



## Clinical trial results:

### Phase III Study Evaluating the Efficacy and Safety of Olmesartan Medoxomil/Hydrochlorothiazide 40/12.5 mg Combination Therapy versus Olmesartan Medoxomil 40 mg Monotherapy in Patients with Essential Hypertension

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-005556-32 |
| Trial protocol           | DK DE CZ IT    |
| Global end of trial date | 28 May 2008    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 15 November 2018 |
| First version publication date | 15 November 2018 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CS866CM-B-E303 |
|-----------------------|----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Menarini Ricerche S.p.A.   |
| Sponsor organisation address | Via Sette Santi, 1, Florence, Italy, 50131   |
| Public contact               | Corporate Clinical Sciences, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it |
| Scientific contact           | Corporate Clinical Sciences, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it |

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                       | 28 May 2008 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 28 May 2008 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 28 May 2008 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

To assess the anti-hypertensive effect of Olmesartan Medoxomil/Hydrochlorothiazide (OM/HCTZ) 40/12.5 mg combination therapy compared to Olmesartan Medoxomil (OM) 40 mg monotherapy in lowering sitting diastolic blood pressure (dbP) in hypertensive patients after 8 weeks of double-blind treatment (from baseline to the end of the first double-blind treatment phase of the study).

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP which affected the safety of the study participants, the sponsor and the investigator were to take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs were to be informed forthwith about these new events and the measures taken.

For patients participating in the study, Menarini Ricerche S.p.A. had stipulated an insurance policy in accordance with local regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 03 July 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 | Poland: 152         |
| Country: Number of subjects enrolled | Czech Republic: 161 |
| Country: Number of subjects enrolled | Denmark: 62         |
| Country: Number of subjects enrolled | Germany: 137        |
| Country: Number of subjects enrolled | Italy: 76           |
| Country: Number of subjects enrolled | Romania: 145        |
| Country: Number of subjects enrolled | Israel: 53          |
| Country: Number of subjects enrolled | Croatia: 60         |
| Worldwide total number of subjects   | 846                 |
| EEA total number of subjects         | 793                 |

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)                      | 665 |
| From 65 to 84 years                       | 181 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients were to be screened for eligibility. Eligible patients were entered into a two-phase pre-randomisation period consisting of

- a) 2 weeks for tapering off the current anti-hypertension treatment and a
- b) 2 weeks single-blinded placebo run-in phase.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Phase A   |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | OM 40 mg |

Arm description: -

|  |                      |
|--|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Olmesartan Medoxomil |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Tablet               |
| Routes of administration               | Oral use             |

Dosage and administration details:

Tablet containing 40 mg Olmesartan, once daily for 8 weeks

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | OM/HCTZ 40/12.5 mg |
|------------------|--------------------|

Arm description: -

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Olmesartan Medoxomil/Hydrochlorothiazide |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Tablet                                   |
| Routes of administration               | Oral use                                 |

Dosage and administration details:

Tablet containing 40 mg Olmesartan Medoxomil and 12.5 mg Hydrochlorothiazide, once daily for 8 weeks

| <b>Number of subjects in period 1<sup>[1]</sup></b> | OM 40 mg | OM/HCTZ 40/12.5 mg |
|---|----------|--------------------|
| Started   | 282      | 556                |
| Completed   | 268      | 523                |
| Not completed                                       | 14       | 33                 |
| BP out of specifications                            | 2        | -                  |

|                              |   |    |
|------------------------------|---|----|
| Consent withdrawn by subject | 7 | 18 |
| unk                          | 2 | 6  |
| Adverse event, non-fatal     | 2 | 9  |
| 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: Reported data are from ITT population. Eight patients were randomized and but did not provide efficacy data and are therefore not considered in the baseline number.

**Period 2**

|                              |   |
|------------------------------|---|
| Period 2 title               | Phase B   |
| Is this the baseline period? | No  |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | OM 40 mg responders |

Arm description:

Patients that received 40 mg OM in Phase A and responded to treatment

|  |                      |
|--|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Olmesartan Medoxomil |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Tablet               |
| Routes of administration               | Oral use             |

Dosage and administration details:

Tablet containing 40 mg Olmesartan, once daily for 8 weeks

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | OM 40 mg non-responders |
|------------------|-------------------------|

Arm description:

Patients that received 40 mg OM in Phase A and did not respond to treatment

|  |  |
|--|--|
| Arm type                               | Experimental                             |
| Investigational medicinal product name | Olmesartan Medoxomil/Hydrochlorothiazide |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Tablet                                   |
| Routes of administration               | Oral use                                 |

Dosage and administration details:

Tablet containing 40 mg Olmesartan Medoxomil and 12.5 mg Hydrochlorothiazide, once daily for 8 weeks

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | OM/HCTZ 40/12.5 mg responders |
|------------------|-------------------------------|

Arm description:

Patients that received OM/HCTZ 40/12.5 mg in Phase A and responded to treatment

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |  |
|--|--|
| Investigational medicinal product name | Olmesartan Medoxomil/Hydrochlorothiazide |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Tablet                                   |
| Routes of administration               | Oral use                                 |

Dosage and administration details:

Tablet containing 40 mg Olmesartan Medoxomil and 12.5 mg Hydrochlorothiazide, once daily for 8 weeks

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | OM/HCTZ 40/12.5 mg non responders |
|------------------|-----------------------------------|

Arm description:

Patients that received OM/HCTZ 40/12.5 mg in Phase A and did not respond to treatment

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | OM/HCTZ 40/25 mg |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Tablet containing 40 mg olmesartan medoxomil and 25 mg hydrochlorothiazide, once daily for 8 weeks

| <b>Number of subjects in period 2</b> | OM 40 mg responders | OM 40 mg non-responders | OM/HCTZ 40/12.5 mg responders |
|---------------------------------------|---------------------|-------------------------|-------------------------------|
| Started                               | 129                 | 139                     | 336                           |
| Completed                             | 128                 | 137                     | 333                           |
| Not completed                         | 1                   | 2                       | 3                             |
| Consent withdrawn by subject          | -                   | 2                       | -                             |
| unk                                   | -                   | -                       | 1                             |
| Adverse event, non-fatal              | 1                   | -                       | 1                             |
| Lost to follow-up                     | -                   | -                       | 1                             |

| <b>Number of subjects in period 2</b> | OM/HCTZ 40/12.5 mg non responders |
|---------------------------------------|-----------------------------------|
| Started                               | 187                               |
| Completed                             | 186                               |
| Not completed                         | 1                                 |
| Consent withdrawn by subject          | 1                                 |
| unk                                   | -                                 |
| Adverse event, non-fatal              | -                                 |
| Lost to follow-up                     | -                                 |

## Baseline characteristics

### Reporting groups

|                                |                    |
|--------------------------------|--------------------|
| Reporting group title          | OM 40 mg           |
| Reporting group description: - |                    |
| Reporting group title          | OM/HCTZ 40/12.5 mg |
| Reporting group description: - |                    |

| Reporting group values                       | OM 40 mg | OM/HCTZ 40/12.5 mg | Total |
|--|----------|--------------------|-------|
| Number of subjects                           | 282      | 556                | 838   |
| Age categorical                              |          |                    |       |
| Units: Subjects                              |          |                    |       |
| 18 years or older                            | 282      | 556                | 838   |
| Age continuous                               |          |                    |       |
| Units: years                                 |          |                    |       |
| arithmetic mean                              | 56.0     | 55.4               |       |
| standard deviation                           | ± 11.5   | ± 10.6             | -     |
| Gender categorical                           |          |                    |       |
| Units: Subjects                              |          |                    |       |
| Female                                       | 127      | 264                | 391   |
| Male   | 155      | 292                | 447   |
| Smoking habits                               |          |                    |       |
| Units: Subjects                              |          |                    |       |
| Smoker                                       | 45       | 119                | 164   |
| Non-smoker                                   | 186      | 334                | 520   |
| Ex-smoker                                    | 51       | 103                | 154   |
| Alcohol consumption                          |          |                    |       |
| Units: Subjects                              |          |                    |       |
| None   | 91       | 186                | 277   |
| Sporadic                                     | 174      | 333                | 507   |
| Regular                                      | 17       | 37                 | 54    |
| Trough sitting dBp                           |          |                    |       |
| sitting diastolic blood pressure at baseline |          |                    |       |
| Units: mmHG                                  |          |                    |       |
| arithmetic mean                              | 104.5    | 104.6              |       |
| standard deviation                           | ± 4.0    | ± 4.2              | -     |
| Trough sitting sBP                           |          |                    |       |
| Sitting systolic blood pressure              |          |                    |       |
| Units: mmHg                                  |          |                    |       |
| arithmetic mean                              | 168.0    | 168.5              |       |
| standard deviation                           | ± 7.7    | ± 8.4              | -     |
| BMI  |          |                    |       |
| Body Mass Index                              |          |                    |       |
| Units: kg/m²                                 |          |                    |       |
| arithmetic mean                              | 29.67    | 29.18              |       |
| standard deviation                           | ± 4.8    | ± 4.7              | -     |

## End points

### End points reporting groups

|   |                                   |
|---|-----------------------------------|
| Reporting group title   | OM 40 mg                          |
| Reporting group description: -  |                                   |
| Reporting group title   | OM/HCTZ 40/12.5 mg                |
| Reporting group description: -  |                                   |
| Reporting group title   | OM 40 mg responders               |
| Reporting group description:  |                                   |
| Patients that received 40 mg OM in Phase A and responded to treatment                 |                                   |
| Reporting group title   | OM 40 mg non-responders           |
| Reporting group description:  |                                   |
| Patients that received 40 mg OM in Phase A and did not respond to treatment           |                                   |
| Reporting group title   | OM/HCTZ 40/12.5 mg responders     |
| Reporting group description:  |                                   |
| Patients that received OM/HCTZ 40/12.5 mg in Phase A and responded to treatment       |                                   |
| Reporting group title   | OM/HCTZ 40/12.5 mg non responders |
| Reporting group description:  |                                   |
| Patients that received OM/HCTZ 40/12.5 mg in Phase A and did not respond to treatment |                                   |

### Primary: dBP change after 8 weeks Phase A

|  |                                  |
|--|----------------------------------|
| End point title  | dBP change after 8 weeks Phase A |
| End point description:   |                                  |
| Reduction in Mean Trough Sitting dBP (mmHg) from Baseline (Week 0) to Week 8 |                                  |
| End point type   | Primary                          |
| End point timeframe:   |                                  |
| Eight weeks  |                                  |

| End point values                     | OM 40 mg        | OM/HCTZ 40/12.5 mg |  |  |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type                   | Reporting group | Reporting group    |  |  |
| Number of subjects analysed          | 282             | 556                |  |  |
| Units: mmHG                          |                 |                    |  |  |
| arithmetic mean (standard deviation) | -15.8 (± 9.71)  | -18.9 (± 9.32)     |  |  |

### Statistical analyses

|                            |                                    |
|----------------------------|------------------------------------|
| Statistical analysis title | dBP change after 8 weeks (Phase A) |
| Comparison groups          | OM 40 mg v OM/HCTZ 40/12.5 mg      |



|   |               |
|---|---------------|
| Number of subjects included in analysis | 838           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001      |
| Method                                  | ANCOVA        |

### Primary: sBP change after 8 weeks Phase A

|                        |  |
|------------------------|--|
| End point title        | sBP change after 8 weeks Phase A   |
| End point description: | Reduction in Mean Trough Sitting sBP (mmHg) from Baseline (Week 0) to Week 8 |
| End point type         | Primary  |
| End point timeframe:   | Eight weeks  |

| End point values                     | OM 40 mg        | OM/HCTZ 40/12.5 mg |  |  |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type                   | Reporting group | Reporting group    |  |  |
| Number of subjects analysed          | 282             | 556                |  |  |
| Units: mmHg                          |                 |                    |  |  |
| arithmetic mean (standard deviation) | -26.5 (± 14.56) | -31.9 (± 14.76)    |  |  |

### Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | sBP change after 8 weeks (Phase A) |
| Comparison groups                       | OM 40 mg v OM/HCTZ 40/12.5 mg      |
| Number of subjects included in analysis | 838                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | < 0.0001                           |
| Method                                  | ANCOVA                             |

### Secondary: dBP change after 8 weeks Phase B

|                        |   |
|------------------------|---|
| End point title        | dBP change after 8 weeks Phase B  |
| End point description: | Reduction in trough sitting diastolic blood pressure after 8 weeks of additional treatment, depending on Phase A treatment and outcome (responder/non-responder). |
| End point type         | Secondary   |
| End point timeframe:   | Eight weeks   |

| End point values                     | OM 40 mg responders | OM 40 mg non-responders | OM/HCTZ 40/12.5 mg responders | OM/HCTZ 40/12.5 mg non responders |
|--------------------------------------|---------------------|-------------------------|-------------------------------|-----------------------------------|
| Subject group type                   | Reporting group     | Reporting group         | Reporting group               | Reporting group                   |
| Number of subjects analysed          | 129                 | 139                     | 336                           | 187                               |
| Units: mmHg                          |                     |                         |                               |                                   |
| arithmetic mean (standard deviation) | -0.5 (± 6.95)       | -9.3 (± 7.91)           | -0.3 (± 6.68)                 | -8.0 (± 8.56)                     |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | dBp change after 8 weeks (Phase B)  |
| Comparison groups                       | OM 40 mg responders v OM 40 mg non-responders v OM/HCTZ 40/12.5 mg responders v OM/HCTZ 40/12.5 mg non responders |
| Number of subjects included in analysis | 791   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |

## Secondary: sBP change after 8 weeks Phase B

|                        |  |
|------------------------|--|
| End point title        | sBP change after 8 weeks Phase B   |
| End point description: | Reduction in trough sitting systolic blood pressure after 8 weeks of additional treatment, depending on Phase A treatment and outcome (responder/non-responder). |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Eight weeks            |  |

| End point values                     | OM 40 mg responders | OM 40 mg non-responders | OM/HCTZ 40/12.5 mg responders | OM/HCTZ 40/12.5 mg non responders |
|--------------------------------------|---------------------|-------------------------|-------------------------------|-----------------------------------|
| Subject group type                   | Reporting group     | Reporting group         | Reporting group               | Reporting group                   |
| Number of subjects analysed          | 129                 | 139                     | 336                           | 187                               |
| Units: mmHg                          |                     |                         |                               |                                   |
| arithmetic mean (standard deviation) | -0.5 (± 6.95)       | -12.4 (± 11.64)         | -0.4 (± 9.32)                 | -12.1 (± 12.69)                   |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | sBP change after 8 weeks (Phase B)  |
| Comparison groups                       | OM 40 mg responders v OM 40 mg non-responders v OM/HCTZ 40/12.5 mg responders v OM/HCTZ 40/12.5 mg non responders |
| Number of subjects included in analysis | 791   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from first double-blinded study dose (start of Phase A) to EOS visit (end of Phase B)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 11 |
|--------------------|----|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Phase B OM/HCTZ 40/12.5 mg non-responders |
|-----------------------|---|

Reporting group description: -

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Phase B OM/HCTZ 40/12.5 mg responders |
|-----------------------|---------------------------------------|

Reporting group description: -

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Phase B OM 40 mg non-responders |
|-----------------------|---------------------------------|

Reporting group description: -

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Phase B OM 40 mg responders |
|-----------------------|-----------------------------|

Reporting group description: -

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Phase A OM/HCTZ 40/12.5 mg |
|-----------------------|----------------------------|

Reporting group description: -

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Phase A OM 40 mg |
|-----------------------|------------------|

Reporting group description: -

| <b>Serious adverse events</b>                                       | Phase B OM/HCTZ<br>40/12.5 mg non-<br>responders | Phase B OM/HCTZ<br>40/12.5 mg<br>responders | Phase B OM 40 mg<br>non-responders |
|---|--|---|------------------------------------|
| Total subjects affected by serious adverse events                   |  |   |                                    |
| subjects affected / exposed   | 1 / 188 (0.53%)                                  | 3 / 336 (0.89%)                             | 0 / 139 (0.00%)                    |
| number of deaths (all causes)                                       | 0  | 0   | 0                                  |
| number of deaths resulting from adverse events                      | 0  | 0   | 0                                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |   |                                    |
| Uterine leiomyoma   |  |   |                                    |
| subjects affected / exposed   | 0 / 188 (0.00%)                                  | 0 / 336 (0.00%)                             | 0 / 139 (0.00%)                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0                                       | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                                       | 0 / 0                              |
| Duodenal ulcer  |  |   |                                    |
| subjects affected / exposed   | 0 / 188 (0.00%)                                  | 0 / 336 (0.00%)                             | 0 / 139 (0.00%)                    |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0                                       | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0                                       | 0 / 0                              |
| Injury, poisoning and procedural complications                      |  |   |                                    |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Anal fissure                                    | Additional description: worsening and surgery |                 |                 |
| subjects affected / exposed                     | 1 / 188 (0.53%)                               | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Humerus fracture                                |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)                               | 1 / 336 (0.30%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Upper limb fracture                             |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)                               | 1 / 336 (0.30%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |   |                 |                 |
| Atrial flutter                                  |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)                               | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |   |                 |                 |
| Ischaemic cerebral infarction                   |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)                               | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Syncope   |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)                               | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Brain contusion                                 |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)                               | 1 / 336 (0.30%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |   |                 |                 |
| Gastritis                                       |   |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 188 (0.00%) | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incontinence                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 1 / 336 (0.30%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 1 / 336 (0.30%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%) | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Pneumonia viral                                 |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)   | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Parotid abscess                                 |   |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)   | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Erysipeloid                                     | Additional description: Erysipel B / Erysipel Crus Left |                 |                 |
| subjects affected / exposed                     | 0 / 188 (0.00%)   | 0 / 336 (0.00%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |

| Serious adverse events  | Phase B OM 40 mg responders                   | Phase A OM/HCTZ 40/12.5 mg | Phase A OM 40 mg |
|---|---|----------------------------|------------------|
| Total subjects affected by serious adverse events                   |   |                            |                  |
| subjects affected / exposed   | 2 / 129 (1.55%)                               | 4 / 561 (0.71%)            | 5 / 285 (1.75%)  |
| number of deaths (all causes)                                       | 0   | 0                          | 0                |
| number of deaths resulting from adverse events                      | 0   | 0                          | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                            |                  |
| Uterine leiomyoma   |   |                            |                  |
| subjects affected / exposed   | 0 / 129 (0.00%)                               | 1 / 561 (0.18%)            | 0 / 285 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1                      | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                      | 0 / 0            |
| Duodenal ulcer  |   |                            |                  |
| subjects affected / exposed   | 0 / 129 (0.00%)                               | 0 / 561 (0.00%)            | 1 / 285 (0.35%)  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 0                      | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                      | 0 / 0            |
| Injury, poisoning and procedural complications                      |   |                            |                  |
| Anal fissure  | Additional description: worsening and surgery |                            |                  |
| subjects affected / exposed   | 0 / 129 (0.00%)                               | 0 / 561 (0.00%)            | 0 / 285 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 0                      | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0                      | 0 / 0            |
| Humerus fracture  |   |                            |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Ischaemic cerebral infarction                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 561 (0.18%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain contusion                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 561 (0.18%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incontinence                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%) | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 1 / 561 (0.18%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia viral                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Parotid abscess                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 129 (0.00%) | 0 / 561 (0.00%) | 1 / 285 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Erysipeloid                                     | Additional description: Erysipel B / Erysipel Crus Left |                 |                 |
| subjects affected / exposed                     | 1 / 129 (0.78%)   | 0 / 561 (0.00%) | 0 / 285 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Phase B OM/HCTZ<br>40/12.5 mg non-<br>responders | Phase B OM/HCTZ<br>40/12.5 mg<br>responders | Phase B OM 40 mg<br>non-responders |
|---|--|---|------------------------------------|
| Total subjects affected by non-serious adverse events |  |   |                                    |
| subjects affected / exposed                           | 24 / 188 (12.77%)                                | 38 / 336 (11.31%)                           | 21 / 139 (15.11%)                  |
| Vascular disorders                                    |  |   |                                    |
| Hypertension  |  |   |                                    |
| subjects affected / exposed                           | 2 / 188 (1.06%)                                  | 2 / 336 (0.60%)                             | 0 / 139 (0.00%)                    |
| occurrences (all)                                     | 2  | 2   | 0                                  |
| Nervous system disorders                              |  |   |                                    |
| Dizziness   |  |   |                                    |
| subjects affected / exposed                           | 0 / 188 (0.00%)                                  | 0 / 336 (0.00%)                             | 0 / 139 (0.00%)                    |
| occurrences (all)                                     | 0  | 0   | 0                                  |
| Headache  |  |   |                                    |
| subjects affected / exposed                           | 1 / 188 (0.53%)                                  | 2 / 336 (0.60%)                             | 2 / 139 (1.44%)                    |
| occurrences (all)                                     | 1  | 2   | 2                                  |
| Gastrointestinal disorders                            |  |   |                                    |
| Abdominal pain upper                                  |  |   |                                    |
| subjects affected / exposed                           | 0 / 188 (0.00%)                                  | 1 / 336 (0.30%)                             | 0 / 139 (0.00%)                    |
| occurrences (all)                                     | 0  | 1   | 0                                  |
| Respiratory, thoracic and mediastinal disorders       |  |   |                                    |
| Cough   |  |   |                                    |
| subjects affected / exposed                           | 0 / 188 (0.00%)                                  | 0 / 336 (0.00%)                             | 0 / 139 (0.00%)                    |
| occurrences (all)                                     | 0  | 0   | 0                                  |
| Musculoskeletal and connective tissue disorders       |  |   |                                    |
| Arthralgia  |  |   |                                    |
| subjects affected / exposed                           | 2 / 188 (1.06%)                                  | 1 / 336 (0.30%)                             | 0 / 139 (0.00%)                    |
| occurrences (all)                                     | 2  | 1   | 0                                  |
| Infections and infestations                           |  |   |                                    |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 188 (1.06%)<br>2 | 2 / 336 (0.60%)<br>2 | 0 / 139 (0.00%)<br>0 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 188 (0.00%)<br>0 | 2 / 336 (0.60%)<br>2 | 2 / 139 (1.44%)<br>2 |
| Metabolism and nutrition disorders  |                      |                      |                      |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 188 (1.06%)<br>2 | 2 / 336 (0.60%)<br>2 | 1 / 139 (0.72%)<br>1 |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 188 (0.00%)<br>0 | 4 / 336 (1.19%)<br>4 | 1 / 139 (0.72%)<br>1 |

| <b>Non-serious adverse events</b>   | Phase B OM 40 mg<br>responders | Phase A OM/HCTZ<br>40/12.5 mg | Phase A OM 40 mg     |
|---|--------------------------------|-------------------------------|----------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 22 / 129 (17.05%)              | 41 / 561 (7.31%)              | 42 / 285 (14.74%)    |
| Vascular disorders  |                                |                               |                      |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 129 (0.00%)<br>0           | 0 / 561 (0.00%)<br>0          | 0 / 285 (0.00%)<br>0 |
| Nervous system disorders  |                                |                               |                      |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 129 (0.00%)<br>0           | 10 / 561 (1.78%)<br>10        | 0 / 285 (0.00%)<br>0 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 129 (0.78%)<br>1           | 9 / 561 (1.60%)<br>9          | 6 / 285 (2.11%)<br>6 |
| Gastrointestinal disorders  |                                |                               |                      |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                | 2 / 129 (1.55%)<br>2           | 0 / 561 (0.00%)<br>0          | 0 / 285 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal<br>disorders                                      |                                |                               |                      |
| Cough<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 129 (0.00%)<br>0           | 2 / 561 (0.36%)<br>2          | 5 / 285 (1.75%)<br>5 |
| Musculoskeletal and connective tissue<br>disorders                                      |                                |                               |                      |

|   |                      |                        |                      |
|---|----------------------|------------------------|----------------------|
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 129 (0.00%)<br>0 | 0 / 561 (0.00%)<br>0   | 0 / 285 (0.00%)<br>0 |
| Infections and infestations   |                      |                        |                      |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 129 (1.55%)<br>2 | 6 / 561 (1.07%)<br>6   | 3 / 285 (1.05%)<br>3 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)       | 2 / 129 (1.55%)<br>2 | 14 / 561 (2.50%)<br>14 | 5 / 285 (1.75%)<br>5 |
| Metabolism and nutrition disorders  |                      |                        |                      |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 129 (0.78%)<br>1 | 0 / 561 (0.00%)<br>0   | 0 / 285 (0.00%)<br>0 |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 129 (0.00%)<br>0 | 0 / 561 (0.00%)<br>0   | 0 / 285 (0.00%)<br>0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 12 October 2007 | Non-substantial amendment: to detail the electronic SUSAR reporting to the EMEA and to all CAs where electronic submission was in place. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported