Clinical trial results:
Prevention and Treatment of Steroid-Induced Osteopenia in children and adolescents with rheumatic diseases

Summary

EudraCT number	2005-003129-23
Trial protocol	GB
Global end of trial date	27 February 2015

Results information

Result version number	v1 (current)
This version publication date	17 June 2022
First version publication date	17 June 2022

Trial information

Trial identification

Sponsor protocol code	04/MR/111

Additional study identifiers

ISRCTN number	ISRCTN66814619
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust
Sponsor organisation address	Research Office, 2nd Floor King Edward Building, Royal Hospital Site, Belfast, United Kingdom, BT12 6BA
Public contact	Alison Murphy, Research Office, Belfast Health and Social Care Trust, ResearchSponsor@belfasttrust.hscni.net
Scientific contact	Research Office, Research Office, Belfast Health and Social Care Trust, ResearchSponsor@belfasttrust.hscni.net
Sponsor organisation name	Queen's University Belfast (QUB)
Sponsor organisation address	Research Governance, Ethics and Integrity, QUB, 63 University Road, Belfast, United Kingdom, BT7 1NN
Public contact	Research Governance, Research Governance, Ethics and Integrity, QUB, +44 90972572, researchgovernance@qub.ac.uk
Scientific contact	Research Governance, Research Governance, Ethics and Integrity, QUB, +44 90972572, researchgovernance@qub.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of this study is to demonstrate whether 1-hydroxycholecalciferol or the Bisphosphonate Risedronate is superior to placebo in preventing osteopaenia in children with rheumatic diseases commencing or established on steroids.

Protection of trial subjects:

All patients and parents / guardians provided written informed consent. All female participants of child bearing age undertook a pregnancy test at each visit. Renal function was undertaken prior to and during the trial. Blood testing was kept to the minimum required to address efficacy and safety issues. All patients, parents/guardians were informed of their freedom to withdraw at any time from the trial. Treatment of their underlying rheumatological conditions continued during the trial according to clinical need as perceived by the local PI

Background therapy:

All patients received Calcium and vitamin D supplements. All medications including steroids continued according to clinical need

Evidence for comparator:

There was limited evidence of the benefit of either interventions to improve bone mineral density in children. There is a large body of evidence for the use of bisphosphonates for improving bone density and reducing fracture risk in adults treated with steroids. Paediatric rheumatologists used active vitamin D metabolites in an attempt to prevent bone loss in children treated with steroids. Thus the comparators were placebo and the active Vitamin D metabolite One Alpha

Actual start date of recruitment	22 August 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 217
Worldwide total number of subjects	217
EEA total number of subjects	217

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	88
Adolescents (12-17 years)	129
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 11 centres throughout the UK. Centres commenced recruitment in a sequential fashion. Recruitment began on 22nd Aug 2007.

Pre-assignment

Screening details:

PI were advised to identify all children and young people commencing or already treated with steroids for a rheumatic disease. Screening logs were introduced during the trial in order to improve patient identification and recruitment. 516 patient were screened in 11 centres

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a multicentre double-blind randomised placebo-controlled trial. Patients were randomised to take one of two active treatments or one of two placebos. To reduce the amount of placebos the children would have to take, and improve recruitment and compliance the two placebo arms were then combined for the analysis, so that there were 3 groups. Patients were randomised centrally into one of three treatment arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

1 alpha hydroxycholecalciferol and risedronate placebos

Arm type	Placebo
Investigational medicinal product name	Identical Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Coated tablet, Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Matching placebo for Hydroxycholecalciferol or Risedronate

Arm title	1-Alphahydroxycholecalciferol

Arm description:

1-Alphahydroxycholecalciferol 15ng/kg/day

Arm type	Experimental
Investigational medicinal product name	1-Alphahydroxycholecalciferol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

15ng/kg per day (max 1mg)

Arm title	Risedronate

Arm description:

risedronate 1mg/kg for 15-30kg weekly
risedronate >30kg, 35mg weekly

Arm type	Experimental
Investigational medicinal product name	Risedronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

15-30mg if <30kgs
35mg weekly if >30kgs

Number of subjects in period 1	Placebo	1-Alphahydroxycholecalciferol	Risedronate
Started	77	71	69
Completed	72	67	59
Not completed	5	4	10
Patient receives other vitamin D supplements	-	-	1
Consent withdrawn by subject	3	2	5
Adverse event, non-fatal	-	-	2
Cannot get time off	-	-	1
Migrated to another country	1	-	-
Protocol deviation	1	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
1 alpha hydroxycholecalciferol and risedronate placebos	
Reporting group title	1-Alphahydroxycholecalciferol
Reporting group description:	
1-Alphahydroxycholecalciferol 15ng/kg/day	
Reporting group title	Risedronate
Reporting group description:	
risedronate 1mg/kg for 15-30kg weekly risedronate >30kg, 35mg weekly	

Reporting group values	Placebo	1-Alphahydroxycholecalciferol	Risedronate
Number of subjects	77	71	69
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	34	26	28
Adolescents (12-17 years)	43	45	41
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	12.1	12.1	12.0
standard deviation	± 3.5	± 3.7	± 3.4
Gender categorical Units: Subjects			
Female	55	48	53
Male	22	23	16
Steroid dose Units: Subjects			
<= 0.2 mg/kg	37	30	32
> 0.2 mg/kg	40	41	37
Ethnic origin Units: Subjects			
Caucasian	59	54	55
Black	4	4	6
Oriental	0	1	0
Asian	11	10	6
Other	3	2	2
Relevant medical conditions			

Units: Subjects			
Yes	42	39	43
No	35	32	26
Prior fracture history Units: Subjects			
Yes	13	9	8
No	64	62	61
Medication at baseline - DMARDS Units: Subjects			
Yes	71	64	62
No	6	7	7
Medication at baseline - Biologics Units: Subjects			
Yes	8	17	7
No	69	54	62
Disease group - JIA Units: Subjects			
Yes	21	30	20
No	56	41	49
Disease group - JSLE Units: Subjects			
Yes	31	21	24
No	46	50	45
Disease group - JDM Units: Subjects			
Yes	17	13	16
No	60	58	53
Disease group - Vasculitis Units: Subjects			
Yes	11	12	13
No	66	59	56
Tanner score Units: score			
median	2	2	2
inter-quartile range (Q1-Q3)	1 to 4	1 to 4	1 to 3
Cumulative Steroid dose Units: mg/kg			
arithmetic mean	8403.7	9108.7	8090.4
standard deviation	± 9206.9	± 7528.0	± 9390.1

Reporting group values	Total		
Number of subjects	217		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	88		
Adolescents (12-17 years)	129		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	156		
Male	61		
Steroid dose			
Units: Subjects			
<= 0.2 mg/kg	99		
> 0.2 mg/kg	118		
Ethnic origin			
Units: Subjects			
Caucasian	168		
Black	14		
Oriental	1		
Asian	27		
Other	7		
Relevant medical conditions			
Units: Subjects			
Yes	124		
No	93		
Prior fracture history			
Units: Subjects			
Yes	30		
No	187		
Medication at baseline - DMARDS			
Units: Subjects			
Yes	197		
No	20		
Medication at baseline - Biologics			
Units: Subjects			
Yes	32		
No	185		
Disease group - JIA			
Units: Subjects			
Yes	71		
No	146		
Disease group - JSLE			
Units: Subjects			
Yes	76		
No	141		
Disease group - JDM			
Units: Subjects			
Yes	46		
No	171		
Disease group - Vasculitis			

Units: Subjects			
Yes	36		
No	181		
Tanner score			
Units: score			
median			
inter-quartile range (Q1-Q3)	-		
Cumulative Steroid dose			
Units: mg/kg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
1 alpha hydroxycholecalciferol and risedronate placebos	
Reporting group title	1-Alphahydroxycholecalciferol
Reporting group description:	
1-Alphahydroxycholecalciferol 15ng/kg/day	
Reporting group title	Risedronate
Reporting group description:	
risedronate 1mg/kg for 15-30kg weekly risedronate >30kg, 35mg weekly	

Primary: Lumbar Spine Bone Mineral Density

End point title	Lumbar Spine Bone Mineral Density
End point description:	
The change from baseline to year 1 was calculated and the difference between the three groups were compared using analysis of variance.	
End point type	Primary
End point timeframe:	
Baseline to Year 1	

End point values	Placebo	1-Alphahydroxycholecalciferol	Risedronate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	67	58	
Units: gram(s)/square centimeter				
arithmetic mean (standard deviation)	0.034 (± 0.047)	0.031 (± 0.052)	0.069 (± 0.057)	

Statistical analyses

Statistical analysis title	Lumbar Spine BMD - ANOVA
Comparison groups	Risedronate v 1-Alphahydroxycholecalciferol v Placebo
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA

Primary: Lumbar Spine Bone Mineral Density (Z Score)

End point title	Lumbar Spine Bone Mineral Density (Z Score)

End point description:

The change from baseline to year 1 was calculated and the difference between the three groups were compared using analysis of variance technique.

End point type	Primary

End point timeframe:

Change from Baseline to year 1

End point values	Placebo	1-Alphahydroxycholecalciferol	Risedronate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	64	56	
Units: gram(s)/square meter				
arithmetic mean (standard deviation)	-0.036 (± 0.435)	-0.109 (± 0.516)	0.229 (± 0.556)	

Statistical analyses

Statistical analysis title	Lumbar Spine BMD (Z Score) - ANOVA

Statistical analysis description:

Analysis of variance (ANOVA)

Comparison groups	Risedronate v 1-Alphahydroxycholecalciferol v Placebo
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	ANOVA

Primary: Total Body Bone Mineral Density

End point title	Total Body Bone Mineral Density

End point description:

The change from baseline and year 1 was calculated and the difference between groups were compared using analysis of variance.

End point type	Primary

End point timeframe:

The change from baseline to year 1

End point values	Placebo	1-Alphahydroxycholecalciferol	Risedronate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	65	59	
Units: gram(s)/square centimeter				
arithmetic mean (standard deviation)	0.016 (± 0.032)	0.029 (± 0.034)	0.040 (± 0.030)	

Statistical analyses

Statistical analysis title	Total Body BMD - ANOVA
Comparison groups	Risedronate v 1-Alphahydroxycholecalciferol v Placebo
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA

Primary: Total Body Bone Mineral Density (Z Score)

End point title	Total Body Bone Mineral Density (Z Score)

End point description:

The change from baseline and year 1 was calculated and the difference between groups were compared using analysis of variance.

End point type	Primary

End point timeframe:

The change from baseline to year 1

End point values	Placebo	1-Alphahydroxycholecalciferol	Risedronate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	62	57	
Units: gram(s)/square centimeter				
arithmetic mean (standard deviation)	-0.129 (± 0.458)	-0.052 (± 0.403)	0.151 (± 0.409)	

Statistical analyses

Statistical analysis title	Total Body BMD (Z Score) - ANOVA
Comparison groups	Risedronate v 1-Alphahydroxycholecalciferol v Placebo

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	ANOVA

Secondary: Fracture rate

End point title	Fracture rate

End point description:

End point type	Secondary

End point timeframe:

Year 1

End point values	Placebo	1-Alphahydroxycholecalciferol	Risedronate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	71	68	
Units: Percentage	4	2	5	

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Placebo v 1-Alphahydroxycholecalciferol v Risedronate
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Fisher's exact test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data was captured at each patient visit and serious adverse events was to be reported within 24 hours.

Assessment type	Systematic

Dictionary used

Dictionary name	NA
Dictionary version	NA

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	One-alpha
Reporting group description: -	
Reporting group title	Risedronate
Reporting group description: -	

Serious adverse events	Placebo	One-alpha	Risedronate
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 77 (23.38%)	14 / 71 (19.72%)	21 / 69 (30.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Trauma			
subjects affected / exposed	0 / 77 (0.00%)	2 / 71 (2.82%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Biochemistry			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematology test			

subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MAS			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weakness			
subjects affected / exposed	2 / 77 (2.60%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Raised IoP			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatosplenomegaly			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea and Vomiting			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
GUT			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			

subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease flare			
subjects affected / exposed	4 / 77 (5.19%)	8 / 71 (11.27%)	5 / 69 (7.25%)
occurrences causally related to treatment / all	0 / 4	0 / 9	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enthesitis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reflex Sympathetic Dystrophy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Fever			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 77 (1.30%)	5 / 71 (7.04%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			

subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Infection			
subjects affected / exposed	2 / 77 (2.60%)	1 / 71 (1.41%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			
subjects affected / exposed	3 / 77 (3.90%)	0 / 71 (0.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 77 (1.30%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	One-alpha	Risedronate
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 77 (77.92%)	55 / 71 (77.46%)	57 / 69 (82.61%)
Vascular disorders			
Depression			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Allergic reaction			
subjects affected / exposed	1 / 77 (1.30%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	1	1	0
Allergy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	5 / 77 (6.49%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	5	1	3
Fever			
subjects affected / exposed	3 / 77 (3.90%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	3	1	0
Lethargy			
subjects affected / exposed	2 / 77 (2.60%)	4 / 71 (5.63%)	2 / 69 (2.90%)
occurrences (all)	2	4	2
Pyrexia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	2	0	0
Weakness			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			
Respiratory sob			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Hyperventilation			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	5 / 77 (6.49%)	2 / 71 (2.82%)	4 / 69 (5.80%)
occurrences (all)	6	2	5
Overdose			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Oedema			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0

Raynaud's phenomenon			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
Vasculitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Epislaxis			
subjects affected / exposed	4 / 77 (5.19%)	0 / 71 (0.00%)	3 / 69 (4.35%)
occurrences (all)	4	0	3
Nervous system disorders			
Central nervous system			
subjects affected / exposed	3 / 77 (3.90%)	2 / 71 (2.82%)	2 / 69 (2.90%)
occurrences (all)	7	2	2
Headache			
subjects affected / exposed	21 / 77 (27.27%)	12 / 71 (16.90%)	15 / 69 (21.74%)
occurrences (all)	28	16	23
Seizure			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	3
Tremor			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Biochemistry			
subjects affected / exposed	4 / 77 (5.19%)	2 / 71 (2.82%)	6 / 69 (8.70%)
occurrences (all)	5	3	6
Haematology test abnormal			
subjects affected / exposed	1 / 77 (1.30%)	1 / 71 (1.41%)	2 / 69 (2.90%)
occurrences (all)	1	1	2
Enlarged thymus			

subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Eye disorders			
Eye damage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	2	0	0
Eye damage/Pathology			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Eyes			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Raised lop			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	0 / 77 (0.00%)	2 / 71 (2.82%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	13 / 77 (16.88%)	9 / 71 (12.68%)	12 / 69 (17.39%)
occurrences (all)	15	9	13
Anorexia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	2 / 69 (2.90%)
occurrences (all)	1	0	2
Constipation			
subjects affected / exposed	3 / 77 (3.90%)	2 / 71 (2.82%)	2 / 69 (2.90%)
occurrences (all)	3	2	2
Diarrhoea			
subjects affected / exposed	5 / 77 (6.49%)	5 / 71 (7.04%)	2 / 69 (2.90%)
occurrences (all)	6	8	3
Gastritis			

subjects affected / exposed	2 / 77 (2.60%)	2 / 71 (2.82%)	1 / 69 (1.45%)
occurrences (all)	2	2	1
GI upset			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	2 / 69 (2.90%)
occurrences (all)	0	1	3
GIT			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Mouth			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	1 / 77 (1.30%)	2 / 71 (2.82%)	2 / 69 (2.90%)
occurrences (all)	1	2	2
Nausea			
subjects affected / exposed	5 / 77 (6.49%)	1 / 71 (1.41%)	4 / 69 (5.80%)
occurrences (all)	5	1	4
Nausea and Vomiting			
subjects affected / exposed	9 / 77 (11.69%)	4 / 71 (5.63%)	6 / 69 (8.70%)
occurrences (all)	10	4	7
Mouth pain			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Weight Gain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 71 (2.82%)	1 / 69 (1.45%)
occurrences (all)	0	2	1
Bruising			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	2 / 69 (2.90%)
occurrences (all)	0	1	2

Calcinosis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	3	0
Itching			
subjects affected / exposed	2 / 77 (2.60%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	2	1	1
Pigmentation			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	6 / 77 (7.79%)	13 / 71 (18.31%)	5 / 69 (7.25%)
occurrences (all)	8	16	6
Skin abnormality			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	2
Skin lesion			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	0	1	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	2 / 77 (2.60%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	3	0	1
Nephritis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	1 / 77 (1.30%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	1	1	1
Testicular torsion			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Urinary			

subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
BXO			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 77 (20.78%)	16 / 71 (22.54%)	18 / 69 (26.09%)
occurrences (all)	27	32	23
Arthritis			
subjects affected / exposed	6 / 77 (7.79%)	10 / 71 (14.08%)	6 / 69 (8.70%)
occurrences (all)	8	13	10
Bone pain			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Decreased movement			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	0	2	1
Inflammation			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Muscle spasm			
subjects affected / exposed	1 / 77 (1.30%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 71 (1.41%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Tendinitis			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Infections and infestations			

Conjuctivitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 71 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	24 / 77 (31.17%)	19 / 71 (26.76%)	21 / 69 (30.43%)
occurrences (all)	37	27	35
Fungal infection			
subjects affected / exposed	3 / 77 (3.90%)	1 / 71 (1.41%)	1 / 69 (1.45%)
occurrences (all)	3	1	1
Bacterial infection			
subjects affected / exposed	3 / 77 (3.90%)	5 / 71 (7.04%)	6 / 69 (8.70%)
occurrences (all)	3	5	6
Skin infection			
subjects affected / exposed	0 / 77 (0.00%)	0 / 71 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	17 / 77 (22.08%)	18 / 71 (25.35%)	19 / 69 (27.54%)
occurrences (all)	25	26	24
Upper respiratory tract infection			
subjects affected / exposed	17 / 77 (22.08%)	10 / 71 (14.08%)	14 / 69 (20.29%)
occurrences (all)	21	11	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2007	Protocol amendment V4.0: Ethics reference corrected. Contact page updated to include new trial statistician and specification of PI at a site. Trial interventions paragraph update for dose for sub groups <30kgs and inclusion of patient support networks as a recruitment source. Administrative amends to table of contents, abbreviations, revision to allow for clearer instructions and addition of appendices. Schedule of events includes exact requirement and time points for conduct events. Treatment schedule update for clarification. Concomitant treatment allowed – inclusion of immunosuppressant's point. Revision of section to include changes to clinical measures. X-rays will be read chronologically. Adverse reporting will end 3 months after stopping study medication. Assessment of causality has been added. 15 years has been added as the recommended time to retain records. Updates to Patient Information Sheets, Parent and Patient Information Sheets and consent form.
27 February 2007	Protocol amendment V5.0. Addition of 2 PIs. Updates to Patient Information Sheets, Parent and Patient Information Sheets and consent form.
19 July 2007	Protocol amendment V5.1: Contact page updated to include new trial statistician and 2 PIs. Additional point giving permission for any sample remaining after genetic studies carried out to be stored and sued for future research purposes only, into rheumatic diseases in children and adolescents. Updates to Patient Information Sheets, Parent and Patient Information Sheets.
15 December 2008	Protocol amendment V5.2: Addition of new PI and site and removal of PI. PI working on 2 sites and another PI seeking approval to recruit from her second hospital. Change of Trial Coordinator surname. Inclusion of '2.5 years' for methodology and study duration 'at each centre'.
20 January 2010	Change of sponsor to the Belfast Health and Social Care Trust.
01 June 2010	Protocol amendment V6.0: The required sample size initially was 270 children. In order to detect an improvement between the treatment groups of 6.25 and between the treatment groups and the control groups of 6.25, using a SD of 12.5 (observed in our 1 year growth hormone study), recruitment of 75 children in each of the three study arms offers 80% power to detect a significant difference at the 5% level of significance, allowing for a 15% dropout rate. It was further expected that approximately 20% of this population will not receive steroids for one year. Thus to ensure that an adequate number of children do complete the study on steroids will require 90 children per treatment group; a total of 270. However following interim analysis the dropout rate was ~ 8% and there were no reports of patients being taken off steroids very early in the study. Taking a conservative position it was estimated that the dropout rate would be 10%. This would imply an overall recruitment target of 216 patients. A protocol amendment was therefore requested and obtained.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31388666