# Clinical trial results:
# Efficacy and tolerability clinical trial of Lantigen B (A bacterial lysate having immunostimulating activity) in the prophylaxis of respiratory infections, with special reference to patients with allergy to perennial inhalants. Double-blind multicenter, randomized study vs. placebo.

## Summary

| | |
|---|---|
| EudraCT number | 2011-003239-76 |
| Trial protocol | IT |
| Global end of trial date | 28 October 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 February 2020 |
| First version publication date | 21 February 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | LAN-BR-11-001 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Bruschettini S.r.l. |
| Sponsor organisation address | Via Isonzo, Genoa, Italy, 16127 |
| Public contact | Clinical Research Department, Medi Service SRL, 0039 039-6057074, medi@mediservice.it |
| Scientific contact | Clinical Research Department, Medi Service SRL, 0039 039-6057074, medi@mediservice.it |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 10 October 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Evaluation of the efficacy of LANTIGEN B vs. placebo, in reducing, during a 8-month period, the number of infective episodes of the respiratory tract .

Protection of trial subjects:

During the study follow-up, to minimise the patients pain/distress, it was permitted to take the following concomitant medications:
antibiotics, decongestant, mucolytics.

Background therapy:

During the two weeks preceding the randomization the following drugs were not allowed: Immune-stimulants, gamma-globulines, etc. of the ATC group J06 and J07AX; Anti-neoplastic drugs of the ATC group L01; Cytokines, interleukins, interferon, immune-suppressants of the ATC group L03 and L04.

After the randomization and during the study (including the follow-up period) the following drugs were not permitted: Immune-stimulants of the ATC group J07AX; Anti-neoplastic drugs of the ATC group L01; Cytokines, interleukins, interferon, immune-suppressants of the ATC group L03 and L04; Systemic steroids (if used for more than 2 weeks); Any drug product or dietary supplement containing zinc (if used for more than one week); Any other product with immune-stimulant features.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 September 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Italy: 160 |
| Worldwide total number of subjects | 160 |
| EEA total number of subjects | 160 |

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) | 151 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 160 subjects were enrolled in 12 Italian Clinical Centres in the period September 2012 - January 2013.

### Pre-assignment

Screening details:

Run-in and/or screening periods were not planned in the study design. Randomization visit (Visit 1) was considered as baseline period.
Wash-out period: during the two weeks preceding the randomization the following drugs were not allowed: ATC groups J06, J07AX, L01, L03 and L04.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Lantigen B |

Arm description:

Lantigen B is a suspension of bacterial antigens obtained from Streptococcus pneumoniae type 3, Streptococcus pyogenes Group A, Branhamella catarrhalis, Staphylococcus aureus, Hemophilus influenzae type b and Klebsiella pneumoniae.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lantigen B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops |
| Routes of administration | Oral use |

Dosage and administration details:

Administration: 15 oral drops twice daily (morning and evening) for 4 weeks, followed by 2 weeks off + 4 weeks of treatment + 6 weeks off, for a total of 16 weeks in two cycles.

| | |
|---|---|
| **Arm title** | placebo |

Arm description:

placebo

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral drops |
| Routes of administration | Oral use |

Dosage and administration details:

Administration: 15 oral drops twice daily (morning and evening) for 4 weeks, followed by 2 weeks off + 4 weeks of treatment + 6 weeks off, for a total of 16 weeks in two cycles

| **Number of subjects in period 1** | Lantigen B | placebo |
|---|---|---|
| Started | 79 | 81 |
| Completed | 62 | 58 |
| Not completed | 17 | 23 |
| Familiar reasons | - | 1 |
| Consent withdrawn by subject | 10 | 13 |
| Adverse event, non-fatal | 1 | 2 |
| Patient not contactable | - | 1 |
| Lost to follow-up | 1 | 4 |
| Protocol deviation | 5 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Lantigen B |
| Reporting group description: | |
| Lantigen B is a suspension of bacterial antigens obtained from Streptococcus pneumoniae type 3, Streptococcus pyogenes Group A, Branhamella catarrhalis, Staphylococcus aureus, Hemophilus influenzae type b and Klebsiella pneumoniae. | |

| | |
|---|---|
| Reporting group title | placebo |
| Reporting group description: | |
| placebo | |

| Reporting group values | Lantigen B | placebo | Total |
|---|---|---|---|
| Number of subjects | 79 | 81 | 160 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 42.38 | 42.43 | |
| standard deviation | ± 13.937 | ± 15.146 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 54 | 58 | 112 |
| Male | 25 | 23 | 48 |
| Number of previous infectious episodes | | | |
| Number of infectious episodes of the respiratory tract in the previous year. | | | |
| Units: number | | | |
| arithmetic mean | 3.67 | 3.84 | |
| standard deviation | ± 1.615 | ± 1.337 | - |
| Number of previous allergic episodes | | | |
| Number of allergic episodes in the previous year. | | | |
| Units: number | | | |
| arithmetic mean | 1.57 | 1.25 | |
| standard deviation | ± 4.376 | ± 2.467 | - |

## End points

### End points reporting groups

| Reporting group title | Lantigen B |
|---|---|

Reporting group description:

Lantigen B is a suspension of bacterial antigens obtained from Streptococcus pneumoniae type 3, Streptococcus pyogenes Group A, Branhamella catarrhalis, Staphylococcus aureus, Hemophilus influenzae type b and Klebsiella pneumoniae.

| Reporting group title | placebo |
|---|---|

Reporting group description:

placebo

### Primary: Number of respiratory infectious episode

| End point title | Number of respiratory infectious episode |
|---|---|

End point description:

An infectious episode was defined as "new" if at least 72 hours had passed, in the complete absence of symptoms, from the resolution of the previous episode.

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

End point timeframe:

Respiratory infectious episodes during the 8 months of follow-up

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59[1] | 58[2] | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 0.86 (± 1.238) | 1.43 (± 1.613) | | |

Notes:

[1] - ITT Population

[2] - ITT population

### Statistical analyses

| Statistical analysis title | Independent-Samples t-test / GLM analysis |
|---|---|

Statistical analysis description:

Independent-Samples t-test.
ANCOVA Analysis, adjusting for the number of previous infectious episodes and gender.

| Comparison groups | Lantigen B v placebo |
|---|---|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.036 [4] |
| Method | t-test, 2-sided |
| Parameter estimate | Cox proportional hazard |

Notes:

[3] - ITT Population: Primary end-point analysis

[4] - ANCOVA, applied by adjusting for the number of previous infectious episodes and gender, confirmed this finding (p=0.019).
Wilcoxon Rank-sum Test p-value = 0.080.

## Secondary: Number of days with respiratory infectious episodes

| End point title | Number of days with respiratory infectious episodes |
|---|---|

End point description:

Number of days with respiratory infectious episodes during 8 months

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

End point timeframe:

8 months follow-up study

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59[5] | 58[6] | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 5.83 (± 9.839) | 10.14 (± 15.575) | | |

Notes:

[5] - ITT Population

[6] - ITT Population

### Statistical analyses

| Statistical analysis title | Independent-Samples t-test / GLM analysis |
|---|---|

Statistical analysis description:

Independent-Samples t-test.
ANCOVA Analysis, adjusting for the number of previous infectious episodes and gender.

| Comparison groups | Lantigen B v placebo |
|---|---|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.076 [8] |
| Method | t-test, 2-sided |

Notes:

[7] - Secondary end-point analysis.

[8] - The ANCOVA, applied by adjusting for the number of previous infectious episodes and gender, confirmed this finding (p=0.102).

## Secondary: Number of days with episodes of allergy

| End point title | Number of days with episodes of allergy |
|---|---|

End point description:

Number of days with episodes of allergy during the 8 months of follow-up.

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

End point timeframe:

During the 8 months of follow-up study.

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59[9] | 58[10] | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 12.69 (± 31.701) | 2.84 (± 7.991) | | |

Notes:

[9] - ITT Population

[10] - ITT Population

### Statistical analyses

| Statistical analysis title | Independent-Samples t-test / GLM analysis |
|---|---|

Statistical analysis description:

Independent-Samples t-test.
ANCOVA Analysis, adjusting for the number of previous infectious episodes and gender.

| Comparison groups | Lantigen B v placebo |
|---|---|
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.024 [12] |
| Method | t-test, 2-sided |

Notes:

[11] - Secondary end-point analysis

[12] - The ANCOVA, applied by adjusting for the number of previous infectious episodes and gender, not confirmed this finding (p=0.056).

## Secondary: Number of days lost at work or school

| End point title | Number of days lost at work or school |
|---|---|

End point description:

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

End point timeframe:

Period: 8 months follow-up study.

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59[13] | 57[14] | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 0.75 (± 2.570) | 0.79 (± 2.433) | | |

Notes:

[13] - ITT Population

[14] - ITT Population (missing value for 1 subject)

### Statistical analyses

| Statistical analysis title | Independent-Samples t-test |
|---|---|
| Comparison groups | Lantigen B v placebo |

| | |
|---|---|
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.925 |
| Method | t-test, 2-sided |

Notes:
[15] - Secondary end-point analysis

## Secondary: General well-being

| | |
|---|---|
| End point title | General well-being |

End point description:
Evaluated by the subjects using a VAS scale (from 0 to 10).

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

End point timeframe:
End of Study: after 2 treatment cycles.

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59[16] | 56[17] | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 7.28 (± 1.708) | 7.47 (± 1.283) | | |

Notes:
[16] - ITT population
[17] - ITT population: missing values for 2 subjects.

### Statistical analyses

| Statistical analysis title | Independent-Samples t-test |
|---|---|
| Comparison groups | Lantigen B v placebo |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[18] |
| P-value | = 0.496 |
| Method | t-test, 2-sided |

Notes:
[18] - Secondary end-point analysis

## Secondary: Global efficacy

| | |
|---|---|
| End point title | Global efficacy |

End point description:
The global efficacy was evaluated by the Investigator using a 5-item scale.

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

End point timeframe:
End of Study Visit

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58[19] | 57[20] | | |
| Units: number | | | | |
| Worsened | 2 | 3 | | |
| Unchanged | 25 | 22 | | |
| Improved | 31 | 32 | | |

Notes:

[19] - ITT Population: missing value for 1 subject

[20] - ITT Population: missing value for 1 subject

### Statistical analyses

| Statistical analysis title | Chi Square test |
|---|---|
| Comparison groups | Lantigen B v placebo |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.686 |
| Method | Chi-squared |

Notes:

[21] - Secondary end-point analysis

## Secondary: Global safety

| End point title | Global safety |
|---|---|

End point description:

The global safety was evaluated by the Investigator using a 5-item scale.

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

End point timeframe:

End of Study Visit

| End point values | Lantigen B | placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59[22] | 57[23] | | |
| Units: number | | | | |
| Excellent | 24 | 21 | | |
| Good | 30 | 29 | | |
| Fair | 5 | 7 | | |

Notes:

[22] - ITT Population

[23] - ITT Population: missing value for 1 subject

### Statistical analyses

| Statistical analysis title | Chi Square test |
|---|---|
| Comparison groups | Lantigen B v placebo |

| | |
|---|---|
| Number of subjects included in analysis | 116 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.735 |
| Method | Chi-squared |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events reported during the study (from baseline to the last visit) were taken into account.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Lantigen B |

Reporting group description:

Lantigen B is a suspension of bacterial antigens obtained from Streptococcus pneumoniae type 3, Streptococcus pyogenes Group A, Branhamella catarrhalis, Staphylococcus aureus, Hemophilus influenzae type b and Klebsiella pneumoniae.

| | |
|---|---|
| Reporting group title | placebo |

Reporting group description:

placebo

| Serious adverse events | Lantigen B | placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 74 (1.35%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung Cancer | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Nasopharynx biopsy | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Hip prosthesis insertion | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0.1 %

| **Non-serious adverse events** | Lantigen B | placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 10 / 76 (13.16%) | 15 / 74 (20.27%) | |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all) | 0 / 76 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 | |
| Surgical and medical procedures<br>Cryosurgery of turbinates<br>subjects affected / exposed<br>occurrences (all) | 1 / 76 (1.32%)<br>1 | 0 / 74 (0.00%)<br>0 | |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br>Migraine<br>subjects affected / exposed<br>occurrences (all) | 2 / 76 (2.63%)<br>2<br>1 / 76 (1.32%)<br>2 | 0 / 74 (0.00%)<br>0<br>0 / 74 (0.00%)<br>0 | |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 76 (0.00%)<br>0 | 2 / 74 (2.70%)<br>2 | |
| Social circumstances<br>Premenopause<br>subjects affected / exposed<br>occurrences (all) | 0 / 76 (0.00%)<br>0 | 1 / 74 (1.35%)<br>1 | |
| Gastrointestinal disorders<br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)<br>Nausea | 0 / 76 (0.00%)<br>0 | 1 / 74 (1.35%)<br>2 | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Duodenogastric reflux | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 74 (2.70%) | |
| occurrences (all) | 2 | 3 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| skin rush | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Genitourinary tract infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 74 (1.35%) | |
| occurrences (all) | 3 | 1 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain ankle | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 74 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lipoma | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 74 (1.35%) | |
| occurrences (all) | 2 | 1 | |
| Herpes labialis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 74 (1.35%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 74 (1.35%) | |
| occurrences (all) | 1 | 1 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported