



## 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,<br>clinicaltrials@biogen.com |
| Scientific contact           | Biogen Study Medical Director, Biogen,<br>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- $\beta$  (IFN- $\beta$ ).

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- $\beta$  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 |
|------------------------------|-----|

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | 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- $\beta$ . Dosage of cetirizine depended on the type of IFN- $\beta$  used by the study subject (ie, the number of injections of IFN- $\beta$  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- $\beta$ .

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | 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 |
| 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- $\beta$ . Dosage of cetirizine depended on the type of IFN- $\beta$  used by the study subject (ie, the number of injections of IFN- $\beta$  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- $\beta$ .

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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) <sup>[1]</sup> |
|-----------------|------------------------------------------------------------------------------------------|

## 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 <sup>[2]</sup>    | 39 <sup>[3]</sup>    |  |  |
| 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:<br>Baseline | Placebo: 4/6<br>Hour | Placebo: 12/15<br>Hour | Cetirizine:<br>Baseline |
|--------------------------------------|----------------------|----------------------|------------------------|-------------------------|
| Subject group type                   | Subject analysis set | Subject analysis set | Subject analysis set   | Subject analysis set    |
| Number of subjects analysed          | 41 <sup>[4]</sup>    | 41 <sup>[5]</sup>    | 41 <sup>[6]</sup>      | 41 <sup>[7]</sup>       |
| 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<br>Hours | Cetirizine:<br>12/15 Hours |  |  |
|--------------------------------------|--------------------------|----------------------------|--|--|
| Subject group type                   | Subject analysis set     | Subject analysis set       |  |  |
| Number of subjects analysed          | 41 <sup>[8]</sup>        | 41 <sup>[9]</sup>          |  |  |
| 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  $\geq 2$  FLS-S Compared With Pre-injection Values**

---

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects (Responders) With a Decrease of $\geq 2$ 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  $\geq 2$ .

|                |           |
|----------------|-----------|
| 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 <sup>[10]</sup>   | 40 <sup>[11]</sup>   |  |  |
| 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  $\geq 2$  FLS-S Compared to Pre-injection Values**

---

|                 |                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With an Increase of $\geq 2$ FLS-S Compared to Pre-injection Values |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

FLS incidence was defined as an increase of  $\geq 2$  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

---

| <b>End point values</b>       | Placebo              | Cetirizine           |  |  |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed   | 40 <sup>[12]</sup>   | 40 <sup>[13]</sup>   |  |  |
| 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    |                                                         |                                                            |                                                            |

| <b>Serious adverse events</b>                     | Cetirizine / Placebo:<br>Period 2 (Treatment<br>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 %

| <b>Non-serious adverse events</b>                     | Placebo / Cetirizine:<br>Period 1 (Treatment<br>With Placebo) | Placebo / Cetirizine:<br>Period 2 (Treatment<br>With Cetirizine) | Cetirizine / Placebo:<br>Period 1 (Treatment<br>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                                                                |

| <b>Non-serious adverse events</b>                     | Cetirizine / Placebo:<br>Period 2 (Treatment<br>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