Clinical trial results:
Effect of Oral Ladarixin 400 mg Twice a Day on Insulin Sensitivity. A Phase 2, Randomized, Double-blind, Placebo-controlled Explorative Study in Obese Patients With Prediabetes Eligible to Bariatric Surgery.

Summary

EudraCT number	2020-003296-18
Trial protocol	IT
Global end of trial date	26 May 2023

Results information

Result version number	v1 (current)
This version publication date	01 December 2024
First version publication date	01 December 2024

Trial information

Trial identification

Sponsor protocol code	LDX0119

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dompé farmaceutici S.p.A.
Sponsor organisation address	Via Santa Lucia, 6, Milan, Italy, 20122
Public contact	Dompé farmaceutici S.p.A., Clinical Development, Dompé farmaceutici S.p.A., +39 02 583831, clinical.trials@dompe.com
Scientific contact	Dompé farmaceutici S.p.A., Clinical Development, Dompé farmaceutici S.p.A., +39 02 583831, clinical.trials@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	30 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2023
Global end of trial reached?	Yes
Global end of trial date	26 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to explore whether ladarixin may improve insulin sensitivity in participants with prediabetes eligible for bariatric surgery with body mass index (BMI) ≥35 kg/m2. The safety of ladarixin was also evaluated.

The study also aimed to explore changes in relevant metabolic and inflammatory markers/variables after ladarixin treatment.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki (October 2013), ICH GCP E6(R2), IEC guidance, and all other applicable local regulatory requirements.

Background therapy: -

Evidence for comparator:

A total of 25 participants (13 in the ladarixin arm and 12 in the placebo arm) received IMP; all completed IMP treatment including completion of the End of Cycle 1 and Follow-up visits. A total of 23 participants (12 randomized to ladarixin and 11 randomized to placebo) underwent bariatric surgery; 1 participant in each treatment group did not undergo surgery.

Actual start date of recruitment	23 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	25
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

40 participants were screened for the study. Of these, 14 did not meet all inclusion/exclusion criteria.The remaining 26 were randomized: 13 to ladarixin and 13 to placebo. One patient randomized to placebo did not complete the Baseline visit due to unavailability of veins, and so didn't receive IMP and wasn't included in the analyses.

Pre-assignment

Screening details:

Potential participants were identified from those on the waiting list for bariatric surgery at one of the participating Surgery Units. After the surgeon had explained and discussed the study with a participant, any willing potential participants were referred to the CCS for consent and screening.

Period 1

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

Blinding implementation details:

The appearance, including packaging and labelling, of IMP capsules (ladarixin and placebo) were matched so that the actual treatment could not be identified.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ladarixin

Arm description:

In this arm participants received Ladarixin 400 mg (2 x200 mg capsule), administered twice a day orally for 3 cycles
of 14 days each, with a 14-day wash-out between cycles, for a total of 10 weeks from first to last dose. Please note that n=13 patients of this arm completed both End of Cycle 1 visit, and Follow-up visit.

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

Dosage and administration details:

Ladarixin was provided as hard gelatine capsules for oral administration. Each active capsule contained 200 mg ladarixin.
Capsules were to be taken at least two hours before or after meals.

Arm title	Placebo

Arm description:

In this arm participants received matched placebo, administered twice a day orally for 3 cycles of 14 days each, with a 14-day wash-out between cycles, for a total of 10 weeks from first to last dose. Please note 1: One participant randomized to placebo did not complete the Baseline visit due to unavailability of veins, and consequently did not receive IMP. Please note 2: n=12 Completed both End of Cycle 1 visit and Follow-up visit.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Matched placebo capsules were administered twice a day orally for 3 cycles of 14 days each, with a 14-day interval between cycles. Hence placebo was indistinguishable compared to active drug with respect of formulation, time and way of administration and posologic scheme.

Number of subjects in period 1[1]	Ladarixin	Placebo
Started	13	12
Completed	13	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 40 participants were screened for the study. Of these, 14 did not meet all inclusion/exclusion criteria.The remaining 26 were randomized: 13 to ladarixin and 13 to placebo. One patient randomized to placebo, though, did not complete the Baseline visit due to unavailability of veins, and so didn't receive IMP and wasn't included in the analyses (n=25).

Baseline characteristics

Reporting groups

Reporting group title	Ladarixin

Reporting group description:

In this arm participants received Ladarixin 400 mg (2 x200 mg capsule), administered twice a day orally for 3 cycles
of 14 days each, with a 14-day wash-out between cycles, for a total of 10 weeks from first to last dose. Please note that n=13 patients of this arm completed both End of Cycle 1 visit, and Follow-up visit.

Reporting group title	Placebo

Reporting group description:

In this arm participants received matched placebo, administered twice a day orally for 3 cycles
of 14 days each, with a 14-day wash-out between cycles, for a total of 10 weeks from first to last dose. Please note 1: One participant randomized to placebo did not complete the Baseline visit due to unavailability of veins, and consequently did not receive IMP. Please note 2: n=12 Completed both End of Cycle 1 visit and Follow-up visit.

Reporting group values	Ladarixin	Placebo	Total
Number of subjects	13	12	25
Age categorical			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: Subjects			
Adults (18-64 years)	12	12	24
From 65-84 years	1	0	1
Age continuous			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: years			
arithmetic mean	50.4	47.7	
standard deviation	± 9.16	± 6.02	-
Gender categorical			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: Subjects			
Female	6	4	10
Male	7	8	15

Subject analysis sets

Subject analysis set title	Ladarixin - ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Participants were analyzed according to their
randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.

Subject analysis set title	Ladarixin - SAF

Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis (SAF) set: Defined as all participants in the RND set who received any IMP (either ladarixin or placebo). Subjects were analyzed according to the treatment they actually received. The SAF set was used to present safety data.

Subject analysis set title	Placebo - ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Participants were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.

Subject analysis set title	Placebo - SAF set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis (SAF) set: Defined as all participants in the RND set who received any IMP (either ladarixin or placebo). Subjects were analyzed according to the treatment they actually received. The SAF set was used to present safety data.

Reporting group values	Ladarixin - ITT set	Ladarixin - SAF	Placebo - ITT set
Number of subjects	13	13	12
Age categorical			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: Subjects			
Adults (18-64 years)	12	12	12
From 65-84 years	1	1	0
Age continuous			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: years			
arithmetic mean	50.4	50.4	47.7
standard deviation	± 9.16	± 9.16	± 6.02
Gender categorical			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: Subjects			
Female	6	6	4
Male	7	7	8

Reporting group values	Placebo - SAF set		
Number of subjects	12		
Age categorical			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: Subjects			
Adults (18-64 years)	12		
From 65-84 years	0		

Age continuous			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: years			
arithmetic mean	47.7		
standard deviation	± 6.02		
Gender categorical			
Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Subjects were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.			
Units: Subjects			
Female	4		
Male	8		

End points

End points reporting groups

Reporting group title	Ladarixin

Reporting group description:

In this arm participants received Ladarixin 400 mg (2 x200 mg capsule), administered twice a day orally for 3 cycles
of 14 days each, with a 14-day wash-out between cycles, for a total of 10 weeks from first to last dose. Please note that n=13 patients of this arm completed both End of Cycle 1 visit, and Follow-up visit.

Reporting group title	Placebo

Reporting group description:

In this arm participants received matched placebo, administered twice a day orally for 3 cycles
of 14 days each, with a 14-day wash-out between cycles, for a total of 10 weeks from first to last dose. Please note 1: One participant randomized to placebo did not complete the Baseline visit due to unavailability of veins, and consequently did not receive IMP. Please note 2: n=12 Completed both End of Cycle 1 visit and Follow-up visit.

Subject analysis set title	Ladarixin - ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Participants were analyzed according to their
randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.

Subject analysis set title	Ladarixin - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis (SAF) set: Defined as all participants in the RND set who received any IMP (either ladarixin or placebo). Subjects were analyzed according to the treatment they actually received. The SAF set was used to present safety data.

Subject analysis set title	Placebo - ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to Treat (ITT) set: Defined as all participants who were randomized and received at least 1 dose of IMP (either ladarixin or placebo). Participants were analyzed according to their randomized treatment, regardless of the treatment actually received. The ITT set was used to present efficacy data.

Subject analysis set title	Placebo - SAF set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis (SAF) set: Defined as all participants in the RND set who received any IMP (either ladarixin or placebo). Subjects were analyzed according to the treatment they actually received. The SAF set was used to present safety data.

Primary: Change from baseline to follow-up in Insulin Sensitivity Index – Matsuda (ISI-M) from 3-hours Oral Glucose Tolerance Test (OGTT), calculated by Matsuda 1999

End point title	Change from baseline to follow-up in Insulin Sensitivity Index – Matsuda (ISI-M) from 3-hours Oral Glucose Tolerance Test (OGTT), calculated by Matsuda 1999

End point description:

As the trial was exploratory, no primary endpoint was defined.
The insulin sensitivity Index by Matsuda (ISI-M) in general is assessed via the 3h-OGTT, the main analysis, but also via the 2h-OGTT. Generally speaking, these are standard diagnostic tests for diabetes and is commonly used to evaluate whole body glucose tolerance. Participation in the trial requires a somewhat more frequent and prolonged (up to 3 hours) sampling to betted define post-load changes in glucose, insulin, proinsulin and c-peptide levels for research purposes.

Insulin Sensitivity Index-Matsuda (ISI-M) calculated by [Matsuda, 1999]:
ISI– M= 10,000 / √(FPG*FPI) * (MPG*MPI)

where FPG = fasting plasma glucose (mmol/dL); FPI = fasting plasma insulin (mIU/L)
MPG = mean plasma glucose (mmol/dL); MPI = mean plasma Insulin (mIU/L)

End point type	Primary

End point timeframe:

Follow-up (Day 72). More precisely ISI-M from 2h-(OGTT) is calculated considering the timepoints Basal, 30, 60, 90, 120 minutes and ISI-M from 3h-(OGTT) is calculated considering the timepoints Basal, 10, 20, 30, 60 , 90, 120 and 180 minutes.

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	11		
Units: Index of sensitivity				
arithmetic mean (standard deviation)				
ISI-M	0.37 (± 0.925)	0.25 (± 1.057)		
ISI-M (2h OGTT)	0.32 (± 0.923)	0.19 (± 0.992)		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:
ISI- M (3-hours OGTT)

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39 [1]
Method	t-test, 1-sided

Notes:
[1] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:
ISI-M from 2-hours OGTT

Comparison groups	Placebo - ITT set v Ladarixin - ITT set
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375 [2]
Method	t-test, 1-sided

Notes:
[2] - The comparison between treatment groups will be carried-out using t-test for unpaired data.

Other pre-specified: Change from baseline to follow-up in Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR).

End point title	Change from baseline to follow-up in Homeostasis Model of

	Assessment of Insulin Resistance (HOMA-IR).

End point description:

As the trial was exploratory, no primary endpoint was defined.
Homeostasis model assessment of insulin resistance (HOMA-IR) is a method to measure insulin resistance, an early stage of type 2 diabetes that increases the risk of many chronic diseases. The index practically says how much insulin the body needs to keep blood sugar levels in check.
HOMA-IR calculated by [Mari, 2001] is defined as:
(fasting plasma insulin(mIU/L)x fasting plasma glucose (mg/dL))/405 where fasting plasma glucose (mg/dL) and fasting plasma insulin (mIU/L) are defined as above in the ISI-M formula details.
In general, HOMA-IR values between 0.5 and 1.4 are considered normal, ≥1.9 are indicative of early IR, and ≥2.9 indicate IR.

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72).

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: index of insulin resistance				
arithmetic mean (standard deviation)	0.64 (± 3.999)	-0.98 (± 3.404)		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.144
Method	t-test, 1-sided

Other pre-specified: Change from baseline to follow-up in C-peptide area under the curve (AUC) from 3-hours OGTT.

End point title	Change from baseline to follow-up in C-peptide area under the curve (AUC) from 3-hours OGTT.

End point description:

As the trial was exploratory, no primary endpoint was defined.
Area under the curve (AUC) values for plasma C-peptide (CP) concentration/level is a common method to measure beta cell loss in Type 1 diabetes (T1D). CP typically rises in the first weeks to months after diagnosis and then falls over time. Both the starting level of CP, reflecting beta cell reserve, and its rate of decline, indicating disease progression, vary considerably between patients. In the study C-peptide AUC was assessed through 3h-OGTT (meaning that C-peptide AUC was calculated considered the timepoints: Basal, 10 min, 20 min, 30 min, 60 min, 90 min, 120 min, 180 min). More in detail, C-peptide AUC was calculated using the trapezoidal rule.

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72).

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	11		
Units: ng*H/ml				
arithmetic mean (standard deviation)	4.84 (± 352.279)	-70.68 (± 348.731)		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306 [3]
Method	t-test for unpaired data

Notes:

[3] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Other pre-specified: Change from baseline of mean Proinsulin / C-peptide ratio

End point title	Change from baseline of mean Proinsulin / C-peptide ratio

End point description:

As the trial was exploratory, no primary endpoint was defined.
Proinsulin/C-peptide ratio was calculated using the following formula [Truyen, 2005]:
Proinsulin/C-peptide ratio (%) = 100 × proinsulin (pmol/l; ELISA) / [total C-peptide (pmol/l;ECLIA)−proinsulin (pmol/l; ELISA)].
Note: in this study the method ECLIA (Electrochemiluminescence Immunoassay) was used for the laboratory range of C-peptide, but this was confirmed by the Sponsor to be comparable to the TRFIA (Time Resolved Fluorescence Immunoassay) reported in the paper reference [Truyen, 2005].
Please note: Basal value is defined as the mean of Basal #1 (i.e., 15 min before glucose administration) and Basal #2 (i.e., Time 0, just before glucose administration);

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72). More precisely Proinsulin / C-peptide ratio is calculated considering the timepoints Basal and 10 min, 20 min, 30 min, 60 min, 90 min, 120 min, 120 and 180 min post-dose.

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[4]	11		
Units: ratio				
arithmetic mean (standard deviation)				
Basal	0.350 (± 1.7621)	-0.525 (± 2.4090)		

10 min post-dose	0.632 (± 1.4440)	-0.538 (± 1.8403)		
20 min post-dose	0.333 (± 0.9718)	-0.423 (± 1.4235)		
30 min post-dose	0.208 (± 0.8459)	-0.250 (± 1.4432)		
60 min post-dose	-0.046 (± 0.6417)	0.004 (± 1.2131)		
90 min post-dose	0.023 (± 0.6575)	0.057 (± 1.0675)		
120 min post-dose	0.233 (± 0.9068)	-0.380 (± 1.6122)		
180 min post-dose	0.265 (± 1.0406)	-1.378 (± 2.9115)		

Notes:

[4] - Please note : for 10, 20 and 30 min post-dose n=12

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of participants with Impaired Glucose Tolerance (IGT)

End point title	Number of participants with Impaired Glucose Tolerance (IGT)

End point description:

IGT, defined as Nathan 2007, is a post-load glucose [level] of 140-199 mg/dL, inclusive, at 2 hours of the OGTT. This means that For each study visit, a patient was considered having IGT when at 2-hour post-load glucose level of 140-199 mg/dL was observed during OGTT.

End point type	Other pre-specified

End point timeframe:

At Baseline (Day 0) and Follow-up (Day 72) visits.

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: count of partecipants				
number (not applicable)				
Baseline (Day 0)	6	3		
Follow-up (Day 72)	4	5		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Baseline

Comparison groups	Ladarixin - ITT set v Placebo - ITT set

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.271 [5]
Method	Chi-squared

Notes:

[5] - Comparison between treatment groups is carried out using a Chi-square test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Folllow-up (Day 72)

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.459 [6]
Method	Chi-squared

Notes:

[6] - Comparison between treatment groups is carried out using a Chi-square test

Other pre-specified: Change from Baseline in Hormones values [Amylin (active & total), Ghrelin, Incretines (GIP, GLP-1), Glucagon, Leptin, Pancreatic Polypeptide, Adiponectin, Resistin, Adipsin, Plasminogen Activator Inhibitor (PAI 1)].

End point title	Change from Baseline in Hormones values [Amylin (active & total), Ghrelin, Incretines (GIP, GLP-1), Glucagon, Leptin, Pancreatic Polypeptide, Adiponectin, Resistin, Adipsin, Plasminogen Activator Inhibitor (PAI 1)].

End point description:

Blood sampling for assey of hormones values [Amylin (active & total), Ghrelin, Incretines (GIP, GLP-1), Glucagon, Leptin, Pancreatic Polypeptide, Adiponectin, Resistin, Adipsin, Plasminogen Activator Inhibitor (PAI 1)]were collected at the Baseline and Follow-up visits. Statistical tests on hormone parameters were performed as post-hoc analyses.

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72)

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12[7]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Amylin (active)	0.59 (± 10.729)	-1.59 (± 5.178)		
Amylin (total)	1.76 (± 5.330)	-3.17 (± 9.059)		
Ghrelin	-5.96 (± 38.635)	-7.13 (± 48.601)		
GIP	2.77 (± 6.735)	-18.15 (± 45.297)		
GLP-1	-0.69 (± 24.662)	-27.16 (± 40.790)		

Glucagon	-2.88 (± 10.379)	-2.58 (± 33.154)		
Leptin	2291.66 (± 5951.559)	-3059.87 (± 6456.941)		
Pancreatic Polypeptide	3.04 (± 16.624)	-14.23 (± 55.437)		
Adiponectin	2014165.5 (± 9888777.93)	-2640019.05 (± 8322851.81)		
Resistin	-2067.7 (± 14974.71)	-7762.0 (± 12019.82)		
Adipsin	163756.9 (± 2060489.70)	-1875034.7 (± 1991483.67)		
PAI1	2088.0 (± 18852.63)	-8772.3 (± 29861.88)		

Notes:

[7] - please note that for Amylin (active) n=11

Statistical analyses

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Amylin (active) - please note that the total number of subjects in this comparison are 24 and not the 25 automatically reported by the system, since in the placebo arm n=11.

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.643 [8]
Method	Kruskal-wallis

Notes:

[8] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Amylin (total)

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.231 [9]
Method	Kruskal-wallis

Notes:

[9] - The comparison between treatment groups was carried-out using Kruskal-Wallis test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Ghrelin

Comparison groups	Ladarixin - ITT set v Placebo - ITT set

Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.474 [10]
Method	t-test for unpaired data

Notes:

[10] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

GIP

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.014 [11]
Method	Kruskal-wallis

Notes:

[11] - The comparison between treatment groups was carried-out using Kruskal-Wallis test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

GLP-1

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.092 [12]
Method	Kruskal-wallis

Notes:

[12] - The comparison between treatment groups was carried-out using Kruskal-Wallis test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Glucagon

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.415 [13]
Method	Kruskal-wallis

Notes:

[13] - The comparison between treatment groups was carried-out using Kruskal-Wallis test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Leptin

Comparison groups	Ladarixin - ITT set v Placebo - ITT set

Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.021 [14]
Method	t-test for unpaired data

Notes:

[14] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Pancreatic Polypeptide

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.277 [15]
Method	Kruskal-wallis

Notes:

[15] - The comparison between treatment groups was carried-out using Kruskal-Wallis test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Adiponectin

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority[16]
P-value	= 0.109
Method	t-test for unpaired data

Notes:

[16] - Treatment groups were compared using t-test for unpaired data

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Resistin

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.624 [17]
Method	Kruskal-wallis

Notes:

[17] - The comparison between treatment groups was carried-out using Kruskal-Wallis test

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

Adipsin

Comparison groups	Ladarixin - ITT set v Placebo - ITT set

Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.01 [18]
Method	t-test for unpaired data

Notes:

[18] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

PAI-1

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.142 [19]
Method	t-test for unpaired data

Notes:

[19] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Other pre-specified: Percent Change from baseline in Inflammatory Chemokine/cytokine [Interleukin IL-6, IL-8, IL-10, IP-10, MCP-1, GROα, MIP- 1α, and TNFα] and C-reactive protein values

End point title	Percent Change from baseline in Inflammatory Chemokine/cytokine [Interleukin IL-6, IL-8, IL-10, IP-10, MCP-1, GROα, MIP- 1α, and TNFα] and C-reactive protein values

End point description:

Blood sampling for assay of Inflammatory Chemokine/cytokine [Interleukin IL-6, IL-8, IL-10, IP-10, MCP-1, GROα, MIP- 1α, and TNFα] and C-reactive protein values. Please note that C-reactive protein unit of measure is mg/L. Statistical test for differences in inflammatory chemokines/cytokines and C-reactive protein levels between the 2 treatment groups were analyzed as post-hoc analyses.

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72)

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: pg/ml				
arithmetic mean (standard deviation)				
IL-6	-0.29 (± 1.852)	2.94 (± 16.432)		
IL-8	0.08 (± 0.642)	0.57 (± 6.121)		
IL-10	1.48 (± 7.505)	-3.27 (± 7.945)		
IP-10	-439.14 (± 2459.770)	-14.85 (± 112.707)		
MCP-1	16.95 (± 65.767)	-29.95 (± 126.927)		

GROα	-2.59 (± 3.956)	1.32 (± 17.881)		
MIP-1α	1.21 (± 13.042)	16.19 (± 75.687)		
TNFα	6.42 (± 18.309)	0.66 (± 36.345)		
C-Reactive Protein	-2.53 (± 2.378)	-2.07 (± 5.908)		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: IL-6	
Comparison groups	Placebo - ITT set v Ladarixin - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.744 [20]
Method	Kruskal-wallis

Notes:

[20] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: IL-8	
Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.479 [21]
Method	Kruskal-wallis

Notes:

[21] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: IL-10	
Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.504 [22]
Method	Kruskal-wallis

Notes:

[22] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:
IP-10

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.514 [23]
Method	Kruskal-wallis

Notes:
[23] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo
Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.134 [24]
Method	t-test for unpaired data

Notes:
[24] - The comparison between treatment groups was carried-out using t-test for unpaired data.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:
GROα

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.061 [25]
Method	Kruskal-wallis

Notes:
[25] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:
MIP-1α

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.956 [26]
Method	Kruskal-wallis

Notes:
[26] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:
TNFα

Comparison groups	Ladarixin - ITT set v Placebo - ITT set

Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.624 [27]
Method	Kruskal-wallis

Notes:

[27] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Statistical analysis title	Ladarixin vs placebo

Statistical analysis description:

C-reactive protein

Comparison groups	Ladarixin - ITT set v Placebo - ITT set
Number of subjects included in analysis	25
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.174 [28]
Method	Kruskal-wallis

Notes:

[28] - The comparison between treatment groups was carried-out using Kruskal-Wallis test.

Other pre-specified: Mean percent change from baseline in gut (faeces) Microbioma/microbiota Diversity Index values

End point title	Mean percent change from baseline in gut (faeces) Microbioma/microbiota Diversity Index values

End point description:

Gut (faeces) microbiome/microbiota “Diversity” defined as [Pellegrini, 2017]: The richness and evenness distribution of distinct types of organisms, calculated by the Shannon’s Diversity Index; should the Diversity be different between treatment groups, additional taxonomic details will be obtained from the centralized laboratory and presented (separate report attached to the CSR) up to the level where the difference between groups is evident

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72)

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: mean percent				
arithmetic mean (standard deviation)	4.40 (± 16.966)	2.08 (± 23.296)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change from baseline in waist and waist/hip

measurements.

End point title	Percent Change from baseline in waist and waist/hip measurements.

End point description:

The waist and hip circumference are measures of the distribution of body fat (both subcutaneous and intra-abdominal). The Waist /Hip Ratio is calculated by dividing waist measurement by hip measurement.The formula is: WHR= waist circumference / hip circumference.

End point type	Other pre-specified

End point timeframe:

Follow-up (Day 72)

End point values	Ladarixin - ITT set	Placebo - ITT set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: cm				
arithmetic mean (standard deviation)				
Waist Circumference	0.88 (± 2.900)	-1.748 (± 2.454)		
Waist/Hip Circumference	0.471 (± 1.7869)	-0.66 (± 5.558)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Adverse events

End point title	Adverse events

End point description:

An AE was defined as any untoward medical occurrence in a patient/clinical investigation participant administered a medicinal product and which did not
necessarily have a causal relationship with that treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding),
symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product. Any AEs which were
considered to be reasonably likely to have been caused by the IMP were considered Adverse Drug Reactions (ADRs). Any AE reported as having had a possible, probable, or highly probable relationship to the study medication qualified as an ADR.

End point type	Other pre-specified

End point timeframe:

AEs were monitored and recorded throughout the study, from the date of informed consent signed (week 0) to the end of study participation (early discontinuation or follow-up visit during week 11 (day 71-75))

End point values	Ladarixin - SAF	Placebo - SAF set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	12		
Units: Count of partecipants				
number (not applicable)				
TEAE	9	4		
Non-serious TEAE	9	4		
Treatment-emergent SAE	0	0		
Serious ADR	0	0		
TEAE leading to treatment discontinuation	0	0		
TEAE leading to study discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored and recorded throughout the study, from the date of informed consent signed (week 0) to the end of study participation (early discontinuation or follow-up visit during week 11 (day 71-75))

Adverse event reporting additional description:

All TEAEs were mild or moderate in severity and none led to treatment or study discontinuation.
The most frequently reported TEAEs in the ladarixin group were gastrointestinal disorders, most of which were considered ADRs. All ADRs in the ladarixin treatment group were mild in severity and treatment with ladarixin was continued unchanged.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Ladarixin
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Ladarixin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Ladarixin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)	4 / 12 (33.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 13 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	6	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Hepatobiliary disorders			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 13 (23.08%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Autoimmune thyroid disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Helicobacter infection			

subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2021	Extension of IMP shelf-life from 24 to 36 months.
09 November 2021	Addition of INCO operational unit. INCO stands for Istituto Nazionale di Cura dell'Obesità (National Institute of Obesity Treatment)
07 October 2022	Extension of IMP shelf-life from 36 to 48 months
07 November 2022	Transfer of INCO operational unit from IRCCS Policlinic San Donato to IRCCS Galeazzi Hospital. IRCCS stands for Istituto di Ricovero e Cura a Carattere Scientifico (Scientific Institute for Research, Hospitalization and Healthcare)

Notes:

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: