NOVARTIS

Global Clinical Development - General Medicine

ZOL446 / zoledronic acid

Clinical Trial Protocol CZOL446H2337E1 / NCT01197300

A 1-year, multicenter, open-label, extension to CZOL446H2337 to evaluate safety and efficacy of zoledronic acid twice yearly in osteoporotic children treated with glucocorticoids

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List of abbreviations

AE	Adverse Event
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AP	Anterior-posterior
AST	Aspartate Aminotransferase
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BSAP	Bone Specific Alkaline Phosphatase
CQA	Compliance Quality Assurance
CRO	Contract Research Organization
DAR	Dose administration record
DMD	Duchenne muscular dystrophy
DXA	Dual Energy X-ray Absorptiometry
eCRF	Case Report/Record Form (electronic)
[redacted]	[redacted]
EOS	End of Study
FAS	Full Analysis Set
FPS-R	Faces Pain Scale - revised
GC	Glucocorticoids
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GIO	Glucocorticoid-induced osteoporosis
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
i.v.	intravenous
IRB	Institutional Review Board
ISCD	International Society for Clinical Densitometry
JRA	Juvenile rheumatoid arthritis
LS	Lumbar Spine
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MCHC	Mean cell hemoglobin concentration
NTX	Cross-linked N-telopeptide
OC/RDC	Oracle Clinical/Remote Data Capture
OI	Osteogenesis Imperfecta
ONJ	Osteonecrosis of the Jaw
P1NP	Procollagen type 1 amino-terminal propeptide

[redacted]

[redacted]	[redacted]
PMO	Postmenopausal Osteoporosis
RBC	Red Blood Cell
RDA	Recommended Daily Allowance
SAE	Serious Adverse Event
SAF	Safety population
SLE	Systemic Lupus Erythematosus
SUSAR	Suspected Unexpected Serious Adverse Reactions
TRAP-5b	Tartrate-resistant Acid Phosphatase Isoform 5b
TNF	Tumor Necrosis Factor
TD	Study Treatment Discontinuation
UK	United Kingdom
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication pack number	A unique identifier on the label of each investigational drug package
Patient ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 3

Amendment rationale

- The rationale for this amendment is to reflect the changes in the Core protocol (CZOL446H2337) v05 which has been amended [redacted] to provide a Risk Benefit statement (Section 3.6), and allow more countries to apply the contraceptive wording originally provided for UK sites only.
  - The introduction (Section 1) has been revised with more recent references that reflect the increase in knowledge of childhood osteoporosis since the protocol was first proposed.
  - The investigational plan (Section 3) and statistical sections (Section 9) have been clarified.
  - In addition, the DMC concerns regarding potential for transient symptomatic hypocalcemia after first infusion are addressed by adding additional calcium supplementation at the recommended daily allowance (RDA) for age in Table 5-1 for up to 10 days around time of infusion (in line with Institutional clinical practice guidelines).
  - Table 5-1 has been revised in line with the current minimum RDAs for vitamin D and calcium from the Institute of Medicine.
  - Visit 9 for Group 1 is now defined as up to 10 months after Visit 5 (month 6) of the Core study, to allow patients who are deteriorating at the time of the second infusion during the Core study to enter the Extension study rather than be treated off-label.
  - This amendment includes clarification of the list of eligible medical conditions other than chronic rheumatologic conditions or inflammatory bowel disease or Duchenne muscular dystrophy (DMD) already specified previously. These additional conditions are listed in Appendix 6 and the exclusion criteria for Group 2 have been revised to address these as follows:
    - Due to the inclusion of some of these additional medical conditions, e.g. nephrotic syndrome, the exclusion criterion of renal impairment previously defined as an estimated glomerular filtration rate (GFR) < 35 mL/min/1.73 m^2 at screening has been increased to normal renal function defined as < 60 mL/min/1.73 m^2 based on the Schwartz formula at Visit 8 (Group 1) or Visit 8A (Group 2).
    - Schwartz formula has been added under Section 6.5.4.2
    - In addition ‘serious renal disease’ in DMD has been removed as this is included under the GFR exclusion criterion.
    - In DMD patients, chronic muscle breakdown results in elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (frequently higher than 10 fold); hence total bilirubin and gamma-glutamyl transpeptidase (GGT) have been added as additional markers to detect any potential liver toxicity.

[redacted]

- The exclusion criterion 'symptomatic cardiac abnormality' in DMD has been redefined because other conditions or concomitant medications, including glucocorticoids can contribute to cardiac disease: Uncontrolled symptoms of cardiac failure or arrhythmia.
- Serum 25-hydroxy vitamin D concentrations have been revised to the currently accepted definition of normal i.e. < 20 ng/mL or < 50 nmol/L at Visit 8A for Group 2.
- The blood volume required (Appendix 7) for the analysis of specialized bone markers has been reduced from 8.5 mL to 3 mL.

- The local serum creatinine before the second infusion of zoledronic acid has been removed because of the need for normal renal function as an eligibility criterion. Renal function is reviewed centrally before and 10 days after each infusion.
- Inconsistencies have been corrected within the protocol and across supporting documents especially with respect to Serious Adverse Event/Adverse Event reporting in Group 2 and central laboratory analyses.
- In this 12 month study, visit windows have been removed and replaced with a requirement to perform the visit as close to the designated day as possible. For Group 2 only, the time between Visit 8A and Visit 9 should be as close to 28 days as possible, but cannot be longer than 8 weeks.

The latest Novartis protocol template has been used to aid the reader in navigating the protocol and more some procedures have been revised in line with our current processes.

Status of the study as of 10-May-2016:

Twelve (12) patients have been enrolled onto this study, all were enrolled into Group 1; the proposed changes will have no impact on the interpretation of the data.

Changes to the protocol

Changes to specific sections of the protocol are shown by track changes in the track changes version of the protocol using ~~strike through red font for deletions~~, and red underlined for insertion.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments:

Amendment 2

The rationale for this amendment (dated 15-Jan-2014) was to reflect the changes in the Core (CZOL446H2337) protocol v04 which extended the study population to include subjects with

[redacted]

underlying conditions other than chronic inflammatory disorders e.g. Duchenne muscular dystrophy (DMD).

- Include (Group 2): patients not eligible to enroll into the Core study because of clinically significant back pain (significant symptoms) from vertebral fracture and the preexisting clinical care at the Investigator's site is to treat this type of patient with a bisphosphonate. Therefore two Baselines are used in the study:
  - Baseline 1: First visit of the Core for Group 1
  - Baseline 2: First visit of the Extension for Group 2.
- Align with the Core study changes in the Inclusion/Exclusion criteria:
  - Relax the LS BMD Z-score inclusion criteria from -1.0 to -0.5 or worse.
  - Modify the exclusion criteria of patients with any prior use of osteoporosis/bone modifying therapy. Bisphosphonates and sodium fluoride will be kept in the exclusion criteria. Calcitonin, calcitriol, SERMS, LHRH agonists, Growth Hormone and medroxyprogesterone will be taken out from the exclusion criteria
  - Modify the exclusion criteria of patients with any prior use of osteoporosis/bone modifying therapy and to allow non-ambulatory patients who require wheelchair assistance for mobility to enter the study.
  - Add exclusion criteria for history of serious renal disease and symptomatic cardiac involvement in DMD patients.
- Align with the Core study changes in the assessments by adding the following:
  - [redacted]
  - Serum 25-hydroxy vitamin D concentration at Month 12 of the Extension.
- Eliminated 24-hours and 48-hours post-first dose local serum ionized calcium measurements.

Amendment 1

This amendment (dated 29-Nov-2012) applied to United Kingdom (UK) sites only, regarding contraception and pregnancy in female patients of child bearing potential.

[redacted]

Protocol Summary

Protocol number	**CZOL446H2337E1**
Title	A 1-year, multicenter, open-label, extension to CZOL446H2337 to evaluate safety and efficacy of zoledronic acid twice yearly in osteoporotic children treated with glucocorticoids
Brief title	A 12-month observational study of zoledronic acid in children and adolescents with osteoporosis
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the safety of zoledronic acid plus vitamin D and calcium in osteoporotic children treated with glucocorticoids
Primary Objective(s)	To demonstrate that zoledronic acid given long-term, over an additional 12 months from the Core study (CZOL446H2337), is safe for the treatment of osteoporotic children treated with glucocorticoids (Group 1 only)
Secondary Objectives	Group 1: 1. To evaluate the change from baseline (Visit 1 of the Core study) in LS BMD Z-score at Month 18 and 24 by core treatment group. 2. To evaluate the change from baseline 1 (Visit 1 of the Core study) in LS and total body BMC at Month 18 and 24 by core treatment group. 3. To evaluate the change from baseline 1(Visit 1 of the Core study) in serum N-terminal propeptide type I collagen (P1NP), cross linked N-telopeptide (NTX), bone specific alkaline phosphatase (BSAP) and tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) at Month 18 and 24 by core treatment group. 4. To evaluate the proportion of patients with new clinical vertebral fractures during the 12 month extension period by core treatment group. 5. To evaluate the proportion of patients with new morphometric vertebral fracture during the 12 month extension period by core treatment group. 6. To evaluate the change from baseline 1 (Visit 1 of the Core study) in pain using the Faces Pain Scale-Revised (FPS-R) at Month 15, 18, 21 and 24 by core treatment group. 7. To evaluate the change from baseline 1 (Visit 1 of the Core study) in 2nd metacarpal cortical width at month 24 by core treatment group. 8. To evaluate the change from baseline 1(Visit 1 of the Core study) in bone age and 2nd metacarpal cortical width at month 24 by core treatment group. Group 2: 1. To evaluate the change from (Extension) baseline 2 (Visit 8A) in LS-BMD Z-score at Month 6 and 12. 2. To evaluate the change from (Extension) baseline 2 (Visit 8A) in LS and total body BMC at Month 6 and 12. 3. To evaluate the relative change from (Extension) Baseline 2 in serum N-terminal propeptide type I collagen (P1NP), cross linked N-telopeptide (NTX), bone specific alkaline phosphatase (BSAP) and tartrate-resistant acid phosphatase

	isoform 5b (TRAP-5b) at Month 6 and 12. 4. To evaluate the proportion of patients with new clinical vertebral fractures during the 12 month period. 5. To evaluate the proportion of patients with new morphometric vertebral fracture during the 12 month period. 6. To evaluate the change from (Extension) baseline 2 in pain using the Faces Pain Scale-Revised (FPS-R) at Month 3, 6, 9 and 12. 7. To evaluate the change from (Extension) baseline 2 in bone age and 2nd metacarpal cortical width at Month 12. 8. To demonstrate that zoledronic acid is safe for the treatment of osteoporotic children (with symptomatic vertebral fracture) treated with glucocorticoids, through the monitoring of relevant clinical and laboratory safety parameters.
Study design	This will be an international multi-center, 1-year open-label extension to the CZOL446H2337 Core study with a single treatment arm (zoledronic acid); there will be no placebo or active control group. All patients will have received glucocorticoid therapy of any duration within the 12 months preceding screening.
Population	The trial population will consist of male and female children and adolescents with a confirmed diagnosis of non-malignant conditions requiring treatment with systemic glucocorticoids. All patients who complete the Core study (Group 1) will be eligible. Those patients who were found to be eligible for the Core study but not enrolled due to clinically significant back pain associated with the fracture (Group 2). Approximately 100 patients will be eligible for enrollment into the extension, for both groups. Patient recruitment in Group 2 will stop once enrollment in the Core study is completed.
Key Inclusion criteria	Written informed consent before any study-related procedure. **Group 1:** 1. Children and adolescents, male or female, 6-19 years old, who met the inclusion criteria for entry into the Core study and who took at least one dose of study drug and have completed Visit 8 of the CZOL446H2337 Core study. 2. Patient must be enrolled into the extension at Visit 9 up to 10 months after Visit 5 (month 6) of the Core study. 3. Patients who followed the regimen of calcium and vitamin D intake as required in the Core study through diet or supplementation. **Group 2:** 1. Children and adolescents, male or female, 5 - 17 years old who met the inclusion criteria for entry into the Core study but were not enrolled because of clinically significant back pain from vertebral fracture and the preexisting clinical care at the Investigator site is to treat this type of patient with a bisphosphonate. 2. Confirmed diagnosis of non-malignant conditions (including but not limited to rheumatic conditions, inflammatory bowel disease, Duchenne muscular dystrophy, nephrotic syndrome), treated with systemic glucocorticoids (i.v. or oral) within the 12 months preceding enrollment in the study (any duration) 3. LS-BMD Z-score of -0.5 or worse confirmed by the central imaging vendor 4. Evidence of at least 1 vertebral compression fracture (at least Genant Grade 1 vertebral compression or radiographic signs of vertebral compression) confirmed by central reading OR At least one lower OR 2 upper extremity long-bone, low-trauma, fracture which occurred sometime within the 2 years or preceding enrollment in the study, confirmed by radiological report. (*Low trauma fracture is defined as falling from standing height or less).
Key Exclusion	1. Major protocol violation in the Core Study (Group 1 only).

[redacted]

criteria	2. Prior use of bisphosphonates (Group 2 only) or sodium fluoride (doses for osteoporosis not for dental hygiene). 3. Hypocalcemia and hypophosphatemia: any value (age-matched) below the normal range at Visit 8 or 8A. 4. Vitamin D deficiency (serum 25-hydroxy vitamin D concentrations of < 20 ng/mL or < 50 nmol/L) at Visit 8 (Group 1) or Visit 8A (Group 2). 5. Renal impairment defined as an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 at screening based on the Schwartz formula at Visit 8 or 8 A; a serum creatinine above the normal range at Visit 9 (Group 1) or an increase between Visit 8A and Visit 9 greater than 0.5 mg/dL (44.2 µmol/L) for Group 2. 6. Female patients of child bearing potential are eligible only if they are not pregnant/non-lactating. Females of child bearing potential must be practicing a medically acceptable form of birth control for greater than 2 months prior to screening visit and consent to pregnancy tests during the study.
Study treatment	i.v. zoledronic acid (ZOL446) 5.0 mg/100 mL solution, supplied in a ready-to-infuse plastic bottle
Efficacy assessments	The efficacy variables will be measured using the following techniques: • vertebral morphometric fractures [redacted] • DXA measurements • bone marker analysis [redacted] • bone age and metacarpal cortical width assessment • pain assessment
Key safety assessments	Adverse event monitoring, Physical examinations, Monitoring of laboratory markers in blood and urine; and bone safety monitoring.
[redacted]	
Data analysis	Data analyses will be performed separately for the two populations (Group 1 [SAF-1] and Group 2 [SAF-2]), if not otherwise specified. For the patients in Group 2 (SAF-2); only descriptive statistics will be reported for the single treatment arm.
Key words	Osteoporosis, children and adolescents, zoledronic acid, chronic inflammation, Duchenne muscular dystrophy, glucocorticoids

[redacted]

1 Introduction

1.1 Background

Osteoporosis in children is a very different disease to osteoporosis in adults. Children have not attained peak bone mass, and sufficient data correlating bone density with fractures are not available. The role of lumbar spine bone mineral density (LS-BMD) in the risk of fracture has been evaluated in some childhood illnesses, particularly osteogenesis imperfecta (OI) (primary osteoporosis). Although the diagnosis of osteoporosis in adults is based on BMD, Sbrocchi et al 2011 reported a child with glucocorticoid (GC) responsive nephrotic syndrome and fragility fracture; bone biopsy revealed signs of osteoporosis with marked thinning of the cortices and decreased trabecular bone volume, suggesting that dual X-ray absorptiometry (DXA)-based, LS-BMD should not be relied upon exclusively for assessing bone health in children, and that a LS-BMD Z-score of -0.5 is sufficient. Further, the International Society for Clinical Densitometry (ISCD) now defines pediatric osteoporosis as the finding of one or more low impact vertebral compression fractures (Genant Grade 1 or more) in the absence of a change in BMD (Bishop et al 2014).

Patients receiving high doses of GCs are at increased risk of significant bone loss and fractures; GC-induced osteoporosis (GIO) is now recognized as one of the most important reasons for secondary osteoporosis in adults as well as children. Prior GC use confers a substantial increase in fracture risk in adults, and this risk is largely independent of BMD or a prior fragility fracture (Kanis et al 2004). Studies in adults suggest that GC treatment for 3 months is sufficient to increase fracture risk, and similar data have been collected in children and adolescents where almost one-half of the patients with fractures were asymptomatic (Leblanc et al 2015). The earliest observation of vertebral fractures in children with rheumatic disorders is 4 months after starting systemic GCs (Rodd et al 2012).

The etiology of secondary osteoporosis in children with inflammatory disorders is multifactorial and varies with the particular disease. Overlapping risk factors seen in chronic inflammatory conditions include poor nutrition and malabsorption of both calcium and fat-soluble vitamins. Direct detrimental effects on bone due to high circulating levels of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor (TNF)-alpha have been reported. The treatment of inflammatory bowel disease (IBD), juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), Duchenne muscular dystrophy (DMD), and nephrotic syndrome includes GC therapy which can further worsen bone mineral status.

While there is no primary bone involvement in DMD, the reduced mechanical loading and poor ambulation lead to osteoporosis, which is further compounded by the side effects of chronic GC therapy. Osteoporosis is most profound in the lower extremities of boys with DMD and begins to develop early while still ambulatory (Larson and Henderson 2000). Other examples of diseases of children treated with intermittent high doses of glucocorticoids where osteoporosis is also a risk include asthma, myasthenia gravis and Becker's dystrophy, and etc. (see Appendix 7).

There is no established treatment for secondary osteoporosis in children, although treatment for adult osteoporosis including GIO is currently well established for bisphosphonates.

[redacted]

Placebo controlled trials using bisphosphonates such as risedronate and alendronate have been shown to increase BMD and reduce the risk of vertebral fractures in patients initiating glucocorticoids or receiving such a treatment for a longer period of time. In adults, regulatory approval for treatment and prevention of osteoporosis has been granted for bisphosphonates. Although bisphosphonates have been used experimentally in the treatment of specific pediatric metabolic bone disease, only one, neridronate is currently approved in Italy for osteogenesis imperfecta (OI). Pamidronate is provided as an example of bisphosphonates for consideration in the management of DMD boys with ‘bone demineralization and increased fracture risk (Bushby et al 2010).

Zoledronic acid

Zoledronic acid is a third generation bisphosphonate and is the most potent bisphosphonate marketed. In a variety of assays of bone metabolism, zoledronic acid has demonstrated inhibition of bone resorption in vitro at concentrations of 0.3-30 nM and in vivo at doses of 0.3-30 μ g/kg without exerting any untoward effects on either bone formation or mineralization. A large difference exists between various bisphosphonates in terms of potency and effects on mineralization. There is an inverse relationship between potency and mineralization defects. These mineralization defects have occurred in patients treated with the upper therapeutic dose range of etidronate. In animal models, zoledronic acid has demonstrated extremely high potency in terms of antiresorptive effect without adverse effects on mineralization even at high doses; hence there appears to be a large therapeutic window between the desired inhibition of resorption and unwanted inhibition of mineralization in these models [see Investigator’s Brochure (IB)].

Zoledronic acid is marketed as Aclasta® outside of the US and for Paget’s disease of bone and PMO as Reclast® within the US. As Aclasta, ZOL is approved as a single infusion for the treatment of Paget’s disease of bone and as once annual dosing for the treatment of postmenopausal osteoporosis (PMO), treatment of osteoporosis in men, prevention and treatment of adult glucocorticoid-induced osteoporosis (GIO), prevention of postmenopausal osteoporosis (PMO) and prevention of clinical fractures after hip fracture in men and women. Moreover, it is approved for the prevention of skeletal-related events (pathological fractures, spinal compression, radiation or surgery to bone) or tumor-induced treatment of hypercalcemia of malignancy as Zometa® using approximately a 10-fold higher dose on a yearly basis (4 mg once monthly).

A 2007 Cochrane Review (Ward et al 2007) of bisphosphonate therapy for children and adolescents with secondary osteoporosis concluded that though there was not enough information in the studies included within the review to determine whether bisphosphonates would make a difference to children’s bone mineral content (BMC), further use of bisphosphonates in the context of pediatric trials was justified.

1.2 Purpose

The purpose of this study is to extend the period of observation in patients who have completed one year of evaluation in the Core study (CZOL446H2337) to evaluate the long-term safety and efficacy of zoledronic acid in osteoporotic children or adolescents treated with GCs. Patients who completed the Core study are referred to in this protocol as patients in Group 1. This study will also add to the information available on the management of

secondary osteoporosis in children (Hogler and Ward 2015) and will help to determine if there is added benefit of a second year of treatment with zoledronic acid.

In addition, the study will evaluate safety and efficacy of zoledronic acid in patients who are not eligible to be randomized to the Core study due to clinically significant back pain (significant symptoms) from vertebral fracture when the preexisting clinical care at the investigator's site is to treat this type of patient with a bisphosphonate. These patients are included in this protocol in Group 2.

2 Study objectives

2.1 Primary objective

The primary objective of this study is to demonstrate that zoledronic acid given long-term, over an additional 12 months from the Core study (CZOL446H2337), is safe for the treatment of osteoporotic children treated with glucocorticoids. This objective applies only to patients who completed the Core study (these patients are referred to as Group 1).

2.2 Secondary objective(s)

Group 1 secondary objectives:

1. To evaluate the change from baseline 1 (Visit 1 of the Core study) in LS-BMD Z-score at Month 18 and 24 by core treatment group.
2. To evaluate the change from baseline 1 (Visit 1 of the Core study) in LS and total body BMC at Month 18 and 24 by core treatment group.
3. To evaluate the change from baseline 1(Visit 1 of the Core study) in serum N-terminal propeptide type I collagen (P1NP), cross linked N-telopeptide (NTX), bone specific alkaline phosphatase (BSAP) and tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) at Month 18 and 24 by core treatment group.
4. To evaluate the proportion of patients with new clinical vertebral fractures during the 12 month extension period by core treatment group.
5. To evaluate the proportion of patients with new morphometric vertebral fracture during the 12 month extension period by core treatment group.
6. To evaluate the change from baseline 1 (Visit 1 of the Core study) in pain using the Faces Pain Scale-Revised (FPS-R) at Month 15, 18, 21 and 24 by core treatment group.
7. To evaluate the change from baseline 1 (Visit 1 of the Core study) in 2nd metacarpal cortical width at month 24 by core treatment group.
8. To evaluate the change from baseline 1(Visit 1 of the Core study) in bone age and 2nd metacarpal cortical width at month 24 by core treatment group.

Group 2 secondary objectives:

1. To evaluate the change from (Extension) baseline 2 (visit 8A) in LS- BMD Z-score at Month 6 and 12.
2. To evaluate the change from (Extension) baseline 2 (visit 8A) in LS and total body BMC at Month 6 and 12.

[redacted]

3. To evaluate the relative change from (Extension) baseline 2 in serum N-terminal propeptide type I collagen (P1NP), cross linked N-telopeptide (NTX), bone specific alkaline phosphatase (BSAP) and tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) at Month 6 and 12.
4. To evaluate the proportion of patients with new clinical vertebral fractures during the 12 month period.
5. To evaluate the proportion of patients with new morphometric vertebral fracture during the 12 month period.
6. To evaluate the change from (Extension) baseline 2 in pain using the Faces Pain Scale-Revised (FPS-R) at Month 3, 6, 9 and 12.
7. To evaluate the change from (Extension) baseline 2 in bone age and 2nd metacarpal cortical width at Month 12.
8. To demonstrate that zoledronic acid is safe for the treatment of osteoporotic children (with symptomatic vertebral fracture) treated with GCs, through the monitoring of relevant clinical and laboratory safety parameters.

3 Investigational plan

3.1 Study design

This study is a 1-year open-label extension to the CZOL446H2337 Core study. The study uses a single treatment arm (zoledronic acid); there will be no placebo or active control group. All patients will be osteoporotic children and adolescents receiving GC therapy of any duration within the 12 months preceding Baseline (Visit 1 of the Core study for Group 1; Visit 8A of this study for Group 2). All patients must manifest a LS-BMD Z-score of -0.5 or worse and have evidence of low impact/fragility fracture at either the Baseline of the Core Study (Group 1) or this study (Group 2).

Group 1: Patients who have received at least one dose of study drug and who have completed the Core study and who meet the inclusion/exclusion criteria for this Extension study will be eligible to enroll. The final visit of the Core study (Visit 8) will serve as the first (screening) visit for the Extension study. At Visit 8A, which may take place on the same day as Visit 8, patients will complete additional screening assessments for the Extension study. Patients will return at Visit 9 (which can also be on the same day as Visit 8 of the Core study) and all patients will receive zoledronic acid. The allowed window for Visit 9 is up to10 months after Visit 5 (month 6) of the Core study (up to 4 months after Visit 8 of the Core study). Note that Visit 8 and Visit 9 can be combined if the patients or parents or legal guardians have provided informed consent to enter into the Extension study prior to Visit 8 and undergone the appropriate screening procedures as outlined in Section 6. Central labs from Visit 8 will be utilized for the Extension Visit 9, provided the lab samples have been collected within 30 days prior to the Visit 9 infusion. Otherwise, the labs must be redrawn and the results reviewed for eligibility, prior to infusion at Visit 9. The DXA scans (hip, spine and distal femur) from Visit 8 will be used for the extension Visit 9 provided the DXAs have been obtained within 3 months of the Visit 9 infusion; otherwise, the DXA scans must be repeated at Visit 9.

Group 2: Children, male or female, 5 to 17 years of age who otherwise met the inclusion criteria for entry into the Core study but did not complete screening on the Core study because of clinically significant back pain due to vertebral fracture and the preexisting clinical care at the Investigator's site is to treat this type of patient with a bisphosphonate.

Visit 8 A will serve as the first (screening) visit for Group 2. Patients will return at Visit 9 and all patients will receive zoledronic acid. The allowed screening window between Visit 8 A and Visit 9 is 30 days. Central labs from Visit 8 A will be utilized for Visit 9, provided the lab samples have been collected within 30 days prior to the Visit 9 infusion. Otherwise, the labs must be redrawn and the results reviewed for eligibility, prior to infusion at Visit 9. The DXA scans (hip, spine and distal femur) and X-rays collected at Visit 8 A will be read centrally and if the child/adolescent is eligible, used for Baseline provided the DXAs have been obtained within 3 months of Visit 9; otherwise, the DXA scans must be repeated at Visit 9.

All Patients (Group 1 and Group 2) will receive two infusions of i.v. zoledronic acid (0.05 mg/kg) with an interval of 6 months at Visit 9 and at Visit 12.

Safety and efficacy will be assessed at 6 (Visit 12) and 12 months (Visit 15), with additional visits 10 days after each infusion to evaluate on renal and calcium (Visit 10 and 13) as well as

[redacted]

telephone visits to assess pain, adverse events [redacted] and concomitant medication at 3 (Telephone Visit 11) and 9 (Telephone Visit 14) months.

3.2 Rationale of study design

The study is an open-label study where all patients will be receiving active study drug (zoledronic acid 0.05mg/kg).

Group 1: The Core study, CZOL446H2337, is part of a Pediatric Investigational Plan (EMEA-000057-PIP01-07), [redacted]. This one-year study will extend the period of observation in patients who have completed the Core protocol and will collect long-term safety and efficacy data (Group1). The primary objective of the study will focus on general safety. The Extension study is an open-label study where all patients will receive active study drug (zoledronic acid 0.05 mg/kg). Given the rapid bone loss associated with the use of GCs and the fracture inclusion criteria for enrollment in the Core study, an open-label study design addresses ethical considerations for those patients who were randomized to receive placebo in the Core study who may deteriorate and require an active intervention, while at the same time allowing for the primary objective to be assessed.

Group 2: The study will capture additional safety and efficacy data on zoledronic acid from patients who presented with clinically significant back pain (significant symptoms) from vertebral fracture who were not enrolled into the Core study (Group 2) because the pre-existing clinical care at the Investigator's site is to treat this type of patient with a bisphosphonate.

3.3 Rationale of dose/regimen, duration of treatment

Zoledronic acid dose selection for Study CZOL446H2337E1 is based on several sources of information, including safety and efficacy data from completed Novartis clinical trials in adults with postmenopausal osteoporosis and GIO, pediatric patients with severe OI, long-term safety in pediatric patients with OI, and a PK study in pediatric patients with severe OI. Published data is available from trials in patients with postmenopausal osteoporosis (Reid et al 2002; Black et al 2007). Adults with benign disease (Paget's and PMO) have received safely up to 5 mg i.v. by slow injection (over 15 minutes) over various dosing frequencies. Cancer patients have received up to 4 and 8 mg i.v. monthly, in long term studies (> 1 year). In the zoledronic acid clinical development program in pediatrics to date, the dose selection was an infusion of 0.05 mg/kg (max 4mg) administered quarterly. This dose was extrapolated from a comparison with a pamidronate infusion in patients with tumor-induced hypercalcemia that showed that 4 mg zoledronic acid was more effective than 90 mg pamidronate. The 4 mg dose of zoledronic acid represents an approximate adult dose of zoledronic acid of 0.07 mg/kg or a dose of pamidronate of 1.5 mg/kg for a 60 kg adult. Pamidronate 1.5 or 3.0 mg/kg administered every 6 months was the dose range and interval used in the long-term pamidronate OI study (Glorieux et al 1998). In this pivotal trial, the pamidronate dosing interval was changed to an every 4 month dosing regimen as monthly evaluations of serum alkaline phosphatase concentration and urinary calcium excretion increased after 4 months.

The Study CZOL446H2202 is the largest NVS-sponsored trial in pediatric patients with metabolic bone disease. This 12-month study compared the efficacy and safety of i.v. zoledronic acid 0.05 mg/kg administered quarterly to i.v. pamidronate 1.0 mg/kg on each of 3

[redacted]

successive days administered quarterly in 155 patients with severe OI. The results showed that zoledronic acid was superior to pamidronate in increasing LS -BMD at month 12 and in reducing markers of bone turnover, both formation and resorption. [redacted] The overall incidence rate of adverse events was similar between the two treatment groups. There was no evidence of a long-term effect on renal function following the administration of zoledronic acid in this patient population. In addition to efficacy and safety evaluations, Study CZOL446H2202 assessed the pharmacokinetics of zoledronic acid. The pharmacokinetics of a single infusion of zoledronic acid 0.05 mg/kg, in children and adolescents aged 3-8 years and 9-17 years, were similar to those observed in adult oncology patients at approximately the same mg/kg dose. Plasma concentrations in the pediatric patients were generally at or below the median concentrations in adults, which may be an advantage in consideration of drug safety and tolerability in children. In a second trial with OI patients (Study CZOL446H2202E1), the 12-month Extension study to CZOL446H2202, long-term safety was assessed in 103 patients receiving 0.05 mg/kg zoledronic acid either as an annual infusion or twice yearly (6 months apart). In this study, median increases in LS-BMD were approximately 1.3% higher in patients who received the twice yearly dosing of zoledronic acid. Though these data from Study CZOL446H2202E1 should be interpreted with caution as the sample sizes are too small to make definitive conclusions, it is established that there is an effect of puberty on bone degradation, with children demonstrating high bone resorption relative to adults.

Therefore, the zoledronic acid dose and interval selected for the on-going Core protocol, 0.05 mg/kg as two i.v. infusions with a 6 month interval, is expected to provide superior efficacy (as measured by change in LS-BMD Z-score) compared to placebo in pediatric patients with osteoporosis. This same dose and regimen will be used into this protocol.

The maximum allowable zoledronic acid dose of 5 mg (regardless of patient weight), does not exceed the doses already used in adults and is well within the maximum zoledronic acid dose tested in Phase I Novartis Oncology trials: zoledronic acid 16 mg by slow i.v. infusion. In this study in children with secondary osteoporosis, zoledronic acid will be administered as at least a 30 minute i.v. infusion. Dose limitation and a 30 minute infusion time are designed to reduce the risk of possible adverse effects while maintaining efficacy.

3.4 Rationale for choice of comparator

No placebo-treatment arm will be used in this Extension study.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Benefit

The potential benefit of zoledronic acid in children at risk of osteoporosis due to underlying disease or intermittent high dose GCs is outlined in Section 1.1 and in the Investigator's Brochure.

[redacted]

Additional evidence suggests that bisphosphonates have anti-apoptotic effects on osteoblasts and osteocytes which may lead to increased trabecular thickness and thus, may partly explain why bisphosphonates produce a greater reduction in fracture risk than that expected from BMD gains alone (Plotkin 1999).

The skeletal toxicity of GC is confirmed in adults and children. Furthermore, BMD is greatly influenced by sex steroids, and puberty can be delayed in the presence of GC which can also result in short stature which may be offset by the use of bisphosphonates (Glorieux et al 1998).

Risks

Known risks of zoledronic acid

Since this protocol was first written in 2010, there have been more publications on the potential use of bisphosphonates in children with kidney diseases including nephrotic syndrome (Gruppen et al 2013, Sbrocchi et al 2011).

Zoledronic acid is concentrated and excreted via the kidney and, like other bisphosphonates, has the potential to produce renal injury. Thus, care should be taken when administering the compound to patients with renal insufficiency. Although case reports have been published in adults regarding the nephrotoxicity of zoledronic acid with an incidence of acute kidney injury (AKI) between 9% and 13%, bisphosphonate-induced AKI in children remains undocumented (Patzer 2008).

- In this protocol, patients are excluded if they have an estimated glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2. In addition patients considered for Group 2 who have nephrotic syndrome with osteoporosis, who do not meet this exclusion criterion, have been stable for 3 months prior to enrollment, and meet the remaining eligibility criteria, can be considered for this study.

Post-infusion acute phase reactions are more common after the first infusion and can include pyrexia, muscle and joint pain,

- To reduce the risk of these reactions, children will be instructed to eat and drink as usual, NSAIDs or acetaminophen (paracetamol) will be prescribed and an anti-emetic may be provided to reduce the risk of symptomatic hypocalcemia if the child develops nausea or starts to vomit. Further calcium supplements will be provided for up to 10 days at the time of infusion and parent/legal guardian instructions provided on the signs to watch for as well as an emergency number, if needed.

A rare risk in patients who receive bisphosphonates is osteonecrosis of the jaw (ONJ). This condition has been reported in cancer patients whose complex treatment regimens include higher doses and frequencies of bisphosphonates, typically administered with other treatments such as radiation, chemotherapy and GCs. To date, ONJ has not been reported in the literature in children or adolescents who have received bisphosphonates. Based on available evidence, a causal relationship between ONJ and bisphosphonates, including ZOL, has not been established.

- In this study a lower dose and short duration of zoledronic acid is used than has been reported in cases of ONJ in adults, and all children will have an examination of their oral cavity during the study and referred to a dentist if necessary.

[redacted]

Potential risks of zoledronic acid in a pediatric population

Based on the results from animal studies showing inhibition of bone calcification by first generation bisphosphonates (Mashiba et al 2000), there are theoretical concerns about negative effects on growth in children. In growing children, each bisphosphonate treatment cycle leads to the accumulation of a thin band of mineralized tissue at the interface between growth plate and metaphysis which is evident as a metaphyseal line on the radiograph (Land et al 2006a). These lines represent persistent calcified cartilage in the horizontal trabeculae which later remodels into secondary bone. This interface between weaker bone and stronger bisphosphonate-treated bone could represent a site for potential fracture. However, in clinical trials with i.v. bisphosphonates, linear growth in children and adolescents has not been observed to be negatively impacted with no observed increase in fracture. To the contrary, cyclical i.v. treatment with pamidronate has been shown to be beneficial in children with severe forms of OI (Glorieux et al 1998).

- To investigate this potential risk, all subjects will have DXA examination at 6 and 12 months and in the event of clinical worsening or diagnosis of new fracture, an X-ray will be performed.

Another concern in children is effects on the reproductive organs. The animal reproduction studies of zoledronic acid are described in [Section 4.3.5 of the Investigator's Brochure]. Teratogenicity was observed in the rat, but not the rabbit when treatment during the perinatal period resulted in delayed parturition likely resulting from the calcium lowering effect of the compound outside of bone, which negatively affects uterine contraction. There were no effects reported in males.

- Consequently this protocol requires contraception in all girls who are pubertal and may become pregnant and in some countries additional pregnancy checks will be made.

There are potential concerns regarding the i.v. infusion in children. Apart from the potential risks at the infusion site of pain, infection, phlebitis, hematoma and extravasation, the infusion may also cause fluid overload if the rate is too high and this can result in hypertension, heart failure or pulmonary edema. Additional risks of the infusion can include electrolyte imbalance and embolism.

- The infusion is administered in a hospital or clinic by staff experienced in administering i.v. infusions to children. The infusion line is flushed with saline before and after administration and the infusion given over at least 30 minutes e.g. in a 25 kg child, 100 mL may be administered over one hour at a rate of 5 mL/minute.

Protocol procedures: blood draws and radiology

The number of blood draws and frequency of hospital visits in this protocol is within the usual limit of clinical practice for children with these serious underlying diseases. The radiation exposure is increased over routine clinical practice, but within the limits for children who have suffered a fracture and no greater than the exposure during a transatlantic flight. Repeat blood draws and X-rays/DXA will only be requested when absolutely necessary i.e. safety, baseline or end-of-study visits.

In summary, the risks to the children and adolescents in this trial will be minimized by compliance with the eligibility criteria and study procedures, particularly adequate hydration at the time of the infusion, adherence to a diet rich in calcium and vitamin D, regular renal

[redacted]

monitoring and contraception in girls of child bearing potential. A maximum dose of 5 mg zoledronic acid (regardless of patient weight) and a minimum 30 minute infusion time 6 monthly are designed to reduce the risk of possible adverse effects. This dose regimen has been used in children with primary and secondary osteoporosis and has shown a favorable risk-benefit profile.

4 Population

Group 1: Patients who have received at least one dose of study drug, have completed participation in the Core study and who meet the inclusion/exclusion criteria for this extension, will be eligible to participate. These patients have been previously diagnosed with non-malignant conditions (including but not limited to rheumatologic conditions, IBD, DMD, nephrotic syndrome) and have been treated with systemic GCs (i.v. or oral) prior to the Core study and have evidence of at least 1 vertebral compression fracture confirmed by central reading or one or more low-trauma lower extremity long bone fractures or two or more low trauma upper extremity long bone fractures confirmed by radiology report.

Group 2: Patients who were not eligible for the Core study because of clinically significant back pain from vertebral fracture and the preexisting clinical care at the Investigator's site is to treat this type of patient with a bisphosphonate.

Approximately 100 patients will be eligible for enrollment into the extension, for both groups. Patient recruitment in Group 2 will stop once enrollment in the Core study is completed

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

- Written informed consent must be obtained before any assessment is performed. An assent needs to be provided in accordance with ICH and local regulations.

Group 1:

1. Children and adolescents, male or female, between 6 to 19 years of age who met the inclusion criteria for entry into the Core study and who took at least one dose of study drug and have completed Visit 8 of the CZOL446H2337 Core study.
2. Patient must be enrolled into the extension at Visit 9 up to 10 months after Visit 5 (month 6) of the Core study.
3. Patients who followed the regimen of calcium and vitamin D intake as required in the Core study (at least 1000 mg calcium for 6-8 years of age or at least 1300 mg calcium for 9-19 years of age and at least 600 IU daily vitamin D, through diet or supplementation).

Group 2:

1. Children and adolescents, male or female, between 5 to 17 years of age who met the inclusion criteria for entry into the Core study but were not enrolled because of clinically significant back pain from vertebral fracture and the preexisting clinical care at the Investigator's site is to treat this type of patient with a bisphosphonate.
2. Confirmed diagnosis of non-malignant conditions (including but not limited to rheumatic conditions, inflammatory bowel disease, Duchenne muscular dystrophy, nephrotic syndrome who have stable normal renal function for at least 3 months prior to screening or

[redacted]

other subtype of secondary osteoporosis in children taking GCs, except patients with oncologic conditions (such as lymphoma and leukemia) see Appendix 6), treated with systemic GCs (i.v. or oral) within the 12 months preceding enrollment in the study (any duration)

3. Lumbar Spine areal BMD Z-score of - 0.5 or worse confirmed by central imaging
4. Evidence of at least 1 vertebral compression fracture (at least Genant Grade 1 vertebral compression or radiographic signs of vertebral compression*) seen on X-ray within 1 month of or at screening visit confirmed by central reading.

*Radiographic signs of vertebral compression fracture include loss of endplate parallelism, vertebral buckling and endplate interruption.

4.2 Exclusion criteria

1. Patients who demonstrated a major protocol violation in the Core study (Group 1 only)
2. Patients for whom the investigator considers participation in the Extension study is not appropriate (Group 1 only).

(For both groups)

3. Hypocalcaemia and hypophosphatemia: any value (age-matched) below the normal range at Visit 8 or 8 A.
4. Vitamin D deficiency (serum 25-hydroxy vitamin D concentrations < 20 ng/mL or < 50 nmol/L) at Visit 8 for Group 1, Visit 8 A for Group 2.
5. Local serum ionized calcium below the normal range at Visit 9.
6. Renal impairment defined as an estimated GFR < 60 ml/min/1.73 m^2 based on the Schwartz formula at screening Visit 8 or 8 A (in the case of DMD additional methods may have been recorded in the source documents). Serum creatinine above the normal range at Visit 9 (Group 1) or an increase between Visit 8 A and Visit 9 greater than 0.5 mg/dL (44.2 μ mol/L) for Group 2.
7. Uncontrolled symptoms of cardiac failure or arrhythmia
8. Any prior use of bisphosphonates (other than study drug during the Core study for Group 1 only) or sodium fluoride (doses for osteoporosis not for dental hygiene).
9. Current active hyperparathyroidism or hyper/hypothyroidism or during the Core study.
10. New diagnosis of sarcoidosis currently or during the Core study.
11. New malignancy diagnosis currently or during the Core study.
12. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
13. History of primary bone disease (OI, idiopathic juvenile osteoporosis, rickets/ osteomalacia).
14. Female patients of child bearing potential are eligible only if they are: (1) not pregnant/ non-lactating; (2) are sexually abstinent or are surgically sterile or (3) if sexually active, must be practicing a medically acceptable form of birth control for greater than 2 months prior to screening visit.

[redacted]

- Females of child bearing potential who are sexually active must agree to continue to practice their birth control during the trial and at least 1 year after completing the trial and must consent to a pregnancy test prior to every dose administration and at the End of Study (EOS) Visit.
- [For sites where additional safeguards are required only: Female patients of child bearing potential are eligible only if they are not pregnant/non-lactating. Females of child bearing potential must be practicing a medically acceptable form of birth control for greater than 2 months prior to screening visit. At least one and preferable two complementary forms of contraception including a barrier method should be used and be continued throughout the trial and for at least 1 year after completing the trial. They must also consent to a pregnancy test prior to every dose administration and at the EOS visit. An additional supervised urine pregnancy test will be assessed at Visit 11 (Month 15) (See Section 6.5.5).

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Zoledronic acid 5.0 mg/100 ml solution supplied in a ready-to-infuse plastic bottle, twice yearly.

5.1.2 Additional treatment

Adequate intake of vitamin D and calcium is mandatory for the four weeks prior to randomization and throughout the duration of the study, either through adequate dietary intake or via supplementation, or a combination of both diet and supplementation. Described below are the recommended guidelines for vitamin D and calcium intake. It is the responsibility of the investigator to ensure that each patient receives the adequate recommended daily allowance (RDA) of vitamin D and calcium (through diet and/or supplementation)(Ross et al 2011).

Table 5-1 Recommended minimum daily dietary allowances

Age	Vitamin D	Calcium
≥ 5 years to ≤ 8 years	600 IU	1000 mg
≥ 9 years to ≤ 20 years	600 IU	1300 mg

All patients should take at least 600 IU vitamin D daily from Visit 8/8A until the final extension study visit through diet and/or supplementation.

Elemental calcium, at least 1000 mg for 5-8 years of age or at least 1300 mg for 9-20 years of age, daily will be taken beginning at Visit 8/8A and during the total duration of the trial, through diet and/or supplementation. Calcium carbonate is the preferred form of calcium

[redacted]

supplementation. If calcium carbonate is not well tolerated, another form of oral calcium would be acceptable.

Any vitamin D and calcium supplements will be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

In addition, transient hypocalcemia has been reported following the first infusion and it can cause symptoms in rare cases. To prevent the development of symptomatic hypocalcemia, the parent or legal guardian of each child will receive an information sheet and all patients will receive calcium supplementation at the doses recommended in Table 5-1 starting at least from the day of infusion and for a minimum of 5 days after the infusion (for sites where this calcium supplementation usually starts prior to the infusion, the total treatment period is approximately 10 days in total) (Hogler et al 2004).

5.2 Treatment arms

All patients will be given open-label zoledronic acid.

5.3 Treatment assignment

Not applicable, as this is an open-label trial.

5.4 Treatment blinding

This is an open-label study and treatment blinding is not applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Group 1: Each patient entering this Extension study will continue to be identified by the patient number assigned in the Core study, CZOL446H2337.

Group 2: Patient number consists of a four digit Center number (e.g. 0001) followed by a five digit patient number. The five digit patient number for the first patient starts at 101 (e.g. 00101). Example of patient number in Group 2: 0001_00101.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and

[redacted]

designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug, but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

At physician's discretion, vitamin D and calcium supplementation may be managed by diet alone, and this should be recorded in the source records.

When dietary supplements are recommended, this non-study treatment has to be recorded in the Concomitant medications/Significant non-drug therapies of the eCRF specifically:

- Calcium supplements at the time of infusion (all patients)
- Multivitamins that contain the RDA for calcium and vitamin D from Visit 8/8A to Visit 15 in line with Table 5-1
- Calcium or calcium plus vitamin D supplements from Visit 8/8A to Visit 15 in line with Table 5-1
- Vitamin D as a single supplement from Visit 8/8A to Visit 15 in line with Table 5-1

Details are described in the CRF completion guidelines.

5.5.4 Instructions for prescribing and administering study treatment

Patients will receive a single dose of zoledronic acid of 0.05 mg/kg, administered as a slow infusion of 100 ml over 30 minute, at Visit 9 and Visit 12.

AGE	DOSE of ZOLEDRONIC ACID	TIME OF INFUSION
≥ 5 years to 20 years	0.05 mg/kg diluted in 100 ml of normal saline	30 minute infusion

The zoledronic acid dose is not to exceed 5.0 mg.

[redacted]

A peripheral intravenous site must be used for the zoledronic acid 30 minute infusion. The i.v. infusion will be preceded by and followed by a 10 ml normal saline flush of the intravenous line.

As an example, the following table demonstrates how to prepare drug for a patient who weighs 46 kg.

Table 5-2 Preparation of i.v. zoledronic acid infusion

Pt Weight (kg)	Patient dose based on 0.05 mg/kg	Total number of 5.0 mg/100ml vials	Volume of zoledronic acid to add to the normal saline	Volume of normal saline	Total volume of prepared infusion
46 kg	Y = 2.3 mg	1 vial	46 ml	100 ml	146 ml
X kg	X kg * 0.05 mg/kg = Y or Patient dose	1 vial	Y / 5 mg / 100 ml= Patient dose	100 ml	100 ml + volume of reconstituted zoledronic acid to add
Note: The maximum dose is 5 mg therefore the maximum volume from the 5mg/100ml zoledronic acid vial to be used in this study is 100ml					

The investigator should promote compliance by instructing the patient to take the study drug exactly and additional treatment as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant medication

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

5.5.7.1 Treatment of study drug related adverse events

As with other bisphosphonates, zoledronic acid has been associated with post-dose symptoms that may include fever, nausea, myalgia, arthralgia and bone pain, with onset occurring within the first 72 hours after the infusion. Typically these symptoms occur with the first infusion of bisphosphonate. The symptoms are usually mild to moderate and rarely severe. These symptoms may be adequately managed, at the discretion of the investigator, with non-steroidal anti-inflammatory agents (e.g. acetaminophen/paracetamol or ibuprofen) and/or anti-

emetics by local treatment standards and according to approved local labeling. Based on data from controlled trials, treatment with non-steroidal anti-inflammatory agents will reduce the incidence of these symptoms by approximately 50%. In managing these symptoms it is important to encourage adequate hydration and food intake. An anti-emetic may be provided to reduce the risk of symptomatic hypocalcemia if the child develops nausea or starts to vomit. Further calcium supplements will be provided for up to 10 days at the time of infusion and parent or legal guardian instructions provided on the signs to watch for as well as an emergency number, if needed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the concomitant medications/significant non-drug therapies eCRF after start of study treatment.

5.5.8 Prohibited medication

Use of the following treatments is NOT allowed throughout the duration of the trial: bisphosphonates, high dose sodium fluoride, denosumab.

5.5.9 Emergency breaking of assigned treatment code

Not applicable in this open-label study.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed all the assessments in the last visit planned in the protocol (Visit 15, Month 24).

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. This care may include:

- Alternative therapy may be prescribed at the discretion of the treating physician at Visit 15 (EOS).

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration i.e. before Visit 12, Month 18, and can be initiated by either the patient, parent/legal guardian or the investigator.

The investigator must discontinue study treatment for a given patient if he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient or parent/legal guardian's wish
- Pregnancy (see Section 6.5.5 and Section 7.4)
- Use of prohibited treatment as per recommendations in Section 5.5.8
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following adverse events:

[redacted]

- ONJ
- Renal failure
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation (TD) visit. Treatment discontinuation visit assessments detailed in Visit 15 (Month 24) in Table 6-1 or Table 6-2 should be completed and recorded in the CRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage administration record CRF and the study completion CRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events (AEs)/serious adverse events (SAEs)

If the patient, parent/legal guardian cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient and parent/legal guardian, or with a person pre-designated by the patient or parent/legal guardian. This telephone contact should preferably be done according to the study visit schedule and changes recorded in the relevant pages of the CRF.

5.6.3 Withdrawal of informed consent

Patients and/or parents/legal guardians may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) from the study is defined as when a patient, parent/legal guardian:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's or parent's/legal guardian's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

[redacted]

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1 and Table 6-2.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all of the assessments and indicate with an "X" when the visits are performed.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

[redacted]

Table 6-1 Group 1 Assessment schedule

	Final visit of Core study		Infusion visit		Tele-phone	Infusion visit		Tele-phone		Notes
Visit	**8**	**8A**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EOS and TD and/or PSW**	Visit 8 is the Core study completion visit. Visit 8A lists the additional assessments which need to be completed for the Extension study. Visits 8 and 8A assessments must be completed on the same day. Visits 8, 8A, and 9 can occur on the same day
Months relative to the Core study (after Visit 9 - Baseline of Extension study)			**up to 10 months after V5 (Core study)**	**10 days after V9**	**15 (3 months after V9)**	**18 (6 months after V9)**	**10 days after V12**	**21 (9 months after V9)**	**24 (12 months after V9)**	
Obtain informed consent (D) and assent (S)		X								
Inclusion/exclusion criteria (S)		X	X							
Prior/concomitant medications including GCs (D)	X	X	X	X	X	X	X	X	X	
Adverse events (D)	X	X	X	X	X	X	X	X	X	Any AEs that occur after Visit 8 but prior to first dose of Extension study (Visit 9) will be collected on the AE (e)CRF
Vital signs (D)	X		X			X			X	Pulse rate and blood pressure only
Physical examination (S)	X		X			X			X	Including an oral examination for exposed bone
Tanner staging (D), if applicable	X								X	
[redacted]										
Weight (D)	X		X			X			X	
Pain assessment	X		X		X	X		X	X	Pain is assessed using Faces Pain Scale-Revised (FPS-R)
[redacted]										
Central laboratory test (hematology, biochemistry including urinalysis)	X		X	X		X	X		X	All patients will have limited blood chemistry assessments, GFR and urinalysis performed at

[redacted]

	Final visit of Core study		**Infusion visit**		**Tele-phone**	**Infusion visit**		**Tele-phone**		**Notes**
Visit	**8**	**8A**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EOS and TD and/or PSW**	Visit 8 is the Core study completion visit. Visit 8A lists the additional assessments which need to be completed for the Extension study. Visits 8 and 8A assessments must be completed on the same day. Visits 8, 8A, and 9 can occur on the same day
Months relative to the Core study (after Visit 9 - Baseline of Extension study)			**up to 10 months after V5 (Core study)**	**10 days after V9**	**15 (3 months after V9)**	**18 (6 months after V9)**	**10 days after V12**	**21 (9 months after V9)**	**24 (12 months after V9)**	
										Visit 10 and Visit 13
Serum creatinine (local lab)			X							For exclusion purposes
Ionized calcium (local lab)			X							Measured pre-dose, (local lab) prior to first infusion of Extension study
Bio-markers (Serum P1NP, NTX, BSAP, Trap-5b)	X		X			X			X	Not required at Visit 9 if it occurs within 30 days of Visit 8
Serum 25 hydroxy vitamin D	X		X						X	
Pregnancy Test	X		X		[X]	X			X	To be performed for females with childbearing potential only [Only for sites where additional safeguards are required: Supervised urine pregnancy test]
i.v. drug administration (zoledronic acid)			X			X				
Dispense calcium and vitamin D, if required		X	X			X				
DXA measurements (lumbar spine, total body and distal femur)	X		X			X			X	Not required if obtained 3 months prior to Visit 9
X-ray	X								X	Lateral thoraco-lumbar spine and postero-anterior left hand/wrist
[redacted]										
Study completion	X								X	
S = Source data, D = Database, TD = study treatment discontinuation, PSW = premature patient withdrawal										

[redacted]

Table 6-2 Group 2 Assessment schedule

	Screening Visit	Infusion Visit[1]		Tele-phone	Infusion Visit		Tele-phone		Notes
Visit	**8A**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EOS and TD and/or PSW**	Screening period from Visit 8A to Visit 9 should be as close to 28 days as possible, but cannot be longer than 8 weeks
Months relative to the Core study (after Visit 9 - Baseline of Extension study)		**28 days from V8A**	**10 days after V9**	**3 months after V9**	**6 months after V9**	**10 days after V12**	**9 months after V9**	**12 months after V9**	
Obtain informed consent (D) and assent (S)	X								
Inclusion/exclusion criteria (S)	X	X							
Medical History (D)	X	X							
Prior/concomitant medication, including GCs (D)	X	X	X	X	X	X	X	X	
Vital signs (D)	X	X			X			X	Pulse and blood pressure
Physical examination (S)	X	X			X			X	Including an oral examination for exposed bone
Tanner staging (D), if applicable		X						X	
[redacted]									
Weight (D)	X	X			X			X	
Pain assessment		X		X	X		X	X	Pain is assessed using Faces Pain Scale-Revised (FPS-R)
[redacted]									
Central laboratory test (hematology, biochemistry including urinalysis)	X	[X]	X		X	X		X	All patients will have limited blood chemistry, GFR and urinalysis performed at Visit 10 and Visit 13. [Visit 9 lab draw only if more than 4 weeks from Visit 8A].
Serum creatinine (local lab)	X	X							For exclusion purposes
Ionized calcium (local lab)		X							Measured pre-dose (local lab) prior to first infusion

[redacted]

	Screening Visit	Infusion Visit[1]		Tele-phone	Infusion Visit		Tele-phone		Notes
Visit	**8A**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EOS and TD and/or PSW**	Screening period from Visit 8A to Visit 9 should be as close to 28 days as possible, but cannot be longer than 8 weeks
Bio-markers (Serum P1NP, NTX, BSAP, Trap-5b)		X			X			X	
Serum 25 hydroxy vitamin D	X							X	
Pregnancy Test	X	X		[X]	X			X	To be performed for females with childbearing potential only [Only for sites where additional safeguards are required: Supervised urine pregnancy test]
i.v. drug administration (zoledronic acid)		X			X				
Dispense calcium and vitamin D, if required	X	X			X				
DXA measurements (lumbar spine, total body and distal femur	X				X			X	
X-ray	X							X	Lateral thoraco-lumbar spine and postero-anterior left hand/wrist
[redacted]									
Adverse events and SAEs (D)	X	X	X	X	X	X	X	X	SAEs only collected between Visit 8A and Visit 9 (AEs during this time recorded as medical history)
Study completion								X	
S = Source data, D = Database, TD = study treatment discontinuation, PSW = premature patient withdrawal									

[redacted]

6.1 Information to be collected on screening failures

Patients may discontinue from the study from Visit 8/8A through Visit 9, prior to any open-label medication being administered.

Patients discontinuing prior to first infusion in the Extension study are considered screening failures.

If a patient discontinues before entering the open-label treatment period, the demographic information, reason for non-eligibility and screening log should be completed on the eCRF.

6.2 Patient demographics/other baseline characteristics

Group 1: Baseline demographical information for continuing patients was collected at the beginning of the Core study and will not be collected again in the Extension study. Visit 1 of the Core study will be considered as Baseline 1. Any adverse events that occur after Visit 8 of the Core study but prior to the first dose of the Extension study (Visit 9) will be also collected on the adverse event eCRF.

Group 2: Baseline demographical information, medical history, concomitant medications, physical exam and laboratory/imaging assessments will be collected at Screening visit (Visit 8A) or Visit 9; this will be considered as Baseline 2.

6.3 Treatment exposure and compliance

Concomitant Medications/Non-drug therapy prior to the first dose of study medication in the Extension study and after start of study drug will be collected, including medication name and reason. More details (including dose and dates of intake) will be provided for the following categories of treatments: osteoporosis-related medications**,** nutritional supplements (vitamin D/ calcium), and GCs. A Dosage Administration Record will be completed for each i.v. dose of zoledronic acid. Information collected will include the date of dose, start and stop times of infusion and the reason for each dose.

Compliance with vitamin D/calcium will be assessed by the investigator and/or study personnel at each visit using information on diet and supplement use provided by the patient/caregiver. This information should be captured in the source document, at each visit, and in the Concomitant Medication/Non-significant therapy eCRF. All study treatment and any additional treatment (i.e. vitamin D and/or calcium provided by Novartis or designee) dispensed and returned must be recorded in the Drug accountability log.

6.4 Efficacy

The efficacy variables will be measured using the following techniques:

- vertebral morphometric fractures

[redacted]

- DXA measurements
- bone marker analysis

[redacted]

[redacted]

- bone age and metacarpal cortical width assessment
- pain assessment

6.4.1 Vertebral morphometric fractures

Group 2 only:

At Visit 8A, anterior-posterior (AP) and lateral X-rays of the lumbar and thoracic spine will be taken to evaluate the presence of vertebral fractures of Genant grade 1 or higher or radiographic signs of vertebral compression fracture. AP spine X-ray will be employed at baseline, in order to identify fractures that may not be readily visualized on the lateral spine because of rotation/scoliosis/other.

Radiographic signs of fracture include loss of endplate parallelism, vertebral buckling and endplate interruption. Patient's eligibility must be confirmed by the central imaging laboratory before the patient can be enrolled. AP and lateral thoracolumbar spine X-rays taken within 1 month of Visit 8A (screening) can be used. The film and report must be sent to central imaging for fracture confirmation.

All patients:

Lateral thoraco-lumbar spine X-ray will be performed at the final visit of the Extension study (Visit 15) to assess incident vertebral fractures. Vertebral fractures present at baseline or occurring during the study will be defined according to the Semi-Quantitative (SQ) method and confirmed with the Quantitative Morphometric (QM) method for vertebral fracture assessment:

1. A mild (Grade 1) vertebral fracture is defined as greater than or equal to (≥)20% and less than or equal to (≤) 25% reduction in anterior, middle, and/or posterior vertebral height.
2. A moderate (Grade 2) vertebral fracture is defined as greater than (>) 25% and less than or equal to (≤) 40% reduction in any vertebral height.
3. A severe (Grade 3) vertebral fracture is defined as greater than **(>)** 40% reduction in any vertebral height.

or based on radiographic signs of fracture, including: loss of endplate parallelism, vertebral buckling and endplate disruption.

Specific instructions for sending radiographic images will be distributed to investigators prior to the start of study.

Vertebral morphometry (or concave index) will be calculated using the average ratio between mid-height and posterior height from the first to the fourth lumbar vertebrae (L1 to L4) (Land et al 2006b)

[redacted]

[redacted]

[redacted]

6.4.3 DXA measurements

DXA measurements of the lumbar spine (LS), total body and distal femur will be performed on all patients. LS- BMD Z-score, LS bone mineral content (BMC), Total body BMC [redacted] will be assessed at the final visit of the Core study (for Group 1) or Visit 8A-Screening Visit (for Group 2), Visit 9 (Month 18) and Visit 15 (Month 24) (final extension study visit/EOS). DXA will be acquired locally and the results will be sent to a central reader for evaluation.

Group 1: The DXA scans (hip, spine and distal femur) from Visit 8 will be used for the extension Visit 9 provided the DXAs have been obtained within 3 months of the Visit 9 infusion; otherwise, the DXA scans must be repeated at Visit 9.

Group 2: Lumbar Spine-BMD-Z score of -0.5 or worse at Visit 8A needs to be confirmed by central imaging vendor.

6.4.4 Bone marker analysis

Specialized serum tests for BSAP, P1NP, TRAP-5b and NTX will be performed. Blood will be drawn from patients at the final visit Core study (for Group 1) or Visit 9 (for Group 2), at Visit 12 (Month 18) and Visit 15 (Month 24) (final extension study visit/EOS). Detailed shipping instructions will be provided in the Investigator Laboratory Manual.

[redacted]

[redacted]

6.4.6 Bone age and metacarpal cortical width assessment

Left postero-anterior (PA) hand/wrist X-ray will be taken at the final visit of Core study (for Group 1) or Visit 8A-Screening visit for Group 2 and at Visit 15/EOS (Month 24) for both Groups to assess bone age. The change in 2nd metacarpal cortical width at Month 24 relative to the respective baseline will be calculated.

If a fracture of the left upper extremity precludes radiographic imaging, (or precluded this X-ray in the Core study for Group 1) then the right hand will be evaluated for this purpose. In this case, the right hand should be imaged at both Visit 8 and at Visit 15/EOS (Month 24). The information will be used in the assessment of bone density.

6.4.7 Pain assessment

A Faces Pain Scale Revised (FPS-R) will be used for this purpose.

Pain will be evaluated at each visit (at office and telephone visit) at the final visit of the Core study (Group 1 only) and first visit of the Extension study (Visit 9), Visits 11, 12, 14 and 15.

6.4.8 Appropriateness of efficacy assessments

Fracture determination by X-ray is the standard endpoint for long-term studies in osteoporosis. However, in studies of 12 months duration, change in BMD has become an acceptable surrogate and has been shown to be a strong indicator of the efficacy of anti-resorptive therapies, including bisphosphonates such as ZOL. Bone marker assessments of change in BSAP, P1NP, TRAP-5b and NTX often parallel the change in BMD over the same time course. NTX and TRAP-5b measure bone resorption while BSAP and P1NP measure bone

formation. In the growing child, height and bone age also indicate the overall effectiveness of an intervention, but in this study, only trends may be observed over the 12 month period. Bisphosphonates are considered effective in managing bone pain, including fracture pain, and the FPS-R is a scale used to measure pain in children.

The efficacy measurements listed above are therefore expected to be appropriate for this study.

6.5 Safety

Safety assessments will consist of:

- monitoring and recording of all adverse events and serious adverse events,
- renal function (serum creatinine and GFR),
- the regular laboratory monitoring of hematology, blood chemistry and urinalysis, regular measurement of vital signs, and
- the performance of physical examinations including oral examinations for exposed bone.

6.5.1 Physical examination

Physical examination, including an oral exam of the gums and roof of the mouth, will be performed at Visits 9, 12 and 15. If the investigator is concerned about the patient's oral health then the patient may be referred to a dentist.

Significant findings made after the start of study drug which meet the definition of an AE must be recorded in the Adverse Event case report form. Significant findings prior to study drug would be entered on the Medical History CRF for Group 2 only.

Tanner staging will be performed at Visit 8 (Group 1 only), Visit 9 (Group 2 only) and the end of the extension study visit (Visit 15/EOS), when applicable.

6.5.2 Vital signs

Measurements will be made of sitting blood pressure and pulse rate at Visits 8 (Group 1 only), 8A (Group 2 only), 9, 12 and 15.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 [redacted] weight

Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be performed at Visits 8 (Group 1 only), 8A (Group 2 only), 9, 12 and 15 and recorded on the Vital sign eCRF.

[redacted]

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected except for ionized calcium and serum creatinine (for exclusion purposes). Details on the collections, shipment of

[redacted]

samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

EMLA cream may be used at all blood draws. EMLA Cream is a topical anesthetic which numbs the skin and decreases the sensation of pain. There should be up to three attempts to obtain a serum sample from the patient at any blood draw.

A central laboratory will collect and evaluate blood and urine samples for hematology, biochemistry and urinalysis at Visit 8A (Group 2 only) and Visits 9, 12 and 15.

An additional lab test for renal monitoring will be performed at Visits 9, 10, 12, 13 and 15.

6.5.4.1 Hematology

Hemoglobin, hematocrit, platelet count, red blood cell count (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), RBC morphology, white blood cell count (WBC) and differential white blood cell counts.

6.5.4.2 Clinical chemistry

Non-fasting specimens will be obtained for glucose, creatinine, serum urea, uric acid, total protein, SGOT (AST), SGPT (ALT), alkaline phosphatase, sodium, potassium, chloride, phosphorus, magnesium, albumin, total bilirubin, gamma-glutamyl transpeptidase (GGT) and calcium.

Glomerular Filtration Rate (GFR) will be calculated using the Schwartz equation at all visits where serum creatinine will be measured (Visits 8A (Group 2 only) 9, 10, 12, 13 and 15) by the Central Laboratory.

Schwartz Formula to calculate Glomerular Filtration

GFR (mL/min/1.73 $m^{2)}$ = k [Height (m)] / Serum Creatinine (mg/dL)

k = Constant

k=0.41

Specialized (non-fasting) testing for serum 25-hydroxy vitamin D will be performed at Visit 8/8A and Visit 15. Additional local laboratory evaluation of serum ionized calcium will be evaluated in the local laboratory at pre-dose (first infusion). If local serum ionized calcium at Visit 9 is less than the normal range, the infusion must not be given. The patient may retest once at the investigator's discretion. If the serum ionized calcium retest is in the normal range, the patient may be dosed.

Also, local laboratory evaluation of serum creatinine will be performed at Visit 8A (Group 2 only) and Visit 9 for exclusion purposes. If local serum creatinine at Visit 9 is less than the normal range, the infusion must not be given. The patient may retest once at the investigator's discretion. If the serum creatinine retest is in the normal range, the patient may be dosed.

[redacted]

Patients with laboratory tests containing clinically significant abnormal values will be followed regularly until the values return to normal ranges or until a valid reason for the abnormality, other than study drug related adverse event, is identified

6.5.4.3 Urinalysis

A urine specimen will be obtained at Visit 8A (Group 2 and Group 1 if more than 28 days has lapsed since Visit 8 of the Core study), Visits 9, 10, 12, 13 and 15 for routine urinalysis, including microscopic examination.

6.5.5 Pregnancy and assessments of fertility

Serum pregnancy tests (β-hCG) will be performed at Visit 8 of the Core study or Screening visit (for Group 2) and at the final visit (Visit 15) of the Extension study. Urine pregnancy tests will be performed at Visit 9 and Visit 12, prior to study drug infusion. The test will be conducted for all female patients of childbearing potential.

[For sites where additional safeguards are required only due to local regulations e.g. UK, Italy, Germany, Sweden & etc.,: an additional supervised urine pregnancy test will be conducted at Visit 11 (Month 15) 90 days after first study drug administration. In case of a positive test, the patient must contact the investigator immediately.]

6.5.6 Bone safety monitoring

Measurement of LS-BMD Z-score at Visit 12 and 15 will be subject to monitoring from the central imaging lab for the detection of excessive changes in BMD. Repeat scans may be requested if technical factors are suspected to be involved. The investigator will be notified in the case of an absolute change in LS-BMD greater than -0.5 compared with screening at the Month 6 or 12 visits or an absolute increase of LS-BMD of greater than +2.0. In either event, the investigator should further assess the patient for secondary causes (e.g. underlying disease). If it is in the best interests of the patient to discontinue the study, discontinuation procedures should be followed as described in Section 5.6.2

6.5.7 Appropriateness of safety measurements

Safety assessments consist of monitoring and recording of all adverse events and serious adverse events, including those known to be associated with bisphosphonate use; renal function (serum creatinine and GFR), regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations including oral examinations for exposed bone. An oral examination of the gums and roof of the mouth will be performed as part of the physical examination at screening, randomization, Month 6 and Month 12 visits to assess for signs of ONJ. ONJ is characterized by exposed bone in the maxillofacial area that occurs in association with dental surgery, or occurs spontaneously, with no evidence of healing. See Section 3.6.

Tanner staging assesses the sexual maturity of the patient and is important to indicate child-bearing potential in girls as these girls will require pregnancy tests before each infusion.

Vitamin D (25-hydroxy-D) and calcium will be measured before the first infusion in the Extension study to ensure that all patients have adequate vitamin D and calcium levels at

[redacted]

study entry, as a precaution to minimize the risk of developing hypocalcemia with the first zoledronic acid administration. In addition, ionized calcium will be monitored locally, before the first infusion to ensure that the patients have normal serum calcium level. Families will be counselled on the importance of a diet rich in calcium and vitamin D, and supplements recommended based at the investigators discretion.

Bone safety is monitored by the central imaging laboratory via DXA at Visits 12 and 15. In case of excessive change in LS-BMD Z-scores compared with the relevant baseline for each Group, the investigator will be alerted.

Patients may be hospitalized at the discretion of the primary investigator for observation following the first study drug infusion. Alternatively, they may be treated in an out-patient setting. Ionized calcium will be monitored pre-dose during this visit.

The safety assessments selected are standard for this indication/patient population.

[redacted]

[redacted]

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 DNA Sampling

Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.5 Other biomarkers

Not applicable.

7 Safety Monitoring

7.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a patient or clinical investigation subject occurring after starting the study drug even if the event is not considered to be related to study drug. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

Group 1: all AEs following completion of the Core study (Visit 8) will be recorded in the eCRF of this extension study.

Group 2: due to the long screening period (at least 4 weeks), although SAEs are collected from signing the informed consent, the AE page of the eCRF is only completed from the first day of study drug; any events that occur prior to receiving study treatment, should be recorded in the eCRF as Medical History.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patients and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities.

There may be cases where a severe AE that is life-threatening may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

- its relationship to
  - study treatment (no/yes), or
  - other treatment (no/yes). or
  - both or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding investigational treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment dosage temporarily adjusted/interrupted
- investigational treatment permanently discontinued due to this adverse event
- concomitant medication
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)

[redacted]

- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient/parent/legal guardian informed consent and should be discussed with the patient/parent/legal guardian during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient/parent/legal guardian.

The investigator must also instruct each patient and parent/legal guardian to report any new adverse event (beyond the protocol observation period) that the patient or parent/legal guardian, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

[redacted]

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

All diagnosed cases of ONJ should be considered as "medically significant" irrespective of whether the event meets the definition of "Serious Adverse Event" under current health authority guidelines. These cases are therefore reported to Novartis Integrated Medical Safety (IMS) as well as local health authorities under the guideline of SAE reporting.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient or parent/legal guardian has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day period after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs *(either initial or follow up information)* is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of study treatment (if study treatment consists of several components)*, complete the SAE Report Form in English, and submit the completed, signed form within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department specific to the site, and listed in the investigator folder provided to each site. The original copy of the SAE Report Form must be kept with the case report form documentation at the study site.

[redacted]

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of

[redacted]

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data will be employed. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient or parent(s)/legal guardian(s) [a signed copy is given to the patient or parent(s)/legal guardian(s)].

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that

[redacted]

the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and forward to the CRO. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Radiographic images will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be implemented to safeguard patient safety. All members will be independent from the sponsor and study investigators. The DMC will conduct regularly scheduled meetings to review study progress and any potential emerging safety signals in the study population

8.5 Adjudication Committee

Not required.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Data analyses will be performed separately for two group populations (Group 1 and Group 2), if not otherwise specified. No inferential statistical analysis or treatment group comparison will be performed for the patients in Group 2; only descriptive statistics will be reported for the single treatment arm. Baseline comparison will be performed with respect to baseline 1

[redacted]

and baseline 2 for Group 1 population whereas the same will be performed with respect to baseline 2 for Group 2 population.

9.1 Analysis sets

The following analysis sets are described:

Group 1 (patients who were randomized into the Core protocol)

- Full Analysis Set-1 (FAS-1)
- Safety Analysis Set-1 (SAF-1)

Group 2 (patients who were not randomized into the Core protocol)

- Full Analysis Set-2 (FAS-2)
- Safety Analysis Set-2 (SAF-2)

Full Analysis Set-1(FAS-1)

FAS-1 includes all patients who have completed the Core study and have received at least one dose of study medication in the Extension study.

Screen failure patients are not considered as enrolled and excluded from FAS-1. Patients will be analyzed according to the treatment they were assigned to at the Core study randomization.

Full Analysis Set-2 (FAS-2)

FAS-2 includes all patients who are enrolled in this Extension study and were not eligible to be randomized to the Core study because of having symptomatic (significant back-pain) vertebral fracture. Patients will be analyzed according to the treatment received at the Extension study.

All efficacy analyses will be performed separately using FAS-1 and FAS-2.

Safety Analysis Set-1 (SAF-1)

SAF-1 includes all patients who have completed the Core study and have received at least one dose of study medication in the Extension study. Patients will be analyzed according to the treatment received during the Core study. Patients will be analyzed as receiving zoledronic acid in the Core study if they received at least one dose of zoledronic acid in the Core study.

Safety Analysis Set-2 (SAF-2)

SAF-2 includes all patients those were not eligible to be randomized to the core study because of having symptomatic (significant back- pain) vertebral fractures and receive at least one dose of study medication in the Extension study.

- All safety analyses will be performed separately using SAF-1 and SAF-2.

9.2 Patient demographics and other baseline characteristics

Descriptive statistics (mean, median, standard deviation, minimum, and maximum for continuous variables and number and percentage for categorical variables) for the

[redacted]

demographic and other baseline characteristics variables will be provided for the 2 randomized Core treatment groups. In addition, the baseline comparability between these two treatment groups will be evaluated for key demographic and other baseline characteristics variables for Group 1. Categorical variables will be evaluated using Fisher's exact test, and the continuous variables will be evaluated using a one-way analysis of variance (ANOVA).

Note that these tests of comparability are performed for descriptive purpose only, and will not be considered to define any formal basis for determining factors which should be included in statistical analysis models. However, when these tests yield significant results they can be used as extra information in interpreting any treatment-by-factor interactions that are observed in the sensitivity analyses performed on the key secondary efficacy variables.

All analyses will be performed based on the FAS-1 for Group 1.

Similar descriptive statistics for single treatment arm will be reported on FAS-2 for Group 2 also.

The relevant medical history/current medical conditions for the Extension study include relevant medical history/current medical conditions recorded in the Core study and adverse events occurring during the Core study or after the end of Core study but before the first study drug infusion in the Extension study for Group 1. The number and percentage of patients with relevant medical history/current medical conditions for the Extension study will be presented for each core treatment by primary system organ class and preferred term of the MedDRA dictionary. The number and percentages of adverse events that started before the Extension study and is still present at the first drug infusion in the Extension study will be presented for each core treatment by primary system organ class and preferred term. Similar medical history/current medical conditions except adverse events will also be recorded for Group 2. The number and percentage of patients with relevant medical history/current medical conditions for the Extension study will be presented for single treatment arm by primary system organ class and preferred term of the MedDRA dictionary.

All analyses will be performed separately based on the FAS-1 and FAS-2.

9.3 Treatments

Study drug and compliance

Descriptive statistics will be provided by core treatment group for duration of infusion and volume of infusion.

Concomitant therapy

Concomitant medications will be coded using the WHO Drug Reference List that employs the Anatomical Therapeutic Chemical (ATC) classification system. Summary tables will be provided that present the number and percent of patients receiving those medications by preferred term and treatment for medications prior to the first dose in the extension and during the 12-month extension period. The medications will be sorted in decreasing order of frequency with respect to usage in the zoledronic acid group.

[redacted]

Descriptive statistics will be provided by core treatment group for the dose and duration of use of GCs prior to the first dose in the extension and during the 12-month extension period for Group 1. The number and percentage of patients receiving different types of GC therapy will be presented by preferred term and Core treatment group (zoledronic acid or placebo).

Similar summary tables will be provided that present the number and percent of patients receiving those medications by preferred term and treatment for medications prior to the first dose in the extension and during the 12-month extension period for Group 2.

9.4 Analysis of the primary variable(s)

9.4.1 Variable

This study is designed to observe the long-term safety of zoledronic acid in pediatric patients who were treated with GCs and completed the Core study CZOL446H2337 (Group 1) and those who were not enrolled onto Core study due to symptomatic vertebral fracture but enrolled in this Extension study CZOL446H2337E1 (Group 2). Particular attention will be given to general safety and renal safety.

All safety evaluations will be performed separately using SAF-1 and SAF-2. The assessment of safety will be based mainly on the frequency of adverse events, serious adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. vital signs and special tests) will also be reported.

Adverse events and serious adverse events will be summarized by presenting the number and percentage of patients in which events occur, by primary system organ class, preferred term, and severity. If a patient reports more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reports more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity. Death, serious adverse events, adverse events causing permanently discontinuation of study drug, and adverse events causing concomitant medication taken will be presented by the core treatment group.

Laboratory data will be presented with respect to three groups of laboratory tests (hematology, serum chemistry, and urinalysis).

Summary statistics (means, medians, standard deviations, ranges) of raw data and change from baseline values) will be presented. In addition, shift tables using extended normal ranges (baseline to post-baseline value) will be provided in order to compare a patient's baseline laboratory evaluation relative to each study visit. For the shift tables, the normal laboratory values will be used to evaluate whether a particular laboratory test value is normal, low, or high for each visit value relative to whether or not the baseline value is normal, low, or high. These summaries will be presented by laboratory test and by the core treatment group. For Group 1, both changes from Baseline 1 (first visit of the Core) and Baseline 2 (first visit of the Extension) will be reported. The number and percentage of patients who have lab values that meet the criteria for being clinically notable after the first dose of study medication will be presented by the Core treatment group. Patient listings that present each patient's lab profile for those tests that are outside of the clinically notable ranges will also be provided.

[redacted]

The ranges of the normal laboratory values as well as the alert values for the safety monitoring will be provided in the Laboratory Manual, which will be attached to the protocol as an exhibit.

Data from other assessments (e.g. vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. The number and percentage of patients who have vital sign values that meet the criteria for being clinically notable after the first dose of study medication will be presented by the Core treatment group. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

No statistical test will be performed for Group 2.

Details will be available in statistical analysis plan.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical analyses conducted will be descriptive with summary statistics (mean, standard deviation, median, minimum, maximum) presented by the Core treatment group for continuous variables and the number and percentage of patients presented by the Core treatment group for categorical variables for Group 1. Similar statistics will be presented for the single treatment arm for Group 2.

9.4.3 Handling of missing values/censoring/discontinuations

All patients in the SAF-1 and SAF-2 will be included to calculate the percentage of adverse events. Laboratory tests and vital signs will be summarized based on the available data.

9.4.4 Sensitivity analyses

All supportive analyses are included in Section 9.4.1.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

If otherwise not specified, the efficacy data for Group 1 will be summarized and analyzed with respect to Baseline 1 (first visit of the Core) and Baseline 2 (first visit of the Extension) will be presented by the Core treatment group and visit. However only summary statistics will be presented with respect to Baseline 2 and will be presented only for the single treatment. Data will be presented in summary tables, graphs, and listings to give an overview of the long-term efficacy maintenance. The mean, median, standard deviations, and range of each variable and its change from baseline measured on a continuous scale, will be presented by treatment group and visit. Frequency tables will be provided for categorical variables by treatment group and visit. All hypothesis tests (only for Group 1) will be evaluated at a 0.05 level of significance, and the p-values will be rounded to the 4th decimal place. Change from baseline at Month 18/24 is defined as value at Month 18/24 – value at baseline. Percentage change baseline is defined as 100 times the change from baseline divided by the baseline value. Missing values will not be imputed or replaced.

All efficacy analysis will be performed using FAS-1 and FAS-2 separately.

[redacted]

Data from all centers will be combined so that an adequate number of patients are available for analysis. Small centers will be pooled using an algorithm specified before database lock.

9.5.1.1 Change in lumbar spine areal BMD Z-score at Months 18 and 24 relative to baseline

Group 1: the percentage change in LS-BMD Z-score at Months 18 and 24 relative to both baselines between zoledronic acid and placebo (the Core treatment groups) will be evaluated using an ANCOVA model with treatment, pooled center, underlying condition treated with GCs and baseline LS-BMD Z-score as explanatory variables. The 2-sided 95% confidence intervals for the difference in least squares means between zoledronic acid and placebo will be provided.

Group 2: percentage changes in LS-BMD Z-score at Months 18 and 24 relative to Baseline 2 (Visit 8A/9) for zoledronic acid will be evaluated.

9.5.1.2 Change in lumbar spine and total body BMC at Months 18 and 24 relative to baseline

Group 1: change in BMC at the lumbar spine and total body at Months 18 and 24 relative to both baselines between zoledronic acid and placebo will be evaluated using an ANCOVA model with treatment, pooled center, underlying condition treated with GCs and baseline BMC (Visit 1 of Core study) as explanatory variables. The 2-sided 95% confidence intervals for the difference in least squares means between zoledronic acid and placebo will be provided.

Group 2: change from Baseline 2 (Visit 8A/9) in BMC at the lumbar spine and total body at Months 18 and 24 in zoledronic acid group will be presented.

9.5.1.3 Relative change in biochemical markers of bone turnover (Serum NTX, TRAP-5b, BSAP and P1NP)

Group 1: a transformation of the log ratio of treatment value vs. baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) at each visit will be used to normalize the distribution of the biochemical marker parameters. An ANCOVA model with treatment group, pooled center, underlying condition treated with GCs, and $\log_e$ (baseline value), as explanatory variables will be performed on the transformed data at each post-baseline time point.

The 2-sided 95% confidence intervals for the difference in least squares means of transformed data between zoledronic acid and placebo will be provided using the described ANCOVA model and then back transformed to the original scale.

Group 2: summary statistics and relative change from Baseline 2 (Visit 8A/9) of biochemical markers of bone turnover will be presented.

9.5.1.4 Incidence of new clinical vertebral fractures and new morphometric vertebral fractures during the 12 month extension period

Group 1: The number and percentage of patients with new vertebral fractures and new morphometric vertebral fractures during the 12 month extension period will be presented by

Core treatment group. Between-treatment differences will be evaluated using Fisher's exact test. A new morphometric vertebral fractures during the 12 month extension period is defined as a morphometric vertebral fracture present at Month 24 X-ray which is not present at the extension baseline (Core Visit 8 and Visit 1 X-rays).

Group 2: number and percentage of patients with new vertebral fractures and new morphometric vertebral fractures during the 12 month extension period will be presented.

9.5.1.5 Change in metacarpal cortical width at Month 24 relative to baseline

Group 1: the change in metacarpal cortical width at Month 12 relative to both baselines will be evaluated using an ANCOVA model with treatment, pooled center, underlying condition treated with GCs and baseline bone age as explanatory variables. The 2-sided 95% confidence intervals in difference in least squares means between zoledronic acid and placebo will be provided.

Group 2: summary statistics will be reported.

9.5.1.6 Reduction in pain from baseline

The reduction in pain from baseline by visit will be evaluated based on whether or not patients have a decrease in their Faces Pain Scale-Revised from baseline. If pain remains the same or worsens from baseline a patient will be classified as '0' and if the pain scale decreased then the patient will be classified as '1'. Whether or not a patent experiences a decrease in pain will be evaluated using a logistic regression model with treatment, pooled center, underlying condition treated with GCs and baseline pain score as explanatory variables.

Regression analysis will be carried out for Group 1 with respect to both the baselines. However the number and percentage of patients with classified status of pain with respect to baseline 2 will be reported for Group 2.

[redacted]

[redacted]

9.5.1.10 Other analyses

The following Core data for the patients in the extension FAS-1 will be summarized and analyzed similarly at Core visits to give an overall profile during the 24 months core and extension combined period:

- Change in LS-BMD Z-score relative to baseline
- Change in lumbar spine and total body BMC relative to baseline
- Relative change in biochemical markers of bone turnover (Serum NTX, TRAP-5b, BSAP and P1NP)
- Change in metacarpal cortical width relative to baseline

[redacted]

Similar analyses will be performed for FAS-2 for the zoledronic acid group.

9.5.2 Safety variables

Safety is the primary objective. Analysis of safety variables are described in Section 9.4.

9.5.3 Resource utilization

Not applicable.

[redacted]

[redacted]

[redacted]

9.5.6 Pharmacokinetics

Not applicable.

9.5.7 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

9.5.8 Biomarkers

Biochemical markers of bone turnover are secondary efficacy variables. The analyses are described in Section 9.5.1.3

9.5.9 PK/PD

Not applicable.

9.6 Sample size calculation

Participation in the Extension study will be available to all patients completing the Core study CZOL446H2337 and also for the patients who were not eligible to be enrolled to the Core study due to clinically significant back pain from vertebral fracture. Approximately 100 patients in total will be enrolled into the Extension study. Patient recruitment in Group 2 will stop once randomization in the Core study is completed.

9.7 Interim analyses

An interim analysis will not be conducted for this study.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC and a copy of the approved version must be provided to the Novartis monitor or designee after IRB/IEC approval.

[redacted]

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

[redacted]

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values and vital signs

Table 13-1 Clinical notable criteria for selected laboratory tests

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
Systolic Blood Pressure	mmHg	< 12 yrs	(70.0, 125.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		12 yrs/male	(90.0, 127.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		13 yrs/male	(90.0, 130.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		14 yrs/male	(90.0, 132.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		15 yrs/male	(90.0, 135.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		16 yrs/male	(90.0, 138.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		17 – 20 yrs/ male	(90.0, 140.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		12 yrs/female	(90.0, 126.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		13 yrs/female	(90.0, 128.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		14 yrs/female	(90.0, 130.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		15 yrs/female	(90.0, 131.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		16 yrs/female	(90.0, 132.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		17-20 yrs/ female	(90.0, 132.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
Diastolic Blood Pressure	mmHg	< 12 yrs	(40.0, 85.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		12 yrs/male	(50.0, 83.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		13 yrs/male	(50.0, 84.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		14 yrs/male	(50.0, 85.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		15 yrs/male	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		16 yrs/male	(50.0, 87.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		17-20 yrs/male	(50.0, 89.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		12 yrs/female	(50.0, 82.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		13 yrs/female	(50.0, 84.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change

[redacted]

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		14 yrs/female	(50.0, 85.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		15 yrs/female	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		16 yrs/female	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		17-20 yrs/ female	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
Heart Rate	bpm	< 12 yrs	(70.0, 130.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		≥ 12 yrs	(50.0, 120.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
Clinical Chemistry				
Blood Urea Nitrogen (serum urea)	mg/dL	≤ 20 yrs	(4.0, 24.0)	Outside the normal range
Calcium	mg/dl	> 2 - 20 yrs	(8.4, 10.3)	Outside the normal range
Chloride	mEq/L	≤ 20 yrs	(94.0, 112.0)	Outside the normal range
Creatinine	mg/dl	5 - 7 yrs/ Female	(0.2, 0.5)	Outside the normal range
		> 7- 10 yrs/ Female	(0.2, 0.6)	Outside the normal range
		> 10 - 13 yrs/ Female	(0.3, 0.7)	Outside the normal range
		> 13 - 16 yrs/ Female	(0.4, 0.8)	Outside the normal range
		> 16 - 20 yrs/ Female	(0.5, 0.9)	Outside the normal range
		5 - 7 yrs/ Male	(0.2, 0.5)	Outside the normal range
		> 7- 10 yrs/ Male	(0.3, 0.6)	Outside the normal range
		> 10 - 13 yrs/ Male	(0.3, 0.7)	Outside the normal range
		> 13 - 16 yrs/ Male	(0.4, 0.8)	Outside the normal range

[redacted]

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		> 16 - 20 yrs/ Male	(0.5, 0.9)	Outside the normal range
Magnesium	mg/dl	5 - 7 yrs/ Female	(1.7, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 7- 10 yrs/ Female	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 10 - 13 yrs/ Female	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 13 - 16 yrs/ Female	(1.6, 2.3)	Clinically significantly low, if < 1.0 mg/dL
		> 16 - 20 yrs/ Female	(1.5, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		5 - 7 yrs/ Male	(1.7, 2.4)	Clinically significantly low, if < 1.0 mg/dL
		> 7- 10 yrs/ Male	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 10 - 13 yrs/ Male	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 13 - 16 yrs/ Male	(1.6, 2.3)	Clinically significantly low, if < 1.0 mg/dL
		> 16 - 20 yrs/ Male	(1.5, 2.2)	Clinically significantly low, if < 1.0 mg/dL
Potassium	mEq/L	> 1 - 20 yrs	(3.4, 5.4)	Outside the normal range
Phosphorus	mg/dl	5 - 10 yrs	(3.2, 6.1)	Outside the normal range
		> 10 - 15 yrs	(3.1, 6.0)	Outside the normal range
		> 15 - 20 yrs	(2.2, 5.1)	Outside the normal range
Sodium	mEq/L	≤ 20 yrs	(132.0, 147.0)	Outside the normal range
ALT	U/L	5- 20 yrs	(6 , 200)	Outside the normal range
AST	U/L	5- 20 yrs	(10 , 200)	Outside the normal range
Alkaline Phosphatase	U/L	5- 20 yrs	(51 , 315)	Outside the normal range
Albumin	g/dL	5- 20 yrs	(2.9 – 4.7)	Outside the normal range
GGT	U/L	5 – 10 yrs/ Female	(0, 24)	Outside the normal range
		10 – 18 yrs/ Female	(0, 33)	Outside the normal range
		18 – 20 yrs/ Female	(4, 49)	Outside the normal range
		5 – 10 yrs/ Male	(0, 24)	Outside the normal range
		10 – 18 yrs/ Male	(0, 51)	Outside the normal range
		18 – 20 yrs/ Male	(10, 61)	Outside the normal range
Total bilirubin	µmol/L	5 - 20 yrs	(3, 21)	Outside the normal range
Hematology				

[redacted]

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
Hemoglobin	g/dl	5 - 12 yrs/ Female	(11.2, 15.5)	Outside the normal range
		> 12 - 20 yrs/ Female	(11.6, 16.4)	Outside the normal range
		5 - 12 yrs/ Male	(11.2, 15.5)	Outside the normal range
		> 12 - 20 yrs/ Male	(12.7, 18.1)	Outside the normal range
Hematocrit	%	5- 6 yrs/ Female	(35.0, 44.0)	Outside the normal range
		> 6 - 12 yrs/ Female	(34.0, 44.0)	Outside the normal range
		> 12 - 20 yrs/ Female	(34.0, 48.0)	Outside the normal range
		5 - 6 yrs/ Male	(33.0, 43.0)	Outside the normal range
		> 6 - 12 yrs/ Male	(34.0, 44.0)	Outside the normal range
		> 12 - 20 yrs/ Male	(39.0, 54.0)	Outside the normal range
RBC	10^6/uL	> 3 - 6 yrs/ Female	(4.1, 5.2)	Outside the normal range
		> 6 - 12 yrs/ Female	(3.7, 6.0)	Outside the normal range
		> 12 - 20 yrs/ Female	(4.1, 5.6)	Outside the normal range
		5- 6 yrs/ Male	(4.1, 5.3)	Outside the normal range
		> 6 - 12 yrs/ Male	(3.7, 6.0)	Outside the normal range
		> 12 - 20 yrs/ Male	(4.5, 6.4)	Outside the normal range
WBC	10^3/uL	5- 6 yrs	(4.00, 12.00)	Outside the normal range
		> 6 - 12 yrs	(4.35, 13.65)	Outside the normal range
		> 12 - 20 yrs	(4.35, 13.15)	Outside the normal range
Lymphocytes	10^3/uL	5- 6 yrs/ Female	(1.50, 8.00)	Outside the normal range
		> 6 - 12 yrs/ Female	(1.15, 6.65)	Outside the normal range
		> 12 - 20 yrs/ Female	(0.95, 5.25)	Outside the normal range
		5- 6 yrs/ Male	(1.50, 8.00)	Outside the normal range
		> 6 - 12 yrs/ Male	(1.15, 6.65)	Outside the normal range
		> 12 - 20 yrs/ Male	(0.95, 5.25)	Outside the normal range
Neutrophils	10^3/uL	5- 6 yrs/ Female	(1.00, 9.00)	Outside the normal range

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		> 6 - 12 yrs/ Female	(1.35, 8.15)	Outside the normal range
		> 12 - 20 yrs/ Female	(1.65, 8.15)	Outside the normal range
		5- 6 yrs/ Male	(1.35, 8.65)	Outside the normal range
		> 6 - 12 yrs/ Male	(1.35, 8.65)	Outside the normal range
		> 12 - 20 yrs/ Male	(1.65, 8.15)	Outside the normal range
Eosinophils	10^3/uL	< 20 yrs	(0.00, 0.57)	Outside the normal range
MCV	fL	5 – 6 yrs/ Female	(74, 89)	Outside the normal range
		6 – 12 yrs/ Female	(76, 93)	Outside the normal range
		12 – 20 yrs/ Female	(79, 98)	Outside the normal range
		5 – 6 yrs/ Male	(74, 89)	Outside the normal range
		6 – 12 yrs/ Male	(76, 93)	Outside the normal range
		12 – 20 yrs/ Male	(79, 96)	Outside the normal range
MCHC	g/L	5 - 20 yrs	(310, 380)	Outside the normal range
RBC Morph		5 - 20 yrs	Normal	Outside the normal range
Urinalysis		5 – 20 yrs	Normal	Outside the normal range

Lab normal ranges provided by Covance Labs

[redacted]

14 Appendix 2: Tanner Staging

Male patients - Development of external genitalia

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length; these has been further growth of testes and scrotum

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin

Stage 5: Genitalia adult in size and shape

Female patients - Breast development

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

The girls will be asked at each visit if they had begun to menstruate.

Male and female patients - Pubic hair

Stage 1: Pre-adolescent (can see velus hair similar to abdominal wall).

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia or the base of the penis.

Stage 3: Considerably darker, coarser and more curled hair. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by is still considerably smaller than in most adults. There is no spread to the medial surface of thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs (about age 15 years).

(Marshall and Tanner 1970; Marshall and Tanner 1969)

[redacted]

15 Appendix 3: Faces Pain Scale

Faces Pain Scale – Revised (FPS-R)

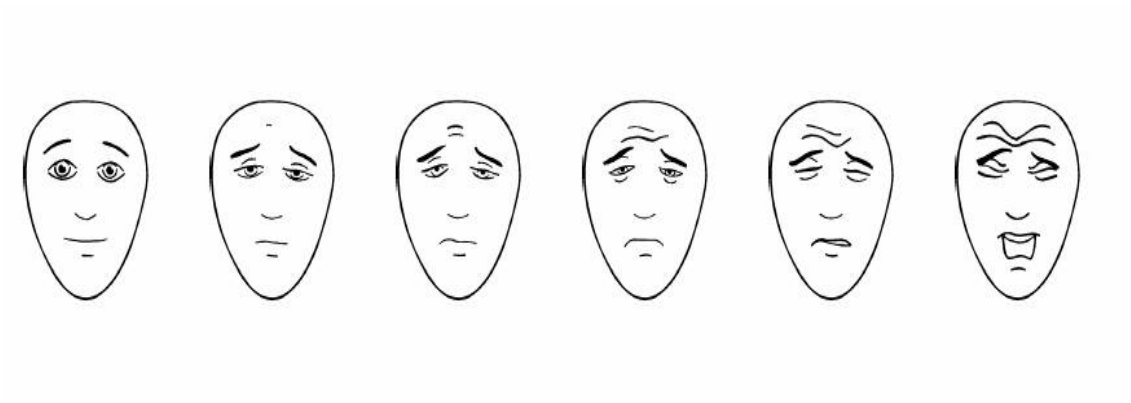
From *Pediatric Pain Sourcebook*, **www.painsourcebook.ca**
Version: 7 Aug 2007 CL von Baeyer

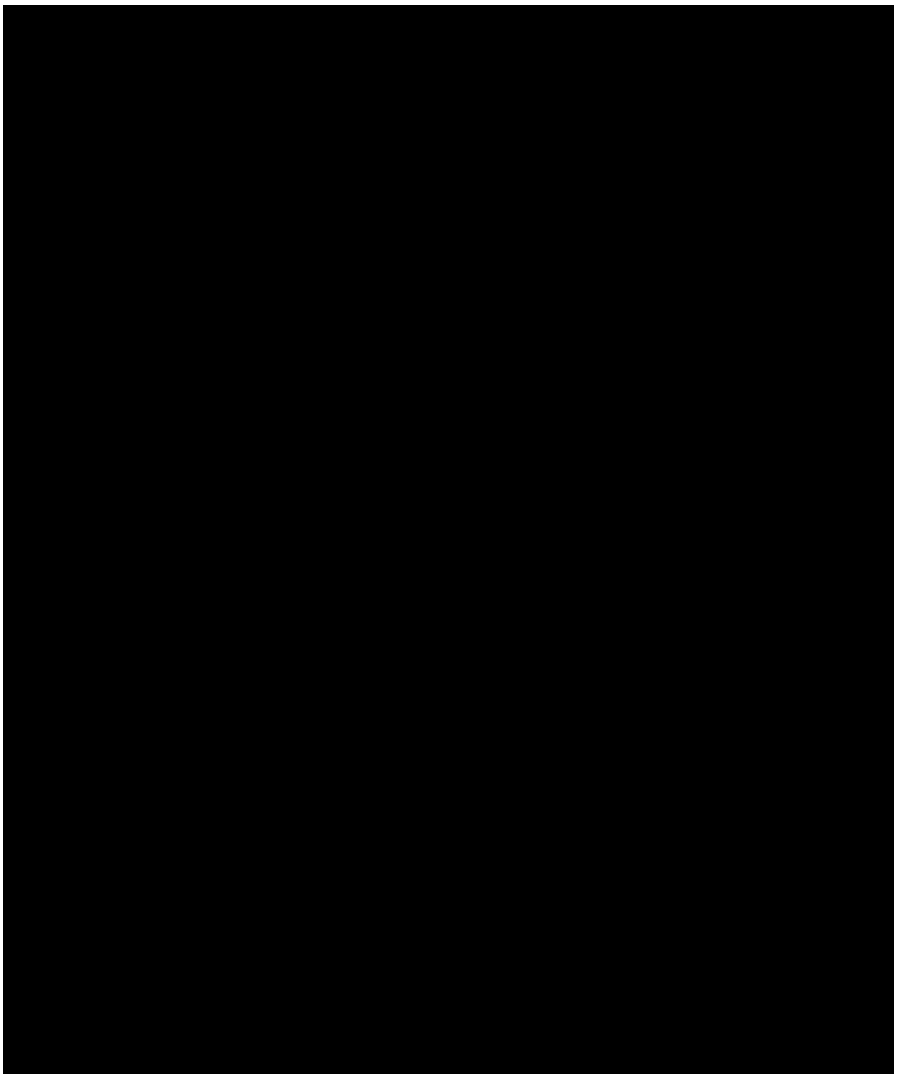
In the following instructions, say "hurt" or "pain," whichever seems right for a particular child.

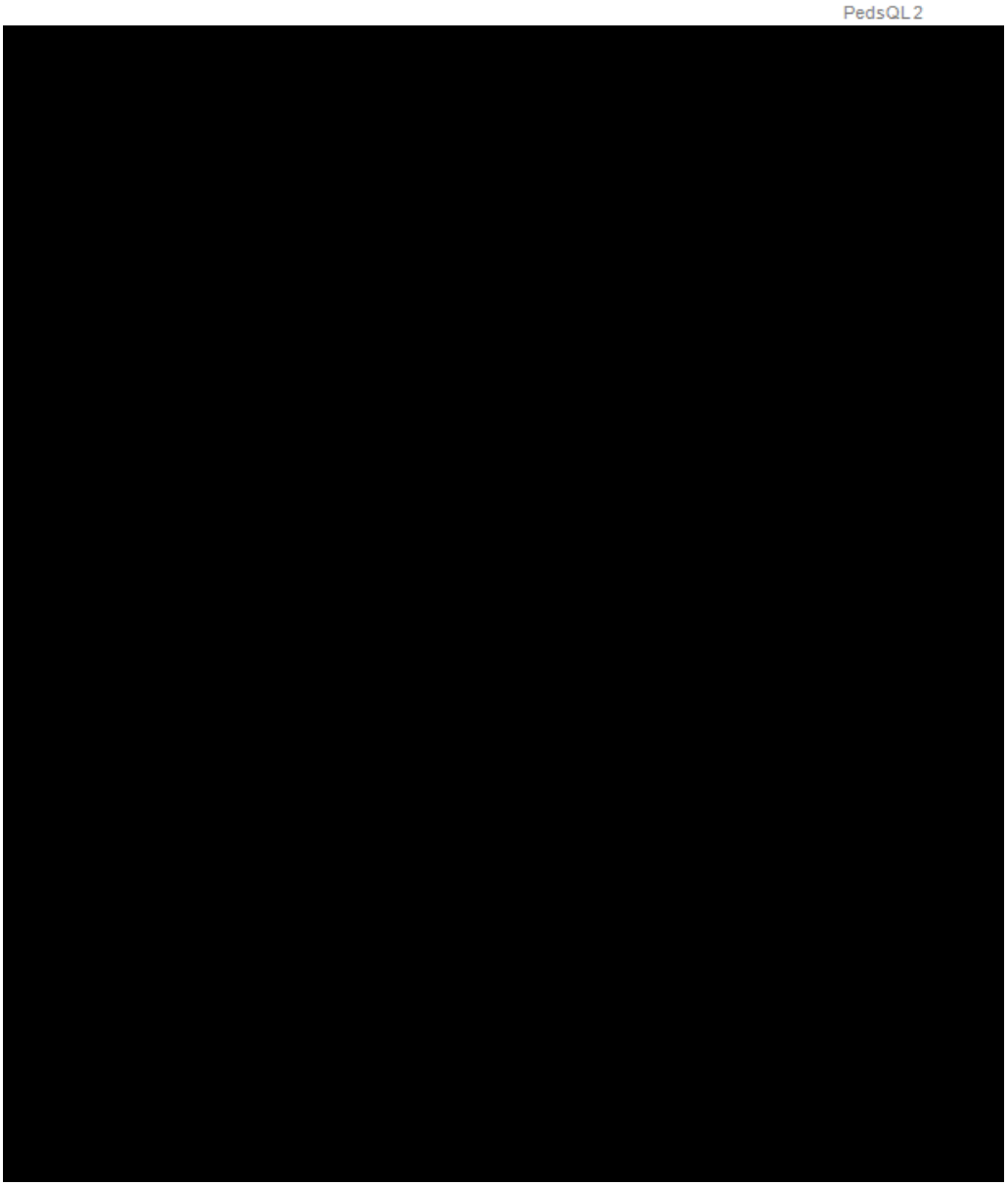
"These faces show how much something can hurt. This face *[point to left-most face]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to right-most face]* **– it shows very much pain. Point to the face that shows how much you hurt** [right now]**."**

Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so '0' = 'no pain' and '10' = 'very much pain.' Do not use words like 'happy' and 'sad'. This scale is intended to measure how children feel inside, not how their face looks.

0 2 4 6 8 10







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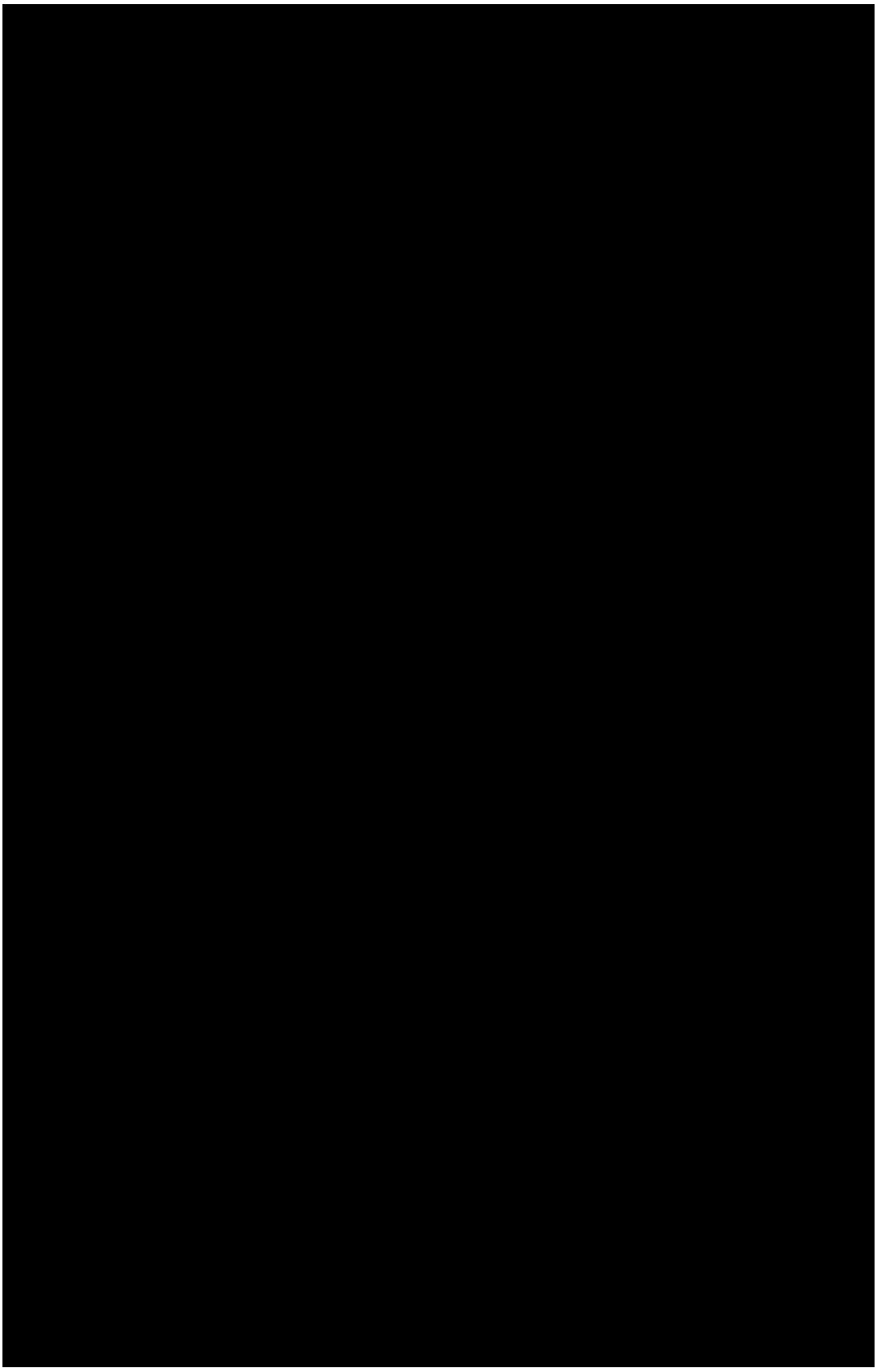

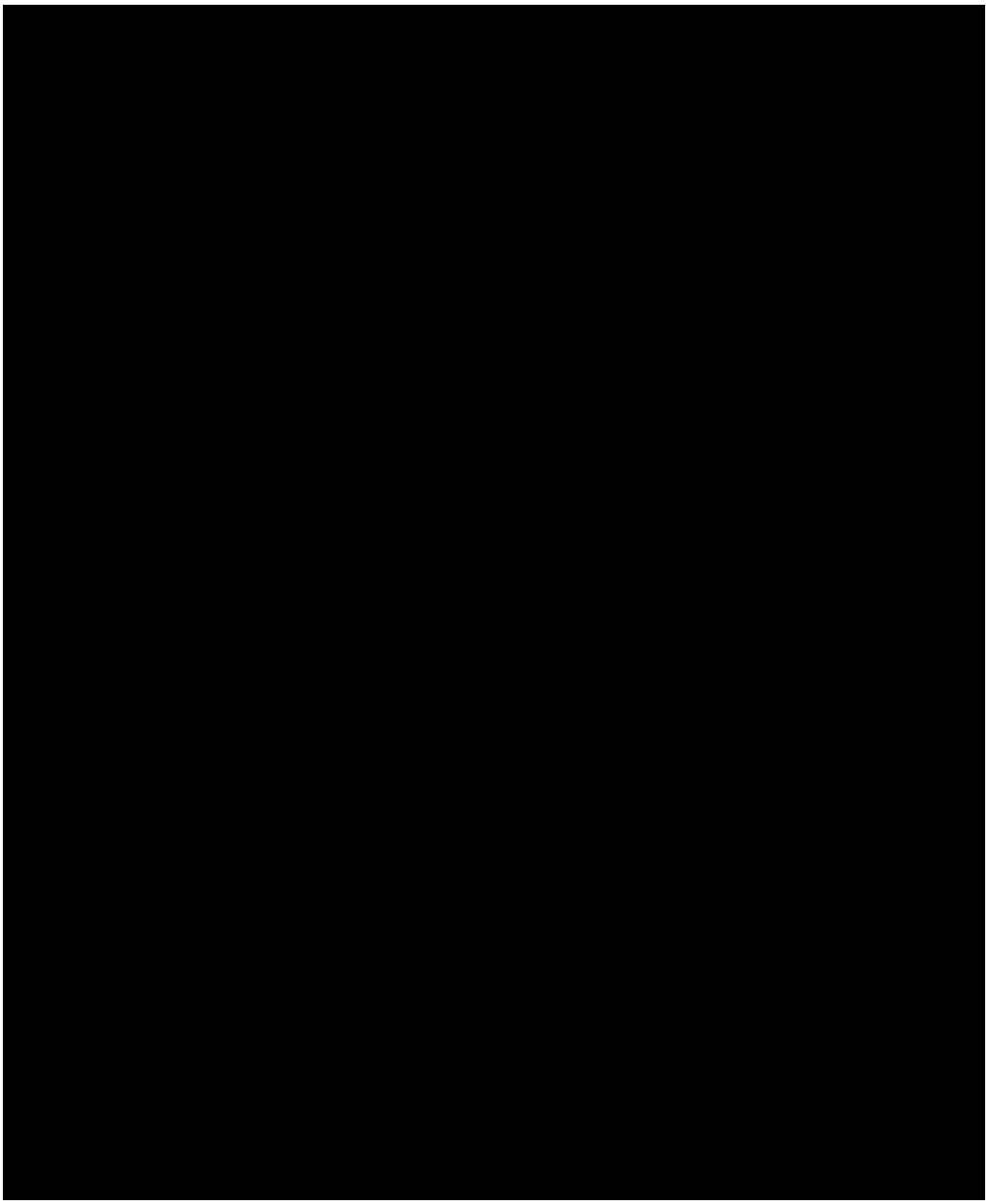

18 Appendix 6: Other subtypes of osteoporosis in children

Allowed	Disallowed
Cerebral palsy	Leukemia or lymphoma
Becker's dystrophy	Solid tumors
Diabetes mellitus	Thalassemia
Celiac disease	Mastocytosis
Cystic fibrosis	Hypogonadism
	Growth Hormone deficiency
	Hyperthyroidism
	Vitamin D deficiency
	Anorexia nervosa
	Chronic kidney disease
	Secondary hyperparathyroidism
	Organ transplant recipient
	Biliary atresia
	Female athletic triad
	Spinal cord injury

19 Appendix 7: Amount of blood to-be Drawn

Only the laboratory samples which apply to the Visits in the Extension study are included.

Period								
Visit	**8A**	**9**	**10**	**11^{T}**	**12**	**13**	**14^{T}**	**15/EOS and TD and/or PSW**
Day	**-60 to -30**	**0**	**10 days after V9**	**90 days after V9**	**180 days after V9**	**190 days after V9**	**270 days after V9**	**365 days after V9**
Week	**-8 to-4**			**12**	**26**		**39**	**52**
Central Laboratory - All Patients								
Hematology	3 mL				3 mL			3 mL
Chemistry	3.5 ml [6 mL (Australia only)]				3.5 mL			3.5 mL [6 mL (Australia only)]
Renal & Ca monitoring[1]			3.5 mL			3.5 mL		
Serum pregnancy[2]	2.5mL							2.5mL
Specialized serum bone-markers		3 mL[3]			3 mL			3 mL
Vitamin D	2.5 mL							2.5 mL
Local Laboratory - All Patients								
Serum creatinine		2.5 mL						
Serum ionized calcium		2.5 mL						
TOTALS	**14 mL [16.5mL (Australia only)]**	**8 mL**	**3.5mL**	**-**	**9.5mL**	**3.5mL**	**-**	**14.5 mL [17.0mL (Australia only)]**

[1]Serum creatinine, urea, electrolytes, calcium, magnesium, phosphorus only

[2]Only in girls of child bearing potential

[3]Only repeated in Group 1 if more than 30 days after Visit 8 of the Core study

[redacted]