Clinical trial results:
A prospective, multicenter, double-blind, placebo-controlled randomized study to assess efficacy and safety of LAIS® Grass pollen tablets in patients with seasonal grass pollen-induced allergic rhinoconjunctivitis

Summary

EudraCT number	2019-001532-65
Trial protocol	IT
Global end of trial date	24 September 2020

Results information

Result version number	v1 (current)
This version publication date	22 April 2022
First version publication date	22 April 2022

Trial information

Trial identification

Sponsor protocol code	LGT03-19

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	CRO, CD PHARMA GROUP SRL, +39 02581981,
Scientific contact	CRO, CD PHARMA GROUP SRL, +39 02581981,

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	15 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy and safety of tablet-based sublingual immunotherapy (SLIT) with the monomeric allergoid LAIS® Grass tablets compared to placebo in patients with grass pollen-induced allergic rhinoconjunctivitis with or without controlled asthma.

Protection of trial subjects:

The study was conducted in accordance with the protocol, under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).
With the exception of those drugs listed among non-permitted medications participants were allowed to use any concomitant medication (necessary for the treatment of preexisting concomitant pathologies or for intercurrent diseases), that did not interfere with the study evaluation parameters.
Decongestants (oral, nasal spray, drops) were allowed for symptom relief for short term needs (i.e. to provide relief after the TNPT, in occurrence of a cold or flu).
Asthma medications not influencing the study outcomes (i.e. inhaled corticosteroids, short-acting and long acting beta-2-agonists) were admitted to maintain asthma control along the whole trial duration.

Background therapy:

Standard rescue therapy with anti-symptomatic medication during the grass pollen season: Desloratadine (oral) , Levocabastine (eyedrops), Mometasone furoate (nasal) 50 mcg , Prednisone (oral) 5 mg.
The score was assigned as follows:
Score = 1: use of oral/ocular antihistamines;
Score = 2: use of nasal corticosteroids;
Score = 3: use of oral corticosteroids.
The assumption of Rescue Medications was reported on the patient diary.
For adolescents included in the trial, parents were responsible for the management of rescue medications and careful clinical diary completion

Evidence for comparator: -

Actual start date of recruitment	18 November 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	17
Adults (18-64 years)	81
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Territory: Italy
The total number of partecipants in each treatment group was recruited and screened for inclusion and exclusion criteria. Recruitment was greatly slower than planned. Limitation of a reduced sample size was due to the premature termination of the study enrolment.

Pre-assignment

Screening details:

Patients with a confirmed diagnosis of moderate to severe ARC based on medical history underwent a skin prick test and nasal allergen provocation challenge with Grass pollen extract and serum specific IgE (>0.7 kU/l) for Phl p1-5.

Period 1

Period 1 title	Grass pollen (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The randomization was implemented in eCRF according to an algorithm generated and validated by CINECA. A paper copy of the complete randomization list was placed in a sealed envelope and retained in a secure, fire-proof room with restricted-access at the CRO. The MED.ID was then printed on the label of the medication prescribed by the randomization list. Breaking of this code was only valid under certain circumstances

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo - Group 1

Arm description:

Sublingual placebo preparation (one tablet once daily) for about 7-9 months pre-/coseasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season. Placebo and verum preparation were identical except of the active ingredient

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

Dosage and administration details:

Independent of the assigned tratment group, the patients ingested one sublingual tablet per day. The first dose had to be self-administered at the randomization visit (V1) at study site and patient was monitored for at least 30 minutes after tablet intake.

Arm title	Lais Grass - Group 2

Arm description:

Sublingual immunotherapy with grass pollen extract (one tablet of 1,000 UA once daily) for about 7-9 months pre-/co-seasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season.

Arm type	Experimental

Investigational medicinal product name	Lais Grass sublingual tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Independent of the assigned tratment group, the patients ingested one sublingual tablet per day. The first dose had to be self-administered at the randomization visit (V1) at study site and patient was monitored for at least 30 minutes after tablet intake.

Number of subjects in period 1[1]	Placebo - Group 1	Lais Grass - Group 2
Started	47	47
Completed	38	37
Not completed	9	10
No evaluable post-randomization data	9	10

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: Overall, 98 patients were randomised to receive the assigned treatment: 49 patients were randomised to receive LAIS grass and 49 patients were randomised to receive placebo. Two randomised patients in each treatment group did not receive at least one dose of the study medication and there therefore excluded. The study comprised 94 patients overall (95.9% of randomized), 47 (95.9%) in each treatment group.

Baseline characteristics

Reporting groups

Reporting group title	Grass pollen

Reporting group description:

Female or male patients aged 12–64 years with a history of at least 2 years of grass pollen induced allergic rhinoconjunctivitis (ARC) with or without seasonal controlled allergic asthma; moderate/severe (interfering with usual daily activities or sleep) ARC defined according to ARIA guidelines; positive clinical history of grass pollen allergy; compliance and ability of the patient to complete a patient's diary for self-evaluation of the symptoms and antisymptomatic medication and treatment compliance; signed and dated patient's informed consent.

Reporting group values	Grass pollen	Total	
Number of subjects	94	94	
Age categorical			
Female or male patients aged 12–64 years			
Units: Subjects			
12-64 years	94	94	
Age continuous			
Units: years			
median	28		
full range (min-max)	12 to 54	-	
Gender categorical			
The demographic characteristics were similar in the two groups, except for a slightly higher proportion of males in the LAIS group than in the placebo group			
Units: Subjects			
Female	45	45	
Male	49	49	

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Randomized patients who met key eligibility and evaluability criteria. This dataset was defined by the availability of evaluable post-randomization data for at least one of the primary efficacy variables (dSS and dMS during the 14-days of highest pollen load)
The analysis of ITT population was based on 37 subjects in the treatment group and 38 in the control group from all investigational centers.All p-values reported refer to the analysis of variance.

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

Subject analysis set description:

All patients in the FAS with no major protocol deviations, which would impact the primary efficacy (defined as 'critical'), and delivering a sufficient data set of measurements and evaluations of the primary efficacy variables: a maximum of two subsequent missing single evaluations of the rhinoconjunctivitis symptom score (dSS) was acceptable. The total number of missing single evaluations of the dSS had not to exceed 25 % over the entire course of the 14-days of highest pollen load within the peaks of the grass pollen season.
The analysis was based on 31 subjects in the treatment group and 32 in the control group from all investigational centers.

Subject analysis set title	Safety evaluation set- SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety evaluation set (SES), which included all randomized patients who received at least one dose of the study medication. This population was used for all safety analyses.
The analysis was based on 47 subjects in the treatment group and 47 in the control group from all investigational centers.

Reporting group values	ITT population	Per-Protocol-Set (PP-set)	Safety evaluation set- SES
Number of subjects	75	63	94
Age categorical			
Female or male patients aged 12–64 years			
Units: Subjects			
12-64 years	75	63	94
Age continuous Units: years median full range (min-max)	12 to 54	12 to 54	12 to 54
Gender categorical			
The demographic characteristics were similar in the two groups, except for a slightly higher proportion of males in the LAIS group than in the placebo group			
Units: Subjects			
Female	34	31	45
Male	41	32	49

End points

End points reporting groups

Reporting group title	Placebo - Group 1

Reporting group description:

Sublingual placebo preparation (one tablet once daily) for about 7-9 months pre-/coseasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season. Placebo and verum preparation were identical except of the active ingredient

Reporting group title	Lais Grass - Group 2

Reporting group description:

Sublingual immunotherapy with grass pollen extract (one tablet of 1,000 UA once daily) for about 7-9 months pre-/co-seasonally (from at least 16 weeks before the expected start of the pollen season to 30 June 2020) and standard rescue therapy with anti-symptomatic medication during the grass pollen season.

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Randomized patients who met key eligibility and evaluability criteria. This dataset was defined by the availability of evaluable post-randomization data for at least one of the primary efficacy variables (dSS and dMS during the 14-days of highest pollen load)
The analysis of ITT population was based on 37 subjects in the treatment group and 38 in the control group from all investigational centers.All p-values reported refer to the analysis of variance.

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

Subject analysis set description:

All patients in the FAS with no major protocol deviations, which would impact the primary efficacy (defined as 'critical'), and delivering a sufficient data set of measurements and evaluations of the primary efficacy variables: a maximum of two subsequent missing single evaluations of the rhinoconjunctivitis symptom score (dSS) was acceptable. The total number of missing single evaluations of the dSS had not to exceed 25 % over the entire course of the 14-days of highest pollen load within the peaks of the grass pollen season.
The analysis was based on 31 subjects in the treatment group and 32 in the control group from all investigational centers.

Subject analysis set title	Safety evaluation set- SES
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety evaluation set (SES), which included all randomized patients who received at least one dose of the study medication. This population was used for all safety analyses.
The analysis was based on 47 subjects in the treatment group and 47 in the control group from all investigational centers.

Primary: CSMS - 14D - Efficacy

End point title	CSMS - 14D - Efficacy

End point description:

Assessment of the efficacy on the average daily total Combined Symptom-Medication score (CSMS) based on an equal weight of the dSS and dMS (maximum score 3 + 3 = 6) for the 14 days of highest pollen load within the peaks of the grass pollen season taking into account:
- Daily rhinoconjunctivitis total Symptom Score (dSS) of the six rhinoconjunctivitis symptoms over the previous 24 hours, which included itching, sneezing, rhinorrhea, obstruction, ocular itching/grittiness/redness and ocular tearing with scale from 0-3 per symptom (maximum score 18 points / divided by 6 symptoms = 3 points)

- Daily Medication Score (dMS) over the previous 24 hours:
0 = no rescue medication taken
1 = use of antihistamines (oral, ophthalmic, or both);
2 = use of nasal corticosteroids;
3 = use of oral corticosteroids
If more than 1 class of rescue medication was used on a particular day, the highest score was to be

retained for the dMS of that day (maximum score = 3).

End point type	Primary

End point timeframe:

14-days of highest pollen load within the peaks of the grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	1.04 (± 1.25)	0.84 (± 1.10)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [1]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.16

Notes:

[1] - The difference in LMSs was -0.30 (95% CI, -0.44 to -0.16) that corresponds to a difference of -28% relative to to placebo, and was statistically significant.

Secondary: Average CSMS during the peak

End point title	Average CSMS during the peak

End point description:

Average CSMS

End point type	Secondary

End point timeframe:

During the days with ≥ 50 pollen/m3

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	1.02 (± 1.29)	0.55 (± 0.96)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.41

Notes:

[2] - The difference in LMSs was -0.49 (95% CI, -0.58 to -0.41) and was statistically significant (p<0.0001 between groups)

Secondary: Average CSMS during the entire grass pollen season

End point title	Average CSMS during the entire grass pollen season

End point description:

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.96 (± 1.25)	0.75 (± 1.04)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	-0.22

Notes:

[3] - The difference in LMSs was -0.28 (95% CI, -0.33 to -0.22) and was statistically significant (p<0.0001 between groups)

Secondary: Average dSS -14D

End point title	Average dSS -14D

End point description:

End point type	Secondary

End point timeframe:

14-days of highest pollen load within the peaks of the grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.47 (± 0.62)	0.44 (± 0.61)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference.
The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	-0.01

Notes:

[4] - The difference in LMSs was -0.08 (95% CI, -0.16 to -0.01) and was statistically significant (p=0.0058 between groups)

Secondary: Average dSS during the peak

End point title	Average dSS during the peak

End point description:

End point type	Secondary

End point timeframe:

During the days with ≥ 50 pollen/m3

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.49 (± 0.67)	0.30 (± 0.52)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.17

Notes:

[5] - The difference in LMSs was -0.21 (95% CI, -0.26 to -0.17) and was statistically significant (p<0. 0001 between groups)

Secondary: Average dSS during the entire grass pollen season

End point title	Average dSS during the entire grass pollen season

End point description:

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.48 (± 0.62)	0.41 (± 0.59)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	-0.08

Notes:

[6] - The difference in LMSs was -0.11 (95% CI, -0.13 to -0.08) and was statistically significant (p<0. 0001 between groups)

Secondary: Average dMS - 14D

End point title	Average dMS - 14D

End point description:

End point type	Secondary

End point timeframe:

14-days of highest pollen load within the peaks of the grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.57 (± 0.83)	0.40 (± 0.63)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [7]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.12

Notes:

[7] - The difference in LMSs was -0.21 (95% CI, -0.30 to -0.12) and was statistically significant (p=0.0004 between groups)

Secondary: Average dMS during the peak

End point title	Average dMS during the peak

End point description:

End point type	Secondary

End point timeframe:

during the days with ≥ 50 pollen/m3

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.52 (± 0.82)	0.25 (± 0.65)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.23

Notes:

[8] - The difference in LMSs was -0.28 (95% CI, -0.34 to -0.23) and was statistically significant (p<0.0001 between groups)

Secondary: Average dMS during the entire grass pollen season

End point title	Average dMS during the entire grass pollen season

End point description:

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	0.48 (± 0.80)	0.34 (± 0.65)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %

Notes:

[9] - The difference in LMSs was -0.17 (95% CI, -0.21 to -0.13) and was statistically significant (p<0.0001 between groups)

Secondary: Average 6 individual symptom scores of dSS - 14D

End point title	Average 6 individual symptom scores of dSS - 14D

End point description:

Each six individual symptom score of dSS were analyzed using a general linear mixed model having the same independent variable side structure as described for CSMS to reach the primary objective (treatment group as fixed effect, pollen region as random effect).

End point type	Secondary

End point timeframe:

14-days of highest pollen load within the peaks of the grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)				
Nasal itching mean 14D	0.54 (± 0.87)	0.43 (± 0.70)		
Rhinorrhoea mean 14D	0.49 (± 0.79)	0.47 (± 0.80)		
Nasal obstruction 14D	0.56 (± 0.83)	0.50 (± 0.78)		
Sneezing mean 14D	0.62 (± 0.80)	0.59 (± 0.79)		
Ocular itching/grittiness/redness mean 14D	0.39 (± 0.73)	0.42 (± 0.73)		
Ocular tearing	0.23 (± 0.60)	0.23 (± 0.64)		

Statistical analyses

Statistical analysis title	Nasal itching mean 14D
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6145 [10]
Method	Mixed models analysis

Notes:

[10] - The difference between groups was not statistically significant

Statistical analysis title	Rhinorrhoea mean 14D
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5905 [11]
Method	Mixed models analysis

Notes:

[11] - The difference between groups was not statistically significant.

Statistical analysis title	Nasal obstruction mean 14D
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7007 [12]
Method	Mixed models analysis

Notes:

[12] - The difference between groups was not statistically significant.

Statistical analysis title	Sneezing mean 14D
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.829 [13]
Method	Mixed models analysis

Notes:

[13] - The difference between groups was not statistically significant.

Statistical analysis title	Ocular itching/grittiness/redness mean 14D

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5564 [14]
Method	Mixed models analysis

Notes:

[14] - The difference between groups was not statistically significant.

Statistical analysis title	Ocular tearing mean 14D
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4247 [15]
Method	Mixed models analysis

Notes:

[15] - The difference between groups was not statistically significant.

Secondary: Average 6 individual symptom scores of dSS - during the peak

End point title	Average 6 individual symptom scores of dSS - during the peak

End point description:

Average six individual symptom scores of the dSS: during the days with ≥ 50 pollen/m3

End point type	Secondary

End point timeframe:

during the days with ≥ 50 pollen/m3

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)				
Nasal itching mean peak	0.59 (± 0.88)	0.32 (± 0.62)		
Rhinorrhoea mean peak	0.53 (± 0.84)	0.30 (± 0.65)		
Nasal obstruction mean peak	0.57 (± 0.90)	0.35 (± 0.66)		
Sneezing mean peak	0.60 (± 0.78)	0.41 (± 0.69)		
Ocular itching/grittiness/redness mean peak	0.42 (± 0.76)	0.29 (± 0.60)		
Ocular tearing mean peak	0.25 (± 0.62)	0.15 (± 0.49)		

Statistical analyses

Statistical analysis title	Nasal itching mean peak
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5722 [16]
Method	Mixed models analysis

Notes:

[16] - The difference between groups was not statistically significant.

Statistical analysis title	Rhinorrhoea mean peak
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6146 [17]
Method	Mixed models analysis

Notes:

[17] - The difference between groups was not statistically significant.

Statistical analysis title	Nasal obstruction mean peak
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6852 [18]
Method	Mixed models analysis

Notes:

[18] - The difference between groups was not statistically significant.

Statistical analysis title	Sneezing mean peak
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7894 [19]
Method	Mixed models analysis

Notes:

[19] - The difference between groups was not statistically significant.

Statistical analysis title	Ocular itching/grittiness/redness mean peak
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7014 [20]
Method	Mixed models analysis

Notes:

[20] - The difference between groups was not statistically significant.

Statistical analysis title	Ocular tearing mean peak
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3058 [21]
Method	Mixed models analysis

Notes:

[21] - The difference between groups was not statistically significant.

Secondary: Average 6 individual symptom scores of dSS - during entire grass pollen season

End point title	Average 6 individual symptom scores of dSS - during entire grass pollen season

End point description:

Average six individual symptom scores of the dSS: over the entire grass pollen season until the study end

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)				
Nasal itching mean entire grass season	0.51 (± 0.79)	0.43 (± 0.71)		
Rhinorrhoea mean entire grass season	0.51 (± 0.79)	0.46 (± 0.78)		
Nasal obstruction mean entire grass season	0.54 (± 0.85)	0.47 (± 0.75)		
Sneezing mean entire grass season	0.62 (± 0.83)	0.57 (± 0.80)		
Ocular itching/grittiness/redness mean - season	0.44 (± 0.79)	0.35 (± 0.67)		
Ocular tearing mean entire grass season	0.24 (± 0.58)	0.19 (± 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: well days

End point title	well days

End point description:

The “well days”, being defined as days of the entire grass pollen season with a maximum ARC

symptom score of 2 and no rescue medication use according to Dahl (Dahl et al., 2006) and Durham (Durham et al., 2006) (verum vs. placebo)

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	67.33 (± 21.68)	69.56 (± 22.89)		

Statistical analyses

Statistical analysis title	LMSs difference (Lais-Placebo)

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the difference in adjusted means between the 2 groups was presented as well as the coherent p-value vs. the H0 stating the null value for such difference. The adjusted difference was obtained as least squares mean (LSM) estimated within the previously cited linear mixed model framework

Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1702 [22]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.11

Notes:

[22] - The difference in LMSs was 0.04 (95% CI, -0.02 to 0.11) and was not statistically significant (p = 0.1702 between groups)

Secondary: VAS score

End point title	VAS score

End point description:

The VAS on ‘nasal symptoms’ was included as a simple, reliable, and fully validated subjective psychometric response scale in adults for symptoms in many indication areas to evaluate disease severity including AR and was, therefore, recommended by the EAACI. In this study, VAS was determined during the control visits to show differences between the treatment groups. the VAS score was analysed as described for the primary endpoints (i.e. applying the hierarchical testing procedure in case of statistically significant result for CSMS). The VAS score was the distance (in millimetres) from the left end of the line to the point where the patient’s mark crossed the line

End point type	Secondary

End point timeframe:

entire grass season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: millimetre(s)				
arithmetic mean (standard deviation)	19.50 (± 21.40)	22.14 (± 23.96)		

Statistical analyses

Statistical analysis title	Vas score
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5331 [23]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	7.69

Notes:

[23] - The difference between the groups was 1.84 mm (95% CI, -4.01 to 7.69 mm) and was not statistically significant (p = 0.5331)

Secondary: Global evaluation for the entire grass pollen season

End point title	Global evaluation for the entire grass pollen season

End point description:

A global evaluation was carried out by the patient for the entire grass pollen season, to evaluate the Treatment Satisfaction (verum vs placebo) with the scale: 0 = unsatisfied, 1 = little satisfied, 2 = satisfied, 3 = very satisfied.

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	3.13 (± 0.58)	2.95 (± 0.66)		

Statistical analyses

Statistical analysis title	Global evaluation
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2186 [24]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.1

Notes:

[24] - The difference between the groups was - 0.19 (95% CI, -0.47 to 0.10) and was not statistically significant (p= 0.2186)

Secondary: Global evaluation comparison of the current season versus the previous year

End point title	Global evaluation comparison of the current season versus the previous year

End point description:

A global evaluation carried out by the patient in the overall comparison of the current grass pollen season versus the previous season (previous year); in order to permit a computation of a responder analysis, this aspect was investigated at the end of the treatment period, by asking subjects the following question "Compared to your symptoms in previous grass seasons, how have you felt overall in this grass pollen season?" with possible response categories: 0 = worsening; 1 = no change; 2 = slight to moderate improvement; 3 = good to excellent improvement

End point type	Secondary

End point timeframe:

entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: score				
arithmetic mean (standard deviation)	3.03 (± 0.69)	2.95 (± 0.87)		

Statistical analyses

Statistical analysis title	Global evaluation comparison between seasons
Comparison groups	Placebo - Group 1 v Lais Grass - Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7184 [25]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.44

Notes:

[25] - The difference between the groups was 0.08 (95% CI - 0.28 to 0.44) and was not statistically significant.

Secondary: Excellence of rhinoconjunctivitis control during entire grass pollen season

End point title	Excellence of rhinoconjunctivitis control during entire grass pollen season

End point description:

Excellence of rhinoconjunctivitis control during the entire grass pollen season = more than 50% well days in the grass pollen season;

End point type	Secondary

End point timeframe:

Entire grass pollen season

End point values	Placebo - Group 1	Lais Grass - Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: %				
number (not applicable)	78.9	78.4		

Statistical analyses

Statistical analysis title	Excellence of rhinoconjunctivitis control
Comparison groups	Lais Grass - Group 2 v Placebo - Group 1

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9688 [26]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	1.26

Notes:

[26] - The difference between groups was -0.02% (95% CI, -1.31 to 1.26%) and was not statistically significant (p= 0.9688 between groups).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 to end of follow up (observation period between V1 and V5)

Adverse event reporting additional description:

The patient diary for the recording of the Adverse Events was dispensed to patients. All treatment emergent adverse events (TEAEs) were assigned to a Preferred Term (PT) and classified by primary System Organ Class (SOC) according to the MedDRA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Placebo - Group 1

Reporting group description:

groups of subjects to whom placebo was administered

Reporting group title	Lais Grass - Group 2

Reporting group description:

groups of subjects to whom Lais sublingual tablets (verum) was administered

Serious adverse events	Placebo - Group 1	Lais Grass - Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous	Additional description: Patient was a male subject aged 17 years . On 02 Mar 2000, the patient had preumothorax spontaneous, which was of moderate intensity and required hospitalization. Treatment with IMP was discontinued and the event resolved on 15 Mar 2000		
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
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: 0 %

Non-serious adverse events	Placebo - Group 1	Lais Grass - Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 47 (57.45%)	29 / 47 (61.70%)	
Vascular disorders			

Hypotension			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Premenstrual pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	9 / 47 (19.15%)	8 / 47 (17.02%)	
occurrences (all)	9	8	
Cough			
subjects affected / exposed	3 / 47 (6.38%)	5 / 47 (10.64%)	
occurrences (all)	3	5	
Sneezing			
subjects affected / exposed	1 / 47 (2.13%)	4 / 47 (8.51%)	
occurrences (all)	1	4	
Throat irritation			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			

subjects affected / exposed	1 / 47 (2.13%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Nasal inflammation			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Nasal discomfort			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Nasal obstruction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Asthma			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Apnoea			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Rhinorrhoea			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Influenza virus test negative			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Ligament sprain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Arthropod sting			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 47 (8.51%)	8 / 47 (17.02%)	
occurrences (all)	4	8	
Migraine without aura			
subjects affected / exposed	4 / 47 (8.51%)	3 / 47 (6.38%)	
occurrences (all)	4	3	
Paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Neurological symptom			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	5 / 47 (10.64%)	3 / 47 (6.38%)	
occurrences (all)	5	3	
Eyelid irritation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	

Eye pruritus			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 47 (6.38%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Oral pruritus			
subjects affected / exposed	2 / 47 (4.26%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Anal fissure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Urticaria			

subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Dermatitis contact			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 47 (2.13%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Neck pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 47 (8.51%)	4 / 47 (8.51%)	
occurrences (all)	4	4	
Conjunctivitis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Cystitis			

subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Bacterial rhinitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Acute sinusitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2019	The protocol initially submitted to the Italian Health Authority ('Agenzia Italiana del Farmaco', AIFA) was that named Version 1.3 of 23 April 2019. Then the IEC of the coordinating centre evaluated the study before AIFA and required changes and integrations that led to Protocol Version 1.4 of 12 July 2019, which was re-submitted to AIFA. Changes from Protocol Version 1.3 of 23 April 2019 to Version 1.4 of 12 July 2019 - Addition of information on the stepwise management of rescue medication; - Change of time of waiting for the next incremental dosage in case of a negative TNPT result; - Addition of specifications on the management of asthma exacerbations and on the management of treatments for asthma.
23 July 2019	AIFA examined Protocol Version 1.4 of 12 July 2019 and required further changes and integrations that led to Protocol Version 1.5 of 23 July 20219 Changes from Protocol Version 1.4 to Version 1.5 - Addition and specification of the secondary objective of the study; - Addition of phone contact control visits; - Addition of further specifications on the stepwise management of rescue medication; - Addition of a clarification on highly effective method of contraception as inclusion criterion; - Change from urine to serum pregnancy test at inclusion in the study; - Minor formal changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported