Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

RISEDRONATE SODIUM

UK/W/009/pdWS/002

Marketing Authorisation Holder: Sanofi-aventis / Warner Chilcott

Rapporteur:	UK
Finalisation procedure (day 120):	20 December 2012
Date of finalisation of PAR	4 January 2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Actonel
INN (or common name) of the active substance(s):	Risedronate sodium
MAH:	Sanofi-aventis / Warner Chilcott
Currently approved Indication(s)	Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis. To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5 mg/day prednisone or equivalent. Treatment of Paget's disease of bone
Pharmaco-therapeutic group (ATC Code):	Drugs affecting bone metabolism Bisphosphonate
Pharmaceutical form(s) and strength(s):	Film-coated tablets 5mg,30mg,35mg and 75mg risedronate sodium Film-coated tablets 35 mg risedronate sodium + 500mg calcium Film-coated tablets 35 mg risedronate sodium + sachet 1000 mg calcium/880 IU vitamin D3

I. EXECUTIVE SUMMARY

Bisphosphonates, as potent inhibitors of bone resorption, are currently the class of drugs of first choice in the management of skeletal disorders with high bone turnover, whether localised or generalised. Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. This anti-resorptive activity leads to the consequent decrease in bone turnover, which constitute the rationale for the use of this drug in many disorders of bone metabolism.

Osteogenesis imperfecta (OI) is characterized by genetic alterations in type I collagen. This alteration is associated with an increase in bone turnover and an uncoupling between the processes of bone resorption and formation of new bone, responsible for the worsening features of the skeleton. Recently several bisphosphonates have been investigated for the treatment of patients with OI.

Risedronate sodium has been approved in several dose strengths (5, 30, 35, and 75 mg film-coated tablets) for the indications of postmenopausal osteoporosis (treatment and prevention), for steroid-induced osteoporosis in postmenopausal women and for Paget's disease.

No specific paediatric formulation is available as risedronate is not currently licensed in children.

According to Article 46 of the Regulation (EC) No 1901/2006, as amended, the MAHs submitted a data package which included the complete clinical study report of a randomized, double-blind, placebo-controlled, multicenter, parallel group study of one-year duration followed by 2 years of open-label treatment to determine the safety and efficacy of orally administered 2.5 mg or 5 mg daily risedronate in children >4 to <16 years old with OI as well as the Addendum report with results of the blinded re-reading of Xrays from this paediatric trial. The year 1 study report of this trial was submitted and assessed in a European paediatric work-sharing procedure (UK/W/009/pdWS/001) under Article 45 which was finalized in 2010 and led to additional wording in SmPC as follows:

4.2 Posology and method of administration
Paediatric population: Risedronate sodium is not recommended for use in children below age 18 years due to insufficient data on safety and efficacy (also see section 5.1).

5.1 Pharmacodynamic properties
Paediatric population: The safety and effectiveness of risedronate sodium is being investigated in an on-going study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. After completion of its one-year randomized, double-blind, placebo controlled period, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however an increased number of at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. Overall, results do not support the use of risedronate sodium in paediatric patients with osteogenesis imperfecta.

The MAHs concluded that overall the findings of this study support positive anti-absorption and a favourable bone safety profile of risedronate when used in paediatric OI patients. However there are no robust data to confirm that the improvement in lumbar spine BMD due to treatment with risedronate also results in a consequent improvement in the incidence of fractures. As stated by the MAH "because of the retrospective nature of the re-reads for the double-blind phase of the study, the contradictory results of the independent re-reads during that phase, and the failure to

demonstrate a vertebral fracture benefit in risedronate-treated patients, these data still do not support the use of risedronate in children with mild to moderate OI."

The rapporteur agreed that based on the evidence submitted for the completed 3 years paediatric OI study, the use of risedronate should not be recommended. However the information currently included in section 5.1 of the SmPC should be amended to reflect the overall data from the completion of this study.

SmPC changes are proposed in section 5.1. No changes are proposed for the PIL of risedronate containing products.

II. RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that for all products containing Risedronate across the EU, it is recommended that SmPCs contain the following wording:

4.2 Posology and method of administration

Paediatric population: Risedronate sodium is not recommended for use in children below 18 years of age due to insufficient data on its efficacy and safety (also see section 5.1).

5.1 Pharmacodynamic properties

Paediatric population: The safety and efficacy of risedronate sodium has been investigated in a 3 year study (a randomized, double-blind, placebo-controlled, multicenter, parallel group study of one-year duration followed by 2 years of open-label treatment) in paediatric patients aged 4 to less than 16 years with mild to moderate osteogenesis imperfecta. In this study, patients weighing 10-30 kg received risedronate 2.5 mg daily and patients weighing more than 30 kg received risedronate 5 mg daily.
After completion of its one-year randomized, double-blind, placebo controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated ; however an increased number of patients with at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. During the one year double blind period, the percentage of patients who reported clinical fractures was 30.9% in the risedronate group and 49.0% in the placebo group. In the open label period when all patients received risedronate (month 12 to month 36), clinical fractures were reported by 65.3% of patients initially randomized to the placebo group and by 52.9% of patients initially randomized to the risedronate group. Overall, results do not support the use of risedronate sodium in paediatric patients with mild to moderate osteogenesis imperfecta.

The MAHs are therefore requested to submit a Type IB variation to update the SmPCs of products containing the active ingredient Risedronate sodium in line with the above work-sharing recommendations within 60 days of the report.

III. INTRODUCTION

In March 2012, the MAHs submitted the following documents from a completed paediatric study for Risedronate sodium, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use:

- a cover letter with a proposal of SmPC update for section 5.1
- the year-3 Clinical study report
- the Addendum report with results of the x-ray re-reads.

The MAH stated that the submitted data from the completed OI paediatric study provided further information regarding the safety of risedronate in paediatric patients with this condition. It was concluded that "*The results of the blinded re-reading of x-rays from children with OI who received double-blind treatment with placebo or risedronate for 12 months followed by open label treatment with risedronate for 2 years varied somewhat from those of the original x-ray reads. The conclusion from the consensus re-read was that there was no meaningful difference between the treatment groups in the percentage of patients with vertebral fractures.*"

However the MAH was still of the view that the evidence from this study is not robust enough to support the use of risedronate in children with OI and consequently an update for section 5.1 of the SmPC was proposed as follows:

5.1 Pharmacodynamic properties

Paediatric population: The safety and efficacy of risedronate sodium has been ~~is being~~ investigated in a three-year ~~an on-going~~ study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. After completion of its one-year randomized, double-blind, placebo controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however no significant difference ~~an increased number of at least 1 new morphometric (identified by x-ray)~~ in vertebral fracture rates (identified by x-ray) was found in the risedronate group compared to placebo. Overall, results do not support the use of risedronate sodium in paediatric patients with osteogenesis imperfecta.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Risedronate is an orally administered third generation pyridinyl bisphosphonate currently licensed in Europe and the United States. It is suggested that it is approximately 100 times more potent than pamidronate in terms of inhibiting bone resorption. Risedronate sodium has been approved in several dose strengths (5, 30, 35, and 75 mg film-coated tablets). In addition, the 35 mg film-coated tablets are also approved under 2 combination packs with calcium and calcium/vitamin D3.

IV.2 Clinical aspects

1. Introduction

Osteogenesis imperfecta (OI) is a disease associated with very low bone mass. Children with OI suffer recurrent fractures resulting in pain, deformity, and disability. In the past, treatment of children with OI focused on fracture management and surgical correction of deformities. Following the publication of a paper by Glorieux et al (Glorieux 1998), therapy with pamidronate has become a treatment option for children with moderate-to-severe OI. Risedronate is an orally administered third generation pyridinyl bisphosphonate. It is considered to be approximately 100

times more potent than pamidronate in terms of inhibiting bone resorption. It has been demonstrated that risedronate 5 mg daily decreases the incidence of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis (PMO) and significantly increases bone mass.
A Phase I clinical study was conducted to determine risedronate pharmacokinetics (PK) following a single oral dose in children with OI (An Open Label, Randomized, Multi-centre, Parallel Group Study to Investigate the Safety, Tolerability and Pharmacokinetics of Risedronate Administered as a Single Oral Dose of 2.5 mg or 5 mg in Children ≤ 30 kg and 5 mg or 10 mg in Children > 30 kg with OI). This study was reviewed during the previous European paediatric work-sharing procedure under Article 45. The results of this study confirmed that exposures for risedronate doses of 2.5 mg for patients weighing 10-30 kg and 5 mg for patients weighing > 30 kg were similar to those previously observed in adults. The results of this study also demonstrated that risedronate was well tolerated in children with OI.

Rapporteur's Comments for this study (extract from Final PdAR UK/W/009/pdWS/001)
In the assessor's opinion the main finding of this study is that the PK parameters in the tested paediatric population appear to be extremely and unpredictably variable, although the MAH concludes that the mean values are comparable to those of adults. The initial selection of the doses under investigation is not adequately justified. As the results of this study were use to provide the dosing regime for the safety and efficacy OI study, a proper dose finding design should have been utilized as part of the whole paediatric development plan. As mentioned earlier in this report, the literature is also inconclusive for the most appropriate dosing regime for the paediatric population. However the assessor agrees that based on the findings of the PK study, the used dosing in phase III study of 2.5 mg/day for children with body weight 10-30 kg and 5mg/day for children with body weight >30 kg appears to be appropriate to ensure safety; nevertheless it is unclear if it is the optimal dose for efficacy demonstration in long-term use in OI paediatric patients.

2. Clinical study

A randomized, double-blind, placebo-controlled, multicenter, parallel group study of one-year duration followed by 2 years of open-label treatment to determine the safety and efficacy of orally administered 2.5 mg or 5 mg daily risedronate in children >4 to <16 years old with OI.

- Introduction

This phase III efficacy and safety study was still on-going in 2010 (the first year was completed and the 2-year open label period was on-going) when the year 1, double-blind study report was submitted to EMA by the MAHs and was assessed as part of the work-sharing procedure under Article 45 as it was considered that provided important paediatric clinical information which led to amendments of the SmPC for the use of risedronate in paediatric OI patients. At that time the MAHs informed the MSs that the final study report would be submitted to the competent authorities in accordance with the Article 46 of Regulation 1901/2006 within 6 months of its completion.

Rapporteur's Comments for this study (extract from Final PdAR UK/W/009/pdWS/001)
The results of this study support the previously documented effects of risedronate in children with OI. The anti-resorptive effects and favourable safety profile are consistent with those demonstrated in risedronate clinical trials in adults with osteoporosis using various doses and dosing regimens. However, a higher percentage of patients had new morphometric vertebral fractures in the risedronate group versus placebo; these data were unexpected and are difficult to explain given that the rate of new vertebral fractures was similar in the risedronate and placebo groups. The present study was neither designed nor powered to estimate the efficacy of risedronate on fractures. In the assessor's opinion the effect of risedronate on BMD should

provide robust evidence on the advantages of treatment for these patients. The results are rather disappointing as the demonstrated increase of the BMD in the lumbar spine does not appear to have clinical significance and does not appear to protect the patients from new vertebral fractures. The MAHs states that the following 2 years of the study will offer additional safety data that will help clarify the finding of the increased vertebral fractures. However the design for this period of the study is open label without a placebo comparator group. The efficacy endpoints including lumbar BMD are going to be reviewed against the findings from baseline, which will offer very limited additional proof of risedronate's effect. The incidence and rate of new fractures will be recorded but the uncontrolled model of this period of the study will limit the robustness of these findings. Additionally the findings of the first year of the study revealed that the patients' life does not appear to be improved from treatment as the overall quality of life evaluation did not demonstrate any difference from the placebo group. A fracture outcome study would have been the study of choice as the efficacy data are based on changes in bone mineral density, which are surrogates for bone health rather than indicators of reduction in fracture events. It is noted that very young patients (<4 years) which often have much serious type of the disease and suffer more commonly from atraumatic fractures are not included. Overall the follow up period (currently 1 year) is limited in order to assess a likely positive long term effect of treatment in the progress of the disease. Also regarding the safety of the paediatric use of risedronate, surprisingly, both in the PK and in the efficacy study occurrence of Crohn's disease as a serious adverse event has been reported. The relevance of this finding is not further discussed by the MAH.

In September 2010 the MAH provided the line-listing for the completed study 2003100. However it was communicated that "the final results of this study are currently undergoing re-evaluation of the x-rays that were conducted at several time points of the study." Based on this information the UK was appointed as the rapporteur for this Article 46 paediatric work-sharing procedure and it was agreed to delay the initiation of this procedure until the time when the final x-rays results analysis became available.

- **Methods**

- **Objective(s)**

The primary objective of this study was to determine the efficacy of risedronate compared to placebo in children ≥ 4 to < 16 years of age with OI as assessed by percent change from Baseline in lumbar spine bone mineral density (BMD) at Month 12.

Open-label Period Objectives

The objectives of the open label period of the study (2nd and 3rd years of study) were to evaluate risedronate treatment in children 4 to 16 years with OI in terms of the BMD, the incidence and rate of fractures, reported adverse events and growth.

- **Study design**

This was a 1-year, randomized, double-blind, placebo-controlled, multicenter, parallel group study with 2 additional years of open-label treatment. At the end of 1 year of treatment, without the unblinding of individual patients, all patients took open-label risedronate for 2 additional years.

- **Study population /Sample size**

One-hundred forty-seven (147) children ≥ 4 to < 16 years of age with OI were enrolled at 20 study centres in North America, Australia, Europe, South America, and South Africa.

Children (≥ 4 to < 16 years of age) were eligible to participate in this study if they were diagnosed with OI as based on a modified classification scale (Sillence 1979, Glorieux 2000) and at an increased risk of fractures as defined by:

- a history of at least 1 radiographically confirmed, non-traumatic or low impact fracture, plus low BMD (Z-score ≤ -1 at either total body or lumbar spine sites);

or

- very low BMD (Z-score ≤ -2.0 at either total body or lumbar spine sites) with or without a history of fractures

Participants also needed to shown to have at least 2 evaluable lumbar spine vertebral bodies (L1-L4), namely without fracture or degenerative disease.

Patients were excluded if they had body weight <10kgr, had a history of using any of the following medications, regardless of dose, for at least 1 month, within 3 months of enrolment:

- anabolic agents
- estrogen (except contraceptives)
- progestogens (except contraceptives)
- calcitriol, calcidiol, or alfacalcidol
- calcitonin
- fluoride (except dental health products)
- glucocorticoids (does not include inhaled glucocorticoids)
- growth hormones or parathyroid hormone (PTH)
- strontium

Patients were also excluded if they had a history of using any bisphosphonates within 1 year of enrolment, except for a single dose of oral bisphosphonate, such as risedronate or alendronate or suffered from osteoporosis, secondary to diseases other than OI or drug therapies

- **Treatments**

During the double-blind period (Year 1), patients weighing 10-30 kg received risedronate 2.5 mg or placebo daily and patients weighing more than 30 kg received risedronate 5 mg or placebo daily. Patients younger than 4 years of age were not studied due to the inability of the patient to take the volume of water needed to ensure safe and accurate dosing. During the open-label period (Years 2 and 3), all patients received risedronate; doses were again 2.5 or 5mg based on body weight but were adjusted only once at the beginning of the second year if appropriate; doses remained unchanged throughout the 2 years of the open-label period.

Throughout the study, all patients were required to take a daily supplement of calcium and vitamin D; patients were encouraged to remain on their present formulation of calcium and vitamin D, as long as the dose fell within a range of 500-1000 mg of calcium and 200-600 IU of vitamin D.

Selection of Risedronate Doses in the Study

It is reported that the doses selected were based on risedronate PK data showing similar results for adults and children (study 2002020 see table 1), gastrointestinal (GI) safety considerations, the efficacious dose used for treatment of women with osteoporosis, other data (i.e. alendronate).

Table 1
Risedronate Pharmacokinetics in Children and Adults
(Year 1 Report)

	Children with OI				Adults Normal and with PMO
PK parameter	2.5 mg Ris 10-30 kg body weight	5 mg Ris 10-30 kg body weight	5 mg Ris > 30 kg body weight	10 mg Ris > 30 kg body weight	5 mg Ris
Cmax (ng/mL)	0.25-1.66	0.91-1.96	1.32-1.56	1.26-3.68	0.32-4.13
AUC (ng*h/mL)	3.49-9.37	4.16-7.74	12.54-14.48	10.27-19.18	1.11-20.44
t1/2,z (hr)	78-745	123-579	100-406	238-661	36-955

*Data presented as ranges.
Data taken from 2003100 Year 1 CSR, Table 1.

In this current Phase III risedronate study in children, the highest potential dose is 0.25 mg/kg and the lowest potential dose is 0.08 mg/kg (Table 2). The effective daily dose in postmenopausal women was approximately 0.17 mg/kg for a 30-kg woman (lowest body weight in the PMO studies) and 0.08 mg/kg for a 60-kg woman (average body weight from risedronate postmenopausal studies was 60-65 kg).

Table 2
Summary of Dose Levels by Body Weight (mg/kg)
(Year 1 Report)

Body Weight (kg)	2.5 mg	5 mg*
Children		
10 kg	0.25 mg/kg	
30 kg	0.08 mg/kg	0.17 mg/kg
60 kg		0.08 mg/kg
Adults (60 kg)		0.08 mg/kg

*Approved dose for postmenopausal osteoporosis.
Data taken from 2003100 Year 1 CSR, Table 2.

- **Outcomes/endpoints**

The primary objective of this study was to determine the efficacy of risedronate compared to placebo in children ≥ 4 to < 16 years with OI as assessed by percent change from baseline in lumbar spine BMD at Month 12.

The secondary objectives of the year 1, placebo-controlled period of study were:

a) to evaluate the efficacy of risedronate compared to placebo in children ≥4 to < 16 years with OI as assessed by:

- percent change from baseline in lumbar spine BMD at Month 6
- percent change from baseline in total body BMD
- percent change from baseline in total body and lumbar spine BMC
- change and percent change from baseline in total body and lumbar spine BMD Z-score
- percent change from baseline in lumbar spine and total body bone area
- incidence and rate of new vertebral fractures (Genant 1993)
- incidence and rate of clinical vertebral and non-vertebral fractures
- percent change from baseline in bone turnover markers (BTMs) (serum bone-specific alkaline phosphatase [BAP] and urine type-I collagen N-telopeptide [NTX])
- improvement from baseline in musculoskeletal pain relief as determined by FACES (Wong 2001) pain rating scale
- improvement from baseline in quality of life (QOL) as determined by PedsQL (Varni 2001, Varni 1999) Pediatric QOL questionnaire.

b) to evaluate the safety and tolerability of risedronate treatment in children ≥ 4 to < 16 years with OI as assessed by:

- ❖ adverse events
- ❖ laboratory profiles including bone biopsy
- ❖ change from baseline in bone age
- ❖ annualized growth velocity from baseline.

The variables for Years 2 and 3 (open-label period) of the study include the following:

- percent change from Baseline in lumbar spine BMD
- percent change from Baseline in total body BMD
- percent change from Baseline in total body and lumbar spine BMC
- change and percent change from Baseline in total body and lumbar spine BMD Z-score
- percent change from Baseline in lumbar spine and total body bone area
- incidence and rate of new vertebral fractures
- incidence and rate of clinical vertebral and non-vertebral fractures
- percent change from Baseline in bone turnover markers (BAP and NTX)
- adverse events
- laboratory profiles
- change from Baseline in bone age
- annualized growth velocity from Baseline

- **Statistical Methods**

The data from the open-label period were to be analyzed and reported separately. All analyses were analyzed/displayed using the intent-to-treat (ITT) population. The open-label period of the study was not powered for statistical testing. Statistical tests that were performed were exploratory; thus, p-values were not adjusted for multiplicity.

A total of 123 patients were to be randomized to the risedronate and placebo groups in a 2:1 ratio. This sample size allowed detection of a difference of at least 5% in lumbar spine BMD percent change from Baseline at 12 months between the risedronate and placebo groups with 90% power. The calculation was based on the assumptions that the common within-group standard deviation (SD) would be approximately 7% and the dropout rate within Year 1 would be 20%. A difference of 5% in lumbar spine BMD percent change from Baseline was considered a clinically meaningful difference. Historical data based on placebo-controlled studies on adults have suggested the within-group SD for lumbar spine BMD percent change at Month 12 is approximately 1.04-1.12 times the observed mean. The 7% SD assumed in this study was below 1.2 times the observed mean we assumed in the risedronate group (6%).

➢ **Results**

- **Recruitment/ Number analysed**

A total of 231 patients were screened, and 147 patients were randomized. Of the patients randomized, 143 received at least one dose of study drug. During the double-blind period (Baseline to Month 12), no patients in the placebo group and 7 (7.4%) patients in the risedronate group discontinued on or prior to Month 12. All of the patients who completed the double-blind period (49 patients, placebo/ris; 87 patients, ris/ris group) were treated during the open-label period. Of these, 43 (87.8%) in the placebo/ris group and 82 (94.3%) in the ris/ris group completed Month 36 of the study. Six (12.2%) patients in the placebo/ris group, and 5 (5.7%) in the ris/ris group discontinued the study prior to Month 36

- **Baseline data**

More than 80% of patients were Caucasian, and the median age was 9.0 years in the placebo/ris group and 8.5 years in the ris/ris group. The percentages of patients in the 4- to 9-year age group and the 10- to 15- year age group were similar for the 2 treatment groups. The range of ages was also similar for the 2 treatment groups (4-14 years, placebo/ris; 4-15 years,

ris/ris). Over 80% of the patients in each treatment group had Type I OI. Approximately 94% of patients in each group had any prior fracture reported on their medical history; most (~83%) patients in each group had 3 or more fractures reported on their medical history. The groups did not differ significantly with respect to any of these demographic and baseline characteristics. The 2 groups were generally similar with respect to their medical and surgical history. The prevalent lower limb fractures and dislocations overall were similar for the 2 treatment groups (69.4%, placebo; 69.1%, risedronate).

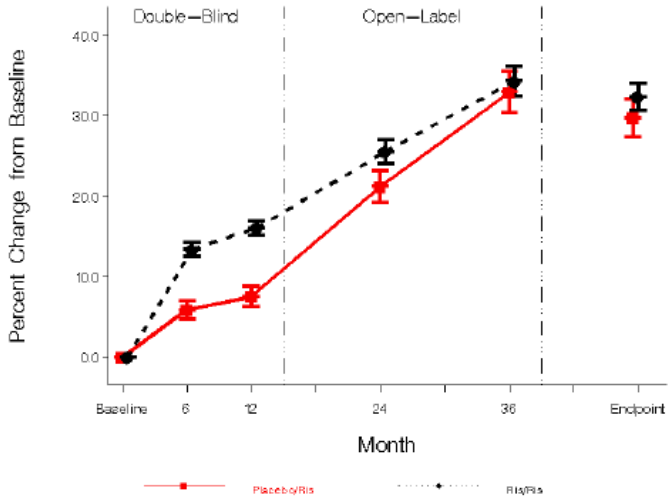
The Z-scores for lumbar spine BMD at Baseline were similar in the 2 treatment groups. There was a statistically significant difference between the 2 groups for the total body Z-score ($p = 0.0444$). Among patients with known fracture status, the placebo/ris and ris/ris groups were similar at Baseline with respect to the percentages of patients who had at least 1 prevalent vertebral fracture (67.4%, placebo/ris; 61.3%, ris/ris) and the percentages of patients who had ≥ 2 prevalent vertebral fractures (39.0%, placebo/ris; 43.8%, ris/ris).

- **Efficacy results**

Lumbar Spine BMD

During the double-blind period (Baseline to Month 12), both groups had a statistically significant mean percent increase from Baseline in lumbar spine BMD at Months 6 and 12 (Figure 1). The mean percent increases were 5.9% in the placebo/ris group and 13.5% in the ris/ris group at Month 6, and 7.6% in the placebo/ris group and 16.2% in the ris/ris group at Month 12. The mean percent increase in the ris/ris group was significantly greater than that in the placebo/ris group at both time points. During the open-label period (Month 12 to Month 36), further mean percent increases from baseline were noted in both groups (Figure 1). At the Endpoint, the mean percent increases were 29.9% in the placebo/ris group and 32.6% in the ris/ris group.

Figure 1: Least Square Means (+/- SE) for Lumbar Spine BMD Percent Change from Baseline (Intent-to-treat)

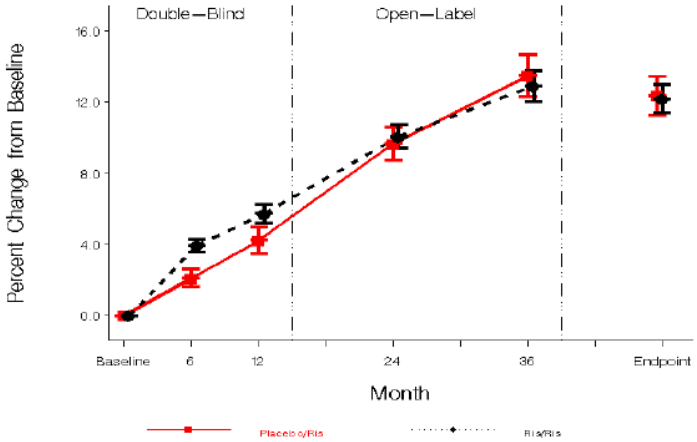


Total Body BMD

During the double-blind period (Baseline to Month 12), both groups had a statistically significant mean percent increase from Baseline in total body BMD at Months 6 and 12 (Figure 2). The mean percent increases were 2.1% in the placebo/ris group and 4.0% in the ris/ris group at Month 6 and 4.3% in the placebo/ris group and 5.8% in the ris/ris group at Month 12. The mean percent increase from Baseline was significantly greater in the ris/ris group than in the placebo/ris group at Month 6. During the open-label period (Month 12 to Month 36), further

mean percent increases from Baseline were noted in both groups. During this period, the mean percent increases were similar in the 2 groups.

Figure 2: Least Square Means (+/- SE) for Total Body BMD Percent Change from Baseline (Intent-to-treat)



New Morphometric Vertebral Fractures

During the double-blind period, 31.8% of patients in the ris/ris group experienced at least 1 new vertebral fracture, compared with 16.7% of patients in the placebo/ris group. During the open-label period, similar percentages of patients in the placebo/ris and ris/ris groups experienced at least 1 new vertebral facture from Month 12 to Month 24 (20.0%, placebo/ris; 24.1%, ris/ris) and from Month 12 to Month 36 (26.7%, placebo/ris; 22.2%, ris/ris). Over the entire study (Baseline to Month 36), the percentages of patients who experienced new vertebral deformities were similar in the 2 treatment groups (31.1%, placebo/ris; 24.4%, ris/ris).

During the double-blind period, 20 new morphometric vertebral fractures were experienced by 8 placebo-treated patients (average of 2.5 vertebral fractures/placebo patient who had a new vertebral fracture). On the other hand, there were a total of 45 new morphometric vertebral fractures experienced by 29 risedronate-treated patients (average of 1.6 vertebral fractures/risedronate patient who had a new vertebral fracture). There was no significant difference between treatment groups in the rate of new morphometric vertebral fractures for risedronate patients as compared to patients in the placebo group. The estimated risedronate to placebo odds ratio was 1.39 (95% CI [0.60, 3.23]) at Endpoint (p = 0.45). The rate of new vertebral fractures was not analyzed for the open-label period

The percentages of patients who experienced new or worsening vertebral fractures (based on X-ray measurements) were similar in placebo/ris and ris/ris groups during the double-blind period (Baseline to Month 12), during the open-label period (Month 12 to Month 24 and Month 12 to Month 36), and over the entire study (Baseline to Month 36).

Clinical Vertebral and Non-vertebral Fractures

Clinical vertebral and non-vertebral fractures are fractures reported as treatment-emergent adverse events (TEAEs) and include all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures that occurred after randomization. During the double-blind period, no patients reported a clinical vertebral fracture. During the open-label period (Month 12 to Month 36), clinical vertebral fractures were experienced by 1 (2.0%) patient in the placebo/ris group (cervical vertebral fracture) and 3 (3.4%) in the ris/ris group (lumbar vertebral fracture, spinal compression fracture, and spinal fracture).

The analysis of time-to-first clinical fracture during the double-blind period shows a significantly lower proportion of patients with clinical fractures (non-vertebral) in the risedronate group versus

placebo with a relative risk reduction of 47% (hazard ratio [HR] = 0.53, 95% CI 0.31 – 0.92; log-rank p = 0.0253). Similarly, there was a lower proportion of patients with long-bone fractures in the risedronate group versus placebo with a relative risk reduction of 51% (HR = 0.49, 95% CI 0.25 – 0.95; logrank p = 0.0501) (see Table 3)

TABLE 3

Clinical Fractures - Time to First Event (Intent-to-treat; Year 1 Report)

Fracture Type Statistic	Placebo (N = 49)	Risedronate (N = 94)	Hazard Ratio	95% CI	p-value
All Fractures					
Number of patients with fractures	24	29			
Kaplan-Meier Cumulative Incidence	0.5043	0.314	0.534	(0.310,0.922)	0.0253
Vertebral Fracture					
Number of patients with fractures	0	0	-	-	-
Kaplan-Meier Cumulative Incidence	-	-	-	-	-
All Non-Vertebral Fracture					
Number of patients with fractures	24	29			
Kaplan-Meier Cumulative Incidence	0.5043	0.314	0.534	(0.310,0.922)	0.0253
Long Bone Non-Vertebral Fracture					
Number of patients with fractures	17	18			
Kaplan-Meier Cumulative Incidence	0.3618	0.1954	0.487	(0.250,0.950)	0.0501
Other Non-Vertebral Fracture					
Number of patients with fractures	10	12			
Kaplan-Meier Cumulative Incidence	0.204	0.1311	0.608	(0.262,1.410)	0.2141

Hazard Ratio and 95% CI based on Cox proportional hazards model stratified by age group with treatment and pooled-country as covariates.
P-values correspond to the log-rank test.
Long bones include radius, ulna, humerus, tibia, fibula, femur, upper limb fracture, and lower limb fracture.
Data taken from 2003100 Year 1 CSR, Table 25.

The analysis of time-to-recurrent clinical fracture during the double-blind period shows a significant reduction in the proportion of patients with recurrent clinical fractures in the risedronate group versus placebo with a relative risk reduction of 42% (HR=0.58, 95% CI 0.35 - 0.98; p = 0.0416). Similarly, there was a lower proportion of patients with recurrent long-bone clinical fractures in the risedronate group versus placebo with a relative risk reduction of 46% (HR = 0.54, 95% CI 0.27 – 1.08; p = 0.08). (see table 4)

TABLE 4

Clinical Fractures - Time to Recurrent Events (Intent-to-treat; Year 1 Report)

Fracture Type Statistic	Placebo (N = 49)	Risedronate (N = 94)	Hazard Ratio	95% CI	p-value
All Fractures					
Number of fractures	38	42			
Number of patients with fractures	24	29	0.584	(0.348,0.980)	0.0416
Vertebral Fracture					
Number of fractures	0	0	-	-	-
Number of patients with fractures	0	0	-	-	-
All Non-Vertebral Fracture					
Number of fractures	38	42			
Number of patients with fractures	24	29	0.584	(0.348,0.980)	0.0416
Long Bone Non-Vertebral Fracture					
Number of fractures	27	28			
Number of patients with fractures	17	18	0.543	(0.274,1.076)	0.0799
Other Non-Vertebral Fracture					
Number of fractures	11	14			
Number of patients with fractures	10	12	0.682	(0.304,1.532)	0.3540

Hazard Ratio and 95% CI based on Andersen-Gill mean intensity model stratified by age group with treatment and pooled-country as covariates.
P-values correspond to the Wald test.
Long bones include radius, ulna, humerus, tibia, fibula, femur, upper limb fracture, and lower limb fracture.
Data taken from 2003100 Year 1 CSR, Table 26.

Bone Turnover Markers

During the open-label period (Month 12 to Month 36), there were mean percent decreases from Baseline in serum Bone-specific Alkaline Phosphatase (BAP) in both treatment groups at Month 24, Month 36, and Endpoint, and the mean percent decreases were similar in the 2 groups at each of these time points. During the open-label period, further mean percent decreases from Baseline in Type I Collagen N-telopeptide Adjusted for Creatinine (NTX/Cr) were noted in both groups, and the decreases were similar in the placebo/ris and ris/ris groups.

Other End-points

A majority of patients in the placebo group reported no change in their pain score based on the Wong-Baker FACES pain rating scale; a higher percentage of patients in the risedronate group compared to placebo reported an "improvement" at all time points (eg, 22.9%, placebo; 32.6%, risedronate at Month 12); however, there was no statistically significant differences between the 2 groups at any time point. The Wong-Baker FACES Pain Rating Scale was not utilized during the open-label period.

The change from baseline in overall quality of life was assessed by the PedsQLPediatric QOL questionnaire at Month 12. The risedronate group had a statistically significant increase from baseline in the Emotional Function Domain Score, School Function Domain Score, Psychological Health Summary Score, and Total Scale Score; the placebo group had no statistically significant changes from baseline. There were no statistically significant differences between the 2 groups for any of the domain scores, including the mean change from baseline in Total Scale Score (100 point score). The Pediatric Quality of Life Questionnaire was not utilized during the open-label period.

- **Safety results**

During the double-blind period, no patients in the placebo group and 7 (7.4%) patients in the risedronate group discontinued on or prior to Month 12 (Table 4). The most common reason for discontinuation prior to Month 12 was voluntary withdrawal (0%, placebo; 4 patients, 4.3%, risedronate); 1 was lost in follow up, 1 had a protocol violation and 1 discontinued due to an AE (Crohn's disease).

All of the patients who completed the double-blind period (49 patients, placebo/ris; 87 patients, ris/ris group) were treated during the open-label period. Of these, 43 (87.8%) in the placebo/ris group and 82 (94.3%) in the ris/ris group completed Month 36 of the study. Six (12.2%) patients in the placebo/ris group, and 5 (5.7%) in the ris/ris group discontinued the study prior to Month 36. The most common reason for discontinuation prior to Month 36 was adverse event in the placebo/ris group (3 patients, 6.1%) and voluntary withdrawal in the ris/ris group (4 patients, 4.6%). During the open-label period (Month 12 to Month 36), 3 (6.1%) patients in the placebo/ris group and 1 (1.1%) in the ris/ris group withdrew because of an AE. The TEAEs leading to withdrawal were abdominal pain, abdominal pain upper, and benign bone neoplasm in 1 patient each in the placebo/ris group and pharyngitis in 1 patient in the ris/ris group.

During the double-blind period (Baseline to Month 12), over 90% of patients in each group experienced a Treatment-emergent Adverse Event (TEAE), and 1 patient (risedronate group) was withdrawn from the study due to a TEAE.

During the open-label period (Month 12 to Month 36), over 90% of patients in each group experienced a TEAE, and 3 (6.1%) patients in the placebo/ris group and 1 (1.1%) in the ris/ris group were withdrawn from the study because of a TEAE. Overall, the percentages of patients with TEAEs were similar in the 2 treatment groups. However, the percentages of patients with serious TEAEs, TEAEs that led to withdrawal, upper gastrointestinal (GI) TEAEs, and selected musculoskeletal TEAEs were lower in the ris/ris group than in the placebo/ris group. There were no deaths during the study. Most TEAEs were mild to moderate in severity.

During both the double-blind and open-label periods, the treatment groups were generally similar overall in the percent of patients with the most frequently reported TEAEs (Table 5).

TABLE 5

Most Common (>= 2 Patients in Either Treatment Group) Serious Treatment-emergent Adverse Events by MedDRA SOC and PT (Intent-to-treat)

	Double Blind		Open Label		
System Organ Class Preferred Term	Placebo (N=49) n (%) nAE	Risedronate (N=94) n (%) nAE	Placebo/Ris (N=49) n (%) nAE	Ris/Ris (N=87) n (%) nAE	p-value
OVERALL	8 (16.3%) 16	11 (11.7%) 18	13 (26.5%) 21	16 (18.4%) 24	0.2825
Injury, poisoning and procedural complications	8 (16.3%) 16	8 (8.5%) 14	10 (20.4%) 17	12 (13.8%) 18	0.3391
Femur fracture	7 (14.3%) 8	4 (4.3%) 7	6 (12.2%) 7	3 (3.4%) 5	0.0704
Tibia fracture	2 (4.1%) 2	2 (2.1%) 2	1 (2.0%) 1	2 (2.3%) 2	1.0000
Ulna fracture	2 (4.1%) 2	1 (1.1%) 1	2 (4.1%) 2	2 (2.3%) 3	0.6191
Forearm fracture	0 (0.0%) 0	2 (2.1%) 2	1 (2.0%) 1	1 (1.1%) 1	1.0000
Radius fracture	2 (4.1%) 2	0 (0.0%) 0	2 (4.1%) 2	0 (0.0%) 0	0.1281
Infections and infestations	0 (0.0%) 0	2 (2.1%) 2	1 (2.0%) 1	3 (3.4%) 3	1.0000
Gastrointestinal disorders	0 (0.0%) 0	2 (2.1%) 2	0 (0.0%) 0	0 (0.0%) 0	

Placebo/Ris: Placebo during the 1-year double-blind period and risedronate 2.5 or 5 mg daily during the 2-year open-label period.
Ris/Ris: Risedronate 2.5 or 5 mg daily during the 1-year double-blind period and the 2-year open-label period.
N=number of intent-to-treat patients within specified treatment.
n(%) = number (percent) of patients within specified category and treatment.
nAE = number of adverse events within the specified category and treatment.
P-value from Fisher's Exact Test on Open Label Period for descriptive purposes only (no adjustment for multiple comparisons).
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During the double-blind period, the most frequently reported TEAEs (≥ 10%) by PT were the following:

- Placebo group: gastroenteritis, fall, femur fracture, pain in extremity, back pain, arthralgia, abdominal pain, nausea, and pain
- Risedronate group: fall, pain in extremity, back pain, vomiting, abdominal pain upper, pain, and headache.

During the open-label period, femur fracture was experienced by 18.4% of patients in the placebo/ris group and by 4.6% of patients in the ris/ris group. The most frequently reported TEAEs (≥ 10%) by PT during this period were the following:

- Placebo/ris group: fall, hand fracture, femur fracture, arthralgia, back pain, pain in extremity, tibia fracture, pyrexia, abdominal pain, abdominal pain upper, ulna fracture, foot fracture, vomiting, forearm fracture.
- Ris/ris group: fall, back pain, hand fracture, pain in extremity, radius fracture, nasopharyngitis, ulna fracture.

Clinical Fractures Reported as TEAEs

Clinical vertebral and non-vertebral fractures are fractures reported as TEAEs and include all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures that occurred after randomization. During the double-blind period (Baseline to Month 12), clinical fractures were reported by 49.0% of patients in the placebo group and by 30.9% of patients in the risedronate group. The difference between the groups was due in part to a lower percentage of patients with femur fracture in the risedronate group than in the placebo group (16.3%, placebo; 9.6%, risedronate). No patients reported a clinical vertebral fracture during the double-blind period.

During the open-label period (Month 12 to Month 36), clinical fractures were reported by 65.3% of patients in the placebo/ris group and by 52.9% of patients in the ris/ris group. The percentage of patients reporting femur fracture was 18.4% in the placebo/ris group and 4.6% in the ris/ris group (Table 6). Clinical vertebral fractures were experienced by 1 (2.0%) patient in the placebo/ris group (cervical vertebral fracture) and 3 (3.4%) in the ris/ris group (lumbar vertebral fracture, spinal compression fracture, and spinal fracture).

TABLE 6

All Long Bone Clinical Fractures Reported as Treatment-emergent Adverse Events by PT (Intent-to-treat)

All Fractures Long Bone Type Preferred Term	Double Blind Placebo (N=49) n (%) nAE	 Risedronate (N=94) n (%) nAE	Open Label Placebo/Ris (N=49) n (%) nAE	 Ris/Ris (N=87) n (%) nAE	p-value
All Long Bone Fractures	16 (32.7%) 27	18 (19.1%) 28	23 (46.9%) 43	29 (33.3%) 58	0.1424
Upper Extremity	9 (18.4%) 13	8 (8.5%) 9	13 (26.5%) 18	22 (25.3%) 38	1.0000
Radius fracture	4 (8.2%) 5	1 (1.1%) 1	3 (6.1%) 3	11 (12.6%) 11	0.3782
Ulna fracture	4 (8.2%) 5	2 (2.1%) 3	5 (10.2%) 6	9 (10.3%) 12	1.0000
Humerus fracture	0 (0.0%) 0	1 (1.1%) 1	3 (6.1%) 3	5 (5.7%) 6	1.0000
Forearm fracture	2 (4.1%) 2	3 (3.2%) 3	5 (10.2%) 6	3 (3.4%) 3	0.1363
Upper limb fracture	0 (0.0%) 0	1 (1.1%) 1	0 (0.0%) 0	3 (3.4%) 4	0.5529
Hand fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Wrist fracture	1 (2.0%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Lower Extremity	10 (20.4%) 14	11 (11.7%) 19	14 (28.6%) 25	13 (14.9%) 20	0.0732
Tibia fracture	2 (4.1%) 3	5 (5.3%) 5	7 (14.3%) 10	7 (8.0%) 7	0.2568
Femur fracture	8 (16.3%) 9	9 (9.6%) 12	9 (18.4%) 11	4 (4.6%) 7	0.0136
Fibula fracture	2 (4.1%) 2	2 (2.1%) 2	4 (8.2%) 4	2 (2.3%) 2	0.1880
Lower limb fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	2 (2.3%) 2	0.5356
Avulsion fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Pain in extremity	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000

N=number of intent-to-treat patients within specified treatment.
n(%) = number (percent) of patients within specified category and treatment.
nAE = number of adverse events within the specified category and treatment.
P-value from Fisher's Exact Test on Open Label Period for descriptive purposes only (no adjustment for multiple comparisons).
Corresponding data can be found in Appendix 13.2.7 Listing 1.
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TZ6411.

During the double-blind period, in the placebo group, clinical fractures were experienced by 42.9% of patients in the 4- to 9-year age group and by 57.1% of patients in the 10- to 15-year age group. In the risedronate group, clinical fractures were experienced by 41.5% of patients in the younger age group and by 17.1% of patients in the older age group. During the open-label period, in the placebo/ris group, clinical fractures were experienced by 71.4% of patients in the younger age group and by 57.1% of patients in the older age group. In the ris/ris group, clinical fractures were experienced by 54.2% of patients in the younger age group and by 51.3% of patients in the older age group. There was one report of abnormal healing time during the double-blind period (delayed union of a distal femur fracture in a 6 year old girl in the risedronate group) but there were reports of abnormal healing times during the open label period.

During the double-blind period, there were mean percent increases from Baseline in height in both treatment groups. At Month 12, the mean percent increase in height was 4.5% in the placebo group and 5.5% in the risedronate group. When patients who sustained at least 1 new vertebral fracture during the study were evaluated separately, both treatment groups continued to have a mean percent increase from Baseline in height. Among these patients, the mean percent increase in height at Month 12 was 3.1% in the placebo group and 4.2% in the risedronate group. During the open-label period, mean height increased in both groups, and the mean changes from Baseline were similar in the placebo/ris and ris/ris groups. Mean percent changes in height were not analyzed during the open-label period. Mean bone age increased at each time point in both treatment groups. The mean increases in bone age were similar in the 2 treatment groups, as was the change from Baseline in annualized growth velocity.

3. Discussion on clinical aspects

During the double-blind period, the mean percent increases in lumbar spine BMD were 7.6% in the children with OI treated with placebo and 16.1% in those treated with risedronate. There were no differences between the placebo and risedronate groups in the Wong-Baker FACES pain score and Pediatric Quality of Life endpoints, which were assessed during the double-blind period only. As evaluated with adult methodology (the Genant (1993) semi-quantitative (SQ) scoring System), the percentage of patients who experienced at least one new morphometric

(identified by x-ray) vertebral fracture was 31.8% in the risedronate group compared with 16.7% in the placebo group (p = 0.0680).

The MAH concluded that the data from the 2-year open-label period were consistent with and supported the findings from the 1-year double-blind period of the study. During the period of open-label treatment, patients in the placebo/ris group experienced increases in BMD similar to those experienced after 1 year of double-blind treatment by patients in the ris/ris group. As soon as all patients were on risedronate, the percentages of patients who experienced new morphometric vertebral fractures, scored according to the Genant SQ-scoring system, become more equal. Therefore over the whole study period the occurrences in the second and third year tend to outweigh the differences in the first year double-blind period thereby reducing the two-fold difference. However this cannot remove the concern that in the first double-blind comparison there was a much larger percentage in the active group. Also it should be noted that in the second and third years, when considered as separate time periods, between 20 and 27% of patients had at least one new fracture while receiving risedronate treatment.

Looking at Table 25 it would appear that younger children were having more fractures and certainly there were more fractures in patients treated with risedronate than with placebo.

Table 25
Incidence of New Vertebral Fractures by SQ Score Stratified by Age Group
(Intent-to-treat; Year 1 Report)

Category	4 - 9 years		10 - 15 years	
	Placebo N=28	Risedronate N=53	Placebo N=21	Risedronate N=41
Number of patients with new vertebral fractures	7	19	1	10
Number of new vertebral fractures	19	32	1	13
Number of patients with new vertebral fractures and mild SQ score (change from 0 to Grade 1)	7	17	1	10
Number of patients with new vertebral fractures and moderate & severe SQ score (change from 0 to Grade 2 or 3)	3	3	0	1

SQ=semi-quantitative
Note: Numbers in the columns are not additive as a patient may have had both mild and moderate/severe fractures.
Data taken from 2003100 Year 1 CSR, Table 23.

The MAH stated that the safety data from the open-label period were similar and supported those from the double-blind period. Data from both study periods showed that risedronate treatment was generally safe and well tolerated in children with OI. The MAH states that during the open-label period, there were no clinically relevant differences between the placebo/ris and ris/ris groups except that the percentage of patients who reported clinical fractures was lower in the ris/ris group than in the placebo/ris group. This difference was partly due to a lower percentage of patients with femur fracture in the ris/ris group than in the placebo/ris group.

When looking at the percentages of clinical fractures reported as treatment-emergent AEs, it is difficult to reach any robust conclusion as the sample size is considered very limited to assess any safety issues and therefore any p-values quoted are unlikely to be meaningful due to lack of statistical power. However it is noted from the table below (Table 48) that during the double blind period 49% of patients in the placebo group reported a clinical fracture compared to 30.9% in the risedronate group. During the open label period the lack of a placebo comparator limits the value of the data; however after 2 years of risedronate treatment (in the placebo/risedronate group), 65.3% of the patients reported a clinical fracture and 52.9% of patients after 3 years of risedronate treatment (in the ris/ris group) reported clinical fractures. Based on these data it is difficult to establish that the improvement in the BMD from the risedronate treatment also results in a consequent improvement in the incidence of fractures which is considered the clinically meaningful outcome in these patients.

Table 48
Clinical Fractures Reported as Treatment-emergent Adverse Events by PT
(Intent-to-treat)

All Fractures Preferred Term	Double Blind Placebo (N=49) n (%) nAE	Risedronate (N=94) n (%) nAE	Open Label Placebo/Ris (N=49) n (%) nAE	Ris/Ris (N=87) n (%) nAE	p-value
All Fractures	24 (49.0%) 39	29 (30.9%) 42	32 (65.3%) 66	46 (52.9%) 96	0.2064
Hand fracture	3 (6.1%) 3	5 (5.3%) 6	11 (22.4%) 11	12 (13.8%) 17	0.2357
Radius fracture	4 (8.2%) 5	1 (1.1%) 1	3 (6.1%) 3	11 (12.6%) 11	0.3782
Ulna fracture	4 (8.2%) 5	2 (2.1%) 3	5 (10.2%) 6	9 (10.3%) 12	1.0000
Foot fracture	1 (2.0%) 1	6 (6.4%) 7	5 (10.2%) 5	7 (8.0%) 7	0.7559
Tibia fracture	2 (4.1%) 3	5 (5.3%) 5	7 (14.3%) 11	7 (8.0%) 7	0.2568
Humerus fracture	0 (0.0%) 0	1 (1.1%) 1	3 (6.1%) 3	5 (5.7%) 6	1.0000
Femur fracture	8 (16.3%) 9	9 (9.6%) 12	9 (18.4%) 11	4 (4.6%) 7	0.0136
Upper limb fracture	1 (2.0%) 1	1 (1.1%) 1	0 (0.0%) 0	4 (4.6%) 6	0.2964
Forearm fracture	2 (4.1%) 2	3 (3.2%) 3	5 (10.2%) 6	3 (3.4%) 3	0.1363
Clavicle fracture	2 (4.1%) 2	0 (0.0%) 0	3 (6.1%) 3	2 (2.3%) 2	0.3507
Fibula fracture	2 (4.1%) 2	2 (2.1%) 2	4 (8.2%) 4	2 (2.3%) 2	0.1880
Lower limb fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	2 (2.3%) 2	0.5356
Patella fracture	0 (0.0%) 0	0 (0.0%) 0	1 (2.0%) 1	2 (2.3%) 2	1.0000
Rib fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	2 (2.3%) 2	0.5356
Wrist fracture	3 (6.1%) 3	0 (0.0%) 0	0 (0.0%) 0	2 (2.3%) 2	0.5356
Avulsion fracture	1 (2.0%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Ilium fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Lumbar vertebral fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Pain in extremity	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Pelvic fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Scapula fracture	0 (0.0%) 0	1 (1.1%) 1	1 (2.0%) 1	1 (1.1%) 1	1.0000
Spinal compression fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Spinal fracture	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (1.1%) 1	1.0000
Ankle fracture	2 (4.1%) 2	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	
Cervical vertebral fracture	0 (0.0%) 0	0 (0.0%) 0	1 (2.0%) 1	0 (0.0%) 0	0.3603

Placebo/Ris: Placebo during the 1-year double-blind period and risedronate 2.5 or 5 mg daily during the 2-year open-label period.
Ris/Ris: Risedronate 2.5 or 5 mg daily during the 1-year double-blind period and the 2-year open-label period.
N=number of intent-to-treat patients within specified treatment.
n(%) = number (percent) of patients within specified category and treatment.
nAE = number of adverse events within the specified category and treatment.
P-value from Fisher's Exact Test on Open Label Period for descriptive purposes only (no adjustment for multiple comparisons).
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Blinded Re-reading of X-rays from Study Number: 2003100 Addendum to Year 3 Final Report

A secondary objective of the study was to determine the incidence and rate of new morphometric vertebral fractures over 12, 24, and 36 months. Morphometric vertebral fractures were determined by lateral radiographs according to the Genant (1993) semi-quantitative (SQ) scoring system (see Annex 1). This methodology has been used in adults and has become standard in osteoporosis research. Both semi-quantitative assessment and quantitative assessment have been employed in pediatric trials.
Minor changes on vertebral x-rays for children with OI are difficult to read and score. As a result, vertebral x-rays are difficult to interpret in children with OI, and enumeration of vertebral fractures may be unreliable in these instances (Sakkers et al., 2004). To account for intra- and inter-reader variability in SQ-scores, an additional analysis of "new or worsening vertebral deformities" was introduced in the open-label period of the study (years 2 and 3). New or orsening fractures were defined as any vertebrae that had more than a +2 change from Baseline (month 12) or a baseline (month 12) score of 2 that increased to 3.

Following a review of the unblinded, 1- year efficacy data by the DSMB, questions were raised regarding the reliability of the reading of the x-ray films. A qualitative review by DSMB members indicated that some of the vertebral xray films may have been unclear or not interpreted consistently by the central vendor. Following a recommendation of the DSMB, the MAH

proposed that a new read of the vertebral x-ray films be performed by 2 independent readers experienced in reviewing x-rays from children with OI.

This report describes the procedures for re-read of the vertebral x-ray images obtained in this study, summaries of the results of the re-reads of the vertebral x-ray images captured throughout the course of this study, and a comparison of these results with the results of the original reads.

Methodology

To ensure consistency, study specific review instructions were created, and were signed off by the Readers prior to the first read session and start of each read session. The purpose of the read rules document was to describe the processes (primary read, consensus/adjudication), services, and issues related to the independent blinded review of the x-ray data.

In a first session, the 2 primary readers read 100% of cases independently.

In a second session, the 2 primary readers performed an open consensus adjudication (consensus read) together in those cases where a significant discrepancy occurred between the 2 primary readers' SQ scores for any vertebral level (T4-L4) within a time point. If the 2 primary readers were unable to agree on a SQ score during their consensus read, the adjudicator assessed the case in question and made the final decision.

Results

Consensus-reads were performed for 48 of 49 patients in the placebo/ris group and for 88 of 94 patients in the ris/ris group. Although Readers 1 and 2 came to conflicting conclusions after their independent reads, they reached agreement during the consensus reads in all cases.

During the double-blind period, 31.8% of patients in the risedronate group experienced at least 1 new vertebral fracture, compared with 33.3% of patients in the placebo group (Table 7). During the open-label period, there were no significant differences between the placebo/ris and ris/ris groups with respect to the percentages of patients who experienced at least 1 new vertebral fracture from Month 12 to Month 24 (20.0%, placebo/ris; 13.3% ris/ris), from Month 12 to Month 36 (20.0%, placebo/ris; 13.6%, ris/ris), or over the entire study from Baseline to Month 36 (33.3%, placebo/ris; 24.4%, ris/ris).

TABLE 7

Incidence of New Vertebral Deformities, X-ray Re-read (Final Consensus) (Intent-to-treat)

Visit Deformity Status	Placebo/Ris (N=49)	Ris/Ris (N=94)	p-value
Double Blind Baseline to Month 12			
n	48	88	
At Least 1 New Deformed Vertebra	16 (33.3%)	28 (31.8%)	0.8506
No New Deformed Vertebra	32 (66.7%)	60 (68.2%)	
Open Label Month 12 to Month 24			
n	45	83	
At Least 1 New Deformed Vertebra	9 (20.0%)	11 (13.3%)	0.3207
No New Deformed Vertebra	36 (80.0%)	72 (86.7%)	
Open Label Month 12 to Month 36			
n	45	81	
At Least 1 New Deformed Vertebra	9 (20.0%)	11 (13.6%)	0.4459
No New Deformed Vertebra	36 (80.0%)	70 (86.4%)	
Entire Study Baseline to Month 36			
n	45	82	
At Least 1 New Deformed Vertebra	15 (33.3%)	20 (24.4%)	0.3044
No New Deformed Vertebra	30 (66.7%)	62 (75.6%)	

N=number of intent-to-treat patients within specified treatment.
n=number of patients with at least one vertebra evaluated at the specified start and end visits.
New Deformity=SQ score is 0 at the specified start visit and >0 at the specified end visit within each study category.
P-value refers to Fisher's Exact Test.
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There were no statistically significant differences between the placebo/ris and ris/ris groups with respect to the percentages of patients who experienced 0, 1, 2, or ≥ 3 new vertebral fractures during the double-blind period (Baseline to Month 12), during the open-label period (Month 12 to Month 24 and Month 12 to Month 36), or over the entire study (Baseline to Month 36).

There were no statistically significant differences between the placebo/ris and ris/ris groups with respect to the percentages of patients who experienced new or worsening vertebral fractures (based on x-ray measurements) during the double-blind period (Baseline to Month 12), during the open-label period (Month 12 to Month 24 and Month 12 to Month 36), or over the entire study (Baseline to Month 36). There were no statistically significant differences between the placebo/ris and ris/ris groups with respect to the percentages of patients with 0, 1, 2, or ≥ 3 new or worsening morphometric vertebral fractures during the double-blind period (Baseline to Month 12), during the open-label period (Month 12 to Month 24 and Month 12 to Month 36), or over the entire study (Baseline to Month 36).

It is stated by the MAH that after the consensus read, the re-readers arrived at the conclusion that there was no meaningful difference between placebo- and risedronate-treated patients in terms of fracture incidence. As noted above, vertebral x-rays are difficult to interpret in children with OI. Because many microfractures and small collapses of vertebral bodies are difficult to detect and may not be discovered (Sakkers et al., 2004), readers have had difficulty distinguishing between an SQ-score of 0 and 1. As a result, minor changes on vertebral x-rays for children with OI are difficult to interpret. Thus, the Genant scoring system may not be appropriate in paediatric cases. The MAH states that another factor possibly contributing to this difficulty is that treatment with risedronate enhances the density of newly formed bone close to the growth plates that are present on the superior and inferior surfaces of every vertebra in the growing spine. This may enable radiologists to visualize pre-existing deformities more clearly.
It is concluded by the MAH that, the findings from the consensus reread support the original conclusion of the study that the anti-resorptive effects and favourable bone safety profile of risedronate were consistent with those demonstrated in risedronate clinical trials in adults with osteoporosis using various doses and dosing regimens.

Statistical Assessor's Comments

It is important to consider the reliability of the reading of the x-rays. The agreement between the two original readers is low (Kappa score of 0.419) for morphometric vertebral fractures. However both readers assessed that there were more patients with at least one new fracture in the risedronate group than the placebo group although each reader read x-rays for a different half of the patients. It should be noted that the p-values are not necessarily meaningful probably due to low statistical power.

The addendum to the clinical study report described independent reading of the x-rays by two primary readers and an adjudicator. Results from the two readers were not consistent in the direction of the imbalance between the two groups, although the majority of x-rays were read by both. In fact while Reader 1 identified a higher percentage of patients with fractures in the placebo group than in the risedronate group, Reader 2 identified a higher percentage in the risedronate group.

New vertebral deformities from x-ray re-read for double blind period (Extracted from Tables 1 and 2 of the addendum by the statistical assessor)

	Reader 1		*Reader 2*	
	Placebo n (%) N=48	*Risedronate n (%) N=88*	*Placebo n (%) N=45*	*Risedronate n (%) N=87*
At least one new deformed vertebra	*13 (27)*	*16 (18)*	*6 (13)*	*21 (24)*

Although the two readers came to conflicting conclusions after their independent reads, they reached agreement during the consensus reads in all cases without using the adjudicator. Remarkably the final results showed no difference between the two treatments.

New vertebral deformities from x-ray final consensus for double blind period (Extracted from Table 3 of the addendum by the statistical assessor)

	Placebo N=48	*Risedronate N=88*
At least one new deformed vertebra	*16 (33)*	*28 (32)*

This must raise serious concerns over the reliability of the x-ray data. Although it is understood that the two readers conducting the independent re-read were blinded at all times to the study treatments received by the patients, the results of this exercise are surprising. Therefore it is difficult to consider the findings of the investigation of this endpoint with any level of confidence especially as this was a post hoc investigation.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The use of bisphosphonates in children with OI has become a common clinical practice, although there is no drug licensed specifically for this indication in UK. A systematic review of the effects of bisphosphonate treatment in children with OI (Castillo et al 2009) concluded that despite a large body of published literature, there have been only eight studies with a sufficiently high level of internal validity to be truly informative. These studies confirm improvement in bone density. Some, but not all studies, demonstrate reduction in fracture rate and enhanced growth. There has been extremely limited evaluation of broader treatment impacts such as deformity, need for orthopaedic surgery, pain, functioning, or quality of life. As an example a 2-year randomized placebo-controlled trial (Kok et al 2007) has found only slight differences in quality of life in favour of the bisphosphonate group. Short-term side effects were minimal. More recent studies raise even more doubts for the efficacy of bisphosphonates in paediatric OI. Ward et al (2011) conducted a multicenter, double-blind, randomized, placebo-controlled study, including 139 children (aged 4-19 yr) with type I, II,IV OI and concluded that “oral alendronate for 2 years in significantly decreased bone turnover and increased spine areal BMD but was not associated with improved fracture outcomes.” However a retrospective case-control study of a population of children with primarily neuromuscular disease (Dominquez-Bartness et al 2012) concluded that “Alendronate does not reliably improve bone density in children and young adults with primarily neuromuscular disease and without osteogenesis imperfecta.” Rauch et al (2009) conducted a single-centre randomized double-blind placebo-controlled trial in a total of 26 children and adolescents (age, 6.1-17.7 yr) with OI type I, randomized to either placebo (n = 13) or risedronate (n = 13) for 2 yr. Risedronate doses were 15 mg once per week in patients weighing <40 kg and 30 mg once per week in patients weighing >40 kg. After 2 yr of treatment, risedronate decreased serum levels of the bone resorption marker collagen type I N-telopeptide by 35% compared with a 6% reduction with placebo (p = 0.003). Risedronate increased lumbar spine areal BMD Z-scores by 0.65, whereas patients receiving placebo experienced a decrease of 0.15 (p = 0.002). In contrast, no significant treatment differences in bone mass and density were found at the radial metaphysis and diaphysis, the hip, and the total body. The authors concluded that “These results suggest that the skeletal effects of oral risedronate are weaker than those that are commonly observed with intravenous pamidronate treatment but still lead to an increase in lumbar spine areal BMD.” Even in adults the results from bisphosphonate treatment with OI is not very promising as Bradbury et al (2012) concluded that “Risedronate in adults with OI type I results in modest but significant increases in BMD at LS, and decreased

bone turnover" but fracture incidence remained high suggesting that this increase in BMD may be insufficient to make a clinically significant difference to fracture incidence.

- **Overall conclusion**

The MAH concluded that the findings of this study support positive anti-absorption and a favourable bone safety profile of risedronate when used in paediatric OI patients. However there are no robust data to confirm that the improvement in lumbar spine BMD due to treatment with risedronate also results in a consequent improvement in the incidence of fractures. As it is stated by the MAH "because of the retrospective nature of the re-reads for the double-blind phase of the study, the contradictory results of the independent re-reads during that phase, and the failure to demonstrate a vertebral fracture benefit in risedronate-treated patients, these data still do not support the use of risedronate in children with mild to moderate OI."

The rapporteur agrees that based on the evidence submitted for the completed 3 years paediatric OI study 2003100, the use of risedronate should not be recommended.
However the information currently included in section 5.1 of the SmPC should be amended to reflect the overall data from the completion of this study. The rapporteur does not support the MAH's conclusion that based on the re-read of the spinal X-rays there was no meaningful difference between placebo- and risedronate-treated patients in terms of fracture incidence. Regardless of the difficulties in assessing reliably the spinal x-rays, serious concerns have been raised regarding the reliability of this post hoc investigation. On these grounds the rapporteur does not agree that the wording in the SmPC regarding the incidence of new morphometric spinal fractures as previously agreed during the Article 45 work-sharing procedure can be replaced. However the rapporteur considers that additional information on the overall incidence of clinical fractures has to be included in section 5.1 to provide the prescribers a more complete overview of the evidence generated from this study.

- **Recommendation**

Type Ib variation to be requested from the MAH within 60 days from circulation of this final assessment report.

4.2 Posology and method of administration

Paediatric population: Risedronate sodium is not recommended for use in children below 18 years of age due to insufficient data on its efficacy and safety (also see section 5.1).

5.1 Pharmacodynamic properties

Paediatric population: The safety and efficacy of risedronate sodium has been investigated in a 3 year study (a randomized, double-blind, placebo-controlled, multicenter, parallel group study of one-year duration followed by 2 years of open-label treatment) in paediatric patients aged 4 to less than 16 years with mild to moderate osteogenesis imperfecta. In this study, patients weighing 10-30 kg received risedronate 2.5 mg daily and patients weighing more than 30 kg received risedronate 5 mg daily.
After completion of its one-year randomized, double-blind, placebo controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated ; however an increased number of patients with at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. During the one year double blind period, the percentage of patients who reported clinical fractures was 30.9% in the risedronate group and 49.0% in the placebo group.

In the open label period when all patients received risedronate(month 12 to month 36), clinical fractures were reported by 65.3% of patients initially randomized to the placebo group and by 52.9% of patients initially randomized to the risedronate group. Overall, results are insufficient to support the use of risedronate sodium in paediatric patients with mild to moderate osteogenesis imperfecta.

PIL INFORMATION

The MAH informed the rapporteur that in the section 2 of the PIL of risedronate 'What you need to know before you take Optinate", the following statement regarding paediatric use was already added further to completion of Article 45 paediatric procedure in 2009:

"Children and adolescents
Risedronate sodium is not recommended for use in children below 18 due to insufficient data on safety and efficacy."

This information is considered sufficient in the PIL by the MAH and no further update is envisaged. The rapporteur agrees with the MAH's conclusion and has no further comments.