

**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 | <ul style="list-style-type: none">• 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 occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 6 (33.33%) 2 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 6 (0.00%) 0 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Injury, poisoning and procedural complications Foot fracture subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Skin abrasion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Nervous system disorders Presyncope subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 6 (33.33%) 2 |
| Ageusia | | | |

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

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

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Infections and infestations | | | |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 6 (0.00%) 0 |
| Postoperative wound infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 6 (16.67%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 6 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 6 (16.67%) 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 occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Nasal congestion subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 2 (50.00%) 1 | 0 / 1 (0.00%) 0 |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Injury, poisoning and procedural complications Foot fracture subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Skin abrasion subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Nervous system disorders Presyncope subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Ageusia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 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 occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Ileus subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Intestinal obstruction subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Hepatobiliary disorders Gallbladder obstruction subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Intertrigo subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Night sweats subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Psoriasis subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 2 (50.00%) 1 | 0 / 1 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Pain in extremity | | | |

| | | | |
|---|---------------------|--------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Infections and infestations | | | |
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Postoperative wound infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 0 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 2 (0.00%) 0 | 0 / 1 (0.00%) 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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.

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| 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) |
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Notes: