



Clinical trial results:

Phase II randomized trial of MEK inhibitor MSC1936369B or placebo combined with gemcitabine in metastatic pancreas cancer subjects.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2009-011992-61
Trial protocol	ES BE FR DE GB
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	EMR200066_003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01016483
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250,, Darmstadt, Germany, 64293
Public contact	Merck KGaA, Communication Centre Merck KGaA, Merck Serono, +49 6151725200, service@merckgroup.com
Scientific contact	Merck KGaA, Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2013
Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of MSC1936369B (pimasertib) when combined with gemcitabine in subjects with metastatic pancreatic adenocarcinoma for each of the 2 treatment regimens.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Serbia: 24
Worldwide total number of subjects	141
EEA total number of subjects	96

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)	88
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Nov 2009/Jul 2013. Clinical data cut off: Dec 2013, Study completion date: April 2015

Pre-assignment

Screening details:

Safety Run-In Part: Total of 68 subjects were enrolled out of which 53 subject were treated (27 Subject in Regimen 1 and 26 Subject in Regimen 2).

Phase II: Total 104 subjects were screened. 88 subjects were randomized: 44 subjects each in Arm 1 and Arm 2 respectively.

Period 1

Period 1 title	Safety Run-in Part
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-in Part: Regimen 1

Arm description:

Subjects received pimasertib capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Arm type	Experimental
Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pimasertib was administered as capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Arm title	Safety Run-in Part: Regimen 2
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Arm description:

Subjects received pimasertib capsule orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle and gemcitabine 1000 mg/m² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Arm type	Experimental
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Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pimasertib capsule was administered orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as 1000 mg/m² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Arm title	Part II: Arm 1
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Arm description:

Subjects received gemcitabine 1000 mg/m² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen. Subjects with disease progression in Arm 1 were allowed crossover to receive pimasertib capsule orally 60 mg bid - continuous regimen.

Arm type	Active comparator
Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pimasertib capsule was administered orally twice daily (bid) doses of 60 - continuous regimen.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen.

Arm title	Part II: Arm 2
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Arm description:

Subjects received gemcitabine 1000 mg/m² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and pimasertib capsule orally 60 mg bid - continuous regimen.

Arm type	Active comparator
Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pimasertib capsule was administered orally twice daily (bid) doses of 60 mg - continuous regimen.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as 1000 mg/m² IV infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.

Number of subjects in period 1	Safety Run-in Part: Regimen 1	Safety Run-in Part: Regimen 2	Part II: Arm 1
Started	27	26	44
Completed	27	26	44

Number of subjects in period 1	Part II: Arm 2
Started	44
Completed	44

Period 2

Period 2 title	Phase II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-in Part: Regimen 1

Arm description:

Subjects received pimasertib capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Arm type	Experimental
Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pimasertib was administered as capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Gemcitabine was administered as 1000 milligram per square meter (mg/m ²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Arm title	Safety Run-in Part: Regimen 2
Arm description:	
Subjects received pimasertib capsule orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Arm type	Experimental
Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Pimasertib was administered as capsule orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle and gemcitabine 1000 mg/m ² .	
Arm title	Part II: Arm 1
Arm description:	
Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen. Subjects with disease progression in Arm 1 were allowed crossover to receive pimasertib capsule orally 60 mg bid - continuous regimen.	
Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Gemcitabine was administered as 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received matching placebo as Gemcitabine orally as continuous regimen.	
Arm title	Part II: Arm 2
Arm description:	
Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and pimasertib capsule orally 60 mg bid - continuous regimen.	
Arm type	Experimental

Investigational medicinal product name	Pimasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pimasertib capsule was administered orally twice daily (bid) doses of 60 mg - continuous regimen.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered as 1000 mg/m² IV infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.

Number of subjects in period 2	Safety Run-in Part: Regimen 1	Safety Run-in Part: Regimen 2	Part II: Arm 1
Started	27	26	44
Completed	27	26	44

Number of subjects in period 2	Part II: Arm 2
Started	44
Completed	44

Baseline characteristics

Reporting groups

Reporting group title	Safety Run-in Part: Regimen 1
Reporting group description: Subjects received pimasertib capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m ²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Reporting group title	Safety Run-in Part: Regimen 2
Reporting group description: Subjects received pimasertib capsule orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Reporting group title	Part II: Arm 1
Reporting group description: Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen. Subjects with disease progression in Arm 1 were allowed crossover to receive pimasertib capsule orally 60 mg bid - continuous regimen.	
Reporting group title	Part II: Arm 2
Reporting group description: Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and pimasertib capsule orally 60 mg bid - continuous regimen.	

Reporting group values	Safety Run-in Part: Regimen 1	Safety Run-in Part: Regimen 2	Part II: Arm 1
Number of subjects	27	26	44
Age categorical Units: Subjects			
Between 18 and 65 years	16	19	25
>=65 years	11	7	19
Gender, Male/Female Units: subjects			
Female	9	8	22
Male	18	18	22

Reporting group values	Part II: Arm 2	Total	
Number of subjects	44	141	
Age categorical Units: Subjects			
Between 18 and 65 years	28	88	
>=65 years	16	53	
Gender, Male/Female Units: subjects			
Female	17	56	
Male	27	85	

End points

End points reporting groups

Reporting group title	Safety Run-in Part: Regimen 1
Reporting group description: Subjects received pimasertib capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m ²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Reporting group title	Safety Run-in Part: Regimen 2
Reporting group description: Subjects received pimasertib capsule orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Reporting group title	Part II: Arm 1
Reporting group description: Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen. Subjects with disease progression in Arm 1 were allowed crossover to receive pimasertib capsule orally 60 mg bid - continuous regimen.	
Reporting group title	Part II: Arm 2
Reporting group description: Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and pimasertib capsule orally 60 mg bid - continuous regimen.	
Reporting group title	Safety Run-in Part: Regimen 1
Reporting group description: Subjects received pimasertib capsule orally once daily (qd) doses of 15, 30, 45, 68, 90, and 120 milligram (mg) on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m ²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Reporting group title	Safety Run-in Part: Regimen 2
Reporting group description: Subjects received pimasertib capsule orally twice daily (bid) doses of 60 and 75 mg continuously for a 28-day cycle and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Reporting group title	Part II: Arm 1
Reporting group description: Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen. Subjects with disease progression in Arm 1 were allowed crossover to receive pimasertib capsule orally 60 mg bid - continuous regimen.	
Reporting group title	Part II: Arm 2
Reporting group description: Subjects received gemcitabine 1000 mg/m ² IV infusion on for 30 minutes on Day 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and pimasertib capsule orally 60 mg bid - continuous regimen.	
Subject analysis set title	Regimen 1: 15 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received pimasertib capsule orally once daily (qd) doses of 15, mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m ²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Subject analysis set title	Regimen 1: 30 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 30, mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 45 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 45, mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 68 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 68, mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 90 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 90 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 120 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 120 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 15 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 15 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 68 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib orally once daily (qd) 5-days-on / 2-days-off, continuously (Days 1 to 5, 8 to 12, 15 to 19, 22 to 26, and so on) dose of 68 mg and gemcitabine 1000 milligram per square meter (mg/m²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.

Subject analysis set title	Regimen 1: 90 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib orally once daily (qd) 5-days-on / 2-days-off, continuously (Days 1 to 5, 8 to 12, 15 to 19, 22 to 26, and so on) dose of 90 mg and gemcitabine 1000 milligram per square meter (mg/m²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.

Subject analysis set title	Regimen 1: 120 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received pimasertib orally once daily (qd) 5-days-on / 2-days-off, continuously (Days 1 to 5, 8 to 12, 15 to 19, 22 to 26, and so on) dose of 120 mg and gemcitabine 1000 milligram per square meter

(mg/m²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.

Subject analysis set title	Regimen 1: 30 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 30 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 45 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 45 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 68 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 68 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 15 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 15 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 120 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 120 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 15 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 15 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 30 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 30 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 45 mg
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Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib capsule orally once daily (qd) doses of 45 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).

Subject analysis set title	Regimen 1: 120 mg
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Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received pimasertib capsule orally once daily (qd) doses of 120 mg on Day 1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26 and gemcitabine 1000 milligram per square meter (mg/m ²) intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (1 Cycle = 8 weeks).	
Subject analysis set title	Regimen 2: 60 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject received pimasertib capsule orally twice daily (bid) continuously for a 28-day cycle (60 mg bid - continuous regimen) and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks).	
Subject analysis set title	Regimen 2: 75 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject received pimasertib capsule orally twice daily (bid) continuously for a 28-day cycle (75 mg bid - continuous regimen) and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks).	
Subject analysis set title	Regimen 1: 75 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject received pimasertib capsule orally twice daily (bid) continuously for a 28-day cycle (75 mg bid - continuous regimen) and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks).	
Subject analysis set title	Regimen 2: 60 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received pimasertib orally twice daily (bid) continuously without a break for a 28-day cycle (60 mg bid - continuous regimen) and gemcitabine 1000 milligram per square meter (mg/m ²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.	
Subject analysis set title	Regimen 2: 75 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received pimasertib orally twice daily (bid) continuously without a break for a 28-day cycle (75 mg bid - continuous regimen) and gemcitabine 1000 milligram per square meter (mg/m ²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.	
Subject analysis set title	Regimen 2: 60 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject received pimasertib capsule orally twice daily (bid) continuously for a 28-day cycle (60 mg bid - continuous regimen) and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks).	
Subject analysis set title	Regimen 2: 75 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject received pimasertib capsule orally twice daily (bid) continuously for a 28-day cycle (75 mg bid - continuous regimen) and gemcitabine 1000 mg/m ² intravenous (IV) infusion for 30 minutes on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks).	
Subject analysis set title	Regimen 2: 60 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received pimasertib orally twice daily (bid) continuously without a break for a 28-day cycle (60 mg bid - continuous regimen) and gemcitabine 1000 milligram per square meter (mg/m ²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.	
Subject analysis set title	Regimen 2: 75 mg

Subject analysis set type	Full analysis
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Subject analysis set description:

Subjects received pimasertib orally twice daily (bid) continuously without a break for a 28-day cycle (75 mg bid - continuous regimen) and gemcitabine 1000 milligram per square meter (mg/m²) 30 minutes intravenous (IV) infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1 = 8 weeks) then on Days 1, 8, and 15 of a 28-day cycle.

Primary: Safety Run-In Part: Number of Subjects With Dose Limiting Toxicities (DLTs)

End point title	Safety Run-In Part: Number of Subjects With Dose Limiting Toxicities (DLTs) ^{[1][2]}
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End point description:

DLT using NCI- CTCAE v3.0, defined as toxicities at any dose level, judged to be possibly related to trial medication by Investigator/ Sponsor relevant for combination treatment: Grade 3/more non-hematological toxicity excluding: Subjects with liver involvement: Grade 4 asymptomatic increases liver function tests (LFT) or without liver involvement: Grade 3 asymptomatic increases LFT reversible within 7 days. Grade 3 vomiting encountered despite adequate therapy. Grade 3 diarrhoea encountered despite anti diarrhoea therapy. Grade 4 neutropenia >5 days duration/febrile neutropenia lasting for more than 1 day. Grade 4 thrombocytopenia >1 day/Grade 3 with bleeding. Grade 4 anaemia: treatment delay >2 weeks due to drug-related adverse effects. DLT population: all subjects of safety run-in part received any dose of pimasertib: least 18 out of 20/25 of 28 planned days on pimasertib & least 3 gemcitabine weekly IV during first 28 days of treatment: experienced DLT during 28 first days of treatment.

End point type	Primary
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End point timeframe:

Day 1, 2, 8, 15, 22, 29 of Cycle 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistics were performed for this endpoint, only descriptive statistics was reported for this endpoint.

[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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Safety Run-in Part: Regimen 1	Safety Run-in Part: Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: subjects				
number (not applicable)	0	3		

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: Progression-Free Survival (PFS) time

End point title	Phase II: Progression-Free Survival (PFS) time ^{[3][4]}
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End point description:

PFS: Defined as time from randomization to first documentation of objective tumor progression (Complete Response (CR): Disappearance of all target lesions, Partial Response (PR): At least 30% decrease in sum of the longest diameter of target lesions, taking as reference sum of longest diameter at baseline, Progressive Disease (PD): At least 20% increase in sum of longest diameter of target lesions, taking as reference smallest sum of longest diameter recorded since treatment started, or appearance of 1 or more new lesions and SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of longest diameter since treatment started)/to death due to any cause, whichever occurred first. PFS calculated as (Months) = Date of first

PD or death or censoring date minus date of randomization +1) divided by 30.4375. ITT analysis set included all subjects who had been randomized for the phase II part, as per the IVRS

End point type	Primary
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End point timeframe:

From the time of randomization to every 8 weeks up to end of treatment (EOT) (6 years)

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: No inferential statistics were performed for this endpoint, only descriptive statistics was reported for this endpoint.

[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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: months				
median (confidence interval 95%)	2.83 (1.77 to 3.88)	3.75 (2.63 to 5.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Permanent Treatment Discontinuation

End point title	Safety Run-In Part: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Permanent Treatment Discontinuation ^[5]
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subjects who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. All AEs (serious and non-serious) except AEs recorded with an onset date prior to the first day of drug administration unless a worsening of the event was recorded after the first dosing date, in which case the event was counted as a TEAE. Safety analysis set (SAF) for the safety run-in part included all subjects who had received at least 1 administration of the trial medication (pimasertib or gemcitabine).

End point type	Secondary
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End point timeframe:

Baseline up to post treatment follow-up period (28 days after last trial drug administration)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Safety Run-in Part: Regimen 1	Safety Run-in Part: Regimen 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26		
Units: subjects				
number (not applicable)				
TEAEs	27	26		
Serious TEAEs	18	20		
Permanent treatment discontinuation of pimasertib	12	16		
Permanent treatment discontinuation of gemcitabine	14	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Maximum Concentration (C_{max}) of MSC1936369B, gemcitabine, its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU), and its main active metabolite 2',2'-difluorodeoxycytidine 5'-triphosphate (dFdCTP) for Regimen 1

End point title	Safety Run-In Part: Maximum Concentration (C _{max}) of MSC1936369B, gemcitabine, its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU), and its main active metabolite 2',2'-difluorodeoxycytidine 5'-triphosphate (dFdCTP) for Regimen 1
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End point description:

Maximum observed plasma concentration (C_{max}) was calculated for MSC1936369B, gemcitabine, its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU), and its main active metabolite 2',2'-difluorodeoxycytidine 5'. Pharmacokinetic set (PKS) of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 1: 15 mg	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
MSC1936369B on Days 1 (n=4,3,3,3,11)	32.3 (± 107.5)	131 (± 32.9)	205.8 (± 30)	151.3 (± 40.1)
MSC1936369B on Days 22 (n= 3,3,3,2,3,10)	29.6 (± 39.8)	174.2 (± 29.6)	261.8 (± 52)	212.5 (± 16.9)
Gemcitabine (dFdC) on Day 1 (n=4,3,3,3,11)	69540.5 (± 1729.4)	21207.3 (± 21)	17759.9 (± 34.1)	29762.1 (± 76.7)
Gemcitabine (dFdC) on Day 22 (n= 2,3,3,2,3,9)	24115.8 (± 71.9)	11799.7 (± 167.7)	181.9 (± 39158542.7)	163196.2 (± 3183.3)

Gemcitabine (dFdU) on Day 1 (n=4,3,3,3,3,11)	29359.8 (± 8.5)	33171.6 (± 21.2)	34868.9 (± 12.8)	33804.4 (± 16.7)
Gemcitabine (dFdU) on Day 22 (n=2,3,3,2,3,10)	29677.6 (± 3)	38265.2 (± 54.3)	10569.2 (± 449.2)	32869.2 (± 8.7)

End point values	Regimen 1: 90 mg	Regimen 1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
MSC1936369B on Days 1 (n=4,3,3,3,3,11)	485.3 (± 58.7)	484.3 (± 39.8)		
MSC1936369B on Days 22 (n=3,3,3,2,3,10)	409.1 (± 44.1)	252.9 (± 477)		
Gemcitabine (dFdC) on Day 1 (n=4,3,3,3,3,11)	15606.3 (± 23.1)	23880.7 (± 83.8)		
Gemcitabine (dFdC) on Day 22 (n=2,3,3,2,3,9)	669.5 (± 3278825923)	23207.2 (± 99.5)		
Gemcitabine (dFdU) on Day 1 (n=4,3,3,3,3,11)	37786.4 (± 13.6)	34038.7 (± 29.7)		
Gemcitabine (dFdU) on Day 22 (n=2,3,3,2,3,10)	17135 (± 227.5)	21077.5 (± 179.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Time to Reach Maximum Concentration (tmax) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 1

End point title	Safety Run-In Part: Time to Reach Maximum Concentration (tmax) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 1
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End point description:

PKS set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 1: 15 mg	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: hours				
median (full range (min-max))				
Tmax: MSC1936369B on Day 1 (n=4,3,3,3,3,11)	1.25 (1 to 1.5)	1 (1 to 2.5)	1.533 (1 to 2)	2 (0.67 to 8)
Tmax: MSC1936369B on Day 22 (n=3,3,3,2,3,10)	2.017 (1.28 to 4)	1 (0.5 to 2.5)	1 (0.5 to 1.58)	1.75 (1 to 2.5)
Tmax: Gemcitabine (dFdC) on Day 1 (n=4,3,3,3,3,11)	0.38 (0.25 to 0.5)	0.5 (0.25 to 0.5)	0.25 (0.25 to 0.5)	0.25 (0.25 to 1.17)
Tmax: Gemcitabine (dFdC) on Day 22 (n=2,3,3,2,3,9)	0.42 (0.33 to 0.5)	0.5 (0.5 to 1.58)	0.53 (0.25 to 2)	1.04 (1 to 1.08)
Tmax: Gemcitabine (dFdU) on Day 1 (n=4,3,3,3,3,11)	0.64 (0.5 to 1)	0.5 (0.5 to 0.75)	0.5 (0.5 to 0.77)	0.75 (0.67 to 1)
Tmax: Gemcitabine (dFdU) on Day 22 (n=2,3,3,2,3,10)	0.54 (0.33 to 0.75)	0.75 (0.5 to 1.58)	1 (0.73 to 2)	0.67 (0.33 to 1)

End point values	Regimen 1: 90 mg	Regimen 1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: hours				
median (full range (min-max))				
Tmax: MSC1936369B on Day 1 (n=4,3,3,3,3,11)	1.083 (1 to 2)	1.5 (0.5 to 4)		
Tmax: MSC1936369B on Day 22 (n=3,3,3,2,3,10)	1.5 (1 to 1.75)	2 (0.83 to 8)		
Tmax: Gemcitabine (dFdC) on Day 1 (n=4,3,3,3,3,11)	0.25 (0.25 to 0.38)	0.27 (0.25 to 0.75)		
Tmax: Gemcitabine (dFdC) on Day 22 (n=2,3,3,2,3,9)	0.25 (0.23 to 24)	0.5 (0.25 to 0.75)		
Tmax: Gemcitabine (dFdU) on Day 1 (n=4,3,3,3,3,11)	0.5 (0.38 to 0.5)	0.5 (0.25 to 0.75)		
Tmax: Gemcitabine (dFdU) on Day 22 (n=2,3,3,2,3,10)	0.75 (0.5 to 24)	0.75 (0 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Time to Reach Apparent Terminal Half-Life (t_{1/2}) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 1

End point title	Safety Run-In Part: Time to Reach Apparent Terminal Half-Life (t _{1/2}) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 1
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End point description:

Plasma decay half-life was the time measured for the plasma concentration to decrease by one half. PKs set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at

specified time point.

End point type	Secondary
End point timeframe:	
0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1	

End point values	Regimen 1: 15 mg	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: hours				
median (full range (min-max))				
t1/2: MSC1936369B on Day 1 (n=4,3,3,2,3,11)	4.008 (2.539 to 6.131)	3.807 (3.373 to 6.648)	3.833 (3.612 to 6.477)	4.232 (3.382 to 5.083)
t1/2: MSC1936369B on Day 22 (n=2,2,3,2,3,8)	8.66 (4.709 to 12.61)	6.1 (4.878 to 7.322)	3.254 (3.048 to 6.999)	5.744 (3.829 to 7.658)
t1/2: Gemcitabine (dFdC) on Day 1 (n=4,3,3,3,3,11)	4.274 (2.1 to 7.519)	2.461 (1.239 to 6.821)	2.421 (0.707 to 5.709)	5.327 (5.148 to 5.338)
t1/2: Gemcitabine (dFdC) on Day 22 (n=2,2,1,2,2,9)	7.449 (6.032 to 8.866)	4.553 (2.403 to 6.702)	0.9152 (0.9152 to 0.9152)	4.493 (2.721 to 6.266)
t1/2: Gemcitabine (dFdU) on Day 1 (n=4,3,3,3,3,11)	8.956 (8.129 to 14.68)	10.49 (4.336 to 10.7)	9.836 (9.383 to 14.69)	11.52 (9.344 to 12.36)
t1/2: Gemcitabine (dFdU) on Day 22 (n=2,2,2,2,2,10)	7.731 (6.978 to 8.483)	8.925 (8.299 to 9.552)	8.843 (5.427 to 12.26)	11.14 (9.119 to 13.17)

End point values	Regimen 1: 90 mg	Regimen 1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: hours				
median (full range (min-max))				
t1/2: MSC1936369B on Day 1 (n=4,3,3,2,3,11)	5.036 (4.361 to 5.12)	4.58 (3.394 to 6.938)		
t1/2: MSC1936369B on Day 22 (n=2,2,3,2,3,8)	3.162 (2.903 to 6.341)	4.825 (2.829 to 8.642)		
t1/2: Gemcitabine (dFdC) on Day 1 (n=4,3,3,3,3,11)	8.94 (5.565 to 9.982)	6.242 (0.8913 to 11.9)		
t1/2: Gemcitabine (dFdC) on Day 22 (n=2,2,1,2,2,9)	8.213 (6.665 to 9.762)	4.68 (0.8685 to 8.49)		
t1/2: Gemcitabine (dFdU) on Day 1 (n=4,3,3,3,3,11)	8.349 (7.191 to 9.551)	10.93 (8.802 to 15.48)		
t1/2: Gemcitabine (dFdU) on Day 22 (n=2,2,2,2,2,10)	10.21 (6.782 to 13.64)	12.17 (3.468 to 211.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Area Under Curve (AUC: 0 to Infinity) of

MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU)

End point title	Safety Run-In Part: Area Under Curve (AUC: 0 to Infinity) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU)
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End point description:

AUC: 0 to Infinity was a measure of the serum concentration of the drug over time. It was used to characterize drug absorption. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point and "99999" signifies Geometric Mean and Geometric Coefficient of Variation was not estimable as no subject was analyzed.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg	Regimen 1: 90 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
AUC: MSC1936369B on Day 1	162.8 (± 25.3)	516.3 (± 30.1)	881.1 (± 37.1)	774.8 (± 58.9)
AUC: MSC1936369B on Day 22	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
AUC: Gemcitabine metabolite (dFdU) on Day 1	245795.5 (± 10.8)	228032.9 (± 27.6)	276968.3 (± 28.9)	259816.2 (± 9.2)
AUC: Gemcitabine metabolite (dFdU) on Day 22	190952.6 (± 9.3)	376280.5 (± 13)	217930.8 (± 70.4)	327424.8 (± 2)

End point values	Regimen 1:15 mg	Regimen1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
AUC: MSC1936369B on Day 1	1729.9 (± 32.3)	2175.1 (± 53)		
AUC: MSC1936369B on Day 22	99999 (± 99999)	99999 (± 99999)		
AUC: Gemcitabine metabolite (dFdU) on Day 1	239902.9 (± 27.1)	240293.8 (± 15)		
AUC: Gemcitabine metabolite (dFdU) on Day 22	248496.4 (± 5.2)	247430.7 (± 29.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Apparent Oral Clearance (CL/f) of MSC1936369B: Regimen 1

End point title	Safety Run-In Part: Apparent Oral Clearance (CL/f) of MSC1936369B: Regimen 1
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End point description:

Clearance of a drug was a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) was influenced by the fraction of the dose absorbed. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. PKs set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg	Regimen 1: 90 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: Liter per hour (L/h)				
geometric mean (geometric coefficient of variation)				
CL/f: MSC1936369B on Day 1 (n=4,3,3,2,3,11)	58.104 (± 32.9)	51.072 (± 37.1)	87.765 (± 58.9)	52.025 (± 32.3)
CL/f: MSC1936369B on Day 22 (n=2,2,3,2,3,9)	42.484 (± 31.2)	44.579 (± 23.1)	56.502 (± 7.5)	50.873 (± 59.6)

End point values	Regimen 1: 120 mg	Regimen 1: 15 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	4		
Units: Liter per hour (L/h)				
geometric mean (geometric coefficient of variation)				
CL/f: MSC1936369B on Day 1 (n=4,3,3,2,3,11)	55.171 (± 53)	92.152 (± 25.3)		
CL/f: MSC1936369B on Day 22 (n=2,2,3,2,3,9)	55.723 (± 57.8)	74.143 (± 43.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Oral volume of distribution (V/f) of MSC1936369B:

Regimen 1

End point title	Safety Run-In Part: Oral volume of distribution (V/f) of MSC1936369B: Regimen 1
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End point description:

PKS set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 1: 15 mg	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: liter				
geometric mean (geometric coefficient of variation)				
V/f: MSC1936369B of Day 1 (n=4,3,3,2,3,11)	528.62 (± 63.1)	369.12 (± 5)	329.8 (± 28.4)	524.96 (± 26.2)
V/f: MSC1936369B of Day 22 (n=2,2,3,2,3,8)	824.33 (± 156.8)	366.3 (± 1.8)	264.31 (± 43.8)	441.4 (± 43.4)

End point values	Regimen 1: 90 mg	Regimen 1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: liter				
geometric mean (geometric coefficient of variation)				
V/f: MSC1936369B of Day 1 (n=4,3,3,2,3,11)	362.29 (± 34)	367.25 (± 50.5)		
V/f: MSC1936369B of Day 22 (n=2,2,3,2,3,8)	284.42 (± 35.1)	414.38 (± 66.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Apparent volume of distribution (V) of gemcitabine: Regimen 1

End point title	Safety Run-In Part: Apparent volume of distribution (V) of gemcitabine: Regimen 1
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End point description:

Apparent volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after oral dose (V_z/F) was influenced by the fraction absorbed. PKS set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e.,

gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point and "99999" signifies Geometric Coefficient of Variation was not estimable as data for only 1 subject was collected.

End point type	Secondary
End point timeframe:	
0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1	

End point values	Regimen 1: 15 mg	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: liter				
geometric mean (geometric coefficient of variation)				
V: Gemcitabine (dFdC) of Day 1 (n=4,3,3,3,3,11)	359.55 (± 635.6)	531.23 (± 64.7)	587.64 (± 206.3)	729.65 (± 46.3)
V: Gemcitabine (dFdC) of Day 22 (n=2,2,1,2,2,9)	1723.6 (± 55.9)	908.5 (± 56.5)	251.79 (± 99999)	149.65 (± 1453.7)

End point values	Regimen 1: 90 mg	Regimen 1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: liter				
geometric mean (geometric coefficient of variation)				
V: Gemcitabine (dFdC) of Day 1 (n=4,3,3,3,3,11)	2402.1 (± 59.5)	1270.1 (± 82)		
V: Gemcitabine (dFdC) of Day 22 (n=2,2,1,2,2,9)	2140.8 (± 15.5)	805.15 (± 138)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Total Clearance (CL) of MSC1936369B and Gemcitabine: Regimen 1

End point title	Safety Run-In Part: Total Clearance (CL) of MSC1936369B and Gemcitabine: Regimen 1
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End point description:

Clearance was described as a quantitative measure of the rate at which a drug substance is removed from the body. PKs set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "99999" signifies Geometric Coefficient of Variation was not estimable as data for only 1 subject was collected.

End point type	Secondary
End point timeframe:	
0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1	

End point values	Regimen 1: 15 mg	Regimen 1: 30 mg	Regimen 1: 45 mg	Regimen 1: 68 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	3	3	3
Units: liter/hour				
geometric mean (geometric coefficient of variation)				
CL: MSC1936369B of Day 1	92.152 (\pm 25.3)	58.104 (\pm 32.9)	51.072 (\pm 37.1)	87.765 (\pm 58.9)
CL: MSC1936369B of Day 22	74.143 (\pm 43.6)	42.484 (\pm 31.2)	44.579 (\pm 23.1)	56.502 (\pm 7.5)
CL: Gemcitabine of Day 1	60.537 (\pm 483.4)	133.88 (\pm 45.1)	190.52 (\pm 26)	95.96 (\pm 47.7)
CL: Gemcitabine of Day 22	163.37 (\pm 93.7)	156.93 (\pm 20.1)	190.69 (\pm 99999)	25.123 (\pm 431.2)

End point values	Regimen 1: 90 mg	Regimen 1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	11		
Units: liter/hour				
geometric mean (geometric coefficient of variation)				
CL: MSC1936369B of Day 1	52.025 (\pm 32.3)	55.171 (\pm 53)		
CL: MSC1936369B of Day 22	50.873 (\pm 59.6)	55.723 (\pm 57.8)		
CL: Gemcitabine of Day 1	210.25 (\pm 27.9)	151.93 (\pm 54.7)		
CL: Gemcitabine of Day 22	183.97 (\pm 11.6)	164.6 (\pm 71.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Levels of Pharmacodynamic (Pd) Markers (Phosphorylated- Extracellular Signal-Regulated Kinase (ERK) in Peripheral Blood Mononuclear Cells [PBMCs]) Regimen 1

End point title	Safety Run-In Part: Levels of Pharmacodynamic (Pd) Markers (Phosphorylated- Extracellular Signal-Regulated Kinase (ERK) in Peripheral Blood Mononuclear Cells [PBMCs]) Regimen 1
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End point description:

ERK phosphoprotein in peripheral blood monocytes (PBMCs) was analyzed from blood samples of all subjects in the SAF analysis set (safety-run part) only. Pharmacodynamic population included SAF analysis set for the safety run-in part include all subjects who received at least 1 (non-zero) administration of the trial medication (pimasertib or gemcitabine). Here "9999" signifies data for standard deviation was not estimable as only one patient analyzed, No subjects were evaluable hence the mean ad standard deviation was not analyzed and "n" signifies number of subjects evaluable for

each category at specified time point.

End point type	Secondary
End point timeframe:	
Days 1, 2, and 22 of Cycle 1	

End point values	Regimen 1: 68 mg	Regimen 1: 90 mg	Regimen 1:15 mg	Regimen 1: 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	2
Units: Fluorescence Intensity				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 Pre-dose (n=3,2,2,3,3,7)	6.509 (± 2.24)	4.608 (± 0.197)	5.389 (± 0.797)	6.476 (± 0.997)
Cycle 1 Day 1 Post-dose (n=3,2,2,3,2,6)	3.881 (± 5.387)	1.059 (± 0.042)	1.611 (± 0.537)	2.061 (± 0.825)
Cycle 1 Day 2 Pre-dose (n=3,2,1,2,2,6)	2.768 (± 0.33)	4.874 (± 2.119)	4.818 (± 0.808)	6.719 (± 2.835)
Cycle 1 Day 22 Pre-dose (n=2,1,2,1,3,5)	8.653 (± 9999)	4.252 (± 1.259)	5.242 (± 0.21)	6 (± 9999)
Cycle 1 Day 22 Post-dose (n=0,0,0,0,2)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)

End point values	Regimen 1: 45 mg	Regimen1: 120 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	7		
Units: Fluorescence Intensity				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 Pre-dose (n=3,2,2,3,3,7)	4.767 (± 0.114)	4.229 (± 1.719)		
Cycle 1 Day 1 Post-dose (n=3,2,2,3,2,6)	0.837 (± 0.149)	0.946 (± 0.248)		
Cycle 1 Day 2 Pre-dose (n=3,2,1,2,2,6)	3.902 (± 9999)	3.636 (± 1.755)		
Cycle 1 Day 22 Pre-dose (n=2,1,2,1,3,5)	1.978 (± 2.539)	3.453 (± 0.86)		
Cycle 1 Day 22 Post-dose (n=0,0,0,0,2)	9999 (± 9999)	4.13 (± 1.772)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Maximum Concentration (C_{max}) of MSC1936369B, gemcitabine, its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU), and its main active metabolite 2',2'-difluorodeoxycytidine 5'-triphosphate (dFdCTP) for Regimen 2

End point title	Safety Run-In Part: Maximum Concentration (C _{max}) of MSC1936369B, gemcitabine, its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU), and its main active metabolite 2',
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End point description:

Maximum observed plasma concentration (C_{max}) was calculated for MSC1936369B, gemcitabine, its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU), and its main active metabolite 2',2'-difluorodeoxycytidine 5'. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
MSC1936369B on Days 1 (n= 12,13)	175.7 (± 65)	345.5 (± 52.8)		
MSC1936369B on Days 22 (n=10,9)	228.2 (± 59)	244.8 (± 31.9)		
Gemcitabine (dFdC) on Day 1 (n=11,14)	27849.2 (± 344)	17663.9 (± 173.3)		
Gemcitabine (dFdC) on Day 22 (n=9,4)	21589.7 (± 118.8)	18733.4 (± 88.6)		
Gemcitabine (dFdU) on Day 1 (n=11, 10)	33033.3 (± 11.8)	31623.9 (± 25.4)		
Gemcitabine (dFdU) on Day 22 (n=10,5)	13455.5 (± 546)	18298.7 (± 247.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Area Under Curve (AUC: 0 to Infinity) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU) Regimen 2

End point title	Safety Run-In Part: Area Under Curve (AUC: 0 to Infinity) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU) Regimen 2
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End point description:

AUC: 0 to Infinity is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point and "99999" signifies Geometric Mean and Geometric Coefficient of Variation was not estimable as no subject was analyzed.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
AUC: MSC1936369B on Day 1	704.3 (± 69.4)	1427 (± 30)		
AUC: MSC1936369B on Day 22	99999 (± 99999)	99999 (± 99999)		
AUC: Gemcitabine metabolite (dFdU) on Day 1	189007 (± 40.6)	234934.8 (± 29.9)		
AUC: Gemcitabine metabolite (dFdU) on Day 22	177504.5 (± 171.5)	256714.9 (± 37.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Time to Reach Maximum Concentration (tmax) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 2

End point title	Safety Run-In Part: Time to Reach Maximum Concentration (tmax) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 2
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End point description:

PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: hours				
median (full range (min-max))				
Tmax: MSC1936369B on Day 1 (n=12,13)	2 (0.5 to 3.98)	1.583 (0.5 to 7.98)		
Tmax: MSC1936369B on Day 22 (n=10,9)	1.5 (0.25 to 4.4)	2 (0.58 to 4)		
Tmax: Gemcitabine (dFdC) on Day 1 (n=11,14)	0.5 (0.25 to 0.73)	0.38 (0.25 to 0.75)		

Tmax: Gemcitabine (dFdC) on Day 22 (n=9,4)	0.25 (0 to 0.5)	0.25 (0.25 to 0.5)		
Tmax: Gemcitabine (dFdU) on Day 1 (n=11,13)	0.67 (0.5 to 0.75)	0.67 (0.25 to 1)		
Tmax: Gemcitabine (dFdU) on Day 22 (n=10,5)	0.5 (0 to 2)	0.5 (0.5 to 0.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Time to Reach Apparent Terminal Half-Life (t_{1/2}) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 2

End point title	Safety Run-In Part: Time to Reach Apparent Terminal Half-Life (t _{1/2}) of MSC1936369B, gemcitabine, and its inactive metabolite 2',2'-difluorodeoxyuridine (dFdU): Regimen 2
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End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: hours				
median (full range (min-max))				
t _{1/2} : MSC1936369B on Day 1 (n=10,11)	2.757 (2.183 to 3.557)	2.603 (1.775 to 4.91)		
t _{1/2} : MSC1936369B on Day 22 (n=8,5)	3.425 (2.584 to 10.6)	3.188 (2.296 to 4.617)		
t _{1/2} : Gemcitabine (dFdC) on Day 1 (n=11,14)	5.258 (0.796 to 8.757)	5.376 (0.6681 to 11.64)		
t _{1/2} : Gemcitabine (dFdC) on Day 22 (n=9,4)	5.522 (3.759 to 11.45)	5.249 (0.3198 to 9.505)		
t _{1/2} : Gemcitabine (dFdU) on Day 1 (n=11,13)	9.471 (6.559 to 13.1)	10.26 (7.123 to 12.92)		
t _{1/2} : Gemcitabine (dFdU) on Day 22 (n=10,5)	10.68 (6.543 to 441.9)	13.58 (7.575 to 17.535)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Apparent Oral Clearance (CL/f) of MSC1936369B: Regimen 2

End point title	Safety Run-In Part: Apparent Oral Clearance (CL/f) of MSC1936369B: Regimen 2
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End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 24 (post-dose) on Day 1, 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: Liter per hour (L/H)				
geometric mean (geometric coefficient of variation)				
CL/f: MSC1936369B on Day 1 (n=10,11)	85.186 (± 69.4)	52.558 (± 30)		
CL/f: MSC1936369B on Day 22 (n=8,5)	70.163 (± 63.2)	68.312 (± 24.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Apparent volume of distribution (V) of gemcitabine: Regimen 2

End point title	Safety Run-In Part: Apparent volume of distribution (V) of gemcitabine: Regimen 2
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End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after oral dose (V_z/F) is influenced by the fraction absorbed. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

Days 1 and 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: liter				
geometric mean (geometric coefficient of variation)				
V: Gemcitabine of Day 1 (n=11,14)	716.12 (\pm 343.3)	1059 (\pm 196.6)		
V: Gemcitabine of Day 22 (n=9,4)	1590.8 (\pm 120.5)	801.9 (\pm 130.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Oral Volume of Distribution (V/f) of MSC1936369B: Regimen 2

End point title	Safety Run-In Part: Oral Volume of Distribution (V/f) of MSC1936369B: Regimen 2
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End point description:

Volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after oral dose (V_z/F) was influenced by the fraction absorbed. PKs of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1. Here "n" signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

Days 1 and 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: liter				
geometric mean (geometric coefficient of variation)				
V/f: MSC1936369B of Day 1 (n= 10,11)	335.56 (\pm 66.3)	213.24 (\pm 37.7)		
V/f: MSC1936369B of Day 22 (n=8,5)	389.56 (\pm 47.1)	319.02 (\pm 35.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Levels of Pharmacodynamic (Pd) Markers

(Phosphorylated- Extracellular Signal-Regulated Kinase (ERK) in Peripheral Blood Mononuclear Cells [PBMCs]) Regimen 2

End point title	Safety Run-In Part: Levels of Pharmacodynamic (Pd) Markers (Phosphorylated- Extracellular Signal-Regulated Kinase (ERK) in Peripheral Blood Mononuclear Cells [PBMCs]) Regimen 2
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End point description:

ERK phosphoprotein in peripheral blood monocytes (PBMCs) was analyzed from blood samples of all subjects in the SAF analysis set (safety-run part) only. Pharmacodynamic population included SAF analysis set for the safety run-in part include all subjects who received at least 1 (non-zero) administration of the trial medication (pimasertib or gemcitabine). Here "9999" signifies data for standard deviation was not estimable as only one patient analyzed and 'n' signifies number of subjects evaluable for each category at specified time point.

End point type	Secondary
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End point timeframe:

Days 1, 2, and 22 of Cycle 1

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	4		
Units: Fluorescence Intensity				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 Pre-dose (n=7,4)	6.081 (± 0.827)	5.874 (± 2.239)		
Cycle 1 Day 1 Post-dose (n=5,3)	1.52 (± 0.109)	1.048 (± 0.155)		
Cycle 1 Day 2 Pre-dose (n=7,3)	3.877 (± 2.099)	2.263 (± 0.593)		
Cycle 1 Day 22 Pre-dose (n=6,2)	2.728 (± 0.818)	2.295 (± 0.51)		
Cycle 1 Day 22 Post-dose (n=3,1)	1.443 (± 0.458)	1.111 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-In Part: Total Clearance (CL) of MSC1936369B and Gemcitabine: Regimen 2

End point title	Safety Run-In Part: Total Clearance (CL) of MSC1936369B and Gemcitabine: Regimen 2
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End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. PKs set of the safety run in part included subjects who had received at least the first dose of both drugs (i.e., gemcitabine and pimasertib), and provided PK samples as per the protocol for at least 24 hours following first dosing on Day 1.

End point type	Secondary
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End point timeframe:

Days 1 and 22 of Cycle

End point values	Regimen 2: 60 mg	Regimen 2: 75 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	11		
Units: liter/hour				
geometric mean (geometric coefficient of variation)				
CL: MSC1936369B of Day 1	85.186 (\pm 69.4)	52.558 (\pm 30)		
CL: MSC1936369B of Day 22	70.163 (\pm 63.2)	68.312 (\pm 24.9)		
CL: Gemcitabine of Day 1	145.65 (\pm 363.2)	221.46 (\pm 186)		
CL: Gemcitabine of Day 22	164.68 (\pm 81.4)	183.85 (\pm 73.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Permanent Treatment Discontinuation

End point title	Part 2: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Permanent Treatment Discontinuation ^[6]
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End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. All AEs (serious and non-serious) except AEs recorded with an onset date prior to the first day of drug administration unless a worsening of the event was recorded after the first dosing date, in which case the event was counted as a TEAE. SAF for the Part II included all subjects who had received at least 1 administration of the trial medication .Gemcitabine or Placebo if the subject is in the gemcitabine + Placebo treatment arm (Arm 1) and MSC1936369B or gemcitabine in the MSC1936369B + gemcitabine treatment arm (Arm 2)

End point type	Secondary
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End point timeframe:

Baseline up to post treatment follow-up period (28 days after last trial drug administration)

Notes:

[6] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: subjects				
number (not applicable)				
TEAEs	40	44		
Serious TEAEs	27	34		
TEAEs Leading to Treatment Discontinuation	10	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Best Overall Response (BOR)

End point title	Part 2: Percentage of Subjects With Best Overall Response (BOR) ^[7]
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End point description:

Best overall response was defined as the presence of at least one CR, PR or Stable Disease (SD) (using RECIST v1.0) during treatment. CR: Disappearance of all target lesions, PR: At least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the sum of the longest diameter at baseline and SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since treatment started and non evaluable (NE) subjects. ITT analysis set included all subjects who had been randomized for the phase II part, as per the interactive voice response system (IVRS).

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks up to end of treatment (EOT i.e. 6 years)

Notes:

[7] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: percentage of subjects				
number (not applicable)				
CR	0	0		
PR	9.1	9.1		
SD	36.4	50		
PD	29.5	20.5		
NE	25	20.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Clinical Benefit

End point title	Part 2: Percentage of Subjects With Clinical Benefit ^[8]
End point description:	
Clinical Benefit was defined as the presence of at least one CR, PR or Stable Disease (SD) (using RECIST v1.0) during treatment. CR: Disappearance of all target lesions, PR: At least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the sum of the longest diameter at baseline and SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since treatment started. ITT analysis set included all subjects who had been randomized for the phase II part, as per the interactive voice response system (IVRS).	
End point type	Secondary
End point timeframe:	
Baseline, every 8 weeks up to end of treatment (EOT i.e. 6 years)	

Notes:

[8] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: percentage of subjects				
number (not applicable)	45.5	59.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to progression (TTP)

End point title	Part 2: Time to progression (TTP) ^[9]
End point description:	
Time to progression (TTP) is defined as the time (in months) from the randomization date to the date of progression prior to the start of any subsequent therapy for the primary disease, as reported and documented by the Investigator (i.e. radiological progression per RECIST). ITT analysis set included all subjects who had been randomized for the phase II part, as per the interactive voice response system (IVRS).	
End point type	Secondary
End point timeframe:	
From randomization every 8 weeks up to EOT (6 years)	

Notes:

[9] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: months				
median (confidence interval 95%)	3.78 (1.87 to 5.55)	5.09 (3.75 to 6.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Overall Survival (OS) Time

End point title	Part 2: Overall Survival (OS) Time ^[10]
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End point description:

Overall survival (OS) time is defined as the time (in months) from randomization to death. ITT analysis set included all subjects who had been randomized for the phase II part, as per the interactive voice response system (IVRS). Here "99999" signifies data not evaluated as upper limit of 95% Confidence Interval (CI) not estimable.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks up to EOT (6 years)

Notes:

[10] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	44		
Units: months				
median (confidence interval 95%)	6.64 (5.06 to 99999)	9.33 (3.71 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Absorption rate constant (ka) of MSC1936369B

End point title	Part 2: Absorption rate constant (ka) of MSC1936369B ^[11]
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End point description:

Due to change in planned analysis "Reduction of PK investigations for the phase II part of the trial: Removal of PK sampling for gemcitabine and its metabolites and replacement of intense sampling with a sparse sampling scheme for pimasertib". outcome measure was not analyzed.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks up to EOT (6 years)

Notes:

[11] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[12]	0 ^[13]		
Units: days				
number (not applicable)				

Notes:

[12] - MANDATORY COMMENT

[13] - MANDATORY COMMENT

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Clearance from central compartment (CL/f) and Intercompartmental Clearance (Q/f) of MSC1936369B

End point title	Part 2: Clearance from central compartment (CL/f) and Intercompartmental Clearance (Q/f) of MSC1936369B ^[14]
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End point description:

Clearance is a quantitative measure of the rate at which a drug substance is removed from the body. Due to change in planned analysis " Reduction of PK investigations for the phase II part of the trial: Removal of PK sampling for gemcitabine and its metabolites and replacement of intense sampling with a sparse sampling scheme for pimasertib". outcome measure was not analyzed.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks up to EOT (6 years)

Notes:

[14] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[15]	0 ^[16]		
Units: milliliter per minute (mL/min)				
geometric mean (standard deviation)	()	()		

Notes:

[15] - MANDATORY COMMENT

[16] - MANDATORY COMMENT

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Volume of central compartment (V1/f) volume of peripheral compartment (V2/f) of MSC1936369B

End point title	Part 2: Volume of central compartment (V1/f) volume of peripheral compartment (V2/f) of MSC1936369B ^[17]
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End point description:

Due to change in planned analysis " Reduction of PK investigations for the phase II part of the trial: Removal of PK sampling for gemcitabine and its metabolites and replacement of intense sampling with a sparse sampling scheme for pimasertib". outcome measure was not analyzed.

End point type	Secondary
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End point timeframe:

Baseline, every 8 weeks up to EOT (6 years)

Notes:

[17] - 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: Subject analysis set has been created for various dose regimen to capture the data.

End point values	Part II: Arm 1	Part II: Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[18]	0 ^[19]		
Units: liter				
geometric mean (standard deviation)	()	()		

Notes:

[18] - MANDATORY COMMENT

[19] - MANDATORY COMMENT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug administration until EOT (6 years)

Adverse event reporting additional description:

SAF for the Part II included all subjects who had received at least 1 administration of the trial medication .Gemcitabine or Placebo if the subject is in the gemcitabine + Placebo treatment arm (Arm 1) and MSC1936369B or gemcitabine in the MSC1936369B + gemcitabine treatment arm (Arm 2)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Part II: Arm 2
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Reporting group description:

Subjects received gemcitabine 1000 mg/m² for 30 minutes IV infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and pimasertib orally 60 mg bid - continuous regimen.

Reporting group title	Part II: Arm 1
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Reporting group description:

Subjects received gemcitabine 1000 mg/m² for 30 minutes IV infusion on Days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest (Cycle 1) then on Days 1, 8, and 15 of a 28-day cycle and placebo orally bid - continuous regimen. Subjects with disease progression in Arm 1 were allowed crossover to receive pimasertib orally 60 mg bid - continuous regimen.

Serious adverse events	Part II: Arm 2	Part II: Arm 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 45 (75.56%)	27 / 42 (64.29%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertension alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (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			
Pyrexia			
subjects affected / exposed	5 / 45 (11.11%)	5 / 42 (11.90%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	4 / 45 (8.89%)	5 / 42 (11.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 45 (6.67%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 45 (4.44%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
alternative dictionary used: MedDRA 15.0			
subjects affected / exposed	2 / 45 (4.44%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
alternative assessment type: Systematic			

subjects affected / exposed	5 / 45 (11.11%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 45 (6.67%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 45 (8.89%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemoid reaction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular detachment			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 45 (8.89%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gingival bleeding			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	2 / 45 (4.44%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperbilirubinaemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice extrahepatic obstructive			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin toxicity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchitis				
alternative assessment type: Systematic				
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enterobacter sepsis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatic infection				
alternative assessment type: Systematic				
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pharyngitis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sepsis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Viral infection				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Metabolism and nutrition disorders			
Hypophosphataemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 45 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Part II: Arm 2	Part II: Arm 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 45 (97.78%)	37 / 42 (88.10%)	
Vascular disorders			
Hypotension			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 45 (8.89%)	1 / 42 (2.38%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 45 (35.56%)	17 / 42 (40.48%)	
occurrences (all)	16	17	
Oedema peripheral			
alternative assessment type: Systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Asthenia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>21 / 45 (46.67%)</p> <p>21</p> <p>16 / 45 (35.56%)</p> <p>16</p> <p>8 / 45 (17.78%)</p> <p>8</p>	<p>7 / 42 (16.67%)</p> <p>7</p> <p>12 / 42 (28.57%)</p> <p>12</p> <p>6 / 42 (14.29%)</p> <p>6</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Dyspnoea</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 45 (11.11%)</p> <p>5</p> <p>3 / 45 (6.67%)</p> <p>3</p>	<p>3 / 42 (7.14%)</p> <p>3</p> <p>3 / 42 (7.14%)</p> <p>3</p>	
<p>Investigations</p> <p>Gamma-glutamyltransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood creatine phosphokinase increased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alanine aminotransferase increased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aspartate aminotransferase increased</p> <p>alternative assessment type: Systematic</p>	<p>4 / 45 (8.89%)</p> <p>4</p> <p>9 / 45 (20.00%)</p> <p>9</p> <p>4 / 45 (8.89%)</p> <p>4</p>	<p>7 / 42 (16.67%)</p> <p>7</p> <p>1 / 42 (2.38%)</p> <p>1</p> <p>4 / 42 (9.52%)</p> <p>4</p>	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood bilirubin increased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood alkaline phosphatase increased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ejection fraction decreased</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 45 (8.89%)</p> <p>4</p> <p>2 / 45 (4.44%)</p> <p>2</p> <p>4 / 45 (8.89%)</p> <p>4</p> <p>5 / 45 (11.11%)</p> <p>5</p> <p>1 / 45 (2.22%)</p> <p>1</p> <p>3 / 45 (6.67%)</p> <p>3</p>	<p>3 / 42 (7.14%)</p> <p>3</p> <p>5 / 42 (11.90%)</p> <p>5</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>1 / 42 (2.38%)</p> <p>1</p> <p>4 / 42 (9.52%)</p> <p>4</p> <p>0 / 42 (0.00%)</p> <p>0</p>	
<p>Nervous system disorders</p> <p>Dizziness</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 45 (13.33%)</p> <p>6</p>	<p>1 / 42 (2.38%)</p> <p>1</p>	
<p>Blood and lymphatic system disorders</p> <p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>17 / 45 (37.78%)</p> <p>17</p> <p>16 / 45 (35.56%)</p> <p>16</p>	<p>16 / 42 (38.10%)</p> <p>16</p> <p>9 / 42 (21.43%)</p> <p>9</p>	

<p>Anaemia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>13 / 45 (28.89%)</p> <p>13</p>	<p>6 / 42 (14.29%)</p> <p>6</p>	
<p>Leukopenia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 45 (8.89%)</p> <p>4</p>	<p>6 / 42 (14.29%)</p> <p>6</p>	
<p>Hypochromic anaemia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 45 (6.67%)</p> <p>3</p>	<p>2 / 42 (4.76%)</p> <p>2</p>	
<p>Eye disorders</p> <p>Retinal detachment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Macular degeneration</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Visual acuity reduced</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Visual impairment</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eyelid oedema</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vision blurred</p> <p>alternative assessment type: Systematic</p>	<p>10 / 45 (22.22%)</p> <p>10</p> <p>8 / 45 (17.78%)</p> <p>8</p> <p>4 / 45 (8.89%)</p> <p>4</p> <p>4 / 45 (8.89%)</p> <p>4</p> <p>3 / 45 (6.67%)</p> <p>3</p>	<p>1 / 42 (2.38%)</p> <p>1</p> <p>0 / 42 (0.00%)</p> <p>0</p> <p>1 / 42 (2.38%)</p> <p>1</p> <p>0 / 42 (0.00%)</p> <p>0</p> <p>0 / 42 (0.00%)</p> <p>0</p>	

subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	20 / 45 (44.44%)	8 / 42 (19.05%)	
occurrences (all)	20	8	
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 45 (15.56%)	9 / 42 (21.43%)	
occurrences (all)	7	9	
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 45 (13.33%)	8 / 42 (19.05%)	
occurrences (all)	6	8	
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 45 (8.89%)	6 / 42 (14.29%)	
occurrences (all)	4	6	
Dry mouth			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 45 (6.67%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 45 (51.11%)	15 / 42 (35.71%)	
occurrences (all)	23	15	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 45 (46.67%)	10 / 42 (23.81%)	
occurrences (all)	21	10	
Stomatitis			
alternative assessment type: Systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspepsia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphagia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>15 / 45 (33.33%)</p> <p>15</p> <p>3 / 45 (6.67%)</p> <p>3</p> <p>3 / 45 (6.67%)</p> <p>3</p>	<p>4 / 42 (9.52%)</p> <p>4</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>0 / 42 (0.00%)</p> <p>0</p>	
<p>Hepatobiliary disorders</p> <p>Hepatotoxicity</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Jaundice</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 45 (8.89%)</p> <p>4</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>0 / 42 (0.00%)</p> <p>0</p> <p>3 / 42 (7.14%)</p> <p>3</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alopecia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dermatitis acneiform</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry skin</p> <p>alternative assessment type: Systematic</p>	<p>20 / 45 (44.44%)</p> <p>20</p> <p>4 / 45 (8.89%)</p> <p>4</p> <p>5 / 45 (11.11%)</p> <p>5</p>	<p>4 / 42 (9.52%)</p> <p>4</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>1 / 42 (2.38%)</p> <p>1</p>	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 45 (8.89%)</p> <p>4</p> <p>3 / 45 (6.67%)</p> <p>3</p>	<p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 45 (2.22%)</p> <p>1</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>3 / 42 (7.14%)</p> <p>3</p> <p>3 / 42 (7.14%)</p> <p>3</p>	
<p>Infections and infestations</p> <p>Urinary tract infection</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 45 (2.22%)</p> <p>1</p>	<p>3 / 42 (7.14%)</p> <p>3</p>	
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypokalaemia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypoalbuminaemia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyperglycaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>13 / 45 (28.89%)</p> <p>13</p> <p>6 / 45 (13.33%)</p> <p>6</p> <p>3 / 45 (6.67%)</p> <p>3</p> <p>0 / 45 (0.00%)</p> <p>0</p>	<p>9 / 42 (21.43%)</p> <p>9</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>2 / 42 (4.76%)</p> <p>2</p> <p>4 / 42 (9.52%)</p> <p>4</p>	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2010	1. To update the dose and dose escalation scheme. 2. To introduce a new investigational medical product strength of 30 mg.
27 June 2011	1. To explore safety, PK and Pd effects, and activity signals of pimasertib when administered in a new oral dosing regimen: bid as a continuous dosing regimen (bid - continuous regimen).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported