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 β-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
Arm title	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.

Arm title	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.

Number of subjects in period 1	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:	
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.	

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:	
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:	
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[1]
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[2]	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[3]
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.

Statistical analysis title	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[4]
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[5]	25[6]		
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

Statistical analysis title	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) glycemic 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: logaritm (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

Statistical analysis title	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[7]
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.

Statistical analysis title	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[8]
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.

Statistical analysis title	Ladarixin vs placebo - week 52
Statistical analysis description: 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[9]
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[10]	11[11]		
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[12]	11[13]		
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

n=10 wk 52

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 overal 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[14]	25[15]		
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

n=25 wk 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	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0779
Method	Fisher exact

Statistical analysis title	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

Statistical analysis title	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[16]	11[17]		
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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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[18]	26[19]		
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[20]
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.

Statistical analysis title	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[21]
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.

Statistical analysis title	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[22]
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

End point values	Ladarixin - ITT/SAF	Placebo - ITT/SAF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[23]	25[24]		
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

Statistical analysis title	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[25]
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.

Statistical analysis title	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[26]
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.

Statistical analysis title	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[27]
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 β-cell function

End point title	Proportion of patients maintaining a residual β-cell function

End point description:

Maintenance of a residual ß-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±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[28]	26[29]		
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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 %

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

Increased viscosity of upper respiratory secretion			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Oropharyngeal pain			
subjects affected / exposed	4 / 50 (8.00%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Vocal cord inflammation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Emotional distress			
subjects affected / exposed	2 / 50 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 50 (4.00%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Blood iron decreased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	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 poinsoning			
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	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Skin wound			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	0 / 50 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 50 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 50 (6.00%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Headache			
subjects affected / exposed	14 / 50 (28.00%)	6 / 26 (23.08%)	
occurrences (all)	20	8	
Migrane			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 50 (2.00%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Eosinophilia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 26 (0.00%)	
occurrences (all)	1	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 subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 26 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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: