NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy supplement
Application Number(s)	BLA 125320/S-219
Priority or Standard	Standard
Submit Date(s)	July 25, 2024
Received Date(s)	July 25, 2024
PDUFA Goal Date	May 25, 2025
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology and Nephrology
Review Completion Date	See DARRTS stamped date
Established/Proper Name	Denosumab
Trade Name	Prolia
Pharmacologic Class	Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) Inhibitor
Code name	AMG 162
Applicant	Amgen, Inc.
Dosage form	Single-dose prefilled syringe containing denosumab 60 mg in a 1 mL solution.
Applicant proposed Dosing Regimen	Not applicable
Applicant Proposed Indication(s)/Population(s)	Not applicable
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not applicable
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	390833005 |Osteoporosis caused by corticosteroid (disorder)
Recommended Dosing Regimen	Not applicable

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OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health

Signatures

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Division Director (Clinical)	Theresa Kehoe, MD	OCHEN/DGE	Sections: All sections	**Select one:** ___ Authored _x_ Approved
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BMD	Bone Mineral Density
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHAQ	Childhood Health Assessment Questionnaire
CHQ-PF-50	Childhood Health Questionnaire – Parent Form – 50
CMC	chemistry, manufacturing, and controls
COA	Clinical outcome assessments
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DXA	Dual Energy X-Ray Absorptiometry
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GC	glucocorticoid
GCP	good clinical practice
GIOP	Glucocorticoid-induced osteoporosis
GRMP	good review management practice
GQ	grouped queries
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISCD	International Society for Clinical Densitometry
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OCMQ	Office of New Drug Custom Medical Queries
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAS	Prior Approval Supplement
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
WBFPRS	Wong-Baker Faces Pain Rating Scale

1 Executive Summary

1.1. Product Introduction

Prolia (denosumab), a monoclonal antibody inhibitor of Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL), was approved on June 01, 2010, for the treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Subsequently, Prolia was approved for following indications:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

On July 28, 2017, Amgen, Inc. (the Applicant) submitted an efficacy supplement (S-186) to the Biologics License Application (BLA) for a new indication of the treatment of glucocorticoid-induced osteoporosis (GIOP) in men and women at high risk for fracture. This submission was based on a phase 3 trial in adults with GIOP. Supplement 186 was approved on May 18, 2018.

The approval of Prolia for the treatment of GIOP triggered Pediatric Research Equity Act (PREA) (21 U.S.C.355c). Upon review, the team determined that Prolia would pose safety concerns in children under 5 years of age due to high rates of skeletal growth and the potential for Prolia to adversely affect long-bone growth and dentition in this age group. Hence, the approval letter for S-186 included a waiver for a pediatric study requirement for ages 0 to 4 years. For the age group of 5 to 17 years, the pediatric study was deferred, and the approval letter included the following post-marketing requirement (PMR):

PMR 3422-1 A phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of denosumab in pediatric subjects with glucocorticoid-induced osteoporosis (Study 20140444).

On July 24, 2024, to satisfy PMR 3422-1, the Applicant submitted a Prior Approval Supplement (PAS) to the biologics license application (BLA) for Prolia (BLA 125320, supplement 219) under section 351(a) of the Public Health Service Act (PHS Act). In this supplement, the Applicant has included results of Trial 20140444. The Applicant proposes to update Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS in the Prolia United States Prescribing Information (USPI) to reflect that safety and effectiveness were not established in the phase 3 clinical trial evaluating the effect of denosumab on glucocorticoid-induced osteoporosis (GIOP) in children aged 5 to 17 years old (Study 20140444).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness of Prolia for the treatment of glucocorticoid induced osteoporosis in children aged 5 to 17 years old has not been established. Due to challenges with recruitment, the Applicant was unable to enroll an adequate number of subjects in the pivotal phase 3 Trial 20140444. Hence, an indication of treatment of glucocorticoid induced osteoporosis in children cannot be granted for Prolia at this time.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In this supplement, the Applicant has included data from a phase 3 trial assessing the safety and efficacy of 1 mg/kg (maximum 60 mg) denosumab every 6 months to treat glucocorticoid induced osteoporosis (GIOP) in children aged 5 to 17 years old (Trial 20140444). The primary endpoint was change from baseline in lumbar spine (LS) bone mineral density (BMD) z-scores as assessed by dual energy x-ray absorptiometry (DXA), evaluating for superiority of denosumab compared to placebo to improve LS BMD.

The safety and efficacy of denosumab 1 mg/kg (maximum 60 mg) every 6 months in pediatric patients with GIOP were not adequately demonstrated, because even though the Applicant initially intended to enroll 150 subjects, ultimately, only 24 subjects were enrolled in the trial due to challenges with recruitment. This limits the interpretation of the safety and efficacy data obtained from this trial. However, in the context of these limitations, this review team did not identify significant new safety signals or additional information pertinent to the safety profile of denosumab as described in the Prolia USPI.

The review team recognizes the challenges faced in recruiting eligible subjects. These challenges include the requirement that only subjects with a prior history of osteoporotic fracture were included in this trial. In general, glucocorticoid use is low in pediatric patients, and the prevalence of pediatric patients on chronic glucocorticoid therapy with a prior osteoporotic fracture is even lower. Given that the American College of Rheumatology guidance recommending against routine use of antiresorptives in pediatric patients with no prior history of fracture, modification of these criteria to allow enrollment of subjects without a prior history of fractures may not be justified.[1] Hence, Applicant's decision to terminate the trial early was appropriate.

In conclusion, the Applicant appears to have made a good faith attempt to fulfill the PMR. Hence, the clinical review team recommends that PMR 3422-1 is considered fulfilled. Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the Prolia USPI will be updated to reflect that safety and effectiveness were not established in the phase 3 clinical trial. The Pediatric Review Committee (PeRC) discussed this supplement on April 8, 2025, and concurred with the Division's recommendations.

[1] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Osteoporosis is characterized by low bone mass and structural deterioration of bone, leading to bone fragility and increased fracture risk. Primary osteoporosis is the more common form and is due to typical age-related loss of bone. Secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss. The most common cause of secondary osteoporosis is glucocorticoid therapy, i.e., glucocorticoid-induced osteoporosis (GIOP). • In children, glucocorticoids are commonly used to treat a variety of rheumatologic, gastrointestinal, respiratory, oncologic, renal, and endocrine disorders, as well as other acute and chronic inflammatory diseases, and are also an important part of immunosuppressive regimens. • In children, glucocorticoids adversely affect bone strength, growth, and peak bone mass, with increased fracture risk, though children and young adults often regain lost bone when glucocorticoids are discontinued.	Glucocorticoids are commonly used to treat multiple disorders and diseases in children. The use of glucocorticoids in children can lead to glucocorticoid-induced osteoporosis and adversely affect bone strength, growth, and peak bone mass, with increased fracture risk.
Current Treatment Options	• Guidelines from the American College of Rheumatology on prevention and treatment of GIOP recommend adequate calcium and vitamin D intake for all adults and children beginning or continuing chronic glucocorticoid therapy. Anti-resorptive therapy is not recommended in pediatric patients who do not have a prior history of fracture. However, in children aged 4 to 17 years old with osteoporotic fracture who continue treatment with chronic glucocorticoids, the guidelines conditionally recommend starting oral or intravenous (IV) bisphosphonate therapy, over no therapy. • Studies have suggested that calcium, vitamin D, and oral bisphosphonates are relatively weak modulators of BMD in	Given tolerability concerns with bisphosphonates and the fact that none are approved for use in children, there is a need for additional therapeutic options for the treatment of children with GIOP.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	glucocorticoid-treated children, and do not appear to be effective in preventing fragility fractures. Intravenous bisphosphonates are the recommended first line therapy for treating pediatric GIOP with a history of osteoporotic fracture. However, while several bisphosphonates are FDA-approved for the treatment of GIOP in adults, there are no FDA-approved bisphosphonates for use in children, so such treatment remains off-label.	
Benefit	• Denosumab was evaluated in a phase 3 trial (Trial 20140444) that compared the effect of denosumab 1 mg/kg (maximum 60 mg) every 6 months to placebo on GIOP in pediatric subjects. The primary endpoint was change from baseline in lumbar spine (LS) bone mineral density (BMD) z-scores as assessed by dual energy x-ray absorptiometry (DXA), evaluating for superiority of denosumab compared to placebo to improve LS BMD. • Due to challenges with recruitment, the Applicant was not able to enroll an adequate number of pediatric subjects with GIOP to appropriately evaluate efficacy of denosumab, compared to placebo, to treat GIOP in this population. Due to poor recruitment, the trial was terminated early and benefit of denosumab use in children with GIOP was not established. The observed effect size based on the treated subjects also appears smaller than expected, which contributed to the inclusiveness of the study.	The results of the phase 3 trial did not adequately establish effectiveness of denosumab for the proposed indication, patient population, or dosage regimen.
Risk and Risk Management	• Due to challenges with recruitment, the Applicant was not able to enroll an adequate number of pediatric subjects with GIOP to appropriately evaluate safety of denosumab, compared to placebo, to treat GIOP in this population. Due to poor recruitment, the trial was terminated early and the safety of denosumab use in children	The safety database from the single phase 3 trial is not adequate for a comprehensive safety assessment of denosumab for the proposed indication, patient population, or dosage regimen at the time of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with GIOP was not established. However, no new safety signals were identified.	supplemental BLA submission. However, in the context of these limitations, this safety review did not identify significant new safety signals or additional information pertinent to the safety profile of denosumab as described in the Prolia USPI.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1.2.12
		X	Observer reported outcome (ObsRO)	Section 8.1.2.12
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Osteoporosis is characterized by low bone mass and structural deterioration of bone, leading to bone fragility and increased fracture risk. The International Society for Clinical Densitometry (ISCD) note that osteoporosis should not be diagnosed solely on the basis of of bone density criteria, and a clinically significant fracture history is also required.[2] The ISCD definition of osteoporosis includes non-traumatic vertebral fractures, without the need for bone mineral density (BMD) criteria, which acknowledges that low-trauma vertebral fractures represent an osteoporotic event in childhood. Without vertebral fractures, the ISCD definition of osteoporosis involves both a clinically significant fracture history (≥ 2 long bone fractures by the age of 10 years, or ≥ 3 long bone fractures by 19 years of age), and a gender- and age-matched BMD z-score of ≤ -2.0.[3] However, measurement of BMD is useful for tracking bone health in children over time.[4]

Primary osteoporosis is the more common form and is due to typical age-related loss of bone. Secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss. The most common cause of secondary osteoporosis is glucocorticoid therapy.

In children, glucocorticoids are commonly used to treat a variety of rheumatologic, gastrointestinal, respiratory, oncologic, renal, and endocrine disorders, as well as other acute and chronic inflammatory diseases; such disorders and diseases include asthma, juvenile idiopathic arthritis, inflammatory bowel disease, systemic lupus erythematosus, adrenal insufficiency, nephrotic syndrome, and leukemia.[5,6,7] Glucocorticoids are also important part of immunosuppressive regimens, such as with organ transplantation.[8] Glucocorticoid use in these diseases and disorders is largely due to the anti-inflammatory and immunosuppressive effects

[2] Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. *Front Endocrinol (Lausanne)*. 2020 Dec 16;11:576. doi: 10.3389/fendo.2020.00576. PMID: 33391179; PMCID: PMC7772619.
[3] International Society for Clinical Densitometry (ISCD) Official Pediatric Positions: https://iscd.org/learn/official-positions/pediatric-positions/
[4] Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. *Front Endocrinol (Lausanne)*. 2020 Dec 16;11:576. doi: 10.3389/fendo.2020.00576. PMID: 33391179; PMCID: PMC7772619.
[5] Ferrara G, et al. Clinical Use and Molecular Action of Corticosteroids in the Pediatric Age. *Int J Mol Sci*. 2019 Jan 21;20(2):444. doi: 10.3390/ijms20020444. PMID: 30669566; PMCID: PMC6359239.
[6] Velentza L, et al. Bone health in glucocorticoid-treated childhood acute lymphoblastic leukemia. *Crit Rev Oncol Hematol*. 2021 Dec;168:103492. doi: 10.1016/j.critrevonc.2021.103492. Epub 2021 Oct 13. PMID: 34655742.
[7] Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. *Front Endocrinol (Lausanne)*. 2020 Dec 16;11:576. doi: 10.3389/fendo.2020.00576. PMID: 33391179; PMCID: PMC7772619.
[8] Tsampalieros A, et al. Corticosteroid Use and Growth After Pediatric Solid Organ Transplantation: A Systematic Review and Meta-Analysis. *Transplantation*. 2017 Apr;101(4):694-703. doi: 10.1097/TP.0000000000001320. PMID: 27736823; PMCID: PMC7228591.

of glucocorticoid, though, in the case of adrenal insufficiency, administration of glucocorticoid is for replacement therapy of deficient endogenous steroids.

Patients treated with supraphysiologic doses of glucocorticoids are at an increased risk of developing osteoporosis for several reasons. The primary mechanism involves promotion of osteoblast apoptosis and osteoclast survival by supraphysiologic glucocorticoids, resulting in increased bone resorption.[9] Additional mechanisms include decreased intestinal calcium absorption and increased urinary calcium excretion, leading to negative calcium balance, secondary hypoparathyroidism, and decreased sex hormone levels. Ultimately, glucocorticoids can contribute to disruption of the normal bone remodeling process with a rapid and transient increase in bone resorption and decreased bone formation. Given that glucocorticoids increase expression of RANKL, denosumab, a RANKL inhibitor, may be beneficial in treatment of GIOP.[10]

Studies in adults have demonstrated that glucocorticoids cause rapid, dose-dependent bone loss and increased fracture risk. The growing skeleton may be especially vulnerable to adverse glucocorticoid effects on bone formation, which could possibly compromise trabecular and cortical bone accretion.[11] In children, glucocorticoids adversely affect bone strength, growth, and peak bone mass, with increased fracture risk, though children and young adults often regain lost bone when glucocorticoids are discontinued.[12] A population-based study reported that fracture risk was increased in children using ≥ 30 mg daily prednisone (adjusted odds ratio [OR] 1.24 [95% CI, 1-1.52]) and among children receiving four or more courses of oral corticosteroids (OR 1.32 [95% CI 1.03-1.69]).[13] Given the complications associated with osteoporotic fractures, glucocorticoid-induced bone loss demands attentive management.

2.2. Analysis of Current Treatment Options

Guidelines from the American College of Rheumatology on prevention and treatment of GIOS recommend adequate calcium and vitamin D intake for all adults and children beginning or continuing chronic glucocorticoid therapy. In children aged 4 to 17 years old treated with glucocorticoids and who have low or moderate risk for fracture (definition of which includes a lack of clinically significant fracture history), the guidelines conditionally recommend against starting bisphosphonate therapy; while in children aged 4 to 17 years old with osteoporotic fracture who continue treatment with chronic glucocorticoids, the guidelines recommend

[9] Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. *Front Endocrinol (Lausanne)*. 2020 Dec 16;11:576. doi: 10.3389/fendo.2020.00576. PMID: 33391179; PMCID: PMC7772619.
[10] Hofbauer LC, et al. Prevention of glucocorticoid-induced bone loss in mice by inhibition of RANKL. *Arthritis Rheum*. 2009 May;60(5):1427-37. doi: 10.1002/art.24445. PMID: 19404943.
[11] Leonard MB. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. *Pediatrics*. 2007 Mar;119 Suppl 2:S166-74. doi: 10.1542/peds.2006-2023J. PMID: 17332238.
[12] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.
[13] van Staa TP,et al. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res*. 2003 May;18(5):913-8. doi: 10.1359/jbmr.2003.18.5.913. PMID: 12733732.

starting oral or intravenous (IV) bisphosphonate therapy, over no therapy.[14] However, studies have suggested that calcium, vitamin D, and oral bisphosphonates are relatively weak modulators of BMD in glucocorticoid-treated children, and are not effective in preventing fragility fractures. Hence, IV bisphosphonates are the recommended first line therapy for treating pediatric GIOP.[15] However, because there are no FDA-approved bisphosphonates for use in children, such treatment remains off-label. See Table 1 for details regarding bisphosphonates approved to treat GIOP in adults.

Table 1: Summary of bisphosphonate therapy approved for GIOP in adults (bisphosphonates are recommended, but not approved, for GIOP in children)

Product (s) Name	Year of Approval	Dosing/ Administration	Efficacy Information (mean % increase in lumbar spine BMD at 12 or 24 months)	Important Safety and Tolerability Issues
Alendronate (Fosamax)	1999	5 mg oral daily (or 10 mg oral daily for postmenopausal women not on estrogen)	3.7 (5 mg/day); 5 (10 mg/day) (relative to placebo at 24 months)	Gastrointestinal adverse reactions; hypocalcemia; osteonecrosis of the jaw (ONJ); atypical femoral fracture (AFF)
Risedronate (Actonel)	2000	5 mg oral daily	2.9 (12 months)	Gastrointestinal adverse reactions; hypocalcemia; ONJ; AFF
Zoledronic acid (Reclast)	2009	5 mg IV once yearly	4.1 (treatment population); 2.6 (prevention population) (12 months)	Renal toxicity; hypocalcemia; ONJ; AFF

Source: USPI of Fosamax (NDA 020560), Actonel (NDA 020835), and Reclast (NDA 021817)

Additional therapies approved to treat GIOP in adults include denosumab and teriparatide. However, the guidelines do not list denosumab as a recommended therapy to treat GIOP in children. Denosumab approval for GIOP in adults prompted evaluation of denosumab in

[14] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.
[15] Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. *Front Endocrinol (Lausanne)*. 2020 Dec 16;11:576. doi: 10.3389/fendo.2020.00576. PMID: 33391179; PMCID: PMC7772619.

children with GIOP and the supplement currently under review (refer to Section 3).[16] Additionally, the labels of teriparatide products (i.e., Forteo, NDA 021318; Bonsity, NDA 211939; Yorvipath, NDA 216490; teriparatide, NDA 218771) include warnings against their use in children due to the risk of osteosarcoma in patients with open epiphyses.

Given tolerability concerns with bisphosphonates, and the fact that none are approved for use in children, there is a need for additional therapeutic options for the treatment of children with GIOP. Denosumab is an anti-resorptive agent with similar concerns for hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures as bisphosphonates, but may offer a therapeutic option for use in children and better tolerability.

[16] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Prolia was initially approved on June 01, 2010, in the United States for treatment of postmenopausal women with osteoporosis at high risk of fracture. Subsequent indications include the following:

- Treatment to increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, approved September 16, 2011
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, approved September 16, 2011
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, approved September 20, 2012
- Treatment of GIOP in men and women at high risk for fracture, approved May 18, 2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

On July 28, 2017, the Applicant (Amgen, Inc.) submitted an efficacy supplement (S-186) to the BLA for a new indication of the treatment of GIOP in men and women at high risk for fracture, based on a phase 3 trial in adults with GIOP. Supplement 186 was approved on May 18, 2018. The approval of Prolia for treatment of GIOP triggered PREA (21 U.S.C.355c). Upon review, the team determined that Prolia would pose safety concerns in pediatric patients under 5 years of age due to high rates of skeletal growth and potential for Prolia to adversely affect long-bone growth and dentition in this age group. Hence, the approval letter for S-186 included a waiver for a pediatric study requirement for ages 0 to 4 years. For the age group of 5 to 17 years, the pediatric study was deferred, and the approval letter included the following PMR:

PMR 3422-1 A phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of denosumab in pediatric subjects with glucocorticoid-induced osteoporosis (Study 20140444)

On June 17, 2020, the Applicant requested a meeting with FDA to discuss early termination of Trial 20140444 given the challenges in recruiting an adequate number of subjects (specifically, the low incidence of children with osteoporotic fracture on continuous use of glucocorticoids, reluctance of parents to enroll children in a trial with a placebo group, and a large number of otherwise eligible children with complications from serious underlying disorders resulting in exclusions). Subsequently, with concurrence from the FDA Pediatric Review Committee (PeRC) at a meeting on October 20, 2020, FDA concluded that the Applicant could end enrollment in Study 20140444 early (see clinical review in DARRTS under IND 009837 on October 29, 2020).

In a regulatory letter dated December 01, 2020, this decision was relayed to the Applicant. FDA informed the Applicant that they were allowed to cease recruitment efforts and allow the currently enrolled subjects to complete the trial. Once all currently enrolled subjects complete the trial, the Applicant should submit the complete study report to the BLA as a labeling supplement. A decision regarding the release of the PMR will be made following the labeling

supplement review (see Advice/Information request in DARRTS under IND 009837, submitted December 01, 2020).

On May 31, 2024, the Applicant submitted the Clinical Study Report and datasets for Study 20140444. In response, on June 05, 2024, FDA sent a Prior Approval Supplement Request to the Applicant informing them that submission of the required pediatric postmarketing study must be made as part of a BLA, or as a supplement to the approved BLA with the proposed labeling changes the Applicant believes are warranted based on data from this trial.

On July 25, 2024, the Applicant submitted an efficacy supplement to the BLA (supplement 219) with updated USPI to reflect that safety and effectiveness were not established in the phase 3 clinical trial (Study 20140444) evaluating the effect of denosumab on glucocorticoid-induced osteoporosis (GIOP) in children aged 5 to 17 years old. This supplement is the subject of this review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No additional nonclinical information was submitted in this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

The applicant submitted the final clinical study report for Study 20140444 "A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects with Glucocorticoid-induced Osteoporosis (GIOP)", to fulfill PMR 3422-1.

Study 20140444 ended early due to challenges in enrollment of pediatric patients.

Available PK data from the study were reviewed. No information related to PK of denosumab in pediatric subjects with GIOP was included in product labeling because the safety and efficacy of denosumab in this population is not demonstrated based on limited information from Study 20140444.

6.2. Summary of Clinical Pharmacology Assessment

The planned enrollment for Study 20140444 was 150 subjects in Protocol version 1. The study was delayed due to poor enrollment and the protocol was later amended to reduce number of subjects to 24. Among them, 23 subjects (15 in the denosumab treatment group and 8 in placebo group) completed the 12-month study.

6.2.1. Pharmacokinetics

Individual serum denosumab concentrations after subcutaneous administration of denosumab at 1 mg/kg (max of 60 mg) every 6 month to pediatric subjects (5-17 years old) with GIOP were determined by a validated bioanalytical assay (reviewed under the original BLA submission) and are listed below.

Table 2. Individual Serum Denosumab Concentrations After Subcutaneous Administration of Denosumab at 1 mg/kg to Pediatric Subjects with GIOP (DENOSUMAB 1 MG/KG [MAX 60 MG] SC Q6M)

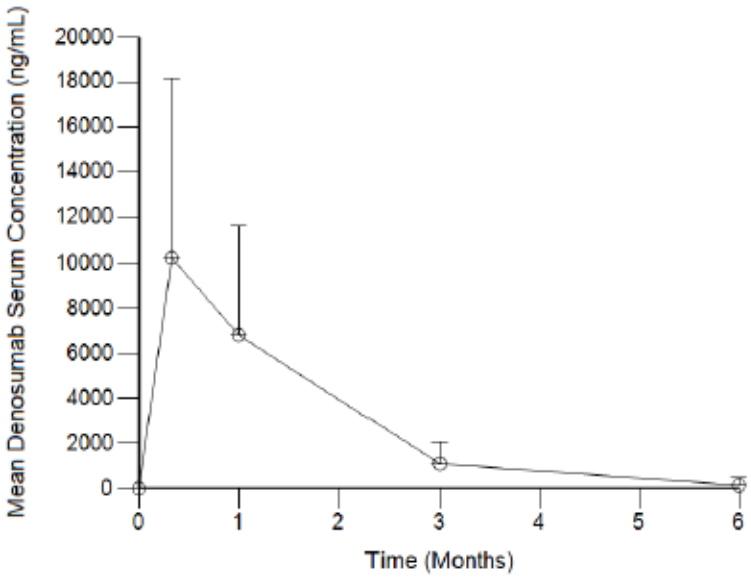
Subject	Nominal Time (day)						
	DAY 1	DAY 10	DAY 30	MONTH 3	MONTH 6	MONTH 12	MONTH 18
(b) (6)	0.00	7570	4310	510	0.00	0.00	0.00
	0.00	10100	6110	1600	0.00	0.00	0.00
	0.00	12200	10000	3370	658	868	535
	0.00	4400	3830	756	0.00	0.00	0.00
	0.00	7830	6690	1310	0.00	ND	0.00
	0.00	32600	18300	489	0.00	0.00	0.00
	0.00	5630	3240	532	0.00	0.00	0.00
	0.00	ND	ND	ND	0.00	0.00	ND
	0.00	3810	ND	ND	0.00[a]	524[a]	0.00
	0.00	11900	ND	ND	1030	855	ND
	ND	6750[a]	ND	ND	0.00	0.00	53.5
	0.00	7430[a]	ND	ND	0.00	0.00	0.00
	0.00	7880	3950	0.00	ND	0.00[a]	0.00[a]
	0.00	ND	ND	1320	0.00	0.00	0.00
	0.00	8970	5020	1100	0.00[a]	ND	0.00
N	14	11	9	10	12	11	12
Mean	0.00	10300	6830	1100	141	157	49.0
SD	0.00	7900	4770	935	338	349	154
Min	0.00	3810	3240	0.00	0.00	0.00	0.00
Median	0.00	7880	5020	928	0.00	0.00	0.00
Max	0.00	32600	18300	3370	1030	868	535
CV%	NR	76.9	69.8	85.1	240.3	222.5	313.6

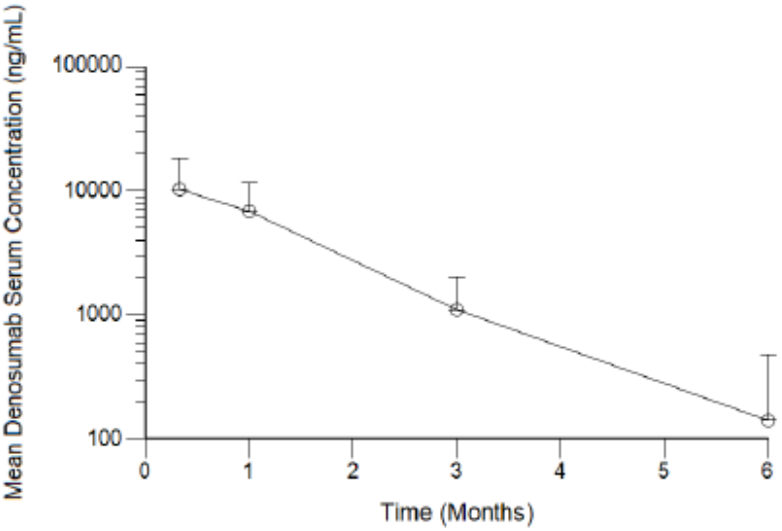
Concentration in ng/mL; LLOQ = 20.0 ng/mL (Values below the LLOQ were set to zero); ND = No data; NR = Not reported;
a Data excluded see Appendix 2 for details.
Day 30 and Month 3 timepoints were part of the PK substudy, which is why there are fewer pediatric subjects at those timepoints

Source: Appendix Table 3-1 of clinical study report for Study 20140444.

Mean (±SD) concentration-time profiles are presented in Figure 1.

Figure 1. Mean (±SD) Serum Concentration-Time Profiles Following Subcutaneous Administration of 1 mg/kg Denosumab in Pediatric Subjects with GIOP





Statistics	Day 1 (Predose)	Day 10	Day 30	Month 3	Month 6 (Predose)
N	14	11	9	10	12
Mean	0.00	10300	6830	1100	141
SD	0.00	7900	4770	935	338

Source: Figure 11-1 of clinical study report for Study 20140444.

Summary of denosumab PK parameter is presented in Table 3.

Table 3. Descriptive Statistics of Serum Denosumab Pharmacokinetic Parameter Table Estimates Following Subcutaneous Administration of 1 mg/kg Denosumab in Pediatric Subjects With GIOP

Statistic	t_{max} (days)	C_{max} (ng/mL)	AUC_{tau} (day*ng/mL)
N	13	13	9
Mean	9.2	9770	539000
SD	2.5	7310	395000
Min	6.0	3810	260000
Median	8.9	7830	383000
Max	13	32600	1460000
CV%	27	75	73
GeoMean	8.9	8340	451000

All descriptive statistics are presented to 3 significant figures except for t_{max} and CV%, which are presented to 2 significant figures and the nearest integer, respectively.
AUC_{tau} = AUC from time zero to the end of the 6-month dosing interval after the first dose; C_{max} = maximum concentration; GeoMean = geometric mean; t_{max} = time to maximum concentration
Source: Table 11-1 of clinical study report for Study 20140444.

Summary of denosumab trough concentrations is presented in Table 4.

Table 4. Descriptive Statistics of Denosumab Trough Concentrations Following Subcutaneous Administration of 1 mg/kg Denosumab in Pediatric Subjects with GIOP

	C_{trough} (ng/mL)		
Statistic	Month 6	Month 12	Month 18
N	12	11	12
Mean	141	157	49.0
SD	338	349	154
Min	0.00	0.00	0.00
Median	0.00	0.00	0.00
Max	1030	868	535
CV%	240	222	314
GeoMean	NA	NA	NA

All descriptive statistics are presented to 3 significant figures except for CV%, which is presented to the nearest integer.
C_{trough} = drug concentration at the end of dosing interval.
Source: Table 11-2 of clinical study report for Study 20140444.

Following administration of denosumab SC at a dose level of 1 mg/kg (up to a maximum of 60 mg), mean (SD) Cmax was 9770 (7310) ng/mL and mean (SD) AUCtau was 539000 (395000) day*ng/mL. Median (range) tmax was 8.9 (6.0-13) days post dose. Mean denosumab trough concentrations (Ctrough) observed from Month 6 to Month 18 ranged from 49.0 to 157 ng/mL.

Compared to denosumab PK in adult subjects with GIOP who received denosumab SC 60 mg Q6W in Study 20101217 (Table 5), mean and standard deviation for Cmax, AUCtau and Ctrough were higher in pediatric subjects with GIOP who received denosumab SC 1mg/kg (max 60 mg) Q6W. The difference may be explained by difference in dosing. Pediatric patients with GIOP received 1 mg/kg, up to a max of 60 mg vs. adult patients with GIOP received 60 mg fixed dose (~0.84 mg/kg based on mean bodyweight at baseline of 71.3 kg). In addition, the adult study had a much larger sample size than the pediatric study (N= 118 vs. N= 24).

Table 5. Descriptive Statistics of Denosumab Pharmacokinetic Parameter Estimates (12-month Primary Analysis) in adult subjects with GIOP in Study 20101217

	GC-C	GC-I	Combined
C_{max} *(mean ±SD) (mcg/mL)*	6.13±2.88 (N=74)	6.01±2.04 (N=44)	6.08±2.59 (N=118)
AUC_{last} *(mean ±SD) (day*mcg/mL)*	314±192 (N=74)	344±182 (N=44)	325±188 (N=118)
T_{max} *(median) (days)*	9.9 (N=74)	9.9 (N=44)	9.9 (N=118)
Half-life (mean ±SD) (days)	17.4±7.36 (N=30)	17.6±4.95 (N=23)	17.5±6.37 (N=53)

GC-C: glucocorticoid-initiating population, GC-I: glucocorticoid-continuing population.
Source: Table 11-1 of Clinical Study Report for 20101217

To avoid misuse of the product, PK information from the pediatric study will not be reflected in the label. The label will state that "Safety and effectiveness were not demonstrated for treatment of glucocorticoid-induced osteoporosis in one multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in 24 pediatric patients with glucocorticoid-induced osteoporosis, aged 5 to 17 years, evaluating change from baseline in lumbar spine BMD z-score."

6.2.2. Immunogenicity

All subjects tested negative for anti-denosumab antibodies. Therefore, no analyses of the relationship between PK and anti-denosumab antibodies could be conducted.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6 summarizes the pediatric clinical development program for denosumab for the indication of GIOP in pediatric subjects.

Table 6: Listing of Clinical Trials Relevant to this supplemental BLA

Trial Identity	IND number	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
Study 20140444	009837	Phase 3, randomized, double-blind, placebo-controlled, parallel group trial	Denosumab: 1 mg/kg (maximum 60 mg) SC every 6 months Placebo SC every 6 months	Primary: Change from baseline in lumbar spine BMD z-score at 12 months Secondary: change from baseline in lumbar spine and proximal femur BMD z-score at 6, 12, 18, 24, and 36 months; incidence of long-bone and vertebral fractures; improvement in vertebral fractures compared to baseline; change from baseline in PROs; change from baseline in growth velocity; serum concentration of denosumab	Subjects randomized 2:1 to denosumab or placebo for 12 months (2 injections), then all subjects were given open label denosumab for 12 months (2 injections), followed by a 12-month off-treatment observation period	Planned to enroll 150 subjects; given difficulties with enrollment, the trial was terminated early after enrollment of a total of 24 subjects (16 in the denosumab arm and 8 in the placebo arm).	Pediatric subjects aged 5 to 17 years with a clinical diagnosis of GIOP	The trial was conducted at 12 centers in 9 countries (Australia, Canada, Colombia, India, Peru, Russia, Turkey, Ukraine, and the United States of America)

7.2. Review Strategy

The phase 3 trial, which is the primary subject of this review, was a randomized, double-blind trial with a 12-month placebo-controlled period in pediatric subjects with GIOP, followed by an open-label 12-month period where all subjects received denosumab. After 24 months of treatment, subjects were followed for 12 months off therapy. The primary endpoint (i.e., change in lumbar spine [LS] BMD after 12 months of denosumab treatment compared to placebo) was appropriate to demonstrate superiority of denosumab to placebo in the treatment of GIOP in pediatric subjects.

Due to challenges with recruitment, the Applicant was unable to enroll an adequate number of pediatric subjects with GIOP in the trial. The trial only included subjects who had a prior history of osteoporotic fracture, because treatment with antiresorptives is not recommended in pediatric patients with GIOP unless they have a prior history of fracture.[17] However, in general, glucocorticoid use is low in pediatric patients, and the prevalence of pediatric patients on chronic glucocorticoid therapy with a prior osteoporotic fracture, is even lower. This resulted in challenges with recruitment, and trial enrollment was terminated early (see Section 3.2). Hence, the Applicant does not propose a new indication or the addition of safety data to the USPI for Prolia. Instead, the Applicant proposes to amend Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the Prolia USPI to reflect that safety and effectiveness were not established in the phase 3 clinical trial.

This review focuses on safety and efficacy data from the phase 3 trial 20140444 and includes an assessment of the Applicant's primary and secondary efficacy results and analyses. The safety review includes an assessment of the Applicant's safety analyses as well as analyses generated by the medical reviewer using JMP, Medical Dictionary for Regulatory Activities (MedDRA)-based Adverse Event Diagnostics (MAED), and Analysis Studio clinical software.

[17] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

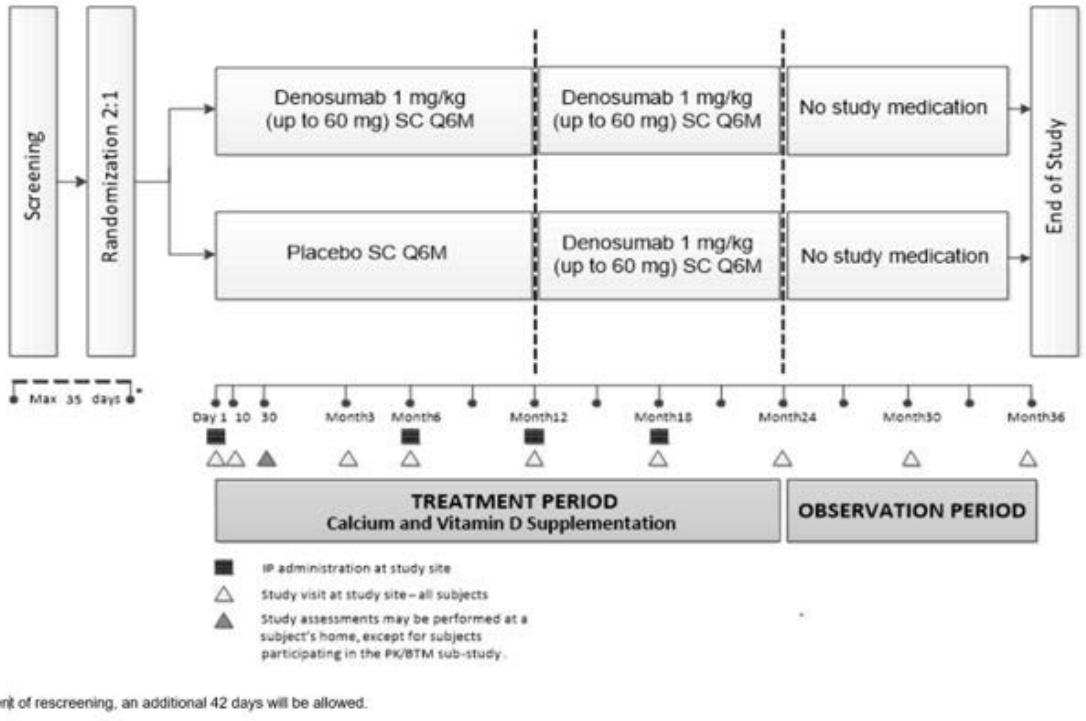
8.1.1. Study 20140444: A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects with Glucocorticoid-induced Osteoporosis

8.1.1.1. Trial design

Study 20140444 was a randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of denosumab administered via subcutaneous (SC) injection every 6 months, compared to placebo, in pediatric subjects aged 5 to 17 years old with GIOP.

The trial consisted of a Screening Period of up to 35 days, a 24-month treatment period and a 12-month observation. During the 24-month treatment period, subjects were randomized 2:1 to receive either 1 mg/kg (maximum 60 mg) denosumab or placebo every 6 months (two doses) for the 12-month placebo-controlled period, followed by an open-label period wherein all subjects received 1 mg/kg denosumab every 6 months (two doses) for 12 months. During the observation period, all subjects were observed off treatment. Refer to Figure 2, below.

Figure 2: Study 20140444 Design and Treatment Schema



* In the event of rescreening, an additional 42 days will be allowed.

Source: Study 20140444 Clinical Study Report, submitted May 31, 2024, Module 5.3.5.1, Figure 8-1, page 21

The dosing of 1 mg/kg denosumab every 6 months was deemed acceptable by the clinical pharmacology team. Based on population PK model-based simulations provided by the Applicant, denosumab steady-state concentrations in children with GIOP at this dosing over a treatment period of 24 months were similar to that of adult subjects with GIOP receiving 60 mg every 6 months (the approved dosing of Prolia as per its USPI; see clinical pharmacology review submitted to DARRTS under IND 009837 on November 17, 2017).

All subjects were required to take daily calcium (30 to 50 mg/kg, not to exceed 1000 mg elemental calcium) and vitamin D (at least 800 IU) supplementation throughout the 12-month double-blind and 12-month open-label periods (i.e., the 24-month treatment periods) of the trial. If deemed medically warranted by the Investigator, daily supplements of calcium and vitamin D were also given during the 12-month observation period.

8.1.1.2. Trial Endpoints

The primary endpoint was change from baseline in LS BMD z-scores as assessed by dual energy x-ray absorptiometry (DXA).

The primary endpoint was appropriate as the evaluation of LS BMD z-scores at 12 months is consistent with the primary endpoints of other approved therapies seeking osteoporosis indications. Evaluation of BMD z-scores is preferred to absolute BMD in children as BMD z-scores allow for interpretation of BMD with respect to age and gender. As discussed in Section 2.1, the ISCD definition of osteoporosis in children includes a gender- and age-matched BMD z-score of ≤ -2.0.[18] The ISCD recommends reporting BMD z-scores when interpreting DXA results in children.[19]

In addition to evaluation of BMD z-scores, development programs of products seeking osteoporosis indications should also evaluate for prevention of fractures, which was included in secondary endpoints in this program.

Relevant secondary endpoints evaluated the effect of denosumab with respect to:

- Change in LS BMD and proximal femur (i.e., total hip and femoral neck) BMD z-scores after 6, 12 (proximal femur BMD), 18, 24, and 36 months.
- Incidence of long-bone fractures and new and worsening vertebral fractures over 12, 24, and 36 months of therapy
- Incidence of improving vertebral fractures compared to baseline at 12, 24, and 36 months of therapy.
- Incidence of new and worsening VF and non-vertebral fractures over 12, 24, and 36 months of therapy.
- Change in growth velocity (GV) at 12, 24, and 36 months (based on age-adjusted z-scores for height, weight, and body mass index [BMI]).

[18] International Society for Clinical Densitometry (ISCD) Official Pediatric Positions: https://iscd.org/learn/official-positions/pediatric-positions/
[19] International Society for Clinical Densitometry (ISCD) Official Pediatric Positions: https://iscd.org/learn/official-positions/pediatric-positions/

- Serum concentration of denosumab over time

8.1.1.3. Eligibility criteria

To qualify for participation, subjects had to be aged 5 to 17 years old with GIOP. To meet the diagnosis of GIOP, these children were required to have a non-malignant condition(s) requiring treatment with systemic glucocorticoids (not as replacement therapy for adrenal insufficiency), have received treatment with systemic glucocorticoids of any duration during the 12 months prior to screening, and have evidence of at least one vertebral compression fracture of Genant grade ≥ 1, or, in the absence of a vertebral compression fracture, have a clinically significant fracture history (i.e., ≥ 2 long bone fractures by the age of 10 years or ≥ 3 long bone fractures by 17 years of age) and LS BMD z-score ≤ - 2.0.

The Applicant's criteria defining osteoporosis are consistent with the ISCD definitions. Genant grading of fractures is a widely used semiquantitative system to assess vertebral compression deformities on x-ray and defines normal as Grade 0; fracture with 20 to 25% loss of vertebral height as Grade 1 (mild); fracture with 26 to 40% loss of vertebral height as Grade 2 (moderate), and fracture with >40% loss of vertebral height as Grade 3 (severe).[20,21]

Only subjects with a prior history of osteoporotic fracture were included in this trial as this is consistent with the American College of Rheumatology guidance, which recommend against routine use of antiresorptives in pediatric patients with no prior history of fracture. [22]

Subjects were not eligible if they had previously received denosumab, strontium, or fluoride. They were also not eligible if they had received bisphosphonate therapy previously, as per the following: zoledronic acid (ZA) within 6 months prior to screening; previous oral or IV bisphosphonate (other than ZA) if at least one dosing interval of the bisphosphonate has not elapsed by the time of study drug administration.

See Appendix 14.3.1 for the full inclusion and exclusion criteria for Study 20140444.

8.1.1.4. Statistical analysis plan

Sample size

The study was initially designed to enroll 150 subjects; however, the enrollment was stopped after 24 subjects due to challenges with recruitment.

Assuming that approximately 30% of subjects would not be evaluable at Month 12 for the primary efficacy endpoint due to dropout, a common standard deviation of 1.24 using a 2-

[20] Burns JE, et al. Vertebral Body Compression Fractures and Bone Density: Automated Detection and Classification on CT Images. *Radiology*. 2017 Sep;284(3):788-797.
[21] Lenchik L, et al. Diagnosis of osteoporotic vertebral fractures: importance of recognition and description by radiologists. *AJR Am J Roentgenol*. 2004 Oct;183(4):949-58.
[22] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.

sample t-test, with a 2:1 ratio of denosumab to placebo, and significance level of two-sided 0.05, the sample size of 150 would provide >95% power to detect a difference of 1.22 in change from baseline lumbar spine BMD z-score at month 12 between denosumab and placebo.

With all assumptions kept the same, and further assuming that all 24 subjects have evaluable data at Month 12, the sample size of 24 would have 58% power to detect a difference of 1.22 in change from baseline lumbar spine BMD z-score at Month 12 between denosumab and placebo. Hence, this study was ultimately not adequately powered to establish efficacy of Prolia in pediatric patients with GIOP.

Primary analysis set

The primary analysis set for the primary efficacy endpoint included all randomized subjects with baseline and at least 1 post baseline lumbar spine provided by the central imaging vendor during the first 12 months (primary DXA analysis set). Subjects were analyzed according to their randomized treatment group.

The applicant prespecified primary analysis set excluded subjects who had lumbar spine measure at baseline only and missing all other post-baseline measures, which is not FDA preferred analysis set. The FDA preferred primary analysis set is the intent-to-treatment set that includes all randomized subjects.

Primary efficacy endpoint analysis

The primary efficacy endpoint was change from baseline in lumbar spine BMD z-score at 12 months. The primary analysis was based on an analysis of covariance (ANCOVA) model with Treatment as a factor baseline age and baseline BMD z-score as covariates. Missing baseline and postbaseline BMD z-scores were not imputed.

The primary analysis prespecified by the Applicant excluded subjects with missing primary endpoint, which is not FDA preferred analysis. The FDA preferred primary analysis includes all randomized subjects and should impute missing data.

Secondary efficacy endpoints analysis

The change from baseline in lumbar spine BMD z-score as assessed by DXA at 6, 18, 24 and 36 months and change from baseline in total hip and femoral neck BMD z-score as assessed by DXA at 6, 12, 18, 24 and 36 months was analyzed by repeated measures model including treatment, study visit, treatment by visit interaction as factors, and corresponding baseline z-score and age as covariates. Missing data were not imputed.

The other secondary endpoints were summarized descriptively for each timepoint of interest.

Multiplicity control

There was no multiplicity adjustment for the analyses of secondary efficacy endpoints.

8.1.1.5. Protocol Amendments

The protocol for Study 20140444 was amended 3 times since its first submission on September 29, 2017.

The first amendment (amendment date May 25, 2018, submitted June 26, 2018) was a result of recommendations from FDA and in conjunction with the Prolia iPSP and served mostly to provide clarifications and consistency. This amendment also included descriptions of additional sensitivity analyses to assess the impact of short stature on BMD z-scores in response to FDA comments.

The second amendment (amendment date April 20, 2021, submitted May 06, 2021) was in response to the fact that only 24 subjects out of a planned 150 subjects, were enrolled between June 2017 and December 2020. As such, following agreement with the European Medicines Agency (EMA) and the FDA, the Applicant ended enrollment in the study (see Section 3.2). This amendment was subsequently submitted which changed the target number of subjects enrolled and revised the statistical analysis plan to reflect the new sample size.

The final amendment (amendment date July 10, 2023, submitted July 25, 2023) was done in order to remove specific endpoints that will not be met for end of study and further revise the statistical analysis plan to reflect the smaller sample size. This amendment also allowed alignment with EMA/Paediatric Committee (EMA/PDCO) Modification Summary Report provided by the EMA.

8.1.2. Study Results

8.1.2.1. Compliance with Good Clinical Practices

The trial was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP) regulations/guidelines.

8.1.2.2. Financial Disclosure

The financial disclosure documents were reviewed. No issues were identified that could influence the outcome of the trials (refer to Section 14.1 of the Appendix).

8.1.2.3. Subject Disposition

A total of 24 subjects were enrolled, and 16 and 8 subjects were randomized to the denosumab/denosumab and placebo/denosumab groups, respectively. A total of 9/16 (56.3%) and 6/8 (75%) subjects originally enrolled in the denosumab/denosumab and placebo/denosumab groups, respectively, participated in the pharmacokinetic (PK)/bone turnover marker (BTM) sub-study.

During the 12-month placebo-controlled period, all subjects in both groups received investigational product. Of these, 2 subjects, both in the denosumab/denosumab group, discontinued treatment early: 1/16 (6.3%) subject discontinued study drug due to an adverse event (AE) of autoimmune hepatitis, though she completed the trial, and 1/16 (6.3%) subject

was lost to follow up and did not complete the 12-month placebo-controlled period. A total of 15/16 (95.8%) and 8/8 (100%) subjects in the denosumab/denosumab and placebo/denosumab groups, respectively, completed all 12 months of the placebo-controlled period and enrolled in the following 12-month open-label period.

During the open-label period, 14/16 (87.5%) and 8/8 (100%) subjects originally enrolled in the denosumab/denosumab and placebo/denosumab groups, respectively, received at least one dose of investigational product. A total of 15/16 (93.8%) and 8/8 (100%) subjects originally enrolled in the denosumab/denosumab and placebo/denosumab groups, respectively, completed the 12-month open label period, and enrolled in and completed the following 12-month untreated observation period.

Refer to Table 7 for subject disposition.

Table 7: Subject Disposition

Treatment:	Denosumab/ Denosumab (N=16) n (%)	Placebo/ Denosumab (N=8) n (%)	Total (N = 24) n (%)
Enrolled	16	8	24
Randomized	16 (100)	8 (100)	24 (100)
Enrolled in PK/BTM sub-study	9 (56.3)	6 (75)	15 (62.5)
12-month placebo-controlled period	16 (100)	8 (100)	24 (100)
Received investigational product	16 (100)	8 (100)	24 (100)
Discontinued investigational product early	2 (12.5)	0	2 (8.3)
Adverse event	1 (6.3)	0	1 (4.2)
Lost to follow up	1 (6.3)	0	1 (4.2)
Completed period	15 (93.8)	8 (100)	23 (95.8)
12-month open-label period	15 (93.8)	8 (100)	23 (95.8)
Received investigational product	14 (87.5)	8 (100)	22 (91.7)
Discontinued investigational product early	0	0	0
Completed period	15 (93.8)	8 (100)	23 (95.8)
12-month observational period	15 (93.8)	8 (100)	23 (95.8)
Completed period	15 (93.8)	8 (100)	23 (95.8)

Source: JMP Clinical, reviewer generated report and information taken from Clinical Study Report for Study 20140444, Table 9-1, page 42

8.1.2.4. Protocol Violations/Deviations

The protocol deviations were reviewed, and do not appear to have an impact on the overall results. All subjects with protocol deviations were included in the full analysis set (FAS).

A total of 6/16 (37.5%) and 4/8 (50%) subjects in the denosumab/denosumab and placebo/denosumab groups, respectively, had at least 1 important protocol deviation. In the denosumab/denosumab group, 1 subject had two protocol deviations listed as “entered study even though entry criteria were not satisfied”, and appears to be due to the fact that that

serum vitamin D was not drawn at an unscheduled screening visit 18 days before the study drug initiation. The second protocol deviation for this subject involved missing lumbar spine DXA data at month 12 (as per Subject Disposition, above, this is the subject that was lost to follow up during the 12-month placebo control period).

The remaining subjects with protocol deviations in both groups were listed as "other deviations", with a coded term of "serious ICH/GCP compliance issue", reported as "missing calcium lab assessment".

8.1.2.5. Baseline Demographic and Disease Characteristics

Baseline demographics regarding sex, ethnicity, race, age, and country were not well balanced between the two treatment groups. This is likely impacted by early termination of trial and a small number of subjects who were ultimately enrolled, making determination of whether there are significant differences in the baseline demographics difficult (see Table 8). While sex was evenly split in the placebo/denosumab (i.e., 50% males and 50% females), the denosumab/denosumab group had 62.5% males compared to 37.5% females. The majority of subject in both groups were white and not Hispanic/Latino, though the proportion was higher in the denosumab/denosumab group (93.8% and 81.3%, respectively) compared to the placebo/denosumab group (62.5% and 62.5%, respectively). The subjects in the denosumab/denosumab were slightly older than those in the placebo/denosumab group, with mean (SD) ages of 13.8 (2.3) and 12.8 (2.1), respectively.

Approximately 8.3% of all subjects were from the United States, while other subjects were from Canada, South America, Europe, or Asia. The predominance of non-US subjects is acceptable. Diagnostic criteria for GIOP in and outside the US are similar, and patients generally have a similar disease etiology. Manifestations of the disease are the same and comorbidities are similar in patients, regardless of area of enrollment.

Table 8: Baseline Demographics

Demographics	Denosumab/ Denosumab (N = 16)	Placebo/ Denosumab (N = 8)	Total (N = 24)
Sex – n (%)			
Male	10 (62.5)	4 (50)	14 (58.3)
Female	6 (37.5)	4 (50)	10 (41.7)
Ethnicity – n (%)			
Hispanic/Latino	1 (6.3)	3 (37.5)	4 (16.7)
Not Hispanic/Latino	15 (93.8)	5 (62.5)	20 (83.3)
Race – n (%)			
Asian	3 (18.8)	0	3 (12.5)
White	13 (81.3)	5 (62.5)	18 (75)
Other	0	3 (37.5)	3 (12.5)
Country			
Australia	1 (6.3)	1 (12.5)	2 (8.3)
Canada	4 (25)	0	4 (16.7)
Colombia	0	1 (12.5)	1 (4.2)
India	2 (12.5)	0	2 (8.3)
Peru	0	1 (12.5)	1 (4.2)
Russia	6 (37.5)	1 (12.5)	7 (29.2)
Türkiye	0	1 (12.5)	1 (8.3)
Ukraine	2 (12.5)	2 (25)	4 (16.7)
United States	1 (6.3)	1 (12.5)	2 (8.3)
Age – years			
Mean (SD)	13.8 (2.3)	12.8 (2.1)	13.4 (2.2)
Median	14	12.5	14
(min, max)	(10, 17)	(10, 15)	(10, 17)

Source: JMP Clinical, reviewer generated report and information taken from Clinical Study Report for Study 20140444, Table 9-3, page 44

In general, the LS, total hip, and femoral neck mean BMD z-scores of subjects in the denosumab/denosumab group (-1.95, -3.14, and -3.35, respectively) were higher at baseline than that of placebo/denosumab group (-3.6, -4.56, and -4.78, respectively), though it is unclear if these differences were significant. Further, endpoints assessed differences in changes from baseline between the two groups and not just final BMD z-scores. Refer to Table 9.

Table 9: Summary of Baseline BMD

Baseline BMD z-scores	Denosumab/ Denosumab (N = 16)	Placebo/ Denosumab (N = 8)	Total (N = 24)
Lumbar Spine			
Mean (SD)	-1.95 (1.03)	-3.6 (1.77)	-2.5 (-1.51)
Median	-1.95	-4.36	-2.34
(min, max)	(-3.58, 0.55)	(-5.59, -0.93)	(-5.59, 0.55)
N	16	8	24
Total hip			
Mean (SD)	-3.14 (1.7)	-4.56 (2.08)	-3.58 (1.9)
Median	-3.2	-3.74	-3.6
(min, max)	(-6.15, -0.45)	(-7.79, -2.38)	(-7.79, -0.45)
N	16	7	23
Femoral neck			
Mean (SD)	-3.35 (1.91)	-4.78 (2.8)	-3.79 (2.25)
Median	-3.02	-3.66	-3.18
(min, max)	(-6.1, -0.53)	(-9.52, -2.28)	(-9.52, -0.53)
N	16	7	23

Source: JMP Clinical, reviewer generated report and information taken from Clinical Study Report for Study 20140444, Table 14-2.5, pages 91 to 93

As required by the inclusion criteria, all subjects had a history of fracture. In the denosumab/denosumab group, 3/16 (18.8%) subjects had a history of nonvertebral fracture, compared to 1/8 (12.5%) subject in the placebo/denosumab group. Of vertebral fractures, 11/16 (68.8%) and 4/16 (25%) subjects denosumab/denosumab group, compared to 6/8 (75%) and 1/8 (12.5%) subjects in the placebo/denosumab group, had ≥ 2 or 1 prevalent vertebral fractures, respectively, based on baseline spine radiographs. Data on baseline vertebral fractures was missing on 1/8 (12.5%) subject in the placebo/denosumab group. Comparable proportions of subjects in the two groups had mild, moderate, or severe Genant grade vertebral fractures at baseline. Refer to Table 10.

Table 10: Summary Prevalent Vertebral Fractures Based on Baseline Spine Radiographs

Prevalent Vertebral Fractures	Placebo / Denosumab 1 mg/kg Q6M (N = 8) n (%)	Denosumab / Denosumab 1 mg/kg Q6M (N = 16) n (%)	All (N = 24) n (%)
Prevalent vertebral fracture			
Yes	7 (87.5)	15 (93.8)	22 (91.7)
No	0 (0.0)	1 (6.3)	1 (4.2)
Not readable	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (12.5)	0 (0.0)	1 (4.2)
Number of prevalent vertebral fractures[a]			
0	0 (0.0)	1 (6.3)	1 (4.2)
1	1 (12.5)	4 (25.0)	5 (20.8)
≥ 2	6 (75.0)	11 (68.8)	17 (70.8)
Not readable / missing	1 (12.5)	0 (0.0)	1 (4.2)
Most severe genant semi-quantitative grade			
Normal	0 (0.0)	1 (6.3)	1 (4.2)
Mild	4 (50.0)	9 (56.3)	13 (54.2)
Moderate	3 (37.5)	6 (37.5)	9 (37.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Not readable / missing	1 (12.5)	0 (0.0)	1 (4.2)

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The full analysis set (FAS) includes all subjects randomized into the study.
N = Number of subjects in the full analysis set. n = Number of subjects with observed data.
Not readable = Unknown fracture status at ≥ 1 vertebra with no fracture at remaining evaluable vertebrae.
[a] A subject has prevalent vertebral fracture if any vertebra from T4 to L4 has a grade of ≥ 1 at baseline.
Percentages based on number of subjects in the full analysis set.
Percentages of subcategories for overall may not add to exact 100 due to rounding.
Snapshot date: 15FEB2024

Source: Clinical Study Report for Study 20140444, Table 14-2.7, page 95

8.1.2.6. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All SC injections were administered by authorized site personnel and administration of all doses was recorded on each subject's case report form.

8.1.2.7. Efficacy Results – Primary Endpoint

There was 1 subject in the denosumab arm who had lumbar spine BMD z-score at baseline only and missing all other post-baseline measures. This subject was excluded from the analysis per pre-specified primary analysis method. At Month 12, the difference in least square mean

change from baseline in lumbar spine BMD z-score between the denosumab and placebo group was not significant: 0.11 (95% CI: -0.45, 0.67), p-value = 0.6819.

The observed difference between denosumab and placebo in change from baseline in lumbar spine BMD z-score at month 12 was 0.11 and standard error was 0.27 (standard deviation 1.32). This observed effect size was much smaller than what was initially assumed for sample size calculation. Therefore, the small effect size along with only 24 subjects with available data could have all contributed to inclusiveness of the study in establishing efficacy.

Table 11. Lumbar Spine BMD z-score Change from Baseline at Month 12

Lumbar spine BMD z-score	**Denosumab 1 mg/kg Q6M N=15**	**Placebo N=8**
Baseline, mean (SD)	-1.92 (1.06)	-3.60 (1.77)
At 12 months, mean (SD)	-1.68 (1.32)	-3.52 (1.66)
Least square mean change from baseline at 12 months (95% CI)	0.23 (-0.05, 0.51)	0.11 (-0.30, 0.53)
Least square mean difference (95% CI)	0.11 (-0.45, 0.67)	
p-value	0.6819	

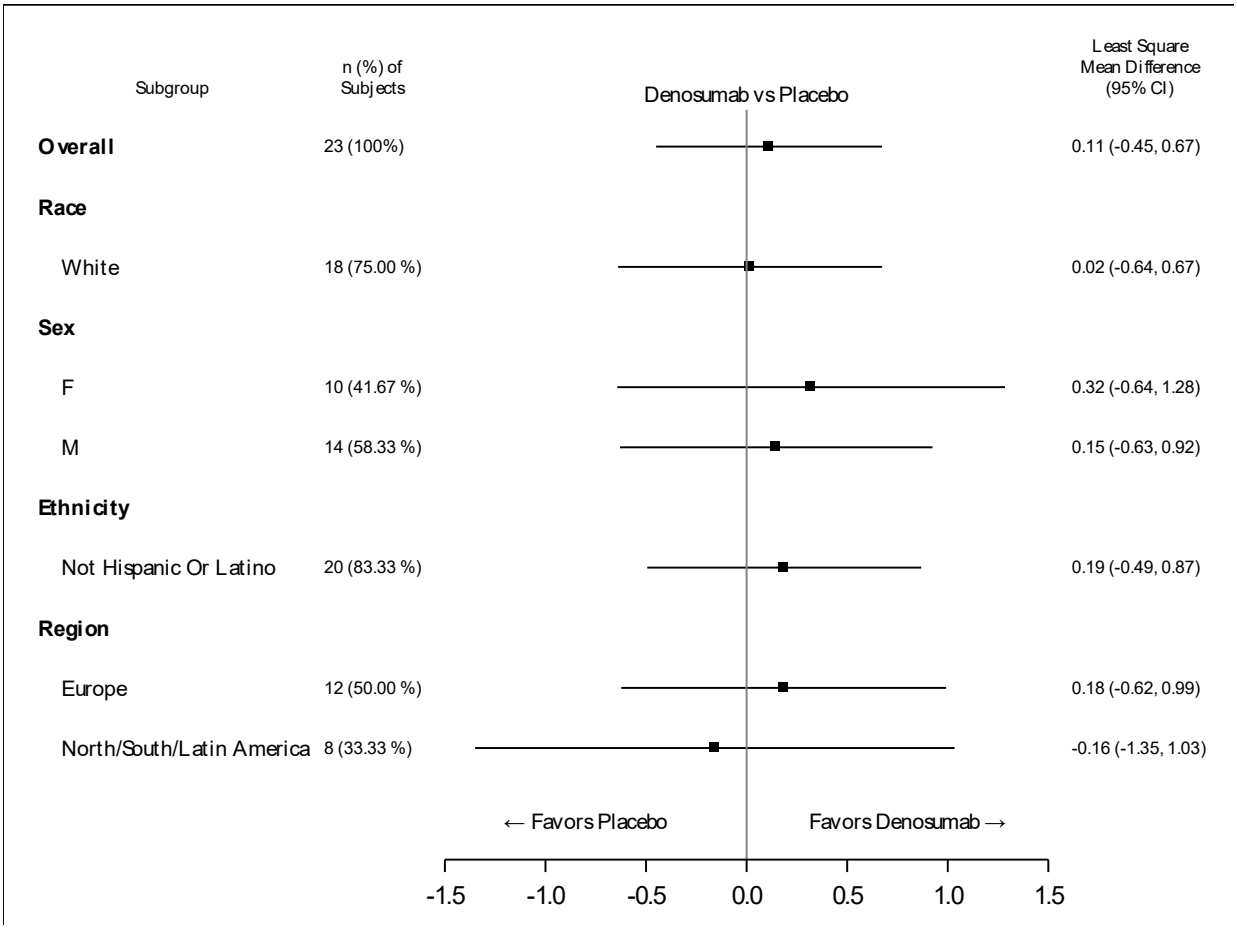
Source: statistical reviewer
The primary analysis set for the primary efficacy endpoint included all randomized subjects with baseline and at least 1 post baseline lumbar spine provided by the central imaging vendor during the first 12 months.
N: Number of subjects in the primary DXA analysis set.
The least square mean changes and difference was based on ANCOVA model adjusting for treatment as fixed effect, baseline age and baseline BMD z-score as covariates.
Abbreviations: SD, standard deviation; CI, Confidence Interval.

The FDA preferred analysis, which included all randomized subjects and imputing primary endpoint for the 1 subject who had lumbar spine BMD z-score at baseline only and missing all other post-baseline measures, did not alter the conclusion.

The primary analysis results were consistent with the sensitivity analysis imputing missing data for the primary endpoint based on placebo data, and the supplementary analysis using mixed model repeated measures approach.

Subgroups analyses by race, sex, ethnicity, and region were performed. These subgroup analyses did not indicate any treatment by subgroup interaction.

Figure 3. Subgroup Analysis of the Primary Endpoint



Source: statistical reviewer
The primary analysis set for the primary efficacy endpoint included all randomized subjects with baseline and at least 1 post baseline lumbar spine provided by the central imaging vendor during the first 12 months.
The least square mean changes and difference was based on ANCOVA model adjusting for treatment as fixed effect, baseline age and baseline BMD z-score as covariates.
Abbreviations: CI, Confidence Interval.

8.1.2.8. Efficacy Results – Secondary and Other Relevant Endpoints

Lumbar spine, femoral neck, and total hip BMD z-scores

The phase 3 trial also assessed secondary efficacy endpoints of change from baseline in LS BMD at Months 18, 24, and 36, and change from baseline in femoral neck BMD and total hip BMD z-scores at Months 12, 18, 24, and 36. There was no statistically significant treatment difference between the two treatment groups for any of these endpoints (see Table 12). The limited number of enrolled subjects in each treatment arm precludes definitive conclusions regarding the results of these secondary efficacy endpoints.

Table 12: Change from baseline in BMD z-scores, Study 201404444 secondary efficacy endpoints

Least squares mean	Timepoint	Denosumab/denosumab	Placebo/denosumab	Treatment difference: Denosumab/denosumab – placebo/denosumab
Lumbar spine[a] (95% CI) n	Month 18	0.32 (-0.03, 0.68) 15	0.3 (-0.21, 0.8) 7	0.03 (-0.19, 0.54) p = 0.34
	Month 24	0.37 (-0.02, 0.76) 13	0.26 (-0.29, 0.8) 7	0.11 (-0.57, 0.8) p = 0.74
	Month 36	-0.23 (-0.83, 0.372) 9	0.57 (-0.27, 1.4) 5	-0.8 (-1.85, 0.24) p = 0.12
Total hip[a] (95% CI) n	Month 12	0.24 (-0.08, 0.55) 14	0.3 (-0.17, 0.76) 7	-0.06 (-0.63, 0.52) p = 0.83
	Month 18	0.48 (0.02, 0.94) 15	0.75 (0.06, 1.43) 6	-0.27 (-1.11, 0.57) p = 0.51
	Month 24	0.52 (0, 1.03) 13	0.69 (-0.06, 1.45) 6	-0.18 (-1.1, 0.75) p = 0.69
	Month 36	0.64 (-0.15, 1.44) 9	0.73 (-0.38, 1.85) 5	-0.09 (-1.47, 1.29) p = 0.89
Femoral neck[a] (95% CI) n	Month 12	0.53 (0.03, 1) 14	0.43 (-0.3, 1.16) 7	0.1 (-0.81, 1) p = 0.83
	Month 18	0.85 (0.26, 1.45) 15	0.48 (-0.39, 1.35) 6	0.37 (-0.7, 1.44) p = 0.48
	Month 24	0.75 (0, 1.5) 13	0.64 (-0.45, 1.72) 6	0.11 (-1.22, 1.44) p = 0.86
	Month 36	1 (-0.01, 2.01) 9	0.63 (-0.8, 2.05) 5	0.38 (-1.38, 2.1) p = 0.66

CI = confidence interval; n = number of subjects who have assessment at baseline and at 12-month assessment.
[a] Based on repeated measures mixed model adjusting for treatment, categorical visits, baseline age, and baseline BMD z-scores as fixed effects and treatment-by-visit included as an interaction.
If DXA assessment is not collected for baseline visit, only the DXA scans obtained on or before Study Day 60 will be considered as baseline values and not the 6-month values.
The DXA analyses set includes all subjects in the Full Analysis Set with baseline and ≥ 1 post-baseline valid DXA assessment.
Source: Information taken from Clinical Study Report for Study 20140444, Table 10-4, page 46 and Table 10-5, page 50 and 51

Long bone fractures and new and worsening vertebral fractures

Evaluation of the proportion of subjects per treatment arm with new and worsening vertebral fractures found on scheduled spine x-rays, in addition to the proportion of subjects with long-bone fractures, confirmed by unscheduled x-ray evaluations, was included as a secondary efficacy endpoint. Thoracic and lumbar spine x-rays were conducted at Months 12, 24, and 36 to evaluate vertebral fractures. Worsening vertebral fractures were defined as those with an increase in semi-quantitative Genant score. The number and proportion of subjects reporting at least 1 long bone fracture or new or worsening vertebral fracture during the phase 3 trial 20140444 are provided in Table 13.

Table 13: Summary of long bone and new and worsening vertebral fractures

Number (%) of subjects with long bone fracture or new or worsening vertebral fracture	Denosumab/Denosumab (N = 16) n(%)	Placebo/Denosumab (N = 8) n(%)	Total (N = 24) n(%)
Placebo-controlled period Months 0 to 12	2 (12.5)	2 (25)	4 (16.7)
Open label period Months 12 to 24	1 (6.3)	2 (25)[b]	3 (12.5)[b]
Observation period Months 24 to 36	2 (12.5)[a]	1 (12.5)	3 (12.5)[a]
Across the entire 36-Month trial Months 0 to 36	3 (18.8)	4 (50)	7 (29.2)

[a] Subjects IDs (b) (6) and (b) (6), both in the denosumab/denosumab group, had also reported long bone or new or worsening fractures in a previous period
[b] Subject ID (b) (6), in the placebo/denosumab group, had also reported long bone or new or worsening fractures in a previous period
Source: JMP Clinical, reviewer generated report and information taken from Clinical Study Report for Study 20140444, Table 10-6, page 52

Placebo-controlled period

In the 12-month, double-blind, placebo-controlled period of the trial, a higher proportion of subjects in the placebo arm, compared to the denosumab arm, had at least 1 long bone fracture or new or worsening vertebral fracture: 2/16 (12.5%) and 2/8 (25%) subjects in the denosumab and placebo arms, respectively. However, because of the small overall population size, definitive conclusions regarding the impact of denosumab therapy on new or worsening fractures cannot be made with the available data.

In the denosumab group, both of these subjects had more than one fracture: 1 subject had 1 new vertebral fracture and 2 new long-bone fractures (femur and tibia, see discussion in Section 8.2.5.6); and the other subject had 1 new vertebral fracture and 1 new long-bone

fracture (femur, see discussion in Section 8.2.5.6). Neither subject had worsening vertebral fracture during this period.

In the placebo group, neither subject had a long bone fracture. One subject had 4 new vertebral fractures; the other subject had 1 new vertebral fracture. Neither subject had worsening vertebral fracture during this period.

Open-label period

In the 12-month, open-label period where all subjects were treated with denosumab from Months 12 to 24, an additional 1/16 (6.3%) and 2/8 (25%) subjects originally randomized to denosumab or placebo, respectively, reported at least 1 long bone fracture or new or worsening vertebral fracture during this period.

In the denosumab/denosumab group, one subject reported 1 new vertebral and no worsening vertebral or new long bone fractures during this period.

In the placebo/denosumab group, each of the two subjects and reported 1 new vertebral and no worsening vertebral or new long bone fractures during this period (one subject had also previously reported 4 new vertebral fractures during the Placebo-controlled period).

Observation period

In the 12-month observation period where all subjects were followed off therapy from Months 24 to 36 (final dose of denosumab at Month 18), 2/16 (12.5%) and 1/8 (12.5%) subjects originally randomized to denosumab or placebo, respectively, reported at least 1 long bone fracture or new or worsening vertebral fracture during this period.

In the denosumab/denosumab group, both subjects had previously reported fractures in previous periods in addition to the new or worsening fractures reported in this period. During this period, one subject had previously reported 1 long bone and 1 new vertebral fracture in the Placebo-controlled period and reported 1 additional vertebral and 1 worsening fracture during this period; the other subject had previously reported 1 new vertebral fracture during the Open-label period and reported an additional 3 new vertebral fractures during this period.

In the placebo/denosumab group, one subject reported 5 new vertebral fractures during, 1 of which was seen to be worsening, during this period.

Conclusion

Overall, a higher proportion of subjects originally randomized to placebo reported at least 1 long bone fracture or new or worsening vertebral fracture in the placebo-controlled period of the trial (2/16 (12.5%) vs. 2/8 (25%) subjects in the denosumab and placebo arms, respectively) and throughout the entire 36-month trial (3/16 [18.8%] subjects in the denosumab/denosumab group vs. 4/8 [50%] subjects from the placebo/denosumab group), (see Table 13). Further, a higher proportion of subjects originally randomized to placebo (2/8 [25%] subjects), compared to denosumab (3/16 [18.8%] subjects), also reported more than 1 long bone fracture or new or worsening vertebral fracture during the 36-month trial. However, because of the small overall

population size, definitive conclusions regarding the impact of denosumab therapy on new or worsening fractures cannot be made with the available data. Additionally, information related to the possibility of decreasing the proportion of new or worsening fractures once all subjects started denosumab therapy in the open-label period can also not be interpreted due to the small number of enrolled subjects.

Not all of these fractures were reported as adverse events (specifically, the vertebral fractures were not reported as adverse events). For a discussion of fractures reported as adverse events in each period of the phase 3 trial, see Section 8.2.5.6.

Incidence of improving vertebral fractures

Evaluation of the proportion of subjects per treatment arm with improving vertebral fractures found on scheduled spine x-rays was included as a secondary efficacy endpoint.

Thoracic and lumbar spine x-rays were conducted at Months 12, 24, and 36 to evaluate vertebral fractures. Improving vertebral fractures were defined as those with a decrease in semi-quantitative Genant score. The incidence of improving vertebral fractures during the phase 3 trial 20140444 are provided in Table 14.

Table 14: Summary of improving vertebral fractures

Number (%) of subjects with improving vertebral fracture	**Denosumab/ Denosumab (N = 15)** n(%)	**Placebo/ Denosumab (N = 7)** n(%)	**Total (N = 22)** n(%)
Placebo-controlled period Months 0 to 12	3 (20)	1 (14.3)	4 (18.2)
Open label period Months 12 to 24	1 (6.7)[a]	1 (14.3)[b]	2 (9.1)[a,b]
Observation period Months 24 to 36	0	2 (28.6)	2 (9.1)
Across the entire 36-Month trial Months 0 to 36	3 (20)	3 (42.9)	6 (27.3)

Percentages are based on the number of subjects in the vertebral fractures set
[a] Subjects ID (b) (6), in the denosumab/denosumab group, had improving vertebral fractures in both the placebo-controlled and open label periods.
[b] Subject ID (b) (6), in the placebo/denosumab group, had improving vertebral fractures in both the placebo-controlled and open label periods
Source: JMP Clinical, reviewer generated report and information taken from Clinical Study Report for Study 20140444, Table 10-7, page 52

Placebo-controlled period

In the 12-month, double-blind, placebo-controlled period of the trial, a higher proportion of subjects in the denosumab arm, compared to the placebo arm, had at least 1 improving vertebral fracture: 3/15 (20%) and 1/7 (14.3%) subjects in the denosumab and placebo arms, respectively. Each of these subjects had more than one vertebral fracture at baseline and in all

but one of these subjects (in the denosumab group), improvement was noted in more than 1 vertebral fracture, though all of these subjects did have other vertebral fractures that did not improve during this period. Additionally, the subject in the placebo arm was the only one of these 4 subjects that had new vertebral fractures during this period. However, because of the small overall population size, definitive conclusions regarding the impact of denosumab therapy on improving vertebral fractures cannot be made with the available data.

Open-label period

In the 12-month, open-label period where all subjects were treated with denosumab from Months 12 to 24, 1/15 (6.7%) and 1/7 (14.3%) subject originally randomized to denosumab or placebo, respectively, had improvement in more than one vertebral fracture during this period, and neither had worsening or new vertebral fractures, though both also had other vertebral fractures that did not improve in this period. Both of these subjects also had improving vertebral fractures in the previous placebo-controlled period. Additionally, the subject in the placebo/denosumab group had fractures that did not improve in the placebo-controlled period, but improved once starting denosumab in the open-label period: subject (ID (b) (6)) had Genant grade 2 fractures of the L3 and L4 vertebrae at baseline and Month 12, that improved to grade 1 by Month 24; and grade 1 fractures of the T7 and T8 vertebrae at baseline and Month 12 that improved to grade 0 by Month 24.

Observation period

In the 12-month observation period where all subjects were followed off therapy from Months 24 to 36 (final dose of denosumab at Month 18), 0 and 2/7 (28.6%) subjects originally randomized to denosumab or placebo, respectively, had improvement of at least 1 vertebral fracture during this period. Both subjects also had other vertebral fractures that did not worsen or improve during the trial.

Conclusion

In the placebo-controlled period of the trial, a higher proportion of subjects in the denosumab arm (20%), compared to the placebo arm (14.3%), had at least 1 improving vertebral fracture. Each of these subjects had more than one vertebral fracture at baseline and in all but one of these subjects (in the denosumab group), improvement was noted in more than 1 vertebral fracture. However, all subjects had other vertebral fractures that did not improve during this period. Additionally, the subject in the placebo arm was the only one of these 4 subjects that had new vertebral fractures during this period. Finally, one subject in the placebo/denosumab group also had fractures that did not improve in the placebo-controlled period but improved once starting denosumab in the open-label period.

However, because of the small overall population size, definitive conclusions regarding the impact of denosumab therapy on improving vertebral fractures during the trial cannot be made with the available data.

8.1.2.9. Dose/Dose Response

As only one dose was studied, dose response cannot be assessed from the phase 3 trial.

8.1.2.10. Durability of Response

The phase 3 trial 20140444 aimed to evaluate the response to denosumab after as many as 4 doses administered every 6 months in children with GIOP, covering 2 years of therapy, allowing for the assessment of changes in BMD z-scores over long-term therapy with denosumab. However, because of difficulties in recruitment, an inadequate number of subjects were enrolled to adequately assess efficacy and the trial was terminated early.

Therefore, while the long-term effects of denosumab for the treatment of osteoporosis indications in adults have been previously established, the current development program cannot provide additional information regarding the long-term effects of denosumab for the treatment of pediatric patients with GIOP.

8.1.2.11. Persistence of Effect

As per the Prolia USPI, approved for the treatment of osteoporosis indications in adults, fracture risk (including vertebral fractures) increases following discontinuation of Prolia and bone mineral density returns to pretreatment values within 18 months after the last injection.

The phase 3 trial 20140444 sought to assess the persistence of drug effect after treatment is stopped or withheld. The trial included evaluation of BMD z-scores 6 (at month 24) and 12 months (at Month 36) after the final dose following 2 years (in the denosumab/denosumab group) or 1 year (in the placebo/denosumab group) of therapy in children with GIOP. The results of these assessments are discussed in Section 8.1.2.8. Because of early termination and inclusion of only a small number of subjects, adequate assessment of persistence of effect upon treatment discontinuation is challenging.

8.1.2.12. COA (PRO) Endpoints

Four measures were used as secondary endpoints to evaluate change from baseline in health-related quality of life, physical function, and pain intensity at Months 12, 24, and 36 of treatment: Childhood Health Questionnaire – Parent Form-50 (CHQ-PF-50) Physical Summary Score, CHQ-PF-50 Psychological Summary Score, Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score, and Wong-Baker Faces Pain Rating Scale (WBFPRS). However, none of these PROs have been validated in the intended population. Also, the trial only included a small number of subjects. Hence, interpretation of information derived from these PROs is challenging. No meaningful conclusions can be drawn, and these data should not be included in the label.

8.1.2.13. Additional Analyses Conducted on the Individual Trial

Not applicable.

8.1.3. Assessment of Efficacy Across Trials

Not applicable, because data from a single trial were included in this supplement.

8.1.4. Integrated Assessment of Effectiveness

Trial 20140444 did not demonstrate that Prolia is effective for treatment of glucocorticoid-induced osteoporosis in pediatric patients. Analyses of primary and secondary efficacy endpoints of this trial did not reveal statistically or clinically significant differences in the change from baseline in L-spine BMD z-score between denosumab and placebo in the 12-month, double blind, controlled period of the pivotal phase 3 trial. Additional analysis during the open-label period (Months 12 to 24) and observation period (Months 24 to 36) also did not reveal an interpretable effect of denosumab therapy on BMD in children with GIOP.

Lack of statistically significant differences between the treatment arms is likely due to the trial including a significantly smaller number of subjects than what was originally planned along with a possible smaller than expected treatment effect. The trial was initially designed to enroll 150 subjects. However, the Applicant experienced recruitment challenges because only subjects who had received glucocorticoid within the prior year and had a prior history of osteoporotic fracture were to be included in the trial. In general, glucocorticoid use is low in pediatric patients, and the prevalence of pediatric patients on chronic glucocorticoid therapy with a prior osteoporotic fracture is even lower. The American College of Rheumatology guidance recommend against initiation of anti-resorptives in pediatric patients who do not have a prior history of fracture. Hence, modification of the inclusion criteria was not justified, and the Agency agreed with the Applicant to terminate the trial early. Ultimately, only 24 subjects were enrolled in the trial.

In conclusion, the efficacy database from the single phase 3 trial is not adequate for a comprehensive assessment of the efficacy of denosumab for the proposed indication, patient population, or dosage regimen.

Therefore, the Division agrees with the Applicant's conclusion that the label for Prolia should be amended to include language stating that the trial did not demonstrate effectiveness of denosumab to treat GIOP in pediatric patients.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data were derived from the double-blind, open-label, and observation periods of the phase 3 trial 20140444. The trial completed (last subject completed follow up) on December 20, 2023, and the Clinical Study Report submitted by the Applicant included analyses with results reflecting data collected as late as February 15, 2024.

The prespecified safety analysis plan and definitions were reviewed during the clinical development program and were acceptable. The safety population was defined by the Applicant as the Safety Analysis Set and in the double-blind and open-label periods, included all

subjects in the FAS who received ≥ 1 dose of investigational product. In the observation period the SAS was defined as all subjects who completed the double-blind and open-label periods and remained in the observation period.

Adverse events were coded using MedDRA version 26.1. The clinical reviewer used the safety data originating from the 52-week double-blind, placebo-controlled period of the phase 3 trial as the primary source of safety assessment which allowed a direct comparison of denosumab to placebo. Supportive long-term safety data were obtained from the following 52-week open-label period and then from the subsequent 52-week observation period. However, the overall analysis of the safety data from these latter two periods is confounded due to different lengths of exposure to denosumab in the two groups. Thus, the supportive safety data should be interpreted with caution.

Clinical trial data were analyzed independently by the clinical reviewer using JMP clinical, Analysis Studio, and the MedDRA-Based Adverse Event Diagnostic (MAED) software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

The review team also conducted an analysis of AEs occurring in the phase 3 trial using Office of New Drug Custom Medical Queries (OCMQ) or grouped queries (GQ). OCMQs were developed by FDA to improve the capture of synonymous AE terms and to improve overall safety signal detection. To further improve safety signal detection, the clinical review team also created GQs which consisted of adverse events that were not already part of an OCMQ but were synonymous. Subjects who reported more than 1 individual preferred term (PT) grouped in a single OCMQ or GQ are only counted once in the number of subjects reporting that combined term.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

All 16 and 8 subjects originally randomized to denosumab or placebo, respectively, received at least 1 dose of investigational product (i.e., either denosumab or placebo). During the 3 total years of the trial, 14 (87.5%) subjects and 8 (100%) subjects originally randomized to denosumab or placebo, respectively, received all four planned doses (i.e., 4 doses of denosumab in subjects originally randomized to denosumab and 2 doses of placebo and denosumab, each, in subjects originally randomized to placebo). During the double-blind period, 2 subjects in the denosumab/denosumab group discontinued treatment: 1 subject received 1 dose, and the other subject received 2 doses, of denosumab before discontinuing treatment. Refer to Table 15.

Table 15: Exposure to Investigational Product, Study 20140444, Safety Analysis Set

Product exposure	Denosumab/Denosumab (N = 16)	Placebo/Denosumab (N = 8)
Total dose duration denosumab or placebo (days)		
n	16	8
Mean (SD)	492.9 (160)	543.8 (5.8)
Median	547	541.5
Min, Max	1, 582	538, 555

The safety analysis set includes all subjects in the Full Analysis Set who received ≥ dose of investigational product. N = number of subjects in the safety analysis set; n = number of subjects with observed data; SD = standard deviation.
Source: Data taken from Clinical Study Report for Study 20140444, Table 12-1, page 66

8.2.2.2. Adequacy of the Safety Database:

The level of exposure to the study drug during the clinical development program does not satisfy the International Council for Harmonisation (ICH) E1 guidelines for safety assessment of a chronically administered drug.[23] As discussed in Section 3.2, due to challenges with recruiting, the Applicant ended enrollment in Study 20140444 early, prior to enrolling an adequate number of subjects to achieve appropriate levels of exposure of denosumab in the proposed indication. Therefore, while the review team completed the following safety review in order to assess for possible safety signals, the safety database from the single phase 3 trial is not adequate for a comprehensive safety assessment of denosumab for the proposed indication, patient population, and dosage regimen at the time of the supplemental BLA submission. Lack of any additional safety findings in this trial does not indicate that the drug is safe in pediatric population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1. Issues Regarding Data Integrity and Submission Quality

The overall data integrity and submission quality were adequate to perform an effective safety review.

[23] Guideline for Industry *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995)

8.2.3.2. Categorization of Adverse Events

The Applicant's definitions of AEs and serious AEs (SAEs) in the protocol were consistent with regulatory definitions and appropriately followed, severity was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and adverse events were coded using MedDRA version 26.1.

8.2.3.3. Routine Clinical Tests

Overall, clinical safety testing was appropriate. Evaluations included hematology, biochemistry, and anti-drug antibodies (ADA). Physical exams and vital signs were also assessed throughout the trial for safety assessments.

8.2.4. Safety Results

8.2.4.1. Deaths

There were no deaths reported during the phase 3 trial Study 20140444.

8.2.4.2. Serious Adverse Events

Comparison of the proportion of subjects who reported SAEs in the two treatment arms is difficult to interpret given the overall low number of subjects enrolled in the trial. Following reviews of the provided narratives, none of the SAEs appear unlikely to be related to study drug. See Table 16 for all treatment emergent SAEs reported during Study 20140444.

Table 16: SAEs reported during Study 201400444

Preferred term	Denosumab/ Denosumab (N=16) n (%)	Placebo/ Denosumab (N=8) n (%)	Total (N = 24) n (%)
Double-blind period			
Any SAE (%)	3 (18.8)	1 (12.5)	4 (16.7)
Autoimmune hepatitis	1 (6.3)	0	1 (4.2)
Brain contusion	1 (6.3)	0	1 (4.2)
Femur fracture	1 (6.3)	0	1 (4.2)
Tibia fracture	1 (6.3)	0	1 (4.2)
Uterine hemorrhage	1 (6.3)	0	1 (4.2)
Cardiomyopathy	0	1 (12.5)	1 (4.2)
Open label period (all subjects on denosumab)			
Any SAE (%)	0	0	0
Observation period			
Any SAE (%)	1 (6.3)	1 (12.5)	2 (8.3)
Urinary tract infection	1 (6.3)	0	1 (4.2)
Ureterolithiasis	0	1 (12.5)	1 (4.2)

Source: JMP Clinical, reviewer generated report

Double-blind period

During the double-blind period of the trial, a slightly higher proportion of subjects in the denosumab/denosumab group (3/16 [18.8%] subjects) reported SAEs compared to the placebo/denosumab group (1/8 [12.5%] subject). All SAEs occurred in 1 subject, each. In the denosumab/denosumab group, 2 subjects reported 2 SAEs each (1 subject reported SAEs with the preferred terms [PTs] of tibia fracture and femur fracture; 1 subject reported SAEs with the PTs of brain contusion and uterine hemorrhage). The third subject in the denosumab/denosumab group, and the only subject in the placebo/denosumab group, who reported SAEs, each only reported 1 SAE.

Open-label period

During the open label period no SAEs were reported.

Observation period

During the Observation period, 1 subject in each group (12.5% and 6.3% in the placebo/denosumab and denosumab/denosumab groups, respectively) reported 1 SAE, each.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant reported that 1 subject, a 12-year-old female, discontinued treatment after 1 dose of denosumab due to an AE (exacerbation of autoimmune hepatitis; serious, grade 3 severity). This subject did complete the entire 36 months of the trial. Upon review of the narrative for this event, causality of denosumab to the AE is unlikely.

8.2.4.4. Significant Adverse Events

Severe adverse events
During the double-blind and observation periods of the trial, there were more severe AEs (i.e., CTCAE Grade 3; no subjects reported AEs of CTCAE ≥ 4) in the group originally randomized to denosumab compared to placebo, though, due to the low number of subjects enrolled in each group, it is unclear that the difference is clinically significant. No subjects in either group reported severe AEs during the open-label period.

It is unlikely that there is causal association with any of these severe AEs and denosumab, especially given that for most cases, the dose of denosumab was not changed or discontinued as a result of the AE and the AE resolved.

Double-blind period

During the double-blind period, 5/16 (31.2%) subjects randomized to denosumab reported 8 AEs of Grade 3 severity (1 subject reported PTs of uterine hemorrhage, anemia, brain contusion, and syncope; and PTs of autoimmune arthritis, autoimmune hepatitis, delayed puberty, and femur fracture [see Section 8.2.5.6 regarding discussion of fractures] were

reported by 1 subject, each), compared to 1/8 (12.5%) subject randomized to placebo who reported a severe AE of cardiomyopathy. None of these AEs were reported with Grade 3 severity by more than 1 subject. No subjects reported an AE with Grade > 3 severity.

Regarding the AEs of Grade 3 severity in subjects taking denosumab, the treatment was withdrawn for the AE of autoimmune hepatitis, as discussed in Section 8.2.4.2, Double-blind period. In all other Grade 3 AEs in this group, the dose of study drug was not changed or withdrawn. The Grade 3 AE of delayed puberty is the only one listed without an end date, while the Grade 3 AEs of femur fracture, anemia, and autoimmune hepatitis had analysis durations of 49, 189, and 296 days, respectively. The remaining Grade 3 AEs had durations from 1 to 7 days. No action was taken for the AEs of brain contusion or syncope, while the others required medication, and, in the cause of the femur fracture, hospitalization and leg immobilization were also required.

Open-label period

No subjects in either group reported severe AEs during the open-label period.

Observation period

During this period, only 1 subject reported a Grade 3 AE, with the PT of urinary tract infection, which was also an SAE. As discussed in Section 8.2.4.2, based on a review of the provided narrative, this AE was unlikely to be causally related to denosumab use.

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, a higher proportion of subjects originally randomized to denosumab, compared to those originally randomized to placebo, reported at least one treatment emergent adverse event (TEAE).

However, while there did not appear to be any significant safety signals of concern or trends in the TEAEs reported, in general, given the low total number of subjects in each group, interpreting clinically meaningful differences in the proportions of TEAEs reported by either group in any of the three periods is difficult and it is unclear that any differences noted are clinically significant.

Double-blind period

TEAEs listed by combined OCMQs or GQs, reported by > 1 subject are listed in Table 17. Overall, a slightly higher proportion of subjects in the denosumab group (11/16 [68.8%] subjects) compared to the placebo group (5/8 [62.5%] subjects), reported at least one TEAE. The 11 subjects randomized to denosumab reported 45 TEAEs while the 5 subjects randomized to placebo reported 18 TEAEs.

Table 17: Adverse events by OCMQ or Grouped Queries and Preferred Terms reported by > 1 subject and arranged by risk difference, Safety Population, Trial 20140444, Double-Blind Period

OCMQs + GQs Preferred Term (PT)	Denosumab/ Denosumab (N=16)	Placebo/ Denosumab (N=8)	Risk Difference (%) (95% CI)
Any TEAE (%)	11 (68.8)	5 (62.5)	6.3 (-34.3, 46.8)
Fracture	2 (12.5)	0	12.5 (-3.7, 28.7)
Femur fracture	*2 (12.5)*	*0*	*12.5 (-3.7, 28.7)*
Tibia fracture	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Hemorrhage	2 (12.5)	0	12.5 (-3.7, 28.7)
Brain contusion	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Epistaxis	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Anemia	2 (12.5)	0	12.5 (-3.7, 28.7)
Back pain	2 (12.5)	0	12.5 (-3.7, 28.7)
Headache	2 (12.5)	1 (12.5)	0 (-28.1, 28.1)
Cataract	1 (6.3)	1 (12.5)	-6.3 (-32.1, 19.6)
Cataract	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Cataract subcapsular	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Diarrhea	1 (6.3)	1 (12.5)	-6.3 (-32.1, 19.6)
Gastrointestinal infection	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Diarrhea	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Pyrexia	1 (6.3)	1 (12.5)	-6.3 (-32.1, 19.6)
Pyrexia	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Hyperthermia	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Nasopharyngitis	1 (6.3)	3 (37.5)	-31.3 (-66.8, 4.3)
Rhinitis	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Nasopharyngitis	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Rhinorrhea	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Vasomotor rhinitis	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Respiratory tract infection	1 (6.3)	3 (37.5)	-31.3 (-66.8, 4.3)
Upper respiratory infection	*1 (6.3)*	*0*	*6.3 (-5.6, 18.1)*
Influenza	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
Respiratory tract infection	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*
COVID-19 pneumonia	*0*	*1 (12.5)*	*-12.5 (-35.4, 10.4)*

Source: MAED analysis using JMP clinical and grouped terms derived from FMQ analysis, clinical reviewer generated report

The only TEAEs by OCMQ analysis reported by > 1 subject in the denosumab group and reported by a higher proportion of subjects in the denosumab group compared to the placebo group were fracture, hemorrhage, anemia, and back pain and are thus discussed briefly below (with the exception of fracture, which is discussed in Section 8.2.5.6). In all TEAEs discussed below, the overall small number of subjects enrolled and limited information provided in this submission precluded assessment of causality. The differences between incidences of the TEAEs

was difficult to interpret and may be due to chance, rather than due to meaningful differences between the products. Additionally, the majority of cases in subjects treated with denosumab were not serious or of Grade ≥ 3 severity or required changes to denosumab dosing or other significant intervention.

Anemia

Of the 2 cases of anemia reported by 2 different subjects in the denosumab/denosumab group, one was reported as Grade 3 severity (beginning on day 359 of the trial with a duration of 189 days and action taken included other medications), the other as Grade 2 severity (beginning on day 1 of the trial with a duration of 90 days and reported with no action taken). Neither case was an SAE and in neither case was the dose of denosumab changed or discontinued. Anemia is already included as an adverse reaction in the label, and no further labeling changes are indicated based on these findings.

Back pain

Both cases of back pain were reported in two different subjects and both with Grade 1 severity. In 1 of these cases, with a duration of 14 days, action taken was listed as 'other', though it is unclear what this involved. In the other case, with a duration of 31 days, no action taken was reported. Neither case was an SAE and in neither case was the dose of denosumab changed or discontinued. Back pain is already included as an adverse reaction in the label, and no further labeling changes are indicated based on these findings.

Hemorrhage

This OCMQ combined the PTs of brain contusion and epistaxis, which were each reported once and by different subjects. The AE of brain contusion was also a Grade 3 SAE and was secondary to being in a traffic accident and unlikely to be related to denosumab. The case of epistaxis was of Grade 1 severity, non-serious, and had a duration of 1 day. In neither case was the dose of denosumab changed or discontinued. Due to a lack of clear causality and given the small number of subjects included in the trial, hemorrhage is not considered to be a newly identified safety signal. Hence, labeling changes are not warranted.

Open-label period

In this period, during which all subjects were treated with denosumab, no new safety signals were identified. A total of 8/24 (33.3%) subjects reported 20 TEAEs, with 6/16 (37.5%) subjects originally randomized to denosumab, compared to 2/8 (25%) subjects originally randomized to placebo, reporting at least 1 TEAE. The TEAEs by FMQ and GQ analyses reported by the most subjects (≥ 5%) were COVID-19 and fungal infection (including the PTs of balanitis candida and fungal skin infection), reported by 2/24 (8.3%) subjects, each. All other TEAEs occurred in < 5% of subjects.

No subjects during this period had the dose of denosumab changed or discontinued due to a TEAE. The majority of the reported TEAEs required no action to be taken (14/20 [70%]), were of Grade 1 severity (17/20 [85%], with the remaining TEAEs being of Grade 2 severity), and none were serious TEAEs.

Observation period

In the observation period, during which all subjects were evaluated off all denosumab therapy, no new safety signals were identified. A total of 11/24 (45.8%) subjects reported 29 TEAEs, with 8/16 (50%) subjects originally randomized to denosumab, compared to 3/8 (37.5%) subjects originally randomized to placebo, reporting at least 1 TEAE. The TEAEs reported by the most subjects (≥ 5%) were nasopharyngitis (reported by 3/24 [12.5%] subjects) and headache (reported by 2/24 [8.3%] subjects). Both nasopharyngitis and headache are common in this age group. All other TEAEs occurred in < 5% of subjects.

Just over half the reported TEAEs required no action to be taken (15/29 [51.7%]). The remaining TEAEs required additional medication to be taken, including two TEAEs (a Grade 2, serious TEAE of ureterolithiasis and a Grade 3, serious TEAE of urinary tract infection, each reported by a separate subject) that required hospitalization. The majority (26/29 [89.7%]) of the TEAEs were of Grade 1 severity, 2 TEAEs were of Grade 2 severity, including 1 (ureterolithiasis) that was serious, and 1 TEAE (urinary tract infection) of Grade 3 severity that was also serious.

8.2.4.6. Laboratory Findings

Safety laboratory testing consisted of hematology and chemistry evaluation and occurred at screening; study day 1 (and, specifically for serum chemistry, days 10 and 30); and study months 3, 6, 12, 18, 24, 30, and 36. There were no clinically meaningful or unexpected changes observed in laboratory parameters during the trial. However, the limited population size of this trial limits interpretation of these data.

During the 24-months of treatment, subjects received investigational product on study day 1, month 6, month 12, and month 18. All subjects were required to take daily calcium and vitamin D supplementation throughout the 12-month double-blind and 12-month open-label periods (i.e., the 24-month treatment periods) of the trial. If deemed medically warranted by the Investigator, daily supplements of calcium and vitamin D were also given during the 12-month observation period.

Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorus and magnesium) and was associated with a higher incidence of anemia in the Prolia post-menopausal osteoporosis indication registration trial in adults. Bone specific alkaline phosphatase (BSALP; typically higher in growing children than in adults) is also often commonly monitored as a marker of bone formation.

Additionally, hypercalcemia was reported during clinical trials evaluating the potential of denosumab use to reduce fracture risk in children with osteogenesis imperfecta; some cases required hospitalization and acute renal injury. Clinical trials in pediatric patients with osteogenesis imperfecta were terminated early due to the occurrence of life-threatening

events and hospitalizations due to hypercalcemia. The risk of hypercalcemia appeared to increase with repeated denosumab treatment as all affected subjects had received at least four doses of denosumab 1 mg/kg every 3 months; the risk was not evident with dosing of denosumab every 6 months.

Therefore, this review includes shift analyses of calcium, phosphorus, magnesium, BSALP, and hemoglobin laboratory parameters. The Prolia package insert advises that calcium, phosphorus, and magnesium be monitored within 14 days of injection, which coincides with the anticipated calcium nadir following denosumab injection. However, in the phase 3 trial, the Applicant only assessed these levels within the recommended time period (i.e., within 14 days) after the first injection of either denosumab or placebo during the double-blind period.

Calcium

The Applicant provided results for both serum and albumin-corrected serum calcium. Because approximately 40% of total body calcium is protein bound, serum calcium may be artificially low in the setting of hypoalbuminemia. In those situations, a correction formula to account for the low albumin is used to estimate actual serum calcium levels. Ionized calcium is the preferred measurement but is not readily available in all laboratories.[24]

Only 2 subjects (a 15-year-old male [randomized to denosumab] and a 13-year-old female [randomized to placebo]) were noted to have hypoalbuminemia during the trial. The subject randomized to denosumab was noted to have low albumin at baseline (36 g/L; lower limit of normal [LLN] 38 g/L), which remained low (nadir of 27 g/L at study day 10) until month 6, when albumin was normal at 40 g/L. This subject also was noted to have low calcium at Day 10 (serum calcium of 1.87 mmol/L, corrected calcium normal; LLN 2.1 mmol/L) and at Day 30 (both serum and corrected calcium were low at 1.9 mmol/L and 2.05 mmol/L, respectively). This subject was subsequently lost to follow up. The subject randomized to placebo had low albumin (36 g/L) on Day 10 only, all other albumin values, and all serum and corrected calcium values, were normal. Because there are reported inaccuracies with various correction formulas, the role for such formulas when albumin levels are normal is unclear, and as there was only a single occurrence of a low serum calcium being reported with a normal, concurrent corrected calcium in the setting of hypoalbuminemia, this review examines only serum calcium measurements, not the corrected calcium values.

Relative to the period of interest, i.e., 14 days after injection as the nadir for serum calcium occurs within the first 2 weeks following denosumab injection, serum calcium was measured at baseline and 10 days after the first injection. The first serum calcium measured after the subsequent injections were a minimum of 6 months after each injection, and thus unlikely to capture the period of calcium nadir after the second injection). The risk of hypocalcemia is greater in patients with severe renal impairment (i.e., glomerular filtration rate < 30

[24] Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. BMJ Open. 2018 Apr 7;8(4):e017703

mL/min/1.73 m^2), and this trial excluded patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.

The difference in median change from baseline in serum calcium between the two treatment groups was not clinically significant at all measurements through all three periods of the trial (see Table 18).

Table 18: Median (min, max) change from baseline in serum calcium (mg/dL) following first study drug administration, Study 20140444

Parameter	Denosumab/denosumab	Placebo/denosumab
DOUBLE-BLIND PERIOD		
Change from baseline at day 10		
Median (min, max)	-0.8 (-1.6, 0.7) N=14	0 (-0.4, 0.4) N=8
Change from baseline at day 30		
Median (min, max)	-0.4 (-1.6, 0.3) N=15	0 (-0.6, 0.04) N=7
Change from baseline at month 3		
Median (min, max)	0 (-0.6, 0.7) N=16	0 (-0.6, 0.4) N=7
Change from baseline at month 6		
Median (min, max)	0 (-0.5, 0.4) N=16	0 (-0.4, 0.5) N=8
Change from baseline at month 12		
Median (min, max)	0.4 (-0.6, 0.7) N=15	0 (-1, 0.4) N=7
OPEN-LABEL PERIOD		
Change from baseline at month 18		
Median (min, max)	0 (-0.5, 0.7) N=13	0 (-0.8, 0.8) N=6
Change from baseline at month 24		
Median (min, max)	0.1 (-0.2, 0.9) N=11	0 (-0.3, 0.5) N=6
OBSERVATION PERIOD		
Change from baseline at month 30		
Median (min, max)	0 (-0.1, 0.6) N=11	0 (-0.7, 0.4) N =5
Change from baseline at month 36		
Median (min, max)	0 (-0.4, 0.9) N=8	-0.1 (-1.1, 0.04) N =5

Source: clinical reviewer analysis; the Applicant provided calcium in units of mmol/L. This reviewer converted to

mg/dL using a conversion factor of mmol/L calcium x4 = mg/dL calcium.[25]

The incidence of hypocalcemia (i.e., calcium noted below the lower limit of normal [LLN]: 8.8 mg/dL and 8.4 mg/dL for subjects < 12 and ≥ 12 years of age, respectively, in subjects with elevated or normal calcium at baseline) during the double-blind period was 4/16 (25%) and 1/8 (12.5%) in the denosumab and placebo groups, respectively. All reports of hypocalcemia in the denosumab group occurred within the first month following denosumab injection, with 3 of the 4 subjects reporting hypocalcemia at the Day 10 visit and continuing to have hypocalcemia at the Day 30 visit. A fourth subject in the denosumab group also reported hypocalcemia for the first time at the Day 30 visit. None of these subjects reported hypocalcemia at any later visit (refer to Table 19). These findings are not unexpected given the anticipated calcium nadir following denosumab injection.

No subjects reported hypocalcemia during the open-label or observation periods.

Table 19: N (%) of subjects with a shift in serum calcium to below the lower limit of normal (< LLN) following first study drug administration, Study 20140444

Parameter	Denosumab/denosumab	Placebo/denosumab
Number of subjects with normal or elevated baseline calcium	16	8
Hypocalcemia at any time	4 (25%)	1 (12.5%)
Double-blind period		
Day 10	3 (18.8%)	0
Day 30	4 (25%)	0
Month 6	0	0
Month 12	0	1 (12.5%)
Open-label period		
Month 18	0	0
Month 24	0	0
Observation period		
Month 30	0	0
Month 36	0	0

Source: clinical reviewer analysis

Of the subjects with laboratory evidence of serum hypocalcemia, the lowest recorded serum calcium value was 1.87 mmol/L and all subjects were asymptomatic.

Across the whole trial, 2/16 (12.5%) and 2/8 (25%) subjects originally randomized to denosumab and placebo, respectively, reported a shift to hypercalcemia (calcium noted above the upper limit of normal [ULN]: 2.7 mmol/L and 2.58 mmol/L for subjects < 12 and ≥ 12 years of age, respectively, in subjects with low or normal calcium at baseline). For subjects originally

[25] Mayo Clinical Laboratories, International System of Units (SI) Conversion: https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

randomized to denosumab, 1 subject reported one episode of hypercalcemia during the double-blind period, at Month 12, and 1 subject reported an episode of hypercalcemia during the open-label (at Month 24) and observation (at Month 36) periods. For subjects originally randomized to placebo, 2 subjects reported one episode of hypercalcemia during the open-label period, at Month 24. Of the subjects with laboratory evidence of serum hypercalcemia the highest reported serum calcium value was 2.66 mmol/L, and all subjects were asymptomatic.

Both hyper- and hypocalcemia were considered by the Applicant to be adverse events of special interest (AESI) and neither were reported as TEAEs by any subject across all three periods of the trial.

In conclusion, no specific safety signals were noted related to calcium and denosumab use given that 1) the difference in median change from baseline in serum calcium between the two treatment groups was not clinically significant at all measurements through all three periods of the trial; 2) there were no unexpected safety signals related to shifts to hypocalcemia after initiation of denosumab therapy; and 3) no concerning safety signal related to hypercalcemia after initiation of denosumab therapy. However, the limited population size of this trial limits interpretation of these data.

Hypophosphatemia, hypomagnesemia, alkaline phosphate, and anemia

The incidence of transition from normal or high at baseline to below the normal range for serum hemoglobin, magnesium, or phosphorus for each period of the phase 3 trial are displayed in Table 20.

Table 20: N (%) of subjects with a shift in hemoglobin, magnesium, or phosphorus to below the lower limit of normal (< LLN) during Study 20140444, Main Period

Parameter (N with normal or elevated values at baseline)	**Denosumab/denosumab**	**Placebo/denosumab**
Double-blind period		
Hemoglobin	3 (21.4%) N=14	1 (12.5%) N=8
Magnesium	0 N=16	1 (12.5%) N=8
Phosphorus	3 (20%) N=15	0 N=8
BSALP	2 (20%) N=10	0 N=8
Open-label period		
Hemoglobin	1 (7.1%) N=14	1 (12.5%) N=8
Magnesium	0 N=16	0 N=8
Phosphorus	0 N=15	0 N=8
BSALP	2 (20%) N=10	0 N=8
Observation period		
Hemoglobin	0 N=14	0 N=8
Magnesium	0 N=16	0 N=8
Phosphorus	0 N=15	0 N=8
BSALP	1 (10%) N=10	0 N=8

BSALP = bone specific alkaline phosphatase
Source: clinical reviewer analysis

During the double-blind period, it is not unexpected that more subjects receiving denosumab than placebo would shift to values of hemoglobin, phosphorus, BSALP, or magnesium that were below the LLN; denosumab can cause disturbances in bone-related mineral levels (i.e., reduced phosphorus and magnesium) and was associated with a higher incidence of anemia in the Prolia post-menopausal osteoporosis indication registration trial. Further, during the open-label period, relatively few subjects in either group, both of whom were treated with denosumab during this period, shifted to below normal values for any of these measurements, with only BSALP noted in a higher proportion in subjects originally randomized to denosumab compared

to placebo. One of the subjects randomized to denosumab who shifted to low BSALP reported low BSALP at least once through all three periods, with only 2 additional subjects randomized to denosumab reporting a shift to low BSALP, 1 subject each for the double-blind and open-label periods. Otherwise, no subjects shifted to below normal values for these measurements during the untreated observation period.

Of these laboratory values, the only related TEAE reported was anemia, in 2/16 (12.5%) vs. 0 subjects in the denosumab and placebo groups, respectively, of the double-blind period and discussed in Section 8.2.4.5, above. During the observation period, only 1 additional subject, originally randomized to placebo reported a non-serious TEAE of anemia, which was of Grade 1 severity.

8.2.4.7. Vital Signs

There were no clinically significant changes is mean or median blood pressure, pulse, temperature, or respiratory rate observed between either treatment group in any of the three periods of the phase 3 trial.

8.2.4.8. Electrocardiograms (ECGs) and QT

Not applicable. ECGs were not conducted during the trial.

8.2.4.9. Immunogenicity

One subject originally randomized to placebo did not have results from anti-denosumab antibodies available. However, no subject with on-trial results in either arm during any of the three treatment periods tested positive for anti-denosumab antibodies.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant included the following as events of interest: hypersensitivity, hypocalcemia, hypercalcemia, osteonecrosis of the jaw, and bacterial cellulitis, all of which are labeled warnings in the USPI for Prolia (in the case of hypercalcemia, the warning is specific to pediatric patients with osteogenesis imperfecta). Analyses of TEAEs related to hyper- and hypocalcemia were discussed in Section 8.2.4.6, above. TEAEs related to each of the other AESIs will be discussed in more detail below, in addition to discussions of TEAEs related to fractures and injection site reactions.

There did not appear to be any significant safety signals of concern or trends in the AESIs reported, though the low total number of subjects in each group precludes a definitive assessment of safety related to these specific events of interest.

8.2.5.1. Hypersensitivity

The clinical reviewer searched the dataset for preferred terms related to anaphylaxis and hypersensitivity. There were no events of anaphylaxis in either treatment group throughout all periods of the trial. Events possibly related to hypersensitivity included only 1/16 (6.3%) subject

in the denosumab arm of the double-blind period who reported a non-serious, Grade 1 TEAE of eczema. This TEAE was first reported on study day 36 and resolved on study day 555 (around the time of the fourth and final scheduled dose of treatment) without any changes to the dose of study drug or other actions taken. This subject also reported a TEAE of dry skin that started on study day 5 and resolved at the same time as the TEAE of eczema, also without any changes to the dose of study drug or other actions taken. As these events improved despite continued therapy, it is unlikely they are related to hypersensitivity to denosumab.

There were no other TEAEs related to hypersensitivity in either treatment group throughout all three periods of the trial.

8.2.5.2. Osteonecrosis of the jaw

No subject in either arm reported a TEAE related to osteonecrosis of the jaw throughout all periods of the trial.

8.2.5.3. Serious infections including skin infections

During the double-blind period, 6/16 (37.5%) and 4/8 (50%) subjects in the denosumab and placebo arms, respectively, reported any TEAEs in the System Organ Class Infections and Infestations. A total of 5/24 (20.8%) subjects reported TEAEs in this System Organ Class during the open-label period. None of these TEAEs were SAEs and all were of either Grade 1 or 2 severity.

Review of these TEAEs did not reveal significant new safety information related to infections.

8.2.5.4. Dermatologic reactions

During the double-blind period, 3/16 (18.8%) and 0 subjects in the denosumab and placebo arms, respectively, reported any TEAEs in the System Organ Class Skin and subcutaneous tissue disorders. No subjects in the open-label period reported relevant TEAEs. None of these TEAEs were SAEs and all were of Grade 1 severity.

Review of these TEAEs did not reveal significant new safety information related to infections.

8.2.5.5. Injection site reaction

Only 1/16 (6.3%) subject in the denosumab arm of the double-blind period reported a non-serious, Grade 2 TEAE of related to an injection site reaction, with the PT of injection site pain. This TEAE was first reported on study day 184 and resolved the same day without any changes to the dose of study drug or other actions taken. Some injection site pain is not unexpected from a drug administered *via* SC injection, and it is reassuring that only 1 subject reported a related TEAE and that it resolved quickly without significant intervention.

There were no other TEAEs related to injection site reactions in either treatment group throughout all three periods of the trial.

8.2.5.6. Fractures

During the double-blind period, 2/16 (12.5%) subjects in the denosumab arm reported 3 TEAEs of fracture: 1 subject reported serious TEAEs of femur (Grade 3) and tibia (Grade 2) fracture and 1 subject reported a non-serious TEAE of femur fracture (Grade 2); compared to 0 subjects in the placebo group. In both subjects, the dose of study drug was not changed or discontinued as a result of the fractures and neither subject ever recorded abnormal calcium values.

- For the subject (a 14-year-old female) reporting serious TEAEs of femur (not considered an atypical femoral fracture) and tibia fracture, both of the right leg, these TEAEs occurred at the same time, 1 month and 3 weeks after the first dose of denosumab and were the result of a falling from bed (greater than 20 inches). LS BMD z-score initially decreased with therapy in this subject, with change from baseline LS BMD z-scores of -0.28, -0.45, and -0.82 after 6, 12, and 18 months of therapy, respectively. At 24 months change from baseline LS BMD z-score was -0.66, and at Month 36, 1 year after the final dose of denosumab, change from baseline in LS BMD z-score was -0.59. Change from baseline in total hip z-score also suggested a lack of improvement with initial therapy (-0.23, -0.2, -0.12, and -0.19 after 6, 12, 18, and 24 months, respectively, with some improvement noted at Month 36, a year after the final dose of denosumab: change from baseline in total hip z-score of 0.65). However, change from baseline in femoral neck z-score suggested improvement with therapy (0.1, 0.55, 0.54, 0.16, and 0.94 Months 6, 12, 18, 24, and 36, respectively). The subject was hospitalized, and the right leg was immobilized with an orthosis.

  The lack of improvement in the primary endpoint (i.e., LS BMD z-score) and secondary endpoint of total hip z-score may suggest that a lack of efficacy contributed to these fracture events, however interpretation is confounded by suggestion of improvement in the secondary endpoint of femoral neck z-score and the report of associated trauma (fall from bed of greater than 20 inches) implying this may be a traumatic fracture.

- An 11-year-old male reported a non-serious TEAE of femur fracture on study day 319, also the result of a fall from more than 20 inches, and the fracture did not result in hospitalization, and no further information related to cause of fracture or action taken to treat the fracture is noted. Analysis of change in LS BMD z-score suggests initial improvement with denosumab therapy (0.29, 0.54, 0.15, and 0.17 at Months 6, 12, 18, and 24, respectively, and -0.5 at Month 36, one year after the final dose of therapy), as did the results of change from baseline in total hip z-score (0.67, 0.38, 0.56, and 0.25 at Months 6, 12, 18, and 24, respectively, and -0.02 at Month 36, one year after the final dose of therapy) and change from baseline in femoral neck z-score (0.21, 0.17, 0.33, and 0.37 at Months 6, 12, 18, and 24, respectively, and 0.38 at Month 36, one year after the final dose of therapy).

> With improvement in primary and secondary efficacy endpoints and a report of associated trauma (fall from more than 20 inches), it is unlikely that a lack of denosumab efficacy contributed to this report of fracture.

No subjects in either arm reported a fracture during the open-label period.

During the observation period, the only TEAE related to fracture was in 1/8 (12.5%) subject in the placebo/denosumab arm who reported a non-serious, Grade 1 TEAE of tooth fracture. As a tooth fracture is not considered to be related to osteoporosis, it is not relevant to the discussion of fractures in this trial.

There were no other TEAEs of fracture (including of vertebral fracture) in either treatment group throughout all three periods of the trial. However, 1/16 (6.3%) subject (a 10-year-old male) originally randomized to denosumab reported a serious, Grade 3, distal femur metaphyseal corner fracture approximately 18 months after the last dose of denosumab administered in the trial and which occurred after falling from a wheelchair. This subject never had an abnormal calcium value recorded. This fracture occurred about 10 days after the end of study visit and was thus not considered a TEAE and therefore also not included in the analyses discussed in Sections 8.2.4.2 and 8.2.4.4. As per the Prolia label, fracture risk (including vertebral fractures) increases following discontinuation of Prolia, and bone mineral density returns to pretreatment values within 18 months after the last injection. While no TEAEs of vertebral fracture were noted, the timing of this post-study, distal femur metaphyseal corner fracture is consistent with this labeled warning.

In conclusion, while there are not enough data to inform definitive causal association between denosumab therapy, or lack of efficacy of denosumab therapy, and fractures, the data available do to suggest a related safety signal.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Clinical outcome assessment analyses informing safety/tolerability were not conducted during the clinical program.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant did not report safety analyses by demographic subgroup in the phase 3 trial 21040444. This reviewer did review safety based on sex (male versus female), race (Asian, white, and other), and ethnicity (Hispanic/Latino versus not Hispanic/Latino) during the 52-week, double-blind period of the trial.

Based on the data available, no significant safety signals were noted based on these safety analyses. However, given the limited number of subjects enrolled in this trial, definitive conclusions regarding safety by demographic subgroup are likely not possible.

Refer to Section 14.3.3, for individual analyses of safety by sex, race, and ethnicity subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies/clinical trials were conducted for denosumab in pediatric subjects with GIOP.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

As per the Prolia label, the carcinogenic potential of denosumab has not been evaluated in long-term animal studies. The Applicant did not provide new non-clinical data in this supplement. There are no previous data to suggest a cancer risk associated with denosumab.

8.2.9.2. Human Reproduction and Pregnancy

There were no known exposures in pregnant or lactating subjects during this development program. The eligibility criteria excluded pregnant or lactating individuals.

Prolia is contraindicated for use in pregnant individuals because it may cause harm to the fetus. As per the Prolia label, there are insufficient data with denosumab use in pregnant individuals to inform drug-associated risks for adverse developmental outcomes. *In utero* exposure of denosumab to cynomolgus monkeys dose monthly through pregnancy with a dose 50-fold higher than the recommended human dose based on body weight resulted in increased fetal loss, stillbirths, postnatal mortality, and absent lymph nodes, abnormal bone growth, and decreased neonatal growth. There is no information regarding the presence of denosumab in human milk, the effects on the breastfed infant, or the effects on milk production.

The information included in this supplemental application does not provide detailed information to inform revisions to information in the product label related to pregnancy or lactation.

8.2.9.3. Pediatrics and Assessment of Effects on Growth

A conclusive assessment of the impact of denosumab on growth in children is likely not possible from this trial because of 1) the limited number of subjects enrolled, 2) the fact that the majority of enrolled children were at an age where the potential for continued linear growth would likely be limited, and 3) the eligibility criterion requiring that subjects received treatment with systemic glucocorticoids of any duration during the 12 months prior to screening.

A phase 3 efficacy and safety trial (Study 20140444) was conducted in pediatric subjects aged 5 to 17 years old with GIOP (refer to Section 8.1.2.7 for a review of the results of the primary efficacy endpoint). A secondary endpoint of this phase 3 trial included evaluation of change from baseline in various parameters of growth (age-adjusted z-scores for height, weight, and BMI) after 12 months, 24 months, and 36 months in the trial. The first 12 months of the trial included the only double-blind, placebo-controlled portion of the trial, and thus allows the best assessment of the effect of denosumab, compared to placebo, on growth in the proposed population, though this assessment is limited by the relatively short-term treatment of a drug

intended for chronic use. Regarding the 24-month assessment of change from baseline in growth parameters, subjects in the denosumab/denosumab group were exposed to denosumab for 24 months, while those in the placebo/denosumab group were exposed to denosumab for only the second 12 months of this period; regarding the 36-month assessment of change from baseline in growth parameters, subjects in both groups were exposed to no treatment for the final 12 months of the trial. Thus, due to differences in the length of exposure to study drug, lack of blinding, and a lack of a control arm in the second two periods of the trial, the 24- and 36-month assessments of change from baseline in growth parameters are less likely to be informative regarding the impact of denosumab on growth.

Children are expected to continue to grow until closure of the epiphyseal plates occurs, which may be as early as 12 to 13 years of age in females and 14 to 15 years of age in males, and until the final few stages of puberty. Information related to pubertal status of enrolled subjects was not included and bone ages were not assessed, thus neither can be used to determine when growth would be expected to stop and the clinical review team could only base assessment of the potential for growth on the age at enrollment.

The phase 3 trial enrolled 10 female subjects, the youngest of whom was 11.6 years old, with the next youngest being 12.8 years old (the oldest was 17.9 years old). The trial enrolled 14 male subjects, of whom the youngest 6 subjects were younger than 14 years of age (10 to 12.1 years old) while the remaining 8 subjects were all ≥ 14 years old (14.2 to 17.7 years old). As such, the majority of subjects enrolled in this trial were either at or near the earliest ages at which continued growth would be limited. Thus, while the Applicant provided data related to change from baseline in various growth parameters after 12 months, 24 months, and 36 months in the trial (see Table 23 in Section 14.3.2), these results (especially height and BMI z-scores) are likely impacted by the potential that many of the enrolled children were already at or nearing final adult height, limiting the amount of growth potential these subjects had during time on treatment.

Additionally, as discussed in Section 2.1, glucocorticoids are known to be able to adversely affect growth in children. One of the eligibility criteria for this trial included systemic glucocorticoid treatment of any duration during the 12 months prior to screening. If glucocorticoids were stopped around the time treatment in this trial was initiated, it would be hard to discern if any improvement in growth would be due to therapy with denosumab itself or to withdrawal of the glucocorticoids, while if glucocorticoids were used during the treatment periods, assessment of the effect of denosumab on growth may be underestimated.

8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not evaluated in this supplement.

8.2.10. Safety in the Postmarket Setting

8.2.10.1. Safety Concerns Identified Through Postmarket Experience

There is extensive marketing experience with denosumab across multiple indications related to osteoporosis in adults; the safety profile is well-characterized and labeled for these indications. However, the safety of denosumab in pediatric patients has not been established.

8.2.10.2. Expectations on Safety in the Postmarket Setting

No potential safety issues have been identified during this review, though the limited number of subjects likely precludes a full assessment of safety in children with GIOP.

8.2.11. Integrated Assessment of Safety

The safety database from the single phase 3 trial 20140444 is not adequate for a comprehensive safety assessment of denosumab for the proposed indication, patient population, or dosage regimen.

As discussed in Section 3.2, due to challenges with recruiting, the Applicant terminated enrollment in the phase 3 Study 20140444 early, prior to enrolling an adequate number of subjects to appropriately characterize the safety profile of denosumab in the proposed indication (i.e., glucocorticoid induced osteoporosis in children aged 5 to 17 years old).

Overall, a higher proportion of subjects originally randomized to denosumab, compared to those originally randomized to placebo in the phase 3 trial reported at least one TEAE. However, given the low total number of subjects in each group, interpreting clinically meaningful differences in the proportions of TEAEs or laboratory parameters reported by either group in any of the three periods (i.e., the double-blind, placebo-controlled period; the open label period; and the observation period) is difficult. It is unclear that any differences noted are clinically significant. However, there did not appear to be any significant safety signals of concern or trends in the TEAEs reported. Likewise, there were no clinically meaningful or unexpected changes observed in laboratory parameters during the trial.

Within the noted limitations of the small population size of the trial, analysis of TEAEs of fractures and post-trial fractures did not raise concerns of additional safety signals for denosumab.

There were no concerning TEAEs related to hypersensitivity, osteonecrosis of the jaw, bacterial cellulitis, or injection site reactions in the phase 3 trial.

While 1 subject originally randomized to placebo did not have results from anti-denosumab antibodies, no subject with on-trial results in either arm during any of the three treatment periods tested positive for anti-denosumab antibodies.

In conclusion, the safety review did not identify significant new safety signals or additional information pertinent to the safety profile of denosumab as described in the Prolia USPI. However, a lack of any additional safety findings in this trial does not indicate that the drug is safe in pediatric population, given that the safety database from the single phase 3 trial was not

adequate. The Division agrees with the Applicant's conclusion that Section 8.4 (Pediatric Use) of the label for Prolia should be amended to include language stating that the trial did not demonstrate the safety of denosumab to treat GIOP in pediatric patients.

8.3. Statistical Issues

There was no major statistical issue identified.

8.4. Conclusions and Recommendations

This supplement includes data from a phase 3 trial assessing safety and efficacy of 1 mg/kg (maximum 60 mg) denosumab every 6 months to treat glucocorticoid induced osteoporosis (GIOP) in children aged 5 to 17 years old (Trial 20140444). The primary endpoint was change from baseline in LS BMD z-scores as assessed by DXA, evaluating for superiority of denosumab compared to placebo to improve LS BMD.

Neither the safety nor the efficacy of denosumab 1 mg/kg (maximum 60 mg) every 6 months in the proposed population were adequately demonstrated, because the Applicant was not able to enroll an adequate number of pediatric subjects with GIOP. The trial was initially designed to enroll 150 subjects, but ultimately only 24 subjects were enrolled in the trial due to challenges with recruitment. Enrollment of a significantly lower number of subjects limits the interpretation of the safety and efficacy data obtained from this trial.

The Applicant appears to have made a good faith attempt to fulfill the PMR, and the review team recognizes the challenges faced in recruiting eligible subjects. These challenges include the requirement that only subjects with a prior history of osteoporotic fracture were included in this trial. In general, glucocorticoid use is low in pediatric patients, and the prevalence of pediatric patients on chronic glucocorticoid therapy with a prior osteoporotic fracture is even lower. Given that the American College of Rheumatology guidance recommend against routine use of antiresorptives in pediatric patients with no prior history of fracture, modification of these criteria to allow enrollment of subjects without a prior history of fractures may not be justified.[26] Hence, the Applicant's decision to terminate the trial early was acceptable.

The Pediatric Review Committee discussed this supplement on April 8, 2025, and concurred with the Division's recommendations.

In conclusion, PMR 3422-1 can be considered fulfilled. Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the Prolia USPI will be updated to reflect that the trial did not demonstrate safety and effectiveness of denosumab to treat GIOP in pediatric patients. The review team also did not identify significant new safety signals or additional information pertinent to the safety profile of denosumab that should be included in the Prolia USPI.

[26] Humphrey MB, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol*. 2023 Dec;75(12):2088-2102. doi: 10.1002/art.42646. Epub 2023 Oct 16. PMID: 37845798.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held, as the application did not raise significant public health questions on the role of the biologic, and there were no controversial issues that would benefit from advisory committee discussion.

10 Pediatrics

A phase 3 efficacy and safety trial was conducted in children aged 5 to 17 years old with GIOP. The Applicant conducted this trial to fulfill PMR 3422-1 that was established under PREA following approval of Prolia for the treatment of GIOP in men and women at high risk for fracture (BLA 125320, S-186; approved May 18, 2018).

Due to challenges with recruitment, the Applicant was not able to enroll an adequate number of pediatric subjects with GIOP and the trial was terminated early (see Section 3.2). Neither the safety nor the efficacy of 1 mg/kg (maximum 60 mg) denosumab every 6 months in the proposed pediatric population were adequately demonstrated in this prematurely terminated trial. Section 8 USE IN SPECIFIC POPULATIONS under 8.4 Pediatric Use of the Prolia (BLA 125320) USPI will thus include language reflecting this conclusion. The Division of Pediatrics and Maternal Health (DPMH) was also consulted regarding the appropriate language to include regarding this conclusion and their recommendations were included in Section 8.4 of the USPI.

11 Labeling Recommendations

11.1. Prescribing information

This Prescribing Information (PI) review includes a summary of the rationale for changes incorporated into the finalized PI as compared to the Applicant's draft PI submitted on July 25, 2024 (see Table 21). The finalized PI was compared to the currently approved PI and the applicant's draft PI. The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 21: Key Labeling Changes and Considerations

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)**
2 DOSAGE AND ADMINISTRATION	**2.3 Recommended Dosage** Updated "healthcare professional" to "healthcare provider" to align with current terminology and with approved denosumab biosimilars.
5 WARNINGS AND PRECAUTIONS	**5.2 Drug Products with Same Active Ingredient** Deleted the sentence "Prolia contains the same active ingredient (denosumab) found in Xgeva." Updated "Patients receiving Prolia should not receive Xgeva" to "Patients receiving Prolia should not receive other denosumab products concomitantly." The deletion and updated sentence were made to reference all available denosumab products, including the approved denosumab biosimilars.
6 ADVERSE REACTIONS	**Beginning of the ADVERSE REACTIONS section** (between Section 6 and subsection 6.1), • "Hypocalcemia" title heading was updated to "Severe Hypocalcemia and Mineral Metabolism Changes" to reflect the title heading used in Section 5 Warnings and Precautions (5.1). • "Hypersensitivity *[see Warnings and Precautions (5.3)]*" was added for completeness. • Clinically significant adverse reactions were reordered based on their presentation in Section 5 WARNINGS AND PRECAUTIONS.

8 USE IN SPECIFIC POPULATIONS	**8.4 Pediatric Use** The following language was incorporated in this section to satisfy the regulatory requirement and guidance recommendations for a trial that did not demonstrate safety and effectiveness in pediatric patients: "Safety and effectiveness were not demonstrated for treatment of glucocorticoid-induced osteoporosis in one multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in 24 pediatric patients with glucocorticoid-induced osteoporosis, aged 5 to 17 years, evaluating change from baseline in lumbar spine BMD z-score." The review team concluded the safety and efficacy of denosumab dosed at 1 mg /kg (maximum dose of 60 mg) every 6 months in the pediatric population were not adequately demonstrated in the prematurely terminated trial due to challenges with recruitment of an adequate number of pediatric subjects with GIOP. Per 21 CFR 201.57 (c)(9)(iv)(E), the regulatory pediatric use statement ("Safety and efficacy were not demonstrated …" language above) must be included the Use in Specific Populations/ Pediatric Use subsection when substantial evidence to support a pediatric indication have not been met. Per *FDA's Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling (2019)*, negative studies should be briefly summarized in subsection 8.4, and not elsewhere in the PI, to avoid implying that PROLIA is safe and effective in pediatric patients with GIOP. No new safety issues were identified in the trial with pediatric patients with GIOP; therefore, no new safety information is included in the summary of the study.

17 PATIENT COUNSELING INFORMATION	Drug Products with Same Active Ingredient Updated "Advise patients that denosumab is also marketed as Xgeva, and if taking Prolia, they should not receive Xgeva *[see Warnings and Precautions (5.2)]*" to "Advise patients that if they receive Prolia, they should not receive other denosumab products concomitantly *[see Warnings and Precautions (5.2)]*." The updated patient counseling information includes reference to other denosumab products and aligns with the updated Warning Precaution 5.2. Hypersensitivity "Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab (Prolia or Xgeva)" to "Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab products." The updated patient counseling information includes reference to other available denosumab products, not Prolia or Xgeva only.

The Office of Prescription Drug Promotion (OPDP) and Division of Medical Policy Programs (DMPP) reviewed the Prescribing Information and Medication Guide, and did not have any comments. Refer to the reviews dated April 15, 2025, and April 16, 2025, in DARRTS.

11.2. Medication Guide

In Supplement 219, the Applicant did not propose changes to the Medication Guide (MG). However, updates have been made to reflect the changes in the Prescribing Information and specifically includes references to other available denosumab products and updated terminology for healthcare providers. The changes are summarized below (see Table 22):

Table 22: Key Labeling Changes and Considerations

Section	Updated Language
What is the most important information I should know about Prolia?	If you receive Prolia, you should not receive other denosumab products at the same time.
Before taking Prolia, tell your doctor about all of your medication conditions, including if you:	Are taking other denosumab products.

How will I receive Prolia?	Prolia is an injection that will be given to you by a healthcare provider.
General information about the safe and effective use of Prolia.	You can ask your doctor or pharmacist for information about Prolia that is written for healthcare providers.

11.3. Carton Labeling

In Supplement 219, the Applicant did not propose changes to the Carton Labeling. However, for consistency with the PI subsection 2.3, DGE requested the Applicant to add the statement "Prolia should be administered by a healthcare provider" to the principal display panel of the Prolia carton labeling. Revised carton labeling will align with the PI and MG for healthcare provider administration instruction of Prolia.

12 Risk Evaluation and Mitigation Strategies (REMS)

There is a REMS in place for BLA 125320. No revision to the REMS is recommended based on the data reviewed for this efficacy supplement.

13 Postmarketing Requirements and Commitment

The review team recommends that PMR 3422-1 is considered fulfilled (refer to Section 8.4 for conclusions leading to decision to release the PMR).

No additional postmarketing requirements or commitments will be issued.

14 Appendices

14.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 20140444

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 135		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.2. Nonclinical Pharmacology/Toxicology

Not applicable

14.1. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable

14.2. Additional Clinical Outcome Assessment Analyses

Not applicable

14.3. Clinical Appendices

14.3.1. Study 20140444 Eligibility Criteria

14.3.1.1. Inclusion criteria

101 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated

102 Male or female subjects, age 5 to 17 years, inclusive, at the time of informed consent

Clinical diagnosis of GiOP as defined by the following (and consistent with the International Society for Clinical Densitometry definition of osteoporosis in children and adolescents [Bishop et al, 2014]):

103 A confirmed diagnosis of non-malignant condition(s) requiring treatment with systemic GC (including, but not limited to, chronic rheumatologic, gastrointestinal, neurologic, respiratory, and/or nephrological conditions)

- Subjects who are on systemic GC only as replacement therapy for adrenal insufficiency are not eligible for the study

104 Treatment with systemic GC (intravenous or oral) of any duration for the underlying non-malignant condition(s) within the 12 months prior to screening

- Prepubertal children should be expected to require significant GC use during the study, per investigator opinion

105 Evidence of at least 1 vertebral compression fracture of Genant grade 1 or higher, as assessed by the central imaging vendor on lateral spine X-rays performed at screening or within 2 months prior to screening; or, in the absence of vertebral compression fractures, presence of both clinically significant fracture history (ie, ≥ 2 long-bone fractures by age 10 years or ≥ 3 long-bone fractures at any age up to 17 years) and lumbar spine BMD Z-score ≤ -2.0, as assessed by the central imaging vendor

Source: Study 20140444 Clinical Study Report, submitted May 31, 2024, Module 16.1.1, Section 4.1.1, pages 31 and 32

14.3.1.2. **Exclusion criteria**

201 Current hyperthyroidism (unless well controlled on stable antithyroid therapy)

202 Current clinical hypothyroidism (unless well controlled on stable thyroid replacement therapy)

203 History of hyperparathyroidism

204 Current hypoparathyroidism

205 Any causes of primary or secondary osteoporosis (other than GC use), or previous exposure to non-GC medications, which the investigator considers to have been a major factor contributing to the patient's fracture(s)

206 Current adrenal insufficiency as the sole indication for GC therapy

207 Duchenne muscular dystrophy with symptomatic cardiac abnormality

208 Current malabsorption (in children with serum albumin < lower limit of normal [LLN], malabsorption should be clinically ruled out by the investigator to confirm eligibility)

209 Known intolerance to calcium or vitamin D supplements

Active infection or history of infections, defined as follows:

210 Any active infection for which systemic anti-infectives were used within 4 weeks prior to screening

211 Serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to screening

212 Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might compromise the safety of the subject

213 History of malignancy

214 History of any solid organ or bone marrow transplant

215 Evidence of untreated oral cavities or oral infections

216 Recent or planned invasive dental procedure

217 Surgical tooth extraction which has not healed by screening

218 Currently unhealed fracture or osteotomy, as defined by orthopedic opinion

219 Osteotomy within 5 months prior to screening

220 Spinal fusion surgery within 5 months prior to screening or not yet healed (per orthopedic surgeon)

221 Rodding surgery within 5 months prior to screening or not yet healed (per orthopedic surgeon)

222 Anticipated major skeletal surgery (eg, rodding surgery, spinal surgery) within the next 12 months from day 1

223 Planned orthopedic surgery that, in the opinion of the investigator, would require missing any dose of investigational product in year 1 or 2 or more doses thereafter

224 History of rare hereditary problems of fructose intolerance

225 History of long QT syndrome

226 History of alcohol or drug abuse

227 History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

228 Serum albumin-corrected calcium < LLN or > 10% above upper limit of normal (ULN) at screening

229 Serum vitamin D < 20 ng/mL at screening (rescreening for vitamin D level < 20 ng/mL will be allowed, after adequate supplementation)

230 Serum phosphorus < LLN at screening

231 Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 x ULN (or > 5 x ULN in subjects with dystrophinopathies) at screening

In subjects with dystrophinopathies, AST or ALT elevation > 5 x ULN may not be exclusionary if

i. It is associated with serum creatine phosphokinase (CPK) elevation

AND

ii. Serum total bilirubin, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and prothrombin time/international normalized ratio (PT/INR) are < ULN, and serum albumin is > LLN

AND

iii. There are no symptoms or signs of hepatic inflammation, such as nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, with no other immediately apparent possible cause (eg, gastroenteritis or constipation)

232 Serum total bilirubin > 1.5 x ULN at screening (subjects with Gilbert syndrome are eligible)

233 Positive blood screen for human immunodeficiency virus (HIV)-1 or -2 antibody

234 Positive blood screen for hepatitis B surface antigen or hepatitis C antibody

235 Estimated glomerular filtration rate < 60 mL/min/1.73 m² at screening (calculated by the bedside Schwartz equation)

236 Less than 2 evaluable vertebrae by DXA evaluation in the region of interest L1-L4, as confirmed by the central imaging laboratory

Prior treatment for bone disease with any of the following at any time:

237 Denosumab

238 Strontium

239 Fluoride

Recent BP treatment, according to the following guidelines:

240 Zoledronic acid (ZA) within 6 months prior to screening (subjects are eligible if 6 months will have elapsed, since the previous ZA dose, by the time of first dose of investigational product)

241 Oral BP or intravenous BP (other than ZA), if the first dose of investigational product would be before their next scheduled BP dose (subjects are eligible if at least 1 BP dosing interval will have elapsed at time of the first dose of investigational product)

Administration of any of the following treatment within 3 months prior to screening:

242 Growth hormone (unless on stable dose for at least 3 months prior to screening)

243 Calcitonin

244 Cathepsin K inhibitor

245 Other bone active drugs including anti-convulsants (except gabapentin and benzodiazepines) and heparin

246 Chronic systemic ketoconazole, androgens (except subjects who have received testosterone therapy for physiologic replacement in the setting of documented hormonal deficiency), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin releasing hormone agonists

Initiation of any of the following biologic agents within 4 weeks prior to screening:

247 Anti-alpha 4 integrin antibody (eg, natalizumab)

248 Anti-CD4/CD8 T-cells (eg, alefacept)

249 Anti-IL-12/IL-23 (eg, ustekinumab)

250 CTLA4 inhibitor (eg, abatacept)

251 IL1 receptor antagonist (eg, anakinra)

252 IL6 inhibitor (eg, tocilizumab)

253 Monoclonal antibody to CD20 (eg, rituximab)

254 Tumor necrosis factor antagonist (eg, adalimumab, certolizumab, golimumab, etanercept, infliximab)

255 Current treatment with > 1 biologic agent for underlying inflammatory disease

256	Currently pregnant or planning a pregnancy during the study and for an additional 5 months after the last dose of investigational product
257	Currently breastfeeding or planning on breastfeeding during the study and for an additional 5 months after the last dose of investigational product
258	For sexually active girls: refusal to use highly effective methods of contraception and to continue this practice for 5 months after the last injection of investigational product
259	Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.
260	Subject's parent or legal representative has any kind of disorder that, in the opinion of the investigator, may compromise the ability to give written parental permission for informed consent
261	Currently receiving treatment in another investigational device or drug study, or < 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

Source: Study 20140444 Clinical Study Report, submitted May 31, 2024, Module 16.1.1, Section 4.1.2, pages 32 to 35

14.3.2. Study 20140444 Assessment of change in growth parameters

Table 23: Change from baseline in age-adjusted z-scores for height, weight, and BMI

	Placebo / Denosumab 1 mg/kg Q6M (N = 8)	Denosumab / Denosumab 1 mg/kg Q6M (N = 15)
Height-for-age z-score		
Change from baseline to Month 12		
n	8	13
Mean	-0.07	-0.18
SD	0.84	0.46
Median	-0.29	-0.02
Q1, Q3	-0.79, 0.57	-0.56, 0.16
Min, Max	-0.8, 1.3	-1.0, 0.4
Change from baseline to Month 24		
n	7	12
Mean	-0.27	-0.11
SD	1.17	0.90
Median	-0.26	-0.03
Q1, Q3	-1.31, 0.69	-0.34, 0.31
Min, Max	-1.7, 1.6	-1.9, 1.6
Change from baseline to Month 36		
n	7	12
Mean	0.01	-0.33

SD	1.35	0.84
Median	0.02	0.04
Q1, Q3	-0.93, 1.24	-1.03, 0.36
Min, Max	-2.4, 1.5	-1.8, 0.6
Weight-for-age z-score		
Change from baseline to Month 12		
n	8	15
Mean	-0.10	-0.12
SD	0.49	0.44
Median	-0.24	-0.14
Q1, Q3	-0.36, -0.03	-0.53, 0.01
Min, Max	-0.6, 1.0	-0.9, 0.8
Change from baseline to Month 24		
n	7	12
Mean	-0.68	-0.22
SD	0.62	0.73
Median	-0.65	-0.47
Q1, Q3	-1.37, -0.30	-0.72, 0.06
Min, Max	-1.5, 0.2	-1.0, 1.4
Change from baseline to Month 36		
n	7	12
Mean	-0.44	-0.32
SD	0.60	0.90
Median	-0.61	-0.49
Q1, Q3	-0.84, 0.06	-0.96, 0.35
Min, Max	-1.4, 0.3	-1.9, 1.1
BMI-for-age z-score		
Change from baseline to Month 12		
n	8	13
Mean	-0.14	-0.03
SD	0.54	0.53
Median	-0.09	0.09
Q1, Q3	-0.33, 0.17	-0.41, 0.40
Min, Max	-1.2, 0.6	-0.8, 0.9
Change from baseline to Month 24		
n	7	12
Mean	-0.75	-0.12
SD	1.02	0.80
Median	-0.57	-0.25
Q1, Q3	-1.11, -0.02	-0.41, 0.16

Min, Max	-2.8, 0.3	-1.6, 1.6
Change from baseline to Month 36		
n	7	12
Mean	-0.72	-0.12
SD	0.97	0.84
Median	-0.59	-0.07
Q1, Q3	-0.93, 0.09	-0.69, 0.34
Min, Max	-2.7, 0.2	-1.5, 1.3

The growth analysis set includes all subjects in the FAS who have non-missing weight, height, BMI, and age in total months at baseline and post baseline. N=number of subjects in the growth analysis set; n=number of subjects with observed data; SD=standard deviation.
Source: Study 20140444 Clinical Study Report, submitted May 31, 2024, Module 5.3.5.1, Section 10.2.10, Table 10-13, pages 58 to 60

14.3.3. Safety analysis by sex, race, and ethnicity subgroups in Trial 21040444

14.3.3.1. Safety by sex

In the 52-week double-blind period of the trial, the safety of denosumab was broadly consistent across sex, though the limited number of subjects in the denosumab and placebo groups likely limits definitive conclusions regarding safety based on sex. The proportion of males and females reporting at least 1 TEAE in the denosumab group was comparable, although a slightly higher proportion of female subjects, compared to male subjects, in this group reported SAEs and 16.7% of females, compared to 0 males, discontinued denosumab due to an AE. Refer to Table 24.

Table 24: Number of subjects, by sex, reporting AEs in the 52-week double-blind period of Trial 21040444

Sex	Denosumab N (%)	Placebo N (%)	Total N (%)
Male			
Number of subjects	10	4	14
Reporting any AEs	7 (70%)	1 (25%)	8 (57.1%)
Reporting serious AEs	1 (10%)	1 (25%)	2 (14.3%)
Treatment discontinued due to AE	0	0	0
Female			
Number of subjects	6	4	10
Reporting any AEs	4 (66.7%)	4 (100%)	8 (80%)
Reporting serious AEs	2 (33.3%)	0	2 (20%)
Treatment discontinued due to AE	1 (16.7%)	0	1 (10%)

Source: Clinical reviewer generated report

14.3.3.2. Safety by race

The small number of subjects per each race exposed to study drug severely limits the ability make meaningful conclusions regarding the impact of race on the safety of denosumab during the 52-week, double-blind period of the trial. Refer to Table 25.

Table 25: Number of subjects, by race, reporting AEs in the 52-week double-blind period of Trial 21040444

Race	Denosumab N (%)	Placebo N (%)	Total N (%)
Asian			
Number of subjects	3	0	3

Race	Denosumab N (%)	Placebo N (%)	Total N (%)
Reporting any AEs	1 (33.3%)	0	1 (33.3%)
Reporting serious AEs	0	0	0
Treatment discontinued due to AE	0	0	0
White			
Number of subjects	13	5	18
Reporting any AEs	10 (76.9%)	3 (60%)	13 (72.2%)
Reporting serious AEs	3 (23.1%)	0	3 (16.7%)
Treatment discontinued due to AE	1 (7.7%)	0	1 (5.6%)
Other			
Number of subjects	0	3	3
Reporting any AEs	0	2 (66.7%)	2 (66.7%)
Reporting serious AEs	0	1 (33.3%)	1 (33.3%)
Treatment discontinued due to AE	0	0	0

Source: Clinical reviewer generated report

14.3.3.3. Safety by ethnicity

During the 52-week, double-blind period of the trial, few subjects overall were enrolled in the trial, and even fewer were of Hispanic/Latino ethnicity, which precludes an assessment of safety based on ethnicity. Refer to Table 26.

Table 26: Number of subjects, by ethnicity, reporting AEs in the 52-week double-blind period of Trial 21040444

Ethnicity	Denosumab N (%)	Placebo N (%)	Total N (%)
Hispanic/Latino			
Number of subjects	1	3	4
Reporting any AEs	1 (100%)	2 (66.7%)	3 (75%)
Reporting serious AEs	0	1 (33.3%)	1 (25%)
Treatment discontinued due to AE	0	0	0
Non Hispanic/Latino			
Number of subjects	15	5	20
Reporting any AEs	10 (66.7%)	3 (60%)	13 (65%)

Ethnicity	Denosumab N (%)	Placebo N (%)	Total N (%)
Reporting serious AEs	3 (20%)	0	3 (15%)
Treatment discontinued due to AE	1 (6.7%)	0	1 (5%)

Source: Clinical reviewer generated report

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/s/

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