



Clinical trial results:

A Dose Finding Study of the Efficacy of LAIS® Mites Sublingual tablets in patients suffering from house dust mite-induced allergic rhinoconjunctivitis

A prospective, double-blind, placebo-controlled randomized multi-centre trial.

Summary

EudraCT number	2013-000617-20
Trial protocol	DE
Global end of trial date	13 May 2014

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021

Trial information

Trial identification

Sponsor protocol code	SMART_2
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Lofarma Spa
Sponsor organisation address	Viale Cassala, 40, Milan, Italy, 20143
Public contact	Scientific Director Lofarma SPA, Institut für Med. Statistik, Informatik u. Epidemiologie, +39 0258198287,
Scientific contact	Scientific Director Lofarma SPA, Institut für Med. Statistik, Informatik u. Epidemiologie, +39 0258198287,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The efficacy of sublingual immunotherapy with the allergoid LAIS® Mites Sublingual tablets will be assessed by the mean improvement in the allergic severity S between baseline and visit V4, comparing the five treatment groups.

Allergic severity S is rated by means of the severity stage integer values $0 \leq c_i \leq 4$. Here i is a number of an attempt (titration stage), made to reach a positive allergic reaction within the Conjunctival Provocation Test (CPT). CPT is considered positive if the response is stage 2 or higher.

The maximum number of attempts (N) is restricted with the titration solutions available. If the severity stage is reached to be $c_i = 2$, the CPT is considered as positive, the test is stopped for the current visit and N is the number of steps to reach a positive result (1, 2, 3).

The titrated conjunctival allergen challenge will be conducted with solutions containing 100, 1,000 and 10,000 SQ-E/ml mite allergens.

Protection of trial subjects:

Before including a patient, the investigator informed the patient in his own words of the nature of the trial, of its aims, of the methods and means to be used, and of the estimated duration of the study. He/she had also informed the patient of the possible risks linked with administration of the products and of the possible effects which to his/her knowledge might occur.

Moreover, the main procedures used to guarantee the subjects' anonymity especially during the analysis of their personal data were profoundly explained.

The patient was allowed to ask questions and had to be satisfied with all the investigator's answers.

Before asking the patient to sign the consent form, the investigator ascertained that the patient entirely understood and agreed to all information provided.

The subject was free to withdraw from the study at any time without prejudicing future medical care and giving a reason.

If any new information became available that might have influenced the subject's decision to stay in the trial, it was transmitted without delay to the subject.

Background therapy:

All patients were supplied with a blister of an oral antihistamine (10 mg Loratadine) to be taken on demand as rescue medication for potentially appearing local side effects like oral pruritus and edema of mouth, tongue or lips.

Evidence for comparator: -

Actual start date of recruitment	01 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 165
Worldwide total number of subjects	165
EEA total number of subjects	165

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	165
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to recruit 150 patients in total, with 30 participants in each treatment group. However, a total number of 165 patients were screened, 131 patients were randomized, with 127 being valid for the ITT analysis subset.

Pre-assignment

Screening details:

Female or male patients aged 18–75 years with a history of at least two years of house dust mites (HDM) induced allergic rhinitis and/or allergic rhinoconjunctivitis with or without controlled asthma upon exposure to house dust mites [From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012]

Period 1

Period 1 title	Lais Mites (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

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

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

Dosage and administration details:

Placebo and verum preparations were identical except of the active substances. i.e. carbamylated, monomeric allergoids of mite.

Arm title	LAIS® Mites 300 UA/Day
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	LAIS® Mites 300 Ua/Day
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

Arm title	Lais Mites 1,000 UA/day
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	LAIS® Mites 1,000 UA/day
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

Arm title	LAIS® Mites 2,000 UA/Day
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	LAIS® Mites 2,000 UA/Day
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

Arm title	LAIS® Mites 3,000 UA/Day
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	LAIS® Mites Sublingual 3,000 UA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

The treatment was randomly allocated to a subject. Each subjects treatment was scheduled for 12 weeks (84±7 days) and each subject ingested one sublingual tablet per day independent of the assigned group. The participants were instructed to place the tablet under the tongue and dissolved for two minutes before swallowing. The first application (day 0) was performed under supervision and the patients remained under the observation of a trained allergologist for at least 30 minutes. Afterwards, trial medication was handed to the patients and administered by him- / herself.

Number of subjects in period 1^[1]	Placebo	LAIS® Mites 300 UA/Day	Lais Mites 1,000 UA/day
Started	29	23	27
Completed	28	23	26
Not completed	1	0	1
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	-

Number of subjects in period 1^[1]	LAIS® Mites 2,000 UA/Day	LAIS® Mites 3,000 UA/Day
Started	26	26
Completed	26	25
Not completed	0	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	-

Notes:

[1] - 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: Since 34 patients resulted as screening failures, 131 patients were randomized into this study.

Baseline characteristics

Reporting groups

Reporting group title	Lais Mites
Reporting group description: -	

Reporting group values	Lais Mites	Total	
Number of subjects	131	131	
Age categorical			
Units: Subjects			
Adults (18–75 years)	131	131	
Age continuous			
Units: years			
arithmetic mean	37.48		
full range (min-max)	18 to 70	-	
Gender categorical			
Units: Subjects			
Female	64	64	
Male	67	67	

Subject analysis sets

Subject analysis set title	Safety set (S-set)/ Exposed Subjects
Subject analysis set type	Safety analysis

Subject analysis set description:

randomized subjects who have been exposed to the study medication at least once. Only safety analyses will be performed in this group.

Subject analysis set title	Intention-To-Treat-set (ITT-set)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Randomized subjects who meet key eligibility and evaluability criteria. This dataset is defined by the existence of evaluable CPT data at baseline and V3 or later.

Subject analysis set title	Per-Protocol-set (PP-set)
Subject analysis set type	Per protocol

Subject analysis set description:

evaluable subjects who comply with the protocol in all points, delivering a complete data set of measurements and evaluations of the primary efficacy variable. A maximum of 25 % deviation from the planned intake of study medication was accepted as per protocol drug intake

Subject analysis set title	Randomized
Subject analysis set type	Full analysis

Subject analysis set description:

all subjects randomized into the study.

Reporting group values	Safety set (S-set)/ Exposed Subjects	Intention-To-Treat- set (ITT-set)	Per-Protocol-set (PP- set)
Number of subjects	131	127	119
Age categorical			
Units: Subjects			
Adults (18–75 years)	131	127	119

Age continuous Units: years arithmetic mean full range (min-max)	37.48 18 to 70	37.48 18 to 70	37.44 18 to 70
Gender categorical Units: Subjects			
Female	64	63	59
Male	67	64	60

Reporting group values	Randomized		
Number of subjects	131		
Age categorical Units: Subjects			
Adults (18–75 years)	131		
Age continuous Units: years arithmetic mean full range (min-max)	37.48 18 to 70		
Gender categorical Units: Subjects			
Female	64		
Male	67		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LAIS® Mites 300 UA/Day
Reporting group description: -	
Reporting group title	Lais Mites 1,000 UA/day
Reporting group description: -	
Reporting group title	LAIS® Mites 2,000 UA/Day
Reporting group description: -	
Reporting group title	LAIS® Mites 3,000 UA/Day
Reporting group description: -	
Subject analysis set title	Safety set (S-set)/ Exposed Subjects
Subject analysis set type	Safety analysis
Subject analysis set description: randomized subjects who have been exposed to the study medication at least once. Only safety analyses will be performed in this group.	
Subject analysis set title	Intention-To-Treat-set (ITT-set)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Randomized subjects who meet key eligibility and evaluability criteria. This dataset is defined by the existence of evaluable CPT data at baseline and V3 or later.	
Subject analysis set title	Per-Protocol-set (PP-set)
Subject analysis set type	Per protocol
Subject analysis set description: evaluable subjects who comply with the protocol in all points, delivering a complete data set of measurements and evaluations of the primary efficacy variable. A maximum of 25 % deviation from the planned intake of study medication was accepted as per protocol drug intake	
Subject analysis set title	Randomized
Subject analysis set type	Full analysis
Subject analysis set description: all subjects randomized into the study.	

Primary: Efficacy (allergic severity score S)

End point title	Efficacy (allergic severity score S)
End point description: The primary outcome parameter of the study was the improvement of the allergic severity S between baseline and V4 (day 84 ± 7). There was a distinct improvement of the allergic severity S between baseline and V3 and a more pronounced improvement between baseline and V4 in each study arm	
End point type	Primary
End point timeframe: between baseline and visit V4.	

End point values	Placebo	LAIS® Mites 300 UA/Day	Lais Mites 1,000 UA/day	LAIS® Mites 2,000 UA/Day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	23	25	26
Units: Score				
arithmetic mean (standard deviation)				
D Baseline - V4	0.30 (± 0.501)	0.21 (± 0.373)	0.37 (± 0.735)	0.33 (± 0.462)
Mean Severity at V4	0.29 (± 0.50)	0.14 (± 0.17)	0.15 (± 0.13)	0.10 (± 0.10)

End point values	LAIS® Mites 3,000 UA/Day			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Score				
arithmetic mean (standard deviation)				
D Baseline - V4	0.27 (± 0.475)			
Mean Severity at V4	0.15 (± 0.09)			

Statistical analyses

Statistical analysis title	Placebo vs. 300 UA
Comparison groups	Placebo v LAIS® Mites 300 UA/Day
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.251
Method	t-test, 2-sided

Statistical analysis title	Placebo vs. 1,000 UA
Comparison groups	Placebo v Lais Mites 1,000 UA/day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.706
Method	t-test, 2-sided

Statistical analysis title	Placebo vs. 2,000 UA
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Statistical analysis description:

In summary, the mean relative improvement of the allergic severity S was highest in the 2,000 UA/d-group (66,8%) with $p < 0.1$ compared to the placebo group. Additionally, the percentage of patients with improved allergic severity between baseline and V4 was the highest in the treatment group with a daily dose of 2,000 UA. Therefore, the results of this clinical trial clearly demonstrated a general efficacy of the treatment with LAIS® mites tablets of 2,000 UA.

Comparison groups	Placebo v LAIS® Mites 2,000 UA/Day
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.093
Method	t-test, 2-sided

Notes:

[1] - The largest amount of patients having improved in the allergic severity S were in the group having received 2,000 UA/d (88,5%) (Table 14.1.5.1.2.2, Figure 11.3). However, comparing the proportion of patients with improvement of the allergic severity S of the placebo group and the actively treated groups statistical significance was not observed.

Statistical analysis title	Placebo vs. 3,000 UA
Comparison groups	LAIS® Mites 3,000 UA/Day v Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.878
Method	t-test, 2-sided

Statistical analysis title	Mean Severity at V4 2000 UA
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Statistical analysis description:

The primary efficacy outcome parameter was the change in the allergic severity between baseline and the final visit V4, calculated from the reaction to the CPT

Comparison groups	LAIS® Mites 2,000 UA/Day v Placebo v LAIS® Mites 300 UA/Day v Lais Mites 1,000 UA/day v LAIS® Mites 3,000 UA/Day
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.1 ^[3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - In the present study, the analysis of the CPT results by means of S (13) favours the active treatment dose of 2000 UA/day when compared to placebo. Likewise, the percentage of patients having an improved CPT threshold at the final visit is significantly higher in the group treated with 2000 UA/day than in the placebo group.

[3] - the mean S in the four active treatment groups was only one-third to one-half of the mean S in the placebo, favouring the treatment group 2000 UA/day, although not significant (P < 0.1)

Secondary: CPT Result Score

End point title	CPT Result Score
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End point description:

As a secondary objective, the changes of the threshold allergen concentration for a positive CPT between baseline and V3 as well as between baseline and V4 were analyzed by means of a CPT result score

End point type	Secondary
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End point timeframe:

Baseline - v3

Baseline - v4

End point values	Placebo	LAIS® Mites 300 UA/Day	Lais Mites 1,000 UA/day	LAIS® Mites 2,000 UA/Day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	23	25	26
Units: Score				
arithmetic mean (standard deviation)				
D Baseline - V3	0.54 (± 0.744)	0.43 (± 0.728)	0.64 (± 0.810)	0.65 (± 0.846)
D Baseline - V4	0.86 (± 0.932)	0.78 (± 0.671)	0.88 (± 0.927)	1.15 (± 0.675)

End point values	LAIS® Mites 3,000 UA/Day			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Score				
arithmetic mean (standard deviation)				
D Baseline - V3	0.28 (± 0.678)			
D Baseline - V4	0.96 (± 0.735)			

Statistical analyses

Statistical analysis title	CPT baseline - V3 Placebo VS 300UA
Comparison groups	Placebo v LAIS® Mites 300 UA/Day
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.908
Method	t-test, 2-sided

Statistical analysis title	CPT baseline - V3 Placebo VS 1,000UA
Comparison groups	Placebo v Lais Mites 1,000 UA/day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.476
Method	t-test, 2-sided

Statistical analysis title	CPT baseline - V3 Placebo VS 2,000UA
Comparison groups	Placebo v LAIS® Mites 2,000 UA/Day

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.496
Method	t-test, 2-sided

Statistical analysis title	CPT baseline - V3 Placebo VS 3,000UA
Comparison groups	Placebo v LAIS® Mites 3,000 UA/Day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	t-test, 2-sided

Statistical analysis title	CPT baseline - V4 Placebo VS 300UA
Comparison groups	Placebo v LAIS® Mites 300 UA/Day
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.958
Method	t-test, 2-sided

Statistical analysis title	CPT baseline - V4 Placebo VS 1,000UA
Comparison groups	Placebo v Lais Mites 1,000 UA/day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	t-test, 2-sided

Statistical analysis title	CPT baseline - V4 Placebo VS 3,000UA
Comparison groups	Placebo v LAIS® Mites 3,000 UA/Day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.544
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 300UA baseline - V3
Statistical analysis description:	
number of patients with improved CPT response threshold between actively treated and placebo group	
Comparison groups	Placebo v LAIS® Mites 300 UA/Day
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.725
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 1,000UA baseline-V3
Statistical analysis description:	
number of patients with improved CPT response threshold between actively treated and placebo group	
Comparison groups	Placebo v Lais Mites 1,000 UA/day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.344
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 2,000UA baseline-V3
Statistical analysis description:	
number of patients with improved CPT response threshold between actively treated and placebo group	
Comparison groups	Placebo v LAIS® Mites 2,000 UA/Day
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.424
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 3,000UA baseline-V3
Statistical analysis description:	
number of patients with improved CPT response threshold between actively treated and placebo group	
Comparison groups	Placebo v LAIS® Mites 3,000 UA/Day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.835
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 300UA baseline - V4
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Comparison groups	Placebo v LAIS® Mites 300 UA/Day
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 1,000UA baseline-V4
Comparison groups	Placebo v Lais Mites 1,000 UA/day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	t-test, 2-sided

Statistical analysis title	n° Pt improved CPT Placebo Vs 2,000UA baseline-V4
Comparison groups	Placebo v LAIS® Mites 2,000 UA/Day
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.04 ^[5]
Method	t-test, 2-sided

Notes:

[4] - The rate of patients who had a worse or unchanged CPT response threshold between baseline and V4 was the lowest (11.5%) in the 2,000 UA/d-group.

[5] - Also, the maximum effect was achieved with a daily dose of 2,000 UA, while higher or lower doses showed less efficacy.

Statistical analysis title	n° Pt improved CPT Placebo Vs 3,000UA baseline-V4
Comparison groups	Placebo v LAIS® Mites 3,000 UA/Day
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358 ^[6]
Method	t-test, 2-sided

Notes:

[6] - Also, the maximum effect was achieved with a daily dose of 2,000 UA, while higher or lower doses showed less efficacy.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The treatment lasted from the 3rd quarter 2013 to the 2nd quarter 2014.

The study protocol defined a treatment duration of 84 ± 7 days. Finally, the minimum of treatment duration (V1-V4) was 56 days and the the maximum duration was 105 days.

Adverse event reporting additional description:

Of 131 patients in the safety analysis set, 37 patients (28%) reported a total number of 50 treatment emerged adverse events (AEs), of which one was a serious adverse event (SAE). The SAE was recorded as a mamma carcinoma in one patient of the placebo group. These numbers are identical for both ITT and safety analysis sets.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	nk

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LAIS® Mites 300 UA/Day
Reporting group description: -	
Reporting group title	Lais Mites 1,000 UA/day
Reporting group description: -	
Reporting group title	LAIS® Mites 2,000 UA/Day
Reporting group description: -	
Reporting group title	LAIS® Mites 3,000 UA/Day
Reporting group description: -	

Serious adverse events	Placebo	LAIS® Mites 300 UA/Day	Lais Mites 1,000 UA/day
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LAIS® Mites 2,000 UA/Day	LAIS® Mites 3,000 UA/Day	
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	LAIS® Mites 300 UA/Day	Lais Mites 1,000 UA/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	9 / 23 (39.13%)	6 / 27 (22.22%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Gastroenteritis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Sensation of pressure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0

Malaise subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 23 (4.35%) 1	0 / 27 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 23 (0.00%) 0	1 / 27 (3.70%) 1
Ear and labyrinth disorders Ear pruritus subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 23 (0.00%) 0	1 / 27 (3.70%) 3
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 23 (4.35%) 1	0 / 27 (0.00%) 0
Gastritis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 23 (4.35%) 1	0 / 27 (0.00%) 0
Oral discomfort subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 23 (0.00%) 0	1 / 27 (3.70%) 2
Glossodynia subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 23 (0.00%) 0	0 / 27 (0.00%) 0
Oral pruritus subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 23 (0.00%) 0	1 / 27 (3.70%) 3
Hypoaesthesia oral subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	0 / 23 (0.00%) 0	0 / 27 (0.00%) 0
Swollen tongue subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 23 (4.35%) 1	0 / 27 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma			

subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal swelling			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Nasal discomfort			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal blistering			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	4
Sneezing			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Increased upper airway secretion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 29 (0.00%)	1 / 23 (4.35%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 29 (3.45%)	2 / 23 (8.70%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Pharyngotonsillitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 23 (8.70%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Acute sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Pulpitis dental			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 23 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	LAIS® Mites 2,000 UA/Day	LAIS® Mites 3,000 UA/Day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)	9 / 26 (34.62%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			

Dysgeusia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
General disorders and administration site conditions			
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Sensation of pressure subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Malaise subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Blood and lymphatic system disorders			
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Ear and labyrinth disorders			
Ear pruritus subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Gastritis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Oral discomfort subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Glossodynia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Oral pruritus			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia oral			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Swollen tongue			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal swelling			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nasal discomfort			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	
occurrences (all)	2	4	
Epistaxis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Oropharyngeal blistering			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Wheezing			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Sneezing			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Increased upper airway secretion			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	
Throat irritation subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	
Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Viral infection subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Pharyngotonsillitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	
Sinusitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 26 (7.69%) 2	
Acute sinusitis subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	3 / 26 (11.54%) 3	
Pulpitis dental subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	
Herpes virus infection subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2014	In the initial version of the study protocol (version 2.0), it was specified that the specific CAP-RAST results to co-allergens had to be less than the CAP-RAST result to mite allergens (the difference had to be ≥ 1) and the results of the skin prick test against co-allergens had to be less than the result of the skin prick test against mite allergens. Allergy against mugwort, alternaria and ambrosia were regarded as exclusion criteria. The final study protocol version 4.1 provided that patients with co-sensitizations to aero-allergens like grass or rye, could be included into the trial irrespective of the skin prick test results. Patients with co-sensitizations against perennial allergens like cat or dog dander could also be included irrespective of the skin prick test results, as long as they were not regularly exposed to these allergens and therefore show no symptoms. Allergy against mugwort, ambrosia and alternaria did not represent an exclusion criterion according to this new version of the study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27068870>