Clinical trial results:
A Randomized, Double-Blind, Parallel-Group Clinical Trial to Assess the Efficacy of Essentiale on Hepatic Steatosis Added to Standard of Care Versus Placebo Added to Standard of Care, in Non-Alcoholic Fatty Liver Disease (NAFLD) Associated with Type 2 Diabetes Mellitus (T2DM) and/or Hyperlipidemia and/or Obesity

Summary

EudraCT number	2021-006069-39
Trial protocol	DE PL
Global end of trial date	06 May 2024

Results information

Result version number	v1 (current)
This version publication date	14 May 2025
First version publication date	14 May 2025

Trial information

Trial identification

Sponsor protocol code	LPS16141

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1244-1278

Notes:

Sponsors

Sponsor organisation name	Sanofi-Aventis Recherche & Developpement
Sponsor organisation address	157 Avenue Charles de Gaulle , Neuilly-sur-Seine Cedex, France, 92200
Public contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-Aventis Recherche & Developpement, 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	06 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Essentiale added to SoC (lifestyle modification [diet and physical activity/exercise]) compared with placebo added to SoC (lifestyle modification [diet and physical activity/exercise]) in patients with NAFLD associated with T2DM and/or hyperlipidemia and/or obesity.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

Background therapy:

Standard of care (lifestyle modification [diet and physical activity/exercise])

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 November 2022
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: 84
Country: Number of subjects enrolled	Germany: 109
Worldwide total number of subjects	193
EEA total number of subjects	193

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)	164
From 65 to 84 years	29

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 237 subjects were assessed for eligibility, of whom 44 subjects (18.6%) were screen failures. A total of 193 subjects were randomized (ITT set) to receive either Essentiale + SoC (n=97) or placebo + SoC (n=96).

Pre-assignment

Screening details:

A total of 237 subjects were assessed for eligibility, 193 of whom were randomized [Essentiale + SoC (n=97) or placebo + SoC (n=96)]. Of the 193 participants enrolled, no participants discontinued the study before receiving treatment in both arms.

Pre-assignment period milestones

Number of subjects started	193
Number of subjects completed	193

Period 1

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

Blinding implementation details:

The IRT system was programmed with blind-breaking instructions. Blinding was maintained throughout the study until the final assessment for the final subject was entered into the database, and the database lock was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Essentiale arm

Arm description:

Essentiale 1800 mg/day orally + SoC (lifestyle modification, ie, diet and physical activity/exercise)

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

Dosage and administration details:

Essentiale 1800 mg/day (2 capsules [300 mg each] thrice daily) for 6 months

Arm title	Placebo arm

Arm description:

Placebo + SoC (lifestyle modification, ie, diet and physical activity/exercise)

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

Dosage and administration details:
Matching placebo (2 capsules thrice daily) for 6 months

Number of subjects in period 1	Essentiale arm	Placebo arm
Started	97	96
Completed	88	84
Not completed	9	12
Consent withdrawn by subject	5	7
Physician decision	1	-
Adverse event, non-fatal	1	1
Not specified	-	2
Noncompliance with study drug	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Essentiale arm
Reporting group description:	
Essentiale 1800 mg/day orally + SoC (lifestyle modification, ie, diet and physical activity/exercise)	
Reporting group title	Placebo arm
Reporting group description:	
Placebo + SoC (lifestyle modification, ie, diet and physical activity/exercise)	

Reporting group values	Essentiale arm	Placebo arm	Total
Number of subjects	97	96	193
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	79	85	164
From 65-84 years	18	11	29
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.6	52.8	
standard deviation	± 12.95	± 11.0	-
Gender categorical Units: Subjects			
Female	45	43	88
Male	52	53	105
Controlled attenuation parameter			
The controlled attenuation parameter (CAP) was measured to assess the severity of liver steatosis at all visits during the study. The CAP technique is a proprietary algorithm based on the ultrasonic attenuation coefficient of the shear wave of transient elastography, an estimate of the total ultrasonic attenuation at 3.5 MHz. It is expressed in dB/meter. At baseline, the majority of subjects in both treatment arms were in a CAP score category S3 (≥280 dB/m)			
Units: Subjects			
S0: CAP score is <248 dB/m	0	0	0
S1: CAP score is ≥248 dB/m and <268 dB/m	6	8	14
S2: CAP score is ≥268 dB/m and <280 dB/m	9	11	20
S3: CAP score is ≥280 dB/m	82	77	159
Not done	0	0	0
Liver Stiffness Measurement			
FibroScan simultaneously assessed liver stiffness by measuring the propagation of an elastic shear wave through the liver parenchyma, and it is expressed in kPa, with higher values indicating greater stiffness. Liver stiffness measurements were performed at all visits during the study. Inclusion criteria allowed recruitment of patients F1 - F3 fibrosis stage as defined by LSM 5-13 kPa. Statistical analysis was done			

to include F4, based on another specific threshold.			
Units: Subjects			
F1: Mild fibrosis (<=7 kPa)	59	58	117
F2: Moderate fibrosis (7.1–8.8 kPa)	22	20	42
F3: Severe fibrosis (8.9–11.6 kPa)	8	14	22
F4: Cirrhosis or advanced fibrosis (>11.6 kPa)	8	4	12
Not done	0	0	0
BMI Category Units: Subjects			
Underweight (<18.5kg/m2)	0	0	0
Normal (18.5kg/m2 to <25kg/m2)	3	3	6
Overweight (25kg/m2 to <30kg/m2)	16	11	27
Obese (>=30kg/m2)	78	82	160
Missing	0	0	0
NAFLD Classification (T2D)			
The NAFLD classifications are made up of T2DM defined as a baseline HbA1c of 8.0% or above.			
Units: Subjects			
Yes	17	10	27
No	80	86	166
NAFLD Classification (Hyperlipidemia)			
The NAFLD classifications are made up of hyperlipidemia defined as baseline triglycerides above 1.6935 mmol/L.			
Units: Subjects			
Yes	58	57	115
No	39	39	78
NAFLD Classification (Obesity)			
The NAFLD classifications are made up of obesity defined as a baseline BMI of 30 kg/m2 or above.			
Units: Subjects			
Yes	78	82	160
No	19	14	33

Subject analysis sets

Subject analysis set title	mITT set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT set included 165 subjects (85.5%) of the enrolled population (82 subjects [84.5%] in the Essentiale + SoC arm and 83 subjects [86.5%] in the placebo + SoC arm). All subjects from the randomization set with evaluable CAP scores at baseline, at least 1 postbaseline CAP measurement, and who received the randomized
treatment (at least 80% of the study drug planned to be given within 6 months). All analyses using the mITT were done according to the randomized treatment.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who received at least 1 dose of the randomized treatment. All analyses using the safety set were done according to the treatment actually received.

Reporting group values	mITT set	Safety set	
Number of subjects	165	193	

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)	140	164	
From 65-84 years	25	29	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.9	52.7	
standard deviation	± 11.48	± 11.99	
Gender categorical Units: Subjects			
Female	75	88	
Male	90	105	
Controlled attenuation parameter			
The controlled attenuation parameter (CAP) was measured to assess the severity of liver steatosis at all visits during the study. The CAP technique is a proprietary algorithm based on the ultrasonic attenuation coefficient of the shear wave of transient elastography, an estimate of the total ultrasonic attenuation at 3.5 MHz. It is expressed in dB/meter. At baseline, the majority of subjects in both treatment arms were in a CAP score category S3 (≥280 dB/m)			
Units: Subjects			
S0: CAP score is <248 dB/m	0	0	
S1: CAP score is ≥248 dB/m and <268 dB/m	12	14	
S2: CAP score is ≥268 dB/m and <280 dB/m	17	20	
S3: CAP score is ≥280 dB/m	136	159	
Not done	0	0	
Liver Stiffness Measurement			
FibroScan simultaneously assessed liver stiffness by measuring the propagation of an elastic shear wave through the liver parenchyma, and it is expressed in kPa, with higher values indicating greater stiffness. Liver stiffness measurements were performed at all visits during the study. Inclusion criteria allowed recruitment of patients F1 - F3 fibrosis stage as defined by LSM 5-13 kPa. Statistical analysis was done to include F4, based on another specific threshold.			
Units: Subjects			
F1: Mild fibrosis (<=7 kPa)	102	117	
F2: Moderate fibrosis (7.1–8.8 kPa)	37	42	
F3: Severe fibrosis (8.9–11.6 kPa)	18	22	
F4: Cirrhosis or advanced fibrosis (>11.6 kPa)	8	12	
Not done	0	0	
BMI Category Units: Subjects			
Underweight (<18.5kg/m2)	0	0	
Normal (18.5kg/m2 to <25kg/m2)	5	6	
Overweight (25kg/m2 to <30kg/m2)	25	27	
Obese (>=30kg/m2)	135	160	
Missing	0	0	

NAFLD Classification (T2D)			
The NAFLD classifications are made up of T2DM defined as a baseline HbA1c of 8.0% or above.			
Units: Subjects			
Yes	22	27	
No	143	166	
NAFLD Classification (Hyperlipidemia)			
The NAFLD classifications are made up of hyperlipidemia defined as baseline triglycerides above 1.6935 mmol/L.			
Units: Subjects			
Yes	100	115	
No	65	78	
NAFLD Classification (Obesity)			
The NAFLD classifications are made up of obesity defined as a baseline BMI of 30 kg/m2 or above.			
Units: Subjects			
Yes	135	160	
No	30	33	

End points

End points reporting groups

Reporting group title	Essentiale arm
Reporting group description:	
Essentiale 1800 mg/day orally + SoC (lifestyle modification, ie, diet and physical activity/exercise)	
Reporting group title	Placebo arm
Reporting group description:	
Placebo + SoC (lifestyle modification, ie, diet and physical activity/exercise)	
Subject analysis set title	mITT set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT set included 165 subjects (85.5%) of the enrolled population (82 subjects [84.5%] in the Essentiale + SoC arm and 83 subjects [86.5%] in the placebo + SoC arm). All subjects from the randomization set with evaluable CAP scores at baseline, at least 1 postbaseline CAP measurement, and who received the randomized treatment (at least 80% of the study drug planned to be given within 6 months). All analyses using the mITT were done according to the randomized treatment.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received at least 1 dose of the randomized treatment. All analyses using the safety set were done according to the treatment actually received.	

Primary: Change in steatosis, as measured by transient elastography (CAP score)

End point title	Change in steatosis, as measured by transient elastography (CAP score)
End point description:	
Change from baseline to 6 month in steatosis measured by transient elastography (CAP score) defined as the CAP score at 6 month minus the CAP score at baseline. Analysis was performed on modified intent-to-treat (mITT) analysis set.	
End point type	Primary
End point timeframe:	
From baseline to 6months	

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: dB/m				
least squares mean (standard error)				
Change from Baseline	-24.6 (± 4.68)	-9.79 (± 4.68)		

Statistical analyses

Statistical analysis title	CAP score
Statistical analysis description:	
For the analysis of the primary efficacy endpoint (change in steatosis, as measured by transient elastography [CAP score] from baseline to 6 months), a mixed-effect model with repeated measures	

(MMRM) was used to test the hypothesis.

Comparison groups	Essentiale arm v Placebo arm
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0269 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-14.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.89
upper limit	-1.72
Variability estimate	Standard error of the mean
Dispersion value	6.63

Notes:

[1] - The level of statistical significance was defined as a P value less than 0.05.

Secondary: Change in QoL total score, as measured by the CLDQ-NAFLD/NASH

End point title	Change in QoL total score, as measured by the CLDQ-NAFLD/NASH

End point description:

Change from baseline to 6 month in Change in QoL total score, as measured by the CLDQ-NAFLD/NASH, from baseline to 6 months. Analysis was performed on modified ittent-to-treat (mITT) analysis set.

End point type	Secondary

End point timeframe:

From baseline to 6 months

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: Score				
least squares mean (standard error)				
Change from Baseline	0.44 (± 0.06)	0.28 (± 0.06)		

Statistical analyses

Statistical analysis title	QoL total score of the CLDQ-NAFLD/NASH

Statistical analysis description:

For the analysis of the secondary efficacy endpoint a mixed-effect model with repeated measures (MMRM) was used to test the hypothesis.

Comparison groups	Essentiale arm v Placebo arm

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.2445 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[2] - The linear mixed model with repeated measures (MMRM) analysis

[3] - The level of statistical significance was defined as a P value less than 0.05.

Secondary: Change in symptom evaluation (global overall symptoms (GOS)) for Asthenia

End point title	Change in symptom evaluation (global overall symptoms (GOS)) for Asthenia

End point description:

Change from baseline to 6 month in in symptom evaluation (using the GOS scale) from baseline to 6 months for Asthenia. Analysis was performed on modified ittent-to-treat (mITT) analysis set.

End point type	Secondary

End point timeframe:

From the baseline to 6 months

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: Score				
least squares mean (standard error)				
Change from Baseline	-0.69 (± 0.12)	-0.46 (± 0.11)		

Statistical analyses

Statistical analysis title	Asthenia (Loss of Energy)

Statistical analysis description:

For the analysis of the secondary efficacy endpoint a mixed-effect model with repeated measures (MMRM) was used to test the hypothesis.

Comparison groups	Placebo arm v Essentiale arm

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5808 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[4] - The linear mixed model with repeated measures (MMRM) analysis

[5] - The level of statistical significance was defined as a P value less than 0.05.

Secondary: Change in symptom evaluation (global overall symptoms (GOS)) for Feeling depressed

End point title	Change in symptom evaluation (global overall symptoms (GOS)) for Feeling depressed

End point description:

Change from baseline to 6 month in in symptom evaluation (using the GOS scale) from baseline to 6 months for Feeling depressed. Analysis was performed on modified intent-to-treat (mITT) analysis set.

End point type	Secondary

End point timeframe:

From baseline to 6 months

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: Score				
least squares mean (standard error)				
Change from Baseline	-0.46 (± 0.12)	-0.46 (± 0.12)		

Statistical analyses

Statistical analysis title	Feeling Depressed

Statistical analysis description:

For the analysis of the secondary efficacy endpoint a mixed-effect model with repeated measures (MMRM) was used to test the hypothesis.

Comparison groups	Essentiale arm v Placebo arm

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[6] - The level of statistical significance was defined as a P value less than 0.05.

Secondary: Change in symptom evaluation (global overall symptoms (GOS)) for Fatigue

End point title	Change in symptom evaluation (global overall symptoms (GOS)) for Fatigue

End point description:

Change from baseline to 6 month in in symptom evaluation (using the GOS scale) from baseline to 6 months for Fatigue. Analysis was performed on modified intent-to-treat (mITT) analysis set.

End point type	Secondary

End point timeframe:

From baseline to 6 months

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: Score				
least squares mean (standard error)				
Change from Baseline	-0.71 (± 0.12)	-0.46 (± 0.12)		

Statistical analyses

Statistical analysis title	Fatigue

Statistical analysis description:

For the analysis of the secondary efficacy endpoint a mixed-effect model with repeated measures (MMRM) was used to test the hypothesis.

Comparison groups	Essentiale arm v Placebo arm

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5808 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[7] - The level of statistical significance was defined as a P value less than 0.05.

Secondary: Change in symptom evaluation (global overall symptoms (GOS)) for Abdominal pain/discomfort

End point title	Change in symptom evaluation (global overall symptoms (GOS)) for Abdominal pain/discomfort

End point description:

Change from baseline to 6 month in in symptom evaluation (using the GOS scale) from baseline to 6 months for abdominal pain/discomfort. Analysis was performed on modified intent-to-treat (mITT) analysis set.

End point type	Secondary

End point timeframe:

From baseline to 6 months

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	83		
Units: Score				
least squares mean (standard error)				
Change from Baseline	-0.53 (± 0.11)	-0.61 (± 0.11)		

Statistical analyses

Statistical analysis title	Abdominal Pain/Discomfort

Statistical analysis description:

For the analysis of the secondary efficacy endpoint a mixed-effect model with repeated measures (MMRM) was used to test the hypothesis.

Comparison groups	Essentiale arm v Placebo arm

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[8] - The level of statistical significance was defined as a P value less than 0.05.

Secondary: Adverse events (AEs), serious adverse events (SAEs), including adverse events of special interest (AESIs).

End point title	Adverse events (AEs), serious adverse events (SAEs), including adverse events of special interest (AESIs).

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily have to have a causal relationship with the treatment. SAEs were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. TEAEs were defined as AEs that developed, worsened or became serious during the TEAE period (from the first administration to the last administration + 5 days).

End point type	Secondary

End point timeframe:

From baseline up to the last administration + 5 days.

End point values	Essentiale arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	96		
Units: Subjects				
Total Patients Exposed At Risk	97	96		
Total Patients Affected by Serious TEAE	5	3		
Total Patients Affected by Non Serious TEAE	23	18		
Total Deaths (all causes)	0	0		
Total Deaths Resulting From AE	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to the last administration + 5 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Essentiale + SOC
Reporting group description: -	
Reporting group title	Placebo + SoC
Reporting group description: -	

Serious adverse events	Essentiale + SOC	Placebo + SoC	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 97 (5.15%)	3 / 96 (3.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal neoplasm			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tibia fracture			

subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (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			
Acute kidney injury			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 96 (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	Essentiale + SOC	Placebo + SoC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 97 (23.71%)	18 / 96 (18.75%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 97 (10.31%)	8 / 96 (8.33%)	
occurrences (all)	18	12	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 97 (9.28%)	8 / 96 (8.33%)	
occurrences (all)	11	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 97 (6.19%)	6 / 96 (6.25%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2022	The protocol was updated with the required statements, measures, and provided benefit-risk discussions with regards to the SARS-COV-2 pandemic in response to the regulatory query.
15 July 2022	Any reference to Russia and China were removed, as these countries were dropped off from the study. Any reference to the investigator's brochure was replaced with summary of product characteristics. The important identified risks for Essentiale were updated to include data on drug-related AEs. Approximate number of sites involved in the study were updated and the information was clarified to be recorded in the eDiary.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported