Clinical trial results:
Blood Glucose Response After Oral Intake of Lactulose (Laevolac®) in Mildly Constipated Patients with Diabetes Mellitus Type 2

Summary

EudraCT number	2018-002359-14
Trial protocol	AT
Global end of trial date	08 March 2019

Results information

Result version number	v1 (current)
This version publication date	10 June 2020
First version publication date	10 June 2020

Trial information

Trial identification

Sponsor protocol code	Lact-004-CP4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03666546
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi Deutschland GmbH
Sponsor organisation address	Else-Kröner-Straße 1, Bad Homburg, Germany, 61346
Public contact	Medical Affairs & Clinical Operations Parenteral Nutrition & Keto-Analogues, Fresenius Kabi Deutschland GmbH, trial-disclosure@fresenius-kabi.com
Scientific contact	Medical Affairs & Clinical Operations Parenteral Nutrition & Keto-Analogues, Fresenius Kabi Deutschland GmbH, trial-disclosure@fresenius-kabi.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	23 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 March 2019
Global end of trial reached?	Yes
Global end of trial date	08 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to investigate whether lactulose, given orally as powder or liquid, increases blood glucose levels in patients with diabetes mellitus type 2. The dose of lactulose given in the trial is normally used for treatment of constipation.

Protection of trial subjects:

Subject protection was ensured by high medical and ethical standards in accordance with Declaration of Helsinki, Good Clinical Practice and applicable national and local laws and regulations. The signed informed consent was obtained from the patient prior to inclusion in the study.

Background therapy:

All study patients had non-insulin requiring diabetes mellitus type 2 and were treated with diet and oral antidiabetic drugs and/or Glucagon-like peptide(GLP)-1 receptor agonists. Diabetes mellitus treatment had to be stable, without any changes in diabetes mellitus related medication within the last 3 months. On days with study treatment, the intake of the antidiabetic medication in the morning was postponed until was postponed until breakfast after the test. Study products were consumed orally as single dose after overnight fast. Over a period of 180 minutes, when blood glucose levels were monitored in capillary blood, patients had to stay fasting and only water was served.

Evidence for comparator:

Water (placebo) was chosen as comparator to estimate normal physiologic variability of capillary blood glucose level over the Observation period of 180 minutes after intake of the study products.
A dose of 30 g glucose (active comparator) was used as reference to evaluate the blood glucose level increase, this dose was chosen because it was considered as a comparable amount to the highest dose of Laevolac®.

Actual start date of recruitment	19 November 2018
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	Austria: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	13
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screened were non-insulin requiring patients with diabetes mellitus type 2, treated with diet and oral antidiabetics and/or GLP1 receptor agonists
- Age 18 - 75 years
- Glycosylated haemoglobin (HbA1c) ≤ 7.5 %
- No change in diabetes mellitus related medication within the last 3 months
- Mild functional constipation for the last 3 months

Period 1

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

Blinding implementation details:

The preparation of study products (blinding, reconstitution and labelling of drinking flasks) was done by unblinded staff by four-eyes principle. Test and control products were dissolved in 250 mL still water in non-transparent dark drinking flasks. The flasks had to bear the same blinded study specific labels which precluded unblinding by visual inspection. The flasks were provided to the blinded site personnel and Investigator to preserve the blind for Investigator and study patients.

Arms

Are arms mutually exclusive?	No
Arm title	Laevolac® liquid 20 g

Arm description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 17 received Laevolac® liquid 20 g as one of 4 different study treatments.

Arm type	Experimental
Investigational medicinal product name	Laevolac® liquid
Investigational medicinal product code	
Other name	Lactulose
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Laevolac® liquid 20 g was dissolved in 250 mL still water. Solution was consumed orally as single dose after overnight fast within 5 minutes.

Arm title	Laevolac® liquid 30 g

Arm description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 15 received Laevolac® liquid 30 g as one of 4 different study treatments.

Arm type	Experimental
Investigational medicinal product name	Laevolac® liquid
Investigational medicinal product code	
Other name	Lactulose
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Laevolac® liquid 30 g was dissolved in 250 mL still water. Solution was consumed orally as single dose

after overnight fast within 5 minutes.

Arm title	Laevolac® crystals 20 g

Arm description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Laevolac® crystals 20 g as one of 4 different study treatments.

Arm type	Experimental
Investigational medicinal product name	Laevolac® crystals
Investigational medicinal product code	
Other name	Lactulose
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Laevolac® crystals 20 g was dissolved in 250 mL still water. Solution was consumed orally as single dose after overnight fast within 5 minutes.

Arm title	Laevolac® crystals 30 g

Arm description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Laevolac® crystals 30 g as one of 4 different study treatments.

Arm type	Experimental
Investigational medicinal product name	Laevolac® crystals
Investigational medicinal product code	
Other name	Lactulose
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Laevolac® crystals 30 g was dissolved in 250 mL still water. Solution was consumed orally as single dose after overnight fast within 5 minutes.

Arm title	Glucose 30 g

Arm description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Glucose 30 g as one of 4 different study treatments.

Arm type	Active comparator
Investigational medicinal product name	Glucose monohydrate
Investigational medicinal product code	
Other name	Glucose
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Glucose 30 g (Glucose monohydrate 33 g) was dissolved in 250 mL still water. Solution was consumed orally as single dose after overnight fast within 5 minutes.

Arm title	Water

Arm description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Water as one of 4 different study treatments.

Arm type	Placebo

Investigational medicinal product name	Still water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

250 mL still water was consumed orally as single dose after overnight fast within 5 minutes.

Number of subjects in period 1	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g
Started	17	15	16
Completed	17	15	16

Number of subjects in period 1	Laevolac® crystals 30 g	Glucose 30 g	Water
Started	16	16	16
Completed	16	16	16

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Phase

Reporting group description:

The study was performed as 4-period cross-over with incomplete block design, stratified by gender. 24 patients were enrolled. Patients were randomized to one of 6 treatment sequences; each patient received 4 of the 6 different study products (6 arms).

Reporting group values	Treatment Phase	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	62.2		
standard deviation	± 7.61	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	16	16	

End points

End points reporting groups

Reporting group title	Laevolac® liquid 20 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 17 received Laevolac® liquid 20 g as one of 4 different study treatments.

Reporting group title	Laevolac® liquid 30 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 15 received Laevolac® liquid 30 g as one of 4 different study treatments.

Reporting group title	Laevolac® crystals 20 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Laevolac® crystals 20 g as one of 4 different study treatments.

Reporting group title	Laevolac® crystals 30 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Laevolac® crystals 30 g as one of 4 different study treatments.

Reporting group title	Glucose 30 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Glucose 30 g as one of 4 different study treatments.

Reporting group title	Water

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Water as one of 4 different study treatments.

Primary: Capillary blood glucose levels as baseline corrected AUC: AUCbaseline_c (0-180 min)

End point title	Capillary blood glucose levels as baseline corrected AUC: AUCbaseline_c (0-180 min)

End point description:

Baseline corrected area under curve (AUC) of blood glucose concentrations from time 0 to 180 minutes after intake of the study products. (AUCbaseline_c is defined as AUC(0-180 min) - (baseline*180 min).

End point type	Primary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: min*mg/dL				
arithmetic mean (standard deviation)	-443.8 (± 1291.52)	-743.8 (± 1577.91)	-964.2 (± 1321.89)	-484.2 (± 1280.63)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: min*mg/dL				
arithmetic mean (standard deviation)	8440 (± 2636.0)	-758.0 (± 1320.23)		

Statistical analyses

Statistical analysis title	Mixed model arm 1 v 6
Comparison groups	Laevolac® liquid 20 g v Water
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	405.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-633.92
upper limit	1444.39

Statistical analysis title	Mixed model arm 2 v 6
Comparison groups	Laevolac® liquid 30 g v Water
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	219.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-855.54
upper limit	1295.12

Statistical analysis title	Mixed model arm 3 v 6
Comparison groups	Laevolac® crystals 20 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	-21.5269
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1095.13
upper limit	1052.08

Statistical analysis title	Mixed model arm 4 v 6
Comparison groups	Laevolac® crystals 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	405.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-667.49
upper limit	1478.51

Statistical analysis title	Mixed model arm 5 v 2
Comparison groups	Glucose 30 g v Laevolac® liquid 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	9024.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7917.58
upper limit	10131

Statistical analysis title	Mixed model arm 5 v 4

Comparison groups	Glucose 30 g v Laevolac® crystals 30 g
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	8838.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	7781.86
upper limit	9895.09

Statistical analysis title	Mixed model arm 5 v 6
Comparison groups	Glucose 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	9243.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	8170.95
upper limit	10317

Statistical analysis title	Mixed model arm 1 v 3
Comparison groups	Laevolac® liquid 20 g v Laevolac® crystals 20 g
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	426.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-627.87
upper limit	1481.39

Statistical analysis title	Mixed model arm 2 v 4
Comparison groups	Laevolac® liquid 30 g v Laevolac® crystals 30 g

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	-185.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1289.75
upper limit	918.31

Secondary: Maximum blood glucose concentration: Cmax

End point title	Maximum blood glucose concentration: Cmax

End point description:

Maximum blood glucose concentration derived from the individual blood glucose concentration time curves from time 0 to 180 minutes after intake of the study products.

End point type	Secondary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: mg/dL				
arithmetic mean (standard deviation)	141.6 (± 16.71)	149.2 (± 19.91)	131.4 (± 17.88)	139.5 (± 25.44)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mg/dL				
arithmetic mean (standard deviation)	236.5 (± 29.95)	136.6 (± 15.76)		

Statistical analyses

Statistical analysis title	Mixed model arm 1 v 6
Comparison groups	Laevolac® liquid 20 g v Water

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	5.5231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.164
upper limit	13.2102

Statistical analysis title	Mixed model arm 2 v 6
Comparison groups	Laevolac® liquid 30 g v Water
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	11.321
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3808
upper limit	19.2611

Statistical analysis title	Mixed model arm 3 v 6
Comparison groups	Laevolac® crystals 20 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	1.0074
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9024
upper limit	8.9172

Statistical analysis title	Mixed model arm 4 v 6
Comparison groups	Laevolac® crystals 30 g v Water

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	5.8679
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.0297
upper limit	13.7655

Statistical analysis title	Mixed model arm 5 v 2
Comparison groups	Glucose 30 g v Laevolac® liquid 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	92.881
Confidence interval	
level	95 %
sides	2-sided
lower limit	84.7739
upper limit	100.99

Statistical analysis title	Mixed model arm 5 v 4
Comparison groups	Glucose 30 g v Laevolac® crystals 30 g
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	98.3341
Confidence interval	
level	95 %
sides	2-sided
lower limit	90.5138
upper limit	106.15

Statistical analysis title	Mixed model arm 5 v 6
Comparison groups	Glucose 30 g v Water

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	104.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.3025
upper limit	112.1

Statistical analysis title	Mixed model arm 1 v 3
Comparison groups	Laevolac® liquid 20 g v Laevolac® crystals 20 g
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	4.5157
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2607
upper limit	12.292

Statistical analysis title	Mixed model arm 2 v 4
Comparison groups	Laevolac® liquid 30 g v Laevolac® crystals 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least squares means
Point estimate	5.4531
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6411
upper limit	13.5472

Secondary: Maximum increase of blood glucose concentration (Cmax minus baseline value): Max_increase

End point title	Maximum increase of blood glucose concentration (Cmax minus baseline value): Max_increase

End point description:

Maximum increase of blood glucose concentration (Cmax minus baseline value) derived from the individual blood glucose concentration time curves from time 0 to 180 minutes after intake of the study products.

End point type	Secondary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: mg/dL				
arithmetic mean (standard deviation)	12.62 (± 7.208)	18.43 (± 10.321)	7.688 (± 7.1969)	12.81 (± 11.180)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mg/dL				
arithmetic mean (standard deviation)	110.9 (± 20.99)	7.875 (± 6.9821)		

Statistical analyses

Statistical analysis title	Mixed model arm 1 v 6
Comparison groups	Laevolac® liquid 20 g v Water
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	5.5231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.164
upper limit	13.2102

Statistical analysis title	Mixed model arm 2 v 6
Comparison groups	Laevolac® liquid 30 g v Water

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	11.321
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3808
upper limit	19.2611

Statistical analysis title	Mixed model arm 3 v 6
Comparison groups	Laevolac® crystals 20 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	1.0074
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9024
upper limit	8.9172

Statistical analysis title	Mixed model arm 4 v 6
Comparison groups	Laevolac® crystals 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	5.8679
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.0297
upper limit	13.7655

Statistical analysis title	Mixed model arm 5 v 2
Comparison groups	Laevolac® liquid 30 g v Glucose 30 g

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	92.881
Confidence interval	
level	95 %
sides	2-sided
lower limit	84.7739
upper limit	100.99

Statistical analysis title	Mixed model arm 5 v 4
Comparison groups	Laevolac® crystals 30 g v Glucose 30 g
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	98.3341
Confidence interval	
level	95 %
sides	2-sided
lower limit	90.5138
upper limit	106.15

Statistical analysis title	Mixed model arm 5 v 6
Comparison groups	Glucose 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	104.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.3025
upper limit	112.1

Statistical analysis title	Mixed model arm 1 v 3
Comparison groups	Laevolac® liquid 20 g v Laevolac® crystals 20 g

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	4.5157
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2607
upper limit	12.292

Statistical analysis title	Mixed model arm 2 v 4
Comparison groups	Laevolac® liquid 30 g v Laevolac® crystals 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	5.4531
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6411
upper limit	13.5472

Secondary: Relative maximum increase of blood glucose concentration (Cmax / baseline value): Max_increase_rel

End point title	Relative maximum increase of blood glucose concentration (Cmax / baseline value): Max_increase_rel

End point description:

Relative maximum increase of blood glucose concentration (Cmax / baseline value) derived from the individual blood glucose concentration time curves from time 0 to 180 minutes after intake of the study products.

End point type	Secondary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: mg/dL / mg/dL				
arithmetic mean (standard deviation)	1.101 (± 0.0610)	1.145 (± 0.0847)	1.063 (± 0.0593)	1.108 (± 0.1005)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: mg/dL / mg/dL				
arithmetic mean (standard deviation)	1.897 (± 0.1891)	1.066 (± 0.0630)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum blood glucose concentration: Tmax

End point title	Time to reach maximum blood glucose concentration: Tmax

End point description:

End point type	Secondary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: minutes				
median (full range (min-max))	30.00 (0.00 to 120.00)	30.00 (0.00 to 60.00)	30.00 (0.00 to 180.00)	30.00 (0.00 to 60.00)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: minutes				
median (full range (min-max))	60.00 (45.00 to 60.00)	22.50 (0.00 to 150.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total AUC from 0 to 180 min for blood glucose concentration: AUC (0-180 min)

End point title	Total AUC from 0 to 180 min for blood glucose concentration: AUC (0-180 min)

End point description:

End point type	Secondary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: min*mg/dL				
arithmetic mean (standard deviation)	22766 (± 3092.3)	22794 (± 3667.5)	21311 (± 2806.7)	22320 (± 4040.1)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: min*mg/dL				
arithmetic mean (standard deviation)	31053 (± 4807.7)	22417 (± 2953.4)		

Statistical analyses

Statistical analysis title	Mixed model arm 1 v 6
Comparison groups	Laevolac® liquid 20 g v Water
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	405.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-633.92
upper limit	1444.39

Statistical analysis title	Mixed model arm 2 v 6
Comparison groups	Laevolac® liquid 30 g v Water
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	219.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-855.54
upper limit	1295.12

Statistical analysis title	Mixed model arm 3 v 6
Comparison groups	Laevolac® crystals 20 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	-21.5269
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1095.13
upper limit	1052.08

Statistical analysis title	Mixed model arm 4 v 6
Comparison groups	Laevolac® crystals 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	405.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-667.49
upper limit	1478.51

Statistical analysis title	Mixed model arm 5 v 2

Comparison groups	Glucose 30 g v Laevolac® liquid 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	9024.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7917.58
upper limit	10131

Statistical analysis title	Mixed model arm 5 v 4
Comparison groups	Glucose 30 g v Laevolac® crystals 30 g
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	8838.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	7781.86
upper limit	9895.09

Statistical analysis title	Mixed model arm 5 v 6
Comparison groups	Glucose 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	9243.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	8170.95
upper limit	10317

Statistical analysis title	Mixed model arm 1 v 3
Comparison groups	Laevolac® liquid 20 g v Laevolac® crystals 20 g

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	426.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-627.87
upper limit	1481.39

Statistical analysis title	Mixed model arm 2 v 4
Comparison groups	Laevolac® liquid 30 g v Laevolac® crystals 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	-185.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1289.75
upper limit	918.31

Secondary: Incremental AUC from 0 to 180 min for blood glucose concentration: iAUC (0-180 min)

End point title	Incremental AUC from 0 to 180 min for blood glucose concentration: iAUC (0-180 min)

End point description:

AUC above baseline levels for blood glucose concentration derived from the individual blood glucose concentration time curves from time 0 to 180 minutes after intake of the study products.

End point type	Secondary

End point timeframe:

From 5 min before (blood glucose baseline value) to 180 min after ingestion of study product. Further blood glucose measurements 15, 30, 45, 60, 90, 150 and 180 min after ingestion of study product.

End point values	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g	Laevolac® crystals 30 g
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	15	16	16
Units: min*mg/dL				
arithmetic mean (standard deviation)	619.7 (± 555.28)	755.7 (± 673.84)	296.3 (± 477.69)	503.4 (± 499.11)

End point values	Glucose 30 g	Water		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: min*mg/dL				
arithmetic mean (standard deviation)	8677 (± 2384.1)	350.7 (± 573.37)		

Statistical analyses

Statistical analysis title	Mixed model arm 1 v 6
Comparison groups	Laevolac® liquid 20 g v Water
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	288.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-482.47
upper limit	1058.49

Statistical analysis title	Mixed model arm 2 v 6
Comparison groups	Laevolac® liquid 30 g v Water
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	425.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-369.73
upper limit	1220.7

Statistical analysis title	Mixed model arm 3 v 6
Comparison groups	Laevolac® crystals 20 g v Water

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	-25.8996
Confidence interval	
level	95 %
sides	2-sided
lower limit	-813.73
upper limit	761.93

Statistical analysis title	Mixed model arm 4 v 6
Comparison groups	Laevolac® crystals 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	165.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-619.67
upper limit	951.57

Statistical analysis title	Mixed model arm 5 v 2
Comparison groups	Laevolac® liquid 30 g v Glucose 30 g
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	7911.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	7108.96
upper limit	8713.89

Statistical analysis title	Mixed model arm 5 v 4
Comparison groups	Laevolac® crystals 30 g v Glucose 30 g

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	8170.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	7386.6
upper limit	8955.33

Statistical analysis title	Mixed model arm 5 v 6
Comparison groups	Glucose 30 g v Water
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	8336.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	7550.95
upper limit	9122.88

Statistical analysis title	Mixed model arm 1 v 3
Comparison groups	Laevolac® liquid 20 g v Laevolac® crystals 20 g
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	872.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-461.79
upper limit	1089.61

Statistical analysis title	Mixed model arm 2 v 4
Comparison groups	Laevolac® liquid 30 g v Laevolac® crystals 30 g

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference least square means
Point estimate	259.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-542.14
upper limit	1061.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of AE reporting began with the fasting period the day before Screening Visit after Informed Consent (i.e. maximum 21 days before the first Treatment Visit) and ended 24 hours after the last of 4 Treatment Visits.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Laevolac® liquid 20 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 17 received Laevolac® liquid 20 g as one of 4 different study treatments.

Reporting group title	Laevolac® liquid 30 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 15 received Laevolac® liquid 30 g as one of 4 different study treatments.

Reporting group title	Laevolac® crystals 20 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Laevolac® crystals 20 g as one of 4 different study treatments.

Reporting group title	Laevolac® crystals 30 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Laevolac® crystals 30 g as one of 4 different study treatments.

Reporting group title	Glucose 30 g

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Glucose 30 g as one of 4 different study treatments.

Reporting group title	Water

Reporting group description:

Due to the 4-period cross-over design of the study, each patient was allocated to 4 arms, with a wash-out phase of 4 to 14 days to avoid carry-over effects. Of the 24 study patients, 16 received Water as one of 4 different study treatments.

Serious adverse events	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Laevolac® crystals 30 g	Glucose 30 g	Water
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Laevolac® liquid 20 g	Laevolac® liquid 30 g	Laevolac® crystals 20 g
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)	15 / 15 (100.00%)	12 / 16 (75.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	8 / 17 (47.06%)	4 / 15 (26.67%)	4 / 16 (25.00%)
occurrences (all)	8	5	4
Abdominal distension			
subjects affected / exposed	6 / 17 (35.29%)	7 / 15 (46.67%)	5 / 16 (31.25%)
occurrences (all)	11	8	5
Abdominal pain			

subjects affected / exposed	3 / 17 (17.65%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Diarrhoea			
subjects affected / exposed	5 / 17 (29.41%)	9 / 15 (60.00%)	7 / 16 (43.75%)
occurrences (all)	5	11	8
Dyspepsia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 15 (6.67%)	2 / 16 (12.50%)
occurrences (all)	1	1	2
Eructation			
subjects affected / exposed	1 / 17 (5.88%)	2 / 15 (13.33%)	2 / 16 (12.50%)
occurrences (all)	1	3	2
Flatulence			
subjects affected / exposed	11 / 17 (64.71%)	9 / 15 (60.00%)	8 / 16 (50.00%)
occurrences (all)	11	9	9
Gastrointestinal sounds abnormal			
subjects affected / exposed	11 / 17 (64.71%)	13 / 15 (86.67%)	8 / 16 (50.00%)
occurrences (all)	14	20	10
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Regurgitation			
subjects affected / exposed	1 / 17 (5.88%)	2 / 15 (13.33%)	2 / 16 (12.50%)
occurrences (all)	1	2	2
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 15 (6.67%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 17 (0.00%)	0 / 15 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Laevolac® crystals 30 g	Glucose 30 g	Water
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)	9 / 16 (56.25%)	7 / 16 (43.75%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	5 / 16 (31.25%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	5	2	1
Abdominal distension			
subjects affected / exposed	7 / 16 (43.75%)	4 / 16 (25.00%)	3 / 16 (18.75%)
occurrences (all)	7	4	3
Abdominal pain			
subjects affected / exposed	3 / 16 (18.75%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Diarrhoea			
subjects affected / exposed	5 / 16 (31.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	6	1	1
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Eructation			
subjects affected / exposed	3 / 16 (18.75%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	3	2	2
Flatulence			
subjects affected / exposed	6 / 16 (37.50%)	4 / 16 (25.00%)	5 / 16 (31.25%)
occurrences (all)	7	5	5
Gastrointestinal sounds abnormal			
subjects affected / exposed	11 / 16 (68.75%)	6 / 16 (37.50%)	4 / 16 (25.00%)
occurrences (all)	13	6	4
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Regurgitation			
subjects affected / exposed	0 / 16 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	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

None reported