# EU Clinical Trials Register

## Clinical trial results:
## A Multicentre, International, Adaptive, Open-label, Repeated Administration Pharmacokinetic Study of Bilastine in Children from 2 to <12 Years of age with Allergic Rhinoconjunctivitis or Chronic Urticaria

### Summary

| | |
|---|---|
| EudraCT number | 2009-012013-22 |
| Trial protocol | DE ES SE |
| Global end of trial date | 12 June 2012 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 01 July 2022 |
| First version publication date | 01 July 2022 |

### Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BILA-3009/PED |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01081574 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | ClinicalTrials.gov identifier: NCT01081574 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | FAES FARMA S.A. |
| Sponsor organisation address | Avda Autonomía, 10, Leioa, Spain, |
| Public contact | Cristina Campo, FAES FARMA S.A., +34 94 481 83 00 , ccampo@faes.es |
| Scientific contact | Cristina Campo, FAES FARMA S.A., +34 94 481 83 00 , ccampo@faes.es |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000347-PIP01-08 |
| 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 | 10 March 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 June 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 June 2012 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to assess the pharmacokinetics of bilastine in children (aged 2 to <12 years) with allergic rhinoconjunctivitis (seasonal allergic rhinitis and/or perennial allergic rhinitis [SAR/PAR]) or chronic urticaria (CU) in order to ascertain whether the proposed dose (10 mg/day or lower) matches the systemic exposure seen in adults with the 20 mg/day dose.

Protection of trial subjects:

- Only children with symptomatic AR or chronic urticaria were enrolled in this study, thus avoiding unnecessary dosing of healthy children not in need of any medication
-To minimise the potential risk of overexposure to bilastine for younger children (2 to <6 years), the study design, includes an ongoing implementation of the PK/PD model with pharmacokinetic data obtained from children 6 to <12 years old, to allow to choose an adequate bilastine dose to be administered to younger children (2 to <6 years) before enrolling this group of children in this study. This model also reduces any risk or discomfort associated with blood sampling, to be drawn from children to a minimum. In addition, appropriate safety monitoring of patients enrolled in the study is conducted throughout the treatment period.
- Given the lower incidence of somnolence due to bilastine compared to cetirizine and levocetirizine, bilastine is expected to show some advantages for the children enrolled in the study, in terms of side effects such as somnolence/drowsiness which represent a common concern for this class of drugs particularly in children where it can negatively affect their school performance and social life.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 15 April 2010 |
| 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 | Sweden: 10 |
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Australia: 2 |
| Worldwide total number of subjects | 31 |
| EEA total number of subjects | 29 |

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) | 31 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details:

41 patients were screened  in 8 sites: Australia (2), Germany (3), Sweden (2)  and Spain (1). 31 patients were recruited and randomized: 24 in Group A (6-12 years) and 7 in Group B (2-6 years) between April 15, 2010 - June 12, 2012. These 31 patients completed the study.

## Pre-assignment

Screening details:

An adaptive design was followed to minimize testing in children and achieve adequate characterization of the PK model.
Study recruitment was terminated early based on the results of the second interim analysis, in accordance with pre-specified rules in the protocol, only 31 subjects were included (instead of the initially planned 44 subjects).

## Period 1

| Period 1 title | Overall trial (overall period) |
|---|---|
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| Are arms mutually exclusive? | No |
|---|---|
| **Arm title** | Final analysis children group |

Arm description:

31 children from groups A (6 to < 12 years ol) and B (2 to 6 years old) treated with Bilastine 10 mg orodispersible tablet, once daily for 7 days.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Bilastine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Orodispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Bilastine 10 mg once daily, administered orally, for 7 days

| **Arm title** | Group A (children 6 to < 12 years) |
|---|---|

Arm description: -

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Bilastine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Orodispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Bilastine 10 mg once daily, administered orally, for 7 days

| **Arm title** | Group B (Children 2 to 6 years) |
|---|---|

Arm description: -

| Arm type | Experimental |
|---|---|

| Investigational medicinal product name | Bilastine |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Orodispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Bilastine 10 mg once daily, administered orally, for 7 days

| **Number of subjects in period 1** | Final analysis children group | Group A (children 6 to < 12 years) | Group B (Children 2 to 6 years) |
|---|---|---|---|
| Started | 31 | 25 | 9 |
| Completed | 31 | 25 | 9 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial |
|---|---|

Reporting group description:

All children in this study received bilastine 10 mg orodispersible tablet, once daily for 7 days, administered orally under fasting conditions. The blood-sampling was performed after 7 days.

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 31 | 31 | |
| Age categorical | | | |
| Group A: 6 to <12 years, subgroups A1 (6-8 years), A2 (8-10 years), A3 (10- <12 years) Group B: 2 to < 6 years | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 31 | 31 | |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 11 | |
| Male | 20 | 20 | |

### Subject analysis sets

| Subject analysis set title | First Interim analysis set |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

Pharmacokinetic analysis of 16 subjects from group A (6 to 12 years old) treated with bilastine 10 mg

| Subject analysis set title | Second Interim analysis set |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

9 children (6 from group A + 3 from group B) + 16 chidren from the first interim analysis

| Subject analysis set title | Final model analysis |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

Total group of 31 children from 4 to <12 years: Groups A (25 children from 6 to < 12 years) + Group B (7 children from 4 to 5 years).
For the final model 2 outliers subjects were removed from the analysis.

| Reporting group values | First Interim analysis set | Second Interim analysis set | Final model analysis |
|---|---|---|---|
| Number of subjects | 16 | 25 | 31 |
| Age categorical | | | |
| Group A: 6 to <12 years, subgroups A1 (6-8 years), A2 (8-10 years), A3 (10- <12 years) Group B: 2 to < 6 years | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 16 | 25 | 29 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | | |
| Male | | | |

## End points

### End points reporting groups

| Reporting group title | Final analysis children group |
|---|---|
| Reporting group description: | |
| 31 children from groups A (6 to < 12 years ol) and B (2 to 6 years old) treated with Bilastine 10 mg orodispersible tablet, once daily for 7 days. | |
| Reporting group title | Group A (children 6 to < 12 years) |
| Reporting group description: - | |
| Reporting group title | Group B (Children 2 to 6 years) |
| Reporting group description: - | |
| Subject analysis set title | First Interim analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Pharmacokinetic analysis of 16 subjects from group A (6 to 12 years old) treated with bilastine 10 mg | |
| Subject analysis set title | Second Interim analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| 9 children (6 from group A + 3 from group B) + 16 chidren from the first interim analysis | |
| Subject analysis set title | Final model analysis |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Total group of 31 children from 4 to <12 years: Groups A (25 children from 6 to < 12 years) + Group B (7 children from 4 to 5 years).<br>For the final model 2 outliers subjects were removed from the analysis. | |

### Primary: Maximum plasma concentration (Cmax)

| End point title | Maximum plasma concentration (Cmax) |
|---|---|
| End point description: | |
| Pharmacokinetics (PK) of bilastine in children (aged 2 to <12 years) with allergic rhinoconjunctivitis (AR) (seasonal allergic rhinitis [SAR] and/or perennial allergic rhinitis [PAR]) or chronic urticaria in order to ascertain that the systemic exposure attained with a dose of 10 mg every day or lower is comparable to that achieved in adults and adolescents administered with a dose of 20 mg/every day. | |
| End point type | Primary |
| End point timeframe: | |
| Group A, prior to dose administration, and at 0.25, 0.5, 0.8, 1.0, 1.2, 1.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours<br>Group B, prior to dose administration, and at0.25, 0.5, 1.0, 1.5, 3.0, 6.0, 8.0, 10.0, and 12.0 hours | |

| End point values | First Interim analysis set | Second Interim analysis set | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 16 | 25 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 241 (± 109) | 347 (± 109) | | |

## Statistical analyses

| Statistical analysis title | Nonlinear mixed-effects modelling (NONMEM) |
|---|---|

Statistical analysis description:

Pharmacokinetic analysis was performed. The paediatric PK dataset of N=31 (Group A and Group B) was analysed by nonlinear mixed-effects modelling methods as implemented in NONMEM® VI (GloboMax LLC, Hanover, MD, USA) (FOCE method). Data exploration, statistical testing external to NONMEM and graphics were performed using S-PLUS version 8 (Insightful Corp, Seattle, WA).

| Comparison groups | First Interim analysis set v Second Interim analysis set |
|---|---|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | < 0.05 |
| Method | Mixed models analysis |

Notes:

[1] - Pharmacokinetic characterization of the IMP in a population of children

## Secondary: Safety and tolerability

| End point title | Safety and tolerability |
|---|---|

End point description:

Describe the safety and tolerability of a repeated administration of bilastine in the aforementioned paediatric subset with allergic rhinoconjunctivitis (SAR/PAR) or chronic urticaria in terms of the number of subjects who presented Adverse Events during the study

| End point type | Secondary |
|---|---|

End point timeframe:

Period from the signature of the Informed Consent to the end of the study

| End point values | Final analysis children group | Group A (children 6 to < 12 years) | Group B (Children 2 to 6 years) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31[2] | 25[3] | 9[4] | |
| Units: number | 15 | 12 | 3 | |

Notes:

[2] - 31 children (total safety population)

[3] - Group A (Children 6 to < 12 y)

[4] - Group B (2 to 6 y)

## Statistical analyses

| Statistical analysis title | S-plus software |
|---|---|

Statistical analysis description:

S-plus software. Descriptive analysis

| Comparison groups | Group A (children 6 to < 12 years) v Group B (Children 2 to 6 years) |
|---|---|

| Number of subjects included in analysis | 34 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.05 [5] |
| Method | Mixed models analysis |
| Parameter estimate | indiviual Bayes parameters |
| Confidence interval | |
| level | 95 % |
| Variability estimate | Standard deviation |

Notes:

[5] - P < 0.05 indicates statistical significance between two values

## Other pre-specified: Pharmacokinetic final model - Absorption constant

| End point title | Pharmacokinetic final model - Absorption constant |
|---|---|

End point description:

This parameter was estimated in 29 pediatric patients. Two patients from Group A3 (10-11 years) were eliminated due to atypical statistical behavior (outliers), probably due to protocol deviations.
The absorption constant (Ka) is measured in h -1, we present the estimated value and the standard error of the estimate as a percentage (%)

| End point type | Other pre-specified |
|---|---|

End point timeframe:

After collecting blood-samples from 31 children included in the study (from Groups A + B).

| **End point values** | First Interim analysis set | Second Interim analysis set | Final model analysis | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 16[6] | 25 | 29 | |
| Units: h -1 | | | | |
| arithmetic mean (standard error) | 1.28 (± 0.000) | 1.49 (± 0.214) | 1.29 (± 0.286) | |

Notes:

[6] - Group A 6-12 years

| **Attachments (see zip file)** | Population pK parameter estimates/EudraCT |
|---|---|

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Pharmacokinetic final model - Clearance

| End point title | Pharmacokinetic final model - Clearance |
|---|---|

End point description:

This parameter was estimated in 29 pediatric patients. Two patients from Group A3 (10-11 years) were eliminated due to atypical statistical behavior (outliers).
The Clearance (Cl/F) is measured in L/h, we present the estimated value and the standard error of the estimate as a percentage (%)

| End point type | Other pre-specified |
|---|---|

End point timeframe:

After collecting blood-samples from 31 children included in the study (from Groups A + B).

| End point values | First Interim analysis set | Second Interim analysis set | Final model analysis | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 16 | 25 | 29 | |
| Units: L/h | | | | |
| arithmetic mean (standard error) | 13.2 (± 1.20) | 13.8 (± 1.23) | 12.5 (± 0.74) | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Pharmacokinetic final model - Volume of distribution (Vd/F)

| End point title | Pharmacokinetic final model - Volume of distribution (Vd/F) |
|---|---|

End point description:

This parameter was estimated in 29 pediatric patients. Two patients from Group A3 (10-11 years) were eliminated due to atypical statistical behavior (outliers).
The Volume of distribution (Vd/F) is measured in L, we present the estimate and the standard error of the estimate as a percentage (%)

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At the end of the sutdy, after collecting blood-samples from 31 children included in the study (from Groups A + B).

| End point values | First Interim analysis set | Second Interim analysis set | Final model analysis | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 16 | 25 | 29 | |
| Units: L | | | | |
| arithmetic mean (standard error) | 19.0 (± 4.34) | 24.6 (± 3.78) | 19.7 (± 2.53) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From informed consent signature till end of trial

Adverse event reporting additional description:

Safety statistical analyses were performed by inVentiv Health Clinical, (formerly PharmaNet/i3, company name change in US only). A safety population was included with all participant children who received at least 1 dose of protocol treatment. The Medical Dictionary for Regulatory Activities (MedDRA), Version 13.0, was used

| Assessment type | Systematic |
|---|---|

### Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 13.0 |

### Reporting groups

| Reporting group title | Safety population (Group A + B) |
|---|---|

Reporting group description:

No deaths, SAEs, severe events, or discontinuations due to AEs were reported.

| Serious adverse events | Safety population (Group A + B) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Safety population (Group A + B) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 31 (48.39%) | | |
| Investigations | | | |
| Blood glucose descreased | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Nervous system disorders | | | |
| Headache | Additional description: 5 children from Group A and 1 kid from group B | | |
| subjects affected / exposed | 6 / 31 (19.35%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 4 | | |
| | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|------|-----------|
| 15 December 2009 | made the following changes based on the request from EC/CA involved in the study protocol evaluation: One inclusion and one exclusion criterion amended for clarification, and 2 exclusion criteria added to exclude mentally disabled minors or those minors who explicitly refuse to take part in the study. In the withdrawal of subjects section, respect of minor's volition was added for emphasis and clarity. Information regarding withdrawing subjects based on abnormal lab results or ECG change from baseline of greater than 30 msec was added to provide the investigator with clear instructions to protect the safety of the subject.<br>A few general changes were made apart from EC/CA request including the deletion of carbon dioxide test in the blood chemistry panel, as this parameter is not required, minor changes in the shipping of sampling information, and a note added to the pharmacokinetic sampling tables for Groups A and B for clarity. |
| 10 November 2010 | changed the inclusion criterion #2 from a majority range of the 25th through 75th percentile to the 10th to 90th percentile. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

 None reported