)
Greece	5	42 (10.4)
Hong Kong	1	5 (1.2)
Hungary	3	6 (1.5)
India	12	75 (18.7)
Italy	3	12 (3.0)
Latvia	2	56 (13.9)
Lithuania	2	3 (0.7)
Mexico	1	1 (0.2)
New Zealand	2	12 (3.0)
Poland	3	16 (4.0)
Romania	2	15 (13.7)
Russia	4	24 (6)
Slovakia	2	15 (13.7)
United Kingdom	4	18 (4.5)
United States	8	35 (8.7)

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TABLE E-II Administration of Investigational Product

		Romosozumab									
		70 mg			140 mg			210 mg			Total
	Placebo N=103	2 Doses N=34	3 Doses N=34	4 Doses N=33	2 Doses N=33	3 Doses N=33	4 Doses N=33	2 Doses N=33	3 Doses N=31	4 Doses N=35	N=299
Number of patients who received ≥ 1 dose of investigational product	100	34	34	32	33	32	31	32	30	35	293
Number of doses received, median (range)	4 (1–4)	4 (1–4)	4 (1–4)	4 (1–4)	4 (2–4)	4 (1–4)	4 (1–4)	4 (1–4)	4 (2–4)	4 (1–4)	4 (1–4)
Patients who received active doses of romosozumab, n (%)											
1 dose	0 (0.0)	1 (2.9)	1 (2.9)	1 (3.1)	0 (0.0)	1 (3.1)	1 (3.2)	1 (3.1)	0 (0.0)	1 (2.9)	7 (2.4)
2 doses	0 (0.0)	33 (97.1)	0 (0.0)	0 (0.0)	33 (100.0)	0 (0.0)	0 (0.0)	31 (96.9)	1 (3.3)	2 (5.7)	100 (34.1)
3 doses	0 (0.0)	0 (0.0)	33 (97.1)	2 (6.3)	0 (0.0)	31 (96.9)	2 (6.5)	0 (0.0)	29 (96.7)	2 (5.7)	99 (33.8)
4 doses	0 (0.0)	0 (0.0)	0 (0.0)	29 (90.6)	0 (0.0)	0 (0.0)	28 (90.3)	0 (0.0)	0 (0.0)	30 (85.7)	87 (29.7)

N = number of randomized patients.

Gray shading indicates patients who received their intended active doses of romosozumab.