Clinical trial results:
Flu-like Syndrome Inhibition Giving Anti-histaminic Therapy

Summary

EudraCT number	2013-001055-12
Trial protocol	IT
Global end of trial date	07 July 2014

Results information

Result version number	v1 (current)
This version publication date	04 February 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	BIIT0212

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.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	07 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this Phase IIIb, crossover, single-centre, randomized, placebo-controlled, double blind trial was evaluation of the efficacy of the administration of cetirizine 10 mg on flu-like syndrome (FLS) in patients with relapsing-remitting multiple sclerosis (RRMS) treated with interferon-β (IFN-β).

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent form and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy:

All subjects in the study continued their treatment with IFN-β and any medications for FLS (standard of therapy), with stable dose and frequency. These drugs were dispensed to patients according to normal procedures of the Centre.

Evidence for comparator: -

Actual start date of recruitment	16 September 2013
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: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a 12-week screening period.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / Cetirizine

Arm description:

Subjects were randomized to a period of standard therapy plus placebo lasting 4 weeks followed by 4 weeks of standard therapy plus cetirizine 10 mg.

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Arm type	Experimental
Investigational medicinal product name	cetirizine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects took one capsule of cetirizine 10 mg one hour before injection of IFN-β. Dosage of cetirizine depended on the type of IFN-β used by the study subject (ie, the number of injections of IFN-β per week).

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects took one capsule of placebo one hour before injection of IFN-β.

Arm title	Cetirizine / Placebo

Arm description:

Subjects were randomized to a period of standard therapy plus cetirizine 10 mg lasting 4 weeks followed by 4 weeks of standard therapy plus placebo.

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Arm type	Experimental

Investigational medicinal product name	cetirizine
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Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects took one capsule of cetirizine 10 mg one hour before injection of IFN-β. Dosage of cetirizine depended on the type of IFN-β used by the study subject (ie, the number of injections of IFN-β per week).

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects took one capsule of placebo one hour before injection of IFN-β.

Number of subjects in period 1[1]	Placebo / Cetirizine	Cetirizine / Placebo
Started	23	22
Completed	21	20
Not completed	2	2
Consent withdrawn by subject	2	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 46 subjects were enrolled into the study; 1 subject was enrolled but not randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Adults (18-64 years)	45	45	
Age continuous Units: years			
arithmetic mean	39.1		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	13	13	

End points

End points reporting groups

Reporting group title	Placebo / Cetirizine

Reporting group description:

Subjects were randomized to a period of standard therapy plus placebo lasting 4 weeks followed by 4 weeks of standard therapy plus cetirizine 10 mg.

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Reporting group title	Cetirizine / Placebo

Reporting group description:

Subjects were randomized to a period of standard therapy plus cetirizine 10 mg lasting 4 weeks followed by 4 weeks of standard therapy plus placebo.

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population: all randomized subjects who received at least one dose of cetirizine or one dose of placebo and have, for both products, at least one evaluation before and after taking the drug.

Subject analysis set title	Cetirizine
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population: all randomized subjects who received at least one dose of cetirizine or one dose of placebo and have, for both products, at least one evaluation before and after taking the drug.

Subject analysis set title	Placebo: Baseline
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population subjects taking placebo, assessed before injection.

Subject analysis set title	Placebo: 4/6 Hour
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population subjects taking placebo, assessed after 4-6 hours post-injection.

Subject analysis set title	Placebo: 12/15 Hour
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population subjects taking placebo, assessed after 12- 15 hours post-injection.

Subject analysis set title	Cetirizine: Baseline
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population subjects taking cetirizine, assessed before injection.

Subject analysis set title	Cetirizine: 4/6 Hours
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population subjects taking cetirizine, assessed after 4-6 hours post-injection.

Subject analysis set title	Cetirizine: 12/15 Hours
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat population subjects taking cetirizine, assessed after 12-15 hours post-injection.

Primary: Mean Change in Subject Visual Analog Scale of Flu Like Symptoms (VAS-FLS)

End point title	Mean Change in Subject Visual Analog Scale of Flu Like Symptoms (VAS-FLS)[1]

End point description:

The mean change in the severity of subjective FLS, evaluated the subjective seriousness of the FLS as assessed by the subject on a visual analog scale (VAS-FLS). The VAS-FLS is 10 cm in length, where 0 = no discomfort due to FLS and 10 = maximum discomfort imaginable due to FLS. The values considered are the VAS scores collected 4 hours after the last injection after 4 weeks of treatment according to the treatment group (Placebo [A] or Cetirizine [B]). These values were then divided by the two sequences of randomization (AB vs BA) to allow assessment of the sequence effect.

End point type	Primary

End point timeframe:

up to 8 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: P-value for placebo vs. cetirizine = 0.6029 (ANOVA; n = 39).

Sequence x treatment p-value for placebo vs. cetirizine = 0.1279 (ANOVA; n = 39).

End point values	Placebo	Cetirizine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39[2]	39[3]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Sequence AB	3.45 (± 3.09)	3.15 (± 2.95)		
Sequence BA	3.37 (± 2.35)	3.97 (± 2.58)		
Total	3.41 (± 2.71)	3.57 (± 2.76)		

Notes:

[2] - Intention to treat population: three subjects were excluded due to missing data

[3] - Intention to treat population: three subjects were excluded due to missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in the Symptom Score of FLS (FLS-S)

End point title	Mean Change in the Symptom Score of FLS (FLS-S)

End point description:

The mean change in severity of FLS (as assessed by the symptom score of FLS [FLS-S]) between the assessments before injection, after 4-6 hours after injection and after 12- 15 hours after injection during the entire study period. Subjects assigned a score to the presence and intensity of muscle pain, chills and weakness, each evaluated separately, according to the following scale: 0=absent; 1=mild, did not interfere with daily activities; 2=moderate, enough to interfere with daily activities; 3=severe, required bed rest. Body temperature was also recorded using the following scale: 0: <37.3° C; 1: ≥37.3° C and <37.8° C; 2: ≥37.8° C and <38.4° C; 3: ≥38.4° C. The scores of individual symptoms (muscle aches, chills, weakness and body temperature) were added together to get the FLS-S, which ranged between 0 (no symptoms) and 12 (worst symptoms). A change in the total score ≥2 points compared to the pre-injection score was considered positive for the presence of FLS.

End point type	Secondary

End point timeframe:

up to 8 weeks

End point values	Placebo: Baseline	Placebo: 4/6 Hour	Placebo: 12/15 Hour	Cetirizine: Baseline
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41[4]	41[5]	41[6]	41[7]
Units: units on a scale				
arithmetic mean (standard deviation)				
First Week: Placebo - Cetirizine	2 (± 2)	3.6 (± 2.8)	2.7 (± 2.2)	2.3 (± 2.7)
First Week: Cetirizine - Placebo	1.7 (± 1.9)	3 (± 2.6)	3 (± 2.5)	2.3 (± 2.2)
First Week: Total	1.8 (± 1.9)	3.3 (± 2.7)	2.8 (± 2.3)	2.3 (± 2.5)
Second Week: Placebo - Cetirizine	1.8 (± 2.1)	3.7 (± 3)	3.1 (± 2.5)	2.4 (± 2.6)
Second Week: Cetirizine - Placebo	2 (± 1.9)	3.2 (± 2.4)	3.2 (± 2.5)	2.4 (± 2.2)
Second Week: Total	1.9 (± 2)	3.5 (± 2.7)	3.1 (± 2.5)	2.4 (± 2.4)
Third Week: Placebo - Cetirizine	2.2 (± 2.3)	3.3 (± 2.9)	2.6 (± 2.4)	2 (± 2.2)
Third Week: Cetirizine - Placebo	1.7 (± 1.8)	2.9 (± 2)	3 (± 2.6)	2.4 (± 2.5)
Third Week: Total	2 (± 2.1)	3.1 (± 2.5)	2.8 (± 2.5)	2.2 (± 2.3)
Fourth Week: Placebo - Cetirizine	2 (± 2.2)	3.3 (± 2.9)	2.7 (± 2.7)	2.3 (± 2.6)
Fourth Week: Cetirizine - Placebo	2.1 (± 2.3)	3.3 (± 2.4)	3.4 (± 2.7)	2.3 (± 2.3)
Fourth Week: Total	2 (± 2.2)	3.3 (± 2.6)	3 (± 2.7)	2.3 (± 2.4)

Notes:

[4] - Intention to treat population: one subject was excluded due to missing data

[5] - Intention to treat population: one subject was excluded due to missing data

[6] - Intention to treat population: one subject was excluded due to missing data

[7] - Intention to treat population: one subject was excluded due to missing data

End point values	Cetirizine: 4/6 Hours	Cetirizine: 12/15 Hours		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[8]	41[9]		
Units: units on a scale				
arithmetic mean (standard deviation)				
First Week: Placebo - Cetirizine	3.5 (± 2.8)	2.7 (± 2.8)		
First Week: Cetirizine - Placebo	3.8 (± 2.6)	3.6 (± 2.5)		
First Week: Total	3.6 (± 2.7)	3.1 (± 2.7)		
Second Week: Placebo - Cetirizine	3.1 (± 2.9)	2.6 (± 2.6)		
Second Week: Cetirizine - Placebo	3.7 (± 2.6)	3.3 (± 3)		
Second Week: Total	3.4 (± 2.7)	3 (± 2.7)		
Third Week: Placebo - Cetirizine	3 (± 3)	2.7 (± 2.6)		
Third Week: Cetirizine - Placebo	4 (± 2.7)	3.5 (± 2.9)		
Third Week: Total	3.5 (± 2.9)	3.1 (± 2.7)		
Fourth Week: Placebo - Cetirizine	3 (± 2.9)	2.6 (± 2.6)		
Fourth Week: Cetirizine - Placebo	4 (± 2.6)	3.5 (± 2.9)		
Fourth Week: Total	3.5 (± 2.7)	3 (± 2.7)		

Notes:

[8] - Intention to treat population: one subject was excluded due to missing data

[9] - Intention to treat population: one subject was excluded due to missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects (Responders) With a Decrease of ≥ 2 FLS-S Compared With Pre-injection Values

End point title	Percentage of Subjects (Responders) With a Decrease of ≥ 2 FLS-S Compared With Pre-injection Values

End point description:

FLS-S scores recorded at baseline and after 4-6 hours from each injection were considered. Subjects for whom the score FLS-S was reduced by 2 or more units were defined as responders. Subjects with more than 1 weekly evaluation were considered responders if at least an evaluation of the difference of the score FLS-S between the value before the injection and the next 4-6 hours after injection was ≥ 2.

End point type	Secondary

End point timeframe:

up to 8 weeks

End point values	Placebo	Cetirizine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[10]	40[11]		
Units: percentage of subjects				
number (not applicable)				
Placebo - Cetirizine	15	20		
Cetirizine - Placebo	10	15		
Total	25	35		

Notes:

[10] - Intention to treat population: two subjects were excluded due to missing data

[11] - Intention to treat population: two subjects were excluded due to missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Increase of ≥ 2 FLS-S Compared to Pre-injection Values

End point title	Percentage of Subjects With an Increase of ≥ 2 FLS-S Compared to Pre-injection Values

End point description:

FLS incidence was defined as an increase of ≥ 2 FLS-S compared to the value before injection after 4-6 hours and after 12-15 hours during the entire study period.

End point type	Secondary

End point timeframe:

up to 8 weeks

End point values	Placebo	Cetirizine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40[12]	40[13]		
Units: percentage of subjects				
number (not applicable)				
Placebo - Cetirizine	75	75		
Cetirizine - Placebo	90	85		
Total	82.5	80		

Notes:

[12] - Intention to treat population: two subjects were excluded due to missing data

[13] - Intention to treat population: two subjects were excluded due to missing data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through the end of study (up to 8 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo / Cetirizine: Period 1 (Treatment With Placebo)

Reporting group description:

Subjects were randomized to a period of standard therapy plus placebo lasting 4 weeks (period 1) followed by 4 weeks of standard therapy plus cetirizine 10 mg (period 2).

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Reporting group title	Placebo / Cetirizine: Period 2 (Treatment With Cetirizine)

Reporting group description:

Subjects were randomized to a period of standard therapy plus placebo lasting 4 weeks (period 1) followed by 4 weeks of standard therapy plus cetirizine 10 mg (period 2).

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Reporting group title	Cetirizine / Placebo: Period 1 (Treatment With Cetirizine)

Reporting group description:

Subjects were randomized to a period of standard therapy plus cetirizine 10 mg (period 1) lasting 4 weeks followed by 4 weeks of standard therapy plus placebo (period 2).

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Reporting group title	Cetirizine / Placebo: Period 2 (Treatment With Placebo)

Reporting group description:

Subjects were randomized to a period of standard therapy plus cetirizine 10 mg (period 1) lasting 4 weeks followed by 4 weeks of standard therapy plus placebo (period 2).

If a subject was already taking drugs for the treatment of the FLS, such as acetaminophen or ibuprofen, he/she was asked to keep the dosage of such therapy stable as much as possible during the study period, always at the discretion of the investigator and in accordance with normal clinical practice.

Serious adverse events	Placebo / Cetirizine: Period 1 (Treatment With Placebo)	Placebo / Cetirizine: Period 2 (Treatment With Cetirizine)	Cetirizine / Placebo: Period 1 (Treatment With Cetirizine)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Cetirizine / Placebo: Period 2 (Treatment With Placebo)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo / Cetirizine: Period 1 (Treatment With Placebo)	Placebo / Cetirizine: Period 2 (Treatment With Cetirizine)	Cetirizine / Placebo: Period 1 (Treatment With Cetirizine)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	0 / 22 (0.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Cetirizine / Placebo: Period 2 (Treatment With Placebo)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

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