



Clinical trial results:

SGI-110 to potentiate platinum response: A phase Ib/randomised IIa open label clinical trial combining SGI-110 with cisplatin and gemcitabine chemotherapy

Summary

EudraCT number	2015-004062-29
Trial protocol	GB
Global end of trial date	01 June 2020

Results information

Result version number	v1 (current)
This version publication date	21 March 2022
First version publication date	21 March 2022

Trial information

Trial identification

Sponsor protocol code	RHMCAN1142
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Additional study identifiers

ISRCTN number	ISRCTN16332228
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation
Sponsor organisation address	Tremona Road, Southampton, United Kingdom,
Public contact	Denise Dunkley, Southampton Clinical Trials Unit, 44 2381205154, ctu@soton.ac.uk
Scientific contact	Denise Dunkley, Southampton Clinical Trials Unit, 44 2381205154, ctu@soton.ac.uk

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	01 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2018
Global end of trial reached?	Yes
Global end of trial date	01 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To find a safe and effective dose of the trial drug when given in combination with gemcitabine and cisplatin chemotherapy.

Protection of trial subjects:

Independent Ethics Committee (REC): The protocol, amendments and informed consent forms (ICFs) for this study were reviewed and approved by the REC prior to implementation. No subject was treated until the REC had provided written approval of the study and the ICF to the investigator and the sponsor. Protocol amendments and all revisions to the ICF after initial REC approval were submitted for REC review and approval before implementation in accordance with regulatory requirements.

Ethical Conduct of the Study: The study was conducted in accordance with the principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, applicable local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Subject Information and Consent: The ICF(s) used for each study centre complied with ICH, the principles enunciated in the Declaration of Helsinki, local regulatory requirements, and ICH GCP guidelines and was approved by the sponsor and the REC. The investigator, or a person delegated by the investigator, explained the medical aspects of the study, including the nature and purpose of the study and the treatment, the procedures involved, and the potential benefits and risks. Other tasks in the informed consent process may have been delegated by the investigator. After having been informed that participation was voluntary and that subjects may withdraw from the study at any time, without prejudice, each subject signed the REC-approved ICF prior to undergoing any study specific procedures and enrolment in the study.

Concomitant medications and therapies deemed necessary for supportive care and safety of the subject were allowed, including antiemetics and intravenous hydration, per local institutional policy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 19
Worldwide total number of subjects	19
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 8 principal investigators at 8 study centres in the UK enrolled 40 eligible patients in this study between May 2016 and September 2019. Phase I = 17 evaluable patients and 3 non-evaluable patients due to rapid disease progression leading to death (were replaced). Phase II = 20 patients with muscle invasive bladder cancer.

Pre-assignment

Screening details:

Screening criteria: age ≥ 16 y, ECOG 0-1, glomerular filtration rate ≥ 60 ml/min, adequate haematological/biochemical parameters, life expectancy > 3 m, written informed consent. Also in Phase I: incurable metastatic solid cancers; and in Phase II: bladder cancer with pure/predominant transitional cell Carcinoma, T2-4a N0 M0, planned GC for 3-4 cycles.

Period 1

Period 1 title	Overall trial Phase I (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 2 - 20 mg + G-CSF

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	SGI-110
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection , Intraabdominal use , Subcutaneous use

Dosage and administration details:

SGI-110 administration has been established as 20 mg/m², daily, on days 1-5, by sub-cutaneous injection to all patients and preferably in the abdominal area.

- Care must be taken to avoid intradermal injection as this may result in injection site pain.
- SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may occasionally be experienced.
- If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pretreatment with topical or systemic analgesics can be considered.

Investigational medicinal product name	Granulocyte Colony Stimulating Factor
Investigational medicinal product code	GCSF
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use, Injection

Dosage and administration details:

300µg GCSF, daily, on days 15-21, by subcutaneous injection

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

Dosage and administration details:

Gemcitabine 1000 mg/m² on days 8 and 15 of each cycle by IV infusion over 30-60 minutes (and prior to cisplatin on day 8)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion , Intravenous use
Dosage and administration details:	
Cisplatin 70 mg/m2 on day 8 of each cycle by IV infusion over 2-4 hours	
Arm title	Cohort 3 - 30 mg + G-CSF
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	SGI-110
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraabdominal use , Subcutaneous use, Injection
Dosage and administration details:	
SGI-110 administration has been established as 30 mg/m2, daily, on days 1-5, by sub-cutaneous injection to all patients and preferably in the abdominal area.	
• Care must be taken to avoid intradermal injection as this may result in injection site pain. • SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may occasionally be experienced. • If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pretreatment with topical or systemic analgesics can be considered.	
Investigational medicinal product name	Granulocyte Colony Stimulating Factor
Investigational medicinal product code	GCSF
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use, Injection
Dosage and administration details:	
300µg GCSF, daily, on days 15-21, by subcutaneous injection	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion , Intravenous use
Dosage and administration details:	
Cisplatin 70 mg/m2 on day 8 of each cycle by IV infusion over 2-4 hours	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use, Infusion
Dosage and administration details:	
Gemcitabine 1000 mg/m2 on days 8 and 15 of each cycle by IV infusion over 30-60 minutes (and prior to cisplatin on day 8)	
Arm title	Cohort 1 20mg
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Guadecitabine
Investigational medicinal product code	SGI-110
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection , Intraabdominal use , Subcutaneous use

Dosage and administration details:

SGI-110 administration has been established as 20 mg/m², daily, on days 1-5, by sub-cutaneous injection to all patients and preferably in the abdominal area.

- Care must be taken to avoid intradermal injection as this may result in injection site pain.
- SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may occasionally be experienced.
- If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pretreatment with topical or systemic analgesics can be considered.

Number of subjects in period 1	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg
Started	9	6	4
Completed	8	5	4
Not completed	1	1	0
Death prior to cycle 2	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 2 - 20 mg + G-CSF
Reporting group description: -	
Reporting group title	Cohort 3 - 30 mg + G-CSF
Reporting group description: -	
Reporting group title	Cohort 1 20mg
Reporting group description: -	

Reporting group values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg
Number of subjects	9	6	4
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	2	2
From 65-84 years	3	3	2
Not recorded	1	1	0
Age continuous			
Age continuous description			
Units: years			
median	56	68	63
inter-quartile range (Q1-Q3)	52.5 to 65	47 to 70	57.5 to 70
Gender categorical			
Units: Subjects			
Female	3	1	2
Male	5	4	2
Not recorded	1	1	0
ECOG Performance Status			
Eastern Cooperative Oncology Group (ECOG) performance status			
Units: Subjects			
0 - Fully Active	5	2	2
1 - Restricted in Physically Strenuous Activity	3	3	2
Not recorded	1	1	0

Reporting group values	Total		
Number of subjects	19		
Age categorical			
Units: Subjects			
Adults (18-64 years)	9		
From 65-84 years	8		
Not recorded	2		
Age continuous			
Age continuous description			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		

Gender categorical			
Units: Subjects			
Female	6		
Male	11		
Not recorded	2		
ECOG Performance Status			
Eastern Cooperative Oncology Group (ECOG) performance status			
Units: Subjects			
0 - Fully Active	9		
1 - Restricted in Physically Strenuous Activity	8		
Not recorded	2		

End points

End points reporting groups

Reporting group title	Cohort 2 - 20 mg + G-CSF
Reporting group description: -	
Reporting group title	Cohort 3 - 30 mg + G-CSF
Reporting group description: -	
Reporting group title	Cohort 1 20mg
Reporting group description: -	

Primary: Dose Limiting Toxicity

End point title	Dose Limiting Toxicity ^[1]
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End point description:

Any of the following events occurring between the first dose administration of SGI-110 and day 1 of the second cycle of treatment will constitute a DLT if, in the opinion of the investigator, the event is defined as definitely or probably related to the combination of SGI-110, cisplatin and gemcitabine:

- Greater than 14 days of delay in commencing a second cycle of treatment due to drug toxicity
- Grade 4 neutropenia $\geq$ 7 days duration
- Grade 3 – 4 neutropenia associated with a temperature $\geq$ 38.5°C
- Grade 3 – 4 neutropenia associated with bacteriologically proven sepsis
- Any grade 4 thrombocytopenia $\geq$ 7 days duration
- Grade 3 thrombocytopenia associated with non-traumatic bleeding
- Any other clinically significant grade 3 or above toxicity except nausea or vomiting

A DLT excludes isolated laboratory changes of any grade (except as specified above) without clinical sequelae or clinical significance.

End point type	Primary
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End point timeframe:

Phase I - Trial Period

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: Phase 1 trial, no statistical analyses

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Subjects				
$\geq$ 14 days of delay commencing 2nd cycle	0	1	0	
Grade 4 Neutropenia $\geq$ 7 days	0	1	1	
Grade 3 or Grade 4 Febrile Neutropenia ($\geq$ 38.5°C)	2	1	1	
Grade 3 or Grade 4 Neutropenic Sepsis	0	0	0	
Grade 4 Thrombocytopenia $\geq$ 7 days	0	2	0	
G3 Thrombocytopenia with non-traumatic bleeding	0	0	0	
Other Clinically Significant G3 or above toxicity	0	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of complete cycles of Guadecitabine

End point title	Number of complete cycles of Guadecitabine
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End point description:

End point type	Secondary
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End point timeframe:

Treatment Period

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Subjects				
1 cycle	1	2	0	
2 cycles	1	2	0	
3 cycles	2	0	1	
4 cycles	1	0	0	
5 cycles	2	0	2	
6 cycles	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Gemcitabine - Number of cycles received

End point title	Gemcitabine - Number of cycles received
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End point description:

End point type	Secondary
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End point timeframe:

Treatment Period

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Cycles				
median (full range (min-max))	3.5 (1.0 to 6.0)	2.0 (1.0 to 6.0)	5 (3 to 6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cisplatin - Number of Cycles Received

End point title Cisplatin - Number of Cycles Received

End point description:

End point type Secondary

End point timeframe:

Treatment Period

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Cycles				
median (full range (min-max))	3.5 (1.0 to 6.0)	2.0 (1.0 to 6.0)	5 (3 to 6)	

Statistical analyses

No statistical analyses for this end point

Secondary: G-CSF Administration as Per Protocol

End point title G-CSF Administration as Per Protocol^[2]

End point description:

End point type Secondary

End point timeframe:

Treatment Period

Notes:

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

Justification: Phase 1 trial, no statistical analyses

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	5		
Units: Subjects				
Yes	7	4		
No	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of deaths on trial

End point title	Number of deaths on trial
End point description:	
End point type	Secondary
End point timeframe:	
Trial Period	

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Line 1 Percentage Methylation from Cycle 1 Day 1

End point title	Mean Change in Line 1 Percentage Methylation from Cycle 1 Day 1
End point description: AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).	
End point type	Secondary
End point timeframe:	
Trial Period	

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Percentage				
arithmetic mean (standard error)	0 ($\pm$ 0)	0 ($\pm$ 0)	0 ($\pm$ 0)	

Attachments (see zip file)	Line-1 plot1.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Hgb-F Fold Change from Cycle 1 Day 1

End point title	Hgb-F Fold Change from Cycle 1 Day 1
End point description:	AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).
End point type	Secondary
End point timeframe:	
Trial Period	

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Percentage				
number (not applicable)	0	0	0	

Attachments (see zip file)	Hbf panel plot1.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in LTR12C

End point title	Mean Change in LTR12C
End point description:	AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).
End point type	Secondary
End point timeframe:	
Trial Period	

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Percentage				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)	0 (± 0)	

Attachments (see zip file)	LTR12C plot1.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in SAT2 percentage methylation

End point title	Mean Change in SAT2 percentage methylation
End point description:	AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).
End point type	Secondary
End point timeframe:	
Trial Period	

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Percentage				
arithmetic mean (standard error)	0 (± 0)	0 (± 0)	0 (± 0)	

Attachments (see zip file)	SAT2 plot1.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in D4Z4 percentage methylation

End point title	Mean Change in D4Z4 percentage methylation
End point description:	AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).
End point type	Secondary

End point timeframe:

Trial Period

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Percentage				
arithmetic mean (standard error)	0 ($\pm$ 0)	0 ($\pm$ 0)	0 ($\pm$ 0)	

Attachments (see zip file)

D4Z4 plot1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in NBL2 percentage methylation

End point title	Mean Change in NBL2 percentage methylation
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End point description:

AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).

End point type	Secondary
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End point timeframe:

Trial Period

End point values	Cohort 2 - 20 mg + G-CSF	Cohort 3 - 30 mg + G-CSF	Cohort 1 20mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	4	
Units: Percentage				
arithmetic mean (standard error)	0 ($\pm$ 0)	0 ($\pm$ 0)	0 ($\pm$ 0)	

Attachments (see zip file)

NBL2 plot1.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting requirement applies for all adverse events occurring up to 4 weeks after the last administration of study drugs. SAEs, SARs and SUSARs should be reported within 24 hours of the site becoming aware of the event.

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Phase I - 20mg + G-CSF
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Reporting group description: -

Reporting group title	Phase I - 20mg
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Reporting group description: -

Reporting group title	Phase I - 30mg + G-CSF
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Reporting group description: -

Serious adverse events	Phase I - 20mg + G-CSF	Phase I - 20mg	Phase I - 30mg + G-CSF
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	3 / 4 (75.00%)	4 / 5 (80.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Peripheral ischaemia	Additional description: Peripheral ischaemia		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure	Additional description: Seizure		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia		

subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric obstruction	Additional description: Ureteric obstruction		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection	Additional description: Infection		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase I - 20mg + G-CSF	Phase I - 20mg	Phase I - 30mg + G-CSF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	4 / 4 (100.00%)	5 / 5 (100.00%)
Vascular disorders	Additional description: Flushing		
Flushing			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hypertension	Additional description: Hypertension		

subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Embolism	Additional description: Embolism		
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Face oedema	Additional description: Face oedema		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injection site pain	Additional description: Injection site pain		
subjects affected / exposed	3 / 8 (37.50%)	2 / 4 (50.00%)	1 / 5 (20.00%)
occurrences (all)	21	17	3
Malaise	Additional description: Malaise		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Injection site discomfort	Additional description: Injection site discomfort		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Injection site bruising	Additional description: Injection site bruising		
subjects affected / exposed	0 / 8 (0.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	0 / 8 (0.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Injection site erythema	Additional description: Injection site erythema		
subjects affected / exposed	0 / 8 (0.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Chills	Additional description: Chills		

subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Fatigue	Additional description: Fatigue		
subjects affected / exposed	8 / 8 (100.00%)	3 / 4 (75.00%)	5 / 5 (100.00%)
occurrences (all)	15	9	8
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site reaction	Additional description: Injection site reaction		
subjects affected / exposed	1 / 8 (12.50%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	1	15	0
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	3 / 8 (37.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia	Additional description: Insomnia		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Investigations			
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	3 / 5 (60.00%)
occurrences (all)	1	1	20
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase	Additional description: Aspartate aminotransferase increased		

increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Monocyte count decreased	Additional description: Monocyte count decreased		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Platelet count increased	Additional description: Platelet count increased		
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	4	1	0
Red blood cell count decreased	Additional description: Red blood cell count decreased		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion	Additional description: Contusion		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Stoma site haemorrhage	Additional description: Stoma site haemorrhage		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Arthropod bite	Additional description: Arthropod bite		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	Additional description: Palpitations		
	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
	1	0	0
Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all) Peripheral motor neuropathy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Extrapyramidal disorder subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all)	Additional description: Paraesthesia		
	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
	1	0	0
	Additional description: Peripheral motor neuropathy		
	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
	0	1	0
	Additional description: Peripheral sensory neuropathy		
	1 / 8 (12.50%)	1 / 4 (25.00%)	1 / 5 (20.00%)
	1	1	1
	Additional description: Headache		
	2 / 8 (25.00%)	2 / 4 (50.00%)	1 / 5 (20.00%)
	2	2	1
	Additional description: Dysgeusia		
	0 / 8 (0.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
	0	4	0
	Additional description: Extrapyramidal disorder		
	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
	0	1	0
	Additional description: Dizziness		
	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 5 (20.00%)
	2	0	1
	Additional description: Lethargy		
	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 5 (20.00%)
	1	0	1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia	Additional description: Anaemia		
	6 / 8 (75.00%)	2 / 4 (50.00%)	2 / 5 (40.00%)
	9	8	19
	Additional description: Thrombocytopenia		
	7 / 8 (87.50%)	4 / 4 (100.00%)	4 / 5 (80.00%)
	25	16	31
	Additional description: Neutropenia		

subjects affected / exposed	5 / 8 (62.50%)	4 / 4 (100.00%)	5 / 5 (100.00%)
occurrences (all)	15	5	12
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Deafness	Additional description: Deafness		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	0 / 8 (0.00%)	2 / 4 (50.00%)	1 / 5 (20.00%)
occurrences (all)	0	3	7
Vestibular disorder	Additional description: Vestibular disorder		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypoacusis	Additional description: Hypoacusis		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Vomiting	Additional description: Vomiting		
subjects affected / exposed	3 / 8 (37.50%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	6	1	1
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	1 / 8 (12.50%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diarrhoea	Additional description: Diarrhoea		

subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	0	3	2
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Melaena	Additional description: Melaena		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea	Additional description: Nausea		
subjects affected / exposed	6 / 8 (75.00%)	4 / 4 (100.00%)	3 / 5 (60.00%)
occurrences (all)	12	13	4
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Constipation	Additional description: Constipation		
subjects affected / exposed	4 / 8 (50.00%)	4 / 4 (100.00%)	1 / 5 (20.00%)
occurrences (all)	4	5	3
Mouth ulceration	Additional description: Mouth ulceration		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oral pain	Additional description: Oral pain		
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Skin induration	Additional description: Skin induration		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dermatitis acneiform	Additional description: Dermatitis acneiform		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Acne	Additional description: Acne		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Purpura subjects affected / exposed occurrences (all)	Additional description: Purpura		
	0 / 8 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Pruritis subjects affected / exposed occurrences (all)	Additional description: Pruritis		
	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	Additional description: Alopecia		
	3 / 8 (37.50%) 3	3 / 4 (75.00%) 4	1 / 5 (20.00%) 1
Erythema subjects affected / exposed occurrences (all)	Additional description: Erythema		
	1 / 8 (12.50%) 1	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	Additional description: Urticaria		
	1 / 8 (12.50%) 5	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	Additional description: Rash		
	0 / 8 (0.00%) 0	1 / 4 (25.00%) 1	1 / 5 (20.00%) 3
Rash macular subjects affected / exposed occurrences (all)	Additional description: Rash macular		
	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Renal and urinary disorders			
Urinary tract pain subjects affected / exposed occurrences (all)	Additional description: Urinary tract pain		
	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Acute kidney injury subjects affected / exposed occurrences (all)	Additional description: Acute kidney injury		
	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Nocturia subjects affected / exposed occurrences (all)	Additional description: Nocturia		
	0 / 8 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Urine odour abnormal subjects affected / exposed occurrences (all)	Additional description: Urine odour abnormal		
	0 / 8 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Haematuria	Additional description: Haematuria		

subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Groin pain	Additional description: Groin pain		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	3
Myalgia	Additional description: Myalgia		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Back pain	Additional description: Back pain		
subjects affected / exposed	3 / 8 (37.50%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	1
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Infections and infestations			
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 8 (12.50%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
Nasopharyngitis	Additional description: Nasopharyngitis		

subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Furuncle	Additional description: Furuncle		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection	Additional description: Viral upper respiratory tract infection		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Lip infection	Additional description: Lip infection		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Corona Virus Infection	Additional description: Corona Virus Infection		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	3	3	1
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	6
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	1
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1

Dehydration subjects affected / exposed occurrences (all)	Additional description: Dehydration		
	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Hypocalcemia subjects affected / exposed occurrences (all)	Additional description: Hypocalcemia		
	1 / 8 (12.50%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2016	MHRA requested changes to the protocol, PIS/ICF updates and addition of a 4th site (Rob Jones).
08 December 2016	Updated IB v07 18 Aug 2016, updated protocol RIS, PIS/ICF side effects and exposure numbers updated in line with new IB.
25 May 2018	-Provide clarification to ensure that, as was the original intention, all patients in the control arm (GC alone) should not have a delay in treatment (Gemcitabine and Cisplatin) administration following randomisation, is clear. -Alter the neutrophil and platelet count criteria for proceeding to subsequent cycles to ensure patients are not unduly delayed. It has been noted in the dose escalation phase that patients were experiencing dose delays enforced by the protocol that would not have usually clinically been implemented and that those patients with reduced neutrophil and platelets counts were returning to within limits within 2 weeks. The TMG have agreed that unnecessary dose delays should be avoided in the neoadjuvant setting that the dose expansion phase will be conducted in. -Request additional sites to be added for dose expansion phase. - Include updates to IMPD previously sent only to the MHRA
07 February 2019	Updated IB v08 18 Aug 2016, updated protocol RIS, PIS/ICF side effects and exposure numbers updated in line with new IB.
02 July 2019	Amendment changes: • Pre-treatment assessments permitted within 3 days prior to Day 1, 8 and 15. • Gemcitabine SmPC updated. • Cisplatin SmPC updated. • RSI table in protocol updated. • PIS – new common side effect of Cisplatin added. • ICF – updated to reflect change in version of PIS. • Changes to predicted timelines – recruitment completion, patient follow-up and final report. Dr Crabb (SPIRE Chief Investigator) has stated 'The changes within this amendment take into account the greater level of safety data now available for this combination of drugs and brings the protocol into line with standard levels of monitoring and toxicity assessment for this form of treatment.'

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33472913>