Clinical trial results:
Comparison of NAABAK® efficacy versus FLUCON® in the treatment of moderate manifestations of allergic conjunctivitis to birch pollen in subjects exposed to birch in ALYATEC's environmental exposure chamber (EEC)

Summary

EudraCT number	2017-001838-26
Trial protocol	FR
Global end of trial date	31 October 2017

Results information

Result version number	v1 (current)
This version publication date	04 July 2021
First version publication date	04 July 2021

Trial information

Trial identification

Sponsor protocol code	THEA-LT0455-PIV-09/16

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	THEA LABORATORY
Sponsor organisation address	12 Rue Louis Blériot, Clermont-Ferrand, France, 63000
Public contact	CORTEVAL François, THEA LABORATORY, francois.corteval@theapharma.com
Scientific contact	CORTEVAL François, THEA LABORATORY, francois.corteval@theapharma.com

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	21 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of NAABAK® compared to FLUCON®, assessed by the measure of the amount of major birch pollen allergen required to trigger a conjunctival response in subjects presenting moderate symptoms of allergic conjunctivitis caused by birch pollen.

Protection of trial subjects:

Adequate information was provided to the subject in both oral and written form and consent was obtained in writing prior to performance of any study specific procedure. The content and process of obtaining informed consent was in accordance with all applicable regulatory and IEC/IRB requirements.

Background therapy:

N/A

Evidence for comparator:

In this non-inferiority study, NAAGA (NAABAK®) was compared to FM (FLUCON®), which is the treatment of severe conjunctivitis, used for short periods and only when allergic conjunctivitis is not controlled under antihistamines and mast cells stabilizers treatment.

Actual start date of recruitment	06 September 2017
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	France: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment lasted two months, from September to October 2017.

Pre-assignment

Screening details:

A total of 31 patients were screened, 28 were included and underwent baseline exposures (expo 1 and expo 2), and 24 were randomized in one of the two sequence groups (expo 3, 4, 5, 6).
Three subjects were screen failures (Arterial hypertension not controlled, IgE<0.7 and ACT score <20).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

In this study, commercialized treatments were used in their own initial packaging so it was not possible to maintain blinding for subjects. However, the random attribution of treatments was done by the pharmacist and blinding was maintained only for the investigators in order to follow the "masked investigator" technique.

Arms

Are arms mutually exclusive?	No
Arm title	NAABAK®

Arm description:

Subjects were treated with N-acetyl aspartyl glutamic acid 4.9% (NAAGA) for 5 days in treatment period 1 or treatment period 2 in a counterbalanced order (cross-over). Treatment period 1 was followed by exposures 3 and 4, and treatment period 2 was followed by exposures 5 and 6. The washout between the 2 treatment periods lasted 14 days.

Arm type	Experimental
Investigational medicinal product name	N-acetyl aspartyl glutamic acid 4.9%
Investigational medicinal product code	NAAGA
Other name	NAABAK®
Pharmaceutical forms	Eye drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

Instillation 1 drop per eye, 3 times/day during 5 days

Arm title	FLUCON®

Arm description:

Subjects were treated with fluorometholone 0.1 % (FM) for 5 days in treatment period 1 or treatment period 2 in a counterbalanced order (cross-over).
Treatment period 1 was followed by exposures 3 and 4, and treatment period 2 was followed by exposures 5 and 6. The washout between the 2 treatment periods lasted 14 days.

Arm type	Active comparator
Investigational medicinal product name	Fluorometholone 0.1 % (FM)
Investigational medicinal product code	FM
Other name	FLUCON®
Pharmaceutical forms	Eye drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

Instillation 1 drop per eye, 3 times/day during 5 days

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: In this study, commercialized treatments were used in their own initial packaging so it was not possible to maintain blinding for subjects. However, the random attribution of treatments was done by the pharmacist and blinding was maintained only for the investigators in order to follow the "masked investigator" technique.

Number of subjects in period 1	NAABAK®	FLUCON®
Started	24	24
Completed	24	24

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	28.3		
standard deviation	± 7.38	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	12	12	

End points

End points reporting groups

Reporting group title	NAABAK®

Reporting group description:

Subjects were treated with N-acetyl aspartyl glutamic acid 4.9% (NAAGA) for 5 days in treatment period 1 or treatment period 2 in a counterbalanced order (cross-over). Treatment period 1 was followed by exposures 3 and 4, and treatment period 2 was followed by exposures 5 and 6. The washout between the 2 treatment periods lasted 14 days.

Reporting group title	FLUCON®

Reporting group description:

Subjects were treated with fluorometholone 0.1 % (FM) for 5 days in treatment period 1 or treatment period 2 in a counterbalanced order (cross-over).
Treatment period 1 was followed by exposures 3 and 4, and treatment period 2 was followed by exposures 5 and 6. The washout between the 2 treatment periods lasted 14 days.

Primary: Estimated mean quantity of allergen responsible of a positive conjunctival response

End point title	Estimated mean quantity of allergen responsible of a positive conjunctival response

End point description:

To study the efficacy of NAABAK® versus FLUCON®, by measuring the amount of birch pollen allergen required to induce a conjunctival response (Abelson score ≥ 5) in subjects with moderate allergic conjunctivitis related to birch pollen.

End point type	Primary

End point timeframe:

Exposures 3 and 5

End point values	NAABAK®	FLUCON®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[1]	24[2]		
Units: ng				
arithmetic mean (confidence interval 95%)	1.165 (0.958 to 1.416)	1.193 (0.981 to 1.450)		

Notes:

[1] - This was a crossover study where all subjects received NAAGA and FM in a counterbalanced order.

[2] - This was a crossover study where all subjects received NAAGA and FM in a counterbalanced order.

Statistical analyses

Statistical analysis title	Quantity of allergen

Statistical analysis description:

The primary efficacy criterion was the quantity of allergen responsible of a conjunctival response. The primary efficacy endpoint was log-transformed and analyzed in a linear mixed model for cross-over designs, i.e. adjusting for fixed effects (period, sequence, treatment) and the within sequence random patient effect.

Comparison groups	NAABAK® v FLUCON®

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	> 0.05
Method	Mixed models analysis
Parameter estimate	Hazard ratio (HR)
Point estimate	0.977
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.812
Variability estimate	Standard deviation

Notes:

[3] - The difference in least-squares means between treatment groups (NAAGA-FM) was estimated in this model along with the two-sided 95% confidence interval (95% CI). The back-transformed difference was expressed as the ratio of geometrical means (NAAGA/FM) and non-inferiority could be claimed if the lower bound of the two-sided 95% CI was above the non-inferiority margin of 0.5.

Secondary: Time to obtain a positive conjunctival response

End point title	Time to obtain a positive conjunctival response

End point description:

Time to conjunctival response was evaluated at baseline (expo 1) and with treatments (expo 3 and 5).

End point type	Secondary

End point timeframe:

Exposure 1, 3 and 5

End point values	NAABAK®	FLUCON®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Minutes				
arithmetic mean (standard deviation)	114.79 (± 54.95)	116.63 (± 51.52)		

Statistical analyses

Statistical analysis title	Time to obtain a conjunctival response

Statistical analysis description:

The secondary endpoint related to the time to conjunctival response was analyzed using a proportional hazard model adapted for cross-over studies.

Comparison groups	NAABAK® v FLUCON®
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	> 0.05
Method	Cox Model
Parameter estimate	Cox proportional hazard
Point estimate	2.191

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.927
upper limit	5.175
Variability estimate	Standard deviation

Notes:

[4] - Hazard ratio between the two groups (NAABAK®/FLUCON®) was estimated with a one-sided 95% CI. The upper bound of the hazard ratio was compared to the non-inferiority threshold which has been set at 2 (meaning that at any time, the risk of conjunctival response in the study group was not superior to two-fold the risk of the reference group). Median survival times predicted in the stratified Cox model and their 95% CI were also calculated.

Secondary: Abelson score after 24h and 48h of treatment

End point title	Abelson score after 24h and 48h of treatment

End point description:

These results are difficult to interpret because, by construction of the study, the subject left the chamber (and the Abelson score was no more measured) when the Abelson score was 5 or higher. The number of subjects present in the chamber decreased at each time point and the less sensible subjects were selected over time. The mean score are meaningless when the number of subjects is low.

End point type	Secondary

End point timeframe:

24h and 48h after treatments

End point values	NAABAK®	FLUCON®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: score				
number (not applicable)				
24h after treatment	1.38	1.21		
48h after treatment	2.29	2.42		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time written informed consent was obtained until the final study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	X

Reporting groups

Reporting group title	NAABAK®

Reporting group description:

Subjects were treated with NAAGA (NAABAK®) for 5 days in treatment period 1 or treatment period 2 in a counterbalanced order.

Reporting group title	FLUCON®

Reporting group description:

Subjects were treated with FM (FLUCON®) for 5 days in treatment period 1 or treatment period 2 in a counterbalanced order.

Serious adverse events	NAABAK®	FLUCON®	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	NAABAK®	FLUCON®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 24 (29.17%)	14 / 24 (58.33%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
General disorders and administration site conditions			

Abdominal pain upper			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 24 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Eye pruritus			
subjects affected / exposed	5 / 24 (20.83%)	7 / 24 (29.17%)	
occurrences (all)	6	7	
Ocular hyperaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Xerophthalmia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hordeolum			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	3	1	

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