



Clinical trial results:

MOSAIC - A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Selonsertib in Subjects with Moderate to Advanced Diabetic Kidney Disease

Summary

EudraCT number	2018-003951-39
Trial protocol	GB ES IT
Global end of trial date	03 September 2021

Results information

Result version number	v2
This version publication date	04 November 2022
First version publication date	16 September 2022
Version creation reason	• Correction of full data set Changes made to a statement in Baseline Characteristics section, Timeframe of an endpoint and Updated title of an endpoint.

Trial information

Trial identification

Sponsor protocol code	GS-US-223-1017
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04026165
WHO universal trial number (UTN)	-
Other trial identifiers	Japan Pharmaceutical Information Center: JapicCTI-194911

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	03 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2021
Global end of trial reached?	Yes
Global end of trial date	03 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate whether selonsertib (SEL) can slow the decline in kidney function in participants with moderate to advanced diabetic kidney disease (DKD).

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	24 July 2019
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	Australia: 6
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Japan: 79
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	United States: 251
Worldwide total number of subjects	384
EEA total number of subjects	0

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)	155
From 65 to 84 years	229
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

961 participants were screened.

Period 1

Period 1 title	Run-in Placebo Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in Placebo
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Arm description:

Participants received placebo to match selonsertib (SEL) tablet orally once daily for at least one week.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match SEL administered once daily for at least one week

Number of subjects in period 1	Run-in Placebo
Started	384
Completed	362
Not completed	22
Withdrew Consent	2
Enrollment Error	13
Significant Non-compliance with Study Drug	1
Protocol Violation	2
Run-in Failure	4

Period 2

Period 2 title	Run-in SEL Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in SEL 18 mg
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Arm description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks.

Arm type	Experimental
Investigational medicinal product name	SEL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered once daily

Number of subjects in period 2^[1]	Run-in SEL 18 mg
Started	357
Completed	311
Not completed	46
Withdrew Consent	10
Enrollment Error	4
Death	1
Investigator's Discretion	2
Protocol Violation	3
Run-in Failure	26

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Five participants discontinued the study after completing the Run-in Placebo (Period 1) and didn't enter the Run-in SEL period (Period 2).

Period 3

Period 3 title	Randomised Period
Is this the baseline period?	Yes ^[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	Randomised SEL 18 mg
Arm description:	
Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received SEL 18 mg tablet orally once daily for at least 48 weeks.	
Arm type	Experimental
Investigational medicinal product name	SEL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
18 mg administered once daily	

Arm title	Randomised Placebo
Arm description:	
Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received placebo-to-match SEL tablet orally once daily for at least 48 weeks.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo to match SEL was administered once daily	

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline characteristics were measured in Period 1. However, baseline characteristics are presented for the Safety analysis set (n=667) by Randomisation status and Randomised treatment group. Therefore, period 3 was selected as the Baseline period due to system constraints so the treatment groups are correctly populated in the system.

Number of subjects in period 3^[3][4]	Randomised SEL 18 mg	Randomised Placebo
Started	154	156
Completed	140	137
Not completed	14	19
Withdrew Consent	5	8
Death	5	7
Lost to Follow-up	2	2
Investigator's Discretion	2	2

Notes:

[3] - 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: Baseline characteristics were reported for the Safety Analysis Set only, which included participants who received at least one dose of Run-in SEL.

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Following the Run-in period, eligible participants were randomised to receive either SEL (18 mg) or placebo.

Baseline characteristics

Reporting groups

Reporting group title	Randomised SEL 18 mg
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Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received SEL 18 mg tablet orally once daily for at least 48 weeks.

Reporting group title	Randomised Placebo
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Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received placebo-to-match SEL tablet orally once daily for at least 48 weeks.

Reporting group values	Randomised SEL 18 mg	Randomised Placebo	Total
Number of subjects	154	156	310
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	65 ± 9.3	66 ± 8.8	-
Gender categorical Units: Subjects			
Female	48	51	99
Male	106	105	211
Race Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	41	44	85
Black or African American	26	22	48
Native Hawaiian or Pacific Islander	5	4	9
White	78	84	162
Other	2	2	4
Ethnicity			
Not Permitted = local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	132	136	268
Hispanic or Latino	21	19	40
Not Permitted	1	1	2

Subject analysis sets

Subject analysis set title	Run-in SEL 18 mg, Not Randomised
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The analysis set included all participants who took at least 1 dose of Run-in SEL and were not randomised.

Reporting group values	Run-in SEL 18 mg, Not Randomised		
Number of subjects	47		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	65 ± 9.7		
Gender categorical Units: Subjects			
Female Male	12 35		
Race Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Pacific Islander White Other	0 4 4 1 36 2		
Ethnicity			
Not Permitted = local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Not Hispanic or Latino Hispanic or Latino Not Permitted	39 8 0		

End points

End points reporting groups

Reporting group title	Run-in Placebo
Reporting group description: Participants received placebo to match selonsertib (SEL) tablet orally once daily for at least one week.	
Reporting group title	Run-in SEL 18 mg
Reporting group description: Participants received SEL 18 mg tablet orally once daily for at least 4 weeks.	
Reporting group title	Randomised SEL 18 mg
Reporting group description: Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received SEL 18 mg tablet orally once daily for at least 48 weeks.	
Reporting group title	Randomised Placebo
Reporting group description: Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received placebo-to-match SEL tablet orally once daily for at least 48 weeks.	
Subject analysis set title	Run-in SEL 18 mg, Not Randomised
Subject analysis set type	Safety analysis
Subject analysis set description: The analysis set included all participants who took at least 1 dose of Run-in SEL and were not randomised.	

Primary: Treatment-specific Baseline Estimated Glomerular Filtration Rate Based on Creatinine (eGFRcr)

End point title	Treatment-specific Baseline Estimated Glomerular Filtration Rate Based on Creatinine (eGFRcr) ^[1]
End point description: The values of eGFRcr were calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Creatinine Equation (2009). $eGFRcr = 141 \cdot \min(\text{Standardized Serum Creatinine (Scr)}/\kappa, 1)^{\alpha} \cdot \max(\text{Scr}/\kappa, 1)^{-1.209} \cdot 0.993^{\text{Age}} \cdot 1.018[\text{if female}] \cdot 1.159[\text{if Black}]$, where $\kappa=0.7(\text{females})$ or $0.9(\text{males})$, $\alpha=-0.329(\text{females})$ or $-0.411(\text{males})$. min indicates the minimum of Scr/ κ or 1, max indicates the maximum of Scr/ κ or 1, and age is in years. Treatment-specific Baselines = the average of Visits A and B values for Placebo, and the average of Visit C and Day 1 values for SEL. Visit A= enrollment, Visit B= 7-14 days after Visit A, Visit C= 21-28 days after Visit B, and Visit 1= 7-14 days after Visit C. The Full Analysis Set included all participants who were randomised in the study, and received at least one dose of study drug in the Randomisation Phase.	
End point type	Primary
End point timeframe: Treatment-specific Baselines (From enrollment (Visit A) up to 14 days after Visit A for placebo and from Visit C up to 14 days after Visit C for SEL)	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analyses was planned for this endpoint.	

End point values	Randomised SEL 18 mg	Randomised Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	156		
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)	32.7 (± 10.59)	34.9 (± 10.81)		

Statistical analyses

No statistical analyses for this end point

Primary: eGFRcr Slope

End point title	eGFRcr Slope
End point description: The values of eGFRcr were calculated using the CKD-EPI Creatinine Equation (2009). $eGFRcr = 141 * \min(Scr/kappa, 1)^\alpha * \max(Scr/kappa, 1)^{-1.209} * 0.993^{Age} * 1.018[\text{if female}] * 1.159[\text{if Black}]$, where $kappa=0.7(\text{females})$ or $0.9(\text{males})$, $\alpha=-0.329(\text{females})$ or $-0.411(\text{males})$. min indicates the minimum of Scr/kappa or 1, max indicates the maximum of Scr/kappa or 1, and age is in years. Treatment specific baselines for eGFRcr: average of Visit A (enrollment) and Visit B (7-14 days after Visit A) values for Placebo, and average of Visit C (21-28 days after Visit B, and Visit 1 (7-14 days after Visit C) values for SEL. Participants in the Full Analysis Set with available data were analysed.	
End point type	Primary
End point timeframe: Treatment-specific Baselines through Week 84	

End point values	Randomised SEL 18 mg	Randomised Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	156		
Units: mL/min/1.73m ² /year				
least squares mean (standard error)	-2.29 (± 0.58)	-3.49 (± 0.58)		

Statistical analyses

Statistical analysis title	Randomised SEL 18 mg, Randomised Placebo
Statistical analysis description: Estimates were from a random slope model with change in eGFRcr from treatment-specific Baselines at Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84 as outcome, including terms for treatment-specific Baseline eGFRcr, pre-run-in urine albumin to creatinine ratio (UACR) category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors at Randomisation, treatment group, week, and treatment-by-week interaction, where week has a random effect.	
Comparison groups	Randomised SEL 18 mg v Randomised Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1439
Method	Random Slope Model
Parameter estimate	Difference in Adjusted Mean
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	2.81
Variability estimate	Standard error of the mean
Dispersion value	0.82

Secondary: Percentage of Participants with Kidney Clinical Events at Week 48

End point title	Percentage of Participants with Kidney Clinical Events at Week 48
End point description:	
Kidney clinical events were defined as any of the following events: confirmed $\geq 40\%$ decline in eGFR _{cr} from baseline, or kidney failure (dialysis performed for at least 4 weeks, kidney transplantation, or confirmed decrease in eGFR _{cr} to < 15 mL/min/1.73 m ² for participants without dialysis or kidney transplantation), or death due to kidney disease. Participants in the Full Analysis Set were analysed.	
End point type	Secondary
End point timeframe:	
Week 48	

End point values	Randomised SEL 18 mg	Randomised Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	156		
Units: percentage of participants				
number (not applicable)	9.1	9.0		

Statistical analyses

Statistical analysis title	Randomised SEL 18 mg, Randomised Placebo
Statistical analysis description:	
95% exact CI based on the Santner-Snell method was presented for the difference in proportions between SEL and placebo arms.	
Comparison groups	Randomised SEL 18 mg v Randomised Placebo
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8353 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Percentage
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	11.4

Notes:

[2] - p-value was based on Cochran-Mantel-Haenszel test stratified by Randomisation stratification factors. Randomisation stratification factors= pre-run-in eGFRcr stratum, pre-run-in UACR category and concomitant use of SGLT-2 inhibitors at Randomisation.

Secondary: Time From Randomization to First Occurrence of a Kidney Clinical Event: Event Rate Per 100 Participant-years for First Occurrence of Kidney Clinical Event

End point title	Time From Randomization to First Occurrence of a Kidney Clinical Event: Event Rate Per 100 Participant-years for First Occurrence of Kidney Clinical Event
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End point description:

Kidney clinical events were defined as any of the following events: confirmed $\geq 40\%$ decline in eGFRcr from baseline, or kidney failure (dialysis performed for at least 4 weeks, kidney transplantation, or confirmed decrease in eGFRcr to < 15 mL/min/1.73 m² for participants without dialysis or kidney transplantation), or death due to kidney disease. This outcome measure was analyzed using event rate per 100 participant-years for first occurrence of kidney clinical event. Participant year was calculated as total follow-up duration across all participants in a given group. Follow-up duration was defined as time from Randomization to the earliest of study completion, premature study discontinuation, death, or event of interest in each row. Participants in the Full Analysis Set were analysed.

End point type	Secondary
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End point timeframe:

From randomisation up to Week 101

End point values	Randomised SEL 18 mg	Randomised Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	156		
Units: events per 100 participant-years				
number (not applicable)	13.4	9.8		

Statistical analyses

Statistical analysis title	Randomised SEL 18 mg, Randomised Placebo
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Statistical analysis description:

Hazard ratio and 95% CI were estimated using a stratified Cox proportional hazard model, stratified by randomisation stratification factors and were reported only for outcomes with more than 10 events, and have at least 1 event in each treatment arm.

Comparison groups	Randomised SEL 18 mg v Randomised Placebo
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201 ^[3]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	2.72

Notes:

[3] - P-value was calculated using a stratified log-rank test, stratified by randomisation stratification factors.

Secondary: Pre-run-in Baseline Estimated Glomerular Filtration Rate Based on Cystatin C (eGFRcys)

End point title	Pre-run-in Baseline Estimated Glomerular Filtration Rate Based on Cystatin C (eGFRcys)
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End point description:

eGFRcys = Estimated Glomerular Filtration Rate calculated by CKD-EPI Cystatin C Equation (2012).
$$eGFR = 133 * \min(\text{Standardized Serum Cystatin (Scys)}/0.8, 1) ^{(-0.499)} * \max(\text{Scys}/0.8, 1) ^{(-1.328)} * 0.996^{\text{Age}} * 0.932[\text{if female}]$$
. min indicates the minimum of Scys/0.8 or 1, max indicates the maximum of Scr/0.8 or 1, and age is in years. Participants in the Full Analysis Set were analysed.

End point type	Secondary
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End point timeframe:

Pre-run-in Baseline (Pre-run in Baseline = Average of visit A (Enrollment) and Visit B (7-14 days after Visit A) eGFRcys values)

End point values	Randomised SEL 18 mg	Randomised Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	156		
Units: mL/min/1.73m ²				
arithmetic mean (standard deviation)	33.6 (± 11.81)	32.4 (± 10.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: eGFRcys Slope

End point title	eGFRcys Slope
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End point description:

eGFRcys = Estimated Glomerular Filtration Rate calculated by CKD-EPI Cystatin C Equation (2012).
$$eGFR = 133 * \min(\text{Scys}/0.8, 1) ^{(-0.499)} * \max(\text{Scys}/0.8, 1) ^{(-1.328)} * 0.996^{\text{Age}} * 0.932[\text{if female}]$$
. min indicates the minimum of Scys/0.8 or 1, max indicates the maximum of Scr/0.8 or 1, and age is in years. Pre-run in Baseline = Average of Visit A (Enrollment) and Visit B (7-14 days after Visit A) eGFRcys values. Participants in the Full Analysis Set with available data were analysed.

End point type	Secondary
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End point timeframe:

Pre-run-in Baseline through Week 84

End point values	Randomised SEL 18 mg	Randomised Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	156		
Units: mL/min/1.73m ² /year				
least squares mean (standard error)	-3.79 (± 0.51)	-4.23 (± 0.51)		

Statistical analyses

Statistical analysis title	Randomised SEL 18 mg, Randomised Placebo
Statistical analysis description:	
Estimates were from a random slope model with change in eGFR _{cys} from pre-run-in Baseline at Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84 as outcome, including terms for pre-run-in Baseline eGFR _{cys} , pre-run-in UACR category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of SGLT-2 inhibitors at Randomisation, treatment group, week, and treatment-by-week interaction, where week has a random effect.	
Comparison groups	Randomised SEL 18 mg v Randomised Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5399
Method	Random Slope Model
Parameter estimate	Difference in Adjusted Mean
Point estimate	0.44
Confidence interval:	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	1.86
Variability estimate	Standard error of the mean
Dispersion value	0.72

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality: Enrollment up to maximum duration of 107.1 weeks; Adverse Events: First dose in Run-in

SEL phase up to last dose (maximum: 101 weeks) plus 30 days

Adverse event reporting additional description:

All-Cause Mortality: The All Enrolled Analysis Set included all participants who were enrolled in the study. There were no deaths in the Run-in Placebo period.

Adverse Events: The Safety Analysis Set included all participants who took at least 1 dose of Run-in SEL.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Run-in SEL 18 mg
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Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks.

Reporting group title	Randomised Placebo
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Reporting group description:

Participants received placebo-to-match SEL tablet orally once daily for at least 48 weeks after randomisation.

Reporting group title	Randomised SEL 18 mg
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Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 48 weeks after randomisation.

Serious adverse events	Run-in SEL 18 mg	Randomised Placebo	Randomised SEL 18 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 357 (4.48%)	45 / 156 (28.85%)	45 / 154 (29.22%)
number of deaths (all causes)	1	7	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer metastatic			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Lipoma			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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			
Orthostatic hypotension			
subjects affected / exposed	0 / 357 (0.00%)	2 / 156 (1.28%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure inadequately ~ controlled			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Hypotension			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Generalised oedema			

subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 357 (0.28%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary ~ disease			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Dyspnoea			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Lung infiltration			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Product issues			
Device end of service			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Arteriogram coronary abnormal			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbon dioxide abnormal			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Electrocardiogram abnormal			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
International normalised ratio ~ increased			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transaminases increased			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Contusion			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural complication			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Rib fracture			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Arteriovenous malformation			

subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	3 / 357 (0.84%)	5 / 156 (3.21%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 357 (0.00%)	5 / 156 (3.21%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 357 (0.00%)	2 / 156 (1.28%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 357 (0.28%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 357 (0.00%)	2 / 156 (1.28%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 357 (0.00%)	2 / 156 (1.28%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cardiogenic shock			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cardiopulmonary failure			

subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Myocardial infarction			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (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
Pulseless electrical activity			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus node dysfunction			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrogenic anaemia			

subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinopathy hypertensive			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 357 (0.00%)	5 / 156 (3.21%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Gastric ulcer			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			

subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Pancreatitis acute			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Hepatobiliary disorders			
Hepatic mass			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Jaundice cholestatic			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
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	3 / 357 (0.84%)	7 / 156 (4.49%)	10 / 154 (6.49%)
occurrences causally related to treatment / all	0 / 3	1 / 9	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 357 (0.00%)	3 / 156 (1.92%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 357 (0.56%)	0 / 156 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Diabetic nephropathy			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Nephropathy			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Renal failure			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Renal mass			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcapsular renal haematoma			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (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
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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			

Pneumonia			
subjects affected / exposed	0 / 357 (0.00%)	3 / 156 (1.92%)	5 / 154 (3.25%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	0 / 357 (0.00%)	2 / 156 (1.28%)	5 / 154 (3.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Covid-19 pneumonia			
subjects affected / exposed	0 / 357 (0.00%)	3 / 156 (1.92%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 357 (0.28%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Bacteraemia			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (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
Bursitis infective			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cellulitis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Cystitis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Escherichia bacteraemia			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Influenza			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (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
Large intestine infection			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Otitis externa			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Scrotal abscess			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Septic shock			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Staphylococcal infection			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Urinary tract infection			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Urosepsis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Wound infection			

subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	0 / 357 (0.00%)	3 / 156 (1.92%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 357 (0.28%)	1 / 156 (0.64%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 357 (0.28%)	1 / 156 (0.64%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 357 (0.00%)	1 / 156 (0.64%)	0 / 154 (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
Hyperglycaemia			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 357 (0.28%)	0 / 156 (0.00%)	0 / 154 (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
Hypovolaemia			

subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency			
subjects affected / exposed	0 / 357 (0.00%)	0 / 156 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Run-in SEL 18 mg	Randomised Placebo	Randomised SEL 18 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 357 (10.36%)	49 / 156 (31.41%)	55 / 154 (35.71%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 357 (2.80%)	7 / 156 (4.49%)	11 / 154 (7.14%)
occurrences (all)	10	7	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 357 (0.28%)	8 / 156 (5.13%)	5 / 154 (3.25%)
occurrences (all)	1	9	5
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	5 / 357 (1.40%)	8 / 156 (5.13%)	11 / 154 (7.14%)
occurrences (all)	5	8	11
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 357 (1.96%)	3 / 156 (1.92%)	11 / 154 (7.14%)
occurrences (all)	7	3	11
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 357 (0.28%)	4 / 156 (2.56%)	10 / 154 (6.49%)
occurrences (all)	1	5	10
Infections and infestations			
Urinary tract infection			

subjects affected / exposed occurrences (all)	6 / 357 (1.68%) 6	9 / 156 (5.77%) 10	5 / 154 (3.25%) 5
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	8 / 357 (2.24%)	11 / 156 (7.05%)	12 / 154 (7.79%)
occurrences (all)	8	12	15
Hypoglycaemia			
subjects affected / exposed	4 / 357 (1.12%)	9 / 156 (5.77%)	6 / 154 (3.90%)
occurrences (all)	4	13	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2019	• To address comments received from regulatory agencies. • To provide further clarifications on guidelines for participants who permanently discontinued study drug and remained on study. • To correct minor errors and inconsistencies throughout the protocol.
13 April 2020	The Phase 3 study was designed based on the hypothesis that the acute decline in eGFR is solely an artefact of SEL's interaction with kidney transporters. Based upon the measured GFR results from the GS-US-223-0110 Phase 1b iohexol study with SEL, this hypothesis was challenged. Importantly, the new data did not alter our understanding of the safety of selonsertib, and the acute changes in kidney function were reversible as expected. Accordingly, Gilead decided to convert the Phase 3 study to a Phase 2b study in order to confirm the results of the prior post-hoc Phase 2 analysis using a Run-in design that prospectively accounted for the acute decline in eGFR associated with SEL. Additionally, efficacy was assessed in multiple ways to evaluate for consistency of effect on kidney outcomes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported