



Clinical trial results:

A Phase 1/2 Study of FPA008, an anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-000547-17 |
| Trial protocol | NL FR PL |
| Global end of trial date | 30 December 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 June 2022 |
| First version publication date | 02 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | FPA008-002 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02471716 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Five Prime Therapeutics, Inc. |
| Sponsor organisation address | 111 Oyster Point Boulevard, South San Francisco, CA, United States, 94080 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 December 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 December 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Phase 1: To determine the recommended dose (RD) of cabiralizumab in patients with PVNS/dt-TGCT.

Phase 2: To estimate the objective response rate (ORR) of cabiralizumab in patients with PVNS/dt-TGCT

Protection of trial subjects:

This study was performed in accordance with Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH) and the Declaration of Helsinki (1989) and in compliance with local legal requirements.

Before the start of the study, the study protocol and/or other relevant documents were approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and Regulatory Authorities, in accordance with local legal requirements. The Sponsor, Sponsor's agents, and Investigator ensured that all ethical and legal requirements were met before the first patient was enrolled in the study.

Written informed consent was obtained from each subject before any study procedures were undertaken.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 09 July 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 1 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | United States: 29 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | France: 23 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 35 |

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) | 62 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This was a Phase 1/2 study in adults with pigmented villonodular synovitis (PVNS)/diffuse type-tenosynovial giant cell tumor (dt-TGCT).

Phase 1 was a dose escalation, open-label, safety, tolerability, and pharmacokinetic (PK) study of cabiralizumab.

Phase 2 was a dose expansion, open-label, efficacy study of cabiralizumab.

Pre-assignment

Screening details:

In Phase 1 participants were enrolled sequentially into successive dose cohorts based on assessment of dose-limiting toxicities, overall safety, and tolerability after the last patient enrolled in each cohort completed the first treatment cycle.

In Phase 2, participants were enrolled at the recommended dose established during Phase 1.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg |

Arm description:

Dose escalation cohort dose level 1: 1 mg/kg cabiralizumab intravenously (IV) every 2 weeks for up to 24 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cabiralizumab |
| Investigational medicinal product code | FPA008 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cabiralizumab administered by IV infusion over approximately 30 minutes every 2 weeks.

| | |
|------------------|--|
| Arm title | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg |
|------------------|--|

Arm description:

Dose escalation cohort dose level 2: 2 mg/kg cabiralizumab IV every 2 weeks for up to 24 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cabiralizumab |
| Investigational medicinal product code | FPA008 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cabiralizumab administered by IV infusion over approximately 30 minutes every 2 weeks.

| | |
|------------------|--|
| Arm title | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg |
|------------------|--|

Arm description:

Dose escalation cohort dose level 3: 4 mg/kg cabiralizumab IV every 2 weeks for up to 24 weeks.

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

| | |
|--|---|
| Investigational medicinal product name | Cabiralizumab |
| Investigational medicinal product code | FPA008 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Cabiralizumab administered by IV infusion over approximately 30 minutes every 2 weeks. | |
| Arm title | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |

Arm description:

Dose Expansion Cohort: participants were treated with 4 mg/kg cabiralizumab IV every 2 weeks in 28-day cycles for up to 12 doses.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cabiralizumab |
| Investigational medicinal product code | FPA008 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cabiralizumab administered by IV infusion over approximately 30 minutes every 2 weeks.

| | |
|------------------|---|
| Arm title | Phase 2: Cabiralizumab Dose Expansion Cohort 2B |
|------------------|---|

Arm description:

Dose Expansion Cohort: participants were treated with 4 mg/kg cabiralizumab IV on Cycle 1 Day 1 and Cycle 1 Day 15 then every 4 weeks thereafter for up to 12 months.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cabiralizumab |
| Investigational medicinal product code | FPA008 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cabiralizumab administered by IV infusion over approximately 30 minutes every 4 weeks.

| Number of subjects in period 1 | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg |
|---------------------------------------|--|--|--|
| Started | 3 | 3 | 3 |
| Completed | 3 | 2 | 3 |
| Not completed | 0 | 1 | 0 |
| Study terminated by sponsor | - | - | - |
| Consent withdrawn by subject | - | 1 | - |
| Death | - | - | - |
| Other | - | - | - |
| Lost to follow-up | - | - | - |

| Number of subjects in period 1 | Phase 2: Cabiralizumab Dose Expansion Cohort 2A | Phase 2: Cabiralizumab Dose Expansion Cohort 2B |
|---------------------------------------|---|---|
| Started | 33 | 24 |

| | | |
|------------------------------|----|----|
| Completed | 18 | 8 |
| Not completed | 15 | 16 |
| Study terminated by sponsor | 1 | - |
| Consent withdrawn by subject | 2 | 5 |
| Death | 1 | - |
| Other | 8 | 9 |
| Lost to follow-up | 3 | 2 |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg |
| Reporting group description: | |
| Dose escalation cohort dose level 1: 1 mg/kg cabiralizumab intravenously (IV) every 2 weeks for up to 24 weeks. | |
| Reporting group title | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg |
| Reporting group description: | |
| Dose escalation cohort dose level 2: 2 mg/kg cabiralizumab IV every 2 weeks for up to 24 weeks. | |
| Reporting group title | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg |
| Reporting group description: | |
| Dose escalation cohort dose level 3: 4 mg/kg cabiralizumab IV every 2 weeks for up to 24 weeks. | |
| Reporting group title | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
| Reporting group description: | |
| Dose Expansion Cohort: participants were treated with 4 mg/kg cabiralizumab IV every 2 weeks in 28-day cycles for up to 12 doses. | |
| Reporting group title | Phase 2: Cabiralizumab Dose Expansion Cohort 2B |
| Reporting group description: | |
| Dose Expansion Cohort: participants were treated with 4 mg/kg cabiralizumab IV on Cycle 1 Day 1 and Cycle 1 Day 15 then every 4 weeks thereafter for up to 12 months. | |

| Reporting group values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg |
|----------------------------------|--|--|--|
| Number of subjects | 3 | 3 | 3 |
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 years | 3 | 2 | 3 |
| ≥ 65 years | 0 | 1 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 37.7 | 40.7 | 41.7 |
| standard deviation | ± 11.24 | ± 23.07 | ± 7.51 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | 1 |
| Male | 0 | 0 | 2 |
| Race | | | |
| Units: Subjects | | | |
| American India/Alaska Native | 0 | 0 | 0 |
| Black | 0 | 0 | 0 |
| Native Hawaiian/Pacific Islander | 0 | 0 | 0 |
| White | 3 | 2 | 2 |
| Asian | 0 | 1 | 0 |
| Other | 0 | 0 | 0 |
| Unknown | 0 | 0 | 1 |

| Reporting group values | Phase 2: Cabiralizumab Dose Expansion Cohort 2A | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | Total |
|------------------------|---|---|-------|
| Number of subjects | 33 | 24 | 66 |

| | | | |
|----------------------------------|---------|---------|----|
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 years | 32 | 22 | 62 |
| ≥ 65 years | 1 | 2 | 4 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 38.0 | 44.1 | |
| standard deviation | ± 12.77 | ± 15.32 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 23 | 10 | 40 |
| Male | 10 | 14 | 26 |
| Race | | | |
| Units: Subjects | | | |
| American India/Alaska Native | 0 | 0 | 0 |
| Black | 0 | 2 | 2 |
| Native Hawaiian/Pacific Islander | 0 | 0 | 0 |
| White | 9 | 9 | 25 |
| Asian | 5 | 1 | 7 |
| Other | 19 | 8 | 27 |
| Unknown | 0 | 4 | 5 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg |
| Reporting group description: | |
| Dose escalation cohort dose level 1: 1 mg/kg cabiralizumab intravenously (IV) every 2 weeks for up to 24 weeks. | |
| Reporting group title | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg |
| Reporting group description: | |
| Dose escalation cohort dose level 2: 2 mg/kg cabiralizumab IV every 2 weeks for up to 24 weeks. | |
| Reporting group title | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg |
| Reporting group description: | |
| Dose escalation cohort dose level 3: 4 mg/kg cabiralizumab IV every 2 weeks for up to 24 weeks. | |
| Reporting group title | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
| Reporting group description: | |
| Dose Expansion Cohort: participants were treated with 4 mg/kg cabiralizumab IV every 2 weeks in 28-day cycles for up to 12 doses. | |
| Reporting group title | Phase 2: Cabiralizumab Dose Expansion Cohort 2B |
| Reporting group description: | |
| Dose Expansion Cohort: participants were treated with 4 mg/kg cabiralizumab IV on Cycle 1 Day 1 and Cycle 1 Day 15 then every 4 weeks thereafter for up to 12 months. | |

Primary: Phase 1: Number of Participants with Dose-limiting Toxicities (DLTs)

| | |
|---|--|
| End point title | Phase 1: Number of Participants with Dose-limiting Toxicities (DLTs) ^{[1][2]} |
| End point description: | |
| DLTs are defined as any Grade ≥ 3 (per Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) related adverse event that occur during Cycle 1 of treatment and assessed by the Investigator with concurrence by the Cohort Review Committee (CRC) as related to cabiralizumab with the following exceptions: | |
| <ul style="list-style-type: none">• In the absence of clinical symptoms and other accompanying changes in bilirubin, serum elevations of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $\leq 12 \times$ upper limit of normal (ULN) were not considered a DLT and serum elevations of creatinine kinase (CK) and/or lactate dehydrogenase (LDH) $\leq 15 \times$ ULN were not considered a DLT.• In the absence of clinical symptoms and other accompanying changes in bilirubin, serum elevations of AST and/or ALT $> 12 \times$ ULN and $\leq 20 \times$ ULN that last for ≤ 7 days were not considered a DLT and serum elevations of CK and/or LDH $> 15 \times$ ULN and $\leq 20 \times$ ULN that last for ≤ 7 days were not considered a DLT. | |
| End point type | Primary |
| End point timeframe: | |
| Cycle 1, 28 days | |

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: Statistical analyses were not planned or conducted.

[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: Dose-limiting toxicities (DLTs) were analyzed during Phase 1 only.

| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 3 | |
| Units: participants | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Participants with Confirmed Objective Response

| | |
|-----------------|---|
| End point title | Phase 2: Number of Participants with Confirmed Objective Response ^[3] ^[4] |
|-----------------|---|

End point description:

Objective response was defined as total number of participants with Investigator-assessed confirmed objective responses of either complete response (CR) or partial response (PR) per response evaluation criteria in solid tumors (RECIST) v1.1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 weeks for Phase 2 dose expansion cohort 2A and 52 weeks for Phase 2 dose expansion cohort 2B.

Notes:

[3] - 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: Statistical analyses were not planned or conducted.

[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: Response was analyzed in Phase 2 only.

| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2A | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 ^[5] | 24 ^[6] | | |
| Units: participants | 8 | 8 | | |

Notes:

[5] - Efficacy-Evaluable Population

[6] - Efficacy-Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) Following First Dose of Cabiralizumab

| | |
|-----------------|---|
| End point title | Maximum Observed Serum Concentration (Cmax) Following First Dose of Cabiralizumab |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 predose, 15 minutes after end of infusion, and 4, 24, and 168 hours after end of infusion.

| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
|---|--|--|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 ^[7] | 3 ^[8] | 3 ^[9] | 30 ^[10] |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 22.494 (± 14.289) | 52.056 (± 22.036) | 91.218 (± 15.005) | 91.801 (± 24.803) |

Notes:

[7] - PK-Evaluable Population

[8] - PK-Evaluable Population

[9] - PK-Evaluable Population

[10] - PK-Evaluable Population

| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | | |
|---|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 ^[11] | | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 86.995 (± 12.553) | | | |

Notes:

[11] - PK-Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-time Curve During the Dosing Interval (AUC_{0-tau}) After First of Cabiralizumab

| | |
|-----------------|---|
| End point title | Area Under the Serum Concentration-time Curve During the Dosing Interval (AUC _{0-tau}) After First of Cabiralizumab |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 predose, 15 minutes after the end of infusion, and 4, 24, and 168 hours after the end of infusion.

| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
|---|--|--|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 28 |
| Units: µg*day/mL | | | | |
| geometric mean (geometric coefficient of variation) | 102 (± 10.2) | 283 (± 26.3) | 593 (± 31.3) | 660 (± 17.7) |

| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | | |
|---|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: µg*day/mL | | | | |
| geometric mean (geometric coefficient of variation) | 593 (± 12.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) Following First Dose of Cabiralizumab

| | |
|-----------------|---|
| End point title | Minimum Observed Serum Concentration (Cmin) Following First Dose of Cabiralizumab |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 at 15 minutes after end of infusion, and 4, 24, and 168 hours after end of infusion.

| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
|---|--|--|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 30 |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 2.18 (± 117) | 7.26 (± 41.8) | 21.2 (± 59.2) | 23.9 (± 38.3) |

| | | | | |
|---|---|--|--|--|
| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | 22.6 (± 28.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

| | |
|-----------------|--|
| End point title | Number of Participants with Adverse Events |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of study drug up to 90 days after last dose; the median (min, max) duration of treatment in Phase 1 was 158 (15, 225) days and in Phase 2 was 127 (1, 365) days.

| | | | | |
|-----------------------------|--|--|--|---|
| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 33 |
| Units: participants | 3 | 3 | 3 | 33 |

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: participants | 24 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinical Laboratory Abnormalities

| | |
|-----------------|---|
| End point title | Number of Participants with Clinical Laboratory Abnormalities |
|-----------------|---|

End point description:

The number of participants with a clinical laboratory result that was outside the normal range at some time point during the study.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

52 weeks

| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
|-----------------------------|--|--|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 33 |
| Units: participants | 3 | 3 | 3 | 33 |

| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: participants | 24 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Electrocardiogram Abnormalities

| | |
|-----------------|---|
| End point title | Number of Participants with Electrocardiogram Abnormalities |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

ECG was performed post-dose on Day 15 for all cycles, and at the 30 days End of Treatment Follow-up Visit.

| End point values | Phase 1: Cabiralizumab Dose Escalation 1 mg/kg | Phase 1: Cabiralizumab Dose Escalation 2 mg/kg | Phase 1: Cabiralizumab Dose Escalation 4 mg/kg | Phase 2: Cabiralizumab Dose Expansion Cohort 2A |
|-----------------------------|--|--|--|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 3 | 33 |
| Units: participants | 0 | 0 | 0 | 0 |

| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 24 | | | |
| Units: participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response

| | |
|-----------------|---|
| End point title | Phase 2: Duration of Response ^[12] |
|-----------------|---|

End point description:

Duration of response (DOR) was calculated as the time from the first documentation of confirmed objective response (CR or PR) per RECIST v 1.1 to the first objective documentation of progressive disease (PD) or to death due to any cause in the absence of documented PD.

The Kaplan-Meier method was used to estimate DOR, and 2-sided 95% CI calculated based on the Brookmeyer and Crowley method. "99999" indicates values that could not be estimated.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 14 months

Notes:

[12] - 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: Duration of response was analyzed for Phase 2 only.

| End point values | Phase 2: Cabiralizumab Dose Expansion Cohort 2A | Phase 2: Cabiralizumab Dose Expansion Cohort 2B | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[13] | 8 ^[14] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.4 (3.2 to 99999) | 99999 (11.5 to 99999) | | |

Notes:

[13] - Confirmed responders

[14] - Confirmed responders

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 90 days after last dose; the median (min, max) duration of treatment in Phase 1 was 158 (15, 225) days and in Phase 2 was 127 (1, 365) days.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Phase 1 2 mg/kg |
|-----------------------|-----------------|

| | |
|--------------------------------|--|
| Reporting group description: - | |
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| Reporting group title | Phase 1 1 mg/kg |
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| Reporting group description: - | |
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| Reporting group title | Phase 2 Cohort 2A |
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| Reporting group description: - | |
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| Reporting group title | Phase 2 Cohort 2B |
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| Reporting group description: - | |
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| Reporting group title | Phase 1 4 mg/kg |
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| Reporting group description: - | |
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| Serious adverse events | Phase 1 2 mg/kg | Phase 1 1 mg/kg | Phase 2 Cohort 2A |
|---|-----------------|-----------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 8 / 33 (24.24%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Sarcoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Congenital, familial and genetic disorders | | | |
| Twin reversed arterial perfusion sequence malformation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Cardiac disorders | | | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Colitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Diverticulum | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 7 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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|---|---------------|---------------|----------------|
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis exfoliative | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Skin atrophy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (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 |
| Viral infection | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Phase 2 Cohort 2B | Phase 1 4 mg/kg | |
|---|-------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 24 (25.00%) | 2 / 3 (66.67%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Sarcoma | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Twin reversed arterial perfusion sequence malformation | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|---------------|--|
| Diverticulum | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis exfoliative | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin atrophy | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Endocarditis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 3 (33.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Phase 1 2 mg/kg | Phase 1 1 mg/kg | Phase 2 Cohort 2A |
|---|-----------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 33 / 33 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 3 |
| General disorders and administration site conditions | | | |

| | | | |
|--|----------------|----------------|------------------|
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 7 / 33 (21.21%) |
| occurrences (all) | 0 | 0 | 7 |
| Face oedema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 22 / 33 (66.67%) |
| occurrences (all) | 1 | 0 | 33 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 11 / 33 (33.33%) |
| occurrences (all) | 1 | 2 | 17 |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 1 | 1 |
| Oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 19 / 33 (57.58%) |
| occurrences (all) | 1 | 4 | 36 |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 5 / 33 (15.15%) |
| occurrences (all) | 0 | 0 | 7 |
| Reproductive system and breast disorders | | | |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Pelvic pain | | | |

| | | | |
|--|--------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 33 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 0 | 3 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 2 | 0 | 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 0 | 5 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 6 / 33 (18.18%) |
| occurrences (all) | 0 | 0 | 9 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 10 / 33 (30.30%) |
| occurrences (all) | 0 | 0 | 14 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 3 |
| Blood cholesterol increased | | | |

| | | | |
|--|----------------|----------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 0 | 4 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 21 / 33 (63.64%) |
| occurrences (all) | 1 | 0 | 49 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 0 | 5 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 1 | 0 | 3 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 7 / 33 (21.21%) |
| occurrences (all) | 0 | 1 | 11 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 3 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 0 | 3 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 5 / 33 (15.15%) |
| occurrences (all) | 0 | 0 | 5 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 0 | 5 |
| Eye disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|------------------|
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Conjunctival oedema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 3 |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 6 / 33 (18.18%) |
| occurrences (all) | 0 | 0 | 7 |
| Eyelid rash | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 0 | 4 |
| Periorbital oedema | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 20 / 33 (60.61%) |
| occurrences (all) | 2 | 4 | 42 |
| Photophobia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Scleritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 3 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 1 | 0 | 5 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 0 | 6 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 1 | 4 |
| Lip oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 3 (66.67%) | 5 / 33 (15.15%) |
| occurrences (all) | 0 | 2 | 5 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 1 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 3 (66.67%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 0 | 7 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 1 | 0 | 2 |

| | | | |
|-----------------------------|----------------|----------------|------------------|
| Erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 5 / 33 (15.15%) |
| occurrences (all) | 0 | 0 | 8 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 17 / 33 (51.52%) |
| occurrences (all) | 1 | 0 | 41 |
| Pruritus generalised | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 5 / 33 (15.15%) |
| occurrences (all) | 1 | 1 | 8 |
| Rash | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 11 / 33 (33.33%) |
| occurrences (all) | 1 | 2 | 14 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 3 / 33 (9.09%) |
| occurrences (all) | 0 | 0 | 7 |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 8 / 33 (24.24%) |
| occurrences (all) | 1 | 0 | 16 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 5 / 33 (15.15%) |
| occurrences (all) | 0 | 6 | 7 |
| Skin atrophy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 4 / 33 (12.12%) |
| occurrences (all) | 0 | 0 | 5 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 33 (6.06%) |
| occurrences (all) | 0 | 0 | 2 |

| | | | |
|---|--------------------|--------------------|------------------------|
| Urticaria subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 3 / 33 (9.09%) 4 |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 3 / 33 (9.09%) 5 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 10 / 33 (30.30%) 17 |
| Arthritis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Joint swelling subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 33 (3.03%) 1 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 3 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 4 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 3 |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Oral candidiasis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |

| | | | |
|---|---------------------|--------------------|-----------------------|
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 7 / 33 (21.21%) 11 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 2 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 4 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 33 (3.03%) 1 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 33 (6.06%) 3 |
| Increased appetite subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 1 / 33 (3.03%) 1 |

| Non-serious adverse events | Phase 2 Cohort 2B | Phase 1 4 mg/kg | |
|--|----------------------|---------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 24 / 24 (100.00%) | 3 / 3 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour pain subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 3 (33.33%) 1 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 3 / 24 (12.50%) 5 | 0 / 3 (0.00%) 0 | |

| | | | |
|--|------------------|-----------------|--|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | 0 / 3 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Face oedema | | | |
| subjects affected / exposed | 12 / 24 (50.00%) | 2 / 3 (66.67%) | |
| occurrences (all) | 21 | 3 | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 24 (33.33%) | 3 / 3 (100.00%) | |
| occurrences (all) | 10 | 6 | |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 24 (33.33%) | 2 / 3 (66.67%) | |
| occurrences (all) | 13 | 4 | |
| Pain | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pelvic pain | | | |

| | | | |
|--|---------------------|--------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 | 0 / 3 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 3 (66.67%) | |
| occurrences (all) | 0 | 3 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 2 / 3 (66.67%) | |
| occurrences (all) | 3 | 6 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood cholesterol increased | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 16 / 24 (66.67%) | 3 / 3 (100.00%) | |
| occurrences (all) | 41 | 10 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Headache | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye disorders | | | |

| | | | |
|-----------------------------|------------------|----------------|--|
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Conjunctival oedema | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 1 | |
| Eyelid oedema | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | 1 / 3 (33.33%) | |
| occurrences (all) | 9 | 1 | |
| Eyelid rash | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | 1 / 3 (33.33%) | |
| occurrences (all) | 6 | 1 | |
| Periorbital oedema | | | |
| subjects affected / exposed | 13 / 24 (54.17%) | 2 / 3 (66.67%) | |
| occurrences (all) | 27 | 6 | |
| Photophobia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Scleritis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | 0 / 3 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 1 / 3 (33.33%) | |
| occurrences (all) | 1 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip oedema | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 1 / 3 (33.33%) | |
| occurrences (all) | 3 | 2 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 3 (33.33%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 3 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 4 / 24 (16.67%) | 2 / 3 (66.67%) | |
| occurrences (all) | 4 | 2 | |

| | | |
|-----------------------------|------------------|----------------|
| Erythema | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pruritus | | |
| subjects affected / exposed | 13 / 24 (54.17%) | 0 / 3 (0.00%) |
| occurrences (all) | 17 | 0 |
| Pruritus generalised | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 |
| Rash | | |
| subjects affected / exposed | 10 / 24 (41.67%) | 0 / 3 (0.00%) |
| occurrences (all) | 18 | 0 |
| Rash erythematous | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rash generalised | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 0 |
| Rash maculo-papular | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 |
| Rash pruritic | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 |
| Skin atrophy | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 |
| Skin disorder | | |
| subjects affected / exposed | 5 / 24 (20.83%) | 2 / 3 (66.67%) |
| occurrences (all) | 6 | 4 |
| Skin exfoliation | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 0 |
| Skin lesion | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|--|---|--|
| Urticaria subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 3 (33.33%) 1 | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 3 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) | 3 / 24 (12.50%) 3 1 / 24 (4.17%) 1 2 / 24 (8.33%) 3 1 / 24 (4.17%) 1 0 / 24 (0.00%) 0 3 / 24 (12.50%) 4 | 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 | |
| Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) | 3 / 24 (12.50%) 3 0 / 24 (0.00%) 0 1 / 24 (4.17%) 1 | 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 | |

| | | | |
|---|---------------------|---------------------|--|
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 3 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 3 (0.00%) 0 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 3 (33.33%) 1 | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Increased appetite subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 3 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 17 April 2015 | <p>Revisions included:</p> <ul style="list-style-type: none">•Eligibility criterion revised to clarify how patients would be characterized as having 'inoperable tumors' or 'potentially resectable tumors' that would result in unacceptable functional loss; determination by a qualified surgeon or multi-disciplinary tumor board to be documented in the CRF at screening.•Added requirement that patients in Phase 1 who developed a DLT during DLT assessment period be discontinued from study treatment. Patients with a DLT after Cycle 1 could continue on study treatment with appropriate dose modification, safety monitoring, and follow-up.•Disallowed intra-patient dose escalation.•Clarified that patients could re-escalate the dose following resolution of an AE, but recurrence of that AE would result in permanent dose reduction.•Clarified that patients who were no longer experiencing clinical benefit must be taken off study treatment.•Removal of drug holidays of 3 months to have planned Treatment Period of 6 cycles only.•To evaluate the duration of FPA008 effect after discontinuation of the treatment, a follow-Up Visit was added for patients who had not progressed at Treatment Completion/Early Termination and agreed to continue participation in the study.•The formatting for ALT, AST, and CPK elevation was revised to clarify that the rules for dose modification in Table 3 were not intended to address ALT, AST, and CK.•The protocol was revised to require a dose reduction by 25% for Grade 3 AEs following recovery to baseline or Grade 1 with the intent of enhancing the safety margin.•Addition of testing for anti-nuclear antibodies at Screening and Treatment Completion/Early Termination Visits to address FDA reviewer comments.•PK parameters of AUC_{0-last}, observed C_{max}, observed, C_{min} (trough concentration) CL, and V_{ss} were changed to AUC, C_{max}, C_{min}, CL V_{ss} to generalize the PK parameter estimation.•Immunohistochemistry (IHC) testing for CD163, T cell markers, and Ki67 removed for consistency. |
| 29 June 2015 | <p>Revisions included the following:</p> <ul style="list-style-type: none">• Retinal findings from the secondary endpoints were removed as it was not a secondary endpoint for this study.• Administrative changes for consistency throughout protocol.• Revision of End-of-Treatment Follow-Up Period for all patients, to follow all patients for at least 90 days following the last dose to assess safety while the antibody was cleared from the body.• Number of study centers updated to include an additional study site.• Addition of 'prothrombin time' and clarified reflex testing for CPK isoenzyme if CPK was elevated for clarification of the coagulation and clinical chemistry tests. |

| | |
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| 09 June 2016 | <p>Revisions included the following:</p> <ul style="list-style-type: none"> • Included latest available safety and pharmacology data from studies with FPA008. • Added risk/benefit language regarding elevation of serum enzymes. • Added "selected serum markers" that could have relevance in PVNS to exploratory PD evaluation. • Added Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Numerical Pain Rating Scale (NPRS) as additional measurements of functional outcome. • Added language to allow exploration of alternative dose levels beyond those defined in the protocol after the RD was declared. • Added language to allow modification of RD in Phase 2. • Added Re-treatment Cohort to allow for collection and further exploration of safety, efficacy, PK, and PD in patients who had previously received treatment and completed the 90 day EOT Follow-Up Period. • Updated the eligibility criteria to allow re-treatment of patients who had received FPA008 at lower doses than the RD and to exclude patients with metastatic disease. • Added assessment of synovium by in situ hybridization (ISH) to evaluate samples for the presence of CSF1, CSF1R, and CD68 (macrophage marker). • Added PET scans as an evaluation procedure to provide further information on clinical assessment of disease. • Updated study schema to reflect addition of re-treatment cohort. • Added language for the modification of DLT criteria so as to provide background and rationale related to the elevation of AST, ALT, CK, and LDH. • Updated the number of study centers participating in the study to 11. • Updated dose modification guidelines in the event of ALT, AST, CPK and LDH elevations. • Removed language regarding timing of assessment of health outcomes. • Added language regarding removal of patients who become pregnant and timing of ECOG evaluation. • Added window for collection of vital signs. • Updated language regarding analysis of data. • Updated approximate enrollment numbers for Phase 2. • Updated 95% CI boundaries. |
| 24 August 2016 | <p>Revisions included the following:</p> <ul style="list-style-type: none"> • Protocol updated to include Baseline, Cycle Day 15 patient reported outcomes (PROs) and change in PRO timing to prior to infusion (not after) for typo correction and to align with schedule of assessments. • Additional PET scan at Cycle 3 Day 1 (\pm 7days) for subgroup of 10 patients who underwent PET scan to account for the fact that change in SUV by PET might be observed earlier than changes in tumor volume by MRI. • Dose modification criterion for AST, ALT, Total Bilirubin level updated to allow patients who had moderate elevation of liver test abnormalities which resolved within 28 days to resume dosing of FPA008 at either full dose (4 mg) or one dose level lower (2 mg) after discussion with medical monitor. • Dose modification criterion for CPK and LDH updated to allow patients who had moderate elevation of CPK abnormalities which resolved within 28 days to resume dosing of FPA008 at either full dose (4 mg) or one dose level lower (2 mg) after discussion with medical monitor. • Protocol was updated to remove PRO and clinical outcomes of EQ-5D-5L, Numeric Pain Rating Scale, and Western Ontario McMasters University Osteoarthritis Index. Protocol was updated to add the Brief Pain Inventory and a Joint Stiffness Numeric Rating Scale as the chosen PROs were more specific to PVNS and/or were less burdensome to patients. • Minor updates for clarifications and for consistency throughout the protocol. |

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| 01 September 2017 | <p>Revisions included:</p> <ul style="list-style-type: none"> • FPA008 replaced with cabiralizumab throughout and product description updated. • Included information regarding serum enzyme elevation seen across cabiralizumab studies. • Addition of study objective to determine the change in analgesic medication use while receiving cabiralizumab. • Clarified that the primary endpoint for Phase 2 was Investigator-assessed, not centrally reviewed. • Exploratory endpoints updated to include ORR by tumor volume score, add language indicating that Ogilvie-Harris was only to be assessed for patients in Cohort 2A, add EQ-5D-5L, Global Impression Scales, PVNS-SSAF, PROMISE_PF, and range of motion measurement. • Phase 2 was updated to include Cohort 2B with 4-week dosing regimen. • Re-treatment Cohort was deleted as patients were to be included as part of the original Phase 2, not as a separate cohort. • Addition of language stating AE and SAE to be collected through 90 days post-treatment or when another PNVS treatment was initiated. • Addition of Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale, and the timing of these assessment for patients in Cohort 2A. Clarified that PET were no longer required for patients on study as the number of patients required with PET scan had been met • Study schema separated into 2 phases and Phase 2 schema updated to include Cohort 2B. • Updated total number of patients to account for Cohort 2B. • Two new inclusion criteria added to reflect the addition of evaluation of pain measurement. • Exclusion criteria updated to allow prior antibody-treated and prior small molecule-treated patients with an appropriate washout; to allow consideration for other ingredient to which patients were intolerable; to allow to allow additional options for TB testing; to add CPK exclusion, add anti-nuclear antibody (ANA) exclusion and exclude patients with autoimmune disease. • Dose modification criteria updated. • Tumor response parameters were updated. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported