



Clinical trial results:

A single arm, open label, dose-escalation study of carbamylated monomeric grass pollen drops in patients with a history of allergic rhinoconjunctivitis

Summary

EudraCT number	2018-004472-35
Trial protocol	IT
Global end of trial date	18 June 2019

Results information

Result version number	v1 (current)
This version publication date	08 August 2021
First version publication date	08 August 2021

Trial information

Trial identification

Sponsor protocol code	DE_LODRO_GR19
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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, Milano, Italy,
Public contact	CRO, CD Pharma Srl, 039 0289051076, info@cdpharma.it
Scientific contact	CRO, CD Pharma Srl, 039 0289051076, info@cdpharma.it

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	27 July 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the safety and clinical tolerability of Lais® Graminacee sublingual drops in patients with grass pollen-induced allergic rhinoconjunctivitis.

Protection of trial subjects:

Measures in place:

Stopping rules:

Treatment with the IMP had to be stopped and patients had to be withdrawn from the study at any time for safety reasons. Criteria for the cessation of treatment and withdrawal of an individual patient by the investigator.

Dose adjustment:

A dose adjustment of the investigational product had to be performed for safety reasons.

Background therapy:

Rescue medication:

rhinoconjunctivitis symptoms: Desloratadine 5mg tablets.

For asthmatic patients, reliever medications were allowed including beta-2-agonists.

Evidence for comparator:

None

Actual start date of recruitment	01 March 2019
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	Italy: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in two Italian sites. The First patient was on the 25th of March 2019. Last patient out was on 18th June 2019.

Pre-assignment

Screening details:

Planned 30 patients female or male aged 18–64 years, with grass pollen-induced allergic rhinoconjunctivitis. 39 patients were enrolled in two Italian sites. 33 patients completed the study.

Period 1

Period 1 title	Escalation and Maintenance (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Lais Graminacee sublingual drops
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Arm description:

Dose escalation phase (day 1 to 21): The IMP doses was increased incrementally to reach the patient's individual maximum tolerable dosage. At V2, the treatment was initiated by an ultra-rush schedule with 2 doses of the IMP (2,000 UA and 5,000 UA) at 60-minute intervals in the investigator's office. From day 2 to 6, the single dose of 5,000 UA daily was be self-administered by the patient at home. At V3 (day 7), two doses were be administered (10,000 UA and 15,000 UA) at 60-minute intervals at the investigator's office. From day 8 to 13, the single dose of 15,000 UA daily was self-administered by the patient at home. At V4 (day 14), one dose of 25,000 UA was administered at the investigator's office. From day 15 to 20, the single dose of 25,000 UA day. From day 22 to day 42, a single maintenance dose of 50,000 UA daily was self-administered by the patient at home.

Arm type	Experimental
Investigational medicinal product name	Lais® grass sublingual drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal drops
Routes of administration	Sublingual use

Dosage and administration details:

During the dose escalation phase outside the peak grass pollen season, the doses will be increased incrementally to reach the patient's individual maximum tolerable dosage. A dose adjustment of the investigational product had to be performed for safety reasons in case of patient experiences a moderate local reaction. Concentration of Lais® Graminacee sublingual drops span from 2000 UA to 50000 UA.

Number of subjects in period 1	Lais Graminacee sublingual drops
Started	39
Completed	33
Not completed	6
Consent withdrawn by subject	3
Physician decision	2
logistics	1

Baseline characteristics

Reporting groups

Reporting group title	Escalation and Maintenance
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Reporting group description: -

Reporting group values	Escalation and Maintenance	Total	
Number of subjects	39	39	
Age categorical			
Adults between 18-64 years			
Units: Subjects			
Adults (18-64 years)	39	39	
Age continuous			
Units: years			
arithmetic mean	32.31		
standard deviation	± 11.10	-	
Gender categorical			
Units: Subjects			
Female	16	16	
Male	23	23	

Subject analysis sets

Subject analysis set title	Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety population includes all patients who received at least one dose of the study treatment.

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Intention-To-Treat (ITT) population includes all patients who receive at least one dose of study treatment and have completed at least one evaluation related to the primary outcome.

Subject analysis set title	PP
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Subject analysis set type	Per protocol
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Subject analysis set description:

Per Protocol (PP) population includes all evaluable patients in the ITT population who have reached their maximum tolerated dose of drug and concluded the treatment course excluding patients with major violations.

Subject analysis set title	Screening
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

all screened patients includes all patients who performed the study visit V1 (Screening).

Reporting group values	Safety	ITT	PP
Number of subjects	34	34	7
Age categorical			
Adults between 18-64 years			
Units: Subjects			
Adults (18-64 years)	34	34	7

Age continuous Units: years arithmetic mean standard deviation	32,47 ±	32,47 ±	30,28 ±
Gender categorical Units: Subjects			
Female	14	14	4
Male	20	20	3

Reporting group values	Screening		
Number of subjects	39		
Age categorical			
Adults between 18-64 years			
Units: Subjects			
Adults (18-64 years)	39		
Age continuous Units: years arithmetic mean standard deviation	32,31 ±		
Gender categorical Units: Subjects			
Female	16		
Male	23		

End points

End points reporting groups

Reporting group title	Lais Graminacee sublingual drops
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Reporting group description:

Dose escalation phase (day 1 to 21): The IMP doses was increased incrementally to reach the patient's individual maximum tolerable dosage. At V2, the treatment was initiated by an ultra-rush schedule with 2 doses of the IMP (2,000 UA and 5,000 UA) at 60-minute intervals in the investigator's office. From day 2 to 6, the single dose of 5,000 UA daily was be self-administered by the patient at home. At V3 (day 7), two doses were be administered (10,000 UA and 15,000 UA) at 60-minute intervals at the investigator's office. From day 8 to 13, the single dose of 15,000 UA daily was self-administered by the patient at home. At V4 (day 14), one dose of 25,000 UA was administered at the investigator's office. From day 15 to 20, the single dose of 25,000 UA day. From day 22 to day 42, a single maintenance dose of 50,000 UA daily was self-administered by the patient at home.

Subject analysis set title	Safety
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety population includes all patients who received at least one dose of the study treatment.

Subject analysis set title	ITT
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Intention-To-Treat (ITT) population includes all patients who receive at least one dose of study treatment and have completed at least one evaluation related to the primary outcome.

Subject analysis set title	PP
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Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

Per Protocol (PP) population includes all evaluable patients in the ITT population who have reached their maximum tolerated dose of drug and concluded the treatment course excluding patients with major violations.

Subject analysis set title	Screening
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

all screened patients includes all patients who performed the study visit V1 (Screening).

Primary: Safety

End point title	Safety ^[1]
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End point description:

The primary safety endpoint was the frequency of solicited adverse events. Twenty-eight patients (82.35%) showed no such AEs, four patients (11.76%) experienced solicited local AEs and 2 patients (5.88%) experienced systemic solicited AE. Eight unsolicited AEs were observed at home and reported by the patients, all of mild severity; one was related to the treatment (itching of oral mucosa), six possibly related (sleepiness, conjunctival hyperaemia, two sneezing, upper lip wheal, nasal obstruction), and one of unknown relationship (cough). Finally, one case of abdominal pain was classified as unknow. As in routine practice, the simple use of oral antihistamine seems sufficient to control the sporadic occurrence of local and systemic reactions during up dosing and maintenance phase.dose-range up to daily 50,000 UA of Lais® Graminacee sublingual drops in a suitable dose escalation scheme was generally safe and well-tolerated, thus acceptable for further investigations.

End point type	Primary
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End point timeframe:

from March 25th, 2019 to June 18th, 2019

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All data summaries and listings were performed using The SAS System version 9.4. No inferential statistics was used.

All qualitative descriptive analyses about frequency and percentage were performed by proc freq

statement.

All quantitative descriptive analyses report N, mean, median, standard deviation, min and max were performed by proc means statement.

End point values	Lais Graminacee sublingual drops	Safety		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	34	34		
Units: solicited AEs				
number (not applicable)				
Systemic AEs	2	2		
Local AEs	4	4		

Attachments (see zip file)	Delodro Appendix/DELODRO APPENDIX.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Safety and clinical Tollerability

End point title	Safety and clinical Tollerability
End point description:	
Safety and clinical tolerability were assessed along the whole subjects' treatment period by descriptive analysis:	
<ul style="list-style-type: none"> • Frequency of unsolicited (spontaneously reported during visits or by AE/CM diary card) adverse events • Proportion of patients who reached the maximum dose • Percentage/frequency of use of rescue medication during treatment phase • Physical examinations and vital signs • Laboratory tests (blood count, renal and liver function parameters) • Pulmonary function for asthmatic patients 	
End point type	Secondary
End point timeframe:	
from March 25th, 2019 to June 18th, 2019	

End point values	Lais Graminacee sublingual drops	ITT	PP	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	34	7	
Units: Number				
number (not applicable)	34	34	7	

Attachments (see zip file)	Delodro Appendix/DELODRO APPENDIX.pdf
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

March 25th, 2019 - June 18th, 2019

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Lais® Graminacee sublingual drops
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Reporting group description: -

Serious adverse events	Lais® Graminacee sublingual drops		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Lais® Graminacee sublingual drops		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 34 (38.24%)		
Nervous system disorders			
Sleepiness and tingling			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Eye disorders			
Conjunctival hyperaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Gastrointestinal disorders			

	Additional description: 2 AEs were solicited, 1 was unsolicited.		
<p>Itching of oral mucosa subjects affected / exposed occurrences (all)</p> <p>Mouth ulcer subjects affected / exposed occurrences (all)</p> <p>Abdominal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)</p>	<p>3 / 34 (8.82%) 3</p> <p>1 / 34 (2.94%) 1</p> <p>1 / 34 (2.94%) 1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)</p> <p>Sneezing burst alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)</p> <p>Sneezing alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)</p> <p>Nasal obstruction alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)</p>	<p>1 / 34 (2.94%) 1</p> <p>1 / 34 (2.94%) 1</p> <p>1 / 34 (2.94%) 1</p> <p>1 / 34 (2.94%) 1</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Itching of lips subjects affected / exposed occurrences (all)</p> <p>Upper lip wheal alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)</p>	<p>1 / 34 (2.94%) 1</p> <p>1 / 34 (2.94%) 1</p>		

Psychiatric disorders sleepiness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported