Clinical trial results:
A one-year placebo-controlled phase III trial evaluating the efficacy and safety of the house dust mite (HDM) SLIT-tablet in children (5-11 years of age) with HDM allergic rhinitis/rhinoconjunctivitis with or without asthma

Summary

EudraCT number	2019-000560-22
Trial protocol	FR SK DE PL ES BG LT
Global end of trial date	21 April 2023

Results information

Result version number	v1 (current)
This version publication date	04 November 2023
First version publication date	04 November 2023

Trial information

Trial identification

Sponsor protocol code	MT-12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04145219
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ALK-Abelló A/S
Sponsor organisation address	Bøge Allé 6-8, Hørsholm, Denmark, 2970
Public contact	Global pharmacovigilance and Clinical Development, ALK-Abelló A/S, 45 45747576, clinicaltrials@alk.net
Scientific contact	Global pharmacovigilance and 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001258-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2023
Global end of trial reached?	Yes
Global end of trial date	21 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the efficacy of the HDM sublingual immunotherapy (SLIT)-tablet compared to placebo in the treatment of HDM allergic rhinitis (AR) in children (5-11 years of age) based on total combined rhinitis symptoms and medication use (TCRS) during the primary efficacy assessment period.

Protection of trial subjects:

Safety surveillance.
Access to rescue/reliever medication.

Background therapy:

Rescue medication: Subjects were provided with medication to treat rhinitis/rhinoconjunctivitis symptoms (antihistamine/intranasal corticosteroid) and asthma symptoms (short-acting β2-agonist, SABA), and, in countries where required, adrenaline auto-injector to treat severe allergic reactions.

Asthma controller and reliever medication: Subjects with a diagnosis of asthma and using low or medium daily dose inhaled corticosteroids (ICS) (with or without long-acting β2-agonists, [LABA]) for asthma control, were allowed to continue with the same medication during the trial. In addition, the use of leukotriene receptor antagonists was permitted as concomitant medication for continued use on same dose only.

Evidence for comparator: -

Actual start date of recruitment	12 October 2019
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	Poland: 353
Country: Number of subjects enrolled	Slovakia: 66
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Bulgaria: 181
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Lithuania: 94
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Russian Federation: 329
Country: Number of subjects enrolled	Ukraine: 330
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	1458
EEA total number of subjects	721

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)	1458
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:

Subjects were recruited from 95 trial sites in 11 countries (Bulgaria, Canada, France, Germany, Lithuania, Poland, Russia, Slovakia, Spain, Ukraine and United States).
First subject first visit: 12-Oct-2019
Last subject last visit/contact: 21-Apr-2023

Pre-assignment

Screening details:

Main criteria:
- 5-11 years of age
- Clinical history of HDM allergic rhinitis/conjunctivitis (AR/C) (+/- asthma) and with AR symptoms despite having received symptom-relieving medication during 1 year prior to screening
- Positive SPT and IgE against D. pteronysimus and/or D. farinae
- FEV1 percent predicted ≥ 70%

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
Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

The subject was instructed to preferably take the tablet in the morning, placed under the tongue, and swallowing should be avoided for approximately 1 minute. Food and beverages should not be taken for 5 minutes after intake of IMP. When the first dose was administered, the subject was under medical supervision for a minimum of 30 minutes after the tablet intake.

Arm title	12 SQ-HDM

Arm description:

HDM SLIT-tablet (12 SQ-HDM)

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

Dosage and administration details:

The subject was instructed to preferably take the tablet in the morning, placed under the tongue, and swallowing should be avoided for approximately 1 minute. Food and beverages should not be taken for 5 minutes after intake of IMP. When the first dose was administered, the subject was under medical supervision for a minimum of 30 minutes after the tablet intake.

Number of subjects in period 1	Placebo	12 SQ-HDM
Started	731	727
Completed	707	691
Not completed	24	36
Consent withdrawn by subject	8	12
Reason stated as "other" in CRF	7	7
Adverse event, non-fatal	6	14
Severe or persistent symptoms of oesophagitis	-	1
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	12 SQ-HDM
Reporting group description:	
HDM SLIT-tablet (12 SQ-HDM)	

Reporting group values	Placebo	12 SQ-HDM	Total
Number of subjects	731	727	1458
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)	731	727	1458
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	254	241	495
Male	477	486	963

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set, defined as all randomised subjects who received at least 1 dose of IMP. Subjects were analysed as randomised, i.e., according to their randomised assignment of treatment.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set, defined as all randomised subjects who received at least 1 dose of IMP. Subjects were analysed as treated, i.e., according to the treatment they actually received.	

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	1458	1458	
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)	1458	1458	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	495	495	
Male	963	963	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	12 SQ-HDM
Reporting group description:	
HDM SLIT-tablet (12 SQ-HDM)	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set, defined as all randomised subjects who received at least 1 dose of IMP. Subjects were analysed as randomised, i.e., according to their randomised assignment of treatment.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set, defined as all randomised subjects who received at least 1 dose of IMP. Subjects were analysed as treated, i.e., according to the treatment they actually received.	

Primary: Average daily total combined rhinitis symptoms and medication use (TCRS) during the primary efficacy assessment period

End point title	Average daily total combined rhinitis symptoms and medication use (TCRS) during the primary efficacy assessment period
End point description:	
The primary endpoint of the trial was the average daily total combined rhinitis symptoms and medication use (TCRS) during the primary efficacy assessment period. The average daily TCRS evaluates the treatment effect based on the reduction in daily rhinitis symptoms and medication use (on a scale of 0-24). Higher scores indicate more severe symptoms and/or more medication use.	
End point type	Primary
End point timeframe:	
8 weeks (primary efficacy assessment period), which started 44-49 weeks after initiation of IMP	

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	706[1]	693[2]		
Units: Adjusted mean				
least squares mean (standard error)	4.4 (± 0.3)	3.4 (± 0.3)		

Notes:

[1] - Subjects from the full analysis set with observations in the primary efficacy assessment period

[2] - Subjects from the full analysis set with observations in the primary efficacy assessment period

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The average daily TCRS was analysed using a linear mixed effect (LME) model with square root transformation. The model includes the square root of the endpoint as response variable, treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM
Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effect (LME)
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Secondary: Average rhinitis daily symptom score (DSS) during the primary efficacy assessment period

End point title	Average rhinitis daily symptom score (DSS) during the primary efficacy assessment period

End point description:

Average rhinitis daily symptom score (DSS) evaluates the treatment effect based on the reduction in daily rhinitis symptoms (on a scale of 0-12). Higher scores indicate more severe symptoms.

End point type	Secondary

End point timeframe:

8 weeks (primary efficacy assessment period), which started 44-49 weeks after initiation of IMP

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	706[3]	693[4]		
Units: Adjusted mean				
least squares mean (standard error)	1.9 (± 0.1)	1.5 (± 0.1)		

Notes:

[3] - Subjects from the full analysis set with observations in the primary efficacy assessment period.

[4] - Subjects from the full analysis set with observations in the primary efficacy assessment period.

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint

Statistical analysis description:

The average rhinitis DSS was analysed using a linear mixed effect (LME) model with square root transformation. The model includes the square root of the endpoint as response variable, treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM

Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effect (LME)
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.6

Secondary: Average rhinitis daily medication score (DMS) during the primary efficacy assessment period

End point title	Average rhinitis daily medication score (DMS) during the primary efficacy assessment period

End point description:

Average rhinitis daily medication score (DMS) evaluates the treatment effect based on the reduction in daily rhinitis medication use (on a scale of 0-12). Higher scores indicate more medication use.

End point type	Secondary

End point timeframe:

8 weeks (primary efficacy assessment period), which started 44-49 weeks after initiation of IMP

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	706[5]	693[6]		
Units: Adjusted mean				
least squares mean (standard error)	1.9 (± 0.2)	1.4 (± 0.2)		

Notes:

[5] - Subjects from the full analysis set with observations in the primary efficacy assessment period.

[6] - Subjects from the full analysis set with observations in the primary efficacy assessment period.

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint

Statistical analysis description:

The average rhinitis DMS was analysed using a linear mixed effect (LME) model with square root transformation. The model includes the square root of the endpoint as response variable, treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM

Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Linear mixed effect (LME)
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.8

Secondary: Average daily total combined score (TCS) during the primary efficacy assessment period

End point title	Average daily total combined score (TCS) during the primary efficacy assessment period

End point description:

Average rhinoconjunctivitis total combined score (TCS) evaluates the treatment effect based on the reduction in daily rhinoconjunctivitis symptoms and medication use (on a scale of 0-38). Higher scores indicate more severe symptoms and/or more medication use.

End point type	Secondary

End point timeframe:

8 weeks (primary efficacy assessment period), which started 44-49 weeks after initiation of IMP

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	706[7]	693[8]		
Units: Adjusted mean				
least squares mean (standard error)	5.2 (± 0.4)	4.0 (± 0.4)		

Notes:

[7] - Subjects from the full analysis set with observations in the primary efficacy assessment period.

[8] - Subjects from the full analysis set with observations in the primary efficacy assessment period.

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint

Statistical analysis description:

The average rhinitis TCS was analysed using a linear mixed effect (LME) model with square root transformation. The model includes the square root of the endpoint as response variable, treatment and cohort as fixed factors, the square root of the baseline value as a covariate, country/region within cohort as a random effect, and with different residual errors specified for each treatment. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM

Number of subjects included in analysis	1399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear mixed effect (LME)
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from consent to last follow-up phone contact. Only treatment-emergent AEs are presented (AEs with start time on or after the time of first IMP administration and no later than 7 days after the last day of IMP administration).

Adverse event reporting additional description:

For the first 28 days of treatment, subjects used an eDiary daily to capture presence/absence of 15 pre-specified signs/symptoms, identified as local side effects of sublingual immunotherapy. These were assessed and reported as AEs in the eCRF at the discretion of the investigator and are included in TEAEs presented.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	12 SQ-HDM

Reporting group description:

HDM SLIT-tablet (12 SQ-HDM)

Serious adverse events	Placebo	12 SQ-HDM	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 731 (0.82%)	16 / 727 (2.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			

subjects affected / exposed	1 / 731 (0.14%)	0 / 727 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 731 (0.14%)	0 / 727 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Attention deficit hyperactivity disorder			

subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucinations, mixed			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis norovirus			
subjects affected / exposed	0 / 731 (0.00%)	2 / 727 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 731 (0.27%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			

subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 727 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 727 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 727 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	12 SQ-HDM	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	534 / 731 (73.05%)	608 / 727 (83.63%)	
Nervous system disorders			
Taste disorder			
subjects affected / exposed	116 / 731 (15.87%)	123 / 727 (16.92%)	
occurrences (all)	218	213	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	135 / 731 (18.47%)	242 / 727 (33.29%)	
occurrences (all)	299	547	
Gastrointestinal disorders			
Oral pruritus			
subjects affected / exposed	185 / 731 (25.31%)	419 / 727 (57.63%)	
occurrences (all)	425	1149	
Abdominal pain upper			

subjects affected / exposed	164 / 731 (22.44%)	243 / 727 (33.43%)	
occurrences (all)	320	512	
Lip swelling			
subjects affected / exposed	38 / 731 (5.20%)	151 / 727 (20.77%)	
occurrences (all)	63	282	
Glossodynia			
subjects affected / exposed	41 / 731 (5.61%)	142 / 727 (19.53%)	
occurrences (all)	54	313	
Nausea			
subjects affected / exposed	81 / 731 (11.08%)	135 / 727 (18.57%)	
occurrences (all)	125	260	
Mouth swelling			
subjects affected / exposed	27 / 731 (3.69%)	99 / 727 (13.62%)	
occurrences (all)	41	210	
Swollen tongue			
subjects affected / exposed	20 / 731 (2.74%)	99 / 727 (13.62%)	
occurrences (all)	29	203	
Diarrhoea			
subjects affected / exposed	74 / 731 (10.12%)	95 / 727 (13.07%)	
occurrences (all)	107	151	
Mouth ulceration			
subjects affected / exposed	53 / 731 (7.25%)	93 / 727 (12.79%)	
occurrences (all)	80	162	
Tongue ulceration			
subjects affected / exposed	27 / 731 (3.69%)	50 / 727 (6.88%)	
occurrences (all)	34	82	
Vomiting			
subjects affected / exposed	33 / 731 (4.51%)	48 / 727 (6.60%)	
occurrences (all)	38	76	
Tooth loss			
subjects affected / exposed	35 / 731 (4.79%)	40 / 727 (5.50%)	
occurrences (all)	61	66	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			

subjects affected / exposed	236 / 731 (32.28%)	401 / 727 (55.16%)	
occurrences (all)	504	1072	
Pharyngeal irritation			
subjects affected / exposed	22 / 731 (3.01%)	68 / 727 (9.35%)	
occurrences (all)	33	134	
Asthma			
subjects affected / exposed	38 / 731 (5.20%)	14 / 727 (1.93%)	
occurrences (all)	49	16	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	164 / 731 (22.44%)	185 / 727 (25.45%)	
occurrences (all)	206	250	
COVID-19			
subjects affected / exposed	38 / 731 (5.20%)	38 / 727 (5.23%)	
occurrences (all)	38	38	
Pharyngitis			
subjects affected / exposed	37 / 731 (5.06%)	38 / 727 (5.23%)	
occurrences (all)	49	44	
Bronchitis			
subjects affected / exposed	45 / 731 (6.16%)	36 / 727 (4.95%)	
occurrences (all)	52	42	
Upper respiratory tract infection			
subjects affected / exposed	37 / 731 (5.06%)	22 / 727 (3.03%)	
occurrences (all)	53	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2019	The amendment was prepared to update selected inclusion criteria and the main changes were: - For subjects for whom medical records of HDM AR/C diagnosis were not available, verbal history from subject/parent/caregiver could be used - Subjects that were 7 years old or younger and did not have asthma were not required to meet the inclusion criterion of FEV1 ≥ 70%, if despite coaching they were not able to perform a reproducible FEV1 manoeuvre
19 March 2021	The trial started before the COVID-19 pandemic and ended during the pandemic. At the outbreak of the COVID-19 pandemic, measures to protect the safety and integrity of trial subjects were implemented in March and April 2020 (see also Section on Trial Interruptions). An amendment was later prepared, in which the main changes included updates to trial procedures to mitigate the risks associated with the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Due to the COVID-19 pandemic, screening and randomisation of cohort 1 was stopped on 20-Mar-2020 prior to the planned deadline of 01-Apr-2020. Subjects screened in Cohort 1 (but not randomised) were screen failed and offered a re-screening in Cohort 2. Screening of subjects for Cohort 2 was initiated as planned on 07-July-2020. A cohort 3 was subsequently added to recruit a sufficient number of subjects. Generally, the following mitigations were implemented due to COVID-19: - Option to convert on-site visits to remote visits via telephone or video was introduced - Introduction of direct-to-patient shipment of IMP and rescue medication, if on-site pick-up was not possible - Option to perform remote monitoring visits over telephone was introduced	07 July 2020

Notes:

Limitations and caveats

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

None.

Notes: