Clinical trial results:
A phase III trial evaluating the efficacy and safety of the house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet in children and adolescents (5-17 years) with HDM allergic asthma

Summary

EudraCT number	2016-004363-39
Trial protocol	DE ES HU BG DK FR PL GB
Global end of trial date	10 August 2022

Results information

Result version number	v1 (current)
This version publication date	12 March 2023
First version publication date	12 March 2023

Trial information

Trial identification

Sponsor protocol code	MT-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03654976
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, 0045 45747576, clinicaltrials@alk.net
Scientific contact	Global pharmacovigilance and Clinical Development, ALK-Abelló A/S, 0045 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	11 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2022
Global end of trial reached?	Yes
Global end of trial date	10 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate efficacy of the HDM SLIT-tablet versus placebo as add-on treatment in children and adolescents (5-17 years) with HDM allergic asthma based on clinically relevant asthma exacerbations after at least 4 months of treatment.

A clinically relevant asthma exacerbation was defined as at least 1 of the following criteria: a) Doubling of ICS dose compared to background treatment, b) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, c) Emergency room visit due to asthma, requiring systemic corticosteroids or d) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

Protection of trial subjects:

Safety surveillance.
Access to rescue medication.

Background therapy:

Background treatment: The asthma background treatment consisted of low dose inhaled corticosteroid (ICS) plus long-acting β2-agonist (LABA) or medium/high dose ICS with/without LABA. In addition, the subject could continue treatment with leukotriene receptor antagonists if this was part of the subject's background treatment when entering the trial. The subject had to stay on the same background treatment and dose throughout the trial as they were on when they entered the trial.
Rescue medication: Subjects were provided with rescue medication to treat asthma symptoms (SABA), asthma exacerbations (ICS and/or prednisolone/prednisone), rhinoconjunctivitis symptoms (antihistamine/intranasal corticosteroid) and, in countries where required, to treat severe allergic reactions (adrenaline auto-injector).

Evidence for comparator: -

Actual start date of recruitment	22 February 2018
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	Russian Federation: 38
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Poland: 291
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 65
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 11

Country: Number of subjects enrolled	Hungary: 37
Worldwide total number of subjects	533
EEA total number of subjects	465

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)	316
Adolescents (12-17 years)	217
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 64 trial sites in Bulgaria, France, Germany, Hungary, Poland, Spain, Russia, United Kingdom and USA.
First subject first visit: 22-February-2018
Last subject last visit: 31-May-2022

Pre-assignment

Screening details:

Main selection criteria:
- 5-17 years at randomisation
- Clinical history of HDM allergic asthma of at least 1 year
- At least 3 clin. relevant asthma exacerbations in past 2 years, 2 clin. relevant asthma exacerbations in past year or 1 severe asthma exacerbation in past year
- Positive SPT and IgE against D. pteronyssinus and/or D. farinae

Period 1

Period 1 title	Overall trial (IMP start and completion) (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 and that food and beverages should not be taken for the following 5 minutes. When the first dose was administered, the subject was under medical supervision for the subsequent ≥ 30 minutes.

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 and that food and beverages should not be taken for the following 5 minutes. When the first dose was administered, the subject was under medical supervision for the subsequent ≥ 30 minutes.

Number of subjects in period 1	Placebo	12 SQ-HDM
Started	263	270
Completed	242	239
Not completed	21	31
Physician decision	1	1
Consent withdrawn by subject	11	11
Reason stated as "other" in CRF	6	10
Adverse event, non-fatal	1	6
3 severe asthma exacerb. within 12 consec. mths.	1	1
Lost to follow-up	-	2
Lack of efficacy	1	-

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	263	270	533
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)	154	162	316
Adolescents (12-17 years)	109	108	217
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	94	88	182
Male	169	182	351

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 included as randomised, i.e., according to their randomised assignment of treatment.
9 randomised subjects were excluded from the full analysis set

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 included as treated, i.e., according to the treatment they actually received.

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	524	533	
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)	315	316	
Adolescents (12-17 years)	209	217	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	178	182	
Male	346	351	

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 included as randomised, i.e., according to their randomised assignment of treatment. 9 randomised subjects were excluded from the full analysis set	
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 included as treated, i.e., according to the treatment they actually received.	

Primary: Annualised rate of clinically relevant asthma exacerbations

End point title	Annualised rate of clinically relevant asthma exacerbations
End point description:	
The primary endpoint of the trial was the annualised rate of clinically relevant asthma exacerbations calculated as the number of exacerbations per year per subject during the efficacy evaluation period (starting 4-10 months after treatment initiation and lasting up to 24-30 months of treatment). A clinically relevant asthma exacerbation had to be medically confirmed and was defined as asthma worsening leading to at least 1 of the following criteria: • Doubling of ICS dose compared to background treatment • Systemic corticosteroids for treatment of asthma symptoms for at least 3 days • Emergency room visit due to asthma, requiring systemic corticosteroids • Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids	
End point type	Primary
End point timeframe:	
The efficacy assessment period for the primary endpoint started 01-sep (4-10 months after treatment initiation) and lasted until the end of trial or discontinuation of treatment.	

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257[1]	252[2]		
Units: Per year per subject				
number (not applicable)	0.21	0.18		

Notes:

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

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

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The number of clinically relevant asthma exacerbations was analysed using a negative binomial regression model with a log-link function and the logarithm of the time in years in the efficacy period as offset. The model included treatment, age group (<12 years, >=12 years) and region (west: DEU, ESP, FRA, GBR and USA; central: POL; east: BGR, HUN and RUS) as fixed factors. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM
Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5412
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.31

Secondary: Proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication

End point title	Proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication

End point description:

The days with nocturnal awakenings due to asthma requiring SABA rescue medication were entered in an eDiary by the subject/caregiver in a 2-week period every 4 months, for up to 24-30 months.
The proportion of days with nocturnal awakenings due to asthma requiring SABA was presented on a range from 0 to 1 (1 indicating that all days in the eDiary period were with nocturnal awakenings due to asthma requiring SABA rescue medication)

End point type	Secondary

End point timeframe:

The efficacy assessment period for the endpoint started 4 months after treatment initiation and lasted until the end of trial or discontinuation of treatment.

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259[3]	253[4]		
Units: Proportion of days				
number (not applicable)	0.0190	0.0147		

Notes:

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

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

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint

Statistical analysis description:

A marginal logistic regression model with a generalised estimating approach was analysed using treatment, visit, treatment*visit, age group (<12 years, >=12 years) and region (west: DEU, ESP, FRA, GBR and USA; central: POL; east: BGR, HUN and RUS) as fixed factors. Baseline visit was included as a covariate. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4156
Method	Marginal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.7713
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.44

Secondary: Proportions of days with SABA use

End point title	Proportions of days with SABA use

End point description:

The days with SABA use were entered in an eDiary by the subject/caregiver in a 2-week period every 4 months, for up to 24-30 months.
The proportion of days with SABA use was presented on a range from 0 to 1 (1 indicating that all days in the eDiary period were with SABA use)

End point type	Secondary

End point timeframe:

The efficacy assessment period for the endpoint started 4 months after treatment initiation and lasted until the end of trial or discontinuation of treatment.

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259[5]	253[6]		
Units: Proportion of days				
number (not applicable)	0.1094	0.0943		

Notes:

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

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

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint

Statistical analysis description:

A marginal logistic regression model with a generalised estimating approach was analysed using treatment, visit, treatment*visit, age group (<12 years, >=12 years) and region (west: DEU, ESP, FRA, GBR and USA; central: POL; east: BGR, HUN and RUS) as fixed factors. Baseline visit is included as a

covariate. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4146
Method	Marginal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.8477
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.26

Secondary: Percentage predicted FEV1

End point title	Percentage predicted FEV1

End point description:

Percentage predicted FEV1 was collected for efficacy assessment at on-site visits every 4 months, for up to 24-30 months.

End point type	Secondary

End point timeframe:

The efficacy assessment period for the endpoint started 4 months after treatment initiation and lasted until the end of trial or discontinuation of treatment.

End point values	Placebo	12 SQ-HDM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259[7]	254[8]		
Units: Percentage predicted				
number (not applicable)	97.05	97.17		

Notes:

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

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

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint

Statistical analysis description:

A 'mixed-effect model repeated measurement' model was analysed using treatment, visit, treatment*visit, age group (<12 years, >=12 years) and region (west: DEU, ESP, FRA, GBR and USA; central: POL; east: BGR, HUN and RUS) as fixed factors. Baseline visit was included as a covariate. No missing data approach was applied.

Comparison groups	Placebo v 12 SQ-HDM

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8829
Method	mixed-effect model repeated measurement
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
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, an eDiary was used daily to capture presence/absence of 15 specific symptoms, identified as local side effects of sublingual immunotherapy (solicited events). These events were reported in the eCRF at the discretion of the investigator and are included in TEAEs presented.
>5% non-serious events are in 12 SQ-HDM.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	12 SQ-HDM

Reporting group description: -

Serious adverse events	Placebo	12 SQ-HDM	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 263 (4.56%)	14 / 270 (5.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Skin wound			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			

subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Eosinophilic oesophagitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic disorder			
subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular cyst			
subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 263 (1.52%)	4 / 270 (1.48%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis allergic			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Growth retardation			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scoliosis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	2 / 263 (0.76%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Salmonellosis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 263 (0.00%)	1 / 270 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 263 (0.38%)	0 / 270 (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	228 / 263 (86.69%)	248 / 270 (91.85%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	44 / 263 (16.73%)	54 / 270 (20.00%)	
occurrences (all)	68	120	
Headache			
subjects affected / exposed	11 / 263 (4.18%)	16 / 270 (5.93%)	
occurrences (all)	13	17	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	60 / 263 (22.81%)	104 / 270 (38.52%)	
occurrences (all)	124	257	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	12 / 263 (4.56%)	14 / 270 (5.19%)	
occurrences (all)	13	19	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	101 / 263 (38.40%)	118 / 270 (43.70%)	
occurrences (all)	194	231	
Aphthous ulcer			
subjects affected / exposed	17 / 263 (6.46%)	16 / 270 (5.93%)	
occurrences (all)	28	28	
Diarrhoea			
subjects affected / exposed	51 / 263 (19.39%)	60 / 270 (22.22%)	
occurrences (all)	77	96	
Glossodynia			
subjects affected / exposed	18 / 263 (6.84%)	74 / 270 (27.41%)	
occurrences (all)	23	134	
Lip swelling			
subjects affected / exposed	14 / 263 (5.32%)	71 / 270 (26.30%)	
occurrences (all)	18	154	
Mouth swelling			
subjects affected / exposed	11 / 263 (4.18%)	67 / 270 (24.81%)	
occurrences (all)	16	159	
Mouth ulceration			
subjects affected / exposed	16 / 263 (6.08%)	26 / 270 (9.63%)	
occurrences (all)	17	44	
Nausea			
subjects affected / exposed	57 / 263 (21.67%)	85 / 270 (31.48%)	
occurrences (all)	96	167	
Oral pruritus			
subjects affected / exposed	65 / 263 (24.71%)	175 / 270 (64.81%)	
occurrences (all)	126	475	
Swollen tongue			
subjects affected / exposed	8 / 263 (3.04%)	55 / 270 (20.37%)	
occurrences (all)	8	98	
Tongue ulceration			
subjects affected / exposed	9 / 263 (3.42%)	19 / 270 (7.04%)	
occurrences (all)	15	34	
Vomiting			
subjects affected / exposed	14 / 263 (5.32%)	33 / 270 (12.22%)	
occurrences (all)	19	49	

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	96 / 263 (36.50%)	80 / 270 (29.63%)	
occurrences (all)	176	158	
Cough			
subjects affected / exposed	20 / 263 (7.60%)	15 / 270 (5.56%)	
occurrences (all)	24	19	
Pharyngeal oedema			
subjects affected / exposed	14 / 263 (5.32%)	58 / 270 (21.48%)	
occurrences (all)	23	113	
Rhinitis allergic			
subjects affected / exposed	23 / 263 (8.75%)	16 / 270 (5.93%)	
occurrences (all)	47	27	
Throat irritation			
subjects affected / exposed	94 / 263 (35.74%)	166 / 270 (61.48%)	
occurrences (all)	178	494	
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	14 / 263 (5.32%)	18 / 270 (6.67%)	
occurrences (all)	14	18	
Nasopharyngitis			
subjects affected / exposed	57 / 263 (21.67%)	63 / 270 (23.33%)	
occurrences (all)	95	110	
Pharyngitis			
subjects affected / exposed	15 / 263 (5.70%)	21 / 270 (7.78%)	
occurrences (all)	21	28	
Upper respiratory tract infection			
subjects affected / exposed	25 / 263 (9.51%)	26 / 270 (9.63%)	
occurrences (all)	31	38	
Viral infection			
subjects affected / exposed	18 / 263 (6.84%)	18 / 270 (6.67%)	
occurrences (all)	22	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2020	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. The COVID-19 pandemic measures were implemented in a protocol amendment dated 11-Nov-2020 and included the main pandemic-related changes: - Screening and randomisation was paused as of 20-March-2020. At this point the last planned cohort was in the screening and randomisation phase - Site-to-patient shipment of IMP and rescue medication was introduced to enable subjects to receive IMP without going to site - Option to convert on-site visits to remote visits via telephone or video was introduced - Option to perform remote monitoring visits over telephone was introduced

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Due to the out-break of the COVID-19 pandemic all screening and randomisation activities were stopped as of 20-March-2020. All subjects in the screening phase were screen failed. During the COVID-19 pandemic the asthma exacerbation rate decreased both in the trial population (blinded data) and in the general asthma population. This was likely due to the widespread adoption of virus containment measures, reducing the circulation of seasonal respiratory viruses, which are known triggers for asthma exacerbations. It was therefore deemed difficult to recruit further subjects based on a history of recent asthma exacerbations and recruitment of subjects was not restarted before the sponsor decided to end the trial with the completed subjects on 10-Aug-2022 due to the severe impact of COVID-19.	-

Notes:

Limitations and caveats

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

The trial was severely impacted by the COVID-19 pandemic, with a rate of clinically relevant asthma exacerbations declining from the period before to the period during the COVID-19 pandemic. Therefore the sponsor decided to end the trial 10-Aug-2022

Notes: