Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial

Nick Bishop, Silvano Adami, S Faisal Ahmed, Jordi Antón, Paul Arundel, Christine P Burren, Jean-Pierre Devogelaer, Thomas Hangartner, Eva Hosszú, Joseph M Lane, Roman Lorenc, Outi Mäkitie, Craig F Munns, Ana Paredes, Helene Pavlov, Horacio Plotkin, Cathleen L Raggio, Maria Loreto Reyes, Eckhard Schoenau, Oliver Semler, David O Sillence, Robert D Steiner

Lancet 2013; 382: 1424–32

Published Online August 6, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61091-0

See Comment page 1388

Academic Unit of Child Health, Department of Human Metabolism, University of Sheffield, Sheffield Children's Hospital, Sheffield, UK (N Bishop MD, P Arundel MD); **Rheumatologic Rehabilitation Unit, University of Verona, Verona, Italy** (S Adami MD); **Royal Hospital for Sick Children, University of Glasgow, Glasgow, UK** (S F Ahmed MD); **Paediatric Rheumatology Unit, Paediatrics Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain** (J Antón MD); **Department of Paediatric Endocrinology and Diabetes, Bristol Royal Hospital for Children, University Hospitals Bristol NHS Foundation Trust, Bristol, UK** (C P Burren MD); **Université Catholique de Louvain, Saint-Luc University Hospital, Brussels, Belgium** (J-P Devogelaer MD); **Biomedical Imaging Laboratory, Wright State University, Dayton, OH, USA** (T Hangartner PhD); **Endocrine Ward, Second Department of Paediatrics, Semmelweis University, Budapest, Hungary** (E Hosszú MD); **Department of Orthopedics and Trauma** (J M Lane MD), **Department of Radiology and Imaging** (H Pavlov MD), **and Department of Pediatric Orthopedics** (C L Raggio MD), **Hospital for Special Surgery, New York, NY, USA; Department of Biochemistry, Radioimmunology, and Experimental Medicine, Children's Memorial Health Institute, Warsaw, Poland** (R Lorenc MD); **Paediatric Endocrinology and Metabolic Bone Diseases, Helsinki University Central Hospital and University of Helsinki, Helsinki,**

Summary

Background Children with osteogenesis imperfecta are often treated with intravenous bisphosphonates. We aimed to assess the safety and efficacy of risedronate, an orally administered third-generation bisphosphonate, in children with the disease.

Methods In this multicentre, randomised, parallel, double-blind, placebo-controlled trial, children aged 4–15 years with osteogenesis imperfecta and increased fracture risk were randomly assigned by telephone randomisation system in a 2:1 ratio to receive either daily risedronate (2·5 or 5 mg) or placebo for 1 year. Study treatment was masked from patients, investigators, and study centre personnel. Thereafter, all children received risedronate for 2 additional years in an open-label extension. The primary efficacy endpoint was percentage change in lumbar spine areal bone mineral density (BMD) at 1 year. The primary efficacy analysis was done by ANCOVA, with treatment, age group, and pooled centre as fixed effects, and baseline as covariate. Analyses were based on the intention-to-treat population, which included all patients who were randomly assigned and took at least one dose of assigned study treatment. The trial is registered with ClinicalTrials.gov, number NCT00106028.

Findings Of 147 patients, 97 were randomly assigned to the risedronate group and 50 to the placebo group. Three patients from the risedronate group and one from the placebo group did not receive study treatment, leaving 94 and 49 in the intention-to-treat population, respectively. The mean increase in lumbar spine areal BMD after 1 year was 16·3% in the risedronate group and 7·6% in the placebo group (difference 8·7%, 95% CI 5·7–11·7; p<0·0001). After 1 year, clinical fractures had occurred in 29 (31%) of 94 patients in the risedronate group and 24 (49%) of 49 patients in the placebo group (p=0·0446). During years 2 and 3 (open-label phase), clinical fractures were reported in 46 (53%) of 87 patients in the group that had received risedronate since the start of the study, and 32 (65%) of 49 patients in the group that had been given placebo during the first year. Adverse event profiles were otherwise similar between the two groups, including frequencies of reported upper-gastrointestinal and selected musculoskeletal adverse events.

Interpretation Oral risedronate increased areal BMD and reduced the risk of first and recurrent clinical fractures in children with osteogenesis imperfecta, and the drug was generally well tolerated. Risedronate should be regarded as a treatment option for children with osteogenesis imperfecta.

Funding Alliance for Better Bone Health (Warner Chilcott and Sanofi).

Introduction

Osteogenesis imperfecta (also known as brittle bone disease) is the most common heritable bone disease with an osteoporotic phenotype.[1] Prevalence is estimated to be between 1 and 2 per 20 000 people.[2,3] Children with osteogenesis imperfecta sustain recurrent fractures, bony deformity, and bone pain.[4–6]

Bisphosphonates are an established treatment for osteoporosis in adults.[7] They increase areal bone mineral density (BMD) and decrease the incidence of osteoporotic fractures. Beneficial effects have also been reported in children with osteogenesis imperfecta.[8–15] In randomised controlled trials, cyclic intravenous neridronate[16] and pamidronate[17] and daily oral olpadronate[18] increased BMD and reduced reported fracture rates in children with osteogenesis imperfecta. However, investigators of a 2008 Cochrane review[19] concluded that it was unclear whether or not treatment with oral or intravenous bisphosphonate reduced fracture incidence in osteogenesis imperfecta.

Treatment with intravenous bisphosphonate requires infusions at regular intervals at home or during hospital stays of up to 3 days. These interludes are disruptive, affect schooling, cause parents to miss time at work, and can be traumatic for children. Oral treatment offers advantages in terms of convenience, cost, and reduced individual distress. Oral administration of alendronate has been shown to lead to substantial improvements in quality of life.[20] However, a large study[21] did not show a substantial improvement in fracture incidence in children with moderate or severe osteogenesis imperfecta treated with alendronate.

Risedronate is an orally administered, third-generation bisphosphonate. Two small studies[15,22] have shown that risedronate was well tolerated and that it significantly

increased BMD in children with mild to severe osteogenesis imperfecta, and reduced long-bone bowing deformities in children with moderate or severe disease. Fracture rates decreased in one of the studies,[22] but not in the other.[15]

The aim of this phase 3 study was to investigate the safety and efficacy of risedronate in children with osteogenesis imperfecta, most of whom had mild disease.

Methods

Study design and participants

In this international, randomised, double-blind, placebo-controlled, multicentre, parallel group study, patients were enrolled at 20 hospital centres in 13 countries across North and South America, Europe, Africa, and Australia. Children with osteogenesis imperfecta[1,23] aged 4–15 years were eligible for inclusion in the study. Patients had either a history of at least one non-traumatic or low-impact fracture and an age-adjusted and sex-adjusted areal BMD *Z* score of –1·0 or less for either total body or lumbar spine sites, or an adjusted areal BMD *Z* score of –2·0 or less irrespective of a history of fractures. Patients were excluded if they weighed less than 10 kg; had a history of cancer within the previous 5 years; had untreated rickets during the previous year; had a serum 25-hydroxyvitamin D concentration of less than 20 nmol/L; had used treatments that could affect interpretation of study findings; or had disease that was severe enough that in their country of origin they would normally have been offered intravenous bisphosphonate treatment.

Patients received their randomly assigned treatment (risedronate or placebo) for 1 year and then open-label treatment with risedronate for 2 additional years. The protocol was approved by the appropriate institutional review boards or independent ethics committees. Investigators obtained assent from the patients and written informed consent from their parents or legal representatives. The appendix lists some additional details of the methods used. The trial ran from Nov 16, 2004, to March 19, 2010, and is registered with ClinicalTrials.gov, number NCT00106028.

Randomisation and masking

Patients were stratified by age (4–9 and 10–15 years) and randomly assigned to receive treatment for 1 year with risedronate tablets or placebo in a 2:1 ratio by a telephone-based interactive voice response system in several permuted blocks of ten to 12 (placebo-controlled phase). Risedronate and placebo tablets were identical in appearance. The study treatment was masked from patients, investigators, and study centre personnel during the first year. After the first year, all patients were given risedronate (open-label phase).

Procedures

During the placebo-controlled phase, patients received doses in accordance with their weight at baseline.

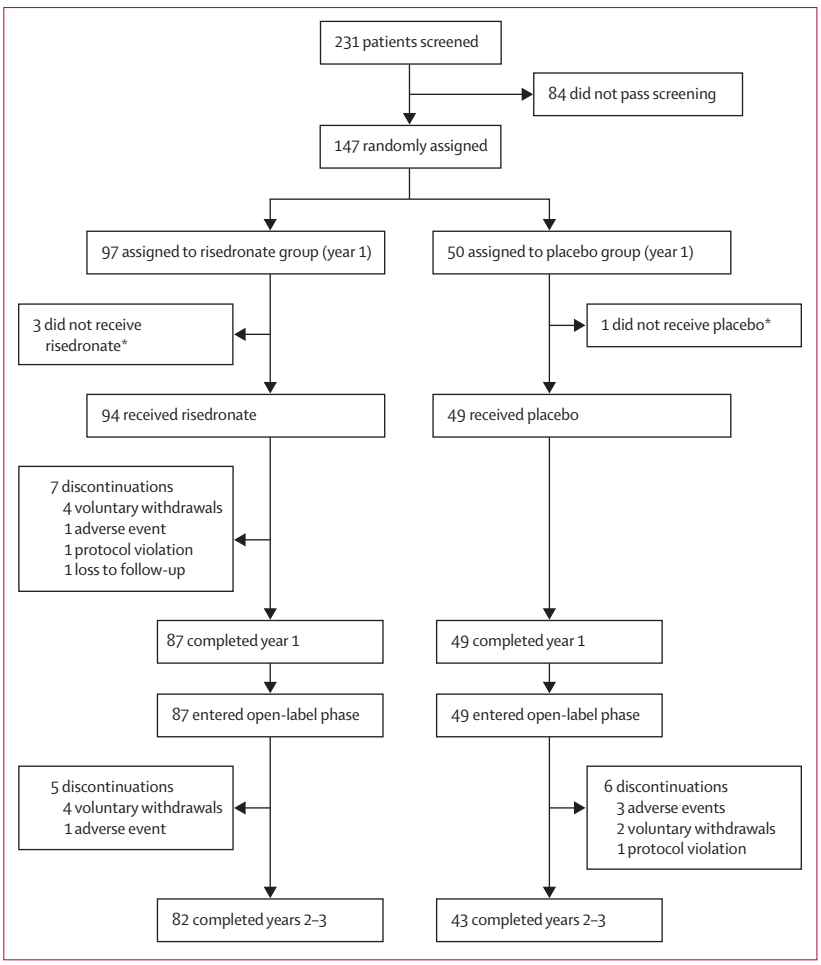

Figure 1: **Trial profile**
*Reasons for withdrawal before treatment were not recorded.

Patients who weighed 10–30 kg received 2·5 mg risedronate or placebo daily; patients who weighed more than 30 kg received 5 mg risedronate or placebo daily. During years 2 and 3, patients received open-label risedronate daily, dosed at 2·5 or 5 mg in accordance with their weight at the end of year 1. The daily dose was based on the approved dosing schedule for adults at the time the study was conceived. Study treatment was given with 120 mL of water. Patients who could not swallow tablets took their study treatment as a solution with a dosing spoon. All patients took study treatment at least 30 min before the first food and drink (apart from plain water) of the day and remained upright for 30 min after dosing. Compliance was assessed by tablet count at each visit. All patients received daily calcium (500–1000 mg) and vitamin D (200–600 IU) appropriate to their weight.

Patients visited the study centre at screening, baseline, and months 3, 6, 12, 15, 18, 24, 30, and 36 for clinical review. Height was measured, at screening and annually, to the nearest 1 mm with a wall-mounted stadiometer.

Finland (O Mäkitie MD); **Bone and Mineral Medicine** (C F Munns MD) **and Connective Tissue Dysplasia Service** (D O Sillence MD), **Sydney Children's Hospital Network, Westmead, NSW, Australia; Herbert Wertheim College of Medicine, Miami Children's Hospital, Miami, FL, USA** (A Paredes MD); **Pediatrics and Orthopedic Surgery, University of Nebraska Medical Center, Children's Hospital, Omaha, NE, USA** (H Plotkin MD); **Pontificia Universidad Católica de Chile, Santiago, Chile** (M L Reyes MD); **Children's Hospital, University of Cologne, Cologne, Germany** (E Schoenau MD, O Semler MD); **and Marshfield Clinic Research Foundation, Marshfield, WI, USA** (R D Steiner MD)

Correspondence to:
Prof Nick Bishop, Academic Unit of Child Health, Department of Human Metabolism, University of Sheffield, Sheffield Children's Hospital, Sheffield S10 2TH, UK
n.j.bishop@sheffield.ac.uk

See Online for appendix

	Risedronate (n=94)	Placebo (n=49)
Age, years	8·9 (3·4)	8·6 (3·1)
Age group		
4–9 years	53 (56%)	28 (57%)
10–15 years	41 (44%)	21 (43%)
Female sex	49 (52%)	22 (45%)
Tanner stage status*		
Stage 1	58 (62%)	37 (76%)
Stage 2	11 (12%)	5 (10%)
Stage 3	16 (17%)	3 (6%)
Stage 4	6 (6%)	2 (4%)
Stage 5	3 (3%)	1 (2%)
Missing data	0	1 (2%)
Race		
Caucasian	77 (82%)	41 (84%)
Hispanic	9 (10%)	4 (8%)
Asian	2 (2%)	2 (4%)
Multiracial	3 (3%)	1 (2%)
Other	3 (3%)	1 (2%)
Height (cm)	128·6 (21·6)	126·8 (20·4)
Height *Z* score, adjusted for age	−0·93 (1·14)	−1·13 (1·12)
Weight (kg)	32·0 (15·4)	30·7 (14·1)
Weight *Z* score, adjusted for age	−0·48 (1·41)	−0·51 (1·21)
Weight group		
≤30 kg	52 (55%)	28 (57%)
>30 kg	42 (45%)	21 (43%)
Osteogenesis imperfecta		
Mild phenotype, without dentinogenesis imperfecta	60 (64%)	29 (59%)
Mild phenotype, with dentinogenesis imperfecta	16 (17%)	8 (16%)
Unknown (mild phenotype, presence of dentinogenesis not recorded)	5 (5%)	3 (6%)
Moderate phenotype (usually type 4)	11 (12%)	6 (12%)
Severe phenotype (type 3)	2 (2%)	3 (6%)
(Continues in next column)		
(Continued from previous column)		
25-hydroxyvitamin D, nmol/L	64·0 (24·8)	59·8 (21·2)
Intact parathyroid hormone, ng/L	22 (12)	22 (9)
Number of previous fractures†		
0	6 (6%)	3 (6%)
1	4 (4%)	4 (8%)
2	6 (6%)	1 (2%)
3	14 (15%)	6 (12%)
4	13 (14%)	5 (10%)
5	14 (15%)	12 (24%)
6	5 (5%)	2 (4%)
>6	30 (32%)	15 (31%)
≥1 fracture (number not known)‡	2 (2%)	1 (2%)
Areal BMD *Z* score for lumbar spine	−2·07 (0·91)§	−2·09 (1·13)¶
Areal BMD *Z* score for total body	−1·42 (1·11)‖	−1·82 (1·06)**
Patients with 13 assessable vertebrae	89	41
0 vertebral fractures	36 (40%)	15 (37%)
1 vertebral fracture	14 (16%)	10 (24%)
≥2 vertebral fractures	39 (44%)	16 (39%)
Patients with orthopaedic hardware	13 (14%)	6 (12%)
Serum bone-specific alkaline phosphatase (U/L)	87·7 (42·6)††	86·8 (36·3)
Urine NTx/creatinine (nmol BCE/mmol creatinine)	557·7 (323·1)‡‡	587·6 (410·6)§§

Data are n, n (%), or mean (SD). BMD=bone mineral density. NTx=type-I collagen N-telopeptide. BCE=bone collagen equivalents. *Tanner stage was assessed on the basis of line drawings. †Previous fractures include both vertebral and non-vertebral fractures. ‡Medical history record refers to more than one fracture without specifying the number of fractures. §n=89 for calculation of areal BMD *Z* score for lumbar spine in the risedronate group. ¶n=48 for calculation of areal BMD *Z* score for lumbar spine in the placebo group. ‖n=88 for calculation of areal BMD *Z* score for total body in the risedronate group. **n=45 for calculation of areal BMD *Z* score for total body in the placebo group. ††n=93 for calculation of serum bone-specific alkaline phosphatase in the risedronate group. ‡‡n=90 for calculation of urine NTx/creatinine in the risedronate group. §§n=48 for calculation of urine NTx/creatinine in the placebo group.

Table 1: **Baseline characteristics of intention-to-treat population**

Dual-energy x-ray absorptiometry scans of the lumbar spine and total body were acquired at screening and months 6, 12, 24, and 36 with Hologic (Bedford, MA, USA) or Lunar (GE Healthcare, Little Chalfont, UK) instruments approved by the central facility (Perceptive Informatics, Waltham, MA, USA) and with appropriate paediatric software. At each site, all scans were done with one instrument. All scans and radiographs (scheduled and unscheduled) were assessed by the central facility. Data from long bones with metal hardware were excluded from analysis of baseline and subsequent scans.

Lateral thoracic and lumbar spine radiographs were taken for assessment of vertebral fracture status at screening and annually. All radiographs were assessed in accordance with the Genant scoring method by one of two readers from whom treatment was masked. This method uses vertebral height loss to grade vertebral collapse, providing a semiquantitative score (0=normal height, 1=mild [about 20–25% loss], 2=moderate [about 25–40% loss], 3=severe [>40% loss]).[24,25] Clinical fractures (defined as symptomatic, radiographically confirmed vertebral fractures and all non-vertebral fractures) that occurred after random assignment were reported as adverse events and as a secondary outcome.

Serum and urine samples for analysis of bone turnover markers were obtained at baseline and at months 3, 6, 12, 24, and 36. Urinary N-terminal crosslinking telopeptide of type I collagen (NTx) was measured by ELISA with the Osteomark assay (Ostex, Seattle, WA, USA) by Vitros ECi (Ortho Clinical Diagnostics, Rochester, NY, USA). Urinary creatinine was measured by standard colorimetric assay. Serum bone-specific

	Lumbar spine areal BMD *Z* score						Total body areal BMD *Z* score					
	Risedronate group		Placebo group		Least-squares mean difference (95% CI)	p value	Risedronate group		Placebo group		Least-squares mean difference (95% CI)	p value
	n	Least-squares mean (95% CI)	n	Least-squares mean (95% CI)			n	Least-squares mean (95% CI)	n	Least-squares mean (95% CI)		
Placebo-controlled phase*												
Baseline	89	−2·130	47	−2·120	..	..	88	−1·462	45	−1·854	..	..
Change from baseline												
6 months	84	0·481 (0·385 to 0·576)†	47	0·094 (−0·034 to 0·221)	0·387 (0·234 to 0·540)	<0·0001	78	0·203 (0·084 to 0·323)†	42	−0·021 (−0·186 to 0·143)	0·225 (0·030 to 0·420)	0·0242
12 months	82	0·427 (0·321 to 0·533)†	46	−0·008 (−0·149 to 0·134)	0·435 (0·265 to 0·604)	<0·0001	77	0·257 (0·117 to 0·397)†	40	0·004 (−0·194 to 0·201)	0·254 (0·024 to 0·483)	0·0308
Open-label phase*												
Change from baseline												
24 months	79	0·550 (0·406 to 0·693)	42	0·351 (0·155 to 0·546)	0·199 (−0·032 to 0·430)	NA	76	0·324 (0·175 to 0·472)	39	0·254 (0·046 to 0·462)	0·069 (−0·174 to 0·313)	NA
36 months	73	0·550 (0·384 to 0·717)	39	0·518 (0·290 to 0·747)	0·032 (−0·239 to 0·303)	NA	74	0·248 (0·087 to 0·409)	39	0·248 (0·025 to 0·472)	0·000 (−0·262 to 0·262)	NA

Change from baseline was calculated from least-squares (adjusted) means and p values are from ANCOVA model with fixed effects for age group, treatment, and pooled centre, with baseline as covariate. BMD=bone mineral density. *Risedronate group received 2·5 or 5 mg risedronate daily during the 1-year placebo-controlled phase and during the 2-year open-label phase; placebo group received placebo pill during the 1-year placebo-controlled phase and 2·5 or 5 mg risedronate daily during the 2-year open-label phase. †Indicates a significant difference from baseline assessed from 95% CI unadjusted for multiple comparisons.

Table 2: **Change from baseline in areal bone mineral density Z-scores for lumbar spine and total body**

alkaline phosphatase was measured by immunochemiluminescence assay (Access Ostase, Beckman Coulter, Brea, CA, USA). Clinical laboratory tests (serum chemistry, haematology, thyroid and parathyroid function tests, 25-hydroxyvitamin D, urinalysis, and serum and urine pregnancy tests [post-menarchal girls only]) were done periodically. All analyses were done by a central laboratory. Radiographs of the left hand and wrist were obtained at screening or baseline and at months 12, 24, and 36 for assessment of bone age (Greulich and Pyle method).[26]

Statistical analysis

We planned to recruit a minimum of 123 patients to be randomly assigned to the risedronate and placebo groups in a 2:1 ratio. This sample size would allow detection of a difference of at least 5% in percentage change from baseline in lumbar spine areal BMD at 12 months between the treatment groups with 90% power. The sample-size calculation was based on the assumptions that the common within-group SD would be about 7% and the withdrawal rate within year 1 would be roughly 15%. We regarded a difference of 5% in percentage change from baseline of lumbar spine BMD as a clinically meaningful difference.

The primary efficacy analysis was based on the placebo-controlled phase of the study. The primary efficacy variable was the percentage change from baseline in lumbar spine areal BMD at the 1-year endpoint, defined as the last measurement obtained during the placebo-controlled phase. Secondary efficacy variables, also analysed statistically up to the 1-year endpoint, included: percentage change from baseline in total body areal

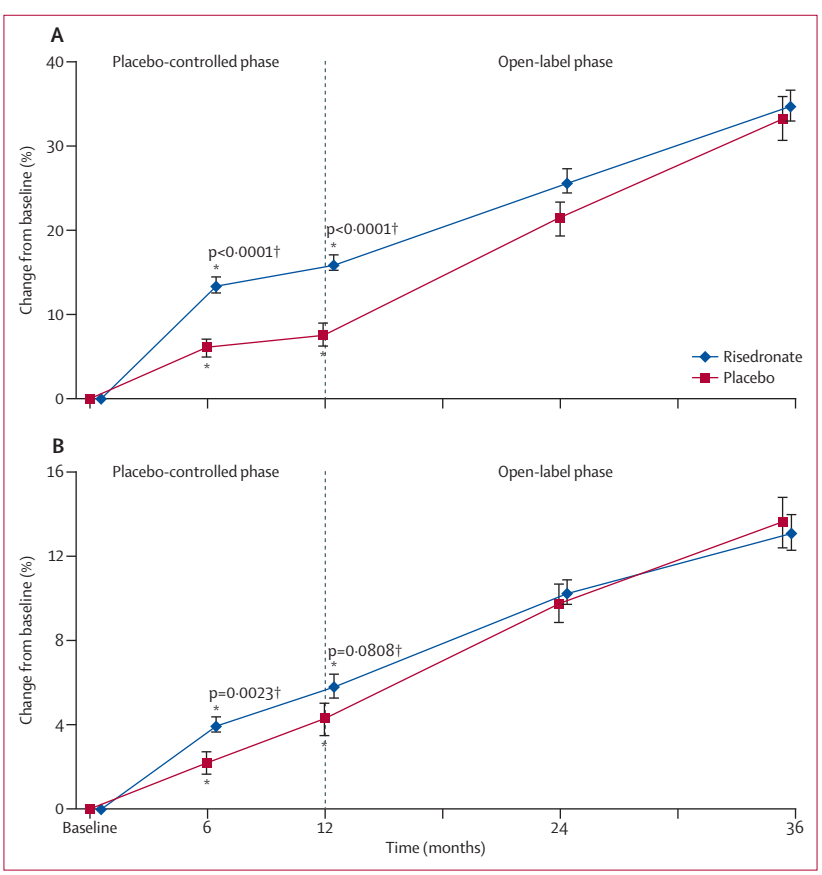

Figure 2: **Changes in areal bone mineral density**

Data are least-squares mean percentage changes in areal bone mineral density from baseline for lumbar spine (A) and total body (B). Error bars show standard error. *Indicates significant difference from baseline, as assessed from 95% CI s unadjusted for multiple comparisons. †p values indicates difference from placebo as assessed from the ANCOVA model with fixed effects for age group, treatment, and pooled centre, with baseline as covariate.

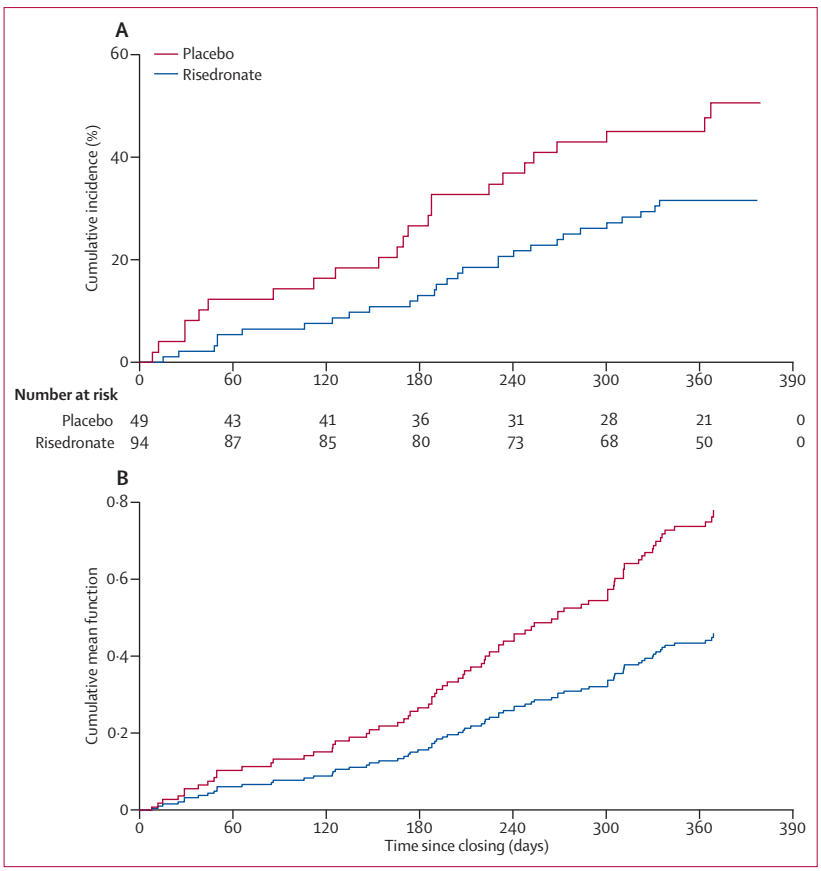

Figure 3: **Time to clinical fractures**
(A) Kaplan-Meier survival curves show cumulative risk of clinical fractures for time to first event (log-rank p=0·0337). (B) Andersen-Gill model shows cumulative mean function of clinical fractures for time to recurrent events (Wald test p=0·0416). The cumulative mean function represents the cumulative risk of recurrent fractures over time.

BMD; change in *Z* scores for lumbar spine and total body areal BMD; incidence and rate of new vertebral collapses; incidence and rate of clinical vertebral and non-vertebral fractures; and percentage change from baseline in bone turnover markers. Safety was assessed on the basis of adverse events, laboratory data, vital signs, and findings of physical examinations.

The primary efficacy analysis was done by ANCOVA, with treatment, age group, and pooled centre as fixed effects, and baseline as covariate. Analyses were based on the intention-to-treat population, which included all patients who were randomly assigned and took at least one dose of assigned study treatment. We summarised continuous variables with descriptive statistics, and discrete variables with counts and percentages for each treatment group. We estimated the time to first clinical fracture from Kaplan-Meier survival curves.[27] The log-rank test to compare the time to first clinical fracture between treatments was adjusted for the stratification factor of age group. We used the Andersen-Gill model to estimate time to recurrent clinical fracture.[28] Formal statistical testing was undertaken only for the placebo-controlled phase, with $\alpha=0\cdot05$. No adjustments were made for multiple comparisons. We report descriptive data for the 2-year open-label phase, which was not powered for statistical testing.

Role of the funding source

The funder designed the study, obtained and helped to analyse and interpret the data, and provided medical writing support. The corresponding author had full access to the data in the study. The authors had final responsibility for the decision to submit for publication.

	Risedronate group	Placebo group	Difference (%)	p value*
Placebo-controlled phase (baseline to 12 months)†				
At least one new vertebral collapse‡	29/91 (31·9%)	8/48 (16·7%)	+15·2%	0·0693
Mild (change in semiquantitative score from grade 0 to 1)§	27/91 (29·7%)	8/48 (16·7%)	..	..
Moderate or severe (change in semiquantitative score from grade 0 to 2 or 3)§	4/91 (4·4%)	3/48 (6·3%)	..	..
No new vertebral collapses‡	62/91 (68·1%)	40/48 (83·3%)	..	..
Open-label phase (12 to 36 months)†				
At least one new vertebral collapse‡	18/81 (22·2%)	12/45 (26·7%)	−4·4%	0·5743
No new vertebral collapses‡	63/81 (77·8%)	33/45 (73·3%)	..	..
Entire study (baseline to 36 months)				
At least one new vertebral collapse‡	20/82 (24·4%)	14/45 (31·1%)	−6·7%	0·3408
No new vertebral collapses‡	62/82 (75·6%)	31/45 (68·9%)	..	..

Data are n/N (%), unless otherwise indicated (N includes all patients who had assessable baseline and follow-up radiographs, irrespective of whether all 13 vertebrae were assessable). Incidence of vertebral collapse is shown as a snapshot at each timepoint during the study, rather than a summation over time. In some cases, vertebrae that seemed to be collapsed at 12 months no longer seemed to be collapsed at 36 months; therefore, incidence of vertebral collapse at 12 months might be greater than that at 36 months. *Fisher's exact test. †Risedronate group received 2·5 or 5 mg risedronate daily during the 1-year placebo-controlled phase and during the 2-year open-label phase; placebo group received placebo pill during the 1-year placebo-controlled phase and 2·5 or 5 mg risedronate daily during the 2-year open-label phase. ‡New vertebral collapses were defined as vertebrae that had a semiquantitative score of 0 at the specified start visit and greater than 0 at the specified end visit within each study category;[24,25] vertebral collapse was graded on the basis of vertebral height loss (0=normal height, 1=mild [about 20–25% loss], 2=moderate [about 25–40% loss], 3=severe [>40% loss]). §Some patients had both mild and moderate fractures.

Table 3: **Incidence of vertebral collapses**

Results

Of the 231 patients screened, 147 met the study criteria and were randomly assigned, 97 to the risedronate group and 50 to the placebo group (figure 1). This number of participants allowed for roughly 15% withdrawals. The groups had similar demographic and disease characteristics (table 1). Lumbar spine areal BMD *Z* scores were similar in the two treatment groups at baseline, whereas the mean total body areal BMD *Z* scores were –1·42 in the risedronate group and –1·82 in the placebo group. Compliance was similar between groups in both the placebo-controlled and open-label phases of the study.

The mean percentage increase in lumbar spine areal BMD at the end of the placebo-controlled phase was greater in the risedronate group (16·3%, 95% CI 14·4–18·2) than in the placebo group (7·6%, 5·1–10·1; difference 8·7%, 5·7–11·7; p<0·0001). The corresponding changes in *Z* scores are shown in table 2. During the placebo-controlled phase, increases from baseline in lumbar spine and total body areal BMD *Z* scores occurred in both groups after 6 and 12 months. During the open-label phase, changes in areal BMD and areal BMD *Z* scores for both lumbar spine and total body measurements were similar in the two groups (figure 2, table 2).

During the placebo-controlled phase, 29 of 94 analysable patients in the risedronate group reported clinical non-vertebral fractures, compared with 24 of 49 in the placebo group (p=0·0446); 18 of the 94 patients in the risedronate group reported clinical long-bone fractures, compared with 17 of the 49 patients in the placebo group. No patients reported a clinical vertebral fracture. During the open-label phase, 46 (53%) of 87 analysable patients who had been in the risedronate group reported clinical vertebral or non-vertebral fractures, compared with 32 (65%) of 49 who had been in the placebo group. Analysis of the time to first clinical fracture during the placebo-controlled phase showed that risedronate reduced the risk of fractures by 47% (hazard ratio [HR] 0·53, 95% CI 0·31–0·92; log-rank p=0·0337). Specifically, Kaplan-Meier estimates of the 1-year fracture rate were 31·4% (22·3–41·1) for the risedronate group and 50·4% (35·3%–63·8%) for the placebo group (figure 3A). Similar results were seen after adjustment for the differences in baseline *Z* scores for total body areal BMD (data not shown).

Risedronate also reduced the risk of recurrent clinical fracture after 12 months by 42% (HR 0·58, 95% CI 0·4–1·0; p=0·0416). The Andersen-Gill model estimates show that the average rate of fracture was roughly 0·46 (0·32–0·66) fractures per patient per year in the risedronate group, compared with 0·78 (0·54–1·12) fractures per patient per year in the placebo group (figure 3B).

At least one new morphometric vertebral collapse (based on radiograph measurements) was reported in almost a third of patients in the risedronate group and about a sixth of patients in the placebo group (table 3). These fractures were mild (change in semiquantitative score from 0 at baseline to 1 at 12 months) in most patients in both treatment groups. Moderate or severe fractures (change in semiquantitative score from 0 at baseline to 2 or 3 at 12 months) were noted in similar proportions of patients in the risedronate and placebo groups. During the open-label phase, at least one new vertebral collapse was reported in similar proportions of patients from the risedronate and placebo groups. Most new morphometric vertebral collapses occurred in the thoracic spine.

Significant mean percentage decreases were noted in urine NTx/creatinine at 3, 6, and 12 months and in serum bone-specific alkaline phosphatase concentration at 3 and 6 months in the risedronate group (figures 4, 5). The differences between the risedronate and placebo

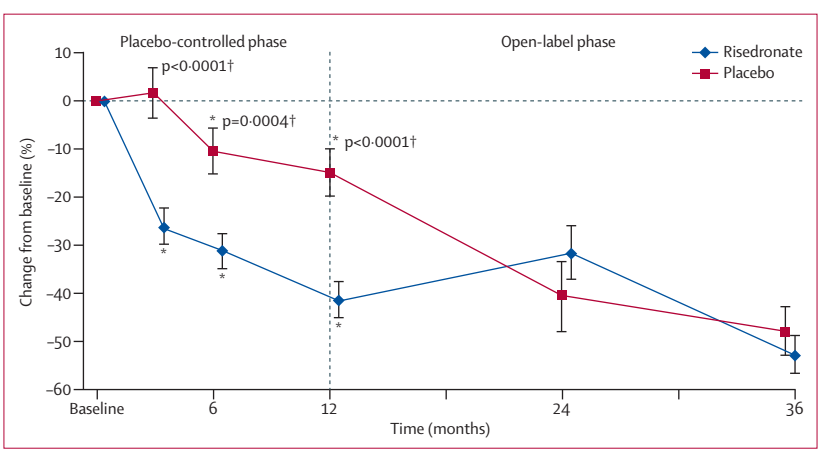

Figure 4: **Changes in urine NTx/creatinine**
Data are least-squares (adjusted) means from the ANCOVA model, adjusted by baseline and with fixed effects for age group, treatment, and pooled centre. NTx=type-I collagen N-telopeptide. *Indicates significant difference from baseline, as assessed from 95% CI s unadjusted for multiple comparisons. †p value indicates difference from placebo, as assessed from the ANCOVA model with fixed effects for age group, treatment, and pooled centre.

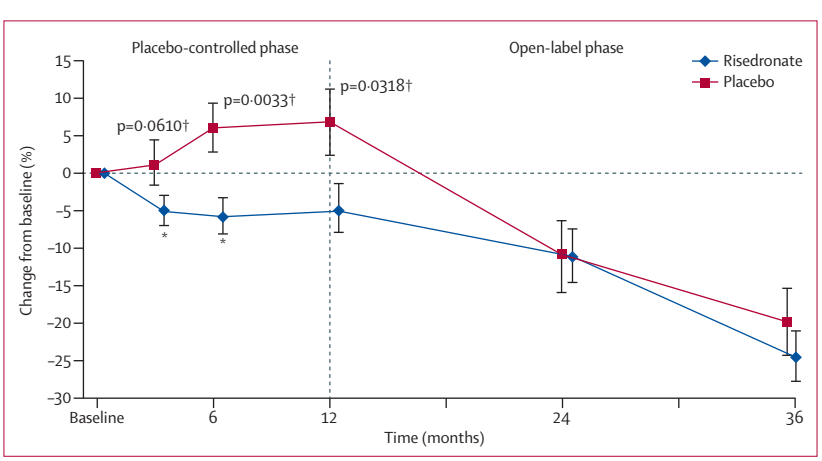

Figure 5: **Changes in serum bone-specific alkaline phosphatase concentration**
Data are least-squares (adjusted) means from the ANCOVA model, adjusted by baseline and with fixed effects for age group, treatment, and pooled centre. *Indicates significant difference from baseline, as assessed from 95% CI s unadjusted for multiple comparisons. †p value indicates difference from placebo, as assessed from the ANCOVA model with fixed effects for age group, treatment, and pooled centre.

	Placebo-controlled phase*		Open-label phase*	
	Risedronate group (N=94)	Placebo group (N=49)	Risedronate group (N=87)	Placebo group (N=49)
Adverse events	86 (91%)	47 (96%)	79 (91%)	46 (94%)
Serious adverse events	11 (12%)	8 (16%)	16 (18%)	13 (27%)
Adverse events leading to death	0	0	0	0
Withdrew from study because of adverse events	1 (1%)	0	1 (1%)	3 (6%)
Possibly or probably study-related adverse events	22 (23%)	15 (31%)	9 (10%)	10 (20%)
Possibly or probably study-related serious adverse events	2 (2%)	0	0	1 (2%)
Upper-gastrointestinal adverse events	23 (24%)	13 (27%)	14 (16%)	13 (27%)
Moderate to severe upper-gastrointestinal adverse events†	2 (2%)	2 (4%)	1 (1%)	3 (6%)
Vertebral clinical fracture adverse events	0	0	2 (2%)	1 (2%)
Non-vertebral clinical fracture adverse events	29 (31%)	24 (49%)	45 (52%)	32 (65%)
Selected musculoskeletal adverse events‡	30 (32%)	13 (27%)	18 (21%)	17 (35%)
Adverse events other than fractures reported by at least 10% of patients in either study group				
Fall	19 (20%)	14 (29%)	36 (41%)	22 (45%)
Pain in arms or legs	20 (21%)	8 (16%)	11 (13%)	7 (14%)
Back pain	16 (17%)	5 (10%)	13 (15%)	7 (14%)
Headache	19 (20%)	4 (8%)	8 (9%)	4 (8%)
Arthralgia	8 (9%)	7 (14%)	5 (6%)	8 (16%)
Abdominal pain	8 (9%)	7 (14%)	5 (6%)	6 (12%)
Vomiting	14 (15%)	3 (6%)	5 (6%)	5 (10%)
Abdominal pain upper	10 (11%)	4 (8%)	3 (3%)	6 (12%)
Pyrexia	8 (9%)	2 (4%)	5 (6%)	7 (14%)
Pain	14 (15%)	5 (10%)	3 (3%)	1 (2%)
Nasopharyngitis	7 (7%)	3 (6%)	9 (10%)	3 (6%)
Nausea	4 (4%)	6 (12%)	4 (5%)	4 (8%)
Gastroenteritis	1 (1%)	5 (10%)	8 (9%)	4 (8%)

Data are n. *Risedronate group received 2·5 or 5 mg risedronate daily during the 1-year placebo-controlled phase and during the 2-year open-label phase; placebo group received placebo pill during the 1-year placebo-controlled phase and 2·5 or 5 mg risedronate daily during the 2-year open-label phase. †No severe upper-gastrointestinal events were reported during the study. ‡Musculoskeletal adverse events included back pain, arthralgia, bone pain, musculoskeletal pain, and neck pain.

Table 4: **Adverse events**

	25-hydroxyvitamin D (nmol/L)		Intact parathyroid hormone (ng/L)	
	Risedronate group	Placebo group	Risedronate group	Placebo group
Placebo-controlled phase*				
Baseline	93 (64·0, 24·8)	47 (59·8, 21·2)	94 (22, 12)	49 (22, 9)
6 months	87 (67·4, 22·4)	48 (66·0, 19·1)	87 (32, 85)	48 (20, 11)
12 months	86 (62·9, 19·5)	48 (67·1, 18·7)	85 (22, 13)	48 (21, 11)
Open-label phase*				
24 months	84 (62·0, 22·1)	46 (60·9, 20·5)	84 (23, 16)	46 (23, 16)
36 months	80 (55·5, 18·5)	45 (53·8, 18·6)	79 (24, 13)	45 (22, 15)

Data are n (mean, SD). *Risedronate group received 2·5 or 5 mg risedronate daily during the 1-year placebo-controlled phase and during the 2-year open-label phase; placebo group received placebo pill during the 1-year placebo-controlled phase and 2·5 or 5 mg risedronate daily during the 2-year open-label phase.

Table 5: **Serum 25-hydroxyvitamin D and intact parathyroid hormone concentrations**

groups were significant at months 6 and 12 for both markers. During the open-label phase, decreases occurred in both markers for both treatment groups. Decreases were similar in the two groups at all timepoints during the open-label phase. Decreases from baseline in either marker during the entire study were greater than 87% in 14 patients. In all but one case, these decreases were in children who were at an age at which reduced bone turnover would be expected because of cessation of longitudinal growth.

During the placebo-controlled phase, more than 90% of patients in each group had an adverse event (table 4). One patient in the risedronate group discontinued the study because of an adverse event, Crohn's disease, which was believed by the investigator to possibly be related to the study drug. During the open-label phase, more than 90% of patients in each group had an adverse event (table 4). No patients died in either group, in either study phase.

During the placebo-controlled phase, mean height increased significantly from baseline in both groups. At 12 months, the mean percentage increase in height was 5·5% in the risedronate group and 4·5% in the placebo group. The two treatment groups did not differ significantly with respect to mean change in *Z* scores for height (risedronate group 0·10 [SD 0·91] *vs* placebo group −0·08 [0·31]; p=0·0788). When patients who sustained at least one new vertebral collapse during the study were analysed separately, patients in both groups continued to have a significant mean percentage increase in height from baseline. For these patients, the mean percentage increase in height at 12 months was 4·2% in the risedronate group and 3·1% in the placebo group. During the open-label phase, mean height increased in both groups, and the mean changes from baseline were similar. Mean bone age increased at the same rate as chronological age in both groups. The mean increases in bone age were similar in the two groups (data not shown).

The mean values for serum 25-hydroxyvitamin D and intact parathyroid hormone were within normal ranges, and the changes from baseline were small at all time-points for both treatment groups (table 5). No associations between initial 25-hydroxyvitamin D or parathyroid hormone and vertebral or non-vertebral fracture rate were noted.

Discussion

Our study has shown significantly greater increases in lumbar spine areal BMD at 6 and 12 months in children with osteogenesis imperfecta treated with oral risedronate than in those given placebo. More importantly, analyses of both time to first fracture and time to recurrent fracture showed that risedronate treatment reduced the risk of clinical fracture. Both analyses suggest that reduction of fracture risk is swift.

Risedronate was generally well tolerated. No difference was seen in the frequency of serious adverse events, or

gastrointestinal or musculoskeletal events (apart from fracture) between the groups; no deaths occurred in either group.

Other studies of risedronate in osteogenesis imperfecta have shown increases in BMD,[15,22,29] but we have now clearly shown that the drug reduces fracture risk (panel). Our results for fracture are consistent with those reported by Sakkers and colleagues[18] for oral olpadronate and by Gatti and colleagues[16] for intravenous neridronate. These results contrast with findings from a study of alendronate in 139 children with moderate to severe osteogenesis imperfecta,[21] which did not show a reduction in fracture incidence despite an increase in lumbar spine areal BMD. Our study and that by Sakkers and colleagues[18] included larger proportions of children with mild forms of the disease. Oral treatment might be better suited to children with mild rather than more severe disease. Intravenous pamidronate has been shown to increase BMD and reduce fracture rates in uncontrolled and observational studies;[10,12] however, so far, no placebo-controlled trials have been done to confirm these findings.

No child with severe vitamin D deficiency was allowed into the study. That the rise in lumbar spine areal BMD in children who received only vitamin D and calcium was steeper in the first 6 months than in the second 6 months of the placebo-controlled phase (figure 2A) implies an effect of such supplementation on filling of the remodelling space. Although mean 25-hydroxyvitamin D concentrations were roughly 60 nmol/L in both groups, we suggest that supplementation with calcium and vitamin D should be given at least during the first year of treatment with risedronate.

New morphometric vertebral collapses occurred in both groups during both the placebo-controlled and open-label phases. During the placebo-controlled phase, these fractures occurred in almost a third of patients in the risedronate group and about a sixth of patients in the placebo group ($p=0\cdot0693$). These findings could be due to improved radiographic visibility of pre-existing fractures that result from increases in mineralised bone or cartilage at vertebral endplates; suboptimum mineral and vitamin D status at the start of the study, initially increasing the risk of fracture in the risedronate group; excessive physical activity in treated children who felt better and therefore did more; or some as yet unidentified factor. Most fractures were mild and occurred in the first 12 months of the study; the proportions of patients with more severe fractures were similar in the two groups.

Radiographs taken between study visits to confirm clinical fractures were obtained by the investigative site and sent to the central facility for assessment. A shortcoming of this fracture surveillance protocol is the possibility that confirmatory radiographs were not obtained or were not sent to the central facility. If such issues occurred, however, they probably did so in similar proportions of patients in each treatment group and therefore would not be expected to affect the results.

***Panel:* Research in context**

Systematic review

We searched PubMed with the keywords "bisphosphonates", "trial", "child", and "osteogenesis imperfecta" for articles published in any language between Jan 1, 1987, and Nov 1, 2012. We also used the reference list of the 2008 Cochrane review by Phillipi and colleagues[19] to ensure that we had not missed any relevant earlier publications. We identified nine randomised controlled trials, four of which[15,18,20,21] studied the effect of oral bisphosphonate treatment for children with osteogenesis imperfecta. All were powered to detect change in bone density as their primary outcome, and their findings showed that areal bone mineral density increased significantly in children treated with oral bisphosphonate. Although the results two of these studies[18,20] suggested a beneficial effect of bisphosphonate treatment on fracture rate, the results of the other two[15,21] did not.

Interpretation

The results of this randomised controlled trial clearly show a reduction in fracture risk from oral bisphosphonate treatment in children with osteogenesis imperfecta. Oral treatment with risedronate seemed to reduce the risk of first and recurrent clinical fractures, and the drug was generally well tolerated. Risedronate should be regarded as a treatment option for children with osteogenesis imperfecta.

We did not identify a difference in either mobility or pain scales between the groups (data not shown). Neither of these measures was taken on a day-by-day basis; hence, we could not adequately capture these data. The absence of an effect on mobility and pain in our study differs from the findings of studies of intravenous bisphosphonates,[10,12] in which patients seemed to have improvements in ambulatory ability or pain. However, these studies either used crude mobility scales or did not quantify the general observations reported. Furthermore, these studies were either uncontrolled or relied on comparison with historical controls. Nevertheless, parents, clinicians, occupational therapists, and physiotherapists have consistently reported increased mobility and physical activity in children with osteogenesis imperfecta after starting bisphosphonate treatment.[10,11] Advising parents that they should limit potentially injurious activity during the initial period of treatment might be appropriate.

In summary, oral risedronate treatment significantly reduced the risk of clinical fracture in children with osteogenesis imperfecta in this study. Risedronate should be regarded as a treatment option for children with osteogenesis imperfecta.

Contributors

NB was the lead investigator for the study; he helped to design the study protocol, recruited children to the study, collected data, discussed the data analysis with the sponsor and the coauthors, wrote and revised the report, and liaised with coauthors about their suggestions and interpretation of the data. SA participated in data collection and review of the report. SFA, JA, J-PD, TH, EH, RL, OM, CFM, AP, HPa, HPl, MLR, ES, OS, and RDS contributed to data collection, analysis, and interpretation, and to revision of the report for intellectual content. PA contributed to data collection and interpretation and to writing of the report. CPB made substantial contributions to the collection and interpretation of data and revised the report for intellectual content. JML contributed to data collection and interpretation and to revision of the report for intellectual content. CLR

contributed to study design; data collection, analysis, and interpretation; and revision of the report for intellectual content. DOS contributed to study design, patient recruitment and enrolment, data collection and interpretation, and writing and editing of the report. All authors approved the final version of the report.

Conflicts of interest

SFA has consultancy arrangements with Alexion and Novartis. NB has received consultancy fees from Procter & Gamble, Novartis, Amgen, GSK, and Roche. J-PD has received consultancy or advisory board fees from Novartis; lecture fees from Merck, Sharp & Dohme, Procter & Gamble, Servier, and Roche; and grant support from Schering-Plough, Abbott, Amgen, Novartis, Servier, Merck, Sharpe & Dohme, Procter & Gamble, and Fonds National de la Recherche Scientifique Médicale Belge. CLR has received grant support from Amgen. ES has received honoraria from Aventis. RDS has received honoraria, consultancy fees, or both from Actelion, Amicus, Biomarin, Genzyme, Shire, and Zacharon. The remaining authors declare that they have no conflicts of interest.

Acknowledgments

This research was supported by the Alliance for Better Bone Health (sponsored by Procter & Gamble Pharmaceuticals [now Warner Chilcott] and Sanofi). Mary Royer, a medical writer who is a paid consultant of Warner Chilcott, assisted with the preparation of the report. Additional technical support for the preparation of the report was provided by Dietrich Wenderoth, who is employed by Warner Chilcott.

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