



## Clinical trial results:

### Randomized, placebo-controlled, double-blind, cross-over trial with Bronchipret and Sinupret to evaluate acceleration of mucociliary clearance (MCC)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-004864-24   |
| Trial protocol           | BE               |
| Global end of trial date | 27 December 2013 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 06 January 2023 |
| First version publication date | 06 January 2023 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | COPD-1 |
|-----------------------|--------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bionorica SE   |
| Sponsor organisation address | Kerschensteinerstraße 11-15, Neumarkt, Germany, 92318                                |
| Public contact               | Head of cooperate communication, Bionorica SE,<br>info@bionorica.de                  |
| Scientific contact           | Head of research and development, Bionorica SE,<br>research.development@bionorica.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 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 09 March 2015    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 27 December 2013 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 27 December 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

The overall aim of this trial was the proof of concept that the herbal drugs Bronchipret® and/or Sinupret® accelerate mucociliary clearance (MCC) of the respiratory tract.

Protection of trial subjects:

This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 17 June 2013 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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**Population of trial subjects****Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 56 |
| Worldwide total number of subjects   | 56          |
| EEA total number of subjects         | 56          |

Notes:

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**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)                      | 56 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Of the 67 screened subjects, 56 were randomised to one of the two treatments (Bronchipret® or Sinupret®). Of the 56 subjects, 28 subjects were treated with Bronchipret® and Bronchipret® placebo and 28 subjects were treated with Sinupret® and Sinupret® placebo. None of the screening failures were treated with trial medication.

### Pre-assignment

Screening details:

Up to 14 days before subject's randomisation to the treatment, a screening visit V 0 was performed to test subject's general eligibility for the trial. It was supposed that trial subjects have already developed a mild to moderate impairment of mucociliary clearance due to their smoking habits.

### Period 1

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

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | No                    |
| <b>Arm title</b>             | Bronchipret Treatment |

Arm description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:  
Group A: Treatment period 1: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day).  
Group B: Treatment period 1: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day).

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

Dosage and administration details:

2 film coated tablets (FCTs) three times daily (TID) for 7 days ( $\pm 1$  day)

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Sinupret Treatment |
|------------------|--------------------|

Arm description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:  
Group C: Treatment period 1: 2 CTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day).  
Group D: Treatment period 1: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day).

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Sinupret® extract mite |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Coated tablet          |
| Routes of administration               | Oral use               |

Dosage and administration details:

2 coated tablets (CTs) TID for 7 days ( $\pm 1$  day)

|  |                               |
|--|-------------------------------|
| <b>Arm title</b>   | Bronchipret-Placebo Treatment |
| Arm description:   |                               |
| At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:<br>Group A: Treatment period 1: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$ day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$ day).<br>Group B: Treatment period 1: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$ day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$ day). |                               |
| Arm type   | Placebo                       |
| Investigational medicinal product name   | Bronchipret® placebo          |
| Investigational medicinal product code   |                               |
| Other name   |                               |
| Pharmaceutical forms   | Film-coated tablet            |
| Routes of administration   | Oral use                      |

Dosage and administration details:

2 film coated tablets (FCTs) three times daily (TID) for 7 days ( $\pm 1$  day)

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Sinupret-Placebo Treatment |
|------------------|----------------------------|

Arm description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:  
Group C: Treatment period 1: 2 CTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day).  
Group D: Treatment period 1: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day).

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

Dosage and administration details:

2 coated tablets TID for 7 days ( $\pm 1$  day)

| Number of subjects in period 1 | Bronchipret Treatment | Sinupret Treatment | Bronchipret-Placebo Treatment |
|--------------------------------|-----------------------|--------------------|-------------------------------|
| Started                        | 28                    | 28                 | 28                            |
| End of treatment with Verum    | 28                    | 28                 | 28                            |
| End of wash-out period         | 28                    | 28                 | 28                            |
| End of treatment with Placebo  | 28                    | 28                 | 28                            |
| Completed                      | 28                    | 28                 | 28                            |

| Number of subjects in period 1 | Sinupret-Placebo Treatment |
|--------------------------------|----------------------------|
| Started                        | 28                         |
| End of treatment with Verum    | 28                         |
| End of wash-out period         | 28                         |
| End of treatment with Placebo  | 28                         |
| Completed                      | 28                         |



## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Bronchipret Treatment |
|-----------------------|-----------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group A: Treatment period 1: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day).

Group B: Treatment period 1: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sinupret Treatment |
|-----------------------|--------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group C: Treatment period 1: 2 CTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day).

Group D: Treatment period 1: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day).

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Bronchipret-Placebo Treatment |
|-----------------------|-------------------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group A: Treatment period 1: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day).

Group B: Treatment period 1: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day).

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Sinupret-Placebo Treatment |
|-----------------------|----------------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group C: Treatment period 1: 2 CTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day).

Group D: Treatment period 1: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day).

| Reporting group values                             | Bronchipret Treatment | Sinupret Treatment | Bronchipret-Placebo Treatment |
|--|-----------------------|--------------------|-------------------------------|
| Number of subjects                                 | 28                    | 28                 | 28                            |
| Age categorical                                    |                       |                    |                               |
| Units: Subjects                                    |                       |                    |                               |
| In utero   | 0                     | 0                  | 0                             |
| Preterm newborn infants (gestational age < 37 wks) | 0                     | 0                  | 0                             |
| Newborns (0-27 days)                               | 0                     | 0                  | 0                             |
| Infants and toddlers (28 days-23 months)           | 0                     | 0                  | 0                             |
| Children (2-11 years)                              | 0                     | 0                  | 0                             |
| Adolescents (12-17 years)                          | 0                     | 0                  | 0                             |
| Adults (18-64 years)                               | 28                    | 28                 | 28                            |
| From 65-84 years                                   | 0                     | 0                  | 0                             |
| 85 years and over                                  | 0                     | 0                  | 0                             |
| Age continuous                                     |                       |                    |                               |
| Units: years                                       |                       |                    |                               |
| arithmetic mean                                    | 32.6                  | 30.9               | 32.6                          |
| standard deviation                                 | $\pm 5.2$             | $\pm 3.8$          | $\pm 5.2$                     |
| Gender categorical                                 |                       |                    |                               |
| Units: Subjects                                    |                       |                    |                               |
| Female   | 15                    | 12                 | 15                            |

|      |    |    |    |
|------|----|----|----|
| Male | 13 | 16 | 13 |
|------|----|----|----|

| Reporting group values                             | Sinupret-Placebo Treatment | Total |  |
|--|----------------------------|-------|--|
| Number of subjects                                 | 28                         | 56    |  |
| Age categorical                                    |                            |       |  |
| Units: Subjects                                    |                            |       |  |
| In utero   | 0                          | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0                          | 0     |  |
| Newborns (0-27 days)                               | 0                          | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0                          | 0     |  |
| Children (2-11 years)                              | 0                          | 0     |  |
| Adolescents (12-17 years)                          | 0                          | 0     |  |
| Adults (18-64 years)                               | 28                         | 56    |  |
| From 65-84 years                                   | 0                          | 0     |  |
| 85 years and over                                  | 0                          | 0     |  |
| Age continuous                                     |                            |       |  |
| Units: years                                       |                            |       |  |
| arithmetic mean                                    | 30.9                       |       |  |
| standard deviation                                 | ± 3.8                      | -     |  |
| Gender categorical                                 |                            |       |  |
| Units: Subjects                                    |                            |       |  |
| Female   | 12                         | 27    |  |
| Male   | 16                         | 29    |  |

### Subject analysis sets

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Bronchipret-FAS |
| Subject analysis set type  | Full analysis   |

Subject analysis set description:

The FAS for the efficacy analysis included all randomised subjects with at least one documented application of the investigational drug and evaluable saccharin tests at the beginning and end of the active treatment period and the beginning and end of the corresponding placebo period.

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | Bronchipret-PP |
| Subject analysis set type  | Per protocol   |

Subject analysis set description:

The PP population for the efficacy analysis included all FAS subjects who did not show protocol deviations which could have a relevant influence on the assessment of the primary endpoint. To be accountable for the PP population a trial subject took 80 – 120% of IMP during each of the both treatment periods and the last three scheduled doses of IMP prior to the saccharin test at the end of treatment period 1 (V 2) and the end of treatment period 2 (V 4).

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Sinupret-FAS  |
| Subject analysis set type  | Full analysis |

Subject analysis set description:

The FAS for the efficacy analysis included all randomised subjects with at least one documented application of the investigational drug and evaluable saccharin tests at the beginning and end of the active treatment period and the beginning and end of the corresponding placebo period.

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Sinupret-PP  |
| Subject analysis set type  | Per protocol |

Subject analysis set description:

The PP population for the efficacy analysis included all FAS subjects who did not show protocol

deviations which could have a relevant influence on the assessment of the primary endpoint.  
To be accountable for the PP population a trial subject took 80 – 120% of IMP during each of the both treatment periods and the last three scheduled doses of IMP prior to the saccharin test at the end of treatment period 1 (V 2) and the end of treatment period 2 (V 4).

| Reporting group values                                | Bronchipret-FAS | Bronchipret-PP | Sinupret-FAS |
|---|-----------------|----------------|--------------|
| Number of subjects                                    | 28              | 25             | 28           |
| Age categorical<br>Units: Subjects                    |                 |                |              |
| In utero  | 0               | 0              | 0            |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0               | 0              | 0            |
| Newborns (0-27 days)                                  | 0               | 0              | 0            |
| Infants and toddlers (28 days-23 months)              | 0               | 0              | 0            |
| Children (2-11 years)                                 | 0               | 0              | 0            |
| Adolescents (12-17 years)                             | 0               | 0              | 0            |
| Adults (18-64 years)                                  | 28              | 25             | 28           |
| From 65-84 years                                      | 0               | 0              | 0            |
| 85 years and over                                     | 0               | 0              | 0            |
| Age continuous<br>Units: years                        |                 |                |              |
| arithmetic mean                                       | 32.6            | 32.8           | 30.9         |
| standard deviation                                    | ± 5.2           | ± 5.3          | ± 3.8        |
| Gender categorical<br>Units: Subjects                 |                 |                |              |
| Female  | 15              | 15             | 12           |
| Male  | 13              | 10             | 16           |

| Reporting group values                                | Sinupret-PP |  |  |
|---|-------------|--|--|
| Number of subjects                                    | 21          |  |  |
| Age categorical<br>Units: Subjects                    |             |  |  |
| In utero  | 0           |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 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)                                  | 21          |  |  |
| From 65-84 years                                      | 0           |  |  |
| 85 years and over                                     | 0           |  |  |
| Age continuous<br>Units: years                        |             |  |  |
| arithmetic mean                                       | 31.1        |  |  |
| standard deviation                                    | ± 4.0       |  |  |
| Gender categorical<br>Units: Subjects                 |             |  |  |
| Female  | 9           |  |  |
| Male  | 12          |  |  |

## End points

### End points reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Bronchipret Treatment |
|-----------------------|-----------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group A: Treatment period 1: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day).

Group B: Treatment period 1: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day).

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sinupret Treatment |
|-----------------------|--------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group C: Treatment period 1: 2 CTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day).

Group D: Treatment period 1: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day).

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Bronchipret-Placebo Treatment |
|-----------------------|-------------------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group A: Treatment period 1: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day).

Group B: Treatment period 1: 2 FCTs of Bronchipret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Bronchipret® (verum) TID for 7 days ( $\pm 1$  day).

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Sinupret-Placebo Treatment |
|-----------------------|----------------------------|

Reporting group description:

At Visit 1 (Day 0), subjects were randomly assigned to the following blinded treatment groups:

Group C: Treatment period 1: 2 CTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day).

Group D: Treatment period 1: 2 CTs of Sinupret® placebo TID for 7 days ( $\pm 1$  day), Wash-out for 7 days (+7 days), Treatment period 2: 2 FCTs of Sinupret® (verum) TID for 7 days ( $\pm 1$  day).

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Bronchipret-FAS |
|----------------------------|-----------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The FAS for the efficacy analysis included all randomised subjects with at least one documented application of the investigational drug and evaluable saccharin tests at the beginning and end of the active treatment period and the beginning and end of the corresponding placebo period.

|                            |                |
|----------------------------|----------------|
| Subject analysis set title | Bronchipret-PP |
|----------------------------|----------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The PP population for the efficacy analysis included all FAS subjects who did not show protocol deviations which could have a relevant influence on the assessment of the primary endpoint.

To be accountable for the PP population a trial subject took 80 – 120% of IMP during each of the both treatment periods and the last three scheduled doses of IMP prior to the saccharin test at the end of treatment period 1 (V 2) and the end of treatment period 2 (V 4).

|                            |              |
|----------------------------|--------------|
| Subject analysis set title | Sinupret-FAS |
|----------------------------|--------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The FAS for the efficacy analysis included all randomised subjects with at least one documented application of the investigational drug and evaluable saccharin tests at the beginning and end of the active treatment period and the beginning and end of the corresponding placebo period.

|                            |             |
|----------------------------|-------------|
| Subject analysis set title | Sinupret-PP |
|----------------------------|-------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The PP population for the efficacy analysis included all FAS subjects who did not show protocol deviations which could have a relevant influence on the assessment of the primary endpoint.

To be accountable for the PP population a trial subject took 80 – 120% of IMP during each of the both treatment periods and the last three scheduled doses of IMP prior to the saccharin test at the end of

**Primary: Relative time to perception of sweetness after 7 days treatment with Bronchipret**

|                 |   |
|-----------------|---|
| End point title | Relative time to perception of sweetness after 7 days treatment with Bronchipret <sup>[1]</sup> |
|-----------------|---|

## End point description:

The primary endpoint was defined as the time to perception of sweetness following the placement of a particle of sodium saccharin on the surface of the inferior nasal concha after 7 days of oral treatment with the investigational products or placebo - relative to the time to perception of sweetness at the beginning of treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

## End point timeframe:

The relative time to perception of sweetness (tps) after 7 days of treatment with the investigational products (relative to the tps before the beginning of treatment) in each treatment period is defined as the primary endpoint.

## Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The overall aim of this trial was to demonstrate the superiority of Bronchipret® and/or Sinupret® over placebo regarding acceleration of MCC . Therefore, 2 analyses were performed for the primary endpoint: one comparing the treatment with Bronchipret vs. Bronchipret placebo and another one comparing the treatment with Sinupret vs. Sinupret placebo regarding the acceleration of MCC.

| End point values                     | Bronchipret Treatment | Bronchipret-Placebo Treatment |  |  |
|--------------------------------------|-----------------------|-------------------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group               |  |  |
| Number of subjects analysed          | 25                    | 25                            |  |  |
| Units: seconds                       |                       |                               |  |  |
| arithmetic mean (standard deviation) | 101.2 (± 59.2)        | 111.6 (± 59.1)                |  |  |

**Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Treatment difference of Bronchipret® and placebo |
|-----------------------------------|--|

## Statistical analysis description:

Treatment difference of Bronchipret® and placebo on relative time to perception of sweetness after 7 days treatment tested by ANOVA

|   |   |
|---|---|
| Comparison groups                       | Bronchipret Treatment v Bronchipret-Placebo Treatment |
| Number of subjects included in analysis | 50  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.364   |
| Method                                  | ANOVA   |
| Parameter estimate                      | Mean difference (final values)                        |
| Point estimate                          | 0.89  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.68  |
| upper limit                             | 1.16  |

## Primary: Relative time to perception of sweetness after 7 days treatment with Sinupret

|                 |  |
|-----------------|--|
| End point title | Relative time to perception of sweetness after 7 days treatment with Sinupret <sup>[2]</sup> |
|-----------------|--|

### End point description:

The primary endpoint was defined as the time to perception of sweetness following the placement of a particle of sodium saccharin on the surface of the inferior nasal concha after 7 days of oral treatment with the investigational products or placebo - relative to the time to perception of sweetness at the beginning of treatment.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

### End point timeframe:

The relative time to perception of sweetness (tps) after 7 days of treatment with the investigational products (relative to the tps before the beginning of treatment) in each treatment period is defined as the primary endpoint.

### Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The overall aim of this trial was to demonstrate the superiority of Bronchipret® and/or Sinupret® over placebo regarding acceleration of MCC. Therefore, 2 analyses were performed for the primary endpoint: one comparing the treatment with Bronchipret vs. Bronchipret placebo and another one comparing the treatment with Sinupret vs. Sinupret placebo regarding the acceleration of MCC.

| End point values                     | Sinupret Treatment | Sinupret-Placebo Treatment |  |  |
|--------------------------------------|--------------------|----------------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group            |  |  |
| Number of subjects analysed          | 21                 | 21                         |  |  |
| Units: seconds                       |                    |                            |  |  |
| arithmetic mean (standard deviation) | 128.6 (± 91.2)     | 107.8 (± 57.2)             |  |  |

## Statistical analyses

|                            |                                     |
|----------------------------|-------------------------------------|
| Statistical analysis title | Relative tps after 7 days treatment |
|----------------------------|-------------------------------------|

### Statistical analysis description:

Treatment difference of Sinupret® and placebo on relative time to perception of sweetness tested by ANOVA

|   |   |
|---|---|
| Comparison groups                       | Sinupret Treatment v Sinupret-Placebo Treatment |
| Number of subjects included in analysis | 42  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.66  |
| Method                                  | ANOVA   |
| Parameter estimate                      | Mean difference (final values)                  |
| Point estimate                          | 1.07  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.77  |
| upper limit                             | 1.51  |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs during the treatment period are reported. All AEs occurring during wash-out periods were added to the preceding active treatment or placebo period, respectively.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Sinupret-Placebo Treatment |
|-----------------------|----------------------------|

|                                |  |
|--------------------------------|--|
| Reporting group description: - |  |
|--------------------------------|--|

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Sinupret Treatment |
|-----------------------|--------------------|

|                                |  |
|--------------------------------|--|
| Reporting group description: - |  |
|--------------------------------|--|

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Bronchipret Treatment |
|-----------------------|-----------------------|

|                                |  |
|--------------------------------|--|
| Reporting group description: - |  |
|--------------------------------|--|

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Bronchipret-Placebo Treatment |
|-----------------------|-------------------------------|

|                                |  |
|--------------------------------|--|
| Reporting group description: - |  |
|--------------------------------|--|

| Serious adverse events                            | Sinupret-Placebo Treatment | Sinupret Treatment | Bronchipret Treatment |
|---|----------------------------|--------------------|-----------------------|
| Total subjects affected by serious adverse events |                            |                    |                       |
| subjects affected / exposed                       | 0 / 28 (0.00%)             | 0 / 28 (0.00%)     | 0 / 28 (0.00%)        |
| number of deaths (all causes)                     | 0                          | 0                  | 0                     |
| number of deaths resulting from adverse events    | 0                          | 0                  | 0                     |

| Serious adverse events                            | Bronchipret-Placebo Treatment |  |  |
|---|-------------------------------|--|--|
| Total subjects affected by serious adverse events |                               |  |  |
| subjects affected / exposed                       | 0 / 28 (0.00%)                |  |  |
| number of deaths (all causes)                     | 0                             |  |  |
| number of deaths resulting from adverse events    | 0                             |  |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | Sinupret-Placebo Treatment | Sinupret Treatment | Bronchipret Treatment |
|---|----------------------------|--------------------|-----------------------|
| Total subjects affected by non-serious adverse events |                            |                    |                       |
| subjects affected / exposed                           | 15 / 28 (53.57%)           | 13 / 28 (46.43%)   | 15 / 28 (53.57%)      |

|   |   |   |   |
|---|---|---|---|
| Vascular disorders<br>Haematoma<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 1 / 28 (3.57%)<br>1   | 0 / 28 (0.00%)<br>0   | 0 / 28 (0.00%)<br>0   |
| Surgical and medical procedures<br>Mole excision<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 28 (0.00%)<br>0   | 0 / 28 (0.00%)<br>0   | 1 / 28 (3.57%)<br>1   |
| General disorders and administration site conditions<br>Fatigue<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza like illness<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 28 (3.57%)<br>1<br><br><br>0 / 28 (0.00%)<br>0<br><br>1 / 28 (3.57%)<br>1 | 1 / 28 (3.57%)<br>1<br><br><br>0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0<br><br><br>1 / 28 (3.57%)<br>1<br><br>0 / 28 (0.00%)<br>0 |
| Reproductive system and breast disorders<br>Breast inflammation<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 28 (0.00%)<br>0   | 1 / 28 (3.57%)<br>1   | 0 / 28 (0.00%)<br>0   |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>alternative assessment type: Non-systematic  | 0 / 28 (0.00%)<br>0   | 0 / 28 (0.00%)<br>0   | 0 / 28 (0.00%)<br>0   |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Dyspnoea exertional                            |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 1 / 28 (3.57%) | 0 / 28 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Increased upper airway secretion               |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 2 / 28 (7.14%) | 0 / 28 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 2              | 0              | 0              |
| Nasal obstruction                              |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 1 / 28 (3.57%) | 0 / 28 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)                              | 1              | 0              | 1              |
| Oropharyngeal pain                             |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 0 / 28 (0.00%) | 1 / 28 (3.57%) | 1 / 28 (3.57%) |
| occurrences (all)                              | 0              | 1              | 1              |
| Rhinorrhoea                                    |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 0 / 28 (0.00%) | 2 / 28 (7.14%) | 2 / 28 (7.14%) |
| occurrences (all)                              | 0              | 2              | 2              |
| Upper-airway cough syndrome                    |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 0 / 28 (0.00%) | 0 / 28 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Psychiatric disorders                          |                |                |                |
| Insomnia                                       |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |
| subjects affected / exposed                    | 1 / 28 (3.57%) | 1 / 28 (3.57%) | 2 / 28 (7.14%) |
| occurrences (all)                              | 1              | 1              | 4              |
| Injury, poisoning and procedural complications |                |                |                |
| Muscle rupture                                 |                |                |                |
| alternative assessment type: Non-systematic    |                |                |                |

|  |   |   |   |
|--|---|---|---|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Wound</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 28 (3.57%)</p> <p>1</p> <p>0 / 28 (0.00%)</p> <p>0</p>                                 | <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p>                                 | <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p>                                 |
| <p>Nervous system disorders</p> <p>Headache</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Migraine</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tremor</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 28 (17.86%)</p> <p>5</p> <p>1 / 28 (3.57%)</p> <p>1</p> <p>1 / 28 (3.57%)</p> <p>1</p> | <p>5 / 28 (17.86%)</p> <p>5</p> <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p> | <p>5 / 28 (17.86%)</p> <p>6</p> <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p> |
| <p>Eye disorders</p> <p>Eye pruritus</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eye swelling</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p>                                 | <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p>                                 | <p>0 / 28 (0.00%)</p> <p>0</p> <p>0 / 28 (0.00%)</p> <p>0</p>                                 |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>alternative assessment type: Non-systematic</p>  | <p>0 / 28 (0.00%)</p> <p>0</p>  | <p>0 / 28 (0.00%)</p> <p>0</p>  | <p>1 / 28 (3.57%)</p> <p>1</p>  |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                 | 1 / 28 (3.57%) | 0 / 28 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                           | 1              | 0               | 0              |
| Diarrhoea                                   |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 1 / 28 (3.57%) | 3 / 28 (10.71%) | 1 / 28 (3.57%) |
| occurrences (all)                           | 1              | 3               | 1              |
| Dry mouth                                   |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 0 / 28 (0.00%) | 0 / 28 (0.00%)  | 1 / 28 (3.57%) |
| occurrences (all)                           | 0              | 0               | 1              |
| Flatulence                                  |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 1 / 28 (3.57%) | 2 / 28 (7.14%)  | 2 / 28 (7.14%) |
| occurrences (all)                           | 1              | 2               | 2              |
| Frequent bowel movements                    |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 1 / 28 (3.57%) | 1 / 28 (3.57%)  | 0 / 28 (0.00%) |
| occurrences (all)                           | 1              | 1               | 0              |
| Gingival inflammation                       |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 0 / 28 (0.00%) | 0 / 28 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                           | 0              | 0               | 0              |
| Haemorrhoids                                |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 1 / 28 (3.57%) | 0 / 28 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                           | 1              | 0               | 0              |
| Nausea                                      |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 0 / 28 (0.00%) | 0 / 28 (0.00%)  | 1 / 28 (3.57%) |
| occurrences (all)                           | 0              | 0               | 1              |
| Reflux gastritis                            |                |                 |                |
| alternative assessment type: Non-systematic |                |                 |                |
| subjects affected / exposed                 | 0 / 28 (0.00%) | 0 / 28 (0.00%)  | 1 / 28 (3.57%) |
| occurrences (all)                           | 0              | 0               | 1              |

|  |   |  |  |
|--|---|--|--|
| Toothache<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 28 (0.00%)<br>0   | 0 / 28 (0.00%)<br>0  | 0 / 28 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Acne<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Hyperhidrosis<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 28 (3.57%)<br>1<br><br>1 / 28 (3.57%)<br>1<br><br>0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>1 / 28 (3.57%)<br>1 | 0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>1 / 28 (3.57%)<br>1<br><br>0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>1 / 28 (3.57%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal pain<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in extremity  | 0 / 28 (0.00%)<br>0<br><br>1 / 28 (3.57%)<br>1<br><br>  | 0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>   | 0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>   |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 | 1 / 28 (3.57%)<br>1 |
| <b>Infections and infestations</b>  |                     |                     |                     |
| Gastroenteritis   |                     |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 | 1 / 28 (3.57%)<br>1 |
| Lower respiratory tract infection   |                     |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 28 (3.57%)<br>1 | 0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Nasopharyngitis   |                     |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Oral herpes   |                     |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 | 1 / 28 (3.57%)<br>1 |
| Pulpitis dental   |                     |                     |                     |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | 1 / 28 (3.57%)<br>1 | 0 / 28 (0.00%)<br>0 |

|   |                               |  |  |
|---|-------------------------------|--|--|
| <b>Non-serious adverse events</b>   | Bronchipret-Placebo Treatment |  |  |
| Total subjects affected by non-serious adverse events   |                               |  |  |
| subjects affected / exposed   | 18 / 28 (64.29%)              |  |  |
| <b>Vascular disorders</b>   |                               |  |  |
| Haematoma   |                               |  |  |
| alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0           |  |  |
| <b>Surgical and medical procedures</b>  |                               |  |  |

|   |   |  |  |
|---|---|--|--|
| Mole excision<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 1 / 28 (3.57%)<br>1   |  |  |
| General disorders and administration site conditions<br>Fatigue<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza like illness<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0<br><br>0 / 28 (0.00%)<br>0<br><br>1 / 28 (3.57%)<br>1 |  |  |
| Reproductive system and breast disorders<br>Breast inflammation<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 28 (0.00%)<br>0   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea exertional<br>alternative assessment type: Non-systematic  | 1 / 28 (3.57%)<br>1<br><br>0 / 28 (0.00%)<br>0<br><br>                    |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>  |  |  |  |
| <p>Increased upper airway secretion</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>   |  |  |  |
| <p>Nasal obstruction</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>1 / 28 (3.57%)</p> <p>occurrences (all)</p> <p>1</p>  |  |  |  |
| <p>Oropharyngeal pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>2 / 28 (7.14%)</p> <p>occurrences (all)</p> <p>2</p>   |  |  |  |
| <p>Rhinorrhoea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>  |  |  |  |
| <p>Upper-airway cough syndrome</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>1 / 28 (3.57%)</p> <p>occurrences (all)</p> <p>1</p>  |  |  |  |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>2 / 28 (7.14%)</p> <p>occurrences (all)</p> <p>3</p>  |  |  |  |
| <p>Injury, poisoning and procedural complications</p> <p>Muscle rupture</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Wound</p> <p>alternative assessment type: Non-systematic</p> |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                 | 1 / 28 (3.57%)  |  |  |
| occurrences (all)                           | 1               |  |  |
| Nervous system disorders                    |                 |  |  |
| Headache                                    |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 3 / 28 (10.71%) |  |  |
| occurrences (all)                           | 3               |  |  |
| Migraine                                    |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%)  |  |  |
| occurrences (all)                           | 0               |  |  |
| Tremor                                      |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%)  |  |  |
| occurrences (all)                           | 0               |  |  |
| Eye disorders                               |                 |  |  |
| Eye pruritus                                |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%)  |  |  |
| occurrences (all)                           | 1               |  |  |
| Eye swelling                                |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%)  |  |  |
| occurrences (all)                           | 1               |  |  |
| Gastrointestinal disorders                  |                 |  |  |
| Abdominal pain                              |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 2 / 28 (7.14%)  |  |  |
| occurrences (all)                           | 2               |  |  |
| Constipation                                |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |
| subjects affected / exposed                 | 2 / 28 (7.14%)  |  |  |
| occurrences (all)                           | 2               |  |  |
| Diarrhoea                                   |                 |  |  |
| alternative assessment type: Non-systematic |                 |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                 | 2 / 28 (7.14%) |  |  |
| occurrences (all)                           | 2              |  |  |
| Dry mouth                                   |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%) |  |  |
| occurrences (all)                           | 0              |  |  |
| Flatulence                                  |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%) |  |  |
| occurrences (all)                           | 1              |  |  |
| Frequent bowel movements                    |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 2 / 28 (7.14%) |  |  |
| occurrences (all)                           | 2              |  |  |
| Gingival inflammation                       |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%) |  |  |
| occurrences (all)                           | 1              |  |  |
| Haemorrhoids                                |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%) |  |  |
| occurrences (all)                           | 0              |  |  |
| Nausea                                      |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%) |  |  |
| occurrences (all)                           | 1              |  |  |
| Reflux gastritis                            |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%) |  |  |
| occurrences (all)                           | 0              |  |  |
| Toothache                                   |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%) |  |  |
| occurrences (all)                           | 1              |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>Skin and subcutaneous tissue disorders</p> <p>Acne</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Dry skin</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Hyperhidrosis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>1 / 28 (3.57%)</p> <p>occurrences (all)</p> <p>1</p> <p>Pruritus</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>1 / 28 (3.57%)</p> <p>occurrences (all)</p> <p>1</p> <p>Rash</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> |  |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Musculoskeletal pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>1 / 28 (3.57%)</p> <p>occurrences (all)</p> <p>1</p> <p>Myalgia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Pain in extremity</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>0 / 28 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>   |  |  |  |
| <p>Infections and infestations</p>   |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Gastroenteritis                             |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%) |  |  |
| occurrences (all)                           | 0              |  |  |
| Lower respiratory tract infection           |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%) |  |  |
| occurrences (all)                           | 0              |  |  |
| Nasopharyngitis                             |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 2 / 28 (7.14%) |  |  |
| occurrences (all)                           | 2              |  |  |
| Oral herpes                                 |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 1 / 28 (3.57%) |  |  |
| occurrences (all)                           | 1              |  |  |
| Pulpitis dental                             |                |  |  |
| alternative assessment type: Non-systematic |                |  |  |
| subjects affected / exposed                 | 0 / 28 (0.00%) |  |  |
| occurrences (all)                           | 0              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 25 October 2013 | <p>The Amendment No. 1 was necessary to implement that the inclusion criterion number 4 is proven by assessing ability to taste sweetness of saccharin on the basis of saccharin test (perception of sweetness within 30 minutes after placement of saccharin behind nasal valve) at V 0. Therefore, placing saccharin particles on the tongue for the "assessment of the ability to taste sweetness of saccharin" as required by protocol at V 0 was not necessary and was deleted. Due to the fact that the taste of saccharin can persist a certain time, it is not adequate to apply saccharin on tongue shortly prior the saccharin test.</p> <p>Furthermore some editorial corrections for clarification were done. Additionally, the planned time lines of trial conduct were adapted.</p> <p>These changes had no substantial implications on the scientific value of the trial, the conduct of the trial or the safety of the trial subjects.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported