Clinical trial results:
Effects of Bilastine on F1 Simulator driving performance in patients affected by allergic rhinitis and/or urticaria

Summary

EudraCT number	2015-001313-26
Trial protocol	IT
Global end of trial date	21 December 2015

Results information

Result version number	v1 (current)
This version publication date	22 February 2017
First version publication date	22 February 2017

Trial information

Trial identification

Sponsor protocol code	MEIN/14/Bil-ARU/001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576041
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini International Operations Luxembourg SA
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg,
Public contact	Medical Director, Medical Scientific Management, Menarini International Operations Luxembourg S.A., +352264976, +352 264976,
Scientific contact	Clinical Operation Manager, Menarini Corporate Medical Department, A. Menarini Industrie Farmaceutiche Riunite, +3905556801, +39 05556801,

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 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2015
Global end of trial reached?	Yes
Global end of trial date	21 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the attention level (wakefulness) by assessing the patients' driving performance (driving ability in stress condition) using the F1 high-speed simulator, following treatment with Bilastine;
- To assess the reactivity level by assessing the patients' psychomotor reactivity during the driving performance test (using the F1-high speed simulator), following treatment with Bilastine.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2015
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: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	18
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment details: Total recruitment period (first patient in to last patient in): 26.10.2015 - 24.11.2015

Pre-assignment

Screening details:

Screening was performed in 2 separate sections, at hospital site (H) and at the simulator (S) centre, divided by 14 days maximum. A total of 19 patients were screened and only one failed screening and was not randomized.

Pre-assignment period milestones

Number of subjects started	19[1]
Number of subjects completed	18

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignement period is the screening period. 19 patients were enrolled and one patient was excluded after the screening visit to evaluate the ability to complete the test without discomfort (V1-S), as the patient did not tollerate to use the simulator.

Period 1

Period 1 title	Placebo (wash-out)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single Arm

Arm description:

This is a single arm design study, with 18 patients enrolled to a Placebo wash out period (7+3 days) followed by a Bilastine active treatment period (7+3 days).

Arm type	Single arm placebo/active treatment
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the wash out period (V0-V1) Placebo was administerd at the dose of one tablet once daily. The tablets should have been administered in the morning at empty stomach at least one hour before breakfast or two hours after intake of food or fruit juice. It was recommended to take the daily dose in one single intake

Investigational medicinal product name	Bilastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the active treatment period (following wash out) Bilastine was administerd at the dose of one

tablet once daily. The tablets should have been administered in the morning at empty stomach at least one hour before breakfast or two hours after intake of food or fruit juice. It was recommended to take the daily dose in one single intake.
At the day of Visit V2S (visit at the simulator centre), bilastine should have been taken approximatively 1 and 1/2 hours before the driving test.

Number of subjects in period 1	Single Arm
Started	18
Completed	18

Period 2

Period 2 title	Bilastine (Active Treatment)
Is this the baseline period?	Yes[2]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single Arm

Arm description:

This is a single arm design study, with 18 patients enrolled to a Placebo wash out period (7+3 days) followed by a Bilastine active treatment period (7+3 days).

Arm type	Single arm placebo/active treatment
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the wash out period (V0-V1) Placebo was administerd at the dose of one tablet once daily. The tablets should have been administered in the morning at empty stomach at least one hour before breakfast or two hours after intake of food or fruit juice. It was recommended to take the daily dose in one single intake

Investigational medicinal product name	Bilastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the active treatment period (following wash out) Bilastine was administerd at the dose of one tablet once daily. The tablets should have been administered in the morning at empty stomach at least one hour before breakfast or two hours after intake of food or fruit juice. It was recommended to take the daily dose in one single intake.
At the day of Visit V2S (visit at the simulator centre), bilastine should have been taken approximatively

1 and 1/2 hours before the driving test.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the wash-out period were patient have taken placebo and not the baseline period with active treatment with Bilastine.

Number of subjects in period 2	Single Arm
Started	18
Completed	18

Baseline characteristics

Reporting groups

Reporting group title	Bilastine (Active Treatment)

Reporting group description:

18 patients who performed a F1-high speed-driving-simulation test before (V1) and after a 7 (+3) days of Bilastine treatment (V2).

Reporting group values	Bilastine (Active Treatment)	Total	
Number of subjects	18	18	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	0	0	
85 years and over	0	0	
Adults	0	0	
Age continuous			
Units: years			
arithmetic mean	38.4		
standard deviation	± 7.3	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	10	10	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subject who received at least one dose of placebo

Subject analysis set title	Safety Population (SP)
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of the study drug Bilastine

Subject analysis set title	Intention to Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all subjects who received at least one dose of the study drug Bilastine and who completed all the study procedures

Subject analysis set title	Per Protocol Population (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from the ITT population who did not present any major protocol violation

Reporting group values	Full Analysis Set (FAS)	Safety Population (SP)	Intention to Treat (ITT)
Number of subjects	18	18	18
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	18	18	18
From 65-84 years			
85 years and over			
Adults			
Age continuous			
Units: years			
arithmetic mean	38.4	38.4	38.4
standard deviation	± 7.3	± 7.3	± 7.3
Gender categorical			
Units: Subjects			
Female	8	8	8
Male	10	10	10

Reporting group values	Per Protocol Population (PP)		
Number of subjects	18		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	18		
From 65-84 years			
85 years and over			
Adults			
Age continuous			
Units: years			
arithmetic mean	38.4		
standard deviation	± 7.3		

Gender categorical Units: Subjects			
Female	8		
Male	10		

End points

End points reporting groups

Reporting group title	Single Arm

Reporting group description:

This is a single arm design study, with 18 patients enrolled to a Placebo wash out period (7+3 days) followed by a Bilastine active treatment period (7+3 days).

Reporting group title	Single Arm

Reporting group description:

This is a single arm design study, with 18 patients enrolled to a Placebo wash out period (7+3 days) followed by a Bilastine active treatment period (7+3 days).

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subject who received at least one dose of placebo

Subject analysis set title	Safety Population (SP)
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of the study drug Bilastine

Subject analysis set title	Intention to Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

all subjects who received at least one dose of the study drug Bilastine and who completed all the study procedures

Subject analysis set title	Per Protocol Population (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from the ITT population who did not present any major protocol violation

Primary: Standard deviation Lateral Position (SDLP)

End point title	Standard deviation Lateral Position (SDLP)

End point description:

SDLP (mainly assessing attention capacities) is a measure of weaving and quality in keeping the requested path. The vehicle position was constantly monitored. The deviation from central position was registered.

End point type	Primary

End point timeframe:

7+3 days of active treatment (Bilastine)

End point values	Single Arm	Single Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: meters				
arithmetic mean (standard deviation)	0.15 (± 0.07)	0.11 (± 0.04)		

Statistical analyses

Statistical analysis title	SDLP statistical analysis

Statistical analysis description:

The t-test for paired data was used to evaluate the differences of performances between the wash-out period of 7(+3) days with placebo intake (V1-S) and the active treatment period of 7(+3) days with Bilastine 20 mg intake (V2S) for every efficacy endpoints.

Comparison groups	Single Arm v Single Arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.002
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.064
upper limit	-0.017
Variability estimate	Standard deviation
Dispersion value	0.047

Notes:

[1] - If the assumption on data collected needed to use a paired t-test were not meet, the correspondent non-parametric test (Wilcoxon's test) was applied.

Secondary: Maintenance of costant speed

End point title	Maintenance of costant speed

End point description:

Different speed were maintained as requested by the simulator. Variations during the test were recorded. The mean deviation from the requested speed was registered.

End point type	Secondary

End point timeframe:

7+3 days of active treatment

End point values	Single Arm	Single Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: Km/h				
arithmetic mean (standard deviation)	5.26 (± 3.36)	3.87 (± 2.03)		

Statistical analyses

Statistical analysis title	Maintenance of constant speed statistical analysis

Statistical analysis description:

The t-test for paired data was used to evaluate the differences of performances between the wash-out period of 7(+3) days with placebo intake (V1-S) and the active treatment period of 7(+3) days with Bilastine 20 mg intake (V2S) for every efficacy endpoints.

Comparison groups	Single Arm v Single Arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.0639
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.397
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.884
upper limit	0.09
Variability estimate	Standard deviation
Dispersion value	2.991

Notes:

[2] - If the assumption on data collected needed to use a paired t-test were not meet, the correspondent non-parametric test (Wilcoxon's test) was applied.

Secondary: Time to reaction

End point title	Time to reaction

End point description:

During the test, at different times, the patient was requested (by led enlighten on the dashboard) to execute actions on the steering-wheel. The delay in executing the requested actions was registered.

End point type	Secondary

End point timeframe:

7+3 days of active treatment (Bilastine)

End point values	Single Arm	Single Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: msec				
arithmetic mean (standard deviation)				
Time reaction to Button A	695 (± 120)	660 (± 167)		
Time reaction to button B	662 (± 144)	644 (± 105)		

Statistical analyses

Statistical analysis title	Time reaction to Button A statistical analysis

Statistical analysis description:

The t-test for paired data was used to evaluate the differences of performances between the wash-out period of 7(+3) days with placebo intake (V1-S) and the active treatment period of 7(+3) days with Bilastine 20 mg intake (V2S) for every efficacy endpoints.

Comparison groups	Single Arm v Single Arm

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.1446
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.1
upper limit	13.1
Variability estimate	Standard deviation
Dispersion value	95.71

Notes:

[3] - If the assumption on data collected needed to use paired t-test were not meet, the correspondent non parametric test (Wilcoxon's test) was applied.

Statistical analysis title	Time reaction to Button B statistical analysys

Statistical analysis description:

The t-test for paired data was used to evaluate the differences of performances between the wash-out period of 7(+3) days with placebo intake (V1-S) and the active treatment period of 7(+3) days with Bilastine 20 mg intake (V2S) for every efficacy endpoints.

Comparison groups	Single Arm v Single Arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.259
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-18.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.21
upper limit	14.72
Variability estimate	Standard deviation
Dispersion value	66.28

Notes:

[4] - If the assumption on data collected needed to use paired t-test were not meet, the correspondent non parametric test (Wilcoxon's test) was applied.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are recorded at each visit from screening visit V-1 (-21 days) to visit 2 at the end of the study active treatment period (15+3 days).

Adverse event reporting additional description:

At each visit the Investigator assessed any occurring subjective or objective AE. Adverse events communicated by the patient or by the patients relatives or delegates through phone calls, letters or emails were also recorded

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Overall trial

Reporting group description:

is the only arm, placebo and then bilastine

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (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	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
Investigations			
Laboratory test abnormal			
subjects affected / exposed	16 / 18 (88.89%)		
occurrences (all)	16		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood alkaline phosphatase			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Blood chloride decreased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Blood potassium decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Eosinophil count decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Globulins decreased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Haemoglobin urine present			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Laboratory test			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
pH urine decreased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Specific gravity urine abnormal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2015	This Protocol Amendment was implemented to add changes requested by Italian Medicines Agency (AIFA) and Ethic Committees. Main change was to leave as the only Primary End-Point the "Standard Deviation Lateral Position - SDLP" and to move to Secondary End-Point the "Maintainance of costant speed". Other changes made were : * Introduction of a more detailed rational of using the driving simulator in patients or in healthy volunteers to asses the effects of the pharmacological treatments and to justify why and how it has been used in this clinical trial. *Implementation of the justification of sample size of 18 patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Note that due to technical limits in the portal the statistical analysis reports 36 patients included in the analysis and not 18 as they effectively are.
36 are indeed the 18 data collected before and the 18 after active treatment intake.

Notes: