Clinical trial results:
A 26-week, Randomized, Open-label, Parallel-group Comparison of SAR341402 Mix 70/30 to NovoMix®30 in Adult Patients with Diabetes Mellitus Using Pre-mix Insulin Analogs

Summary

EudraCT number	2017-000092-84
Trial protocol	PL
Global end of trial date	08 March 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	EFC15082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1202-0910
Other trial identifiers	STUDY NAME: GEMELLI M

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly Mazarin Cedex, 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	16 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of SAR341402 Mix 70/30 in comparison to NovoMix 30 on glycated hemoglobin A1c (HbA1c) change from Baseline to Week 26 in subjects with Type 1 and Type 2 diabetes mellitus (T1DM and T2DM).

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:

Oral antihyperglycemic therapy in subjects with T2DM - if applicable - was to be continued at a stable dose throughout the study.

Evidence for comparator: -

Actual start date of recruitment	03 July 2019
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	Poland: 50
Country: Number of subjects enrolled	India: 210
Country: Number of subjects enrolled	Philippines: 35
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Ukraine: 75
Worldwide total number of subjects	402
EEA total number of subjects	50

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)	300
From 65 to 84 years	102
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 54 active centres in 5 countries. A total of 509 subjects were screened; of which 107 subjects had screen failure. Screen failure was mainly due to HbA1c level outside of eligibility range and incomplete Baseline 7-point self-measured plasma glucose profile.

Pre-assignment

Screening details:

Assigned to treatment in 1:1 ratio (SAR341402 Mix 70/30:NovoMix 30) by using an interactive response technology system. Randomisation: stratified by geographical region (Indian; non-Indian), type of diabetes (T1DM; T2DM), HbA1c obtained at screening visit (less than [<]8.0%; greater than or equal to [>=] 8.0%) and prior use of NovoMix 30 (Yes; No).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SAR341402 Mix 70/30

Arm description:

Subject received SAR341402 Mix 70/30 100 units per millilitre (U/mL) subcutaneous (SC) injection for up to Week 26.

Arm type	Experimental
Investigational medicinal product name	SAR341402 Mix 70/30
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

SAR341402 Mix 70/30, 100 U/mL, twice daily as self-administered SC injection. Dose was adjusted based on investigator's clinical judgement to achieve preprandial plasma glucose between 4.4 and 7.2 millimoles per litre (mmol/L; 80 to 130 milligrams per decilitre [mg/dL]) and a 2-hour postprandial plasma glucose of <10 mmol/L (<180 mg/dL).

Arm title	NovoMix 30

Arm description:

Subject received NovoMix 30 100 U/mL SC injection for up to Week 26.

Arm type	Active comparator
Investigational medicinal product name	NovoMix 30
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

NovoMix 30, 100 U/mL, twice daily as self-administered SC injection. Dose was adjusted based on investigator's clinical judgement to achieve preprandial plasma glucose between 4.4 and 7.2 mmol/L (80 to 130 mg/dL) and a 2-hour postprandial plasma glucose of <10 mmol/L (<180 mg/dL).

Number of subjects in period 1	SAR341402 Mix 70/30	NovoMix 30
Started	204	198
Treated	203	197
Completed	200	191
Not completed	4	7
Randomised and not treated	1	1
Consent withdrawn by subject	1	2
Other unspecified	2	3
Adverse event	-	1

Baseline characteristics

Reporting groups	
Reporting group title	SAR341402 Mix 70/30
Reporting group description:	
Subject received SAR341402 Mix 70/30 100 units per millilitre (U/mL) subcutaneous (SC) injection for up to Week 26.	
Reporting group title	NovoMix 30
Reporting group description:	
Subject received NovoMix 30 100 U/mL SC injection for up to Week 26.	

Reporting group values	SAR341402 Mix 70/30	NovoMix 30	Total
Number of subjects	204	198	402
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	53.2	53.0	
standard deviation	± 14.9	± 15.5	-
Gender categorical			
Units: Subjects			
Female	91	109	200
Male	113	89	202
Baseline Glycated Haemoglobin A1c (HbA1c)			
Units: percentage of HbA1c			
arithmetic mean	8.16	8.28	
standard deviation	± 1.05	± 1.09	-
Baseline Body Mass Index (BMI)			
Units: kilogram per metre square (kg/m^2)			
arithmetic mean	26.61	26.93	
standard deviation	± 4.73	± 4.70	-
Duration of Diabetes			
Units: years			
arithmetic mean	13.47	12.91	
standard deviation	± 8.38	± 8.38	-

End points

End points reporting groups

Reporting group title	SAR341402 Mix 70/30
Reporting group description:	
Subject received SAR341402 Mix 70/30 100 units per millilitre (U/mL) subcutaneous (SC) injection for up to Week 26.	
Reporting group title	NovoMix 30
Reporting group description:	
Subject received NovoMix 30 100 U/mL SC injection for up to Week 26.	

Primary: Change From Baseline to Week 26 in Glycated Hemoglobin A1c (HbA1c)

End point title	Change From Baseline to Week 26 in Glycated Hemoglobin A1c (HbA1c)
End point description:	
Combined least square (LS) means and standard errors (SE) were estimated by analysis of covariance (ANCOVA) model based on data obtained from return-to-baseline multiple imputations for missing data. Analysis was performed on intent-to-treat (ITT) population, which included all randomised subjects (irrespective of compliance with study protocol and procedures) analysed according to treatment group allocated by randomisation, and included all values up to Week 26 (regardless of adherence to treatment).	
End point type	Primary
End point timeframe:	
Baseline to Week 26	

End point values	SAR341402 Mix 70/30	NovoMix 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	198		
Units: percentage of HbA1c				
least squares mean (standard error)	-0.55 (± 0.080)	-0.64 (± 0.080)		

Statistical analyses

Statistical analysis title	SAR341402 Mix 70/30 versus NovoMix 30
Statistical analysis description:	
Analysis was performed using ANCOVA with treatment group (SAR341402 Mix 70/30, NovoMix 30), the randomisation strata of geographical region (Indian, non-Indian), type of diabetes (T1DM, T2DM) and prior use of NovoMix 30 (Yes, No) as fixed categorical effects, as well as the continuous fixed covariate of Baseline HbA1c value.	
Comparison groups	SAR341402 Mix 70/30 v NovoMix 30

Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	LS Mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	0.303
Variability estimate	Standard error of the mean
Dispersion value	0.113

Notes:

[1] - Non-inferiority of SAR341402 Mix 70/30 over NovoMix 30 was demonstrated if upper bound of the 2sided 95% confidence interval of difference between SAR341402 Mix 70/30 and NovoMix 30 on ITT population was <0.3%.

Secondary: Percentage of Subjects With Treatment-induced, Treatment-boosted and Treatment-emergent Anti-insulin Aspart Antibodies (AIAs)

End point title	Percentage of Subjects With Treatment-induced, Treatment-boosted and Treatment-emergent Anti-insulin Aspart Antibodies (AIAs)

End point description:

AIA incidence: 1) Treatment-induced AIAs:subjects who developed AIA following investigational medicinal product (IMP) administration (subjects with at least 1 positive AIA sample at any time during on-treatment period, in those subjects without pre-existing AIA or with missing baseline sample). 2) Treatment-boosted AIAs:subjects with pre-existing AIAs that were boosted to significant higher titer following IMP administration (subjects with at least 1 AIA sample with at least 4-fold increase in titers compared to baseline value at any time during on-treatment period). 3) Treatment-emergent AIA:subjects with treatment-induced/treatment-boosted AIAs. AIA population: all subjects who received at least 1 dose of IMP; had at least 1 AIA sample for analysis during on-treatment period, analysed according to treatment actually received. Here, 'n'=subjects included in the AIA population for each specified category.

End point type	Secondary

End point timeframe:

From first injection of IMP up to last injection of IMP (i.e., Week 26) + 2 days follow-up after last IMP injection

End point values	SAR341402 Mix 70/30	NovoMix 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	195		
Units: percentage of subjects				
number (not applicable)				
Treatment-induced AIA (n = 108, 100)	45.4	45.0		
Treatment-boosted AIA (n = 91, 95)	18.7	17.9		
Treatment-emergent AIA (n = 199, 195)	33.2	31.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With at Least One Hypoglycemic Event

End point title	Number of Subjects With at Least One Hypoglycemic Event

End point description:

Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, because the subject was not capable of helping self. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of less than or equal to (<=) 3.9 mmol/L (70 mg/dL) or plasma glucose level of <3.0 mmol/L (54 mg/dL). Analysis was performed on safety population which included all subjects who took at least 1 dose of IMP and were analysed according to the treatment actually received.

End point type	Secondary

End point timeframe:

From first injection of IMP up to last injection of IMP (i.e., Week 26) + 2 days follow-up after last IMP injection

End point values	SAR341402 Mix 70/30	NovoMix 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	197		
Units: subjects				
Any hypoglycemia	126	138		
Severe hypoglycemia	0	0		
Documented symptomatic <=3.9 mmol/L	80	89		
Documented symptomatic <3.0 mmol/L	47	48		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hypoglycemia Events Per Subject-Year

End point title	Number of Hypoglycemia Events Per Subject-Year

End point description:

Severe hypoglycemia was an event in which the subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, because the subject was not capable of helping self. Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <=3.9 mmol/L (70 mg/dL) or plasma glucose level of <3.0 mmol/L (54 mg/dL). Number of hypoglycemia events (any, severe and documented [both thresholds]) per subject-year of exposure were reported. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

From first injection of IMP up to last injection of IMP (i.e., Week 26) + 2 days follow-up after last IMP injection

End point values	SAR341402 Mix 70/30	NovoMix 30		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	197		
Units: events per subject-year				
number (not applicable)				
Any hypoglycemia	12.62	13.43		
Severe hypoglycemia	0	0		
Documented symptomatic <=3.9 mmol/L	5.50	5.25		
Documented symptomatic <3.0 mmol/L	2.59	1.36		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All treatment-emergent adverse events (TEAEs) were collected from the first injection of IMP up to last injection of IMP (i.e., Week 26) + 2 days follow-up after last IMP injection, regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported AEs and deaths were TEAEs, that is AEs that developed/worsened or became serious and deaths that occurred during 'on-treatment period' (time from the first injection of IMP up to last injection of IMP [i.e., Week 26] + 2 days follow-up after the last injection of IMP). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	SAR341402 Mix 70/30

Reporting group description:

Subject received SAR341402 Mix 70/30 100 U/mL SC injection for up to Week 26.

Reporting group title	NovoMix 30

Reporting group description:

Subject received NovoMix 30 100 U/mL SC injection for up to Week 26.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Since there was no non-serious adverse event with a frequency threshold greater than 5%, no data were available to present in this section.

Serious adverse events	SAR341402 Mix 70/30	NovoMix 30	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 203 (0.99%)	3 / 197 (1.52%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tibia Fracture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	0 / 203 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			

subjects affected / exposed	0 / 203 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden Cardiac Death			
subjects affected / exposed	0 / 203 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 203 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gangrene			
subjects affected / exposed	1 / 203 (0.49%)	0 / 197 (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	SAR341402 Mix 70/30	NovoMix 30	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 203 (0.00%)	0 / 197 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2019	Following changes were done: • Exploratory pharmacokinetic substudy added at the request of the Indian Health Authority in a subset of approximately 14 Indian subjects with T2DM. • Screening period extended by up to a maximum of 3 days after the 2-week period. • Addition of 2 tertiary/exploratory endpoints to assess a) the number of subjects with neutralising anti insulin aspart antibody (NAb) at baseline and specific time-points and b) the clinical effects of NAb on efficacy (HbA1c) and insulin dose. • Clarification of exclusion criteria with regards to use of systemic immunosuppressive agents and glucocorticoids. • Clarification of the process for "direct-to-patient" regulating the delivery of IMP to subjects via a Sponsor's courier in case of emergency. • Clarification of the counter measures in case of hypoglycemia and the use of subject's personal glucose monitoring devices in occasional circumstances. • Clarification of the reporting of hypoglycemia on the electronic case report form; removal of asymptomatic overdose among standard AEs. • Removal of the requirement of fasting state for blood sampling for antibody measurements. • Addition of the events of potential loss of efficacy to the list of events to be adjudicated by allergic reaction assessment committee (ARAC) to be consistent with the ARAC charter. • Update of the time of retention of study records from 15 to 25 years. • Addition of injectable combined hormonal contraception and barrier contraception as permitted contraception.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Upon request of Indian Health Authority an exploratory PK substudy was conducted in a subset of 13 additional Indian subjects with T2DM. Substudy results were exploratory and are not included in main study results.

Notes: