Clinical trial results:
A Phase 2, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study Evaluating the Safety and Efficacy of Semaglutide, and the Fixed-Dose Combination of Cilofexor and Firsocostat, Alone and in Combination, in Subjects with Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2021-001445-12
Trial protocol	ES FR
Global end of trial date	09 December 2024

Results information

Result version number	v1 (current)
This version publication date	28 November 2025
First version publication date	28 November 2025

Trial information

Trial identification

Sponsor protocol code	GS-US-454-6075

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04971785
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	09 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2024
Global end of trial reached?	Yes
Global end of trial date	09 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of this clinical study is to understand whether the study drugs, semaglutide (SEMA) with the fixed-dose combination (FDC) of cilofexor/firsocostat (CILO/FIR), cause fibrosis improvement and Nonalcoholic Steatohepatitis (NASH) resolution in participants with cirrhosis due to NASH.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 349
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Spain: 14
Worldwide total number of subjects	457
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	257
From 65 to 84 years	200
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Canada, France, Japan, Australia and Spain.

Pre-assignment

Screening details:

1595 participants were screened.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SEMA + CILO/FIR FDC

Arm description:

Participants received semaglutide (SEMA) 3.0 mg/mL subcutaneous (SC) injection once weekly and cilofexor and firsocostat (CILO/FIR) 30 mg/20 mg fixed-dose combination (FDC) tablet orally, once daily up to 72 weeks.

Arm type	Experimental
Investigational medicinal product name	Semaglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as subcutaneous injection.

Investigational medicinal product name	Cilofexor/Firsocostat
Investigational medicinal product code	GS-9674/GS-0976
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally.

Arm title	SEMA + PTM CILO/FIR

Arm description:

Participants received SEMA 3.0 mg/mL SC injection, once weekly and Placebo-To-Match (PTM) CILO/FIR FDC tablet orally, once daily up to 72 weeks.

Arm type	Experimental
Investigational medicinal product name	Semaglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as subcutaneous injection.

Investigational medicinal product name	PTM CILO/FIR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally.

Arm title	PTM SEMA + CILO/FIR FDC

Arm description:

Participants received PTM SEMA SC injection, once weekly and CILO/FIR 30 mg/20 mg FDC tablet orally, once daily up to 72 weeks.

Arm type	Experimental
Investigational medicinal product name	PTM SEMA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as subcutaneous injection.

Investigational medicinal product name	Cilofexor/Firsocostat
Investigational medicinal product code	GS-9674/GS-0976
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally.

Arm title	PTM SEMA + PTM CILO/FIR

Arm description:

Participants received PTM SEMA SC injection, once weekly and PTM CILO/FIR FDC tablet orally, once daily up to 72 weeks.

Arm type	Experimental
Investigational medicinal product name	PTM SEMA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as subcutaneous injection.

Investigational medicinal product name	PTM CILO/FIR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally.

Number of subjects in period 1[1]	SEMA + CILO/FIR FDC	SEMA + PTM CILO/FIR	PTM SEMA + CILO/FIR FDC
Started	124	122	123
Completed	103	104	91
Not completed	21	18	32
Withdrew Consent	5	5	17
Adverse Event	7	8	6
Death	-	1	1
Investigator's Discretion	3	1	1
Protocol Violation	3	1	1
Site Terminated by Sponsor	1	1	-
Lost to follow-up	2	1	6

Number of subjects in period 1[1]	PTM SEMA + PTM CILO/FIR
Started	84
Completed	65
Not completed	19
Withdrew Consent	7
Adverse Event	3
Death	-
Investigator's Discretion	-
Protocol Violation	2
Site Terminated by Sponsor	-
Lost to follow-up	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 4 participants who were randomized but not treated were not included in the Safety Analysis Set for Period 1 table reported above.

Baseline characteristics

Reporting groups	
Reporting group title	SEMA + CILO/FIR FDC
Reporting group description:	
Participants received semaglutide (SEMA) 3.0 mg/mL subcutaneous (SC) injection once weekly and cilofexor and firsocostat (CILO/FIR) 30 mg/20 mg fixed-dose combination (FDC) tablet orally, once daily up to 72 weeks.	
Reporting group title	SEMA + PTM CILO/FIR
Reporting group description:	
Participants received SEMA 3.0 mg/mL SC injection, once weekly and Placebo-To-Match (PTM) CILO/FIR FDC tablet orally, once daily up to 72 weeks.	
Reporting group title	PTM SEMA + CILO/FIR FDC
Reporting group description:	
Participants received PTM SEMA SC injection, once weekly and CILO/FIR 30 mg/20 mg FDC tablet orally, once daily up to 72 weeks.	
Reporting group title	PTM SEMA + PTM CILO/FIR
Reporting group description:	
Participants received PTM SEMA SC injection, once weekly and PTM CILO/FIR FDC tablet orally, once daily up to 72 weeks.	

Reporting group values	SEMA + CILO/FIR FDC	SEMA + PTM CILO/FIR	PTM SEMA + CILO/FIR FDC
Number of subjects	124	122	123
Age categorical Units: Subjects			
Adults (18-64 years)	72	73	67
From 65-84 years	52	49	56
Age continuous Units: years			
arithmetic mean	61	61	62
standard deviation	± 10.4	± 9.2	± 9.5
Gender categorical Units: Subjects			
Female	83	85	74
Male	41	37	49
Ethnicity Units: Subjects			
Hispanic or Latino	28	23	30
Not Hispanic or Latino	95	99	90
Not Collected	1	0	3
Race Units: Subjects			
American Indian or Alaska Native	3	1	1
Asian	11	9	15
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	1
White	100	108	98
More than one race	5	2	3
Not Collected	3	1	5

Reporting group values	PTM SEMA + PTM CILO/FIR	Total	
Number of subjects	84	453	
Age categorical Units: Subjects			
Adults (18-64 years)	44	256	
From 65-84 years	40	197	
Age continuous Units: years			
arithmetic mean	63		
standard deviation	± 9.1	-	
Gender categorical Units: Subjects			
Female	50	292	
Male	34	161	
Ethnicity Units: Subjects			
Hispanic or Latino	19	100	
Not Hispanic or Latino	62	346	
Not Collected	3	7	
Race Units: Subjects			
American Indian or Alaska Native	2	7	
Asian	3	38	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	5	9	
White	66	372	
More than one race	4	14	
Not Collected	4	13	

End points

End points reporting groups

Reporting group title	SEMA + CILO/FIR FDC
Reporting group description:	
Participants received semaglutide (SEMA) 3.0 mg/mL subcutaneous (SC) injection once weekly and cilofexor and firsocostat (CILO/FIR) 30 mg/20 mg fixed-dose combination (FDC) tablet orally, once daily up to 72 weeks.	
Reporting group title	SEMA + PTM CILO/FIR
Reporting group description:	
Participants received SEMA 3.0 mg/mL SC injection, once weekly and Placebo-To-Match (PTM) CILO/FIR FDC tablet orally, once daily up to 72 weeks.	
Reporting group title	PTM SEMA + CILO/FIR FDC
Reporting group description:	
Participants received PTM SEMA SC injection, once weekly and CILO/FIR 30 mg/20 mg FDC tablet orally, once daily up to 72 weeks.	
Reporting group title	PTM SEMA + PTM CILO/FIR
Reporting group description:	
Participants received PTM SEMA SC injection, once weekly and PTM CILO/FIR FDC tablet orally, once daily up to 72 weeks.	

Primary: Percentage of Participants Who Achieved ≥ 1-Stage Improvement in Fibrosis Without Worsening of Nonalcoholic Steatohepatitis (NASH) at Week 72 in Semaglutide (SEMA) + Cilofexor/Firsocostat (CILO/FIR) Fixed Dose Combination (FDC) Versus Placebo Groups

End point title	Percentage of Participants Who Achieved ≥ 1-Stage Improvement in Fibrosis Without Worsening of Nonalcoholic Steatohepatitis (NASH) at Week 72 in Semaglutide (SEMA) + Cilofexor/Firsocostat (CILO/FIR) Fixed Dose Combination (FDC) Versus Placebo Groups[1]

End point description:

Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in fibrosis according to the NASH clinical research network (CRN) classification. Worsening of NASH was defined as ≥ 1-point increase from baseline in hepatocellular ballooning or lobular inflammation.
Clopper-Pearson method was used in outcome measure analysis in each arm. Percentages were rounded-off.
Participants in the Full Analysis Set in SEMA + CILO/FIR FDC and PTM SEMA + PTM CILO/FIR were analyzed. The Full Analysis Set included all randomized participants who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Week 72

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned only for arms: SEMA + CILO/FIR vs PTM SEMA + PTM CILO/FIR.

End point values	SEMA + CILO/FIR FDC	PTM SEMA + PTM CILO/FIR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	84		
Units: percentage of participants				
number (confidence interval 95%)	13.7 (8.2 to 21.0)	8.3 (3.4 to 16.4)		

Statistical analyses

Statistical analysis title	SEMA + CILO/FIR FDC vs PTM SEMA + PTM CILO/FIR
Comparison groups	PTM SEMA + PTM CILO/FIR v SEMA + CILO/FIR FDC
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.2289
Method	Stratified Mantel-Haenszel test
Parameter estimate	Difference in percentages
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	14.9

Notes:

[2] - Percentage difference and 95% confidence interval (CI) between each pair of treatment groups were from stratified Mantel-Haenszel test with baseline diabetes status and baseline enhanced liver fibrosis (ELF) category as stratification factors.

Secondary: Percentage of Participants Who Achieved ≥ 1-Stage Improvement in Fibrosis Without Worsening of NASH at Week 72 in SEMA + CILO/FIR FDC Versus SEMA Alone

End point title	Percentage of Participants Who Achieved ≥ 1-Stage Improvement in Fibrosis Without Worsening of NASH at Week 72 in SEMA + CILO/FIR FDC Versus SEMA Alone[3]

End point description:

Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in fibrosis according to the NASH clinical research network classification (CRN) classification. Worsening of NASH was defined as ≥ 1-point increase from baseline in hepatocellular ballooning or lobular inflammation.
Clopper-Pearson method was used in outcome measure analysis in each arm. Percentages were rounded-off.
Participants in the Full Analysis Set in SEMA + CILO/FIR and SEMA + PTM CILO/FIR were analyzed.

End point type	Secondary

End point timeframe:

Week 72

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned only for arms: SEMA + CILO/FIR vs SEMA + PTM CILO/FIR.

End point values	SEMA + CILO/FIR FDC	SEMA + PTM CILO/FIR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	122		
Units: percentage of participants				
number (confidence interval 95%)	13.7 (8.2 to 21.0)	15.6 (9.6 to 23.2)		

Statistical analyses

Statistical analysis title	SEMA + CILO/FIR FDC vs SEMA + PTM CILO/FIR

Statistical analysis description:

Percentage difference and 95% CI between each pair of treatment groups presented were from stratified Mantel-Haenszel test with baseline diabetes status and baseline ELF category as stratification factors.

Comparison groups	SEMA + CILO/FIR FDC v SEMA + PTM CILO/FIR
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6959
Method	Stratified Mantel-Haenszel test
Parameter estimate	Difference in percentages
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	7.4

Secondary: Percentage of Participants With NASH Resolution Without Worsening in Fibrosis at Week 72 in SEMA + CILO/FIR FDC Versus Placebo Groups

End point title	Percentage of Participants With NASH Resolution Without Worsening in Fibrosis at Week 72 in SEMA + CILO/FIR FDC Versus Placebo Groups[4]

End point description:

NASH resolution was defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0.
Worsening of NASH was defined as ≥ 1-point increase from baseline in hepatocellular ballooning or lobular inflammation.
Clopper-Pearson method was used in outcome measure analysis in each arm. Percentages were rounded-off.
Participants in the Full Analysis Set in SEMA + CILO/FIR FDC and PTM SEMA + PTM CILO/FIR with available data were analyzed.

End point type	Secondary

End point timeframe:

Week 72

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned only for arms: SEMA + CILO/FIR FDC vs PTM SEMA + PTM CILO/FIR.

End point values	SEMA + CILO/FIR FDC	PTM SEMA + PTM CILO/FIR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	49		
Units: percentage of participants				
number (confidence interval 95%)	57.3 (45.9 to 68.2)	22.4 (11.8 to 36.6)		

Statistical analyses

Statistical analysis title	SEMA + CILO/FIR FDC vs PTM SEMA + PTM CILO/FIR

Statistical analysis description:

Percentage difference and 95% CI between each pair of treatment groups presented are from stratified Mantel-Haenszel test with baseline diabetes status and baseline ELF category as stratification factors.

Comparison groups	SEMA + CILO/FIR FDC v PTM SEMA + PTM CILO/FIR
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Mantel-Haenszel test
Parameter estimate	Difference in percentages
Point estimate	35.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.8
upper limit	52.6

Secondary: Percentage of Participants With NASH Resolution Without Worsening in Fibrosis In Participants Treated With SEMA + CILO/FIR FDC Versus CILO/FIR Alone Groups

End point title	Percentage of Participants With NASH Resolution Without Worsening in Fibrosis In Participants Treated With SEMA + CILO/FIR FDC Versus CILO/FIR Alone Groups[5]

End point description:

NASH resolution was defined as lobular inflammation of 0 or 1 and hepatocellular ballooning of 0. Clopper-Pearson method was used in outcome measure analysis in each arm. Percentages were rounded-off.
Participants in the Full Analysis Set in SEMA + CILO/FIR FDC and PTM SEMA + CILO/FIR FDC with available data were analyzed.

End point type	Secondary

End point timeframe:

Week 72

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned only for arms: SEMA + CILO/FIR vs PTM SEMA + CILO/FIR

End point values	SEMA + CILO/FIR FDC	PTM SEMA + CILO/FIR FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	88		
Units: percentage of participants				
number (confidence interval 95%)	57.3 (45.9 to 68.2)	31.8 (22.3 to 42.6)		

Statistical analyses

Statistical analysis title	SEMA + CILO/FIR FDC vs PTM SEMA + CILO/FIR FDC

Statistical analysis description:

Percentage difference and 95% CI between each pair of treatment groups presented were from stratified Mantel-Haenszel test with baseline diabetes status and baseline ELF category as stratification factors.

Comparison groups	SEMA + CILO/FIR FDC v PTM SEMA + CILO/FIR FDC
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Stratified Mantel-Haenszel test
Parameter estimate	Difference in percentages
Point estimate	26.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	40.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and Adverse events: Up to 72 weeks plus 35 days

Adverse event reporting additional description:

All-cause mortality: The All Randomized Analysis Set included all participants who were randomized in the study.
Adverse events: The Safety Analysis Set included all participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	SEMA + CILO/FIR FDC

Reporting group description:

Participants received PTM SEMA SC injection, once weekly and PTM CILO/FIR FDC tablet orally, once daily up to 72 weeks.

Reporting group title	SEMA + PTM CILO/FIR

Reporting group description:

Participants received SEMA 3.0 mg/mL SC injection, once weekly and Placebo-To-Match (PTM) CILO/FIR FDC tablet orally, once daily up to 72 weeks.

Reporting group title	PTM SEMA + CILO/FIR FDC

Reporting group description:

Participants received PTM SEMA SC injection, once weekly and CILO/FIR 30 mg/20 mg FDC tablet orally, once daily up to 72 weeks.

Reporting group title	PTM SEMA + PTM CILO/FIR

Reporting group description:

Participants received PTM SEMA SC injection, once weekly and PTM CILO/FIR FDC tablet orally, once daily up to 72 weeks.

Serious adverse events	SEMA + CILO/FIR FDC	SEMA + PTM CILO/FIR	PTM SEMA + CILO/FIR FDC
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 124 (13.71%)	13 / 122 (10.66%)	18 / 123 (14.63%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	2 / 124 (1.61%)	0 / 122 (0.00%)	3 / 123 (2.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer recurrent			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ductal adenocarcinoma of pancreas			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant glioma			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the vulva			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prosthetic cardiac valve stenosis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat exhaustion			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			

subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shoulder fracture			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Sensory loss			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Steatohepatitis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 124 (0.81%)	2 / 122 (1.64%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	3 / 124 (2.42%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			

subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse idiopathic skeletal hyperostosis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	2 / 123 (1.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis intestinal perforated			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			

subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 124 (0.81%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 122 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PTM SEMA + PTM		

	CILO/FIR		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 84 (13.10%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer recurrent			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ductal adenocarcinoma of pancreas			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant glioma			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Squamous cell carcinoma of the vulva				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Shock				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prosthetic cardiac valve stenosis				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Major depression				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heat exhaustion				

subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haematoma				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shoulder fracture				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Atrial septal defect				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sensory loss			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctitis			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Steatohepatitis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Decubitus ulcer				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvi-ureteric obstruction				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue				

disorders				
Arthralgia				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical spinal stenosis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diffuse idiopathic skeletal hyperostosis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal stenosis				
subjects affected / exposed	1 / 84 (1.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal wall abscess			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine infection			

subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural cellulitis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypokalaemia				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 84 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SEMA + CILO/FIR FDC	SEMA + PTM CILO/FIR	PTM SEMA + CILO/FIR FDC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 124 (81.45%)	97 / 122 (79.51%)	85 / 123 (69.11%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 124 (2.42%)	1 / 122 (0.82%)	3 / 123 (2.44%)
occurrences (all)	3	1	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 124 (5.65%)	10 / 122 (8.20%)	9 / 123 (7.32%)
occurrences (all)	8	11	10
Headache			
subjects affected / exposed	7 / 124 (5.65%)	11 / 122 (9.02%)	12 / 123 (9.76%)
occurrences (all)	7	11	22
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 124 (13.71%)	17 / 122 (13.93%)	9 / 123 (7.32%)
occurrences (all)	19	17	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	59 / 124 (47.58%)	49 / 122 (40.16%)	29 / 123 (23.58%)
occurrences (all)	70	58	38
Diarrhoea			
subjects affected / exposed	34 / 124 (27.42%)	25 / 122 (20.49%)	16 / 123 (13.01%)
occurrences (all)	41	33	19
Constipation			

subjects affected / exposed	30 / 124 (24.19%)	26 / 122 (21.31%)	11 / 123 (8.94%)
occurrences (all)	34	27	13
Vomiting			
subjects affected / exposed	27 / 124 (21.77%)	21 / 122 (17.21%)	7 / 123 (5.69%)
occurrences (all)	41	28	10
Abdominal pain			
subjects affected / exposed	11 / 124 (8.87%)	10 / 122 (8.20%)	6 / 123 (4.88%)
occurrences (all)	11	11	6
Abdominal pain upper			
subjects affected / exposed	7 / 124 (5.65%)	11 / 122 (9.02%)	6 / 123 (4.88%)
occurrences (all)	8	12	7
Abdominal distension			
subjects affected / exposed	9 / 124 (7.26%)	10 / 122 (8.20%)	4 / 123 (3.25%)
occurrences (all)	9	11	6
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 124 (5.65%)	13 / 122 (10.66%)	3 / 123 (2.44%)
occurrences (all)	8	13	3
Dyspepsia			
subjects affected / exposed	12 / 124 (9.68%)	2 / 122 (1.64%)	4 / 123 (3.25%)
occurrences (all)	15	2	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 124 (2.42%)	3 / 122 (2.46%)	7 / 123 (5.69%)
occurrences (all)	3	3	7
Dyspnoea			
subjects affected / exposed	0 / 124 (0.00%)	1 / 122 (0.82%)	2 / 123 (1.63%)
occurrences (all)	0	1	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 124 (6.45%)	13 / 122 (10.66%)	12 / 123 (9.76%)
occurrences (all)	9	13	12
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 124 (6.45%)	6 / 122 (4.92%)	12 / 123 (9.76%)
occurrences (all)	8	6	12
Back pain			

subjects affected / exposed	8 / 124 (6.45%)	7 / 122 (5.74%)	8 / 123 (6.50%)
occurrences (all)	8	7	8
Pain in extremity			
subjects affected / exposed	2 / 124 (1.61%)	4 / 122 (3.28%)	7 / 123 (5.69%)
occurrences (all)	2	4	7
Infections and infestations			
COVID-19			
subjects affected / exposed	21 / 124 (16.94%)	15 / 122 (12.30%)	15 / 123 (12.20%)
occurrences (all)	23	15	15
Urinary tract infection			
subjects affected / exposed	13 / 124 (10.48%)	6 / 122 (4.92%)	8 / 123 (6.50%)
occurrences (all)	23	13	8
Upper respiratory tract infection			
subjects affected / exposed	7 / 124 (5.65%)	4 / 122 (3.28%)	12 / 123 (9.76%)
occurrences (all)	7	4	13
Sinusitis			
subjects affected / exposed	8 / 124 (6.45%)	8 / 122 (6.56%)	4 / 123 (3.25%)
occurrences (all)	9	10	4
Nasopharyngitis			
subjects affected / exposed	7 / 124 (5.65%)	4 / 122 (3.28%)	6 / 123 (4.88%)
occurrences (all)	11	6	6
Bronchitis			
subjects affected / exposed	2 / 124 (1.61%)	3 / 122 (2.46%)	5 / 123 (4.07%)
occurrences (all)	2	3	6
Influenza			
subjects affected / exposed	1 / 124 (0.81%)	2 / 122 (1.64%)	3 / 123 (2.44%)
occurrences (all)	1	2	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 124 (15.32%)	20 / 122 (16.39%)	7 / 123 (5.69%)
occurrences (all)	19	20	7
Hypoglycaemia			
subjects affected / exposed	14 / 124 (11.29%)	4 / 122 (3.28%)	3 / 123 (2.44%)
occurrences (all)	42	33	6
Hypertriglyceridaemia			

subjects affected / exposed	2 / 124 (1.61%)	0 / 122 (0.00%)	7 / 123 (5.69%)
occurrences (all)	2	0	7

Non-serious adverse events	PTM SEMA + PTM CILO/FIR		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 84 (71.43%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 84 (7.14%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 84 (9.52%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	3 / 84 (3.57%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 84 (13.10%)		
occurrences (all)	11		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 84 (22.62%)		
occurrences (all)	22		
Diarrhoea			
subjects affected / exposed	15 / 84 (17.86%)		
occurrences (all)	18		
Constipation			
subjects affected / exposed	7 / 84 (8.33%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	6 / 84 (7.14%)		
occurrences (all)	6		
Abdominal pain			

subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	11 / 84 (13.10%) 12 8 / 84 (9.52%) 8 6 / 84 (7.14%) 6 2 / 84 (2.38%) 2 3 / 84 (3.57%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 7 / 84 (8.33%) 7 5 / 84 (5.95%) 5		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 6 / 84 (7.14%) 6		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 11 / 84 (13.10%) 12 7 / 84 (8.33%) 7 3 / 84 (3.57%) 4		
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all)	14 / 84 (16.67%) 15		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 84 (3.57%) 5		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 84 (4.76%) 7		
Sinusitis subjects affected / exposed occurrences (all)	6 / 84 (7.14%) 9		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 84 (4.76%) 4		
Bronchitis subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5		
Influenza subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 6		
Hypoglycaemia subjects affected / exposed occurrences (all)	5 / 84 (5.95%) 15		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	2 / 84 (2.38%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2021	• Included collection of a single pharmacokinetics (PK) blood sample at the early termination (ET) visit (anytime) and at unscheduled visits (anytime) that were performed for the purpose of safety evaluation (eg, serious adverse event follow-up). • "Anthropometric measurements" changed to "measurement of hip and waist circumference" throughout. • Included assessment of any findings related to gallstones or other hepatobiliary disease in addition to hepatocellular carcinoma (HCC) during screening and on-study abdominal ultrasounds. • Data monitoring committee (DMC) to be notified if study drug was withheld. • The protocol synopsis and the study procedures table were updated to align with the updates to the body of the protocol. • Administrative, editorial, and formatting updates, changes, corrections, and clarifications were made, where appropriate, throughout the document.
26 October 2023	• Changed the primary objective to evaluate only whether the combination of SEMA with the fixed-dose combination (FDC) of CILO/FIR causes fibrosis improvement without worsening of NASH compared with placebo; NASH resolution was no longer evaluated as part of the primary objective. The rationale for this change was that increasingly fibrosis improvement was recognized as the biomarker most likely to predict clinical benefit in a cirrhotic NASH study population, and this change allow fibrosis improvement to be tested independently as the highest priority hypothesis. • Added a secondary objective to evaluate whether the combination of SEMA with the FDC of CILO/FIR causes NASH resolution in participants with compensated cirrhosis due to NASH, as compared with placebo. • Changed coprimary endpoints to a single primary endpoint of fibrosis improvement without worsening of NASH in order to test fibrosis improvement independently as the highest priority hypothesis, appropriate for a cirrhotic NASH study population. • Information for statistical testing of the primary and secondary endpoints was changed to order analysis objectives in keeping with the changes to the endpoints, and for consistency with changes made in other sections. • Estimand strategy was added and updated for primary/secondary endpoints based on the modifications made to the endpoints in the protocol. • Statistical considerations section was updated to add "power calculation." • Dose escalation schedule for SEMA was updated. • A list of study interventions and their marketing authorization status was added. • New section regarding definition of serious adverse drug reaction was added. • Section for "Liver-Related Clinical Events" was added. • Pregnancy reporting process and time period was updated. • The text related to "repeating liver-related laboratory assessments (ALT, AST, ALP, GGT, total bilirubin, INR) within 72 hours of initial results (or as soon as possible)" removed from toxicities

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported