

**Clinical trial results:**

A phase 2, multicenter, 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 and preserved -cell function at baseline.

Summary

EudraCT number	2020-002966-15
Trial protocol	DE IT BE
Global end of trial date	11 October 2023

Results information

Result version number	v1 (current)
This version publication date	18 December 2024
First version publication date	18 December 2024

Trial information**Trial identification**

Sponsor protocol code	LDX0419
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04899271
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé farmaceutici S.P.A.
Sponsor organisation address	Via S. Lucia 6, Milan, Italy, 20122
Public contact	dr. Enrico M. Minnella, Dompé farmaceutici S.P.A., Dompé farmaceutici S.P.A., +39 583831, clinical.trials@dompe.com
Scientific contact	dr. Enrico M. Minnella, Dompé farmaceutici S.P.A., 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	29 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2023
Global end of trial reached?	Yes
Global end of trial date	11 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this clinical trial was to assess whether ladarixin treatment is effective to improve glycemic control in newly diagnosed Type 1 Diabetes (T1D) adult patients with preserved β -cell function. The safety of ladarixin in the specific clinical setting was also evaluated

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP; ICH GCP E6(R2)), the Declaration of Helsinki and all other applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2020
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	United States: 2
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	25
EEA total number of subjects	17

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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The number of patients randomized and treated was lower than planned in the study protocol. The Sponsor decided to stop patient enrolment on 28 March 2022, due to the recruitment rate being lower than expected. At the time of recruitment closure, 25 patients had been randomized compared with the 75 planned.

Pre-assignment

Screening details:

Overall, 80 patients were screened and enrolled in the study. Out of these, 55 patients were not randomized due to failure to meet randomization criteria (52, 65.0%) and consent withdrawal (3, 3.8%).

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:

Patients, Investigators and site staff remained blinded to treatment assignment throughout the study. The realization of the double-blind design was made possible by the production of placebo capsules identical in appearance to the active IMP, including packaging and labelling. The treatment assignment info was kept confidential and not disclosed to any other persons than the ones involved in emergency and safety procedures, i.e., Investigators and Dompé Pharmacovigilance contact persons.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ladarixin

Arm description:

The treatment group will receive 400 mg b.i.d. for 13 cycles of 14 days on/14 days off)

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

Dosage and administration details:

Ladarixin was to be administered 400 mg b.i.d. as hard gelatine capsules for oral administration (2 capsules 200 mg each, b.i.d., at least 2 hours apart from breakfast or dinner) for 13 cycles of 14 days on/14 days off

Arm title	Placebo
------------------	---------

Arm description:

The control group received matched placebo with the same schedule of IMP

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

Dosage and administration details:

Placebo was administered orally with the formulation and the same scheme of administration of LDX to preserve blinding.

Number of subjects in period 1	Ladarixin	Placebo
Started	18	7
Completed	15	7
Not completed	3	0
Consent withdrawn by subject	2	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Ladarixin
Reporting group description: The treatment group will receive 400 mg b.i.d. for 13 cycles of 14 days on/14 days off)	
Reporting group title	Placebo
Reporting group description: The control group received matched placebo with the same schedule of IMP	

Reporting group values	Ladarixin	Placebo	Total
Number of subjects	18	7	25
Age categorical Units: Subjects			
Adults (18-64 years)	18	7	25
Age continuous Units: years			
arithmetic mean	25.5	27.3	
standard deviation	± 7.6	± 7.7	-
Gender categorical Units: Subjects			
Female	6	2	8
Male	12	5	17

Subject analysis sets

Subject analysis set title	Ladarixin - FAS
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set: it consisted of all randomized patients who received at least 1 dose of the IMP (either ladarixin or placebo). The FAS was analyzed according to the Intention To Treat (ITT) principle, i.e., by treatment allocation regardless happening of intercurrent events (treatment policy strategy). The FAS was used for the primary analyses of the study and to present results on efficacy data.	
Subject analysis set title	Ladarixin - SAF
Subject analysis set type	Safety analysis
Subject analysis set description: SAF population: The Safety (SAF) population consisted of all randomized patients who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.	
Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set consisted of all randomized patients who received at least one dose of the IMP. The FAS was analyzed according to the ITT principle, i.e., by treatment allocation regardless happening of intercurrent events (treatment policy strategy). The FAS was used for the primary analyses of the study and to present results on efficacy data.	
Subject analysis set title	Placebo - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety (SAF) population consisted of all randomized patients who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Reporting group values	Ladarixin - FAS	Ladarixin - SAF	Placebo - FAS
Number of subjects	18	18	7
Age categorical Units: Subjects			
Adults (18-64 years)	18	18	7
Age continuous Units: years			
arithmetic mean	25.5	25.5	27.3
standard deviation	± 7.6	± 7.6	± 7.7
Gender categorical Units: Subjects			
Female	6	6	2
Male	12	12	5

Reporting group values	Placebo - SAF		
Number of subjects	7		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
Age continuous Units: years			
arithmetic mean	27.3		
standard deviation	± 7.7		
Gender categorical Units: Subjects			
Female	2		
Male	5		

End points

End points reporting groups

Reporting group title	Ladarixin
-----------------------	-----------

Reporting group description:

The treatment group will receive 400 mg b.i.d. for 13 cycles of 14 days on/14 days off)

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

The control group received matched placebo with the same schedule of IMP

Subject analysis set title	Ladarixin - FAS
----------------------------	-----------------

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

Subject analysis set description:

Full Analysis Set: it consisted of all randomized patients who received at least 1 dose of the IMP (either ladarixin or placebo). The FAS was analyzed according to the Intention To Treat (ITT) principle, i.e., by treatment allocation regardless happening of intercurrent events (treatment policy strategy). The FAS was used for the primary analyses of the study and to present results on efficacy data.

Subject analysis set title	Ladarixin - SAF
----------------------------	-----------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

SAF population: The Safety (SAF) population consisted of all randomized patients who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Subject analysis set title	Placebo - FAS
----------------------------	---------------

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

Subject analysis set description:

The Full Analysis Set consisted of all randomized patients who received at least one dose of the IMP. The FAS was analyzed according to the ITT principle, i.e., by treatment allocation regardless happening of intercurrent events (treatment policy strategy). The FAS was used for the primary analyses of the study and to present results on efficacy data.

Subject analysis set title	Placebo - SAF
----------------------------	---------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

The Safety (SAF) population consisted of all randomized patients who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Primary: Proportion of Patients With HbA1c <7% and Daily Insulin Requirement <0.50 IU/Kg/Day at month 12

End point title	Proportion of Patients With HbA1c <7% and Daily Insulin Requirement <0.50 IU/Kg/Day at month 12
-----------------	---

End point description:

The sample size of the study is calculated on the "proportion of patients with a HbA1c < 7% and daily insulin requirement <0.50 IU/Kg/day", a post-hoc composite endpoint derived from data of the phase 2 trial (MEX0114), considering a larger effect size expected from the longer treatment length (one year versus 3 months). The time frame for the primary endpoint has been set at Month 12 (Week 52) in order to evaluate the potential of ladarixin effects on a long-term projection. Please note that proportion is expressed as count of patients.

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

End point timeframe:

Month 12 (52±2 weeks)

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	7		
Units: number of patients	11	5		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Comparison groups	Placebo - FAS v Ladarixin - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807
Method	Chi-squared

Secondary: Proportion of Patients With HbA1c < 7% and Daily Insulin Requirement <0.50 IU/Kg/Day, at months 6 and 18

End point title	Proportion of Patients With HbA1c < 7% and Daily Insulin Requirement <0.50 IU/Kg/Day, at months 6 and 18
-----------------	--

End point description:

The sample size of the study is calculated on the "proportion of patients with a HbA1c < 7% and daily insulin requirement <0.50 IU/Kg/day", a post-hoc composite endpoint derived from data of the phase 2 trial (MEX0114), considering a larger effect size expected from the longer treatment length (one year versus 3 months). Follow-up is extended up to 18 months to evaluate the potential persistency of any glycemic benefit. Please note that proportion is expressed as count of patients.

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

End point timeframe:

Month 6 (26±2 weeks) and Month 18 (78±2 weeks).

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	7		
Units: number of patients				
Month 6	12	6		
Month 18	8	5		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: comparison at month 6	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746
Method	Chi-squared

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: comparison at month 18	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201
Method	Chi-squared

Secondary: Proportion of Patients With a Reduction in HbA1c% > 0.5% From Baseline and Daily Insulin Requirement <0.50 IU/Kg at months 6, 12 and 18

End point title	Proportion of Patients With a Reduction in HbA1c% > 0.5% From Baseline and Daily Insulin Requirement <0.50 IU/Kg at months 6, 12 and 18
End point description: Proportion of patients with a reduction in HbA1c% > 0.5% from baseline and daily insulin requirement <0.50 IU/Kg/day was calculated. Please note that proportion is expressed as count of patients.	
End point type	Secondary
End point timeframe: Months 6 (week 26±2), 12 (week 52±2) and 18 (week 78±2)	

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	7		
Units: number of patients				
Month 6	8	4		
Month 12	8	3		
Month 18	6	2		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 6	
Comparison groups	Placebo - FAS v Ladarixin - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867
Method	Chi-squared

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 12	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769
Method	Chi-squared

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 18	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.776
Method	Chi-squared

Secondary: Change From Baseline in 2-hour AUC of C-peptide Response to the MMTT at months 6, 12 and 18

End point title	Change From Baseline in 2-hour AUC of C-peptide Response to the MMTT at months 6, 12 and 18
-----------------	---

End point description:

C-peptide level is a widely used measure of pancreatic beta-cell function and the MMTT is one of the

methods for its estimation. AUC stands for Area Under the Curve. AUC calculation was based on actual rather scheduled timings and it was calculated using the trapezoidal rule. C-peptide 0-120 min AUC (nmol/L) values were calculated based on all Basal-120min C-peptide values. Unscheduled assessments were excluded from the analysis.

End point type	Secondary
End point timeframe:	
Months 6 (week 26±2), 12 (week 52±2) and 18 (week 78±2)	

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[1]	7		
Units: nmol/L				
arithmetic mean (standard deviation)				
Month 6	-7.17 (± 19.33)	-12.70 (± 16.87)		
Month 12	0.25 (± 23.77)	-0.88 (± 53.61)		
Month 18	-2.07 (± 20.79)	-5.41 (± 32.52)		

Notes:

[1] - month 6: n=16
month 12: n=15
month 18: n=15

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 6 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521 ^[2]
Method	t-test, 2-sided

Notes:

[2] - Assumption of normality was confirmed by Kolmogorov-Smirnov test; the comparison between treatment arms was performed by means of two-sample t-test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 12 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.959 ^[3]
Method	t-test, 2-sided

Notes:

[3] - Assumption of normality was confirmed by Kolmogorov-Smirnov test; the comparison between treatment arms was performed by means of two-sample t-test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: Comparison at month 18 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.773 ^[4]
Method	t-test, 2-sided

Notes:

[4] - Assumption of normality was confirmed by Kolmogorov-Smirnov test; the comparison between treatment arms was performed by means of two-sample t-test.

Secondary: Changes From Baseline in HbA1c Levels at Months 6, 12 and 18.

End point title	Changes From Baseline in HbA1c Levels at Months 6, 12 and 18.
End point description: HbA1c measurement can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. An A1C test measures the percentage of red blood cells that have glucose-coated hemoglobin.	
End point type	Secondary
End point timeframe: Months 6 (week 26±2), 12 (week 52±2) and 18 (week 78±2)	

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[5]	7 ^[6]		
Units: percentage of red blood cells				
arithmetic mean (standard deviation)				
Month 6	-0.67 (± 0.88)	-0.84 (± 1.11)		
Month 12	-0.51 (± 1.24)	-0.77 (± 1.28)		
Month 18	-0.30 (± 1.55)	-0.33 (± 0.67)		

Notes:

[5] - n= 15 at months 6 and 18

n=14 at month 12

[6] - n=6 at months 12 and 18

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description: Comparison at month 6 for change from baseline	

Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.691 ^[7]
Method	t-test, 2-sided

Notes:

[7] - Assumption of normality is confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample t-test.

Statistical analysis title	Ladarixin vs placebo
-----------------------------------	----------------------

Statistical analysis description:

Comparison at month 12 for change from baseline

Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.685 ^[8]
Method	t-test, 2-sided

Notes:

[8] - Assumption of normality is confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample t-test.

Statistical analysis title	Ladarixin vs placebo
-----------------------------------	----------------------

Statistical analysis description:

Comparison at month 18 for change from baseline

Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64 ^[9]
Method	t-test, 2-sided

Notes:

[9] - Assumption of normality is confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample t-test.

Secondary: Proportion of Patients With HbA1c < 7% Who Did Not Experience Severe Hypoglycemic Events during treatment at months 6, 12 and 18

End point title	Proportion of Patients With HbA1c < 7% Who Did Not Experience Severe Hypoglycemic Events during treatment at months 6, 12 and 18
-----------------	--

End point description:

For the purpose of this study, a severe hypoglycaemic event is defined as an event with one of the following symptoms:

memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure,

seizure, loss of consciousness or visual symptoms, in which the subject was unable to treat him/herself and which was

associated with either a blood glucose level <54mg/dL (3.0 mmol/L) or prompt recovery after oral carbohydrate, i.v.

glucose, or glucagon administration. Please note that proportion is expressed as count of patients.

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

End point timeframe:

Months 6 (week 26), 12 (week 52) and 18 (week 78)

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[10]	7 ^[11]		
Units: number of patients				
Month 6	7	3		
Month 12	8	3		
Month 18	7	2		

Notes:

[10] - n=15 at months 6 and 18

n=14 at month 12

[11] - n=6 at month 18

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 6	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867 ^[12]
Method	Chi-squared

Notes:

[12] - Comparison between treatment arms is performed by means of a Chi-squared test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 12	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769 ^[13]
Method	Chi-squared

Notes:

[13] - Comparison between treatment arms is performed by means of a Chi-squared test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 18	
Comparison groups	Ladarixin - FAS v Placebo - FAS

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.577 ^[14]
Method	Chi-squared

Notes:

[14] - Comparison between treatment arms is performed by means of a Chi-squared test.

Secondary: Number of Self-reported Episodes of Severe Hypoglycemia

End point title	Number of Self-reported Episodes of Severe Hypoglycemia
-----------------	---

End point description:

For the purpose of this study, a severe hypoglycaemic event is defined as an event with one of the following symptoms:
memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure,
seizure, loss of consciousness or visual symptoms, in which the subject was unable to treat him/herself and which was
associated with either a blood glucose level <54mg/dL (3.0 mmol/L) or prompt recovery after oral carbohydrate, i.v.
glucose, or glucagon administration.

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

End point timeframe:

From baseline to study termination (month 18, week 78)

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	7		
Units: No of severe hypoglycemic episodes	28	8		

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1.271
Method	Cox proportional hazards model.

Secondary: Change From Baseline in Average (Previous 3 Days) Daily Insulin Requirements (IU/kg/Day) to months 6, 12 and 18

End point title	Change From Baseline in Average (Previous 3 Days) Daily Insulin Requirements (IU/kg/Day) to months 6, 12 and 18
-----------------	---

End point description:

For the purpose of this study, daily insulin is averaged over the previous 3 days. Insulin requirement

(IU/kg/day averaged over the previous 3 days) was to be recorded to Months 6, 12 and 18. Patients were admitted to intensive diabetes management, according to current ADA recommendation [2014]. Patients were instructed to self-monitor their glucose values at least 4 times a day and to report (glucose meter/log) outcome to the diabetes management team. Insulin intake was adjusted to target HbA1c levels of less than 7% and self-monitored (fingerstick):

- pre-prandial blood glucose of 70-130 mg/dL
- post-prandial blood glucose < 180 mg/dL
- bed-time blood glucose of 110-150 mg/dL

End point type	Secondary
End point timeframe:	
Months 6 (week 26±2), 12 (week 52±2) and 18 (week 78±2)	

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[15]	7 ^[16]		
Units: IU/kg/day				
arithmetic mean (standard deviation)				
Month 6	-0.209 (± 0.644)	-0.028 (± 0.228)		
Month 12	-0.183 (± 0.661)	0.024 (± 0.271)		
Month 18	-0.183 (± 0.639)	-0.005 (± 0.342)		

Notes:

[15] - n=16 at month 6
n= 15 at months 12 and 18
[16] - n=6 at month 6

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 6 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 ^[17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - Assumption of normality is not confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 12 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.398 ^[18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - Assumption of normality is not confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Ladarixin vs placebo
-----------------------------------	----------------------

Statistical analysis description:

Comparison at month 18 for change from baseline

Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 ^[19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Assumption of normality is not confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Secondary: Change From Baseline in Estimated Glucose Disposal Rate (eGDR) to months 6, 12 and 18

End point title	Change From Baseline in Estimated Glucose Disposal Rate (eGDR) to months 6, 12 and 18
-----------------	---

End point description:

Estimated Glucose Disposal Rate (eGDR) is a marker for the Assessment of Insulin Resistance and a validated clinical tool for estimating insulin sensitivity in type 1 diabetes.

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

End point timeframe:

Months 6 (week 26±2), 12 (week 52±2) and 18 (week 78±2)

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18 ^[20]	7 ^[21]		
Units: mg/kg/min				
arithmetic mean (standard deviation)				
Month 6	0.418 (± 0.815)	0.367 (± 0.816)		
Month 12	0.067 (± 1.504)	0.623 (± 0.862)		
Month 18	0.242 (± 1.142)	-0.238 (± 1.255)		

Notes:

[20] - n=15 at months 6 and 18

n= 14 at month 12

[21] - n=6 at months 12 and 18

Statistical analyses

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 6 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.892 ^[22]
Method	t-test, 2-sided

Notes:

[22] - Assumption of normality is confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample t-test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 12 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.412 ^[23]
Method	t-test, 2-sided

Notes:

[23] - Assumption of normality is confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample t-test.

Statistical analysis title	Ladarixin vs placebo
Statistical analysis description:	
Comparison at month 18 for change from baseline	
Comparison groups	Ladarixin - FAS v Placebo - FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.371 ^[24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - Assumption of normality is not confirmed by Kolmogorov-Smirnov test; comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Secondary: Number of Patients With at Least One Adverse Events (AEs), Serious or Not Serious

End point title	Number of Patients With at Least One Adverse Events (AEs), Serious or Not Serious
-----------------	---

End point description:

An AE is any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the trial intervention.

A serious adverse event is an adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.

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

End point timeframe:

Throughout the study up to 18 months

End point values	Ladarixin - SAF	Placebo - SAF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	7		
Units: No of patients				
Any TEAE	12	5		
Serious TEAE	1	0		
non-serious TEAE	12	5		
TEAEs leading to IMP discontinuation	1	1		
TEAEs leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemic blood glucose levels for patients reporting severe hypoglycemia

End point title	Hypoglycemic blood glucose levels for patients reporting severe hypoglycemia
-----------------	--

End point description:

A severe hypoglycemic event was defined as an event with 1 of the following symptoms: "memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness, or visual symptoms", in which the subject was unable to treat him/herself and which was associated with either a blood glucose level <54mg/dL or prompt recovery after oral carbohydrate, i.e. glucose, or glucagon administration. Summary statistics of blood glucose level (mg/dL) are provided by treatment group at each time point for patients reporting severe hypoglycemia.

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

End point timeframe:

Months 6 (week 26±2), 12 (week 52±2) and 18 (week 78±2)

End point values	Ladarixin - FAS	Placebo - FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	7		
Units: mg/dL				
arithmetic mean (standard deviation)				
Month 6	48.11 (± 4.73)	51.00 (± 3.94)		
Month 12	48.71 (± 4.75)	49.57 (± 5.71)		
Month 18	48.27 (± 4.90)	50.13 (± 5.51)		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study, from the baseline to the study termination (from cycle 1 up to Month 12) and follow-up (Month 18)

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

Dictionary used

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

Dictionary version	23.0
--------------------	------

Reporting groups

Reporting group title	Ladarixin
-----------------------	-----------

Reporting group description:

The treatment group received 400 mg b.i.d. for 13 cycles of 14 days on/14 days off.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

The control group received matched placebo with the same schedule of IMP

Serious adverse events	Ladarixin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Endocrine disorders			
primary hyperparathyroidism			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	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	12 / 18 (66.67%)	5 / 7 (71.43%)	
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 7 (14.29%) 1	
Reproductive system and breast disorders Amenorrhea subjects affected / exposed occurrences (all) Dysmenorrhea subjects affected / exposed occurrences (all) Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 1 / 7 (14.29%) 2	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Respiratory disorder subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0	
Investigations Occult blood subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2	0 / 7 (0.00%) 0	
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Post procedural hypothyroidism subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 7 (28.57%) 2	
Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 7 (0.00%) 0	
Parosmia subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 7 (14.29%) 1	
Sciatica subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 7 (14.29%) 1	
Taste disorders subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 7 (14.29%) 1	
Blood and lymphatic system disorders Normocytic anemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Gastrointestinal disorders Abnormal faeces subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Diarrhea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	

Dyspepsia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	3	
abdominal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Fixed eruption			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Hyperparathyroidism primary			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
COVID-19			

subjects affected / exposed occurrences (all)	6 / 18 (33.33%) 6	5 / 7 (71.43%) 5	
Influenza subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Nasal herpes subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 7 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 5	1 / 7 (14.29%) 1	
Streptococcal urinary tract infection subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 7 (14.29%) 1	
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	2 / 7 (28.57%) 2	
Metabolism and nutrition disorders Hyperglycemia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 7 (0.00%) 0	
Hypoglycemia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 8	1 / 7 (14.29%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The enrolment was stopped on March,28, 2022 due to low enrolment rate, at the randomization of the 25th patient. Due to the trial early termination, efficacy analyses were reduced given the limited sample size of the study vs the one expected.

Notes: