



## 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          | v1            |
| This version publication date  | 18 April 2022 |
| First version publication date | 18 April 2022 |

#### 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,<br>GileadClinicalTrials@gilead.com |
| Scientific contact           | Gilead Clinical Study Information Center, Gilead Sciences,<br>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 GS-4224 and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of GS-4224 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                                |
| <b>Arm title</b>             | Cohort 1: GS-4224 400 mg (Phase 1) |

Arm description:

Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).

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

Dosage and administration details:

400 mg administered once daily for approximately 21 weeks

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Cohort 2: GS-4224 700 mg (Phase 1) |
|------------------|------------------------------------|

Arm description:

Participants received GS-4224 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

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

Dosage and administration details:

700 mg administered once daily for approximately 10 weeks

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Cohort 3: GS-4224 1000 mg (Phase 1) |
|------------------|-------------------------------------|

Arm description:

Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                                     |
|--|-------------------------------------|
| Investigational medicinal product name                     | GS-4224                             |
| Investigational medicinal product code                     |                                     |
| Other name   |                                     |
| Pharmaceutical forms                                       | Film-coated tablet                  |
| Routes of administration                                   | Oral use                            |
| Dosage and administration details:                         |                                     |
| 1000 mg administered once daily for approximately 39 weeks |                                     |
| <b>Arm title</b>   | Cohort 4: GS-4224 1500 mg (Phase 1) |

Arm description:

Participants received GS-4224 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).

|  |   |
|--|---|
| Arm type   | Experimental                                |
| Investigational medicinal product name                     | GS-4224                                     |
| Investigational medicinal product code                     |   |
| Other name   |   |
| Pharmaceutical forms                                       | Film-coated tablet                          |
| Routes of administration                                   | Oral use                                    |
| Dosage and administration details:                         |   |
| 1500 mg administered once daily for approximately 19 weeks |   |
| <b>Arm title</b>   | Cohort 1 Substudy: GS-4224 400 mg (Phase 1) |

Arm description:

Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

|   |  |
|---|--|
| Arm type  | Experimental                                 |
| Investigational medicinal product name                    | GS-4224                                      |
| Investigational medicinal product code                    |  |
| Other name  |  |
| Pharmaceutical forms                                      | Film-coated tablet                           |
| Routes of administration                                  | Oral use                                     |
| Dosage and administration details:                        |  |
| 400 mg administered once daily for approximately 39 weeks |  |
| <b>Arm title</b>  | Cohort 3 Substudy: GS-4224 1000 mg (Phase 1) |

Arm description:

Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

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

Dosage and administration details:

1000 mg administered once daily for approximately 10 weeks

| <b>Number of subjects in period 1</b> | Cohort 1: GS-4224<br>400 mg (Phase 1) | Cohort 2: GS-4224<br>700 mg (Phase 1) | Cohort 3: GS-4224<br>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                     | -                                     | -                                     | -                                      |

| <b>Number of subjects in period 1</b> | Cohort 4: GS-4224<br>1500 mg (Phase 1) | Cohort 1 Substudy:<br>GS-4224 400 mg<br>(Phase 1) | Cohort 3 Substudy:<br>GS-4224 1000 mg<br>(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: GS-4224 400 mg (Phase 1)           |
| Reporting group description:<br>Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).  |  |
| Reporting group title  | Cohort 2: GS-4224 700 mg (Phase 1)           |
| Reporting group description:<br>Participants received GS-4224 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).  |  |
| Reporting group title  | Cohort 3: GS-4224 1000 mg (Phase 1)          |
| Reporting group description:<br>Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks). |  |
| Reporting group title  | Cohort 4: GS-4224 1500 mg (Phase 1)          |
| Reporting group description:<br>Participants received GS-4224 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks). |  |
| Reporting group title  | Cohort 1 Substudy: GS-4224 400 mg (Phase 1)  |
| Reporting group description:<br>Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).  |  |
| Reporting group title  | Cohort 3 Substudy: GS-4224 1000 mg (Phase 1) |
| Reporting group description:<br>Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks). |  |

| Reporting group values             | Cohort 1: GS-4224 400 mg (Phase 1) | Cohort 2: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 1000 mg (Phase 1) |
|------------------------------------|------------------------------------|------------------------------------|-------------------------------------|
| Number of subjects                 | 3                                  | 3                                  | 6                                   |
| Age categorical<br>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<br>Units: Subjects                |         |         |        |
| Female   | 1       | 0       | 2      |
| Male   | 2       | 3       | 4      |

| Reporting group values             | Cohort 4: GS-4224 1500 mg (Phase 1) | Cohort 1 Substudy: GS-4224 400 mg (Phase 1) | Cohort 3 Substudy: GS-4224 1000 mg (Phase 1) |
|------------------------------------|-------------------------------------|---|--|
| Number of subjects                 | 3                                   | 2   | 1  |
| Age categorical<br>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      |

|                               |       |  |  |
|-------------------------------|-------|--|--|
| <b>Reporting group values</b> | 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: GS-4224 400 mg (Phase 1)           |
| Reporting group description:<br>Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).   |  |
| Reporting group title   | Cohort 2: GS-4224 700 mg (Phase 1)           |
| Reporting group description:<br>Participants received GS-4224 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).   |  |
| Reporting group title   | Cohort 3: GS-4224 1000 mg (Phase 1)          |
| Reporting group description:<br>Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).  |  |
| Reporting group title   | Cohort 4: GS-4224 1500 mg (Phase 1)          |
| Reporting group description:<br>Participants received GS-4224 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).  |  |
| Reporting group title   | Cohort 1 Substudy: GS-4224 400 mg (Phase 1)  |
| Reporting group description:<br>Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).   |  |
| Reporting group title   | Cohort 3 Substudy: GS-4224 1000 mg (Phase 1) |
| Reporting group description:<br>Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).  |  |
| Subject analysis set title  | Cohort 1: GS-4224 400 mg (Phase 1)           |
| Subject analysis set type   | Safety analysis                              |
| Subject analysis set description:<br>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 <sup>[1]</sup> |
| End point description:<br>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 GS-4224•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:<br>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: GS-4224 400 mg (Phase 1) | Cohort 2: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 1000 mg (Phase 1) | Cohort 4: GS-4224 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: GS-4224 400 mg (Phase 1) | Cohort 3 Substudy: GS-4224 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 GS-4224 During the Dose Escalation Phase

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic (PK) Parameter: AUCtau of GS-4224 During the Dose Escalation Phase <sup>[2]</sup> |
|-----------------|---|

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, 0-24 hours (h) post dose (400-1500 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: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 1000 mg (Phase 1) | Cohort 4: GS-4224 1500 mg (Phase 1) | Cohort 1: GS-4224 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 GS-4224 During the Dose Escalation Phase

|                 |   |
|-----------------|---|
| End point title | PK Parameter: Cmax of GS-4224 During the Dose Escalation Phase <sup>[3]</sup> |
|-----------------|---|

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, 0-24 hours (h) post dose (400-1500 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: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 1000 mg (Phase 1) | Cohort 4: GS-4224 1500 mg (Phase 1) | Cohort 1: GS-4224 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: Ctough of GS-4224 During the Dose Escalation Phase

|                 |   |
|-----------------|---|
| End point title | PK Parameter: Ctough of GS-4224 During the Dose Escalation Phase <sup>[4]</sup> |
|-----------------|---|

End point description:

Ctough 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, 0-24 hours (h) post dose (400-1500 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: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 1000 mg (Phase 1) | Cohort 4: GS-4224 1500 mg (Phase 1) | Cohort 1: GS-4224 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 GS-4224 During the Dose Escalation Phase

|                 |   |
|-----------------|---|
| End point title | PK Parameter: Tmax of GS-4224 During the Dose Escalation Phase <sup>[5]</sup> |
|-----------------|---|

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, 0-24 hours (h) post dose (400-1500 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: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 1000 mg (Phase 1) | Cohort 4: GS-4224 1500 mg (Phase 1) | Cohort 1: GS-4224 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



## 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: GS-4224 400 mg (Phase 1) |
|-----------------------|------------------------------------|

Reporting group description:

Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 21 weeks).

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Cohort 2: GS-4224 700 mg (Phase 1) |
|-----------------------|------------------------------------|

Reporting group description:

Participants received GS-4224 700 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Cohort 3: GS-4224 1000 mg (Phase 1) |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Cohort 4: GS-4224 1500 mg (Phase 1) |
|-----------------------|-------------------------------------|

Reporting group description:

Participants received GS-4224 1500 mg once daily for 21 days of each cycle (observed maximum duration was approximately 19 weeks).

|                       |   |
|-----------------------|---|
| Reporting group title | Cohort 1 Substudy: GS-4224 400 mg (Phase 1) |
|-----------------------|---|

Reporting group description:

Participants received GS-4224 400 mg once daily for 21 days of each cycle (observed maximum duration was approximately 39 weeks).

|                       |  |
|-----------------------|--|
| Reporting group title | Cohort 3 Substudy: GS-4224 1000 mg (Phase 1) |
|-----------------------|--|

Reporting group description:

Participants received GS-4224 1000 mg once daily for 21 days of each cycle (observed maximum duration was approximately 10 weeks).

| Serious adverse events  | Cohort 1: GS-4224 400 mg (Phase 1) | Cohort 2: GS-4224 700 mg (Phase 1) | Cohort 3: GS-4224 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          |

|                                    |                                     |   |  |
|------------------------------------|-------------------------------------|---|--|
| <b>Serious adverse events</b>      | Cohort 4: GS-4224 1500 mg (Phase 1) | Cohort 1 Substudy: GS-4224 400 mg (Phase 1) | Cohort 3 Substudy: GS-4224 1000 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 %

| <b>Non-serious adverse events</b>                                   | Cohort 1: GS-4224<br>400 mg (Phase 1) | Cohort 2: GS-4224<br>700 mg (Phase 1) | Cohort 3: GS-4224<br>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<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 2 / 6 (33.33%)<br>2 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 3 (33.33%)<br>1 | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Injury, poisoning and procedural complications<br>Foot fracture<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Nervous system disorders<br>Presyncope<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 3 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  | 2 / 6 (33.33%)<br>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             |

| <b>Non-serious adverse events</b>                                   | Cohort 4: GS-4224<br>1500 mg (Phase 1) | Cohort 1 Substudy:<br>GS-4224 400 mg<br>(Phase 1) | Cohort 3 Substudy:<br>GS-4224 1000 mg<br>(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<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 2 (50.00%)<br>1 | 0 / 1 (0.00%)<br>0 |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Injury, poisoning and procedural complications<br>Foot fracture<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>2 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Nervous system disorders<br>Presyncope<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Ageusia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>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<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Ileus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Intestinal obstruction<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Hepatobiliary disorders<br>Gallbladder obstruction<br>subjects affected / exposed<br>occurrences (all)            | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Intertrigo<br>subjects affected / exposed<br>occurrences (all)  | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Night sweats<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Psoriasis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 1 / 2 (50.00%)<br>1 | 0 / 1 (0.00%)<br>0 |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Pain in extremity   |                     |                     |                    |

|   |                     |                    |                    |
|---|---------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Infections and infestations   |                     |                    |                    |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Postoperative wound infection<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Metabolism and nutrition disorders  |                     |                    |                    |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Hypercalcaemia<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 3 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 3 (33.33%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 1 (0.00%)<br>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"><li>• The protocol was amended to include updated higher dose GS-4224 tablet strengths (200 mg and 500 mg) and the addition of a new formulation for 100 mg strength tablets.</li><li>• 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.</li><li>• 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 GS-4224. 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.</li></ul>   |
| 07 August 2020  | <ul style="list-style-type: none"><li>• 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.</li><li>• The protocol was amended to allow for Phase 1b biopsy substudy subjects receiving GS-4224 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, GS-4224 at the highest dose deemed to be safe by the SRT after completing posttreatment biopsy and Cycle 2.</li><li>• Appendix 5 (Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements) was updated to align with new guidelines for contraception.</li><li>• Appendix 8 was added in response to the COVID-19 pandemic and possible future pandemics that may impact the study.</li></ul>   |
| 02 October 2020 | <ul style="list-style-type: none"><li>• 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.</li><li>• Language in the protocol regarding the administration of GS-4224 was updated as the participants will receive GS-4224 orally once daily in the 400-1500 mg QD cohorts and 1000 mg twice daily in the 1000 mg BID cohort.</li><li>• The protocol was amended to allow for Phase 1b dose escalation subjects receiving GS-4224 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, GS-4224 at the highest dose deemed to be safe by the SRT after completing 4 cycles of treatment and Cycle 5 Day 1 scans.</li><li>• 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.</li></ul> |

|                 |   |
|-----------------|---|
| 02 October 2020 | <ul style="list-style-type: none"> <li>• 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.</li> </ul> |
|-----------------|---|

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: