



## 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,<br>francois.corteval@theapharma.com |
| Scientific contact           | CORTEVAL François, THEA LABORATORY,<br>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 <sup>[1]</sup>    |

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      |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

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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.

| <b>Number of subjects in period 1</b> | 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<br>(gestational age < 37 wks) |               | 0     |  |
| Newborns (0-27 days)                                  |               | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>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:<br>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).<br>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:<br>To study the efficacy of NAABAK® versus FLUCON®, by measuring the amount of birch pollen allergen required to induce a conjunctival response (Abelson score $\geq 5$ ) in subjects with moderate allergic conjunctivitis related to birch pollen. |   |
| End point type  | Primary   |
| End point timeframe:<br>Exposures 3 and 5   |   |

| End point values                          | NAABAK®                | FLUCON®                |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                        | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed               | 24 <sup>[1]</sup>      | 24 <sup>[2]</sup>      |  |  |
| 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:<br>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 <sup>[3]</sup> |
| 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

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | 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 <sup>[4]</sup>         |
| 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<br>subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |  |
| Eye disorders  |                      |                      |  |
| Eye irritation<br>subjects affected / exposed<br>occurrences (all)       | 0 / 24 (0.00%)<br>0  | 3 / 24 (12.50%)<br>3 |  |
| Eye pruritus<br>subjects affected / exposed<br>occurrences (all)         | 5 / 24 (20.83%)<br>6 | 7 / 24 (29.17%)<br>7 |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)    | 1 / 24 (4.17%)<br>2  | 0 / 24 (0.00%)<br>0  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)       | 0 / 24 (0.00%)<br>0  | 2 / 24 (8.33%)<br>2  |  |
| Xerophthalmia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 24 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |  |
| Respiratory, thoracic and mediastinal disorders                          |                      |                      |  |
| Asthma<br>subjects affected / exposed<br>occurrences (all)               | 0 / 24 (0.00%)<br>0  | 1 / 24 (4.17%)<br>1  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 0 / 24 (0.00%)<br>0  | 1 / 24 (4.17%)<br>2  |  |
| Infections and infestations  |                      |                      |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)       | 2 / 24 (8.33%)<br>2  | 0 / 24 (0.00%)<br>0  |  |
| Hordeolum<br>subjects affected / exposed<br>occurrences (all)            | 2 / 24 (8.33%)<br>3  | 1 / 24 (4.17%)<br>1  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported