Clinical trial results:
Double blind, double dummy, placebo controlled, randomized study to compare efficacy of Formoterol (Foradil®) Aerolizer® and Ipratropium Bromide plus Fenoterol (Berodual®) nebulized, in 5 to 12 year old asthmatic patients being treated in emergency rooms with symptoms of bronchial obstruction

Summary

EudraCT number	2015-004464-11
Trial protocol	Outside EU/EEA
Global end of trial date	23 September 2008

Results information

Result version number	v1 (current)
This version publication date	18 November 2016
First version publication date	18 November 2016

Trial information

Trial identification

Sponsor protocol code	CFOR258DVE02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH 4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Study Director, Novartis Pharma AG, 41 613241111,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of two treatment modalities: Fenoterol 0.5 mg plus Ipratropium Bromide, Berodual® (Boeringher Ingelheim Laboratories) nebulized versus Formoterol, Foradil® administered through Aerolizer®, using clinical parameters, Maximum Espiratory Flow or Peek Flow and the One second Forced Espiratory Flow, in pediatric patients being treated in Emergency rooms with bronchial obstruction symptoms

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2007
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	Venezuela, Bolivarian Republic of: 60
Worldwide total number of subjects	60
EEA total number of subjects	0

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)	55
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a multicenter, double-blind, double-dummy, placebo-controlled of parallel groups study of 4 hour duration, assessing and comparing efficacy and tolerability of two treatment schemes in pediatric asthmatic patients being treated in the Emergency room with acute asthma.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Formoterol (Foradil®)

Arm description:

Formoterol (Foradil®) 12 micrograms administered through Aerolizer®.

Arm type	Experimental
Investigational medicinal product name	formoterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

formoterol 12 mcg dry powder capsules inhaled via Aerolizer® after measuring inspiratory flow with specific Aerolizer® resistance.

Arm title	Fenoterol 0.5 mg + Berodual®

Arm description:

Fenoterol 0.5 mg + Ipratropium Bromide (Berodual®) 0.25 mg 20 drops in 3 mL of saline solution nebulized.

Arm type	Active comparator
Investigational medicinal product name	Fenoterol 0.5 mg + Berodual®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

fenoterol, 0.5 mg + Ipratropium Bromide, 0.25 mg delivered by nebulizer;

Number of subjects in period 1	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®
Started	30	30
Completed	28	24
Not completed	2	6
Protocol deviation	2	6

Baseline characteristics

Reporting groups	
Reporting group title	Formoterol (Foradil®)
Reporting group description:	
Formoterol (Foradil®) 12 micrograms administered through Aerolizer®.	
Reporting group title	Fenoterol 0.5 mg + Berodual®
Reporting group description:	
Fenoterol 0.5 mg + Ipratropium Bromide (Berodual®) 0.25 mg 20 drops in 3 mL of saline solution nebulized.	

Reporting group values	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®	Total
Number of subjects	30	30	60
Age Categorical Units: Subjects			
<=18 years	30	30	60
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	7.8	7.8	
standard deviation	± 1.5	± 2.1	-
Gender, Male/Female Units: Subjects			
Female	12	11	23
Male	18	19	37
Study Specific Characteristic | Maximum Inspiratory Flow			
Mean of the Maximum Inspiratory Flow			
Units: Liters/minute			
arithmetic mean	77.7	79.9	
standard deviation	± 16.7	± 17.5	-
Study Specific Characteristic | Maximum Expiratory Flow			
Mean of Maximum Expiratory Flow			
Units: Liters/minute			
arithmetic mean	140.3	150.3	
standard deviation	± 33.1	± 36.6	-
Study Specific Characteristic | Forced Expiratory Flow 1 sec			
Mean of Forced Expiratory Flow one second (FEV1) defined as the volume of air that can be forced out in 1 second after taking a deep breath.			
Units: Liters			
arithmetic mean	1.06	1.12	
standard deviation	± 0.28	± 0.289	-
Study Specific Characteristic | Forced Expiratory Flow 1 sec as a Percentage of Predicted			
Mean Expiratory Flow 1 second as a Percentage of Predicted			
Units: Percentage of Predicted			
arithmetic mean	67.05	71.17	

standard deviation	± 15.22	± 15.76	-
Study Specific Characteristic | Conway Clinical Scale			
Mean of Clinical Scale score measured by assessment of the following: Wheezing, Accessory Muscle Use and Pulse Frequency in a 0 to 3 point scale according to severity for a minimum of 0 points and a total of 9 points in a very severe clinical case.			
Units: score on a scale			
arithmetic mean	4.1	4	
standard deviation	± 1.4	± 1.5	-

End points

End points reporting groups

Reporting group title	Formoterol (Foradil®)
Reporting group description:	
Formoterol (Foradil®) 12 micrograms administered through Aerolizer®.	
Reporting group title	Fenoterol 0.5 mg + Berodual®
Reporting group description:	
Fenoterol 0.5 mg + Ipratropium Bromide (Berodual®) 0.25 mg 20 drops in 3 mL of saline solution nebulized.	

Primary: Mean Change in Maximum Expiratory Flow from Baseline to Final Evaluation

End point title	Mean Change in Maximum Expiratory Flow from Baseline to Final Evaluation
End point description:	
Mean Change from Baseline to Final Evaluation in the Per Protocol population assessed by Maximum Expiratory Flow.	
End point type	Primary
End point timeframe:	
Baseline,4 hours	

End point values	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: Liters/minute				
arithmetic mean (standard deviation)	44 (± 26.87)	43.67 (± 20.48)		

Statistical analyses

Statistical analysis title	MEF
Comparison groups	Formoterol (Foradil®) v Fenoterol 0.5 mg + Berodual®
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.673
Method	Wilcoxon (Mann-Whitney)

Primary: Mean Change in Forced Expiratory Volume in 1 second (FEV1) from baseline to Final Evaluation

End point title	Mean Change in Forced Expiratory Volume in 1 second (FEV1) from baseline to Final Evaluation

End point description:

Mean Change from Baseline to Final Evaluation in the Per Protocol population assessed by Forced Expiratory Volume in 1 second. FEV1 is defined as the volume of air that can be forced out of the lungs in 1 second after taking a deep breath.

End point type	Primary

End point timeframe:

Baseline,4 hours

End point values	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: Liters				
arithmetic mean (standard deviation)	0.32 (± 0.2)	0.34 (± 0.22)		

Statistical analyses

Statistical analysis title	FEV1
Comparison groups	Formoterol (Foradil®) v Fenoterol 0.5 mg + Berodual®
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.89
Method	Wilcoxon (Mann-Whitney)

Primary: Mean Change in Pulse Oxymetry from Baseline to Final Evaluation

End point title	Mean Change in Pulse Oxymetry from Baseline to Final Evaluation

End point description:

Mean Change from Baseline to Final Evaluation in the Per Protocol population assessed by Pulse Oximetry used to monitor the percentage of oxygen saturation of hemoglobin in the blood.

End point type	Primary

End point timeframe:

Baseline, 4 hours

End point values	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: percentage				
arithmetic mean (standard deviation)	2.57 (± 1.67)	2.83 (± 2.51)		

Statistical analyses

Statistical analysis title	MEF
Comparison groups	Formoterol (Foradil®) v Fenoterol 0.5 mg + Berodual®
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.673
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Pulse Oximetry
Comparison groups	Formoterol (Foradil®) v Fenoterol 0.5 mg + Berodual®
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.985
Method	Wilcoxon (Mann-Whitney)

Primary: Mean Change in the Conway Clinical Scale Score from Baseline to Final Evaluation

End point title	Mean Change in the Conway Clinical Scale Score from Baseline to Final Evaluation

End point description:

Mean Change from Baseline to Final Evaluation in the Per Protocol population assessed by the Conway Clinical Scale. Assessment of the following: Wheezing, Accessory Muscle Use and Pulse Frequency in a 0 to 3 point scale according to severity for a minimum of 0 points and a total of 9 points in a very severe clinical case.

End point type	Primary

End point timeframe:

Baseline,4 hours

End point values	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: score on a scale				
arithmetic mean (standard deviation)	-3.18 (± 1.59)	-3.04 (± 1.83)		

Statistical analyses

Statistical analysis title	Clinical Scale
Comparison groups	Formoterol (Foradil®) v Fenoterol 0.5 mg + Berodual®
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.808
Method	Wilcoxon (Mann-Whitney)

Secondary: Pharmacoeconomic Analysis

End point title	Pharmacoeconomic Analysis

End point description:

Pharmacoeconomic analysis comparing the mean direct costs (total cost per prescription) of treatment with Formoterol (Foradil®) to treatment with Fenoterol 0.5 mg + Berodual®.

End point type	Secondary

End point timeframe:

4 hours

End point values	Formoterol (Foradil®)	Fenoterol 0.5 mg + Berodual®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: Cost in US Dollars				
arithmetic mean (full range (min-max))	9.21 (6.19 to 12.93)	25.67 (21.95 to 29.91)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Adverse event reporting additional description:

There were no SAEs or Deaths. No adverse event approached the 5% threshold . Only one AE was recorded for the entire study in the Fomoterol arm of the study. The AE was vomiting and nausea and was not considered drug related.

Assessment type	Non-systematic

Dictionary used

Dictionary name	unknown
Dictionary version	0

Reporting groups

Reporting group title	Formoterol (Foradil®)

Reporting group description:

Formoterol (Foradil®) 12 micrograms administered through Aerolizer®.

Serious adverse events	Formoterol (Foradil®)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (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	Formoterol (Foradil®)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: only one adverse event occurred and this does not reach the 5% threshold for non serious adverse events reporting

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