



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) | EMA-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 β 2-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 β 2-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 $\geq 70\%$

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: <ul style="list-style-type: none">- 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 \geq 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 | <p>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.</p> <p>Generally, the following mitigations were implemented due to COVID-19:</p> <ul style="list-style-type: none">- 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: