



## Clinical trial results:

**A phase 2, multicentre, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 400 mg twice a day oral ladarixin in patients with new-onset type 1 diabetes.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003968-20 |
| Trial protocol           | IT DE BE       |
| Global end of trial date | 15 May 2019    |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 09 August 2020 |
| First version publication date | 09 August 2020 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MEX0114 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02814838 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Dompé Farmaceutici S.p.A.  |
| Sponsor organisation address | Via Santa Lucia, 6, Milano, Italy, 20122   |
| Public contact               | Clinical Development, Dompé Farmaceutici S.p.A., Dompé Farmaceutici S.p.A., +39 02583831, info@dompe.com |
| Scientific contact           | Clinical Development, Dompé Farmaceutici S.p.A., Dompé Farmaceutici S.p.A., +39 02583831, info@dompe.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 03 April 2020 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 15 May 2019   |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 15 May 2019   |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this clinical trial is to investigate whether ladarixin has sufficient activity (preservation of  $\beta$ -cell function and slow-down of the progression of T1D) to warrant its further development (proof of concept trial).

Protection of trial subjects:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and applicable International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP) Guidelines and applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 05 August 2016 |
| 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 | Belgium: 31 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Italy: 27   |
| Worldwide total number of subjects   | 76          |
| EEA total number of subjects         | 76          |

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)                      | 76 |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was to be competitive among the study centres, until the planned number of pts were enrolled. Competitive recruitment was chosen to increase the speed of recruitment and to account for any difference among study centres in the rate and timing of patient referral. Each centre recruited pts as rapidly as possible up to a max of 21 pts.

### Pre-assignment

Screening details:

At Screening, from enrolment to randomisation, the patient's past medical history, disease-specific clinical information and date of first insulin administration were to be recorded. The screening includes the assessment of the baseline values.

### Period 1

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

Blinding implementation details:

This was a randomised, double-blind, placebo-controlled study and the Investigator, study centre staff, patients, Sponsor and designee were blinded to treatment assignment.

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Ladarixin - ITT/SAF |

Arm description:

Ladarixin was administered as oral capsules at a dose of 400 mg (2 capsules) BID, for a total daily dose of 800 mg, for 3 cycles of 14 days on/14 days off.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ladarixin    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

The study treatment consisted of 400 mg of ladarixin (2 oral capsules) BID, for a total daily dose of 800 mg, for 3 cycles of 14 days on/14 days off.

The 2 daily doses were to be administered with a glass of water at about 12-hour intervals (morning and evening; ideally between 8.30/9.30 and 20.30/21.30) and at least 2 hours from breakfast or dinner.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Placebo - ITT/SAF |
|------------------|-------------------|

Arm description:

Matching placebo capsules were administered in the same manner as the test product: 2 oral capsules BID, for 3 cycles of 14 days on/14 days off.

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

Dosage and administration details:

Matching placebo capsules were administered in the same manner as the test product. More specifically,

the placebo was administered orally (2 capsules) BID for 3 cycles of 14 days on/14 days off. The 2 daily doses were to be administered with a glass of water at about 12-hour intervals (morning and evening; ideally between 8.30/9.30 and 20.30/21.30) and at least 2 hours from breakfast or dinner.

| <b>Number of subjects in period 1</b>            | Ladarixin - ITT/SAF | Placebo - ITT/SAF |
|--|---------------------|-------------------|
| Started  | 50                  | 26                |
| Completed  | 48                  | 25                |
| Not completed                                    | 2                   | 1                 |
| Consent withdrawn by subject                     | 1                   | 1                 |
| The pt missed 3 agreed dates for the final visit | 1                   | -                 |

## Baseline characteristics

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Ladarixin - ITT/SAF |
|-----------------------|---------------------|

Reporting group description:

Ladarixin was administered as oral capsules at a dose of 400 mg (2 capsules) BID, for a total daily dose of 800 mg, for 3 cycles of 14 days on/14 days off.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo - ITT/SAF |
|-----------------------|-------------------|

Reporting group description:

Matching placebo capsules were administered in the same manner as the test product: 2 oral capsules BID, for 3 cycles of 14 days on/14 days off.

| Reporting group values | Ladarixin - ITT/SAF | Placebo - ITT/SAF | Total |
|------------------------|---------------------|-------------------|-------|
| Number of subjects     | 50                  | 26                | 76    |
| Age categorical        |                     |                   |       |
| Units: Subjects        |                     |                   |       |
| Adults (18-64 years)   | 50                  | 26                | 76    |
| Age continuous         |                     |                   |       |
| Units: years           |                     |                   |       |
| arithmetic mean        | 27.6                | 26.8              |       |
| standard deviation     | ± 7.06              | ± 6.35            | -     |
| Gender categorical     |                     |                   |       |
| Units: Subjects        |                     |                   |       |
| Female                 | 21                  | 10                | 31    |
| Male                   | 29                  | 16                | 45    |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Ladarixin - ITT/SAF |
| Reporting group description:<br>Ladarixin was administered as oral capsules at a dose of 400 mg (2 capsules) BID, for a total daily dose of 800 mg, for 3 cycles of 14 days on/14 days off. |                     |
| Reporting group title   | Placebo - ITT/SAF   |
| Reporting group description:<br>Matching placebo capsules were administered in the same manner as the test product: 2 oral capsules BID, for 3 cycles of 14 days on/14 days off.            |                     |

### Primary: 2-hour area under the curve (AUC) of C-peptide Response to the Mixed Meal Tolerance Test (MMTT) at week 13

|  |  |
|--|--|
| End point title  | 2-hour area under the curve (AUC) of C-peptide Response to the Mixed Meal Tolerance Test (MMTT) at week 13 |
| End point description:<br>C-peptide level is a widely used measure of pancreatic beta-cell function. The MMTT is one of the methods for its estimation. The MMTT was performed after an overnight fast, at baseline (within 1 week prior to randomization), and at each follow-up visit on weeks 13±1, 26±2, and 52±2. All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead. |  |
| End point type   | Primary  |
| End point timeframe:<br>Follow-up at Week 13±1   |  |

| End point values                     | Ladarixin - ITT/SAF | Placebo - ITT/SAF |  |  |
|--------------------------------------|---------------------|-------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed          | 49                  | 26                |  |  |
| Units: log (x+1)                     |                     |                   |  |  |
| arithmetic mean (standard deviation) | 4.026 (± 0.4852)    | 3.886 (± 0.7446)  |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Ladarixin vs Placebo                    |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 75                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[1]</sup>              |
| P-value                                 | = 0.3303                                |
| Method                                  | Student's t test for unpaired samples   |
| Parameter estimate                      | Mean difference (final values)          |
| Point estimate                          | 0.14                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.14   |
| upper limit         | 0.42    |

Notes:

[1] - Transformed AUC was analyzed with Student t-test for unpaired data using PROC TTEST within SAS® to compare Ladarixin and placebo groups. The estimated treatment difference between Ladarixin and placebo was also presented together with the corresponding 95% confidence interval.

## Secondary: 2-hour AUC of C-peptide Response to the Mixed Meal Tolerance Test (MMTT) at weeks 26 and 52

|                 |   |
|-----------------|---|
| End point title | 2-hour AUC of C-peptide Response to the Mixed Meal Tolerance Test (MMTT) at weeks 26 and 52 |
|-----------------|---|

End point description:

C-peptide level is a widely used measure of pancreatic beta-cell function. The MMTT is one of the methods for its estimation. The MMTT was performed after an overnight fast, at baseline (within 1 week prior to randomization), and at each follow-up visit on weeks 13±1, 26±2, and 52±2.

All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead.

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

End point timeframe:

Follow-ups at Weeks 26±2 and 52±2

| End point values                     | Ladarixin - ITT/SAF | Placebo - ITT/SAF  |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[2]</sup>   | 25                 |  |  |
| Units: Log (x+1)                     |                     |                    |  |  |
| arithmetic mean (standard deviation) |                     |                    |  |  |
| Week 26                              | 3.9351 (± 0.51710)  | 3.8076 (± 0.76473) |  |  |
| Week 52                              | 3.6371 (± 0.75222)  | 3.6380 (± 0.81268) |  |  |

Notes:

[2] - n=47 at week 26 and n=46 at week 52

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Ladarixin vs placebo at FUP week 26     |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 72                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[3]</sup>              |
| P-value                                 | = 0.517                                 |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | 0.0984                                  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.2028 |
| upper limit         | 0.3995  |

Notes:

[3] - The comparisons between groups on 2-hour AUC C-peptide efficacy endpoint was carried-out using a mixed linear model where the  $\log(x+1)$  transformed 2-hour AUC C-peptide was the dependent variable, while treatment group, visit, treatment by visit interaction were the fixed factors of the model and patient will be the random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs placebo at FUP week 52     |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 72                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[4]</sup>              |
| P-value                                 | = 0.7999                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.0486                                 |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.4294                                 |
| upper limit                             | 0.3322                                  |

Notes:

[4] - The comparisons between groups on 2-hour AUC C-peptide efficacy endpoint was carried-out using a mixed linear model where the  $\log(x+1)$  transformed 2-hour AUC C-peptide was the dependent variable, while treatment group, visit, treatment by visit interaction were the fixed factors of the model and patient will be the random effect. An unstructured covariance matrix for each patient is considered and the Kenward-Roger adjustment is used for the degrees of freedom.

## Secondary: Percent change from Baseline of 2-hour AUC of C-peptide response to the MMTT

|                 |  |
|-----------------|--|
| End point title | Percent change from Baseline of 2-hour AUC of C-peptide response to the MMTT |
|-----------------|--|

End point description:

Assessment of percent change is a method to evaluate a response regardless of basal condition. All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead.

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

End point timeframe:

Follow-ups at Weeks 13±1, 26±2 and 52±2

| End point values                     | Ladarixin - ITT/SAF   | Placebo - ITT/SAF     |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed          | 49 <sup>[5]</sup>     | 25 <sup>[6]</sup>     |  |  |
| Units: percentage                    |                       |                       |  |  |
| arithmetic mean (standard deviation) |                       |                       |  |  |
| Week 13                              | 5.7818 (± 36.74477)   | -6.0734 (± 38.22179)  |  |  |
| Week 26                              | -0.8701 (± 42.93044)  | -13.7347 (± 37.41900) |  |  |
| Week 52                              | -22.2532 (± 38.84672) | -24.2215 (± 42.67277) |  |  |

Notes:

[5] - n=49 at week 13; n=47 at week 26; n=46 at week 52

[6] - n=25 at week 13 and n=24 at weeks 26 and 52

## Statistical analyses

| Statistical analysis title   | Ladarixin vs placebo at week 13         |
|--|---|
| Statistical analysis description:  |   |
| Analysis is based on a linear mixed model with percent change from baseline of 2-hour AUC of C-peptide as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect. The baseline value of 2-hour AUC C-peptide is included in the model as covariate. |   |
| Comparison groups  | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis  | 74                                      |
| Analysis specification   | Pre-specified                           |
| Analysis type  | superiority                             |
| P-value  | = 0.2224                                |
| Method   | Mixed models analysis                   |
| Parameter estimate   | adjusted mean difference                |
| Point estimate   | 12.0411                                 |
| Confidence interval  |   |
| level  | 95 %                                    |
| sides  | 2-sided                                 |
| lower limit  | -7.3823                                 |
| upper limit  | 31.4644                                 |

| Statistical analysis title   | Ladarixin vs placebo at week 26         |
|--|---|
| Statistical analysis description:  |   |
| Analysis is based on a linear mixed model with percent change from baseline of 2-hour AUC of C-peptide as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect. The baseline value of 2-hour AUC C-peptide is included in the model as covariate. |   |
| Comparison groups  | Placebo - ITT/SAF v Ladarixin - ITT/SAF |
| Number of subjects included in analysis  | 74                                      |
| Analysis specification   | Pre-specified                           |
| Analysis type  | superiority                             |
| P-value  | = 0.3931                                |
| Method   | Mixed models analysis                   |
| Parameter estimate   | adjusted mean difference                |
| Point estimate   | 8.4803                                  |

|                     |          |
|---------------------|----------|
| Confidence interval |          |
| level               | 95 %     |
| sides               | 2-sided  |
| lower limit         | -11.0935 |
| upper limit         | 28.0541  |

|                                   |                                 |
|-----------------------------------|---------------------------------|
| <b>Statistical analysis title</b> | Ladarixin vs placebo at week 52 |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Analysis is based on a linear mixed model with percent change from baseline of 2-hour AUC of C-peptide as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect. The baseline value of 2-hour AUC C-peptide is included in the model as covariate.

|   |   |
|---|---|
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.7664                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -2.9502                                 |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -22.5476                                |
| upper limit                             | 16.6473                                 |

## Secondary: C-peptide AUC(15 to 120 mins) above fasting value

|                 |   |
|-----------------|---|
| End point title | C-peptide AUC(15 to 120 mins) above fasting value |
|-----------------|---|

End point description:

This parameter is a measure of pancreatic response to stimulus independent from any background (fasting) glycemc control.

All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead.

The means are all "adjusted means".

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

End point timeframe:

Follow-ups at Weeks 13±1 26±2 and 52±2

| End point values                          | Ladarixin - ITT/SAF | Placebo - ITT/SAF |  |  |
|---|---------------------|-------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed               | 50                  | 26                |  |  |
| Units: logarithm (x+1)                    |                     |                   |  |  |
| arithmetic mean (confidence interval 95%) |                     |                   |  |  |

|         |                           |                           |  |  |
|---------|---------------------------|---------------------------|--|--|
| week 13 | 3.3736 (3.1730 to 3.5742) | 3.2334 (2.9568 to 3.5100) |  |  |
| week 26 | 3.2419 (3.0186 to 3.4652) | 3.0649 (2.7562 to 3.3735) |  |  |
| week 52 | 2.9733 (2.7150 to 3.2316) | 2.9282 (2.5720 to 3.2844) |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs placebo - week 13          |
| Statistical analysis description:       |   |
| Comparison at week 13                   |   |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 76                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[7]</sup>              |
| P-value                                 | = 0.4163                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | 0.1402                                  |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.2015                                 |
| upper limit                             | 0.4819                                  |

Notes:

[7] - Analysis is based on a linear mixed model for repeated measures with log(AUC(15-120 minutes) +1) of C-peptide above fasting value as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs placebo - week 26          |
| Statistical analysis description:       |   |
| Comparison at week 26                   |   |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 76                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[8]</sup>              |
| P-value                                 | = 0.3575                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | 0.177                                   |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.2039                                 |
| upper limit                             | 0.558                                   |

Notes:

[8] - Analysis is based on a linear mixed model for repeated measures with log(AUC(15-120 minutes) +1) of C-peptide above fasting value as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|  |   |
|--|---|
| <b>Statistical analysis title</b>                          | Ladarixin vs placebo - week 52          |
| Statistical analysis description:<br>Comparison at week 52 |   |
| Comparison groups  | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis                    | 76                                      |
| Analysis specification                                     | Pre-specified                           |
| Analysis type  | superiority <sup>[9]</sup>              |
| P-value  | = 0.8386                                |
| Method   | Mixed models analysis                   |
| Parameter estimate   | adjusted mean difference                |
| Point estimate   | 0.0451                                  |
| Confidence interval  |   |
| level  | 95 %                                    |
| sides  | 2-sided                                 |
| lower limit  | -0.3948                                 |
| upper limit  | 0.4851                                  |

Notes:

[9] - Analysis is based on a linear mixed model for repeated measures with log(AUC(15-120 minutes) +1) of C-peptide above fasting value as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

### Secondary: AUC(0-2h) of C-peptide MMTT in patients with screening C-peptide < median value

|                 |   |
|-----------------|---|
| End point title | AUC(0-2h) of C-peptide MMTT in patients with screening C-peptide < median value |
|-----------------|---|

End point description:

A subgroup analysis of efficacy endpoints by fasting C-peptide at Screening was performed. The reported data specifically refers to fasting C-peptide at Screening < median value. All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead.

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

End point timeframe:

Follow-up at Weeks 13±1, 26±2, and 52±2.

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| End point values                     | Ladarixin - ITT/SAF | Placebo - ITT/SAF  |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed          | 26 <sup>[10]</sup>  | 11 <sup>[11]</sup> |  |  |
| Units: log(x+1)                      |                     |                    |  |  |
| arithmetic mean (standard deviation) |                     |                    |  |  |
| Week 13                              | 3.8085 (± 0.45692)  | 3.4543 (± 0.86632) |  |  |
| Week 26                              | 3.8202 (± 0.48142)  | 3.3178 (± 0.91906) |  |  |
| Week 52                              | 3.3796 (± 0.68616)  | 3.1562 (± 0.97130) |  |  |

Notes:

[10] - n=26 wk 13  
n=25 wk 26  
n=24 wk 52

[11] - n=11 wk 13  
n=10 wk 26  
n=10 wk 52

## Statistical analyses

| Statistical analysis title  | Ladarixin vs Placebo - Week 13          |
|---|---|
| Statistical analysis description:   |   |
| Transformed AUC was analyzed with Student t-test for unpaired data using PROC TTEST within SAS® to compare Ladarixin and placebo groups. The estimated treatment difference between Ladarixin and placebo was also presented together with the corresponding 95% confidence interval. |   |
| Comparison groups   | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis   | 37                                      |
| Analysis specification  | Pre-specified                           |
| Analysis type   | superiority                             |
| P-value   | = 0.1114                                |
| Method  | t-test, 2-sided                         |
| Parameter estimate  | Mean difference (final values)          |
| Point estimate  | 0.354                                   |
| Confidence interval   |   |
| level   | 95 %                                    |
| sides   | 2-sided                                 |
| lower limit   | -0.09                                   |
| upper limit   | 0.75                                    |

| Statistical analysis title  | Ladarixin vs Placebo - Week 26          |
|---|---|
| Statistical analysis description:   |   |
| Transformed AUC was analyzed with Student t-test for unpaired data using PROC TTEST within SAS® to compare Ladarixin and placebo groups. The estimated treatment difference between Ladarixin and placebo was also presented together with the corresponding 95% confidence interval. |   |
| Comparison groups   | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis   | 37                                      |
| Analysis specification  | Pre-specified                           |
| Analysis type   | superiority                             |
| P-value   | = 0.0411                                |
| Method  | t-test, 2-sided                         |
| Parameter estimate  | Mean difference (final values)          |
| Point estimate  | 0.502                                   |
| Confidence interval   |   |
| level   | 95 %                                    |
| sides   | 2-sided                                 |
| lower limit   | 0.02                                    |
| upper limit   | 0.98                                    |

| Statistical analysis title | Ladarixin vs Placebo - Week 52 |
|----------------------------|--------------------------------|
|----------------------------|--------------------------------|

#### Statistical analysis description:

Transformed AUC was analyzed with Student t-test for unpaired data using PROC TTEST within SAS® to compare Ladarixin and placebo groups. The estimated treatment difference between Ladarixin and placebo was also presented together with the corresponding 95% confidence interval.

|   |   |
|---|---|
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 37                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.4506                                |
| Method                                  | t-test, 2-sided                         |
| Parameter estimate                      | Mean difference (final values)          |
| Point estimate                          | 0.223                                   |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.37                                   |
| upper limit                             | 0.82                                    |

#### Secondary: AUC(15-120) of C-peptide MMTT above fasting value in patients with screening C-peptide < median value

|                 |   |
|-----------------|---|
| End point title | AUC(15-120) of C-peptide MMTT above fasting value in patients with screening C-peptide < median value |
|-----------------|---|

#### End point description:

A subgroup analysis of efficacy endpoints by fasting C-peptide at Screening was performed. The reported data specifically refers to fasting C-peptide at Screening <median value. All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead.

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

#### End point timeframe:

Follow-up at Weeks 13±1, 26±2, and 52±2.

| End point values                     | Ladarixin - ITT/SAF  | Placebo - ITT/SAF    |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 26 <sup>[12]</sup>   | 11 <sup>[13]</sup>   |  |  |
| Units: log(x+1)                      |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Week 13                              | 3.1590 (± 0.56135)   | 2.7959 (± 1.07745)   |  |  |
| Week 26                              | 27.7841 (± 15.10337) | 18.6842 (± 15.46837) |  |  |
| Week 52                              | 2.7993 (± 0.82214)   | 19.9415 (± 16.95597) |  |  |

#### Notes:

[12] - n=26 wk 13

n=25 wk 26

n=24 wk 52

[13] - n=11 wk 13

n=10 wk 26

**Statistical analyses**

| <b>Statistical analysis title</b>  | Ladarixin vs Placebo - Week 13          |
|--|---|
| Statistical analysis description:  |   |
| Analysis is based on a linear mixed model for repeated measures with log(AUC(15-120 minutes)+1) of C-peptide above fasting value as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect. |   |
| Comparison groups  | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis  | 37                                      |
| Analysis specification   | Pre-specified                           |
| Analysis type  | superiority                             |
| P-value  | = 0.1847                                |
| Method   | Mixed models analysis                   |
| Parameter estimate   | Adjusted mean difference                |
| Point estimate   | 0.3631                                  |
| Confidence interval  |   |
| level  | 95 %                                    |
| sides  | 2-sided                                 |
| lower limit  | -0.1817                                 |
| upper limit  | 0.908                                   |

| <b>Statistical analysis title</b>  | Ladarixin vs Placebo - Week 26          |
|--|---|
| Statistical analysis description:  |   |
| Analysis is based on a linear mixed model for repeated measures with log(AUC(15-120 minutes)+1) of C-peptide above fasting value as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect. |   |
| Comparison groups  | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis  | 37                                      |
| Analysis specification   | Pre-specified                           |
| Analysis type  | superiority                             |
| P-value  | = 0.031                                 |
| Method   | Mixed models analysis                   |
| Parameter estimate   | Adjusted mean difference                |
| Point estimate   | 0.6304                                  |
| Confidence interval  |   |
| level  | 95 %                                    |
| sides  | 2-sided                                 |
| lower limit  | 0.0609                                  |
| upper limit  | 1.1998                                  |

| <b>Statistical analysis title</b> | Ladarixin vs Placebo - Week 52 |
|-----------------------------------|--------------------------------|
|-----------------------------------|--------------------------------|



#### Statistical analysis description:

Analysis is based on a linear mixed model for repeated measures with log(AUC(15-120 minutes)+1) of C-peptide above fasting value as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|   |   |
|---|---|
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 37                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.6299                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | Adjusted mean difference                |
| Point estimate                          | 0.1639                                  |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.5202                                 |
| upper limit                             | 0.8479                                  |

#### Secondary: Proportion of patients with HbA1c <7% and absence of episodes of severe hypoglycaemia from the previous visit

|                 |   |
|-----------------|---|
| End point title | Proportion of patients with HbA1c <7% and absence of episodes of severe hypoglycaemia from the previous visit |
|-----------------|---|

#### End point description:

This parameter integrates overall glycemic control (HbA1c) with requirement of as low insulin dose as to avoid hypoglycemia.

Proportion is reported as percentage of patients, despite the measure type indicated is "number". Events per patient are calculated from the date of randomisation.

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

#### End point timeframe:

Follow-up at Weeks 13±1, 26±2, and 52±2.

| End point values                 | Ladarixin - ITT/SAF   | Placebo - ITT/SAF     |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 49 <sup>[14]</sup>    | 25 <sup>[15]</sup>    |  |  |
| Units: percentage                |                       |                       |  |  |
| number (confidence interval 95%) |                       |                       |  |  |
| Week 13                          | 90.0 (78.19 to 96.67) | 73.1 (52.21 to 88.43) |  |  |
| Week 26                          | 78.0 (64.4 to 88.47)  | 50.0 (29.93 to 70.07) |  |  |
| Week 52                          | 62.0 (47.17 to 75.35) | 53.8 (33.37 to 73.41) |  |  |

#### Notes:

[14] - n=49 wk 13

n=48 wk 26

n=47 wk 52

[15] - n=25 wk 13

n=24 wk 26

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - Week 13          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.0779                                |
| Method                                  | Fisher exact                            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - Week 26          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.0248                                |
| Method                                  | Fisher exact                            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - Week 52          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.4504                                |
| Method                                  | Fisher exact                            |

**Secondary: Proportion of patients with HbA1c <7% and absence of episodes of severe hypoglycaemia from the previous visit in patients with screening C-peptide < median value**

|                 |   |
|-----------------|---|
| End point title | Proportion of patients with HbA1c <7% and absence of episodes of severe hypoglycaemia from the previous visit in patients with screening C-peptide < median value |
|-----------------|---|

## End point description:

A severe hypoglycaemic event was defined as an event with one of the following symptoms: memory loss, confusion, uncontrollable behaviour, irrational behaviour, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness, or visual symptoms", in which the patient was unable to treat him/herself and which was associated with either a blood glucose level <54 mg/dL or prompt recovery after oral carbohydrate, i.v. glucose, or glucagon administration.

Proportion is reported as percentage of patients, despite the measure type indicated is "number". Events per patient are calculated from the date of randomisation.

|  |           |
|--|-----------|
| End point type                           | Secondary |
| End point timeframe:                     |           |
| Follow-up at Weeks 13±1, 26±2, and 52±2. |           |

| End point values                 | Ladarixin - ITT/SAF   | Placebo - ITT/SAF     |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 26 <sup>[16]</sup>    | 11 <sup>[17]</sup>    |  |  |
| Units: Percentage                |                       |                       |  |  |
| number (confidence interval 95%) |                       |                       |  |  |
| Week 13                          | 88.5 (69.85 to 97.55) | 63.6 (30.79 to 89.07) |  |  |
| Week 26                          | 88.5 (69.85 to 97.55) | 36.4 (10.93 to 69.21) |  |  |
| Week 52                          | 65.4 (44.33 to 82.79) | 45.5 (16.75 to 76.62) |  |  |

Notes:

[16] - n=26 wk 13  
n=25 wk 26  
n=25 wk 52

[17] - n=11 wk 13  
n=9 wk 26  
n=19 wk 52

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - Week 13          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 37                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.163                                 |
| Method                                  | Fisher exact                            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - Week 26          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 37                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.0074                                |
| Method                                  | Fisher exact                            |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Ladarixin vs Placebo - Week 52          |
| Comparison groups                 | Ladarixin - ITT/SAF v Placebo - ITT/SAF |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 37            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.4437      |
| Method                                  | Fisher exact  |

### Secondary: Average (previous 3 days) insulin requirement

|                        |  |
|------------------------|--|
| End point title        | Average (previous 3 days) insulin requirement              |
| End point description: | Insulin requirement was averaged over the previous 3 days. |
| End point type         | Secondary  |
| End point timeframe:   | Follow-up at Weeks 13±1, 26±2, and 52±2.                   |

| End point values                     | Ladarixin - ITT/SAF | Placebo - ITT/SAF  |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[18]</sup>  | 26 <sup>[19]</sup> |  |  |
| Units: IU/kg/day                     |                     |                    |  |  |
| arithmetic mean (standard deviation) |                     |                    |  |  |
| Week 13                              | 0.270 (± 0.1355)    | 0.310 (± 0.1955)   |  |  |
| Week 26                              | 0.334 (± 0.2624)    | 0.369 (± 0.2114)   |  |  |
| Week 52                              | 0.374 (± 0.2105)    | 0.439 (± 0.2349)   |  |  |

Notes:

[18] - n= 47 at weeks 13 and 26

n=46 at week 52

[19] - n= 26 at week 13;

n=25 at weeks 26 and 52

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Ladarixin vs placebo - week 13          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 73                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[20]</sup>             |
| P-value                                 | = 0.2225                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.048                                  |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.1257                                 |
| upper limit                             | 0.0298                                  |

Notes:

[20] - Analysis is based on a linear mixed model for repeated measures with Daily Insulin Requirement (IU/kg/day) as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs placebo - week 26          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 73                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[21]</sup>             |
| P-value                                 | = 0.551                                 |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.0369                                 |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.1596                                 |
| upper limit                             | 0.0858                                  |

Notes:

[21] - Analysis is based on a linear mixed model for repeated measures with Daily Insulin Requirement (IU/kg/day) as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs placebo - week 52          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 73                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[22]</sup>             |
| P-value                                 | = 0.2501                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.063                                  |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.1712                                 |
| upper limit                             | 0.0453                                  |

Notes:

[22] - Analysis is based on a linear mixed model for repeated measures with Daily Insulin Requirement (IU/kg/day) as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

## Secondary: Glycated haemoglobin (HbA1c) levels

|  |                                     |
|--|-------------------------------------|
| End point title  | Glycated haemoglobin (HbA1c) levels |
| End point description:   |                                     |
| HbA1c is a standard measure of glycemic control in diabetes, that reflects peak blood glucose levels reached in the past 2-3 months. |                                     |
| End point type   | Secondary                           |
| End point timeframe:   |                                     |
| Follow-ups at Weeks 13±1, 26±2 and 52±2  |                                     |

| <b>End point values</b>              | Ladarixin -<br>ITT/SAF | Placebo -<br>ITT/SAF |  |  |
|--------------------------------------|------------------------|----------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed          | 49 <sup>[23]</sup>     | 25 <sup>[24]</sup>   |  |  |
| Units: percentage                    |                        |                      |  |  |
| arithmetic mean (standard deviation) |                        |                      |  |  |
| week 13                              | 6.18 (± 0.735)         | 6.37 (± 0.838)       |  |  |
| week 26                              | 6.41 (± 1.200)         | 6.65 (± 1.138)       |  |  |
| week 52                              | 6.86 (± 1.482)         | 6.65 (± 1.122)       |  |  |

Notes:

[23] - n=49 at week 13

n=48 at week 26

n=47 at week 52

[24] - n=25 at week 13

n=24 at week 26

n=25 at week 52

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - week 13          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[25]</sup>             |
| P-value                                 | = 0.6252                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.1494                                 |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.7514                                 |
| upper limit                             | 0.4526                                  |

Notes:

[25] - Analysis is based on a linear mixed model for repeated measures with HbA1c (%) as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - week 26          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[26]</sup>             |
| P-value                                 | = 0.366                                 |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.2804                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.8904 |
| upper limit         | 0.3297  |

Notes:

[26] - Analysis is based on a linear mixed model for repeated measures with HbA1c (%) as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Ladarixin vs Placebo - week 52          |
| Comparison groups                       | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis | 74                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[27]</sup>             |
| P-value                                 | = 0.5026                                |
| Method                                  | Mixed models analysis                   |
| Parameter estimate                      | adjusted mean difference                |
| Point estimate                          | -0.2063                                 |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.3992                                 |
| upper limit                             | 0.8118                                  |

Notes:

[27] - Analysis is based on a linear mixed model for repeated measures with HbA1c (%) as dependent variable, treatment, visit and treatment by visit interaction as fixed effects and patient as random effect.

### Secondary: Proportion of patients maintaining a residual $\beta$ -cell function

|  |  |
|--|--|
| End point title  | Proportion of patients maintaining a residual $\beta$ -cell function |
| End point description:   |  |
| Maintenance of a residual $\beta$ -cell function is defined as at least one MMTT C-peptide value > 0.2 nmol/L. Proportion is reported as Percentage of patients, despite the measure type indicated is "number". |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Follow-ups at Weeks 13 $\pm$ 1, 26 $\pm$ 2 and 52 $\pm$ 2  |  |

| End point values                 | Ladarixin - ITT/SAF   | Placebo - ITT/SAF     |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 49 <sup>[28]</sup>    | 26 <sup>[29]</sup>    |  |  |
| Units: Percentage                |                       |                       |  |  |
| number (confidence interval 95%) |                       |                       |  |  |
| Week 13                          | 96.0 (86.29 to 99.51) | 88.5 (69.85 to 97.55) |  |  |
| Week 26                          | 86.0 (73.26 to 94.18) | 84.6 (65.13 to 95.64) |  |  |
| Week 52                          | 78.0 (64.04 to 88.47) | 76.9 (56.35 to 91.03) |  |  |

Notes:

[28] - n=49 at week 13

n=46 at week 26

n=45 at week 52

[29] - n=26 at week 13  
n=25 at week 26  
n=25 at week 52

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Ladarixin vs placebo - week 13          |
| Statistical analysis description:   |   |
| Percentages are calculated relative to the number of patients in ITT population |   |
| Comparison groups   | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis   | 75                                      |
| Analysis specification  | Pre-specified                           |
| Analysis type   | superiority                             |
| P-value   | = 0.1171                                |
| Method  | Fisher exact                            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Ladarixin vs placebo - week 26          |
| Statistical analysis description:   |   |
| Percentages are calculated relative to the number of patients in ITT population |   |
| Comparison groups   | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis   | 75                                      |
| Analysis specification  | Pre-specified                           |
| Analysis type   | superiority                             |
| P-value   | = 0.6586                                |
| Method  | Fisher exact                            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Ladarixin vs placebo - week 52          |
| Statistical analysis description:   |   |
| Percentages are calculated relative to the number of patients in ITT population |   |
| Comparison groups   | Ladarixin - ITT/SAF v Placebo - ITT/SAF |
| Number of subjects included in analysis   | 75                                      |
| Analysis specification  | Pre-specified                           |
| Analysis type   | superiority                             |
| P-value   | = 0.5056                                |
| Method  | Fisher exact                            |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were recorded and reported in the CRF from enrolment through patient's participation in the study (last planned visit or early withdrawal date)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Ladarixin SAF |
|-----------------------|---------------|

Reporting group description:

Safety analysis set (SAF) was defined as all patients in the Randomized Analysis Set (RND) who received any study treatment

|                       |             |
|-----------------------|-------------|
| Reporting group title | Placebo SAF |
|-----------------------|-------------|

Reporting group description:

Safety analysis set (SAF) was defined as all patients in the Randomized Analysis Set (RND) who received any study treatment

| Serious adverse events                            | Ladarixin SAF  | Placebo SAF    |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 3 / 50 (6.00%) | 1 / 26 (3.85%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |
| Injury, poisoning and procedural complications    |                |                |  |
| Clavicle fracture                                 |                |                |  |
| subjects affected / exposed                       | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Laceration  |                |                |  |
| subjects affected / exposed                       | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                        |                |                |  |
| Gastrointestinal disorder                         |                |                |  |
| subjects affected / exposed                       | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                             |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Mental disorder                                 |                |                |  |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Hyperglycaemia                                  |                |                |  |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Ladarixin SAF    | Placebo SAF      |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 37 / 50 (74.00%) | 21 / 26 (80.77%) |  |
| Vascular disorders                                    |                  |                  |  |
| Hypertension  |                  |                  |  |
| subjects affected / exposed                           | 0 / 50 (0.00%)   | 1 / 26 (3.85%)   |  |
| occurrences (all)                                     | 0                | 1                |  |
| Surgical and medical procedures                       |                  |                  |  |
| Diabetes mellitus management                          |                  |                  |  |
| subjects affected / exposed                           | 0 / 50 (0.00%)   | 1 / 26 (3.85%)   |  |
| occurrences (all)                                     | 0                | 1                |  |
| Tooth extraction                                      |                  |                  |  |
| subjects affected / exposed                           | 2 / 50 (4.00%)   | 0 / 26 (0.00%)   |  |
| occurrences (all)                                     | 2                | 0                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Asthenia  |                  |                  |  |
| subjects affected / exposed                           | 1 / 50 (2.00%)   | 0 / 26 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                           | 1 / 50 (2.00%)   | 0 / 26 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Injection site reaction                               |                  |                  |  |
| subjects affected / exposed                           | 0 / 50 (0.00%)   | 1 / 26 (3.85%)   |  |
| occurrences (all)                                     | 0                | 1                |  |

|   |                      |                     |  |
|---|----------------------|---------------------|--|
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 0 / 50 (0.00%)<br>0  | 1 / 26 (3.85%)<br>1 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 6 / 50 (12.00%)<br>7 | 2 / 26 (7.69%)<br>3 |  |
| Sensation of foreign body<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 50 (2.00%)<br>1  | 0 / 26 (0.00%)<br>0 |  |
| Immune system disorders<br>Anaphylactic reaction<br>subjects affected / exposed<br>occurrences (all)          | 0 / 50 (0.00%)<br>0  | 1 / 26 (3.85%)<br>1 |  |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 50 (2.00%)<br>1  | 0 / 26 (0.00%)<br>0 |  |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 50 (0.00%)<br>0  | 2 / 26 (7.69%)<br>3 |  |
| Reproductive system and breast disorders<br>Breast pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 50 (0.00%)<br>0  | 1 / 26 (3.85%)<br>1 |  |
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 50 (4.00%)<br>4  | 0 / 26 (0.00%)<br>0 |  |
| Nipple inflammation<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 50 (2.00%)<br>1  | 0 / 26 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all) | 1 / 50 (2.00%)<br>1  | 0 / 26 (0.00%)<br>0 |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 1 / 50 (2.00%)<br>1  | 1 / 26 (3.85%)<br>1 |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Increased viscosity of upper respiratory secretion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 50 (2.00%)<br>4 | 0 / 26 (0.00%)<br>0 |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                   | 4 / 50 (8.00%)<br>5 | 0 / 26 (0.00%)<br>0 |  |
| Vocal cord inflammation<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 50 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 50 (2.00%)<br>1 | 0 / 26 (0.00%)<br>0 |  |
| Emotional distress<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 50 (4.00%)<br>2 | 0 / 26 (0.00%)<br>0 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 50 (4.00%)<br>2 | 0 / 26 (0.00%)<br>0 |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 50 (2.00%)<br>1 | 0 / 26 (0.00%)<br>0 |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 50 (4.00%)<br>2 | 0 / 26 (0.00%)<br>0 |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 50 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |  |
| Blood iron decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 50 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |  |
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 50 (0.00%)<br>0 | 1 / 26 (3.85%)<br>1 |  |
| Eosinophil count decreased   |                     |                     |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                    | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Glycosylated haemoglobin increased             |                |                |  |
| subjects affected / exposed                    | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Haemoglobin increased                          |                |                |  |
| subjects affected / exposed                    | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Vitamin D decreased                            |                |                |  |
| subjects affected / exposed                    | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Weight increased                               |                |                |  |
| subjects affected / exposed                    | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Injury, poisoning and procedural complications |                |                |  |
| Alcohol poisoning                              |                |                |  |
| subjects affected / exposed                    | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Contusion                                      |                |                |  |
| subjects affected / exposed                    | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Fall   |                |                |  |
| subjects affected / exposed                    | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Joint injury                                   |                |                |  |
| subjects affected / exposed                    | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Ligament sprain                                |                |                |  |
| subjects affected / exposed                    | 1 / 50 (2.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)                              | 1              | 1              |  |
| Limb injury                                    |                |                |  |
| subjects affected / exposed                    | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Muscle injury                                  |                |                |  |

|   |                        |                      |  |
|---|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 50 (2.00%)<br>1    | 0 / 26 (0.00%)<br>0  |  |
| Skin wound<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 50 (2.00%)<br>1    | 0 / 26 (0.00%)<br>0  |  |
| Sunburn<br>subjects affected / exposed<br>occurrences (all)   | 0 / 50 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)               | 0 / 50 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)           | 3 / 50 (6.00%)<br>3    | 1 / 26 (3.85%)<br>1  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 14 / 50 (28.00%)<br>20 | 6 / 26 (23.08%)<br>8 |  |
| Migrane<br>subjects affected / exposed<br>occurrences (all)   | 1 / 50 (2.00%)<br>1    | 0 / 26 (0.00%)<br>0  |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)   | 1 / 50 (2.00%)<br>1    | 1 / 26 (3.85%)<br>1  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 50 (2.00%)<br>1    | 0 / 26 (0.00%)<br>0  |  |
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 50 (2.00%)<br>1    | 0 / 26 (0.00%)<br>0  |  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 50 (2.00%)<br>1    | 0 / 26 (0.00%)<br>0  |  |
| lymphadenopathy   |                        |                      |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 2              | 0              |  |
| Lymphocytosis               |                |                |  |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)           | 0              | 2              |  |
| Neutropenia                 |                |                |  |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)           | 1              | 1              |  |
| Polycythaemia               |                |                |  |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences (all)           | 0              | 1              |  |
| Ear and labyrinth disorders |                |                |  |
| Ear discomfort              |                |                |  |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 2              | 0              |  |
| Ear pain                    |                |                |  |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Gastrointestinal disorders  |                |                |  |
| Abdominal discomfort        |                |                |  |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Abdominal pain              |                |                |  |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Abdominal pain upper        |                |                |  |
| subjects affected / exposed | 3 / 50 (6.00%) | 2 / 26 (7.69%) |  |
| occurrences (all)           | 4              | 2              |  |
| Constipation                |                |                |  |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 3              | 0              |  |
| Dental caries               |                |                |  |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Diarrhoea                   |                |                |  |

|                                  |                 |                 |  |
|----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed      | 2 / 50 (4.00%)  | 2 / 26 (7.69%)  |  |
| occurrences (all)                | 2               | 2               |  |
| Dyspepsia                        |                 |                 |  |
| subjects affected / exposed      | 6 / 50 (12.00%) | 0 / 26 (0.00%)  |  |
| occurrences (all)                | 9               | 0               |  |
| Dysphagia                        |                 |                 |  |
| subjects affected / exposed      | 1 / 50 (2.00%)  | 0 / 26 (0.00%)  |  |
| occurrences (all)                | 1               | 0               |  |
| Faeces hard                      |                 |                 |  |
| subjects affected / exposed      | 1 / 50 (2.00%)  | 0 / 26 (0.00%)  |  |
| occurrences (all)                | 1               | 0               |  |
| Gastrooesophageal reflux disease |                 |                 |  |
| subjects affected / exposed      | 1 / 50 (2.00%)  | 1 / 26 (3.85%)  |  |
| occurrences (all)                | 1               | 1               |  |
| Hyperchlorhydria                 |                 |                 |  |
| subjects affected / exposed      | 2 / 50 (4.00%)  | 0 / 26 (0.00%)  |  |
| occurrences (all)                | 2               | 0               |  |
| Nausea                           |                 |                 |  |
| subjects affected / exposed      | 3 / 50 (6.00%)  | 3 / 26 (11.54%) |  |
| occurrences (all)                | 4               | 4               |  |
| Odynophagia                      |                 |                 |  |
| subjects affected / exposed      | 1 / 50 (2.00%)  | 0 / 26 (0.00%)  |  |
| occurrences (all)                | 1               | 0               |  |
| Pancreatitis chronic             |                 |                 |  |
| subjects affected / exposed      | 1 / 50 (2.00%)  | 0 / 26 (0.00%)  |  |
| occurrences (all)                | 1               | 0               |  |
| Toothache                        |                 |                 |  |
| subjects affected / exposed      | 1 / 50 (2.00%)  | 1 / 26 (3.85%)  |  |
| occurrences (all)                | 1               | 1               |  |
| Vomiting                         |                 |                 |  |
| subjects affected / exposed      | 2 / 50 (4.00%)  | 1 / 26 (3.85%)  |  |
| occurrences (all)                | 2               | 1               |  |
| Hepatobiliary disorders          |                 |                 |  |
| Hyperbilirubinaemia              |                 |                 |  |
| subjects affected / exposed      | 0 / 50 (0.00%)  | 1 / 26 (3.85%)  |  |
| occurrences (all)                | 0               | 1               |  |



|   |                             |                |                |  |
|---|-----------------------------|----------------|----------------|--|
| Skin and subcutaneous tissue disorders          | Acne                        |                |                |  |
|   | subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
|   | occurrences (all)           | 1              | 0              |  |
|   | Alopecia                    |                |                |  |
|   | subjects affected / exposed | 1 / 50 (2.00%) | 1 / 26 (3.85%) |  |
|   | occurrences (all)           | 1              | 1              |  |
| Rash  | subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
|   | occurrences (all)           | 0              | 1              |  |
|   |                             |                |                |  |
| Renal and urinary disorders                     |                             |                |                |  |
| Polyuria  | subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
|   | occurrences (all)           | 0              | 1              |  |
|   |                             |                |                |  |
| Musculoskeletal and connective tissue disorders |                             |                |                |  |
| Arthralgia                                      | subjects affected / exposed | 3 / 50 (6.00%) | 0 / 26 (0.00%) |  |
|   | occurrences (all)           | 4              | 0              |  |
|   |                             |                |                |  |
| Back pain                                       | subjects affected / exposed | 1 / 50 (2.00%) | 1 / 26 (3.85%) |  |
|   | occurrences (all)           | 1              | 3              |  |
|   |                             |                |                |  |
| Muscle spasms                                   | subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
|   | occurrences (all)           | 1              | 0              |  |
|   |                             |                |                |  |
| Myalgia   | subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
|   | occurrences (all)           | 3              | 0              |  |
|   |                             |                |                |  |
| Osteoarthritis                                  | subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%) |  |
|   | occurrences (all)           | 1              | 0              |  |
|   |                             |                |                |  |
| Pain in extremity                               | subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%) |  |
|   | occurrences (all)           | 0              | 1              |  |
|   |                             |                |                |  |
| Infections and infestations                     |                             |                |                |  |
| Bronchitis                                      |                             |                |                |  |
|   |                             |                |                |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%)  |
| occurrences (all)           | 0              | 1               |
| Cystitis                    |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Ear infection               |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Eye infection               |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Folliculitis                |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Gastroenteritis             |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Gastroenteritis viral       |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 3 / 26 (11.54%) |
| occurrences (all)           | 1              | 3               |
| Gingivitis                  |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Infected bite               |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 2              | 0               |
| Influenza                   |                |                 |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 26 (3.85%)  |
| occurrences (all)           | 0              | 1               |
| Laryngitis                  |                |                 |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 26 (3.85%)  |
| occurrences (all)           | 1              | 2               |
| Oral herpes                 |                |                 |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 26 (0.00%)  |
| occurrences (all)           | 2              | 0               |
| Pharyngitis                 |                |                 |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed             | 1 / 50 (2.00%)   | 1 / 26 (3.85%)  |  |
| occurrences (all)                       | 1                | 1               |  |
| Sinusitis                               |                  |                 |  |
| subjects affected / exposed             | 0 / 50 (0.00%)   | 1 / 26 (3.85%)  |  |
| occurrences (all)                       | 0                | 2               |  |
| Tinea pedis                             |                  |                 |  |
| subjects affected / exposed             | 1 / 50 (2.00%)   | 0 / 26 (0.00%)  |  |
| occurrences (all)                       | 1                | 0               |  |
| Tonsillitis                             |                  |                 |  |
| subjects affected / exposed             | 1 / 50 (2.00%)   | 0 / 26 (0.00%)  |  |
| occurrences (all)                       | 1                | 0               |  |
| Tooth abscess                           |                  |                 |  |
| subjects affected / exposed             | 1 / 50 (2.00%)   | 0 / 26 (0.00%)  |  |
| occurrences (all)                       | 1                | 0               |  |
| Upper respiratory tract infection       |                  |                 |  |
| subjects affected / exposed             | 3 / 50 (6.00%)   | 1 / 26 (3.85%)  |  |
| occurrences (all)                       | 3                | 1               |  |
| Urinary tract infection                 |                  |                 |  |
| subjects affected / exposed             | 2 / 50 (4.00%)   | 1 / 26 (3.85%)  |  |
| occurrences (all)                       | 2                | 1               |  |
| Viral infection                         |                  |                 |  |
| subjects affected / exposed             | 1 / 50 (2.00%)   | 0 / 26 (0.00%)  |  |
| occurrences (all)                       | 1                | 0               |  |
| Viral upper respiratory tract infection |                  |                 |  |
| subjects affected / exposed             | 13 / 50 (26.00%) | 4 / 26 (15.38%) |  |
| occurrences (all)                       | 19               | 6               |  |
| Metabolism and nutrition disorders      |                  |                 |  |
| Hypercholesterolaemia                   |                  |                 |  |
| subjects affected / exposed             | 1 / 50 (2.00%)   | 1 / 26 (3.85%)  |  |
| occurrences (all)                       | 1                | 1               |  |
| Hyperglycaemia                          |                  |                 |  |
| subjects affected / exposed             | 1 / 50 (2.00%)   | 0 / 26 (0.00%)  |  |
| occurrences (all)                       | 1                | 0               |  |
| Hypoglycaemia                           |                  |                 |  |
| subjects affected / exposed             | 4 / 50 (8.00%)   | 1 / 26 (3.85%)  |  |
| occurrences (all)                       | 7                | 2               |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all) | 1 / 50 (2.00%)<br>1 | 0 / 26 (0.00%)<br>0 |  |
|---|---------------------|---------------------|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|   |
|---|
| No limitations or caveats are applicable to this summary of the results |
|---|

Notes: