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 terminiated 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 terminiated 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: • In the absence of clinical symptoms and other accompanying changes in bilirubin, serum elevations of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 12 x upper limit of normal (ULN) were not considered a DLT and serum elevations of creatinine kinase (CK) and/or lactate dehydrogenase (LDH) ≤ 15 x 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 x ULN and ≤ 20 x ULN that last for ≤ 7 days were not considered a DLT and serum elevations of CK and/or LDH > 15 x ULN and ≤ 20 x 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 (AUC0-tau) After First of Cabiralizumab

End point title	Area Under the Serum Concentration-time Curve During the Dosing Interval (AUC0-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 RECUST 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: -	
Reporting group title	Phase 1 1 mg/kg
Reporting group description: -	
Reporting group title	Phase 2 Cohort 2A
Reporting group description: -	
Reporting group title	Phase 2 Cohort 2B
Reporting group description: -	
Reporting group title	Phase 1 4 mg/kg
Reporting group description: -	

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

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

Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Hypercholesterolaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	7 / 33 (21.21%)
occurrences (all)	0	0	11
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	4
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	3
Increased appetite			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 33 (3.03%)
occurrences (all)	1	0	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	0 / 24 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 24 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	5	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	2 / 24 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	2	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	0 / 24 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 24 (4.17%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Arthritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	2 / 24 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Muscle spasms			
subjects affected / exposed	1 / 24 (4.17%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	3 / 24 (12.50%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	3 / 24 (12.50%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Ear infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2015	Revisions included: •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 AUC0-last, observed Cmax, observed, Cmin (trough concentration) CL, and Vss were changed to AUC, Cmax, Cmin, CL Vss to generalize the PK parameter estimation. • Immunohistochemistry (IHC) testing for CD163, T cell markers, and Ki67 removed for consistency.
29 June 2015	Revisions included the following: • 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.

09 June 2016	Revisions included the following: • 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	Revisions included the following: • 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 (± 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.

01 September 2017	Revisions included: • 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported