



Clinical trial results:

A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-3641, a Ragweed (*Ambrosia artemisiifolia*) Sublingual Immunotherapy Tablet, in Children With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2014-004341-27 |
| Trial protocol | HU HR Outside EU/EEA |
| Global end of trial date | 19 November 2018 |

Results information

| | |
|--------------------------------|-------------|
| Result version number | v1 |
| This version publication date | 31 May 2019 |
| First version publication date | 31 May 2019 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 3641-008 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02478398 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07330 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001881-PIP01-15 |
| 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 | 19 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 November 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of MK-3641 (short ragweed [Ambrosia artemisiifolia] extract, MK-3641, SCH 039641, RAGWITEK™) sublingual immunotherapy tablets in children aged 5 to 17 years with ragweed-induced allergic rhinitis/rhinoconjunctivitis with or without asthma. The primary hypothesis of this study is that administration of MK-3641 sublingual immunotherapy tablets to children 5 to 17 years of age, compared with placebo, will result in a significant reduction in the combination of rhinoconjunctivitis symptoms and medication use over the peak ragweed season (RS).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Only those participants with ragweed pollen-induced rhinoconjunctivitis with or without controlled asthma were eligible for participation in this study. Participants with asthma may have used as-needed short-acting beta2-agonists (SABAs) and/or low or medium daily doses of inhaled corticosteroids (ICS).

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 20 July 2015 |
| 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 | Canada: 246 |
| Country: Number of subjects enrolled | Croatia: 79 |
| Country: Number of subjects enrolled | Hungary: 145 |
| Country: Number of subjects enrolled | Serbia: 161 |
| Country: Number of subjects enrolled | Ukraine: 185 |
| Country: Number of subjects enrolled | United States: 209 |
| Worldwide total number of subjects | 1025 |
| EEA total number of subjects | 224 |

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) | 410 |
| Adolescents (12-17 years) | 606 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who were 17 years old at screening and who turned 18 years old prior to randomization were permitted to continue in the study.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Randomization |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Short ragweed pollen allergen extract |

Arm description:

Participants randomized to short ragweed pollen allergen extract sublingual tablet, to be administered once daily (QD) for up to 35 weeks.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Short ragweed pollen allergen extract |
| Investigational medicinal product code | |
| Other name | SCH 03 9641 (MK-3641) |
| Pharmaceutical forms | Tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

One short ragweed pollen allergen extract sublingual tablet, administered once daily (QD) for up to 35 weeks.

| | |
|--|----------------|
| Investigational medicinal product name | Loratadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Syrup, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants

| | |
|--|----------------|
| Investigational medicinal product name | Olopatadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ophthalmic use |

Dosage and administration details:

Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily

| | |
|--|----------------|
| Investigational medicinal product name | Mometasone |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Nasal spray |

| | |
|--|------------------------|
| Routes of administration | Intranasal use |
| Dosage and administration details: | |
| Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants | |
| Investigational medicinal product name | Epinephrine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement. | |
| Investigational medicinal product name | Albuterol/Salbutamol |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as asthma rescue medication for those participants with asthma | |
| Arm title | Placebo |
| Arm description: | |
| Participants randomized to placebo sublingual tablet, to be administered QD for up to 35 weeks. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Sublingual use |
| Dosage and administration details: | |
| One placebo sublingual tablet, administered QD for up to 35 weeks | |
| Investigational medicinal product name | Loratadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Syrup, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants | |
| Investigational medicinal product name | Olopatadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ophthalmic use |
| Dosage and administration details: | |
| Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily | |

| | |
|--|----------------|
| Investigational medicinal product name | Mometasone |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Nasal spray |
| Routes of administration | Intranasal use |

Dosage and administration details:

Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants

| | |
|--|-------------------|
| Investigational medicinal product name | Epinephrine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement.

| | |
|--|------------------------|
| Investigational medicinal product name | Albuterol/Salbutamol |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as asthma rescue medication for those participants with asthma

| Number of subjects in period 1 | Short ragweed pollen allergen extract | Placebo |
|--------------------------------|---------------------------------------|---------|
| Started | 513 | 512 |
| Completed | 512 | 510 |
| Not completed | 1 | 2 |
| Withdrawal By Parent/Guardian | - | 2 |
| Protocol deviation | 1 | - |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treatment |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

A double-blind/masking technique was used. Short ragweed pollen allergen extract and placebo were packaged identically so blind/masking was maintained. The participant/parent/guardian and the investigator were unaware of the group assignments.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------------------------------------|
| Arm title | Short ragweed pollen allergen extract |
|------------------|---------------------------------------|

Arm description:

One short ragweed pollen allergen extract sublingual tablet, once daily (QD) for up to 35 weeks.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Short ragweed pollen allergen extract |
| Investigational medicinal product code | |
| Other name | SCH 03 9641 (MK-3641) |
| Pharmaceutical forms | Tablet |
| Routes of administration | Sublingual use |

Dosage and administration details:

One short ragweed pollen allergen extract sublingual tablet, administered once daily (QD) for up to 35 weeks.

| | |
|--|----------------|
| Investigational medicinal product name | Loratadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Syrup, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as needed for rhinoconjunctivitis symptoms as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants

| | |
|--|----------------|
| Investigational medicinal product name | Olopatadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ophthalmic use |

Dosage and administration details:

Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily

| | |
|--|----------------|
| Investigational medicinal product name | Mometasone |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Nasal spray |
| Routes of administration | Intranasal use |

Dosage and administration details:

Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants

| | |
|--|-------------------|
| Investigational medicinal product name | Epinephrine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement.

| | |
|--|----------------------|
| Investigational medicinal product name | Albuterol/Salbutamol |
| Investigational medicinal product code | |
| Other name | Rescue therapy |

| | |
|--|------------------------|
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as asthma rescue medication for those participants with asthma | |
| Arm title | Placebo |
| Arm description: | |
| Participants received one placebo sublingual tablet, QD for up to 35 weeks. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Sublingual use |
| Dosage and administration details: | |
| One placebo sublingual tablet, administered QD for up to 28 weeks | |
| Investigational medicinal product name | Loratadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Syrup, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants | |
| Investigational medicinal product name | Olopatadine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ophthalmic use |
| Dosage and administration details: | |
| Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily | |
| Investigational medicinal product name | Mometasone |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Nasal spray |
| Routes of administration | Intranasal use |
| Dosage and administration details: | |
| Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants | |
| Investigational medicinal product name | Epinephrine |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement. | |

| | |
|--|------------------------|
| Investigational medicinal product name | Albuterol/Salbutamol |
| Investigational medicinal product code | |
| Other name | Rescue therapy |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as asthma rescue medication for those participants with asthma

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 was defined as the Baseline period for the study

| Number of subjects in period 2^[2] | Short ragweed pollen allergen extract | Placebo |
|---|---------------------------------------|---------|
| Started | 512 | 510 |
| Completed | 461 | 491 |
| Not completed | 51 | 19 |
| Withdrawal By Participant | 10 | 4 |
| Adverse event, non-fatal | 20 | 5 |
| Withdrawal By Parent/Guardian | 9 | 4 |
| Non-Compliance With Study Drug | 5 | 1 |
| Lost to follow-up | 5 | 4 |
| Protocol deviation | 2 | 1 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of participants globally enrolled was greater than the number of participants who received treatment and entered the baseline period. Period 2 was the Baseline period.

Baseline characteristics

Reporting groups

| | |
|--|---------------------------------------|
| Reporting group title | Short ragweed pollen allergen extract |
| Reporting group description: One short ragweed pollen allergen extract sublingual tablet, once daily (QD) for up to 35 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received one placebo sublingual tablet, QD for up to 35 weeks. | |

| Reporting group values | Short ragweed pollen allergen extract | Placebo | Total |
|---|---------------------------------------|---------|-------|
| Number of subjects | 512 | 510 | 1022 |
| Age Categorical Units: Subjects | | | |
| < 12 years | 206 | 204 | 410 |
| ≥ 12 years | 306 | 306 | 612 |
| Age Continuous Units: years | | | |
| arithmetic mean | 12.1 | 12.2 | |
| standard deviation | ± 3.2 | ± 3.1 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 188 | 191 | 379 |
| Male | 324 | 319 | 643 |
| Race Units: Subjects | | | |
| White | 473 | 477 | 950 |
| Black or African American | 18 | 14 | 32 |
| Asian | 4 | 6 | 10 |
| Native Hawaiian or Other Pacific Islander | 3 | 2 | 5 |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Multiple | 13 | 11 | 24 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 15 | 21 | 36 |
| Not Hispanic or Latino | 490 | 483 | 973 |
| Not Reported | 4 | 5 | 9 |
| Unknown | 3 | 1 | 4 |

End points

End points reporting groups

| | |
|---|---------------------------------------|
| Reporting group title | Short ragweed pollen allergen extract |
| Reporting group description: Participants randomized to short ragweed pollen allergen extract sublingual tablet, to be administered once daily (QD) for up to 35 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Participants randomized to placebo sublingual tablet, to be administered QD for up to 35 weeks. | |
| Reporting group title | Short ragweed pollen allergen extract |
| Reporting group description: One short ragweed pollen allergen extract sublingual tablet, once daily (QD) for up to 35 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received one placebo sublingual tablet, QD for up to 35 weeks. | |
| Subject analysis set title | Short ragweed pollen allergen extract |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants randomized to short ragweed pollen allergen extract sublingual tablet, to be administered once daily (QD) for up to 35 weeks. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants randomized to placebo sublingual tablet, to be administered once daily (QD) for up to 35 weeks. | |

Primary: Total Combined Score (TCS) During the Peak Ragweed Season (RS)

| | |
|---|--|
| End point title | Total Combined Score (TCS) During the Peak Ragweed Season (RS) |
| End point description: TCS is daily symptom score (DSS) plus daily medication score (DMS), assessed in the peak RS (15 consecutive RS days with the highest 15-day average pollen count). The rhinoconjunctivitis (RC) DSS assesses 6 allergy symptoms measured on a scale of 0 to 3 (0=no symptoms, 3=severe symptoms; score range: 0-18). Lower DSS indicates less RC symptoms. The RC DMS is based on use of RC rescue medications (loratadine, olopatadine, mometasone), with different rescue medications being assigned different scores/dose unit (score range: 0-20). Lower DMS indicates less RC medication use. Summed RC DSS+DMS could range from 0 to 38; a lower score indicates less RC symptoms and medication use. Components that contribute to DSS and DMS endpoints are collected in an electronic diary (e-diary) completed by the participant/parent/guardian. Evaluation is based on average TCS during peak RS. The analysis population includes all treated participants with completed e-diary entries. | |
| End point type | Primary |
| End point timeframe: 15 days | |

| | | | | |
|--|---------------------------------------|---------------------|--|--|
| End point values | Short ragweed pollen allergen extract | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 460 | 487 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | 4.39 (3.85 to 4.94) | 7.12 (6.57 to 7.67) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparison of MK-3641 vs Placebo |
| Comparison groups | Short ragweed pollen allergen extract v Placebo |
| Number of subjects included in analysis | 947 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.45 |
| upper limit | -2 |

Secondary: Average TCS During the Entire RS

| | |
|--|----------------------------------|
| End point title | Average TCS During the Entire RS |
| End point description: | |
| <p>TCS is DSS plus DMS, assessed here during the entire RS. This starts from the first day of 3 consecutive days with ragweed pollen counts ≥ 10 grains/m³ through the last day of the last occurrence of 3 consecutive days with ragweed pollen counts ≥ 10 grains/m³. The duration of the entire RS is up to 13 weeks; this duration varies between regions. The RC DSS assesses 6 allergy symptoms measured on a scale of 0 to 3 (score range: 0-18). A lower DSS indicates less RC symptoms. The RC DMS is based on use of RC rescue medications (loratadine, olopatadine, mometasone) with different scores/dose unit (score range: 0-20). A lower DMS indicates less RC medication use. The sum of RC DSS+DMS ranges from 0 to 38, with a lower score indicating less RC symptoms and medication use. Components contributing to the TCS for the entire RS are collected in an e-diary completed by the participant/parent/guardian. The analysis population includes all treated participants with completed e-diary entries.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 13 weeks | |

| | | | | |
|--|---------------------------------------|---------------------|--|--|
| End point values | Short ragweed pollen allergen extract | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 466 | 491 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | 3.88 (3.44 to 4.33) | 5.75 (5.30 to 6.20) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparison of MK-3641 vs Placebo |
| Comparison groups | Short ragweed pollen allergen extract v Placebo |
| Number of subjects included in analysis | 957 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | Difference in LS Mean |
| Point estimate | -1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.46 |
| upper limit | -1.27 |

Secondary: Average Rhinoconjunctivitis (RC) DSS During the Peak RS

| | |
|------------------------|--|
| End point title | Average Rhinoconjunctivitis (RC) DSS During the Peak RS |
| End point description: | <p>This DSS endpoint consists of a total of 6 rhinoconjunctivitis symptoms: 4 rhinitis symptoms (runny nose, stuffy nose, sneezing, itchy nose) and 2 conjunctivitis symptoms (itchy eyes, watery eyes). The components that contribute to the DSS endpoint are collected in an e-diary completed by the participant/parent/guardian. The RC DSS is measured on a 4-point scale from 0 to 3 as follows: 0 (no sign/symptom evident) to 3 (sign/symptom that is hard to tolerate; may cause interference with activities of daily living and/or sleeping). The maximum DSS is 18 points if a participant experiences all 6 symptoms with an intensity of 3 for each symptom. A lower DSS means symptoms are less severe. The evaluation is based on the average DSS during the peak RS. The analysis population includes all treated participants with completed e-diary entries.</p> |
| End point type | Secondary |
| End point timeframe: | 15 days |

| | | | | |
|--|---------------------------------------|---------------------|--|--|
| End point values | Short ragweed pollen allergen extract | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 468 | 494 | | |
| Units: Score on a scale | | | | |
| least squares mean (confidence interval 95%) | 2.55 (2.24 to 2.86) | 3.95 (3.63 to 4.26) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparison of MK-3641 vs Placebo |
| Comparison groups | Short ragweed pollen allergen extract v Placebo |
| Number of subjects included in analysis | 962 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.81 |
| upper limit | -0.99 |

Secondary: Average Rhinoconjunctivitis (RC) DMS During the Peak RS

| | |
|--|---|
| End point title | Average Rhinoconjunctivitis (RC) DMS During the Peak RS |
| End point description: | |
| This DMS endpoint consists of a total of scores for use of RC medications: loratadine syrup or tablets (6 points), olopatadine (6 points), and mometasone (8 points). The maximum possible RC DMS is 20 points, and a lower DMS means that less medication is used. The method used for analysis of the RC DMS is a zero-inflated log-normal model, which takes the average RC DMS during the peak RS as the response and adjusts for the same terms as in the ANOVA model. The components that contribute to the DMS endpoint are collected in an e-diary completed by the participant/parent/guardian. The analysis population includes all treated participants with completed e-diary entries. | |
| End point type | Secondary |
| End point timeframe: | |
| 15 days | |

| | | | | |
|--------------------------------------|---------------------------------------|-----------------|--|--|
| End point values | Short ragweed pollen allergen extract | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 460 | 487 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (confidence interval | 2.01 (1.57 to | 3.85 (3.14 to | | |

| | | |
|------|-------|-------|
| 95%) | 2.46) | 4.57) |
|------|-------|-------|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparison of MK-3641 vs Placebo |
| Comparison groups | Short ragweed pollen allergen extract v Placebo |
| Number of subjects included in analysis | 947 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Zero-Inflated Log-Normal Model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | -1.08 |

Secondary: Percentage of Participants Reporting Pre-specified Local Application Site Reactions

| | |
|---|---|
| End point title | Percentage of Participants Reporting Pre-specified Local Application Site Reactions |
| End point description: | |
| Pre-specified local application site reactions, irrespective of causality, included AEs related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus. The safety population was all treated participants. Participants are grouped by the study treatment actually received. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 35 weeks | |

| End point values | Short ragweed pollen allergen extract | Placebo | | |
|-----------------------------------|---------------------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 513 | 509 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 64.52 | 26.92 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference in % |
| Comparison groups | Placebo v Short ragweed pollen allergen extract |
| Number of subjects included in analysis | 1022 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Difference in % estimates |
| Point estimate | 37.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 31.82 |
| upper limit | 43.12 |

Secondary: Percentage of Participants Reporting Anaphylaxis and/or Systemic Allergic Reactions

| | |
|--|---|
| End point title | Percentage of Participants Reporting Anaphylaxis and/or Systemic Allergic Reactions |
| End point description: For the purposes of this study, systemic allergic reactions are allergic reactions that occur away from the site of study drug application (allergic reactions other than local application site reactions). Anaphylaxis is a severe allergic reaction that typically involves more than one body system. The safety population was all treated participants. Participants are grouped by the study treatment actually received. | |
| End point type | Secondary |
| End point timeframe: Up to 35 weeks | |

| | | | | |
|-----------------------------------|---------------------------------------|----------------------|--|--|
| End point values | Short ragweed pollen allergen extract | Placebo | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 513 ^[1] | 509 ^[2] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 0.58 | 0.20 | | |

Notes:

[1] - No participants reported anaphylaxis. All reported events were systemic allergic reactions.

[2] - No participants reported anaphylaxis. All reported events were systemic allergic reactions.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Difference in % |
| Comparison groups | Short ragweed pollen allergen extract v Placebo |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 1022 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.32 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Difference in % estimates |
| Point estimate | 0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.57 |
| upper limit | 1.53 |

Secondary: Percentage of Participants Treated with Epinephrine

| | |
|------------------------|---|
| End point title | Percentage of Participants Treated with Epinephrine |
| End point description: | Self-injectable epinephrine was provided to each subject/parent/guardian at randomization in countries where it is a regulatory requirement, and was to be available around the time treatment is administered at home. Self-injectable epinephrine was intended for immediate self-administration for an anaphylactic reaction, including symptoms/signs of upper airway obstruction. Instances of treatment with forms of epinephrine other than systemic epinephrine (e.g., inhaled racepinephrine) were counted as use of epinephrine. The safety population was all treated participants. Participants are grouped by the study treatment actually received. |
| End point type | Secondary |
| End point timeframe: | |
| Up to 35 weeks | |

| End point values | Short ragweed pollen allergen extract | Placebo | | |
|-----------------------------------|---------------------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 513 ^[3] | 509 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 0.19 | 0.20 | | |

Notes:

[3] - Participant in this arm received inhaled racepinephrine

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Difference in % |
| Comparison groups | Short ragweed pollen allergen extract v Placebo |
| Number of subjects included in analysis | 1022 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.996 |
| Method | Miettinen & Nurminen |
| Parameter estimate | Difference in % estimates |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.92 |
| upper limit | 0.92 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 35 weeks

Adverse event reporting additional description:

An AE is any physical or clinical change or disease experienced by the participant at any time during the course of the study, whether or not considered related to the use of the study drug. The safety population was all treated participants. Participants are grouped by the study treatment actually received.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants who received placebo sublingual tablet, administered once daily (QD) for up to 35 weeks.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Short ragweed pollen allergen extract |
|-----------------------|---------------------------------------|

Reporting group description:

Participants who received short ragweed pollen allergen extract sublingual tablet, administered once daily (QD) for up to 35 weeks.

| Serious adverse events | Placebo | Short ragweed pollen allergen extract | |
|---|-----------------|---------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 509 (1.77%) | 7 / 513 (1.36%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 509 (0.00%) | 1 / 513 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 509 (0.20%) | 0 / 513 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 509 (0.00%) | 1 / 513 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 509 (0.20%) | 1 / 513 (0.19%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 509 (0.20%) | 0 / 513 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral pruritus | | | |
| subjects affected / exposed | 0 / 509 (0.00%) | 1 / 513 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 3 / 509 (0.59%) | 0 / 513 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Conduct disorder | | | |
| subjects affected / exposed | 1 / 509 (0.20%) | 0 / 513 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 509 (0.00%) | 1 / 513 (0.19%) | |
| 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 / 509 (0.00%) | 1 / 513 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 509 (0.20%) | 0 / 513 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 509 (0.20%) | 0 / 513 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 0 / 509 (0.00%) | 1 / 513 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Short ragweed pollen allergen extract | |
|---|--------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 233 / 509 (45.78%) | 370 / 513 (72.12%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 49 / 509 (9.63%) | 45 / 513 (8.77%) | |
| occurrences (all) | 67 | 100 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 20 / 509 (3.93%) | 29 / 513 (5.65%) | |
| occurrences (all) | 23 | 33 | |
| Ear and labyrinth disorders | | | |
| Ear pruritus | | | |
| subjects affected / exposed | 35 / 509 (6.88%) | 177 / 513 (34.50%) | |
| occurrences (all) | 65 | 750 | |
| Gastrointestinal disorders | | | |

| | | | |
|--|--------------------------|----------------------------|--|
| Abdominal pain upper subjects affected / exposed occurrences (all) | 30 / 509 (5.89%) 53 | 54 / 513 (10.53%) 119 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 21 / 509 (4.13%) 29 | 26 / 513 (5.07%) 55 | |
| Enlarged uvula subjects affected / exposed occurrences (all) | 2 / 509 (0.39%) 2 | 33 / 513 (6.43%) 65 | |
| Glossodynia subjects affected / exposed occurrences (all) | 13 / 509 (2.55%) 29 | 64 / 513 (12.48%) 171 | |
| Lip swelling subjects affected / exposed occurrences (all) | 7 / 509 (1.38%) 14 | 66 / 513 (12.87%) 165 | |
| Nausea subjects affected / exposed occurrences (all) | 43 / 509 (8.45%) 69 | 70 / 513 (13.65%) 167 | |
| Oral pain subjects affected / exposed occurrences (all) | 16 / 509 (3.14%) 29 | 64 / 513 (12.48%) 151 | |
| Oral pruritus subjects affected / exposed occurrences (all) | 62 / 509 (12.18%) 131 | 247 / 513 (48.15%) 1115 | |
| Stomatitis subjects affected / exposed occurrences (all) | 6 / 509 (1.18%) 13 | 34 / 513 (6.63%) 89 | |
| Swollen tongue subjects affected / exposed occurrences (all) | 4 / 509 (0.79%) 5 | 56 / 513 (10.92%) 132 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 30 / 509 (5.89%) 53 | 30 / 513 (5.85%) 39 | |
| Oropharyngeal pain | | | |

| | | | |
|--|--------------------------|----------------------------|--|
| subjects affected / exposed occurrences (all) | 29 / 509 (5.70%) 44 | 25 / 513 (4.87%) 56 | |
| Pharyngeal oedema subjects affected / exposed occurrences (all) | 8 / 509 (1.57%) 14 | 58 / 513 (11.31%) 138 | |
| Throat irritation subjects affected / exposed occurrences (all) | 98 / 509 (19.25%) 223 | 254 / 513 (49.51%) 1048 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 36 / 509 (7.07%) 50 | 38 / 513 (7.41%) 50 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 19 September 2016 | The asthma DSS will be completed daily beginning with Visit 4 by all participants in the study, and decreased blood volume is to be taken at screening |
| 11 September 2018 | Addition of "severe asthma exacerbation" to the list of discontinuation criteria. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported