



## Clinical trial results:

### Effects of Wobenzym® plus in healthy, sportive people after eccentric exercise - a randomized, two-stage, double-blind, placebo-controlled cross-over trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-005003-40 |
| Trial protocol           | DE             |
| Global end of trial date | 13 August 2014 |

#### Results information

|                                   |                        |
|-----------------------------------|------------------------|
| Result version number             | v1 (current)           |
| This version publication date     | 10 July 2016           |
| First version publication date    | 10 July 2016           |
| Summary attachment (see zip file) | Synopsis (Results.pdf) |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | BTS651/12 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01845558 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                                |
|------------------------------|----------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | BioTesys GmbH                                                                                                  |
| Sponsor organisation address | Schelztorstraße 54-56, Esslingen, Germany, 73728                                                               |
| Public contact               | Clinical Trial Information , BioTeSys GmbH, 0049 71131057147, c.reule@biotesys.de                              |
| Scientific contact           | Clinical Trial Information , BioTeSys GmbH, 0049 71131057147, c.reule@biotesys.de                              |
| Sponsor organisation name    | Mucos Pharma GmbH & Co. KG                                                                                     |
| Sponsor organisation address | Bajuwarenring 5, Oberhaching, Germany, 82041                                                                   |
| Public contact               | MUCOS Pharma GmbH & Co. KG<br>, MUCOS Pharma GmbH & Co. KG, +49 89 638372400,<br>info@mucos.de                 |
| Scientific contact           | MUCOS Pharma GmbH & Co. KG<br>, MUCOS Pharma GmbH & Co. KG, Dr. Stefanie Rau, +49 89 638372404, s.rau@mucos.de |

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                                | No |

Notes:

**Results analysis stage**

|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 13 July 2015   |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 13 August 2014 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 13 August 2014 |
| Was the trial ended prematurely?                     | No             |

Notes:

**General information about the trial**

Main objective of the trial:

The aim of the current study is to investigate the therapeutic effect of Wobenzym® plus, an anti-inflammatory drug containing proteolytic enzymes, on exercise induced muscle damage (eiMD) and recovery time in male amateur sportsmen with medium proficiency level compared to placebo. As primary objective, the reduction of maximal isokinetic strength after exercise in the stronger leg and subjective pain after exercise are assumed to be the most promising parameters. Therefore these parameters are combined in a multidimensional approach summarizing different parameters and points of time to strengthen the power. The period after the stress test will be separately calculated for the acute phase (3h, 6h) and the recovery phase (24h-48h).

Protection of trial subjects:

Informed consent after explanation of aims, methods, benefits and potential hazards. Screening visit to exclude patient with diseases, allergic reactions ect (see exclusion criteria). Every volunteer is free to refuse to participate in the study or withdraw their consent at any time and for any reason without incurring any penalty. Study site with Emergency Management Plan and Equipment.

Background therapy:

Not applicable.

Evidence for comparator:

No Comparator used (Placebo-controlled trial).

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 01 February 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 | Germany: 74 |
| Worldwide total number of subjects   | 74          |
| EEA total number of subjects         | 74          |

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)                      | 74 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Monocenter, double-blind, randomized, placebo-controlled, crossover study (stage I) designed to assess acute phase and recovery after eccentric stress test.

Stage II: parallel group design.

### Pre-assignment

Screening details:

Stage I cross-over design:

Group 1 (N=15) Wobenzym plus from day 1 to day 7 and placebo from day 29 to day 35

Group 2 (N=15) Placebo from day 1 to day 7 and Wobenzym plus from day 29 to day 35

Wash-out phase of 21 days.

Stage II: parallel design, 2x22 randomized to Wobenzym plus or Placebo

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Placebo Arm: Stage 1 Crossover Design (15) + stage II parallel design (22)

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Four tablets three times per day. Medication will be taken 30 minutes before each meal on an empty stomach with one glass of water.

|                  |       |
|------------------|-------|
| <b>Arm title</b> | Verum |
|------------------|-------|

Arm description:

Active comparator Wobenzym plus

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Wobenzym plus      |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Four tablets three times per day. Medication will be taken 30 minutes before each meal on an empty stomach with one glass of water.

| <b>Number of subjects in period 1</b> | Placebo | Verum |
|---------------------------------------|---------|-------|
| Started                               | 37      | 37    |
| Completed                             | 33      | 34    |
| Not completed                         | 4       | 3     |
| Consent withdrawn by subject          | 1       | -     |
| Protocol deviation                    | 1       | 3     |
| Not treated                           | 2       | -     |

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values                                | Overall trial | Total |  |
|-------------------------------------------------------|---------------|-------|--|
| Number of subjects                                    | 74            | 74    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero                                              | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 74            | 74    |  |
| From 65-84 years                                      | 0             | 0     |  |
| 85 years and over                                     | 0             | 0     |  |
| Age continuous                                        |               |       |  |
| Units: years                                          |               |       |  |
| arithmetic mean                                       | 31.6          |       |  |
| standard deviation                                    | ± 9.3         | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female                                                | 0             | 0     |  |
| Male                                                  | 74            | 74    |  |

## End points

### End points reporting groups

|                                                                                                            |         |
|------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                      | Placebo |
| Reporting group description:<br>Placebo Arm: Stage 1 Crossover Design (15) + stage II parallel design (22) |         |
| Reporting group title                                                                                      | Verum   |
| Reporting group description:<br>Active comparator Wobenzym plus                                            |         |

### Primary: Acute phase Primary endpoints

|                                                                                                                                                                                                   |                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                                                                                                   | Acute phase Primary endpoints |
| End point description:<br>Multidimensional: Reduction of maximal concentric strenght after stress test + pressure induced pain (Algometry) in the middle of the muscle belly of m. rectus femoris |                               |
| End point type                                                                                                                                                                                    | Primary                       |
| End point timeframe:<br>Acute phase: 3 h and 6 h post stress test                                                                                                                                 |                               |

| End point values            | Placebo         | Verum           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 33              | 34              |  |  |
| Units: NM + NM/cm2          |                 |                 |  |  |
| number (not applicable)     | 33              | 34              |  |  |

### Statistical analyses

|                                                                                                                                                                                      |                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Statistical analysis title                                                                                                                                                           | Multivariate test Stage 1  |
| Statistical analysis description:<br>Multivariate test of first vonfirmatory hypothesis of stage 1 (multidimensional ensemble of peak torque and pressure induced pain at 3h and 6h) |                            |
| Comparison groups                                                                                                                                                                    | Placebo v Verum            |
| Number of subjects included in analysis                                                                                                                                              | 67                         |
| Analysis specification                                                                                                                                                               | Pre-specified              |
| Analysis type                                                                                                                                                                        | superiority <sup>[1]</sup> |
| P-value                                                                                                                                                                              | = 0.0332                   |
| Method                                                                                                                                                                               | Wei-Lachin                 |
| Confidence interval                                                                                                                                                                  |                            |
| level                                                                                                                                                                                | Other: 97.5 %              |
| sides                                                                                                                                                                                | 1-sided                    |
| upper limit                                                                                                                                                                          | 0.4922                     |

Notes:

[1] - one-sided, directional test for superiority, Wei-Lachin procedure

|                                                                        |                         |
|------------------------------------------------------------------------|-------------------------|
| <b>Statistical analysis title</b>                                      | Mann-Whitney stage 1    |
| Statistical analysis description:                                      |                         |
| Associated effect size Mann-Whitney for hypothesis stage 1 acute phase |                         |
| Comparison groups                                                      | Placebo v Verum         |
| Number of subjects included in analysis                                | 67                      |
| Analysis specification                                                 | Pre-specified           |
| Analysis type                                                          | superiority             |
| P-value                                                                | = 0.6153                |
| Method                                                                 | Wilcoxon (Mann-Whitney) |
| Parameter estimate                                                     | Mann-Whitney            |
| Point estimate                                                         | 0.6153                  |
| Confidence interval                                                    |                         |
| level                                                                  | Other: 97.5 %           |
| sides                                                                  | 1-sided                 |
| lower limit                                                            | 0.4922                  |

|                                                                                                    |                           |
|----------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                  | Multivariate test Stage 2 |
| Statistical analysis description:                                                                  |                           |
| multidimensional ensemble of peak torque and pressure induced pain at 3h and 6 hours (acute phase) |                           |
| Comparison groups                                                                                  | Placebo v Verum           |
| Number of subjects included in analysis                                                            | 67                        |
| Analysis specification                                                                             | Pre-specified             |
| Analysis type                                                                                      | superiority               |
| P-value                                                                                            | = 0.8596                  |
| Method                                                                                             | Wei-Lachin                |
| Confidence interval                                                                                |                           |
| level                                                                                              | Other: 97.5 %             |
| sides                                                                                              | 1-sided                   |
| upper limit                                                                                        | 0.325                     |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | Mann-Whitney stage 2    |
| Comparison groups                       | Placebo v Verum         |
| Number of subjects included in analysis | 67                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.4379                |
| Method                                  | Wilcoxon (Mann-Whitney) |
| Parameter estimate                      | Mann-Whitney            |
| Point estimate                          | 0.4379                  |

|                     |               |
|---------------------|---------------|
| Confidence interval |               |
| level               | Other: 97.5 % |
| sides               | 1-sided       |
| lower limit         | 0.325         |

### Primary: Recovery phase: Primary endpoint

|                                                                                                                                                                         |                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| End point title                                                                                                                                                         | Recovery phase: Primary endpoint |
| End point description:                                                                                                                                                  |                                  |
| Multidimensional: Reduction of maximal concentric strenght after stress test + pressure induced pain (Algometry) in the middle of the muscle belly of m. rectus femoris |                                  |
| End point type                                                                                                                                                          | Primary                          |
| End point timeframe:                                                                                                                                                    |                                  |
| 24 h and 48 h after stress test                                                                                                                                         |                                  |

| End point values            | Placebo         | Verum           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 33              | 34              |  |  |
| Units: NM / NM/cm2          |                 |                 |  |  |
| number (not applicable)     | 33              | 34              |  |  |

### Statistical analyses

|                                                                                   |                           |
|-----------------------------------------------------------------------------------|---------------------------|
| Statistical analysis title                                                        | Multivariate test Stage 1 |
| Statistical analysis description:                                                 |                           |
| multidimensional ensemble of peak torque and pressure induced pain at 24h and 48h |                           |
| Comparison groups                                                                 | Placebo v Verum           |
| Number of subjects included in analysis                                           | 67                        |
| Analysis specification                                                            | Pre-specified             |
| Analysis type                                                                     | superiority               |
| P-value                                                                           | = 0.0934                  |
| Method                                                                            | Wei-Lachin                |
| Parameter estimate                                                                | Wei-Lachin                |
| Point estimate                                                                    | 0.0934                    |
| Confidence interval                                                               |                           |
| level                                                                             | Other: 97.5 %             |
| sides                                                                             | 1-sided                   |
| upper limit                                                                       | 0.4556                    |

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Mann-Whitney stage 1 |
| Comparison groups          | Placebo v Verum      |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 67                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.5917                |
| Method                                  | Wilcoxon (Mann-Whitney) |
| Parameter estimate                      | Mann-Whitney            |
| Point estimate                          | 0.5917                  |
| Confidence interval                     |                         |
| level                                   | Other: 97.5 %           |
| sides                                   | 1-sided                 |
| lower limit                             | 0.4556                  |

|                                                                                                                        |                           |
|------------------------------------------------------------------------------------------------------------------------|---------------------------|
| <b>Statistical analysis title</b>                                                                                      | Multivariate test Stage 2 |
| Statistical analysis description:<br>multidimensional ensemble of peak torque and pressure induced pain at 24h and 48h |                           |
| Comparison groups                                                                                                      | Placebo v Verum           |
| Number of subjects included in analysis                                                                                | 67                        |
| Analysis specification                                                                                                 | Pre-specified             |
| Analysis type                                                                                                          | superiority               |
| P-value                                                                                                                | = 0.8783                  |
| Method                                                                                                                 | Wei-Lachin                |
| Parameter estimate                                                                                                     | Wei-Lachin                |
| Point estimate                                                                                                         | 0.8783                    |
| Confidence interval                                                                                                    |                           |
| level                                                                                                                  | Other: 97.5 %             |
| sides                                                                                                                  | 1-sided                   |
| lower limit                                                                                                            | 0.3035                    |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | Mann-Whitney Stage 2    |
| Comparison groups                       | Placebo v Verum         |
| Number of subjects included in analysis | 67                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.4267                |
| Method                                  | Wilcoxon (Mann-Whitney) |
| Parameter estimate                      | Mann-Whitney            |
| Point estimate                          | 0.4267                  |
| Confidence interval                     |                         |
| level                                   | Other: 97.5 %           |
| sides                                   | 1-sided                 |
| lower limit                             | 0.3035                  |

|                                                   |                                 |
|---------------------------------------------------|---------------------------------|
| <b>Secondary: Secondary endpoints: Biomarkers</b> |                                 |
| End point title                                   | Secondary endpoints: Biomarkers |

End point description:

IL-6, Prostaglandin E metabolite derived from cyclooxygenase 2, Creatin kinase, LDH, Lactate, NK-cell-test, Redox-Status (TOS/TAS)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

pre, 0h, 10 min, 30 min, 3h, 6h, 24h - depending on marker

| End point values            | Placebo         | Verum           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 33              | 34              |  |  |
| Units: not applicable       |                 |                 |  |  |
| number (not applicable)     | 33              | 34              |  |  |

## Statistical analyses

| Statistical analysis title              | Multivariate test pooled biomarkers |
|-----------------------------------------|-------------------------------------|
| Comparison groups                       | Placebo v Verum                     |
| Number of subjects included in analysis | 67                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.0001 <sup>[2]</sup>             |
| Method                                  | Wei-Lachin                          |
| Parameter estimate                      | Wei-Lachin                          |
| Point estimate                          | 0.0001                              |
| Confidence interval                     |                                     |
| level                                   | Other: 97.5 %                       |
| sides                                   | 1-sided                             |
| upper limit                             | 0.5407                              |

Notes:

[2] - Combined Stages 1 and 2

| Statistical analysis title              | Mann-Whitney pooled Biomarkers |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Placebo v Verum                |
| Number of subjects included in analysis | 67                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.5847                       |
| Method                                  | Wilcoxon (Mann-Whitney)        |
| Parameter estimate                      | Mann-Whitney                   |
| Point estimate                          | 0.5847                         |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 1-sided                        |
| lower limit                             | 0.5407                         |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

At each visit

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Stage 1 |
|-----------------------|---------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Stage 2 |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | Stage 1        | Stage 2        |  |
|---------------------------------------------------|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 28 (0.00%) | 0 / 44 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |

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

| Non-serious adverse events                            | Stage 1                                             | Stage 2        |  |
|-------------------------------------------------------|-----------------------------------------------------|----------------|--|
| Total subjects affected by non-serious adverse events |                                                     |                |  |
| subjects affected / exposed                           | 13 / 28 (46.43%)                                    | 1 / 44 (2.27%) |  |
| Surgical and medical procedures                       |                                                     |                |  |
| Wisdom teeth extraction                               | Additional description: Assessed as Not Related     |                |  |
| subjects affected / exposed                           | 0 / 28 (0.00%)                                      | 1 / 44 (2.27%) |  |
| occurrences (all)                                     | 0                                                   | 1              |  |
| Nervous system disorders                              |                                                     |                |  |
| Headache                                              | Additional description: All assessed as Not Related |                |  |
| subjects affected / exposed                           | 5 / 28 (17.86%)                                     | 0 / 44 (0.00%) |  |
| occurrences (all)                                     | 5                                                   | 0              |  |
| Gastrointestinal disorders                            |                                                     |                |  |
| Diarrhea                                              | Additional description: Assessed as Possible        |                |  |
| subjects affected / exposed                           | 1 / 28 (3.57%)                                      | 0 / 44 (0.00%) |  |
| occurrences (all)                                     | 1                                                   | 0              |  |

|                                                 |                                                              |                |  |
|-------------------------------------------------|--------------------------------------------------------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders |                                                              |                |  |
| Sore throat                                     | Additional description: Assessed as Not Related              |                |  |
| subjects affected / exposed                     | 2 / 28 (7.14%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 2                                                            | 0              |  |
| Tonsillitis                                     | Additional description: Assessed as Not Related              |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 1                                                            | 0              |  |
| Skin and subcutaneous tissue disorders          |                                                              |                |  |
| Skin eruption                                   | Additional description: Assessed as Unlikely                 |                |  |
| subjects affected / exposed                     | 2 / 28 (7.14%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 2                                                            | 0              |  |
| Rash                                            | Additional description: Acne-like rash, Assessed as Possible |                |  |
| subjects affected / exposed                     | 0 / 28 (0.00%)                                               | 1 / 44 (2.27%) |  |
| occurrences (all)                               | 0                                                            | 1              |  |
| Musculoskeletal and connective tissue disorders |                                                              |                |  |
| Muscle strain                                   | Additional description: Assessed as Not Related              |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 1                                                            | 0              |  |
| Disruption of Clavicle                          | Additional description: Assessed as Not Related              |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 1                                                            | 0              |  |
| Effusion                                        | Additional description: Assessed as Not Related              |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 1                                                            | 0              |  |
| Infections and infestations                     |                                                              |                |  |
| Coryza                                          | Additional description: Assessed as Not Related              |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)                                               | 0 / 44 (0.00%) |  |
| occurrences (all)                               | 1                                                            | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 09 May 2014 | <p>Within the framework of the pre-planned two-stage procedure according to Bauer-Köhne the following decision was made:</p> <ul style="list-style-type: none"><li>- The study will be continued with Stage II.</li><li>- Due to statistically significant carryover effects the stage II of the trial will be based on a simple parallel group scheme with one phase only (no crossover design).</li><li>- The measurement of movement induced pain will be skipped due to zero-dominated data in stage I.</li><li>- The recalculated total sample size for stage II is 2 x 22 patients (sample size reassessment according to protocol and final SAP, one phase, no crossover design in stage II).</li><li>- This decision is established within the framework of the adaptive design features of the two-stage procedure according to Bauer-Köhne and based on the definitions of the protocol and of the final SAP of stage I.</li><li>- Stage I results and rationale for stage II decision are kept confidential as defined in the protocol (section 7.11) and in the final statistical analysis plan (SAP Stage I Version Final 1.0 from January 20th, 2014, Section 5.4.3).</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported