Clinical trial results:
A Multi-center Open-label Parallel Group Randomized Controlled Trial to Compare iGlarLixi Versus Premixed Insulin in Patients With Type 2 Diabetes Who Have Failed to Achieve Glycemic Control With Basal Insulin and Oral Antidiabetic Agents

Summary

EudraCT number	2017-003370-13
Trial protocol	CZ AT ES SE BG GR RO
Global end of trial date	19 July 2020

Results information

Result version number	v1 (current)
This version publication date	28 July 2021
First version publication date	28 July 2021

Trial information

Trial identification

Sponsor protocol code	LPS15017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: Global Premix

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	15 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that in subjects with Type 2 diabetes mellitus (T2DM) failing to achieve control on their current basal insulin combined to 1 or 2 Oral Antidiabetic Drugs (OADs) regimen, iGlarLixi compared to premix insulin Biasp 30/70 twice daily (BID) showed non-inferiority of iGlarLixi in terms of Glycated hemoglobin (HbA1c) reduction or superiority in terms of body weight change at Week 26.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

OAD treatment of Metformin alone or Metformin + Sodium-glucose co-transporter 2 inhibitor (SGLT-2i) was continued at stable doses.

Evidence for comparator: -

Actual start date of recruitment	08 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	North Macedonia: 40
Country: Number of subjects enrolled	Mexico: 90
Country: Number of subjects enrolled	Romania: 30
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Serbia: 78
Country: Number of subjects enrolled	Taiwan: 30
Country: Number of subjects enrolled	Turkey: 18
Country: Number of subjects enrolled	Argentina: 70
Country: Number of subjects enrolled	India: 182
Country: Number of subjects enrolled	Korea, Republic of: 89
Country: Number of subjects enrolled	Kuwait: 25
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 30
Country: Number of subjects enrolled	Austria: 5

Country: Number of subjects enrolled	Bulgaria: 51
Country: Number of subjects enrolled	Czechia: 90
Country: Number of subjects enrolled	Greece: 22
Worldwide total number of subjects	887
EEA total number of subjects	264

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)	573
From 65 to 84 years	313
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 1074 subjects were screened from 08 November 2018 to 02 December 2019 of which 187 were screen failures. Screen failure were mainly due to inclusion criteria not met.

Pre-assignment

Screening details:

A total of 887 subjects were randomised in 1:1 ratio to receive either iGlarLixi or Premixed insulin. Stratification was done at randomisation, based on HbA1c value (less than [<] 8 percentage [%], greater than or equal to [>=] 8%), use of SGLT-2i (Yes/No), and dose of basal insulin (<30 Units [U], >=30 U) at screening visit.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	iGlarLixi

Arm description:

Subjects received iGlarLixi subcutaneously once a day for up to 26 weeks.

Arm type	Experimental
Investigational medicinal product name	iGlarLixi (insulin glargine/lixisenatide)
Investigational medicinal product code	HOE901/AVE0010
Other name	Suliqua
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

iGlarLixi (Fixed ratio combination of insulin glargine and lixisenatide) administered subcutaneously once a day within 1 hour prior to a meal with a prefilled disposable SoloStar® pen-injector. The dose was titrated according to the subject's need for insulin.

Arm title	Premixed insulin

Arm description:

Subjects received Premix BiAsp 30 BID for up to 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Premix BiAsp 30
Investigational medicinal product code	
Other name	NovoMix® 30
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Premixed insulin 3 millilitre (mL) administered subcutaneously BID. The dose was titrated according to the subject's need for insulin and usual practice.

Number of subjects in period 1	iGlarLixi	Premixed insulin
Started	443	444
Treated	442	441
Completed	428	416
Not completed	15	28
Adverse Events (AEs)	4	4
Randomised and not treated	1	3
Other	1	4
Poor compliance to protocol	1	2
Hypoglycemia	-	2
Withdrawal by subject	8	12
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	iGlarLixi
Reporting group description:	
Subjects received iGlarLixi subcutaneously once a day for up to 26 weeks.	
Reporting group title	Premixed insulin
Reporting group description:	
Subjects received Premix BiAsp 30 BID for up to 26 weeks.	

Reporting group values	iGlarLixi	Premixed insulin	Total
Number of subjects	443	444	887
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.8	59.8	
standard deviation	± 10.3	± 10.0	-
Gender categorical Units: Subjects			
Female	219	226	445
Male	224	218	442
Body Mass Index (BMI)			
Data for BMI was collected and analysed for 886 subjects (442 subjects in iGlarLixi arm and 444 in Premixed insulin arm).			
Units: kilogram per metre square (kg/m^2)			
arithmetic mean	29.7	30.0	
standard deviation	± 4.7	± 5.1	-
Duration of T2DM Units: years			
arithmetic mean	13.0	13.0	
standard deviation	± 7.1	± 7.4	-

End points

End points reporting groups	
Reporting group title	iGlarLixi
Reporting group description:	
Subjects received iGlarLixi subcutaneously once a day for up to 26 weeks.	
Reporting group title	Premixed insulin
Reporting group description:	
Subjects received Premix BiAsp 30 BID for up to 26 weeks.	

Primary: Change From Baseline to Week 26 in HbA1c: Non Inferiority Analysis	
End point title	Change From Baseline to Week 26 in HbA1c: Non Inferiority Analysis
End point description:	
Combined estimate for Least square (LS) means and standard errors (SE) were obtained using an analysis of covariance (ANCOVA) (using multiple imputation) to account for missing data using values obtained during the 26-week randomised treatment period. Analysis was performed on intent-to-treat (ITT) population that included all randomised subjects.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	iGlarLixi	Premixed insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	444		
Units: percentage of HbA1c				
least squares mean (standard error)	-1.30 (± 0.06)	-1.05 (± 0.06)		

Statistical analyses

Statistical analysis title	iGlarLixi Versus Premixed insulin
Statistical analysis description:	
Analysis was performed using ANCOVA model including fixed categorical effects of randomisation strata (basal insulin dose at screening visit [<30 U, >=30 U] and SGLT-2i use [Yes, No] at screening visit), treatment group and country as well as fixed continuous covariates of Baseline values HbA1c.	
Comparison groups	iGlarLixi v Premixed insulin
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	ANCOVA (using multiple imputation)
Parameter estimate	LS Mean difference
Point estimate	-0.24

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.41
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	0.07

Notes:

[1] - Non-inferiority of iGlarLixi versus premixed insulin on HbA1c change from Baseline to Week 26 was based on a non-inferiority margin of 0.3%.
[2] - Threshold of significance at 0.025 level.

Primary: Change From Baseline to Week 26 in Body Weight

End point title	Change From Baseline to Week 26 in Body Weight

End point description:

Combined estimate for LS means and SE were obtained using ANCOVA (using multiple imputation) to account for missing data using values obtained during the 26-week randomised treatment period. Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

Baseline, Week 26

End point values	iGlarLixi	Premixed insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	444		
Units: kilograms (kg)				
least squares mean (standard error)	-0.70 (± 0.20)	1.15 (± 0.20)		

Statistical analyses

Statistical analysis title	iGlarLixi Versus Premixed insulin

Statistical analysis description:

Analysis was performed using ANCOVA model including fixed categorical effects of randomisation strata (screening HbA1c value [<8.0% versus >=8.0%], basal insulin dose at screening visit [<30 U, >=30 U] and SGLT-2i use [Yes, No] at screening visit), treatment group and country as well as fixed continuous covariates of Baseline weight values.

Comparison groups	iGlarLixi v Premixed insulin
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-1.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	-1.43
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[3] - Threshold of significance at 0.05 level.

Secondary: Percentage of Subjects With HbA1c <7.0 % Without Body Weight Gain at Week 26

End point title	Percentage of Subjects With HbA1c <7.0 % Without Body Weight Gain at Week 26

End point description:

Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 26

End point values	iGlarLixi	Premixed insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	444		
Units: percentage of subjects				
number (not applicable)	27.5	12.4		

Statistical analyses

Statistical analysis title	iGlarLixi Versus Premixed insulin

Statistical analysis description:

Analysed using logistic regression model adjusted for fixed categorical effects of randomisation strata (basal insulin dose at screening visit [<30 U, >=30 U] and SGLT-2i use [Yes, No] at screening visit), treatment group as well as fixed continuous covariates of Baseline values for each of the primary endpoints (HbA1c and Weight).

Comparison groups	iGlarLixi v Premixed insulin
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Logistic regression model
Parameter estimate	Adjusted Odds Ratio (OR)
Point estimate	2.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	4.04

Notes:

[4] - Threshold of significance at 0.05 level.

Secondary: Percentage of Subjects with HbA1c <7 % Without Hypoglycemia and Without Body Weight Gain at Week 26

End point title	Percentage of Subjects with HbA1c <7 % Without Hypoglycemia and Without Body Weight Gain at Week 26

End point description:

Hypoglycemia was defined as plasma glucose <70 milligrams per decilitre (mg/dL) (<3.9 millimoles per litre [mmol/L]). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Week 26

End point values	iGlarLixi	Premixed insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	444		
Units: percentage of subjects				
number (not applicable)	19.4	7.0		

Statistical analyses

Statistical analysis title	iGlarLixi Versus Premixed insulin

Statistical analysis description:

Analysed using logistic regression model adjusting for fixed categorical effects of randomisation strata (basal insulin dose at screening visit [<30 U, >=30 U] and SGLT-2i use [Yes, No] at screening visit), treatment group as well as fixed continuous covariates of Baseline values for each of the primary endpoints (HbA1c and Weight).

Comparison groups	iGlarLixi v Premixed insulin
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Logistic regression model
Parameter estimate	Adjusted OR
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.19
upper limit	5.28

Notes:

[5] - Threshold of significance at 0.05 level.

Secondary: Change From Baseline to Week 26 in HbA1c: Superiority Analysis

End point title	Change From Baseline to Week 26 in HbA1c: Superiority

	Analysis

End point description:

Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	iGlarLixi	Premixed insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	444		
Units: percentage of HbA1c				
least squares mean (standard error)	-1.30 (± 0.06)	-1.05 (± 0.06)		

Statistical analyses

Statistical analysis title	iGlarLixi Versus Premixed insulin

Statistical analysis description:

Analysis was performed using ANCOVA model including fixed categorical effects of randomisation strata (basal insulin dose at screening visit [<30 U, >=30 U] and SGLT-2i use [Yes, No] at screening visit), treatment group and country as well as fixed continuous covariates of Baseline values HbA1c.

Comparison groups	iGlarLixi v Premixed insulin
Number of subjects included in analysis	887
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	ANCOVA (with multiple imputation)
Parameter estimate	LS mean difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	-0.1

Notes:

[6] - Threshold of significance at 0.05 level.

Secondary: Number of Subjects with Hypoglycemia Event

End point title	Number of Subjects with Hypoglycemia Event

End point description:

Any hypoglycemia event represents the number of subjects with any (severe or documented) hypoglycemia. Documented hypoglycemia was considered when measured plasma glucose concentration less than or equal to (<=) 70 mg/dL (<=3.9 mmol/L) (with or without symptoms). Hypoglycemia defined as plasma glucose level of <54 mg/dL (<3.0 mmol/L) was also considered. Severe hypoglycemia was an event defined as hypoglycemia with severe cognitive impairment (AE preferred term-hypoglycemic unconsciousness) requiring external assistance for recovery. Analysis was performed on the safety population that included randomised population who received at least 1 dose or part of a dose of the investigational medicinal product (IMP) analysed according to the treatment actually received.

End point type	Secondary

End point timeframe:

Up to 26 weeks

End point values	iGlarLixi	Premixed insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	441		
Units: subjects				
number (not applicable)				
Any Hypoglycemia Event	138	187		
Documented Hypoglycemia <=70 mg/dL (<=3.9 mmol/L)	129	179		
Hypoglycemia (<54 mg/dL [<3.0 mmol/L])	28	57		
Severe Hypoglycemia	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the first injection of the IMP up to 3 days after last injection regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that developed, worsened, or became serious during the on-treatment period (time from the first injection of the IMP up to 3 days after the last injection of IMP). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	iGlarLixi

Reporting group description:

Subjects received iGlarLixi subcutaneously once a day for up to 26 weeks.

Reporting group title	Premixed Insulin

Reporting group description:

Subjects received Premix BiAsp 30 BID for up to 26 weeks.

Serious adverse events	iGlarLixi	Premixed Insulin	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 442 (2.71%)	13 / 441 (2.95%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Gastric			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medullary Thyroid Cancer			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Essential Hypertension			

subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis Superficial			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 442 (0.23%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Behaviour			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Eye Contusion			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Injuries			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve Injury			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	1 / 442 (0.23%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic Haemothorax			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			

subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute Myocardial Infarction			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Haemorrhage Intracranial			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	1 / 442 (0.23%)	2 / 441 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 442 (0.23%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 442 (0.23%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 442 (0.00%)	1 / 441 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 442 (0.23%)	0 / 441 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	iGlarLixi	Premixed Insulin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 442 (7.69%)	0 / 441 (0.00%)	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	34 / 442 (7.69%) 39	0 / 441 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2019	Following changes were made: clarified starting dose of Premix BiAsp 30 and distribution of it during the day; clarified that pre breakfast self-monitored plasma glucose (SMPG) value should be used for the adjustment of dinner dose of Premix BiAsp 30, and predinner SMPG for pre-breakfast dose; clarified the difference in SMPG schedule between intervention arms; added recommended hypoglycemia management guidelines following the request of India health authorities; allowed rescreening; clarified the statistical analysis procedure regarding multiplicity considerations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported