Clinical trial results:
A double-blind randomised multi-centre, placebo-controlled trial of combined ACE-inhibitor and beta-blocker therapy in preventing the development of cardiomyopathy in genetically characterised males with DMD without echo-detectable left ventricular dysfunction

EudraCT number	2007-005932-10
Trial protocol	GB
Global end of trial date	23 March 2018

Result version number	v1 (current)
This version publication date	02 December 2019
First version publication date	02 December 2019

Sponsor protocol code	NCTU:ISRCTN50395346

ISRCTN number	ISRCTN50395346
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	NJRO, Level 1, Regent Point, Regent Farm Road, Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
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Notes:

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:

Analysis stage	Final
Date of interim/final analysis	23 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2018
Global end of trial reached?	Yes
Global end of trial date	23 March 2018
Was the trial ended prematurely?	No

Notes:

Main objective of the trial:

To determine whether the introduction of ACE-inhibitor (perindopril) combined with beta-blocker therapy (bisoprolol), before the onset of echo-detectable left ventricular dysfunction, can delay the age of onset and/or slow the rate of progression of cardiomyopathy in males with DMD.

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

Placebo control was chosen in order to maintain power and a simple trial design; hence, the benefits of combination therapy (ACE-inhibitor and beta-blocker) against placebo were evaluated in a two-arm trial.

Actual start date of recruitment	26 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Country: Number of subjects enrolled	United Kingdom: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

Notes:

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)	74
Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Recruitment details:

The recruitment period ran from 25 May 2011 to 22 January 2015, at five NHS hospital sites in the United Kingdom. Sites were in Newcastle upon Tyne, London, Liverpool, Birmingham and Oxford.

Screening details:

Site trial staff screened DMD patients who currently attend neurology or equivalent clinics for supervision of their symptoms, or have regular schedules for cardiac surveillance, for potential participants. Screening logs were kept at each site, recording patient details, satisfaction of eligibility criteria, and reasons for exclusion.

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Assessor, Subject

Blinding implementation details:

Trial IMP tablets were over-encapsulated, and accompanied by matched placebo, to establish the blind from trial start, in bottles numbered according to the blinded randomisation schedule. Sealed codebreak envelopes were stored in the Pharmacy/ISF, and opened only in an emergency. Unblinding was notified to the trial co-ordinating team, and a record kept in the TMF and ISF. The blind was maintained until all trial data were collected and the database locked, when participants were unblinded.

Are arms mutually exclusive?	Yes
	Treatment

Arm description:

Combined capsule containing 2 mg perindopril and 1.25 mg bisoprolol

Arm type	Experimental
Investigational medicinal product name	Bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Boys up to 30 kg body weight at baseline - Months 2-60 (or study end date or until their bodyweight increases to 30 kg or over): one capsule per day, containing 1.25 mg bisoprolol 1.25 mg

Boys 30 kg or over body weight at baseline - Months 2-60 (or study end date): Change to maintenance dosage of two capsules per day, containing 2.5 mg bisoprolol

Boys up to 30 kg body weight at baseline but whose body weight increases to 30 kg or over during the trial – From follow-up appointment where weight increased to 30 kg or over to month 60 (or study end date): Change to maintenance dosage of two capsules per day, containing 2.5 mg bisoprolol

Investigational medicinal product name	Perindopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Boys up to 30 kg body weight at baseline - Months 2-60 (or study end date or until their bodyweight increases to 30 kg or over): Combined capsule containing 2 mg perindopril

Boys 30 kg or over body weight at baseline - Months 2-60 (or study end date): Change to maintenance dosage of two capsules containing 4 mg perindopril

Boys up to 30 kg body weight at baseline but whose body weight increases to 30 kg or over during the trial – From follow-up appointment where weight increased to 30 kg or over to month 60 (or study end date): Change to maintenance dosage of two capsules containing 4 mg perindopril

	Placebo
Arm description:	
Matching placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Boys up to 30 kg body weight at baseline - Months 2-60 (or study end date or until their bodyweight increases to 30 kg or over): Capsule containing matched placebo

Boys 30 kg or over body weight at baseline - Months 2-60 (or study end date): Change to maintenance dosage of two capsules of matched placebo

Boys up to 30 kg body weight at baseline but whose body weight increases to 30 kg or over during the trial – From follow-up appointment where weight increased to 30 kg or over to month 60 (or study end date): Change to maintenance dosage of two capsules of matched placebo

	Treatment	Placebo
Started	42	43
Completed	42	43

Period 2 title	36 months' participation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Trial IMP tablets were over-encapsulated, and accompanied by matched placebo, to establish the blind from trial start, in bottles numbered according to the blinded randomisation schedule. Sealed codebreak envelopes were stored in the Pharmacy/ISF, and opened only in an emergency. Unblinding was notified to the trial co-ordinating team, and a record kept in the TMF and ISF. The blind was maintained until all trial data were collected and the database locked, when participants were unblinded.

Are arms mutually exclusive?	Yes

	Treatment

Arm description:

Combined capsule containing 2 mg perindopril and 1.25 mg bisoprolol

Arm type	Experimental
Investigational medicinal product name	Bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Boys up to 30 kg body weight at baseline - Months 2-60 (or study end date or until their bodyweight increases to 30 kg or over): one capsule per day, containing 1.25 mg bisoprolol 1.25 mg

Boys 30 kg or over body weight at baseline - Months 2-60 (or study end date): Change to maintenance dosage of two capsules per day, containing 2.5 mg bisoprolol

Boys up to 30 kg body weight at baseline but whose body weight increases to 30 kg or over during the trial – From follow-up appointment where weight increased to 30 kg or over to month 60 (or study end date): Change to maintenance dosage of two capsules per day, containing 2.5 mg bisoprolol

Investigational medicinal product name	Perindopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Boys up to 30 kg body weight at baseline - Months 2-60 (or study end date or until their bodyweight increases to 30 kg or over): Combined capsule containing 2 mg perindopril

Boys 30 kg or over body weight at baseline - Months 2-60 (or study end date): Change to maintenance dosage of two capsules containing 4 mg perindopril

Boys up to 30 kg body weight at baseline but whose body weight increases to 30 kg or over during the trial – From follow-up appointment where weight increased to 30 kg or over to month 60 (or study end date): Change to maintenance dosage of two capsules containing 4 mg perindopril

	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Boys up to 30 kg body weight at baseline - Months 2-60 (or study end date or until their bodyweight increases to 30 kg or over): Capsule containing matched placebo

Boys 30 kg or over body weight at baseline - Months 2-60 (or study end date): Change to maintenance dosage of two capsules of matched placebo

Boys up to 30 kg body weight at baseline but whose body weight increases to 30 kg or over during the trial – From follow-up appointment where weight increased to 30 kg or over to month 60 (or study end date): Change to maintenance dosage of two capsules of matched placebo

Reporting group title	Treatment
Reporting group description: Combined capsule containing 2 mg perindopril and 1.25 mg bisoprolol	
Reporting group title	Placebo
Reporting group description: Matching placebo	

	Treatment	Placebo	Total
Number of subjects	42	43	85
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)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
The subject population was children between the ages of five and 12 .			
Units: years			
arithmetic mean	9.6	9.7	
standard deviation	± 1.8	± 2.0	-
Gender categorical			
Subjects were male.			
Units: Subjects			
Female	0	0	0
Male	42	43	85
Genetic mutation type			
Type of genetic mutation that participant exhibits.			
Units: Subjects			
None identified/misssing	9	14	23
Deletion	25	15	40
Duplication	2	3	5
Point mutation	4	7	11
Other	2	4	6
Enrolling centre			
Trial site/centre at which the participant was recruited.			
Units: Subjects			
Newcastle	14	14	28
London	23	22	45
Liverpool	5	5	10

Birmingham	0	1	1
Oxford	0	1	1

Body surface area			
Body surface area of participant.			
Units: Sqrt(weight(kg)*height(cm)/3600)			
arithmetic mean	32.2	31.9	
standard deviation	± 59.6	± 58.1	-

Reporting group title	Treatment
Reporting group description: Combined capsule containing 2 mg perindopril and 1.25 mg bisoprolol	
Reporting group title	Placebo
Reporting group description: Matching placebo	
Reporting group title	Treatment
Reporting group description: Combined capsule containing 2 mg perindopril and 1.25 mg bisoprolol	
Reporting group title	Placebo
Reporting group description: Placebo	

End point title	36 months' participation
End point description: End point description: The primary outcome measure was change in left ventricular ejection fraction (LVEF %), compared to baseline after a minimum of three years of combination therapy or placebo. To assess the robustness of ejection fraction result, similar comparisons will be made for parameters of left ventricular end-systolic dimension, wall motion index and left ventricular fractional shortening (%) and mitral flow to left ventricular tissue Doppler ratios (E/E' ratios).	
End point type	Primary
End point timeframe: 36 months post-randomisation.	

	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	24		
Units: range 0 to 45	33	24		

	LV Ejection Fraction
Statistical analysis description: LV Ejection Fraction (LVEF) at 36 months from baseline (post-randomisation).	
Comparison groups	Treatment v Placebo

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	1.1

	LV end systolic dimensions
Statistical analysis description: LV end systolic dimensions at 36 months from baseline.	
Comparison groups	Treatment v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

	LV end diastolic dimensions
Statistical analysis description: LV end diastolic dimensions at 36 months from baseline.	
Comparison groups	Treatment v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

	LV Ejection Fraction
Statistical analysis description: LV Ejection Fraction (LVEF) up to 36 months	
Comparison groups	Treatment v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA

	LV fractional shortening
Statistical analysis description: LV fractional shortening up to 36 months	
Comparison groups	Treatment v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA

Timeframe for reporting adverse events:
All non-SAEs/SARs occurring during drug treatment were reported on the eCRF system within four weeks of the form being due.
Adverse event reporting additional description:
All Adverse Events were recorded. PIs were responsible for managing all AEs/ARs according to local protocols.

Assessment type	Systematic

Dictionary name	MedDRA
Dictionary version	22.1

Reporting group title	Treatment
Reporting group description:	
Participants receiving active treatment.	
Reporting group title	Placebo
Reporting group description:	
Participants receiving placebo.	

	Treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Fracture	Additional description: The participant suffered fractures of his right and left femurs.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Knee injury	Additional description: The participant suffered a knee injury, and was put in a plaster cast.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Palpitations	Additional description: The participant suffered from palpitations.		

subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fat embolism	Additional description: The participant suffered a fat embolism.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis	Additional description: The participant suffered from acute pericarditis.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Fall	Additional description: Fall from wheelchair with initial recovery, but subsequent seizure, apnoea and failure of resuscitation in A&E.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache	Additional description: The participant suffered with headaches, nausea and visual disturbance.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lethargy	Additional description: The participant suffered from lethargy and was hospitalised.		
subjects affected / exposed	11 / 42 (26.19%)	11 / 43 (25.58%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adverse reaction	Additional description: The participant suffered an adverse reaction to bisphosphonates, specifically zoledronic acid (not the trial medication).		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Overdose	Additional description: The participant suffered an accidental overdose of lisinopril (not trial medication).		

subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: The participant suffered from abdominal pain.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis	Additional description: The participant suffered from gastroenteritis.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric ulcer	Additional description: The participant suffered with superficial gastric ulceration.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation	Additional description: The participant suffered from severe constipation.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chest pain	Additional description: Participant suffered chest pain.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia	Additional description: The participant suffered from pneumonia.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection	Additional description: The participant suffered from a chest infection.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	

Lower respiratory tract infection	Additional description: The participant suffered from a lower respiratory tract infection.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection	Additional description: The participant suffered from a respiratory tract infection (with lethargy, tiredness and cough), and had a delayed recovery.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
ICU admission	Additional description: The participant suffered musculoskeletal symptoms due to his Duchenne muscular dystrophy, and was admitted to the ICU.		
subjects affected / exposed	11 / 42 (26.19%)	13 / 43 (30.23%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

	Treatment	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Verruca			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Vascular disorders			
Flushing			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Hypertension			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Surgical and medical procedures			
Cardiac catheterisation			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Planned hospital admission			

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Sickness			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Adverse reaction			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Constitutional symptoms			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Pyrexia			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Stomach pain, sore throat			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Hay fever			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Respiratory, thoracic and mediastinal disorders			
Cold			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Coryzal symptoms			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Cough			

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Lower respiratory tract infection			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Sore throat			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Upper respiratory tract infection			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Chest pain			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Respiratory infection			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Behaviour disorder			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Insomnia			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Bite			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Fall			

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Fat embolism			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Fracture			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Sprained ankle			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Foot injury			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Knee injury			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Cardiac disorders			
Chest pain, dyspnoea			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Palpitations			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Pericarditis			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Cardiac symptoms			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Increased heart rate			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Nervous system disorders			
Fainting			

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Headache			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Migraine			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)		120	

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Diarrhoea			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Heartburn			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Stomach ache			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Vomiting			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Appendicitis perforated			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Skin and subcutaneous tissue disorders			
Itching			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Pressure sore			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Skin condition			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Pruritus			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Rash			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Neck pain			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Tight achilles tendon			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Knee pain			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Leg pain			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Infections and infestations			
Flu			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Oral thrush			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Pneumonia			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Throat infection			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Toe infection			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Chest infection			

subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Infection			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Ingrowing nail			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	
Tonsillitis			
subjects affected / exposed	29 / 42 (69.05%)	34 / 43 (79.07%)	
occurrences (all)	84	120	

Were there any global substantial amendments to the protocol? Yes

11 March 2010	Personnel changes (Addition of Assistant Trial Manager).

Notes:

Were there any global interruptions to the trial? No

None reported