London, 15 November 2018
EMA/873947/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with Article 46 of regulation (EC) No 1901/2006

Aclasta

zoledronic acid monohydrate

Procedure no.: EMEA/H/C/595 P46 036

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

On 28 Aug 2018, the MAH submitted a completed paediatric study CZOL446H2337 in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. No SmPC update is proposed in this procedure. However, the MAH believes that the results of Study are of clinical relevance and should be reflected in the EU SmPC and a type 2 variation to update the labelling is planned pending discussions with concerned Health Authorities.

2. Scientific discussion

2.1. Information on the development program

Aclasta® (zoledronic acid) was first registered in Europe for Paget's disease of bone on 15 Apr 2005 (via centralized procedure). In 2007, prior to the submission of 2 new indications, (treatment of osteoporosis in men at an increased risk of fracture AND treatment of osteoporosis associated with long-term systemic glucocorticoid therapy), Novartis agreed with the Paediatric Committee (PDCO) of the European Medicines Agency, a Paediatric Investigational Plan (PIP) (EMEA-000057-PIP01-07), in accordance with Article 8 of Regulation EC No 1901/2006, as amended, to assess the use of Aclasta in children at risk for glucocorticoid-induced osteoporosis (GIO). The following measure was part of the agreed PIP:

• A randomized, double-blind, placebo-controlled efficacy and safety study of intravenous zoledronic acid administered twice yearly compared to placebo in children with glucocorticoid-induced osteoporosis (Study CZOL446H2337). This study was initiated in 2008 with Bone Mineral Density (BMD) as the primary endpoint as a surrogate for fracture outcome in the paediatric population. However, the study was terminated (last patient last visit 05 Mar 2018) after 34 of the planned 92 patients were enrolled due to several recruitment challenges (see Section 2.2.1) over the years. The early study termination plan was communicated to the PDCO on 15 Feb 2017.

2.2. Information on the pharmaceutical formulation used in the study

Zoledronic acid 0.05 mg/kg (max 5 mg) was administered as intravenous infusion every 6 months.

2.3. Clinical aspects

2.3.1. Introduction

The treatment of inflammatory bowel disease (IBD), juvenile rheumatoid arthritis, systemic lupus erythematosus, Duchenne's muscular dystrophy, and nephrotic syndrome includes glucocorticoid therapy, which worsens bone mineral status. Glucocorticoid-induced osteoporosis is now recognized as one of the most important reasons for secondary osteoporosis in adults as well as in children. Glucocorticoid use confers a substantial increase in vertebral and hip fracture risk in adults. Studies in adults suggest that glucocorticoid treatment for 3 months is sufficient to increase fracture risk (van Staa et al 2000), and similar data have been collected in children and adolescents where almost one-half of the fractures were asymptomatic (Leblanc et al 2015). The earliest observation of vertebral fractures in children with rheumatic disorders was reported at 4 months after starting systemic glucocorticoids (Rodd et al 2012).

Placebo controlled trials in adults 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. Based on these studies, regulatory approval for the treatment and prevention of osteoporosis, including GIO, has been granted for bisphosphonates. There is no established treatment for secondary osteoporosis in children, although bisphosphonates have been used experimentally in the treatment of specific paediatric metabolic bone disease.

2.3.2. Clinical study

Study H2337: title

Methods

Objective(s)

To study efficacy and safety study of intravenous zoledronic acid in osteoporotic children and adolescents receiving glucocorticoid therapy within the 12 months preceding screening who manifested a lumbar spine BMD Z-score of -0.5 or worse plus evidence of low impact/fragility fracture.

Study design

H2337 was an international, multicentre, randomized, double-blind, placebo controlled study.

Study population /Sample size

The study was designed to recruit 92 patients to obtain 82 evaluable patients for the assessment of the primary endpoint. The sample size was calculated based on the objective to show superiority in improving lumbar spine BMD Z-score by zoledronic acid relative to placebo at Month 12. The sample size estimation considered the standard deviation of 0.93, treatment effect size of 0.63 and a dropout rate of 10%. The effect size of 0.63 increase in lumbar spine BMD Z-score was based on the increase observed with pamidronate-treated children on chronic glucocorticoid therapy presented in (Acott et al 2005). The common standard deviation of 0.93 was considered based on the experience from the pamidronate study by Acott et al 2005 and the standard deviation obtained from the zoledronic acid study in pediatric osteogenesis imperfecta patients (Study CZOL446H2202).

Treatments

Patients were randomized in a 1:1 ratio to receive either a twice yearly 0.05 mg/kg (max 5 mg) i.v. infusion (at least 30 minutes) of zoledronic acid or placebo. Adequate intake of vitamin D and calcium was mandatory for the 4 weeks prior to randomization and throughout the duration of the study (i.e. 12 months) either through adequate dietary intake, supplementation, or a combination of both.

Outcomes/endpoints

The primary objective of the study was to demonstrate that 0.05 mg/kg (max 5 mg) zoledronic acid administered every 6 months is superior to placebo for the change in lumbar spine BMD Z-score at Month 12 relative to baseline.

The secondary objectives were:

• To evaluate between-treatment differences for the change in lumbar spine BMD Z-score at Month 6 relative to baseline.

• To evaluate between-treatment differences for the change in lumbar spine and total body bone mineral content (BMC) at 6 and 12 months.

• To evaluate between-treatment differences for the change in serum N-terminal propeptide type I collagen (P1NP), bone specific alkaline phosphatase (BSAP), cross linked N telopeptide (NTX), and tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) at Month 6 and Month 12 relative to baseline.

• To evaluate between-treatment differences for the proportion of patients with new vertebral fractures at Month 12 relative to baseline.

• To evaluate the between-treatment differences for change in vertebral morphometry at Month 12 relative to baseline.

• To evaluate the between-treatment differences for change in pain using the Faces Pain Scale-Revised (FPS-R) at Months 3, 6, 9 and 12 relative to baseline.

• To evaluate the between-treatment differences for change in 2nd metacarpal cortical width at Month 12 relative to baseline.

• To measure urinary concentration of zoledronic acid at Month 12.

• The safety objective was to demonstrate that zoledronic acid is safe for the treatment of osteoporotic children treated with glucocorticoids through the monitoring of relevant clinical and laboratory safety parameters.

Statistical Methods

The Intention-to-treat (ITT) population consisted of all randomized patients, whereas the Modified Intention-to-treat (MITT) population consisted of all randomized patients who had both baseline and at least one post-baseline lumbar spine BMD Z score. The safety population consisted of all patients that had been exposed to at least one infusion of the study drug. All efficacy analyses were based on the MITT population and safety analyses based on the safety population.

Results

Recruitment/ Number analysed

A total of 92 patients were planned to be randomized from approximately 30 centers, to obtain evaluable data from at least 82 patients for the primary endpoint. However, a total of 34 patients were finally randomized due to the following recruitment challenges over the 9 year course of the study (first patient first visit 04 Dec 2008):

• a screen failure rate of 90% due to patients not meeting inclusion criteria for BMD and/or fractures. In particular, there was a low frequency of fractures in children with glucocorticoid-treated rheumatic disorders and inflammatory bowel disease;

• reluctance of parents to enroll children into a study with a placebo-controlled arm;

• challenges in carrying out a comprehensive bone health study in children with serious underlying disorders which contributed to low enrollment and high screen failure; and

• reduced use of glucocorticoids in children to treat rheumatic disorders and inflammatory bowel disease in recent years;

Of the 34 randomized patients, 30 (88.2%) patients completed the study and 4 (11.8%) patients discontinued:

• 3 patients in the zoledronic acid group withdrew consent (one patient each due to conflict of study visits with school calendar; desire to be treated with zoledronic acid; and participation in another clinical trial)

• 1 patient in the placebo group discontinued as a result of an adverse event (AE) of fracture.

Baseline data

The majority of patients in the MITT population (33 patients) were male, Caucasian, and between 9 to 17 years of age. The key demographic parameters where median differences between zoledronic acid group vs placebo group were observed were as follows: age (15 vs 12.5 years, respectively), standing height (155.00 cm vs 146.00 cm), sitting height (80.50 cm vs 72.00 cm), and weight (50.00 kg vs 42.15 kg). One patient with an extreme weight of 120 kg, sitting height of 141 cm and BMI of 42.52 kg/m2 was included in the zoledronic acid group. There were 4 (66.7%) female patients in the zoledronic acid group with Tanner stage III vs none in the placebo group. Menarche had occurred in 3 (50.0%) female patients in the zoledronic acid group vs none in the placebo group.

The median values of the baseline disease characteristics were as follows: lumbar spine BMD Z-score (-1.992 vs -2.316), lumbar spine BMC (27.653 g vs 22.037 g), total body BMC (1511 g vs 1072 g), Vitamin D (71.0 nmol/L vs 80.5 nmol/L), biomarkers (Serum NTX (29.765 vs 41.630 nmol BCE/L), Serum P1NP (177.90 vs 267.85 ng/mL)), and pain scores (0 vs 2.0). The differences observed were, however, not statistically significant except for total body BMC.

The overall patient population randomized in this study (ITT population) included several sub-types of rheumatic conditions, inflammatory bowel disease, or Duchenne muscular dystrophy patients as summarized in Table 2-1. The number of patients with IBD was higher in the zoledronic acid group than in the placebo group (7 vs 2 patients).

Table -1 Background disease history (ITT population)

Disease type Sub-type	Zoledronic acid (N=18) n (%)	Placebo (N=16) n (%)	Total (N=34) n (%)
Rheumatic conditions	5 (27.8)	7 (43.8)	12 (35.3)
Systemic Onset JIA	0	2 (12.5)	2 (5.9)
Polyarticular Rheumatoid Factor Negative JIA	1 (5.6)	1 (6.3)	2 (5.9)
Oligoarticular Arthritis JIA	0	1 (6.3)	1 (2.9)
Systemic Lupus Erythematosus (SLE)	1 (5.6)	1 (6.3)	2 (5.9)
Juvenile Dermatomyositis	0	1 (6.3)	1 (2.9)
Overlap Syndromes (including mixed connective tissue disease)	0	1 (6.3)	1 (2.9)
Takayasu's arteritis	1 (5.6)	0	1 (2.9)
Polyarteritis nodosa	0	1 (6.3)	1 (2.9)
Other vasculitis*	2 (11.1)	0	2 (5.9)
Inflammatory bowel disease (IBD)	7 (38.9)	2 (12.5)	9 (26.5)
Crohns disease	7 (38.9)	2 (12.5)	9 (26.5)
Duchenne muscular dystrophy	6 (33.3)	7 (43.8)	13 (38.2)
Other	0	1 (6.3)	1 (2.9)

* Other vasculitis included central nervous system vasculitis and inflammatory brain disease.

The ITT population consisted of all randomized patients

A patient could have had more than one disease type or sub-type and was counted once under each disease type or sub-type. The disease types and sub-types were collected on the 'disease-related background/historical information' CRF page.

Source: [H2337 CSR-Table 14.1-3.3]

Efficacy results

Lumbar spine BMD Z-score

The primary endpoint of the Study H2337 was to demonstrate that zoledronic acid administered every 6 months is superior to placebo for the change in lumbar spine bone mineral density (BMD) Z-score at Month 12 relative to baseline. A statistically significant increase was observed between patients in the zoledronic acid group compared to patients in the placebo group (least square (LS) mean difference: 0.425, 95% CI: 0.026, 0.825; p=0.0380) (Table 2-2).

However, no statistically significant difference in lumbar spine BMD Z-score was observed between patients treated with zoledronic acid vs placebo at Month 6 (a secondary endpoint). A between-treatment difference (increase) of 0.290 from baseline to Month 6 in lumbar spine mean BMD Z-score between patients in the zoledronic acid group and patients in the placebo group was observed (95% CI: -0.094, 0.673; p=0.1322).

A larger mean change from baseline (improvement) in the lumbar spine BMD Z-score was observed in the zoledronic acid group compared to the placebo group over time (Figure 2-1).

Table -2 Lumbar spine BMD Z-score – ANCOVA treatment comparison for change from baseline to Month 12 (MITT population)

Statistic	Zoledronic acid N=17	Placebo N=16
Baseline		
N	17	16
Mean (SD)	-2.127 (0.79)	-2.379 (0.90)
Median	-1.992	-2.316
Min, Max	-4.02, -1.05	-3.70, -0.89
Month 12		
n	16	15
Mean (SD)	-1.477 (1.08)	-2.334 (1.03)
Median	-1.223	-2.188
Min, Max	-4.01, 0.04	-4.11, -0.18
Change from baseline to Month 12		
LS mean (SE)	0.607 (0.13)	0.182 (0.15)
Diff (95% CI)		0.425 (0.026, 0.825)
P-value		0.0380

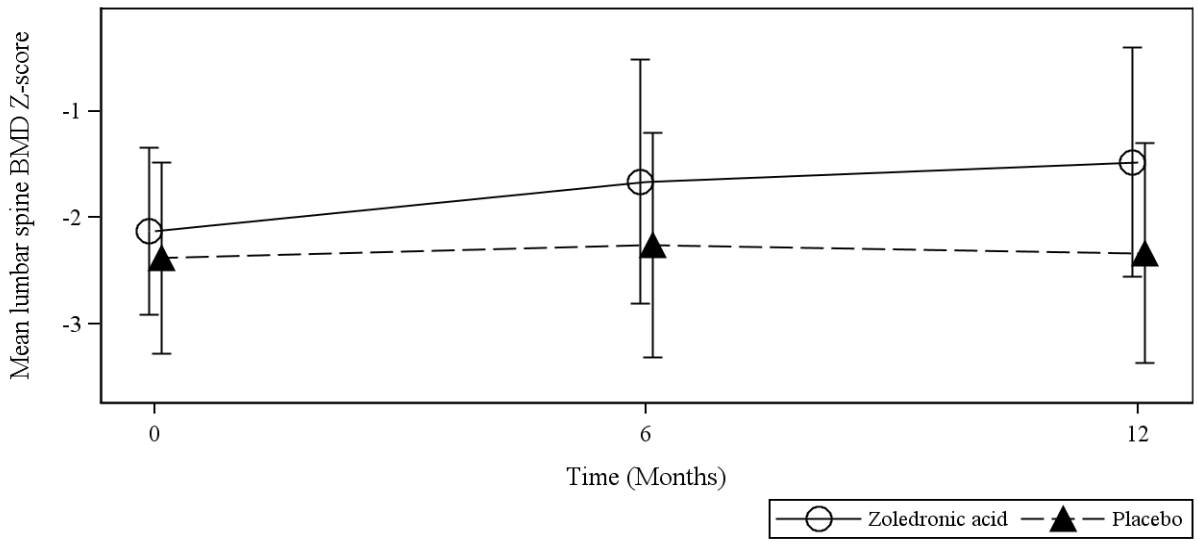
MITT population consisted of all randomized patients who had both baseline and at least one post-baseline lumbar spine BMD Z-score;

An analysis of covariance (ANCOVA) model was used with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Difference in least squares (LS) mean = LS mean for the zoledronic acid group — LS mean for the placebo group.

Source: [H2337 CSR-Table 14.2-1.1]

Figure 1 Least squares mean change from baseline in lumbar spine BMD Z-score over time (MITT population)



This figure shows the LS mean ± SD
Source: [H2337 CSR-Figure 14.2-2.1]

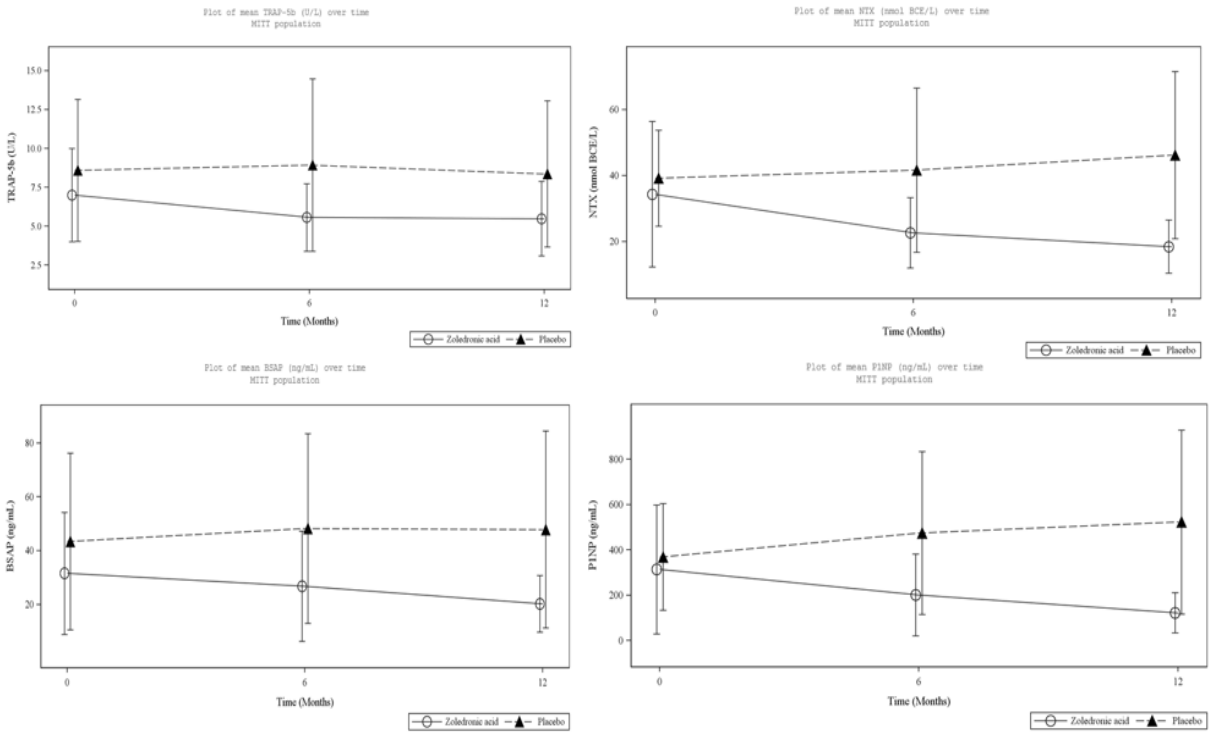
Bone turnover markers

The effect of zoledronic acid and placebo on four serum biomarkers was investigated at Month 6 and Month 12 as secondary endpoints. Changes from baseline in the markers of bone formation (P1NP and BSAP) and the markers of bone resorption (NTX and TRAP-5b) were observed as below:

- At Month 12, a statistically significant ($p<0.05$) reduction in 3 bone turnover markers (P1NP, BSAP, NTX) was observed in the zoledronic acid group as compared to placebo group:
  - P1NP: log-transformed difference= -1.066; 95% CI: -1.770, -0.362; p=0.0049
  - BSAP: log-transformed difference= -0.484; 95% CI: -0.889, -0.079; p=0.0215
  - NTX: log-transformed difference= -0.799; 95% CI: -1.170, -0.428; p=0.0002

  The decrease in serum TRAP-5b levels at Month 12 was not statistically significant (log-transformed difference= -0.207; 95% CI: -0.522, 0.107; p=0.1840).
- At Month 6, a statistically significant between-treatment difference (decrease) of 0.476 was observed from baseline to Month 6 (95% CI: -0.887, -0.065; p=0.0254) between the two groups for serum NTX. For the other 3 biomarkers, the between treatment difference in decrease in log-transformed values did not reach statistical significance at Month 6.

Figure -2 Plot of bone turnover markers over time (MITT population)



Source: [H2337 CSR-Figure 14.2-2.2, Figure 14.2-2.3, Figure 14.2-2.4, Figure 14.2-2.5]

Lumbar spine and total body BMC

- A between-treatment difference of 1.979 was observed between the two groups in lumbar spine BMC at Month 6 (95% CI: 0.089, 3.869; p=0.0409), although this difference (2.155) was not statistically significant at Month 12 (95% CI: -1.488, 5.798; p=0.2340).
- No statistically significant differences in total body BMC were observed between patients treated with zoledronic acid vs placebo at 6 or 12 months.

Vertebral fractures

No new vertebral fractures in the zoledronic acid group were detected as compared to 2 new fractures observed in the placebo group. In a population of patients that met the fracture inclusion criteria for this study, this is an important clinical observation, despite the low numbers of patients.

Other secondary efficacy results

No significant differences in vertebral morphometry, metacarpal cortical width, and reduction in pain were observed between the two groups at Month 12. However, the metacarpal cortical width data showed some numerically higher values for the zoledronic acid group vs placebo. For these endpoints, the number of patients with assessments was low and no conclusions could be made about the differences.

Safety results

Patient exposure

The median duration for 1st and 2nd infusion as well as the median volume of these infusions were similar between the zoledronic acid and placebo groups. There were no patients who required temporary interruption of study drug or dose adjustments due to AEs.

Concomitant medications

A total of 61.1% and 56.3% of patients in the zoledronic acid group and placebo group, respectively, reported the use of concomitant medications and significant non-drug therapies before study start. Corticosteroids of different forms were used most frequently as prior medications in both the zoledronic acid group (27.8%) and placebo group (25.0%).

During the study, all patients in the study were using concomitant medications (ie, those concomitant medications that were started after start of study drug as well as those that were started prior to and continued after start of study drug). Glucocorticoids of various classes were used by patients in both groups, although more patients in the zoledronic acid group used them as compared with those in the placebo group (for example, 61.1% vs 25.0%).

Adverse events

The number of patients with AEs, severe AEs, and serious adverse events (SAEs) was slightly higher in the zoledronic acid group than in the placebo group (Table 2-3). The most commonly reported AEs namely gastrointestinal disorders (vomiting, nausea, diarrhea), pyrexia, arthralgia, myalgia, headache and back pain were related to post-dose symptoms. There were no AEs related to renal or skeletal system (such as osteonecrosis of jaw, non-union, or delayed union).

Table -3 Adverse events (at least 10% in any group), by primary system organ class and preferred term (Safety population)

Primary system organ class Preferred term	Zoledronic acid N=18 n (%)	Placebo N=16 n (%)	Total N=34 n (%)
Number of patients with any adverse event	15 (83.3)	12 (75.0)	27 (79.4)
Cardiac disorders	3 (16.7)	0	3 (8.8)
Tachycardia	3 (16.7)	0	3 (8.8)
Endocrine disorders	3 (16.7)	0	3 (8.8)
Adrenal insufficiency	3 (16.7)	0	3 (8.8)
Gastrointestinal disorders	9 (50.0)	5 (31.3)	14 (41.2)
Vomiting	4 (22.2)	1 (6.3)	5 (14.7)
Nausea	3 (16.7)	2 (12.5)	5 (14.7)
Abdominal discomfort	2 (11.1)	0	2 (5.9)
Crohn's disease	2 (11.1)	0	2 (5.9)
Diarrhoea	2 (11.1)	2 (12.5)	4 (11.8)
General disorders and administration site conditions	7 (38.9)	3 (18.8)	10 (29.4)
Pyrexia	4 (22.2)	1 (6.3)	5 (14.7)
Pain	3 (16.7)	0	3 (8.8)
Acute phase reaction	2 (11.1)	0	2 (5.9)
Fatigue	1 (5.6)	2 (12.5)	3 (8.8)
Infections and infestations	4 (22.2)	8 (50.0)	12 (35.3)
Upper respiratory tract infection	2 (11.1)	3 (18.8)	5 (14.7)
Herpes zoster	0	2 (12.5)	2 (5.9)
Metabolism and nutrition disorders	2 (11.1)	2 (12.5)	4 (11.8)
Hypocalcaemia	2 (11.1)	0	2 (5.9)
Musculoskeletal and connective tissue disorders	10 (55.6)	3 (18.8)	13 (38.2)
Arthralgia	5 (27.8)	1 (6.3)	6 (17.6)
Back pain	4 (22.2)	1 (6.3)	5 (14.7)
Myalgia	3 (16.7)	1 (6.3)	4 (11.8)
Nervous system disorders	4 (22.2)	1 (6.3)	5 (14.7)
Headache	4 (22.2)	1 (6.3)	5 (14.7)

The Safety population consisted of all patients that had been exposed to at least one infusion of the study drug.
Primary system organ classes are presented alphabetically. Preferred terms are presented by descending frequency in the zoledronic acid group.
A patient with multiple occurrences of an AE for the same preferred term or system organ class is counted only once in each specific category.
MedDRA version 20.1 is used for reporting.
Source: [H2337 CSR-Table 14.3.1-1.4]

For additional details on adverse events, refer to [Study H2337 CSR-Section 12.2].

Deaths and discontinuations as a result of an AE

No deaths were reported in this study. One patient in the placebo group discontinued study treatment as a result of an AE (i.e., fracture).

Serious AEs

Overall, more patients reported SAEs in the zoledronic acid group than in the placebo group (5 [27.8%] patients vs 1 [6.3%] patient). A total of 4 (22.2%) patients treated with zoledronic acid experienced gastrointestinal disorders vs none treated with placebo.

Other significant adverse events

Safety topics of interest of hypocalcemia, gastrointestinal AEs and ocular AEs were identified based on the mechanism of action of zoledronic acid, biological plausibility, and information from the existing zoledronic acid database in other indications. The incidence of these AEs observed in this study was consistent with the known safety profile of Aclasta.

Two patients in the zoledronic acid group reported newly occurring hypocalcemia events post-baseline, based on central laboratory values and an additional 2 patients reported hypocalcemia events, based on AEs and central laboratory calcium. In the 2 patients with hypocalcemia AEs, one patient reported the event as an SAE, while the other AE was considered mild in severity. Both of these events were suspected to be related to study drug.

Paediatric safety cumulative data reviews

The results of Study H2337, which included 34 osteoporotic patients aged 5 to 17 years, did not reveal any new safety signals.

As reported in the Periodic Safety Update Report (PSUR) 01 Sep 2016 to 31 Aug 2017, cumulatively, 60 cases of off label use of Aclasta in paediatric patients were reported. No unusual trend or new safety information was identified on review of these cases. The safety profile of zoledronic acid observed in this study in paediatric patients is consistent with that in the overall population in the approved adult indications.

MAH Discussion on clinical aspects

The results of this randomized placebo controlled trial evaluating zoledronic acid in 34 children aged 5 to 17 years with GIO demonstrated a statistically significant improvement in lumbar spine BMD Z-score after 12 months of treatment, relative to baseline. This was associated with significant reduction in other markers of bone turnover (P1NP, BSAP, NTX) at Month 12, a significant increase in lumbar spine BMC at Month 6, and an absence of new vertebral fractures in the zoledronic acid group compared to placebo at the end of study, further supporting a positive treatment effect. The overall efficacy and safety observed in this study was consistent with the known pharmacology of the drug and experience from adult studies with Aclasta.

Novartis believes that the results of Study H2337 are of clinical relevance and should be reflected in the EU SmPC. A type 2 variation to update the labelling is planned pending discussions with concerned Health Authorities. Overall, there are no concerns over the benefit/risk of Aclasta (zoledronic acid) in paediatric GIO patients based upon the results of Study H2337.

3. Rapporteur's overall conclusion and recommendation

The results of this randomized placebo controlled trial evaluating zoledronic acid in 34 children aged 5 to 17 years with GIO demonstrated an improvement in bone mineral density, a surrogate for fracture outcome. More patients reported SAEs in the zoledronic acid group than in the placebo group. The following was described in this study but not specifically mentioned within the current SmPC:

tachycardia, adrenal insufficiency, Crohn's disease and upper respiratory tract infections. The MAH should comment on whether these events are paediatric specific and how they relate to the adult safety profile in the upcoming variation procedure.

The study was terminated after 34 of the planned 92 patients were enrolled due to several recruitment challenges over the years. Whether the 34 patients finally recruited in this study, gives sufficient data to power the study, evaluate endpoints and the objectives will need to be discussed by the MAH in the upcoming variation procedure.

The MAH is asked to submit the study results together with a proposal for the SmPC and PIL for detailed assessment in a type 2 variation. Together with this study, it is recommended that the MAH should also submit all available paediatric data regarding zoledronic acid's use, including any preclinical or adult data supporting a potential benefit for the paediatric population. A decision on B/R in paediatric population should be based upon all available evidence and not solely this study which may have limitations due to underpowering.

X Fulfilled:

No further action required, however further data are expected in the context of a variation prior any conclusion on product information amendments is made. The MAH should commit to submit this variation application no later than 60 days after the receipt of these conclusions.