



Clinical trial results:

A phase II-III trial assessing the efficacy and safety of three doses of the ALK HDM tablet in house dust mite allergic subjects

Summary

EudraCT number	2006-001795-20
Trial protocol	SE DE ES DK GB IT
Global end of trial date	23 April 2008

Results information

Result version number	v1 (current)
This version publication date	16 February 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	MT-02
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló A/S
Sponsor organisation address	Bøge Allé 1, Hørsholm, Denmark, 2970
Public contact	Clinical Development, ALK-Abelló A/S, +45 45747576, ClinicalTrials@alk.net
Scientific contact	Clinical Development, ALK-Abelló A/S, +45 45747576, ClinicalTrials@alk.net

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	23 April 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2008
Global end of trial reached?	Yes
Global end of trial date	23 April 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of specific immunotherapy with three dosages of the ALK HDM tablet given once daily compared to placebo in subjects suffering from house dust mite allergy. The evaluation is based on reduction in inhaled corticosteroid (ICS)

Protection of trial subjects:

Safety surveillance

Subjects had access to symptomatic medications if needed. As regards ICS and medications to relieve asthma and rhinoconjunctivitis symptoms these medications were provided by the sponsor

Background therapy:

Subjects were provided with the asthma rescue medication:

- Budesonide Turbuhalers®, 100 µg or 200 µg.
- Salbutamol inhaler, 200 µg per inhalation. Dosing: Prn.

Subjects were supplied with the following rescue medication:

- Desloratadine 5 mg tablets. Dosing: 1 tablet daily prn.
- Budesonide nasal spray 32 µg micronised budesonide per actuation. Dosing: the lowest dosage acceptable to the subject.

In case of asthma exacerbations or severe rhinoconjunctivitis symptoms which could not be relieved with the asthma medication or rhinoconjunctivitis rescue medication provided, the investigator could treat the subject with an oral corticosteroid. The oral steroid provided was:

- Prednisone/prednisolone 5 mg tablets. Dosing: Up to 50 mg daily for three day

Evidence for comparator:

Placebo comparator

Actual start date of recruitment	18 August 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Denmark: 67
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 128
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Poland: 246

Worldwide total number of subjects	604
EEA total number of subjects	604

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)	0
Adolescents (12-17 years)	39
Adults (18-64 years)	559
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects was recruited from 81 sites in Denmark, France, Germany, Italy, Poland, Spain, Sweden and U.K.

The trial was initiated in the summer of 2006 (first subject first visit – 18 August 2006)

Pre-assignment

Screening details:

Male or female ≥ 14 years, clinical history ≥ 1 year of HDM-induced mild to moderate persistent asthma (steps 2 and 3 according the GINA guidelines) and mild to severe allergic rhinitis (ARIA guidelines), positive SPT (≥ 3 mm) and specific IgE ($\geq$ class 2) to D. pteronyssinus and/or D. farinae, FEV1 > 70% of predicted value with appropriate medication.

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	SQ HDM SLIT-tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP was one lyophilisate [tablet], preferably taken in the morning. The tablet was placed under the tongue, and swallowing was to be avoided for one minute. In addition, eating and drinking was not allowed within 5 minutes after intake of IMP.

Arm title	1 SQ-HDM
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Arm description:

Active IMP, strength 1 SQ-HDM

Arm type	Experimental
Investigational medicinal product name	SQ HDM SLIT-tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP was one lyophilisate [tablet], preferably taken in the morning. The tablet was placed under the tongue, and swallowing was to be avoided for one minute. In addition, eating and drinking was not allowed within 5 minutes after intake of IMP.

Arm title	3 SQ-HDM
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Arm description:

Active IMP, strength 3 SQ-HDM

Arm type	Experimental
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Investigational medicinal product name	SQ HDM SLIT-tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP was one lyophilisate [tablet], preferably taken in the morning. The tablet was placed under the tongue, and swallowing was to be avoided for one minute. In addition, eating and drinking was not allowed within 5 minutes after intake of IMP.

Arm title	6 SQ-HDM
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Arm description:

Active IMP, strength 6 SQ-HDM

Arm type	Experimental
Investigational medicinal product name	SQ HDM SLIT-tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral lyophilisate
Routes of administration	Sublingual use

Dosage and administration details:

The daily dose of IMP was one lyophilisate [tablet], preferably taken in the morning. The tablet was placed under the tongue, and swallowing was to be avoided for one minute. In addition, eating and drinking was not allowed within 5 minutes after intake of IMP.

Number of subjects in period 1	Placebo	1 SQ-HDM	3 SQ-HDM
Started	143	146	159
Completed	126	132	134
Not completed	17	14	25
Consent withdrawn by subject	3	3	6
Adverse event, non-fatal	1	2	8
Not specified	3	3	2
Pregnancy	2	1	2
Non-compliance	3	3	3
Lost to follow-up	5	2	4

Number of subjects in period 1	6 SQ-HDM
Started	156
Completed	140
Not completed	16
Consent withdrawn by subject	3
Adverse event, non-fatal	4
Not specified	1
Pregnancy	-
Non-compliance	5
Lost to follow-up	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	1 SQ-HDM
Reporting group description:	
Active IMP, strength 1 SQ-HDM	
Reporting group title	3 SQ-HDM
Reporting group description:	
Active IMP, strength 3 SQ-HDM	
Reporting group title	6 SQ-HDM
Reporting group description:	
Active IMP, strength 6 SQ-HDM	

Reporting group values	Placebo	1 SQ-HDM	3 SQ-HDM
Number of subjects	143	146	159
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)	0	0	0
Adolescents (12-17 years)	11	7	12
Adults (18-64 years)	131	139	145
From 65-84 years	1	0	2
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	31.4	31.7	31.6
standard deviation	± 12.1	± 12	± 12.4
Gender categorical			
Units: Subjects			
Female	67	71	75
Male	76	75	84

Reporting group values	6 SQ-HDM	Total	
Number of subjects	156	604	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	

Adolescents (12-17 years)	9	39	
Adults (18-64 years)	144	559	
From 65-84 years	3	6	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	31.6		
standard deviation	± 12.9	-	
Gender categorical			
Units: Subjects			
Female	73	286	
Male	83	318	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	-
Reporting group title	1 SQ-HDM
Reporting group description:	Active IMP, strength 1 SQ-HDM
Reporting group title	3 SQ-HDM
Reporting group description:	Active IMP, strength 3 SQ-HDM
Reporting group title	6 SQ-HDM
Reporting group description:	Active IMP, strength 6 SQ-HDM

Primary: reduction of ICS dose from baseline to end of trial after approximately 1 year of treatment

End point title	reduction of ICS dose from baseline to end of trial after approximately 1 year of treatment
End point description:	The primary efficacy analysis defined in the protocol was the comparison of each of the 3 active dose groups to placebo. The approach to this multiple comparisons issue was defined in the protocol as a hierarchical ordering of the null hypotheses, with the following ranking: 1. SQ HDM SLIT-tablet 6 DU versus placebo 2. SQ HDM SLIT-tablet 3 DU versus placebo 3. SQ HDM SLIT-tablet 1 DU versus placebo
End point type	Primary
End point timeframe:	approximately 1 year

End point values	Placebo	1 SQ-HDM	3 SQ-HDM	6 SQ-HDM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	143	146	159	156
Units: microgram(s)/24 hours				
arithmetic mean (standard deviation)	-122 ($\pm$ 279)	-155 ($\pm$ 259)	-116 ($\pm$ 235)	-204 ($\pm$ 274)

Statistical analyses

Statistical analysis title	Reduction in ICS, 6 SQ-HDM versus placebo
Statistical analysis description:	Comparison of the reduction in ICS from baseline with the reduction observed in the placebo group for 6 SQ-HDM, 3 SQ-HDM and 1 SQ-HDM; in that order
Comparison groups	Placebo v 6 SQ-HDM

Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-81.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136.1
upper limit	-26.7
Variability estimate	Standard error of the mean
Dispersion value	27.9

Notes:

[1] - Statistically significant difference between the 6 DU group and placebo

Statistical analysis title	Reduction in ICS, 3 SQ-HDM versus placebo
Comparison groups	Placebo v 3 SQ-HDM
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8544 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.8
upper limit	49.6
Variability estimate	Standard error of the mean
Dispersion value	27.8

Notes:

[2] - No statistically significant differences to placebo were observed for the 3 SQ-HDM group

Statistical analysis title	Reduction in ICS, 1 SQ-HDM versus placebo
Comparison groups	Placebo v 1 SQ-HDM
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1334 ^[3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-42.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-98.4
upper limit	13.1

Variability estimate	Standard error of the mean
Dispersion value	28.4

Notes:

[3] - No statistically significant difference to placebo were observed for the 1 SQ-HDM group

Secondary: IgE-blocking factor at end-of-trial visit versus placebo

End point title	IgE-blocking factor at end-of-trial visit versus placebo
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End point description:

IgE blocking factor specific for Dermatophagoides pteronyssinus.

Samples only collected and analysed from trial sites in Germany and Denmark (30% of the trial population)

End point type	Secondary
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End point timeframe:

Approximately 1 year (change from baseline to end of trial in active versus placebo)

End point values	Placebo	1 SQ-HDM	3 SQ-HDM	6 SQ-HDM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36 ^[4]	34 ^[5]	39 ^[6]	44 ^[7]
Units: arbitrary units				
arithmetic mean (standard error)	0 (± 0.08)	0.08 (± 0.12)	0.09 (± 0.16)	0.17 (± 0.17)

Notes:

[4] - Only analysed for sites in Germany and Denmark

[5] - Only analysed for sites in Germany and Denmark

[6] - Only analysed for sites in Germany and Denmark

[7] - Only analysed for sites in Germany and Denmark

Statistical analyses

Statistical analysis title	6 SQ-HDM versus placebo
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Statistical analysis description:

A mixed model including as fixed effect the visit 4 value, treatment group, visit and treatment group by visit interaction. For each pairwise comparison all available data from all four treatment groups were included. To allow correlation of observations on the same subject a random subject effect was included in the model. Possible different error variance for each treatment group was adjusted for. The error variance was fitted as separate compound symmetry for each treatment group

Comparison groups	6 SQ-HDM v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.116
upper limit	0.215
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[8] - Highly statistical significant difference between 6 SQ-HDM and placebo

Statistical analysis title	3 SQ-HDM versus placebo
Statistical analysis description:	
A mixed model including as fixed effect the visit 4 value, treatment group, visit and treatment group by visit interaction. For each pairwise comparison all available data from all four treatment groups were included. To allow correlation of observations on the same subject a random subject effect was included in the model. Possible different error variance for each treatment group was adjusted for. The error variance was fitted as separate compound symmetry for each treatment group	
Comparison groups	Placebo v 3 SQ-HDM
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[9]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	0.138
Variability estimate	Standard error of the mean
Dispersion value	0.021

Notes:

[9] - Highly statistical significant difference between 3 SQ-HDM and placebo

Statistical analysis title	1 SQ-HDM versus placebo
Statistical analysis description:	
A mixed model including as fixed effect the visit 4 value, treatment group, visit and treatment group by visit interaction. For each pairwise comparison all available data from all four treatment groups were included. To allow correlation of observations on the same subject a random subject effect was included in the model. Possible different error variance for each treatment group was adjusted for. The error variance was fitted as separate compound symmetry for each treatment group	
Comparison groups	Placebo v 1 SQ-HDM
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 ^[10]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.115
Variability estimate	Standard error of the mean
Dispersion value	0.02

Notes:

[10] - Highly statistical significant difference between 1 SQ-HDM and placebo

Secondary: Change from baseline in FEV1

End point title	Change from baseline in FEV1
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End point description:

FEV1 (lung function) was assessed to document the controlled status with respect to asthma of the subjects throughout the trial, in anticipation that all treatment groups would be comparable

End point type	Secondary
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End point timeframe:

approximately 1 year (from baseline to end of trial)

End point values	Placebo	1 SQ-HDM	3 SQ-HDM	6 SQ-HDM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133 ^[11]	138 ^[12]	143 ^[13]	147 ^[14]
Units: percentage of predicted FEV1				
arithmetic mean (standard deviation)	-1.3 (± 8.8)	-0.56 (± 10.2)	-2.09 (± 9.4)	-1.81 (± 8.2)

Notes:

[11] - Number of subjects with end-of-trial visit

[12] - Number of subjects with end-of-trial visit

[13] - Number of subjects with end-of-trial visit

[14] - Number of subjects with end-of-trial visit

Statistical analyses

Statistical analysis title	6 SQ-HDM vs placebo: change from baseline in %FEV1
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Statistical analysis description:

The estimates are based on a repeated measurements analysis with a linear mixed model. Treatment group, baseline value, visit and treatment group by visit interaction are included as fixed effects and centre is included as a random effect.

Comparison groups	Placebo v 6 SQ-HDM
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667 ^[15]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.362
upper limit	1.512
Variability estimate	Standard error of the mean
Dispersion value	0.988

Notes:

[15] - lung function parameters reflect the controlled status with respect to asthma of the subjects throughout the trial, and all treatment groups were completely comparable

Statistical analysis title	3 SQ-HDM vs placebo: change from baseline in %FEV1
Statistical analysis description:	
The estimates are based on a repeated measurements analysis with a linear mixed model. Treatment group, baseline value, visit and treatment group by visit interaction are included as fixed effects and centre is included as a random effect.	
Comparison groups	Placebo v 3 SQ-HDM
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3802 ^[16]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.873
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.823
upper limit	1.077
Variability estimate	Standard error of the mean
Dispersion value	0.995

Notes:

[16] - lung function parameters reflect the controlled status with respect to asthma of the subjects throughout the trial, and all treatment groups were completely comparable

Statistical analysis title	1 SQ-HDM vs placebo: change from baseline in %FEV1
Statistical analysis description:	
The estimates are based on a repeated measurements analysis with a linear mixed model. Treatment group, baseline value, visit and treatment group by visit interaction are included as fixed effects and centre is included as a random effect.	
Comparison groups	Placebo v 1 SQ-HDM
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7433 ^[17]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.329
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.639
upper limit	2.296
Variability estimate	Standard error of the mean
Dispersion value	1.003

Notes:

[17] - lung function parameters reflect the controlled status with respect to asthma of the subjects throughout the trial, and all treatment groups were completely comparable

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the entire trial - approximately 2 months prior to randomisation (screening/baseline phase) and 12 months after randomisation (treatment phase)

Adverse event reporting additional description:

All events meeting the definition of an AE were collected and reported from the first trial-related activity after the subject signed the informed consent and until the end of trial telephone follow-up.

Adverse events were defined according to ICH Harmonised Tripartite Guideline E2A, Step 5

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	1 SQ-HDM
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Reporting group description:

Active IMP, strength 1 SQ-HDM

Reporting group title	3 SQ-HDM
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Reporting group description:

Active IMP, strength 3 SQ-HDM

Reporting group title	6 SQ-HDM
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Reporting group description:

Active IMP, strength 6 SQ-HDM

Serious adverse events	Placebo	1 SQ-HDM	3 SQ-HDM
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 143 (2.80%)	6 / 146 (4.11%)	3 / 159 (1.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	0 / 159 (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
Injury, poisoning and procedural complications			
Spinal fracture			

subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Adenoidectomy			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Paraesthesia			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	0 / 159 (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
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bacterial infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Cellulitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 146 (0.68%)	0 / 159 (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
Chronic tonsillitis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 143 (0.00%)	0 / 146 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	0 / 159 (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
Urethritis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 146 (0.00%)	0 / 159 (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

Serious adverse events	6 SQ-HDM		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 156 (3.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			

subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Adenoidectomy			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			

subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Bone disorder			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic tonsillitis			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urethritis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	1 SQ-HDM	3 SQ-HDM
Total subjects affected by non-serious adverse events subjects affected / exposed	76 / 143 (53.15%)	80 / 146 (54.79%)	105 / 159 (66.04%)
Gastrointestinal disorders Oral pruritus subjects affected / exposed occurrences (all)	5 / 143 (3.50%) 5	16 / 146 (10.96%) 17	31 / 159 (19.50%) 46
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	8 / 143 (5.59%) 8	10 / 146 (6.85%) 11	14 / 159 (8.81%) 17
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	22 / 143 (15.38%) 26 11 / 143 (7.69%) 13 3 / 143 (2.10%) 3	21 / 146 (14.38%) 26 10 / 146 (6.85%) 13 10 / 146 (6.85%) 12	22 / 159 (13.84%) 32 9 / 159 (5.66%) 10 8 / 159 (5.03%) 9

Non-serious adverse events	6 SQ-HDM		
Total subjects affected by non-serious adverse events subjects affected / exposed	102 / 156 (65.38%)		
Gastrointestinal disorders Oral pruritus subjects affected / exposed occurrences (all)	27 / 156 (17.31%) 31		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	14 / 156 (8.97%) 21		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection	25 / 156 (16.03%) 32		

subjects affected / exposed	10 / 156 (6.41%)		
occurrences (all)	10		
Pharyngitis			
subjects affected / exposed	3 / 156 (1.92%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2006	Modification of in- and exclusion criteria
14 December 2006	Change on inclusion criterion regarding ACQ score
05 November 2007	change of trial period from '1-2 years' to '1 year'

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/24797423>