NOVARTIS

Clinical Development

ZOL446 zoledronic acid

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

RAP Module 3 – Detailed Statistical Methodology

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Statistical methods planned in the protocol and determination of sample size

Statistical and analytical plans

This document describes the statistical methodology for analyses of efficacy and safety in Study CZOL446H2337E1. 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 glucocorticoids. To ensure adequate intake of calcium and vitamin D, all children enrolled in this study will be provided with conservative intervention (diet with or without supplements), regardless of their treatment assignment.

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.

The secondary objectives include:
1. To evaluate the change from core baseline in LS-BMD Z-score at Month 18 and 24 by core treatment group.
2. To evaluate the change from core baseline in LS and total body BMC at Month 18 and 24 by core treatment group.
3. To evaluate the change from core baseline 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 core baseline 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 core baseline in 2nd metacarpal cortical width at month 24 by core treatment group.
8. To evaluate the change from core baseline in bone age and 2nd metacarpal cortical width at month 24 by core treatment group.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

General considerations

Baseline definition

Unless otherwise specified, the following general rules will be applied for defining baseline.

- Core baseline: core baseline is defined as the last non-missing measurement on or prior to the date of first study drug infusion in core study.

- Extension baseline: extension baseline is defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study. If no extension assessments are available on or prior to the first drug infusion in the extension study, the last assessment in core study will be used instead.

Study day

The general rules for calculating the study day are as follows:

Core Study Day:

- If the event date occurs before the first infusion date in core study, then the core study day is defined as the date of the event minus the first infusion date in core study;
- If the event date occurs after the first infusion date (inclusive) in core study, then the core study day is defined as the date of the event minus the first infusion date in core study plus 1.

Extension Study Day:

- If the event date occurs before the first infusion date in the extension study, then the extension study day is defined as the date of the event minus the first infusion date in the extension study;
- If the event date occurs after the first infusion date (inclusive) in the extension study, then the extension study day is defined as the date of the event minus the first infusion date in the extension study plus 1.

Visit schedule

Summaries by visit will be based on the visits collected on the CRF and no visit window will be applied. Only scheduled visits will be included in the summary, unless specified otherwise.

Subjects and treatments

The following analysis sets will be defined:

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

Full Analysis Set (FAS)

FAS 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. Patients will be analyzed according to the treatment they were assigned to at the core study randomization.

All efficacy analyses will be performed using FAS.

Safety Analysis Set (SAF)

SAF 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 core study if they received at least one dose of zoledronic acid in core study.

All safety analyses will be performed using SAF.

Pooling of centers

Centers will be pooled into four regions based on the similarity of clinical practice for randomization and analysis purpose. The regions are as follows:

- North America region
  - United States
  - Canada
- EMEA America region
  - Belgium
  - Finland
  - Germany
  - Hungary
  - Italy
  - Poland
  - Romania
  - Russia
  - South Africa
  - Sweden
  - Turkey
  - United Kingdom
- Latin America region
  - Brazil
- APAC region
  - Australia
  - New Zealand

Patient disposition

The number and percentage of patients in the following categories will be tabulated and listed by core treatment group within the FAS:

- Completed extension study
- Discontinued extension study

Discontinuations will be further broken down by reason.

In addition, recruitment will be summarized by country and then center.

A complete listing of patient disposition will be provided for FAS.

Demographic information and reasons for discontinuing will be provided in a listing for screen failure patients.

Protocol deviations

Protocol deviations will be summarized in a table and will be listed for all FAS patients by core treatment group. The number of patients with any protocol deviation will also be summarized.

Patients in each analysis set

The number and percentage of patients in each analysis set (FAS, SAF) will be summarized by core treatment group. Listing of these analysis sets will be provided as well.

Demographic and other baseline characteristics

Demographic variables and baseline characteristics will be summarized at both core and extension baselines.

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.

Descriptive statistics for the following demographic variables and baseline characteristics will be summarized for core period by core treatment group using FAS. Similar summaries will be performed for extension period but sex, race, ethnicity and non-vertebral fractures will be excluded. Vertebral morphometry will be removed as well because it is no longer an endpoint in the extension period.

Age at extension enrollment (years)

- Age group at extension enrollment (> = 6 years to <= 9 years; >=10 years to <=19 years)
- Sex
- Race
- Ethnicity

- Weight (kg)
- BMI (kg/m^2). The baseline standing height will be used in BMI calculation.
- Tanner evaluation (breast development, genital stage, pubic hair, and whether menarche has occurred)
- Lumbar spine BMD Z-score
- Lumbar spine BMD Z-score category
    - <= -2.0
    - > -2.0 to <= -1.0

  - > -1.0 to <= -0.5
- Lumbar spine Bone Mineral Content (BMC) (g)
- Total body BMC (g)
- Serum 25-hydroxy vitamin D (nmol/L)
- Serum calcium level (mmol/L)
- Serum NTX (nmol BCE/L)
- Serum TRAP-5b (U/L)
- Serum BSAP (ng/mL)
- Serum P1NP (ng/mL)
- Vertebral morphometry
- Non-vertebral fractures
- Metacarpal cortical width (mm)

[redacted]

- Pain score

In addition, the core baseline comparability between core treatment groups will be evaluated for demographic and other baseline characteristics variables. Categorical variables will be evaluated using Fisher's exact test, and the continuous variables will be evaluated using a Wilcoxon rank-sum test.

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 primary and secondary efficacy variables.

All demographic and baseline characteristic data will be listed as presented above.

Disease-related background information

Disease-related background and historical information will be summarized by type of disease (Duchenne muscular dystrophy, rheumatic condition or inflammatory bowel disease) and by type (as specified in the CRF) within rheumatic condition and inflammatory bowel disease. Counts and percentages will be provided by core treatment group.

- Rheumatic conditions:
  - Systemic onset Juvenile Idiopathic Arthritis (JIA)
  - Polyarticular rheumatoid factor positive JIA
  - Polyarticular rheumatoid factor negative JIA
  - Psoriatic arthritis JIA
  - Enthesitis-related arthritis JIA

  - Oligoarticular arthritis JIA
  - Unclassified JIA
  - Systemic lupus erythematosus (SLE)
  - Juvenile dermatomyositis
  - Scleroderma (generalized or localized)
  - Overlap syndromes (including mixed connective tissue disease)
  - Sjogren's syndrome
  - Giant cell (temporal) arteritis
  - Takayasu's arteritis
  - Polyarteritis nodosa
  - Wegener's granulomatosis
  - Churg-Strauss syndrome
  - Microscopic polyangiitis
  - Essential cryoglobulinemic vasculitis
  - Cutaneous leukocytoclastic angiitis
  - Behcet's disease
  - Other vasculitis
- Inflammatory bowel disease:
  - Crohn's disease
  - Ulcerative colitis
- Duchenne muscular dystrophy
- Others

Frequency counts will be provided by core treatment group as well as the total in a table. A listing will also be generated.

Relevant medical history and current medical conditions

The relevant medical history/current medical conditions for the extension study include relevant medical history/current medical conditions recorded in 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. 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. A patient with multiple occurrences of a medical condition/adverse event for a preferred term or system organ class is counted only once in each specific category. A corresponding listing will also be provided.

All analyses will be performed separately based on the FAS.

Extent of exposure

A summary table will be provided for the exposure to study medication, including number of patients with any infusion, duration for 1st infusion, duration for 2nd infusion, volume for 1st infusion, and volume for 2nd infusion.

Prior/concomitant medications and significant non-drug therapies

The number and percentage of patients receiving prior and concomitant medications and significant non-drug therapies will be summarized by core treatment group and preferred term according to the WHO Drug Reference List employing the Anatomical Therapeutic Chemical (ATC) classification system. Prior medications are defined as those ending prior to the first infusion of study drug in the extension study; medications ending on or after the first infusion of study drug in the extension study are concomitant medications. Prior medications will be presented separately from concomitant medications. The summary table will first be sorted by ATC class alphabetically and then by preferred term in decreasing order of frequency with respect to usage in the zoledronic acid group.

Furthermore, summarizations by ATC class will be provided with regard to a group of specified concomitant medications/significant non-drug therapies, which include osteoporosis-related medications, nutritional supplements, and glucocorticoids. The summary table will be sorted by ATC class in decreasing order of frequency in the zoledronic acid group.

Missing date convention

If the medication start and end dates are recorded in the CRFs, medications that start on or prior to the first infusion in the extension study and end on or after the first infusion in the extension study including ongoing at end of the extension study were included in both prior to and after start of study drug administration in the study, respectively.

Partial medication start dates will be imputed as follows:

- Only day is missing: the partial start date will be imputed using 15MONYYYY if the month and year indicate that the medication started prior to the first infusion of extension study medication or 01MONYYYY if the month and year indicate that the medication started on or after the first infusion of extension study medication.
- Both day and month are missing: the partial start date will be imputed using 01JULYYYY if the year indicates that the medication started prior to the first infusion of extension study medication or max(01JANYYYY, treatment start date+1) if the year indicates that the medication started on or after the first infusion of extension study medication.

Partial medication end dates will be imputed as follows:

- Only day is missing: the partial end date will be imputed using the last date of the month.
- Both day and month are missing: the partial end date will be imputed as December 31 if the end year is prior to the year of first infusion of extension study medication or one day after the last extension study infusion date if end year is equal to or after the year of first infusion of extension study medication.

Efficacy evaluation

Analyses of all efficacy endpoints will be performed on FAS. All relevant efficacy measurements will be presented in listings. Core study measurements will be listed as well for analyses that require both core and extension study measurements.

Analysis for efficacy variables

If otherwise not specified, the efficacy data will be summarized and analyzed with respect to core baseline only and will be presented by the core treatment group and visit. The mean, median, standard deviations, and range of each variable and its change from baseline measured on a continuous scale, will be presented by core treatment group and visit. Number and percentage of patients will be presented for categorical variables by core treatment group and visit. All hypothesis tests 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 X is defined as value at Month X - value at baseline. Percentage change from baseline is defined as 100 times the change from baseline divided by the baseline value. Missing values will not be imputed or replaced.

The efficacy variables and their analysis methods are described below.

- **Percent change in lumbar spine areal BMD Z-score at Months 18 and 24 relative to baseline, zoledronic acid group vs. placebo**

The percent change in LS-BMD Z-score at Months 18 and 24 relative to core baseline between zoledronic acid and placebo (the core treatment groups) will be evaluated using an ANCOVA model with core treatment, pooled center, underlying condition treated with glucocorticoids and core baseline LS-BMD Z-score as explanatory variables and pooled centers as random effect.

From the model, core treatment difference in least squares means between zoledronic acid group vs. placebo group will be estimated and presented together with two-sided 95% CI and p-value. In the same table, the LS means and standard errors for percent change from baseline in LS-BMD Z-score at Month 18 and Month 24 will be presented for each core treatment group. Descriptive statistics will also be shown for baseline, Month 18 and Month 24 visits.

- **Change in lumbar spine and total body BMC at Months 18 and 24 relative to baseline, zoledronic acid group vs. placebo**

The change in BMC at the lumbar spine and total body at Months 18 and 24 relative to core baseline between zoledronic acid and placebo will be evaluated using an ANCOVA model with core treatment, pooled center, underlying condition treated with glucocorticoids and core baseline BMC as explanatory variables and pooled centers as random effect.

From the model, core treatment difference in least squares means between zoledronic acid group vs. placebo group will be estimated and presented together with two-sided 95% CI and p-value. In the same table, the LS means and standard errors for change from baseline in lumbar spine or total body BMC at Month 18 and Month 24 will be presented for each core treatment group. Descriptive statistics will also be shown for baseline, Month 18 and Month 24 visits.

- **Relative change in biochemical markers of bone turnover (Serum NTX, TRAP-5b, BSAP and P1NP) at Months 18 and 24 relative to baseline, zoledronic acid group vs. placebo**

The analysis of changes from core baseline to Month 18 and Month 24 in the biochemical markers, serum NTX, TRAP-5b, BSAP, and P1NP will be performed as follows: a transformation of the $\log_e$ ratio of post-baseline value vs. baseline value at each visit will be used to normalize the distribution of the biochemical marker parameters. An ANCOVA model with core treatment group, pooled centers, underlying condition treated with glucocorticoids, and $\log_e$ (core baseline value) as explanatory variables and pooled centers as random effect will be used on the transformed data at each post-baseline time point.

From the model, core treatment difference in least squares means between zoledronic acid group vs. placebo group in log scale will be estimated and presented together with two-sided 95% CI and p-value. Estimated core treatment difference and two-sided 95% CI will then be transformed back to the original scale and displayed on the table. In the same table, the LS means and standard errors in both log scale and original scale for change from baseline for the biomarkers at Month 18 and Month 24 will be presented for each core treatment group. Descriptive statistics will also be shown for baseline, Month 18 and Month 24 visits in both original scale and log scale. A plot will be generated for each biochemical marker over core and extension study period respectively.

- **Incidence of new vertebral fractures and new morphometric vertebral fractures during the 12 month extension period, zoledronic acid group vs. placebo**

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. New vertebral fractures are defined as fractures of Genant grade 1 or higher that occur at lumbar or thoracic spine from first extension dose infusion to the end of the extension study. 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 extension baseline.

- **Change in 2nd metacarpal cortical width at Month 24 relative to baseline, zoledronic acid group vs. placebo**

The change in 2nd metacarpal cortical width at Month 24 relative to core baseline will be evaluated using an ANCOVA model with core treatment, pooled center, underlying condition treated with glucocorticoids and core baseline bone age as explanatory variables and pooled centers as random effect.

From the model, core treatment difference in least squares means between zoledronic acid group vs. placebo group will be estimated and presented together with two-sided 95% CI and p-value. In the same table, the LS means and standard errors for change from baseline in 2nd metacarpal cortical width at Month 24 will be presented for each core treatment group. Descriptive statistics will also be shown for baseline and Month 24 visits.

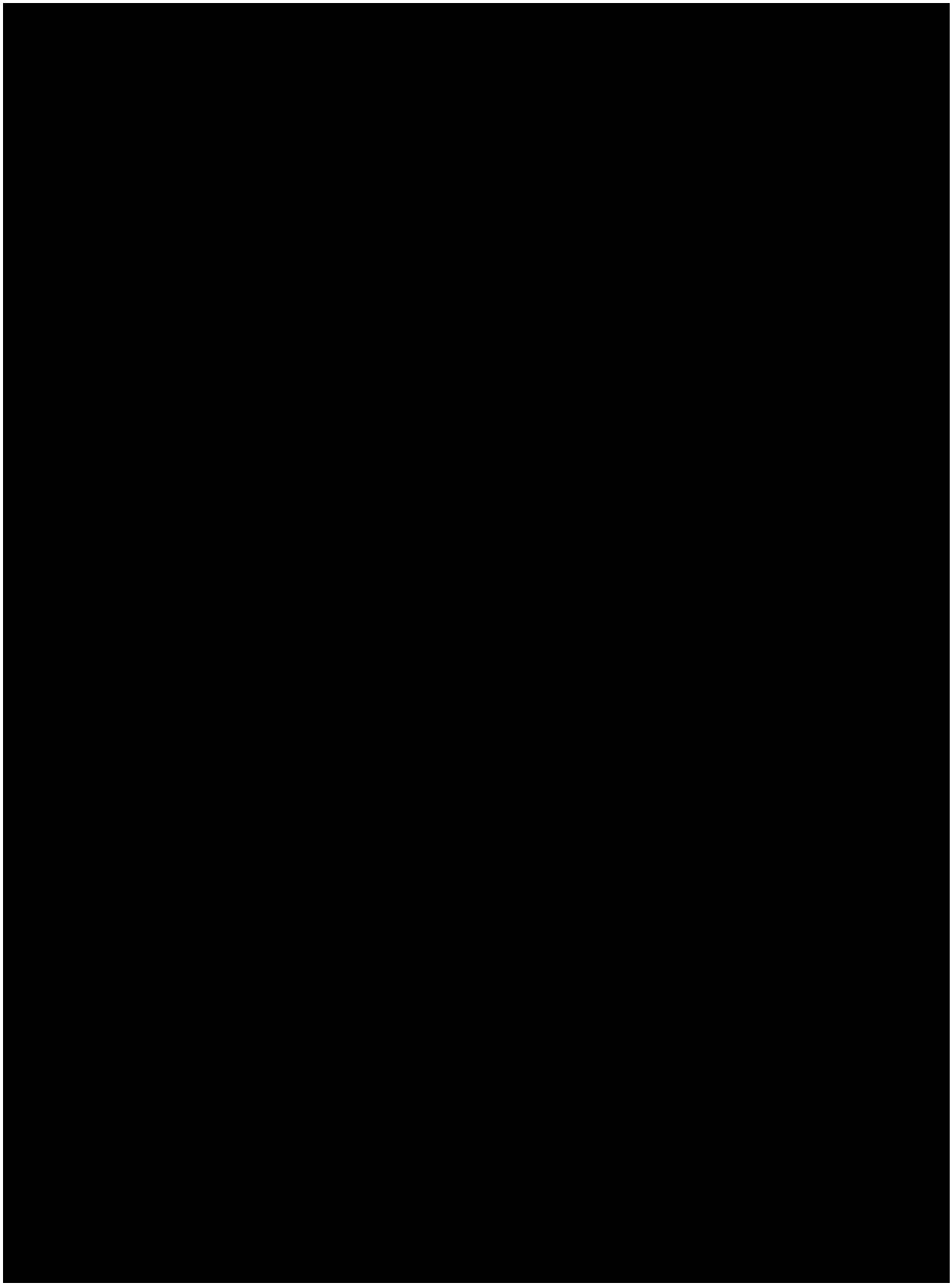
Above analysis will be carried out with respect to both baselines (core baseline as well as extension baseline).

- **Reduction in pain from baseline, zoledronic acid group vs. placebo**

Pain is assessed using Faces Pain Scale-Revised (FPS-R) at first infusion in the extension study (Visit 9), Month 15, 18, 21 and 24, which ranges from 0 (No Pain) to 10 (Very Much Pain). Details of FPS-R can be found in Appendix section "Faces Pain Scale" in the protocol.

The reduction in pain from core baseline by visit will be evaluated based on whether or not patients have a decrease in their FPS-R 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 core treatment, pooled centers, underlying condition treated with glucocorticoids and baseline pain score as explanatory variables.

Regression analysis will be carried out with respect to both baselines (core baseline as well as extension baseline).



[redacted]

Other analyses

The following core data for the patients in the extension FAS 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 2nd metacarpal cortical width relative to baseline

[redacted]

Pharmacokinetic (PK) evaluations

Not applicable.

Safety evaluation

All safety analyses will be performed on the SAF. The assessment of safety will include adverse events, laboratory tests (hematology, blood chemistry and urine values), vital signs, and tanner staging score. Patient listings will be provided for all safety data.

Analysis for the primary objective

The primary objective 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.

Adverse events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject after starting the study drug even if the event is not considered to be related to study drug. Treatment-emergent adverse events will be defined as adverse events that were absent prior to the first infusion in the extension study and occurred after the first infusion during extension study or that were present prior to the first infusion in the extension study and occurred at increased severity after the first infusion during extension study. Summarization will be based on treatment-emergent adverse events.

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA). The number and percentage of patients who report adverse events will be summarized by treatment according to the primary system organ class and preferred term. If a patient reports more than one adverse event within the same primary system organ class (preferred term), the patient will be counted only once with the greatest severity at the system organ class (preferred term) level. Serious adverse events and selected adverse events will be presented by core treatment group code. Listing of these events will be provided.

Adverse event tables will be sorted alphabetically by system organ class and then according to decreasing frequency of preferred term in the zoledronic acid group. If only system organ classes or preferred terms are presented, these will be sorted according to the decreasing frequency in the zoledronic acid group.

The following sets of adverse events will be summarized:

- All adverse events (by primary system organ class and preferred term)
- Adverse events suspected to be related to study drug (by primary system organ class and preferred term)
- Adverse events that occurred after first infusion in the extension study and before second infusion in the extension study (by primary system organ class and preferred term)
- All adverse events (by primary system organ class, preferred term and maximum severity)

- All adverse events (by underlying disease group, primary system organ class and preferred term)
- Adverse events that result in death (by primary system organ class and preferred term)
- Serious adverse events (by primary system organ class and preferred term)
- Adverse events causing permanent discontinuation of study drug (by primary system organ class and preferred term)
- Adverse events causing concomitant medication taken (by primary system organ class and preferred term)
- Adverse events associated with a change in renal function (by preferred term). Time from first infusion in the extension study to first adverse event associated with a change in renal function will be presented separately.

[redacted]

- Hypocalcemia adverse events (by preferred term). Time from first infusion in the extension study to first hypocalcemia occurrence based on AE and central lab calcium will be presented separately.

Incidence of risk as defined in the case retrieval strategy, during the study period, will be summarized by core treatment group, and MedDRA levels. Relative risk of zoledronic acid group vs. placebo (core treatment A vs. core treatment B) will be presented along with corresponding 95% confidence intervals using the Mantel-Haenszel test.

Missing date convention

Please note that for below AE missing date imputation, all infusion dates or treatment dates refer to those in the extension study.

Partial AE start dates: If an AE start date is completely missing, then no imputation is implemented. AEs with completely missing start dates will be treated as treatment emergent. If the year of an AE start date is missing but the month is available, then the date will be imputed as the start date of the first study drug infusion + 1.

If the year is not missing and the month is missing, then date will be imputed as follows:

- If the AE year is less than the year the study drug infusion was administered, then July 1st of the year will be used.
- If the AE year is equal to the year the study drug infusion was administered, then the start date will be imputed as the start date of the first study drug infusion + 1.
- If the AE year is greater than the year the study drug infusion was administered, then the Jan 1st of the year will be used.

If the year is available and the month is non-missing, then the following rules will be applied relative to the month that study drug treatment was given:

- If the month in which the AE started is less than the month that the study drug infusion was administered, then:
    - If the AE year is less than or equal to the year the study drug infusion was administered, then the 15th day of the month will be used.
    - If the AE year is greater than the year the study drug infusion was administered, then the maximum of the first day of the month and the treatment start date + 1 will be used.
- If the month in which the AE started is equal to the month that the study drug infusion was administered, then:
    - If the AE year is less than the year the study drug infusion was administered, then the 15th day of the month will be used.
    - If the AE year is greater than or equal to the year the study drug infusion was administered, then the maximum of the first day of the month and the treatment start date + 1 will be used.
- If the month in which the AE started is greater than the month that the study drug infusion was administered, then:
    - If the AE year is less than the year the study drug infusion was administered, then the 15th day of the month will be used.
    - If the AE year is greater than or equal to the year the study drug infusion was administered, then the maximum of the first day of the month and the treatment start date + 1 will be used.

In case that the AE end date was completed, the AE start date imputed as above was after the AE end date, the AE start date was re-imputed using the AE end date.

Partial AE end dates: There is no STL convention to impute partial AE end date. Partial AE end date was imputed using (a) the last date of the month if only the day of AE end date is missing, (b) December 31 if only the year of AE end date is present. If a patient dies and the imputed end date is after the date of death, the date of death was imputed as the AE end date. When a patient dies, the end date for ongoing AEs was imputed using the date of death.

Adverse events associated with change in renal function

Adverse events associated with change in renal function are defined based on predefined search list which describe a clinically significant change in renal function. A search of the clinical trial database will occur based on this pre-specified list of MedDRA preferred terms. These adverse events will be summarized by preferred term. In addition, the event rate will be summarized. The hazard ratio, 95% CI and p-value based on a Cox proportional hazards model with core treatment and underlying condition treated with glucocorticoids (stratification factor) as explanatory variables will be presented. Meanwhile, to aid in the assessment that the treatment differences are not inconsistent across the strata, the treatment-by-stratification interaction term will be added to the model described above. P-value for the interaction term will be reported. If a patient experiences an adverse event associated with change in renal function, the event time is defined as the earliest of all events if there are

multiple. Otherwise, a patient is considered censored at the last contact date. Kaplan-Meier estimates will be plotted over time if at least 10% of overall population has experienced the event.

Patient listings will be provided for all adverse events associated with clinically significant change in renal function.

Hypocalcemia adverse events and laboratory events

Hypocalcemia adverse events will be searched based on preferred term and summarized. Patients with reported laboratory measurements associated with a signal of hypocalcemia will be summarized by visit. Lab hypocalcemia (low serum calcium levels) is present if the value of serum calcium from central lab is less than the lower limit of normal range provided by the central lab.

The number and percentage of patients who met these criteria will be summarized by core treatment group and overall.

The hazard ratio, 95% CI and p-value based on a Cox proportional hazards model with core treatment and underlying condition treated with glucocorticoids (stratification factor) as explanatory variables will be presented. Meanwhile, to aid in the assessment that the treatment differences are not inconsistent across the strata, the treatment-by-stratification interaction term will be added to the model described above. P-value for the interaction term will be reported. If a patient experiences a hypocalcemia and low calcium value based on the central lab, the event time is defined as the earlier of these events. Otherwise, a patient is considered censored at the last contact date. Kaplan-Meier estimates will be plotted over time if at least 10% of overall population has experienced the event.

Patient listings will be provided for all adverse events associated with hypocalcemia.

Laboratory parameters

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

- Hematology parameters: 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.

- Serum chemistry parameters: non-fasting 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), calcium; and Glomerular Filtration Rate (GFR).

- Urinalysis parameters: amorphous crystals, urine bilirubin, urine blood, calcium oxalate crystals, urine color, urine glucose, urine ketone, urine leukocytes, urine

nitrite, pH, urine protein dipstick, specific gravity, urine urobilinogen, and WBC Casts (Urine) /LPF.

GFR will be calculated using the Schwartz equation at all visits where serum creatinine will be measured (Visits 9, 10, 12, 13 and 15) by the Central Laboratory.

GFR (mL/min/1.73 m^2) =k[Height (m)]/Serum Creatinine (mg/dL), where k=0.41

Descriptive summary statistics for both baselines, each post-baseline visit, and change from both baselines to each visit will be presented by laboratory test group and core treatment group. Note that if either the baseline or the post-baseline value is missing, then the calculation of change from baseline will also be missing.

Also, shift tables for hematology and serum chemistry 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, including changes from both baselines, will be presented by laboratory test group and core treatment group.

In addition, summary tables will be presented based on both baselines for the incidence rates of newly occurring clinically notable laboratory abnormalities, where patients will be counted if they have normal or missing baseline value and with at least one post-baseline assessment satisfying the clinically notable criteria. Incidence rates of newly occurring hypocalcemia (based on central lab) by visit will be summarized similarly for patients who have normal or missing baseline level of serum calcium and clinically notable abnormal serum calcium level at each scheduled post-baseline visit. The definition of clinically notable laboratory abnormalities can be found in Appendix section "Clinically notable laboratory values and vital signs" in the protocol.

Furthermore, summary tables will be provided for the number and percentage of patients with liver enzyme abnormalities by each study visit and with at least one post-baseline assessment satisfying the liver enzyme abnormalities compared against both baselines.

Listings of all laboratory parameter measurements will be displayed. The abnormal value will be flagged, e.g., L/H for a value being below/above normal range, and the lower and upper limit of normal values will be presented as well. Central lab calcium values will also be listed for patients with at least one post-baseline laboratory signal of hypocalcemia and the below normal serum calcium results will be flagged as L.

For each numerical laboratory parameter, the number of decimal places to be used for laboratory values should be the same as that for the normal range. For continuous variables recorded as <*lower limit*>, these will be imputed as being half of the lower limit.

All laboratory parameters will be expressed using SI units.

Vital signs, [redacted] weight

Descriptive summary statistics for the baseline, each study visit, and change from both baselines to each study visit will be presented for sitting systolic blood pressure, sitting diastolic blood pressure, pulse rate, and body weight. [redacted]

[redacted] The number and percentage of patients who have vital sign values that meet the criteria for being clinically notable after the first infusion of study medication in the extension study will be presented by core treatment group. In addition to the listing of all vital sign data, a patient listing will also be provided for patients with newly occurring clinically notable vital signs. The definition of clinically notable vital sign abnormalities can be found in Appendix section "Clinically notable laboratory values and vital signs" in the protocol.

Tanner staging scale

Tanner staging scale data will be summarized at extension Baseline and End of study (Visit 15). The number and percentage of patients in each Tanner staging scale category will be included in the summary. The following tanner staging scales will be summarized:

- Female
    - breast development
    - pubic hair
    - menarche occurrence
- Male
    - genital stage
    - pubic hair

A listing of tanner staging scale by treatment and gender will also be provided.

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.

Handling of missing values/censoring/discontinuations

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

Sensitivity analyses

All supportive analyses are included in analysis of primary objective section.

Determination of sample size

Participation in the extension study will be available to all patients completing the Core study CZOL446H2337.

References

Acott DA, Lang BA, Wong JA, et al (2005) Pamidronate treatment of pediatric fracture patients on chronic steroid therapy. Pediatric Nephrology, vol 20 : 368 - 373

Analysis of covariance (ANCOVA) model

The following is an example of the SAS code used to perform these analyses.

```
ods output lsmeans=lsmeans
           diffs=lsmeandiffcl;
proc mixed data=xxx;
  class treat center gluco ;
random center;
  model CHGVAR = treat center gluco BASVAR;
  lsmeans treat / pdiff=control ('1') alpha=.05 cl;
quit;
```

Adjusted change from baseline

Mean (SE): lsmeans.LSMean (lsmeans.STDERR)

Diff, 95% CI: lsmeandiffcl.DIFFERENCE (lsmeandiffcl.LowerCL, lsmeandiffcl.UpperCL)

p-value (pairwise): lsmeans.ProbtDiff

Logistic regression model

The following is an example of the SAS code used to perform these analyses.

```
ods output parameterestimates=EST oddsratios=ODDS;
proc logistic data=xxx descending;
format _all_;
  class treat center gluco/param=ref ref=first ;
  model RESP = treat center gluco BASVAR;
run;
```

Odds ratio: ODDS.oddsratioest where EFFECT contains 'treat'

95% CI for odds ratio: ODDS.LOWERCL and ODDS.UPPERCL where EFFECT contains 'treat'

P-value: EST.PROBCHISQ where VARIABLE='treat'

Note: In case of non-availability of enough patients, center effect will be dropped from all above statistical methodology.

Appendix