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