Clinical trial results:
Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate-5-lipoxygenase (ALOX5) promoter genotype.

Summary

EudraCT number	2009-015626-11
Trial protocol	GB
Global end of trial date	31 October 2014

Results information

Result version number	v1 (current)
This version publication date	27 August 2017
First version publication date	27 August 2017
Summary attachment (see zip file)	EME Report - WAIT Study (Nwokoro et al. - 2015 - Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate 5-lipoxygen.pdf) Main Publication (LANCET PAPER.pdf) Qualitative Paper (e002750.full.pdf)

Trial information

Trial identification

Sponsor protocol code	006983 QM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01142505
WHO universal trial number (UTN)	-
Other trial identifiers	NIHR-EME Project Number: 08/43/03, NHS Research Ethics Committee Number: 09/H1102/110

Notes:

Sponsors

Sponsor organisation name	Joint Research management Office, Queen mary Innovation Centre
Sponsor organisation address	2 Walden Street, London, United Kingdom, E1 2EF
Public contact	Dr Chinedu Nwokoro, Centre for Paediatrics, Blizard Institute Queen Mary University of London, 0207 8822195, c.nwokoro@qmul.ac.uk
Scientific contact	Dr Chinedu Nwokoro, Centre for Paediatrics, Blizard Institute Queen Mary University of London, 0207 8822195, c.nwokoro@qmul.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	31 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2013
Global end of trial reached?	Yes
Global end of trial date	31 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective of this research is to determine whether intermittent parent-initiated treatment with oral montelukast in preschool children with a history of wheeze, reduces the need for unscheduled medical attention for wheeze. To assess this treatment will be started by parents or guardians i) at the onset of every cold and continued for a minimum of 7 days or until wheeze has resolved for 48 hours, and ii) for every episode of wheeze not associated with a viral cold, and stopped when symptoms have resolved for 48 hours. For each child, the trial will last 12 months.

Protection of trial subjects:

Study was conducted under auspices of an IDMC, and the NHS Research Ethics Committee. All subjects were recruited by their treating medical physician. The investigational medicinal product is already in full licensed use for the indication under study. There were no painful interventions involved in the study.

Background therapy:

Children were under standard treatment for asthma and wheezing disease such as inhaled steroids or beta agonist. These were not imposed as part of study protocol.

Evidence for comparator:

This information is included in the study design section of the report. The comparator was an identical placebo, while the IMP was a known drug used in paediatric asthma.

Actual start date of recruitment	01 October 2010
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: 1346
Worldwide total number of subjects	1346
EEA total number of subjects	1346

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)	463
Children (2-11 years)	883
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were identified in primary and secondary care centres. Recruitment was planned to encompass only three secondary care centres (the Royal London Hospital, University Hospital Leicester and the Royal Aberdeen Children's Hospital), but increased to 41 secondary care centres in England and Scotland. Recruitment spanned Oct 2010 to Dec 2012

Pre-assignment

Screening details:

Eligibility: 10m-5y, >1 wheeze attacks, 1 medically validated, 1 in prev 3m. Exclusions: respiratory comorbidities, sickle cell, BPD, severe developmental delay, montelukast use, other recent trial involvement. 1883 screened, 525 did not ultimately consent, 11 subsequently refused permission for data use, 1 provided no data --> 1346.

Pre-assignment period milestones

Number of subjects started	1883[1]
Intermediate milestone: Number of subjects	Consent: 1366
Intermediate milestone: Number of subjects	Randomisation: 1358
Number of subjects completed	1346

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Refused consent: 517
Reason: Number of subjects	No data collected: 1
Reason: Number of subjects	Withdrew prior to randomisation: 8
Reason: Number of subjects	Withdrew permission to use collected data: 11

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This number (1883) includes all those approached to enter the study.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Novalabs (the primary IMP producer) produced a corresponding randomisation code denoting whether a given IMP box contained active medication or placebo. This was kept sealed and held only by the clinical trials pharmacist and a member of the Independent Data and Safety Monitoring Committee (DSMC), in this way all other clinical investigators and participants remained blinded to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Treatment

Arm description:

Subjects allocated to active treatment

Arm type	Experimental

Investigational medicinal product name	Singulair granules
Investigational medicinal product code	ATC code: R03DC03
Other name	Montelukast
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

IMP was presented as white granules administered either directly into the child's mouth, or mixed with a spoonful of cold or room temperature soft food. The IMP was used according to the primary manufacturer's instructions. Specifically, parents were advised not to open the sachet containing the granules until ready to use. After opening the sachet, the full dose of granules was administered within 15 minutes. If mixed with food, the granules must not be stored for future use. The granules were not intended to be dissolved in liquid for administration however liquids could be taken subsequent to administration. The granules were administered without regard to the timing of food ingestion. The dose was one 4mg sachet per day, started at the start of a viral cold or had wheeze, and stopped after 10 days. Children could start a 2nd course should the wheeze persist. If a child vomited after receiving IMP no additional dose was given, and parents recorded this on the diary card.

Arm title	Placebo

Arm description:

Subjects allocated to receive placebo during the study

Arm type	Placebo
Investigational medicinal product name	Mannitol EP (Pearlitol SD 200)
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

IMP was presented as white granules administered either directly into the child's mouth, or mixed with a spoonful of cold or room temperature soft food. The IMP was used according to the primary manufacturer's instructions. Specifically, parents were advised not to open the sachet containing the granules until ready to use. After opening the sachet, the full dose of granules was administered within 15 minutes. If mixed with food, the granules must not be stored for future use. The granules were not intended to be dissolved in liquid for administration however liquids could be taken subsequent to administration. The granules were administered without regard to the timing of food ingestion. The dose was one 4mg sachet per day, started at the start of a viral cold or had wheeze, and stopped after 10 days. Children could start a 2nd course should the wheeze persist. If a child vomited after receiving IMP no additional dose was given, and parents recorded this on the diary card.

Number of subjects in period 1	Active Treatment	Placebo
Started	669	677
T1 - First Phonecall	652	656
T2 - Second Phonecall	631	636
T3 - Third Phonecall	616	624
T4 - Fourth Phonecall	604	605
T5 - Fifth Phonecall	591	590
T6 - Sixth Phonecall (End of Trial)	579	575
Completed	579	575
Not completed	90	102
Poor Adherence	5	2
Physician decision	51	-

Adverse event, non-fatal	2	6
Other	17	-
Not specified	-	37
Lost to follow-up	-	36
Protocol deviation	14	13
Lack of efficacy	1	8

Baseline characteristics

Reporting groups	
Reporting group title	Active Treatment
Reporting group description:	
Subjects allocated to active treatment	
Reporting group title	Placebo
Reporting group description:	
Subjects allocated to receive placebo during the study	

Reporting group values	Active Treatment	Placebo	Total
Number of subjects	669	677	1346
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			
Age at date of first IMP dispensing.			
Units: years			
arithmetic mean	2.6	2.7	
standard deviation	± 1.1	± 1.1	-
Gender categorical			
Gender.			
Units: Subjects			
Female	243	240	483
Male	426	437	863
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White	514	512	1026
Black	19	18	37
Asian	92	104	196
Other	44	43	87
Preterm birth			
Gestation at birth			
Units: Subjects			
<37 weeks	98	98	196
>37= weeks	571	579	1150
Birthweight			
Birthweight			

Units: Subjects			
<2500g	79	70	149
>= 2500g	590	607	1197
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes	108	111	219
No	561	566	1127
Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes	38	42	80
No	631	635	1266
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes	328	349	677
No	341	328	669
Maternal Asthma History			
History of asthma in mother (self-report)			
Units: Subjects			
Yes	251	230	481
No	418	447	865
Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes	199	207	406
No	470	470	940
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes	192	191	383
No	477	486	963
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes	184	213	397
No	485	464	949
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1	579	554	1133
<=1	90	123	213
Weight			
Weight at recruitment			
Units: kg			
arithmetic mean	14	14.2	
standard deviation	± 3.3	± 3.5	-
Height			
Height at consent to study			

Units: cm			
arithmetic mean	89.9	90.6	
standard deviation	± 10.4	± 11	-
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months			
arithmetic mean	12.8	12.9	
standard deviation	± 10.1	± 10.8	-
Interval between onset of URTI and wheezing			
Onset of URTI to onset of wheezing			
Units: Hours			
arithmetic mean	30.5	27.7	
standard deviation	± 26.6	± 24.4	-
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses			
arithmetic mean	1.9	1.9	
standard deviation	± 1.8	± 2	-
Historic Unscheduled Medical Attendances (USMA)			
USMA in preceding year			
Units: Attendances			
arithmetic mean	5.4	5.6	
standard deviation	± 4.2	± 5.1	-

Subject analysis sets

Subject analysis set title	5/5 ALOX5 stratum - active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/5 ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	5/x + x/y stratum - active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/x or x/y ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	5/5 ALOX5 stratum - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/5 ALOX5 promoter genotype who were allocated to placebo medication	
Subject analysis set title	5/x + x/y stratum - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/x + x/y ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	ICS - Active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Children receiving inhaled corticosteroid and randomised to receive montelukast	
Subject analysis set title	ICS - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Children receiving inhaled corticosteroids at baseline and randomised to receive placebo	

Subject analysis set title	No ICS - Active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Children not on ICS at baseline and randomised to montelukast	
Subject analysis set title	No ICS - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects not on inhaled corticosteroids at baseline and randomised to placebo medication	
Subject analysis set title	5/5 + 5/x stratum - active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with 5/5 or 5/x ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	x/y stratum - Active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with x/y ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	5/5 + 5/x stratum - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with 5/5 or 5/x ALOX5 promoter genotype who were allocated to placebo medication	
Subject analysis set title	x/y stratum - placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects with x/y ALOX5 promoter genotype who were allocated to placebo medication	
Subject analysis set title	Multi trigger wheeze - active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with multi trigger wheeze allocated to montelukast	
Subject analysis set title	Multi trigger wheeze - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with multi trigger wheeze allocated to placebo medication	
Subject analysis set title	Episodic viral wheeze - active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with episodic viral wheeze allocated to montelukast	
Subject analysis set title	Episodic viral wheeze - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with episodic viral wheeze allocated to placebo medication	

Reporting group values	5/5 ALOX5 stratum - active	5/x + x/y stratum - active	5/5 ALOX5 stratum - placebo
Number of subjects	416	253	426
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years)			

Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at date of first IMP dispensing.			
Units: years			
arithmetic mean	2.6	2.5	2.6
standard deviation	± 1.1	± 1.1	± 1.1
Gender categorical			
Gender.			
Units: Subjects			
Female	154	89	150
Male	262	164	276
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White	335	179	338
Black	5	14	4
Asian	55	37	58
Other	21	23	26
Preterm birth			
Gestation at birth			
Units: Subjects			
<37 weeks	58	40	56
>37= weeks	358	213	370
Birthweight			
Birthweight			
Units: Subjects			
<2500g	51	28	42
>= 2500g	365	225	384
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes	64	44	64
No	352	209	362
Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes	26	12	23
No	390	241	403
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes	207	121	215
No	209	132	211
Maternal Asthma History			
History of asthma in mother (self-report)			
Units: Subjects			
Yes	156	95	141
No	260	158	285

Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes	126	73	126
No	290	180	300
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes	120	72	131
No	296	181	295
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes	118	66	144
No	198	187	282
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1	363	216	351
<=1	53	37	75
Weight			
Weight at recruitment			
Units: kg			
arithmetic mean	14	13.9	14
standard deviation	± 3	± 3.7	± 3.3
Height			
Height at consent to study			
Units: cm			
arithmetic mean	90	89.8	89.9
standard deviation	± 10.3	± 10.5	± 10.5
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months			
arithmetic mean	12.4	13.5	12.4
standard deviation	± 9.8	± 10.5	± 10.4
Interval between onset of URTI and wheezing			
Onset of URTI to onset of wheezing			
Units: Hours			
arithmetic mean	31.6	28.8	27.3
standard deviation	± 27.4	± 25.2	± 23.4
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses			
arithmetic mean	2	1.8	1.9
standard deviation	± 1.9	± 1.8	± 1.9
Historic Unscheduled Medical Attendances (USMA)			
USMA in preceding year			
Units: Attendances			
arithmetic mean	5.5	5.4	5.7

standard deviation	± 4.3	± 4.1	± 5.3

Reporting group values	5/x + x/y stratum - placebo	ICS - Active	ICS - Placebo
Number of subjects	251	276	282
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age at date of first IMP dispensing.			
Units: years			
arithmetic mean	2.8		
standard deviation	± 1.2	±	±
Gender categorical			
Gender.			
Units: Subjects			
Female	90		
Male	161		
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White	174		
Black	14		
Asian	46		
Other	17		
Preterm birth			
Gestation at birth			
Units: Subjects			
<37 weeks	42		
>37= weeks	209		
Birthweight			
Birthweight			
Units: Subjects			
<2500g	28		
>= 2500g	223		
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes	47		
No	204		

Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes	29		
No	222		
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes	134		
No	117		
Maternal Asthma History			
History of asthma in mother (self-report)			
Units: Subjects			
Yes	89		
No	162		
Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes	81		
No	170		
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes	60		
No	191		
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes	69		
No	182		
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1	203		
<=1	48		
Weight			
Weight at recruitment			
Units: kg			
arithmetic mean	14.6		
standard deviation	± 3.8	±	±
Height			
Height at consent to study			
Units: cm			
arithmetic mean	91.8		
standard deviation	± 11.7	±	±
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months			
arithmetic mean	13.6		
standard deviation	± 11.5	±	±
Interval between onset of URTI and			

wheezing			
Onset of URTI to onset of wheezing			
Units: Hours			
arithmetic mean	28.2		
standard deviation	± 26	±	±
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses			
arithmetic mean	1.8		
standard deviation	± 2	±	±
Historic Unscheduled Medical Attendances (USMA)			
USMA in preceding year			
Units: Attendances			
arithmetic mean	5.6		
standard deviation	± 4.6	±	±

Reporting group values	No ICS - Active	No ICS - Placebo	5/5 + 5/x stratum - active
Number of subjects	376	374	627
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age at date of first IMP dispensing.			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Gender.			
Units: Subjects			
Female			
Male			
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White			
Black			
Asian			
Other			
Preterm birth			
Gestation at birth			
Units: Subjects			

<37 weeks >37= weeks			
Birthweight			
Birthweight			
Units: Subjects			
<2500g >= 2500g			
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes No			
Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes No			
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes No			
Maternal Asthma History			
History of asthma in mother (self-report)			
Units: Subjects			
Yes No			
Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes No			
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes No			
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes No			
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1 <=1			
Weight			
Weight at recruitment			
Units: kg			

arithmetic mean standard deviation	±	±	±
Height			
Height at consent to study			
Units: cm arithmetic mean standard deviation	±	±	±
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months arithmetic mean standard deviation	±	±	±
Interval between onset of URTI and wheezing			
Onset of URTI to onset of wheezing			
Units: Hours arithmetic mean standard deviation	±	±	±
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses arithmetic mean standard deviation	±	±	±
Historic Unscheduled Medical Attendances (USMA)			
USMA in preceding year			
Units: Attendances arithmetic mean standard deviation	±	±	±

Reporting group values	x/y stratum - Active	5/5 + 5/x stratum - placebo	x/y stratum - placebo
Number of subjects	25	622	34
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at date of first IMP dispensing.			
Units: years arithmetic mean standard deviation	±	±	±

Gender categorical			
Gender.			
Units: Subjects			
Female Male			
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White Black Asian Other			
Preterm birth			
Gestation at birth			
Units: Subjects			
<37 weeks >37= weeks			
Birthweight			
Birthweight			
Units: Subjects			
<2500g >= 2500g			
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes No			
Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes No			
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes No			
Maternal Asthma History			
History of asthma in mother (self-report)			
Units: Subjects			
Yes No			
Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes No			
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes			

No			
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes No			
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1 <=1			
Weight			
Weight at recruitment			
Units: kg arithmetic mean standard deviation	±	±	±
Height			
Height at consent to study			
Units: cm arithmetic mean standard deviation	±	±	±
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months arithmetic mean standard deviation	±	±	±
Interval between onset of URTI and wheezing			
Onset of URTI to onset of wheezing			
Units: Hours arithmetic mean standard deviation	±	±	±
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses arithmetic mean standard deviation	±	±	±
Historic Unscheduled Medical Attendances (USMA)			
USMA in preceding year			
Units: Attendances arithmetic mean standard deviation	±	±	±

Reporting group values	Multi trigger wheeze - active	Multi trigger wheeze - placebo	Episodic viral wheeze - active
Number of subjects	190	183	462
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at date of first IMP dispensing.			
Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
Gender.			
Units: Subjects			
Female Male			
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White Black Asian Other			
Preterm birth			
Gestation at birth			
Units: Subjects			
<37 weeks >37= weeks			
Birthweight			
Birthweight			
Units: Subjects			
<2500g >= 2500g			
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes No			
Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes No			
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes No			
Maternal Asthma History			

History of asthma in mother (self-report)			
Units: Subjects			
Yes			
No			
Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes			
No			
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes			
No			
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes			
No			
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1			
<=1			
Weight			
Weight at recruitment			
Units: kg			
arithmetic mean			
standard deviation	±	±	±
Height			
Height at consent to study			
Units: cm			
arithmetic mean			
standard deviation	±	±	±
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months			
arithmetic mean			
standard deviation	±	±	±
Interval between onset of URTI and wheezing			
Onset of URTI to onset of wheezing			
Units: Hours			
arithmetic mean			
standard deviation	±	±	±
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses			
arithmetic mean			
standard deviation	±	±	±
Historic Unscheduled Medical			

Attendances (USMA)			
USMA in preceding year			
Units: Attendances			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Episodic viral wheeze - placebo		
Number of subjects	473		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age at date of first IMP dispensing.			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Gender.			
Units: Subjects			
Female			
Male			
Ethnicity			
Self-reported ethnicity			
Units: Subjects			
White			
Black			
Asian			
Other			
Preterm birth			
Gestation at birth			
Units: Subjects			
<37 weeks			
>37= weeks			
Birthweight			
Birthweight			
Units: Subjects			
<2500g			
>= 2500g			
Food Allergy			
Parent-reported food allergy status			
Units: Subjects			
Yes			

No			
Drug Allergy			
Patient-recorded drug allergy			
Units: Subjects			
Yes No			
Eczema			
Subjects who have ever had eczema.			
Units: Subjects			
Yes No			
Maternal Asthma History			
History of asthma in mother (self-report)			
Units: Subjects			
Yes No			
Paternal Asthma History			
Paternal asthma history - self-reported			
Units: Subjects			
Yes No			
Multitrigger Wheeze			
Parent-reported multiple trigger wheeze			
Units: Subjects			
Yes No			
Continuous Inhaled Steroids at study entry			
Subjects on continuous inhaled steroids at study entry.			
Units: Subjects			
Yes No			
Historic Hospital Admissions			
Number of hospital admissions for wheeze in preceding 12 months			
Units: Subjects			
>1 <=1			
Weight			
Weight at recruitment			
Units: kg arithmetic mean standard deviation	±		
Height			
Height at consent to study			
Units: cm arithmetic mean standard deviation	±		
Age at first wheeze			
Age at first wheeze - parental reported			
Units: Months arithmetic mean			

standard deviation	±		
Interval between onset of URTI and wheezing			
Onset of URTI to onset of wheezing			
Units: Hours arithmetic mean standard deviation	±		
Historic Oral corticosteroid courses			
Oral corticosteroid courses taken in preceding 12 months			
Units: Courses arithmetic mean standard deviation	±		
Historic Unscheduled Medical Attendances (USMA)			
USMA in preceding year			
Units: Attendances arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Active Treatment
Reporting group description: Subjects allocated to active treatment	
Reporting group title	Placebo
Reporting group description: Subjects allocated to receive placebo during the study	
Subject analysis set title	5/5 ALOX5 stratum - active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/5 ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	5/x + x/y stratum - active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/x or x/y ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	5/5 ALOX5 stratum - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/5 ALOX5 promoter genotype who were allocated to placebo medication	
Subject analysis set title	5/x + x/y stratum - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/x + x/y ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	ICS - Active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Children receiving inhaled corticosteroid and randomised to receive montelukast	
Subject analysis set title	ICS - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Children receiving inhaled corticosteroids at baseline and randomised to receive placebo	
Subject analysis set title	No ICS - Active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Children not on ICS at baseline and randomised to montelukast	
Subject analysis set title	No ICS - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects not on inhaled corticosteroids at baseline and randomised to placebo medication	
Subject analysis set title	5/5 + 5/x stratum - active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with 5/5 or 5/x ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	x/y stratum - Active
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with x/y ALOX5 promoter genotype who were allocated to active medication	
Subject analysis set title	5/5 + 5/x stratum - placebo

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with 5/5 or 5/x ALOX5 promoter genotype who were allocated to placebo medication	
Subject analysis set title	x/y stratum - placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects with x/y ALOX5 promoter genotype who were allocated to placebo medication	
Subject analysis set title	Multi trigger wheeze - active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with multi trigger wheeze allocated to montelukast	
Subject analysis set title	Multi trigger wheeze - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with multi trigger wheeze allocated to placebo medication	
Subject analysis set title	Episodic viral wheeze - active
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with episodic viral wheeze allocated to montelukast	
Subject analysis set title	Episodic viral wheeze - placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with episodic viral wheeze allocated to placebo medication	

Primary: Unscheduled Medical Attendances (USMA) per subject per year

End point title	Unscheduled Medical Attendances (USMA) per subject per year
End point description:	
The number of times a child attends for an unscheduled medical opinion (a summation of hospital admissions, attendances, GP visits,) with respiratory problems over a 12 month period as confirmed from clinical records	
End point type	Primary
End point timeframe:	
12 months	

End point values	Active Treatment	Placebo	5/5 ALOX5 stratum - active	5/x + x/y stratum - active
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	652[1]	656[2]	404	248
Units: USMA/subject				
arithmetic mean (standard deviation)	2 (± 2.6)	2.3 (± 2.7)	2 (± 2.7)	2 (± 2.5)

Notes:

[1] - Previously explained.

[2] - Previously explained

End point values	5/5 ALOX5 stratum - placebo	5/x + x/y stratum - placebo	ICS - Active	ICS - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	410	246	274	282
Units: USMA/subject				

arithmetic mean (standard deviation)	2.4 (± 3)	2 (± 2.3)	2 (± 3)	2 (± 2.3)

End point values	No ICS - Active	No ICS - Placebo	5/5 + 5/x stratum - active	x/y stratum - Active
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	373	368	623	24
Units: USMA/subject				
arithmetic mean (standard deviation)	2 (± 2.2)	2.5 (± 3)	2 (± 2.6)	1.7 (± 1.8)

End point values	5/5 + 5/x stratum - placebo	x/y stratum - placebo	Multi trigger wheeze - active	Multi trigger wheeze - placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	616	34	188	183
Units: USMA/subject				
arithmetic mean (standard deviation)	2.3 (± 2.8)	1.9 (± 2)	2.1 (± 3)	2 (± 2.5)

End point values	Episodic viral wheeze - active	Episodic viral wheeze - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	459	467		
Units: USMA/subject				
arithmetic mean (standard deviation)	2 (± 2.4)	2.3 (± 2.9)		

Attachments (see zip file)	Forest Plot of Primary Outcome incl Stratum/Forest Plot USMA

Statistical analyses

Statistical analysis title	USMA: Montelukast vs Placebo - unstratified

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects.

Comparison groups	Active Treatment v Placebo
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.06
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.01
Variability estimate	Standard deviation

Notes:

[3] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.

Statistical analysis title	USMA: Montelukast vs Placebo (5/5)

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects in the 5/5 promoter polymorphism genotype arm.

Comparison groups	5/5 ALOX5 stratum - active v 5/5 ALOX5 stratum - placebo
Number of subjects included in analysis	814
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.01 [5]
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.95
Variability estimate	Standard deviation

Notes:

[4] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.

[5] - P-value for interaction between genotype and treatment is 0.08 (non-significant).

Statistical analysis title	USMA:Montelukast vs Placebo [5/x + x/y]

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects in the [5/x + x/y] promoter polymorphism genotype arm.

Comparison groups	5/x + x/y stratum - active v 5/x + x/y stratum - placebo
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.79 [7]
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.29
Variability estimate	Standard deviation

Notes:

[6] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.
[7] - P-value for the interaction of genotype (5/5 vs [5/x +x/y])with the primary outcome = 0.08 (non-significant).

Statistical analysis title	USMA: Montelukast vs Placebo (5/5 + 5/x)

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects in the (5/5 + 5/x) promoter polymorphism genotype arm.

Comparison groups	5/5 + 5/x stratum - active v 5/5 + 5/x stratum - placebo v x/y stratum - Active v x/y stratum - placebo
Number of subjects included in analysis	1297
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.93 [9]
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio in each arm
Variability estimate	Standard deviation

Notes:

[8] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.
[9] - P-value for interaction between genotype and treatment is 0.93 (non-significant).

Statistical analysis title	USMA: Montelukast vs Placebo (x/y)

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects in the (x/y) promoter polymorphism genotype arm.

Comparison groups	5/5 + 5/x stratum - active v 5/5 + 5/x stratum - placebo v x/y stratum - Active v x/y stratum - placebo
Number of subjects included in analysis	1297
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.93 [11]
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio in each arm
Variability estimate	Standard deviation

Notes:

[10] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.
[11] - P-value for interaction between genotype and treatment is 0.93 (non-significant).

Statistical analysis title	USMA: Montelukast vs Placebo (ICS at baseline)

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects in children with or without Inhaled Corticosteroids (ICS) at baseline.

Comparison groups	ICS - Active v ICS - Placebo v No ICS - Active v No ICS - Placebo
Number of subjects included in analysis	1297
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.09 [13]
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio in each arm
Variability estimate	Standard deviation

Notes:

[12] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.
[13] - P-value for interaction between inhaled steroid use and treatment is 0.09 (non-significant).

Statistical analysis title	USMA: Montelukast vs Placebo (MTW vs EVW)

Statistical analysis description:

Unscheduled Medical Attendances in Montelukast-treated subjects compared with Placebo-treated subjects in children with multiple trigger wheeze (MTW) vs Episodic Viral Wheeze (EVW) at baseline.

Comparison groups	Multi trigger wheeze - active v Multi trigger wheeze - placebo v Episodic viral wheeze - active v Episodic viral wheeze - placebo
Number of subjects included in analysis	1297
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.19 [15]
Method	Poisson Regression
Parameter estimate	Incidence Rate Ratio in each arm
Variability estimate	Standard deviation

Notes:

[14] - Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.
[15] - P-value for interaction between wheeze phenotype (EVW vs MTW) and treatment is 0.19 (non-significant).

Secondary: Subjects with one or more unscheduled medical attendances

End point title	Subjects with one or more unscheduled medical attendances

End point description:

Subjects with one or more USMA

End point type	Secondary

End point timeframe:

12 months

End point values	Active Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	652[16]	656[17]		
Units: Subjects	426	456		

Notes:

[16] - Intention to treat population

[17] - Intention to treat population

Statistical analyses

Statistical analysis title	Children with one or more USMA by active/placebo

Statistical analysis description:

Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.

Comparison groups	Active Treatment v Placebo
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [18]
Method	Poisson Regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.04

Notes:

[18] - Non-significant

Secondary: Time to first unscheduled medical attendance

End point title	Time to first unscheduled medical attendance

End point description:

Time to first unscheduled medical attendance.

End point type	Secondary

End point timeframe:

12 months

End point values	Active Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	652[19]	656[20]		
Units: days	147	130		

Notes:

[19] - Intention to treat population

[20] - Time to first unscheduled medical attendance in days

Attachments (see zip file)	Kaplan-Meier Curves/Kaplan-Meier Curves - WAIT.jpg

Statistical analyses

Statistical analysis title	Time to first USMA by active/placebo

Statistical analysis description:

Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.

Comparison groups	Active Treatment v Placebo
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [21]
Method	Poisson regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.02

Notes:

[21] - Non-significant

Secondary: Need for rescue oral corticosteroids

End point title	Need for rescue oral corticosteroids

End point description:

Data are analysed using Poisson regression with fixed effects for stratification factor and treatment group, a random effect for individual to account for overdispersion with follow up time fitted as the exposure. Follow up time is based on time from randomisation until either 12 month end of trial date or date of last phonecall. Primary outcome data is taken from the phonecall which occurred every two months, and confirmed from diary cards and primary and secondary care records.

End point type	Secondary

End point timeframe:

12 months

End point values	Active Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	652[22]	656[23]		
Units: Courses/child				
arithmetic mean (standard deviation)	0.26 (± 0.7)	0.33 (± 0.9)		

Notes:

[22] - ITT population

[23] - ITT population

Statistical analyses

Statistical analysis title	Need for oral corticosteroids in follow-up
Comparison groups	Active Treatment v Placebo
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [24]
Method	Poisson regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.98

Notes:

[24] - Significant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reportable for one year from the point of trial entry

Adverse event reporting additional description:

Adverse events were reported on the diary card completed during courses of IMP and sent to the lead centre, reported in the two-monthly telephone questionnaire completed throughout follow-up, or reported as they occurred by telephone to the local research nurse. They were analysed by the local Principal Investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	No dictionary
Dictionary version	0

Reporting groups

Reporting group title	Active Treatment

Reporting group description:

Subjects allocated to active treatment

Reporting group title	Placebo

Reporting group description:

Subjects allocated to receive placebo during the study

Serious adverse events	Active Treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 669 (0.00%)	1 / 677 (0.15%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Cutaneous			
subjects affected / exposed	0 / 669 (0.00%)	1 / 677 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active Treatment	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 669 (29.45%)	235 / 677 (34.71%)	
Injury, poisoning and procedural complications			

Minor Injury	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	27 / 669 (4.04%)	22 / 677 (3.25%)	
occurrences (all)	27	22	
Major Injury	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	2 / 669 (0.30%)	1 / 677 (0.15%)	
occurrences (all)	2	1	
Nervous system disorders			
Central nervous system	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	25 / 669 (3.74%)	46 / 677 (6.79%)	
occurrences (all)	25	46	
Blood and lymphatic system disorders			
Haematological	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	5 / 669 (0.75%)	7 / 677 (1.03%)	
occurrences (all)	5	7	
Immune system disorders			
Allergy	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	16 / 669 (2.39%)	20 / 677 (2.95%)	
occurrences (all)	16	20	
Gastrointestinal disorders			
Gastrointestinal	Additional description: Any GI disturbance Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	86 / 669 (12.86%)	122 / 677 (18.02%)	
occurrences (all)	86	122	
Respiratory, thoracic and mediastinal disorders			
Respiratory	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	34 / 669 (5.08%)	54 / 677 (7.98%)	
occurrences (all)	34	54	
Skin and subcutaneous tissue disorders			
Cutaneous	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	32 / 669 (4.78%)	53 / 677 (7.83%)	
occurrences (all)	32	53	
Renal and urinary disorders			

Genitourinary	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	10 / 669 (1.49%)	6 / 677 (0.89%)	
occurrences (all)	10	6	
Musculoskeletal and connective tissue disorders			
Musculoskeletal	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	0 / 669 (0.00%)	1 / 677 (0.15%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	73 / 669 (10.91%)	103 / 677 (15.21%)	
occurrences (all)	73	103	
Minor infection	Additional description: Number of subjects affected is unknown, only number of occurrences. For purposes of data entry presumption of one occurrence per subject is made.		
subjects affected / exposed	87 / 669 (13.00%)	107 / 677 (15.81%)	
occurrences (all)	87	107	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Nil

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26632627

http://www.ncbi.nlm.nih.gov/pubmed/25212745

http://www.ncbi.nlm.nih.gov/pubmed/23572193