Clinical trial results:
A Phase 1b/2 Dose Escalation/Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GS-4224 in Subjects With Advanced Solid Tumors

Summary

EudraCT number	2019-004605-27
Trial protocol	PL
Global end of trial date	30 March 2021

Results information

Result version number	v2 (current)
This version publication date	25 September 2022
First version publication date	18 April 2022
Version creation reason	• Correction of full data set Updated pharmacokinetic outcome measure timeframe and added generic name of the study drug.

Trial information

Trial identification

Sponsor protocol code	GS-US-494-5484

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04049617
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	30 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2021
Global end of trial reached?	Yes
Global end of trial date	30 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to characterize the safety and tolerability of evixapodlin (formerly GS-4224) and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of evixapodlin in participants with advanced solid tumors.

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	26 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	18
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in New Zealand and the United States. The first participant was screened on 26 August 2019. The last study visit occurred on 30 March 2021.

Pre-assignment

Screening details:

29 participants were screened. The participants took part in the Phase 1 (Dose Escalation) of the study only. No participants were enrolled in the Phase 1 Cohort 5 and Cohort 2 substudy and the study was terminated due to sponsor decision before the planned Dose Expansion Phase 2 started.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Evixapodlin 400 mg (Phase 1)

Arm description:

Participants received evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).

Arm type	Experimental
Investigational medicinal product name	Evixapodlin
Investigational medicinal product code	
Other name	GS-4224
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg administered once daily for approximately 21 weeks

Arm title	Cohort 2: Evixapodlin 700 mg (Phase 1)

Arm description:

Participants received evixapodlin 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

Arm type	Experimental
Investigational medicinal product name	Evixapodlin
Investigational medicinal product code	
Other name	GS-4224
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

700 mg administered once daily for approximately 10 weeks

Arm title	Cohort 3: Evixapodlin 1000 mg (Phase 1)

Arm description:

Participants received Evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

Arm type	Experimental

Investigational medicinal product name	Evixapodlin
Investigational medicinal product code	
Other name	GS-4224
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg administered once daily for approximately 39 weeks

Arm title	Cohort 4: Evixapodlin 1500 mg (Phase 1)

Arm description:

Participants received evixapodlin 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).

Arm type	Experimental
Investigational medicinal product name	Evixapodlin
Investigational medicinal product code	
Other name	GS-4224
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1500 mg administered once daily for approximately 19 weeks

Arm title	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)

Arm description:

Participants received evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

Arm type	Experimental
Investigational medicinal product name	Evixapodlin
Investigational medicinal product code	
Other name	GS-4224
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg administered once daily for approximately 39 weeks

Arm title	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)

Arm description:

Participants received evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

Arm type	Experimental
Investigational medicinal product name	Evixapodlin
Investigational medicinal product code	
Other name	GS-4224
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg administered once daily for approximately 10 weeks

Number of subjects in period 1	Cohort 1: Evixapodlin 400 mg (Phase 1)	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)
Started	3	3	6
Completed	3	3	5
Not completed	0	0	1
Death	-	-	-
Adverse event	-	-	-
Withdrew consent	-	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)
Started	3	2	1
Completed	1	2	0
Not completed	2	0	1
Death	-	-	1
Adverse event	1	-	-
Withdrew consent	-	-	-
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Evixapodlin 400 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).	
Reporting group title	Cohort 2: Evixapodlin 700 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).	
Reporting group title	Cohort 3: Evixapodlin 1000 mg (Phase 1)
Reporting group description:	
Participants received Evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).	
Reporting group title	Cohort 4: Evixapodlin 1500 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).	
Reporting group title	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).	
Reporting group title	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).	

Reporting group values	Cohort 1: Evixapodlin 400 mg (Phase 1)	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)
Number of subjects	3	3	6
Age categorical			
Units: Subjects			
Age continuous			
9999= not reached due to less number of participants			
Units: years			
arithmetic mean	55.3	65.3	61.2
standard deviation	± 28.29	± 15.53	± 5.67
Gender categorical			
Units: Subjects			
Female	1	0	2
Male	2	3	4

Reporting group values	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)
Number of subjects	3	2	1
Age categorical			
Units: Subjects			

Age continuous			
9999= not reached due to less number of participants			
Units: years			
arithmetic mean	70.0	64.0	42.0
standard deviation	± 11.53	± 12.73	± 9999
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	3	2	1

Reporting group values	Total		
Number of subjects	18		
Age categorical			
Units: Subjects			

Age continuous			
9999= not reached due to less number of participants			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	3		
Male	15		

End points

End points reporting groups

Reporting group title	Cohort 1: Evixapodlin 400 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).	
Reporting group title	Cohort 2: Evixapodlin 700 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).	
Reporting group title	Cohort 3: Evixapodlin 1000 mg (Phase 1)
Reporting group description:	
Participants received Evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).	
Reporting group title	Cohort 4: Evixapodlin 1500 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).	
Reporting group title	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).	
Reporting group title	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)
Reporting group description:	
Participants received evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).	
Subject analysis set title	Cohort 1: Evixapodlin 400 mg (Phase 1)
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK Analysis Set included participants in the Safety Analysis Set who had received the study drug and have at least 1 sample with detectable drug concentration. Data for Cohort 1 included participants from Cohort 1 and Substudy Cohort 1.	

Primary: Number of Participants Experiencing Dose Limiting Toxicities (DLTs) During the Dose Escalation Phase

End point title	Number of Participants Experiencing Dose Limiting Toxicities (DLTs) During the Dose Escalation Phase[1]
End point description:	
DLT: any toxicity defined as follows:•Grade ≥4 neutropenia•Grade ≥3 neutropenia with fever•Grade ≥3 thrombocytopenia•Grade ≥2 bleeding •Grade ≥3 anemia•Grade ≥3 or higher non-hematologic toxicity (excluding Grade 3 nausea or emesis or Grade 3 diarrhea)•Grade ≥2 non-hematologic treatment-emergent adverse event that in the opinion of the investigator is of potential clinical significance•Treatment interruption of ≥7days due to unresolved toxicity•Any toxicity event that precludes further administration of evixapodlin•Any Grade 3 or Grade 4 elevation in aspartate aminotransferase or alanine aminotransferase associated with a Grade 2 elevation in bilirubin lasting ≥7days•An immune-related adverse event for which immunotherapy should be permanently discontinued.Safety Analysis Set included data from all participants who received at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received.	
End point type	Primary
End point timeframe:	
Day 1 through Day 21	

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 analysis was planned.

End point values	Cohort 1: Evixapodlin 400 mg (Phase 1)	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)	Cohort 4: Evixapodlin 1500 mg (Phase 1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	3
Units: participants	0	0	0	1

End point values	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Parameter: AUCtau of Evixapodlin During the Dose Escalation Phase

End point title	Pharmacokinetic (PK) Parameter: AUCtau of Evixapodlin During the Dose Escalation Phase[2]

End point description:

AUCtau was defined as area under the concentration-time curve from time zero to the end of the dosing interval. PK Analysis Set included participants in the Safety Analysis Set who had received the study drug and have at least 1 sample with detectable drug concentration. Data for Cohort 1 included participants from Cohort 1 and Substudy Cohort 1. PK data were not collected for Cohort 3 Substudy group due to discontinuation of the development program.

End point type	Secondary

End point timeframe:

Intensive PK: Predose, 0.5, 1, 1.5, 2.5, 4, 6, 24 hours (h) postdose (400-1500 once daily [QD] mg cohorts) on C1D1 & D15

C=Cycle
Day=Day

Notes:

[2] - 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: No statistical analysis was planned.

End point values	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1: Evixapodlin 400 mg (Phase 1)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	6	3	5
Units: h*ng/mL				
arithmetic mean (standard deviation)				
C1D1	8703.8 (± 3717.93)	12241.8 (± 2793.17)	19132.6 (± 596.64)	6543.1 (± 1783.07)

C1D15	13508.4 (± 3126.80)	19380.8 (± 5261.89)	27664.5 (± 7758.37)	9269.8 (± 2693.53)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Cmax of Evixapodlin During the Dose Escalation Phase

End point title	PK Parameter: Cmax of Evixapodlin During the Dose Escalation Phase[3]

End point description:

Cmax was defined as the maximum observed drug concentration. Participants in PK Analysis Set were analyzed. Data for Cohort 1 included participants from Cohort 1 and Substudy Cohort 1. PK data were not collected for Cohort 3 Substudy group due to discontinuation of the development program.

End point type	Secondary

End point timeframe:

Intensive PK: Predose, 0.5, 1, 1.5, 2.5, 4, 6, 24 h postdose (400-1500 QD mg cohorts) on C1D1 & D15

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: No statistical analysis was planned.

End point values	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1: Evixapodlin 400 mg (Phase 1)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	6	3	5
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1	1468.7 (± 497.74)	1918.3 (± 377.59)	2116.7 (± 55.08)	1090.4 (± 355.12)
C1D15	1580.0 (± 245.76)	2051.7 (± 686.89)	2480.0 (± 278.75)	1193.8 (± 605.87)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Ctrough of Evixapodlin During the Dose Escalation Phase

End point title	PK Parameter: Ctrough of Evixapodlin During the Dose Escalation Phase[4]

End point description:

Ctrough is defined as the observed concentration at the end of the dosing interval. Participants in the PK Analysis Set were analyzed. Data for Cohort 1 included participants from Cohort 1 and Substudy Cohort 1. PK data were not collected for Cohort 3 Substudy group due to discontinuation of the development program.

End point type	Secondary

End point timeframe:

Intensive PK: Predose, 0.5, 1, 1.5, 2.5, 4, 6, 24 h postdose (400-1500 QD mg cohorts) on C1D1 & D15

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: No statistical analysis was planned.

End point values	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1: Evixapodlin 400 mg (Phase 1)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	6	3	5
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1	56.2 (± 18.05)	111.9 (± 43.92)	180.3 (± 21.50)	40.3 (± 9.80)
C1D15	198.7 (± 57.98)	318.5 (± 88.44)	472.7 (± 112.88)	109.8 (± 35.61)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of Evixapodlin During the Dose Escalation Phase

End point title	PK Parameter: Tmax of Evixapodlin During the Dose Escalation Phase[5]

End point description:

Tmax is defined as the time to maximum observed concentration. Participants in PK Analysis Set were analyzed. Data for Cohort 1 included participants from Cohort 1 and Substudy Cohort 1. PK data were not collected for Cohort 3 Substudy group due to discontinuation of the development program.

End point type	Secondary

End point timeframe:

Intensive PK: Predose, 0.5, 1, 1.5, 2.5, 4, 6, 24 h postdose (400-1500 QD mg cohorts) on C1D1 & D15

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: No statistical analysis was planned.

End point values	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1: Evixapodlin 400 mg (Phase 1)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	6	3	5
Units: hours				
median (inter-quartile range (Q1-Q3))				
C1D1	1.53 (1.00 to 2.50)	1.52 (1.00 to 1.65)	2.50 (2.50 to 6.00)	1.00 (1.00 to 1.02)
C1D15	1.50 (1.00 to 1.50)	1.51 (1.00 to 2.50)	4.00 (1.50 to 5.95)	1.50 (1.00 to 2.02)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality: Enrollment up to 46.1 weeks;

Adverse Events: First dose date up to last dose (maximum: 39.1 weeks) plus 30 days

Adverse event reporting additional description:

All-Cause Mortality: All Enrolled Analysis Set included all participants who received a study identification number in the study after screening.
Adverse Events: Safety Analysis Set included data from all participants who received at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort 1: Evixapodlin 400 mg (Phase 1)

Reporting group description:

Participants received Evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).

Reporting group title	Cohort 2: Evixapodlin 700 mg (Phase 1)

Reporting group description:

Participants received Evixapodlin 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

Reporting group title	Cohort 3: Evixapodlin 1000 mg (Phase 1)

Reporting group description:

Participants received Evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

Reporting group title	Cohort 4: Evixapodlin 1500 mg (Phase 1)

Reporting group description:

Participants received Evixapodlin 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).

Reporting group title	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)

Reporting group description:

Participants received Evixapodlin 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

Reporting group title	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)

Reporting group description:

Participants received Evixapodlin 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

Serious adverse events	Cohort 1: Evixapodlin 400 mg (Phase 1)	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (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
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Rectal perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Norovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (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
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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	Cohort 4: Evixapodlin 1500	Cohort 1 Substudy: Evixapodlin 400 mg	Cohort 3 Substudy: Evixapodlin 1000

	mg (Phase 1)	(Phase 1)	mg (Phase 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	1 / 1 (100.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (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
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (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
Rectal perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (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
Infections and infestations			
Norovirus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (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
Sepsis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 1 (100.00%)
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	Cohort 1: Evixapodlin 400 mg (Phase 1)	Cohort 2: Evixapodlin 700 mg (Phase 1)	Cohort 3: Evixapodlin 1000 mg (Phase 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Ageusia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	4 / 6 (66.67%)
occurrences (all)	6	3	4
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	4 / 6 (66.67%)
occurrences (all)	2	1	5
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	3
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Abdominal distension			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ileus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Intertrigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psoriasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Back pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Postoperative wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypophosphataemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4: Evixapodlin 1500 mg (Phase 1)	Cohort 1 Substudy: Evixapodlin 400 mg (Phase 1)	Cohort 3 Substudy: Evixapodlin 1000 mg (Phase 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 2 (100.00%)	0 / 1 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Ageusia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0

Migraine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 2 (50.00%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	1 / 2 (50.00%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Ileus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Intertrigo			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Postoperative wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Dehydration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2019	The protocol was amended in response to comments received from FDA on 30 May 2019 and 05 June 2019, and the pre-IND meeting (comments received April 15, 2019) regarding this study protocol.
12 August 2019	The protocol was amended to provide clarification for the Phase 1b starting dose rationale, assessment time points and the addition of non-small cell lung cancer (NSCLC) in the Phase 2 dose expansion basket cohort B1.
04 May 2020	• The protocol was amended to include updated higher dose evixapodlin tablet strengths (200 mg and 500 mg) and the addition of a new formulation for 100 mg strength tablets. • Language in the protocol was updated to allow up to 12 participants to enroll in one of the of the biopsy substudy cohorts. The number of planned participants for Phase 1b and total for the study were adjusted for the 6 additional participants. • Updates were also made to the acid-reducing agent restrictions following a preliminary study on the effects of acid reducing agents on the absorption of evixapodlin. Additionally, requirements for positron emission tomography computed tomography (PET-CT) scans for participants with classical Hodgkin's lymphoma (cHL) as well as Lugano response assessment requirements for cHL were added throughout the protocol.
07 August 2020	• The protocol was amended to include a new dose level (1500 mg) in the dose-escalation portion of the study. The protocol's rationale for dose selection was updated to include the safety information for the added 1500-mg dose level. Protocol language was also updated to reflect the change in the number of subjects that will be enrolled in Phase 1b and the study overall due to the addition of the new dose level. • The protocol was amended to allow for Phase 1b biopsy substudy subjects receiving evixapodlin at a dose level below that which has been deemed to be safe by the study review team (SRT) to receive, at the investigator's discretion, evixapodlin at the highest dose deemed to be safe by the SRT after completing posttreatment biopsy and Cycle 2. • Appendix 5 (Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements) was updated to align with new guidelines for contraception. • Appendix 8 was added in response to the COVID-19 pandemic and possible future pandemics that may impact the study.
02 October 2020	• The protocol was amended to include a new dose level (1000 mg twice daily (BID) in the dose-escalation portion of the study. The safety profile has been manageable at doses up to 1000 mg once daily and no dose-limiting toxicities (DLTs) have been observed. Higher doses are being studied and the protocol's rationale for dose selection was updated to include the safety information for the added 1000 mg twice daily dose level. Protocol language was also updated to reflect the change in the number of participants that will be enrolled in Phase 1b and the study overall due to the addition of the new dose level. • Language in the protocol regarding the administration of evixapodlin was updated as the participants will receive evixapodlin orally once daily in the 400-1500 mg QD cohorts and 1000 mg twice daily in the 1000 mg BID cohort. • The protocol was amended to allow for Phase 1b dose escalation subjects receiving evixapodlin at a dose level below that which has been deemed to be safe by the study review team (SRT) to receive, at the investigator's discretion, evixapodlin at the highest dose deemed to be safe by the SRT after completing 4 cycles of treatment and Cycle 5 Day 1 scans. • Language in the protocol was updated as pharmacodynamic peripheral blood mononuclear cell (PBMC) collection will be required only at select sites in the 1000 mg BID dose escalation cohort.

02 October 2020	• Updates were made to collect intensive pharmacokinetics (PK) samples in all participants in Phase 1b dose cohorts between 400–1500 mg QD. In the 1000 mg BID dose escalation cohort, intensive PK will be collected at select sites in at least 6 participants and a 12-hour time point was added. Predose PK samples will be collected on the indicated days in all participants in Phase 1b who have intensive PK collection (all participants in dose cohorts between 400–1500 mg QD and at least 6 participants in 1000 mg BID dose cohort). Additionally, sparse PK will be collected on the indicated days in all participants in Phase 2 and in those who do not have intensive PK collection in Phase 1b.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This was a planned Phase 1/2 study. However, Phase 2 was not conducted because the study was closed due to sponsor decision prior to opening the dose expansion cohort. Hence, RP2D and any analyses were not performed for Phase 2 (Dose Expansion Phase)

Notes: