SPIRE

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

Short Title: SGI-110 to potentiate platinum response

[redacted]

SPONSOR: University Hospital Southampton NHS Foundation Trust

COORDINATING CENTRE: Southampton Clinical Trials Unit

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Name: [redacted] **Role:** [redacted]
Signature: **Date:**

Name: [redacted] **Role:** [redacted]
Signature: **Date:**

Name: [redacted] **Role:** [redacted]
Signature: **Date:**

MAIN TRIAL CONTACT

[redacted]

Protocol Information

This protocol describes the SPIRE trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering patients for the first time are advised to contact the Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will adhere to the principles of Good Clinical Practice. It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AML	Acute myeloid leukaemia
AR	Adverse reaction
AST	Aspartate transaminase
AUC	Area under the curve
BSA	Body surface area
CRF	Case report form
CI	Chief Investigator
CTA	Clinical trial authorisation
CTCAE	Common terminology criteria for adverse events
CTU	Clinical trials unit
DLT	Dose limiting toxicity
DMEC	Data monitoring and ethics committee
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DSUR	Development safety update report
ECMC	Experimental Cancer Medicine Centre
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
EudraCT	European Clinical Trials Database
GC	Gemcitabine and cisplatin
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
HbF	Haemoglobin F
IB	Investigator brochure
IV	Intravenous
IMP	Investigational medicinal product
ISF	Investigator Site File
LINE-1	Long interspersed nucleotide element-1
MBED	Maximally biologically effective dose
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIBC	Muscle invasive bladder cancer
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIMP	Non Investigational Medicinal Product
NTD	Non tolerated dose
PD	Pharmacodynamic
PI	Principal investigator
PK	Pharmacokinetic
REC	Research Ethics Committee
RP2D	Recommended phase II dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction

SC	Subcutaneous
SCTU	Southampton Clinical Trials Unit
SOP	Standard operating procedure
SmPC	Summary of product characteristics
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TURBT	Transurethral resection of a bladder tumour
UBC	Urothelial bladder cancer
ULN	Upper limit of normal
TMF	Trial master file
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SYNOPSIS

Title:	SGI-110 to potentiate platinum response: A phase Ib/randomised IIa open label clinical trial combining SGI-110 with cisplatin and gemcitabine chemotherapy for solid malignancies including bladder cancer
Short Title:	SGI-110 to potentiate platinum response
Acronym	SPIRE
Sponsor:	University Hospital Southampton NHS Foundation Trust
Funder:	Cancer Research UK and Astex Pharmaceuticals
Trial Phase:	Ib/IIa
Primary Objective:	To establish a safe and biologically effective dose and schedule for SGI-110 in combination with GC chemotherapy for future phase II/III investigation as a neoadjuvant therapy in bladder cancer
Secondary Objectives:	To evaluate the safety and toxicity profile of SGI-110 when combined with GC To provide evidence of the pharmacodynamic effect of SGI-110 in combination with GC in blood and bladder cancer tissue To provide pharmacokinetic data for SGI-110 exposure To evaluate the safety and deliverability of SGI-110 when combined with GC as a neoadjuvant treatment for muscle invasive bladder cancer prior to radical local therapy
Rationale:	SGI-110 is a DNA methyltransferase inhibitor developed for optimised delivery of the active metabolite decitabine. Pre-clinical data support that cisplatin resistance in bladder and other cancers is derived, at least in part, through promotor methylation of silenced genes relevant to a cisplatin resistance phenotype. Experimentally this is reversible through co-administration of DNA hypomethylating agents. The central hypothesis to be tested in this clinical trial is that SGI-110 can be safely combined with GC in bladder cancer at doses able to induce demethylation of genes associated with cisplatin resistance.
Trial Design:	SPIRE is a phase Ib/IIa clinical trial to develop a combination of SGI-110 with GC. It incorporates an initial Dose Escalation Phase in advanced solid tumours (including advanced/metastatic bladder cancer). This will be followed by a randomised Dose Expansion Phase in bladder cancer patients receiving neoadjuvant chemotherapy.
Sample size :	Maximum 56 patients (35-45 likely)
Investigational Medicinal Product:	SGI-110 Gemcitabine Cisplatin
Non-Investigational Medicinal Product:	G-CSF

Inclusion Criteria:	All Patients: 1. Eastern Cooperative Oncology Group (ECOG, see Appendix I) performance status of 0 or 1 2. Glomerular filtration rate estimation of ≥ 60 ml/min according to either the Cockcroft and Gault formula (see Appendix II) or by Cr-51 EDTA or Tc-99m DTPA clearance 3. Adequate haematological parameters • Haemoglobin ≥ 90 g/L • Neutrophil count ≥ 1.5 x10^9/L • Platelets ≥ 100 x10^9/L 4. Adequate biochemical parameters • Bilirubin ≤ 1.5 x ULN • ALT and ALP ≤ 2.5 x ULN (ALP ≤ 5 x ULN if caused by liver or bone metastases) 5. Aged 16 years or over 6. Life expectancy > 3 months 7. Provision of written informed consent Patients In The Dose Expansion Phase: 8. Bladder cancer with a pure or a predominant component of transitional cell carcinoma 9. Clinical stage T2-4a N0 M0 10. Planned to commence GC for 3 or 4 cycles.
Exclusion Criteria:	All Patients: 1. Unresolved toxicities from prior therapy greater than CTCAE v4.03 grade 1 (with the exception of alopecia) at the time of registration 2. Prior radiotherapy to > 30% of bone marrow 3. Major surgery within 30 days 4. Any investigational medicinal product within 30 days 5. Allergy or other known intolerance to any of the proposed study drugs including supportive agents and inclusive of G-CSF and locally utilised anti-emetics 6. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable angina pectoris or congestive cardiac failure (New York Heart Association ≥ grade 2) within the last 6 months 7. Women who are pregnant or breast feeding. (Women of child-bearing potential must have a negative pregnancy test performed within 7 days prior to the start of trial treatment) 8. Patients of child-bearing potential who are not using a highly effective method of contraception as detailed in section 4.7 9. Any patient who, in the judgment of the local investigator, is unlikely to comply with trial procedures, restrictions or requirements 10. Any patient who has received a live vaccine within 4 weeks of initiation of their treatment. Patients In The Dose Expansion Phase: 11. Current separate other malignancy. Current non-melanoma skin cancer, cervical carcinoma in situ or incidental localised prostate cancer is permissible. Other prior malignancy is

	acceptable if the treatment within the SPIRE trial would be given with curative intent.
Treatment (GC chemotherapy):	All patients: • Cisplatin 70 mg/m^2, IV infusion, day 8 of each cycle • Gemcitabine 1000 mg/m^2, IV infusion, days 8 and 15 of each cycle
Treatment (SGI-110):	In the Dose Expansion Phase, patients will be randomised 1:1 in a non-blinded manner to receive either: • Arm A: GC combined with SGI-110 at 20 mg/m^2, daily, on days 1-5 + GCSF (RP2D) • Arm B: GC alone
Treatment (growth factors)	• Arm A: all patients randomised to receive GC in combination with SGI-110 will receive GCSF 300µg, daily, on days 15-21 • Arm B: Patients in the GC alone arm may receive GCSF at the discretion of the local investigator
Concomitant Therapy:	Anti-emetics and suitable intravenous hydration pre- and post-cisplatin will be administered according to local institutional policy. Live vaccines are prohibited during treatment and for at least 4 weeks following the end of treatment. In accordance with the cisplatin SmPC, nephrotoxic and ototoxic drugs are contraindicated during the course of the trial.
Primary Trial Endpoints:	To establish a RP2D for SGI-110 when combined with GC chemotherapy from both: • the MTD based on defined criteria for dose limiting toxicity (DLT) assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and • the Maximally Biologically Effective Dose (MBED) based on plasma/serum DNA LINE-1 methylation and haemoglobin F (HbF) re-expression status
Secondary Trial Endpoints:	The toxicity profile using CTCAE v4.03 of SGI-110 in combination with GC, including a randomised comparison to GC alone at the RP2D. Pharmacokinetics of SGI-110 when combined with GC. The pathological complete response rate of bladder cancer patients enrolled in the dose expansion phase of the trial (not formally statistically powered for this) Investigation of other potential PD biomarkers for SGI-110 target effect in plasma/serum DNA and/or PBMCs and/or in archival pre- and post-treatment tissue samples, potentially including but not limited to: • promoter methylation of MAGE-A1 and other cancer testis antigens • 5-methylcytosine levels • biomarkers of Nrf2 activation including Nrf2, KEAP1, Nrf2 transcriptional targets (e.g., glutathione reductase-1, metallothioneins, NQO-1)

Statistical Methods:	The phase Ib part of the trial utilised a modified rolling 6 dose escalation design. (This part of the trial has now completed recruitment.) In the phase IIa part of the trial, analyses will be conducted in the intent to treat population. These analyses will not be powered for formal statistical comparisons of efficacy. Descriptive statistics will be used to describe rates of toxicity, efficacy and translational endpoints by treatment arm.

Schedule of events: DOSE ESCALATION – THIS PHASE OF THE TRIAL HAS NOW COMPLETED RECRUITMENT

	Screening	Cycles 1 + 2							Cycles 3+			End of Treatment[a]	Follow up[b]
Cycle day	-28 to 1	1[c]	2	3	4	5	8	15	1	8	15		
Informed consent[d]	X												
Eligibility criteria determination	X												
Registration	X												
Medical history	X												
Height	X												
Weight	X	X							X			X	
Physical examination[e]	X	X					X	X	X			X	
Vital signs	X	X	X	X	X	X	X	X	X			X	
ECOG Performance status	X	X					X	X	X			X	
Full blood count	X	X					X	X	X	X	X	X	
Serum biochemistry[f]	X	X					X	X	X	X	X	X	
GFR assessment[g]	X						X			X			
PK samples		X[h]											
Main study & translational blood samples[i]		X					X	X	X	X		X	
Haemoglobin electrophoresis		X					X	X	X	X		X	
Translational tissue sample	X[j]											(X[k])	(X[l])
Disease evaluation[m]	(X)								(X)			(X)	
Toxicity assessment[n]		X					X	X	X	X	X	X	X
Concomitant medication		X							X			X	X
Cisplatin administration							X			X			
Gemcitabine administration							X	X		X	X		
SGI-110 administration		X	X	X	X	X			X[o]				
(G-CSF)[p]								(X)			(X)		
Pregnancy test[q]	X	X							X			X	

[a] To occur 28 ± 7 days after last doses of SGI-110
[b] Assessment of AEs felt to be clinically significant and to have occurred due to SGI-110 or its interaction with chemotherapy should be followed until resolution to CTCAE v4.03 < grade 2 in severity.
[c] If done within the last 7 days during the screening process then weight, physical exam, performance status, full blood count, serum biochemistry and pregnancy test do not need to be repeated on cycle 1 day 1.
[d] Consent may be obtained up to 42 days prior to registration
[e] Physical Examination should include a neurologic and audiology examination according to institutional standards
[f] Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
[g] GFR calculated by the Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice
[h] PK sampling will be undertaken in cycle 1 only. Samples to be taken on day 1 at zero (pre-dose), 15 min, 30 min, 60 min, 90 min and 2 hr, 4 hr, 6 hr and 8 hr post-dose
[i] Main study & translational blood samples should be taken prior to administration of SGI-110 or chemotherapy on the respective days that they are taken
[j] The translational tissue sample during screening will be from the most recent available archival biopsy or surgical sample.
[k] Translational tissue samples will not be routinely taken after chemotherapy in the Dose Escalation Phase of the trial but will be collected if they have been undertaken as part of routine practice.
[l] If post chemotherapy sample not already collected
[m] Disease evaluation is at the discretion of the investigator according to local policy for the relevant disease site at all times. CT scan of the chest, abdomen and pelvis is recommended in most cases.
[n] AE monitoring should occur at the timepoints indicated from screening through to completion of treatment and follow up
[o] SGI-110 administered on each of days 1-5 of each cycle
[p] Only in dose cohorts in which G-CSF is being incorporated. Administered day 15 to 21 of the cycle.
[q] Women of child-bearing potential will have a pregnancy test performed within 7 days prior to the start of trial treatment, at day 1 of each cycle and at the end of treatment.

Schedule of events: DOSE EXPANSION – Arm A (GC + SGI-110 + GCSF)

	Screening	Cycle 1[1]			Cycles 2+[1]			End of Treatment[a]	Follow up[b]
Cycle day	-28 to 1	1[c]	8	15	1	8	15		
Informed consent[d]	X								
Eligibility criteria determination	X								
Registration/randomisation	X								
Medical history	X								
Height	X								
Weight	X				X			X	
Physical examination[e]	X	X	X	X	X			X	
Vital signs[f]	X	X	X	X	X			X	
ECOG Performance status	X	X	X	X	X			X	
Full blood count	X	X	X	X	X	X	X	X	
Serum biochemistry[g]	X	X	X	X	X	X	X	X	
GFR assessment[h]	X		X			X			
Translational blood samples[i]		X	X		X	X		X	
Haemoglobin electrophoresis		X	X		X	X		X	
Translational tissue sample (archival sample)	X[j]							X[k]	X[l]
Disease evaluation[m]	(X)				(X)			(X)	(X)
Toxicity assessment[n]		X	X	X	X	X	X	X	X
Concomitant medication		X			X			X	X
Cisplatin administration			X			X			
Gemcitabine administration			X	X		X	X		
SGI-110 administration[o]		X			X				
G-CSF[p]				X			X		
Pregnancy test[q]	X	X			X			X	
Morbidity/mortality review[r]									X

[1] Specified pre-treatment assessments to be performed within 3 days prior to Day 1, Day 8 and Day 15 (also see footer c for Cycle 1 Day 1)

[a] To occur 28 ± 7 days after last doses of SGI-110

[b] Assessment of AEs felt to be clinically significant and to have occurred due to SGI-110 or its interaction with chemotherapy should be followed until resolution to CTCAE v4.03 < grade 2 in severity.

[c] If undertaken within the last 7 days during screening then weight, physical exam, performance status, full blood count, serum biochemistry and pregnancy test do not need to be repeated within 3 days prior to cycle 1 day 1.

[d] Consent may be obtained up to 42 days prior to registration/randomisation

[e] Physical Examination should include a neurologic and audiology examination according to institutional standards

[f] Vital signs also recorded on days 2-4 in those attending to receive SGI-110

[g] Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles

[h] GFR calculated by Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice

[i] Translational blood samples should be taken prior to administration of SGI-110 or chemotherapy on the respective days that they are taken

[j] The translational tissue sample (archival sample) during screening will be from the most recent available archival biopsy or TURBT sample.

[k] The translational tissue sample (archival sample) following chemotherapy/SGI-110 will be from the cystectomy sample (or if cystectomy not performed from the next cystoscopy sample)

[l] If post chemotherapy sample not already collected

[m] Disease evaluation is at the discretion of the investigator according to local policy for the relevant disease site at all times. CT scan of the chest, abdomen and pelvis is recommended in most cases.

[n] AE monitoring should occur at the timepoints indicated from screening through to completion of treatment and follow up

[o] SGI-110, only in those randomised to receive it, administered on each of days 1-5 of each cycle

[p] Administered day 15 to 21 of the cycle (300µg GCSF, daily)

[q] Women of child-bearing potential will have a pregnancy test performed within 7 days prior to the start of trial treatment, within 3 days prior to day 1 of each cycle and at the end of treatment

[r] To be assessed at 30 days (+/- 2 weeks) after: bladder cystectomy (using Clavien Dindo Grading (see Appendix IV)) or radiotherapy or last trial treatment (if no bladder cystectomy or radiotherapy).

Schedule of events: DOSE EXPANSION – Arm B (GC Alone)

FOLLOWING RANDOMISATION PATIENTS IN ARM B SHOULD PROCEED STRAIGHT TO CYCLE 1 DAY 8 IN THE SCHEDULE TO RECEIVE GEMCITABINE/CISPLATIN. A 7 DAY DELAY IS NOT REQUIRED. (SUBSEQUENT CYCLES ARE OF 21 DAYS AND INCLUDE TRIAL PROCEDURES ON DAY 1 OF EACH CYCLE ACCORDING TO THE SCHEDULE BELOW)

	Screening	Cycle 1[1]		Cycles 2+[1]			End of Treatment[a]	Follow-Up
Cycle day	-28 to 1	8[b]	15	1	8	15		
Informed consent[c]	X							
Eligibility criteria determination	X							
Registration/randomisation	X							
Medical history	X							
Height	X							
Weight	X			X			X	
Physical examination[d]	X	X	X	X			X	
Vital signs	X	X	X	X			X	
ECOG Performance status	X	X	X	X			X	
Full blood count[e]	X	X	X	X	X	X	X	
Serum biochemistry[e]	X	X	X	X	X	X	X	
GFR assessment[ef]	X	X			X			
Translational blood samples[g]		X		X	X		X	
Haemoglobin electrophoresis		X		X	X		X	
Translational tissue sample (archival sample)	X[h]						X[i]	X[n]
Disease evaluation[j]	(X)			(X)			(X)	(X)
Toxicity assessment[k]		X	X	X	X	X	X	X
Concomitant medication		X		X			X	X
Cisplatin administration		X			X			
Gemcitabine administration		X	X		X	X		
Pregnancy test[l]	X	X		X			X	
Morbidity/mortality review[m]								X

[1] Specified pre-treatment assessments to be performed within 3 days prior to Day 1, Day 8 and Day 15 (also see footer b for Cycle 1 Day 8)

[a] To occur 28 ± 7 days after last doses of Gemcitabine

[b] If undertaken within the last 7 days during screening then weight, physical exam, performance status, full blood count, serum biochemistry and pregnancy test do not need to be repeated within 3 days prior to cycle 1 day 8.

[c] Consent may be obtained up to 42 days prior to registration/randomisation

[d] Physical Examination should include a neurologic and audiology examination according to institutional standards

[e] Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles

[f] GFR calculated by Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice

[g] Translational blood samples should be taken prior to administration chemotherapy on the respective days that they are taken

[h] The translational tissue sample(archival sample) during screening will be from the most recent available archival biopsy or TURBT sample.

[i] The translational tissue sample (archival sample) following chemotherapy will be from the cystectomy sample (or if cystectomy not performed from the next cystoscopy sample)

[j] Disease evaluation is at the discretion of the investigator according to local policy for the relevant disease site at all times. CT scan of the chest, abdomen and pelvis is recommended in most cases.

[k] AE monitoring should occur at the timepoints indicated from screening through to completion of treatment and follow up

[l] Women of child-bearing potential will have a pregnancy test performed within 7 days prior to the start of trial treatment, within 3 days prior to day 1 of each cycle and at the end of treatment

[m] To be assessed at 30 days (+/- 2 weeks) after: bladder cystectomy (using Clavien Dindo Grading (see Appendix IV)) or radiotherapy or last trial treatment (if no bladder cystectomy or radiotherapy)

[n] If post chemotherapy sample not already collected

1 INTRODUCTION

1.1 CHEMOTHERAPY FOR BLADDER CANCER

Urothelial bladder cancer (UBC) accounts for 10,000 new diagnoses and 5,000 deaths annually in the UK.[1]

Cisplatin based chemotherapy is a standard of care therapy for UBC for both palliative first line treatment of advanced/metastatic disease and radical neoadjuvant treatment of localised muscle invasive bladder cancer (MIBC).[2-4] In the UK this is most commonly administered as a doublet combination with gemcitabine (GC).[4,5] Attempts to replace cisplatin as a component of chemotherapy regimens, for example with carboplatin, have been unsuccessful to date.[5] For metastatic disease GC results in a median survival and time to progressive disease of approximately 14 months and 7 months respectively. Cisplatin based neoadjuvant chemotherapy prior to either radical cystectomy or radical radiotherapy for MIBC adds an absolute survival advantage of 5-6% to overall cure rates, averaged across T stages, at approximately 50%.[2,3,6]

Cisplatin resistance remains a critical barrier to therapeutic advance in bladder cancer. For example, in a key randomised trial comparing cisplatin based regimens for advanced disease, 17% had primary refractory disease, and by 3 years only 13% were alive and free from progression.[7]

Progression or relapse of UBC following cisplatin based chemotherapy is associated with a dismal prognosis. For patients receiving second line palliative chemotherapy, after a prior platinum based regimen, the median survival is consistently under 1 year with a median progression free survival in the range of 2 to 5 months. To date there has been no clearly established standard of care treatment for UBC patients with clinical cisplatin resistance and no demonstration of survival benefit for any second line palliative therapy.[5] Furthermore, to date no molecularly targeted or stratified treatment strategy has yet been established for use in UBC.[5]

Taken as a whole, the data available for MIBC and metastatic UBC imply a pressing unmet need for improvements to what is currently achieved with systemic therapy.

1.2 USE OF GC CHEMOTHERAPY IN SETTINGS OTHER THAN UBC

Gemcitabine combined with platinum is a standard first-line treatment for non-small cell lung cancer. Four regimens – paclitaxel-cisplatin, gemcitabine-cisplatin, docetaxel-cisplatin and carboplatin-paclitaxel - were shown to be comparable in the early part of the century.[8] Since then pemetrexed has been shown to be superior for those with non-squamous histologies but gemcitabine-platinum treatment remains the treatment of choice for those with squamous cell carcinomas of the lung.[9] The BTOG2 trial compared gemcitabine-carboplatin with gemcitabine-cisplatin at two different doses of cisplatin (50 mg/m^2 and 80 mg/m^2). Carboplatin was clinically equivalent to the higher dose of cisplatin.[10] As with bladder cancer, cisplatin resistance is a major problem and subsequent therapies, such as erlotinib and docetaxel, have low response rates and short durations of response.

1.3 HYPOMETHYLATING DRUGS IN COMBINATION WITH GC CHEMOTHERAPY FOR UBC

Altered gene expression in cancer may arise through structural genomic changes (such as gene mutation or loss/gain of chromosomal content) or through reversible changes in the regulation and expression of genes. The latter, known as epigenetic control, includes biochemical modifications to the histone proteins adjacent to chromatin, and to DNA itself. To date, DNA methylation at CpG di-nucleotides is the best studied epigenetic change in cancer. In general there is a loss of CpG methylation in cancerous cells that can lead to genomic instability and activation of previously silent oncogenes. Conversely, there is often an increase in DNA methylation in the promoter regions around many genes, which can lead to silencing of tumour suppressor genes (TSG) in cancer. In UBC, many genes are affected by promoter hypermethylation. Reversal of this hypermethylation by using DNA methyltrasferase inhibition and siRNA allows TSG re-expression and therefore holds promise as a useful anti-cancer therapy.

To explore this potential therapeutic approach, pre-clinical data from a variety of sources has shown that a strategy to combine a DNA demethylating agent with platinum based chemotherapy might improve on current outcomes for UBC. These data indicate that, in addition to single agent activity, demethylating agents synergise with cisplatin and are able to circumvent cisplatin resistance in experimental models.[11-15]

UBC exhibits abnormal DNA methylation patterns that are associated with disease phenotype (stage, grade and histology), and clinical outcomes. Hyper- and hypo-methylation are associated respectively with invasive and non-invasive tumours, potentially through FOXA1 activation, indicating an epigenetic divergence, in addition to a genetic distinction, between lethal and non-lethal UBC.[16-18] Various gene targets, microRNAs and mirtrons have been associated with poor prognosis when hypermethylated in UBC.[19-21] An epigenetic field defect characterised by hypermethylation has also been described in normal bladder from patients with UBC that is hypothesised to result in a loss of epithelial integrity predisposing to carcinogenesis.[18]

DNA methylation patterns are also linked to cisplatin resistance in pre-clinical models of UBC and other cancers.[22-24] Critically, genetic silencing seen in pre-clinical models as a result of acquired cisplatin resistance has been demonstrated to be reversible through DNA methyltransferase inhibition resulting in reinstatement of cisplatin responsiveness.[22,23]

The DNA methyltransferase inhibitors decitabine, azacitidine and zebularine each have single agent activity in multiple UBC cell lines[11-15] and in xenograft models[12] with demonstration of in–vivo intra-tumoral target gene re-expression.[12] Synergistic inhibition of cell proliferation, and reversal of cisplatin resistance, occurs following co-administration of demethylating agents with cisplatin in bladder cancer cell lines.[14,23]

Data also exist to support investigation of a DNA hypomethylating agent with gemcitabine. Gemcitabine resistant solid tumour cell lines retain sensitivity to both azacytidine and decitabine.[25] Gemcitabine both inhibits and destabilises DNA methyltransferases and reactivates epigenetically silenced genes and has been demonstrated to exhibit synergistic interactions with either azacitidine or decitabine in a variety of solid tumour or lymphoma cell lines.[26-28] In mouse models for HIV-1, a gemcitabine/decitabine combination was found to be both synergistic and active at levels where cumulative toxicity was not seen.[29] Thus in addition to the central

hypothesis that DNA hypomethylating agents will improve efficacy for cisplatin there is justification also to investigate their combination with gemcitabine.

1.4 TARGETING NRF2 ACTIVATION TO ATTENUATE CISPLATIN RESISTANCE

Data support that the transcription factor Nrf2 may play a role in cisplatin resistance in bladder cancer. Nrf2 mediates the cellular oxidative stress response but in some cancers it induces chemo-resistance.[30,31] Many Nrf2 transcriptional targets are linked to bladder cancer prognosis and cisplatin sensitivity and Nrf2 itself is a poor prognostic factor in cisplatin treated bladder cancer. Pre-clinical data indicate that, in part, cisplatin resistance in bladder cancer is regulated by Nrf2 which is reversible experimentally by Nrf2 depletion.[32] Nrf2 is activated by promoter methylation of its up-stream negative regulator Keap1. Consistent with this, DNA methyltransferase inhibition depletes Nrf2 expression and potentiates cisplatin response in cisplatin sensitive (RT112) and resistant (RT112-CP) bladder cancer cells (Crabb, unpublished data). We do not propose that Nrf2 activation via Keap1 methylation is the only mediator of cisplatin resistance in bladder cancer or that it represents the only mechanism by which a favourable interaction might occur in a DNA methyltransferase inhibitor/cisplatin combination. It does however provide a further translational hypothesis for patient selection to test clinically in addition to other markers of methylation status.

1.5 SGI-110 PRE-CLINICAL, PHARMACOKINETIC AND PHARMACODYNAMIC DATA

Information in this section summarises information from the current version of the SGI-110 Investigators Brochure (IB). Investigators should consult the IB for more detailed information.

SGI-110 is a DNA methyltransferase inhibitor composed of a dinucleotide of decitabine and deoxyguanosine formulated for subcutaneous (SC) injection. Decitabine is the active metabolite. As with other agents in class its primary mode of action is DNA hypomethylation leading to re-expression of epigenetically silenced target genes. This approach to decitabine delivery allows for preferable pharmacokinetic (PK) characteristics compared with decitabine alone or other currently available demethylating agents.

SGI-110 induces dose-dependent decrease in global DNA and gene specific methylation in multiple human cancer cell lines. Re-expression of methylation silenced tumour suppressor genes in xenograft models (ovarian and hepatocellular carcinomas) was observed at tolerated and efficacious doses and schedules. SGI-110 depleted global DNA methylation (e.g., at repetitive sequences including long interspersed nucleotide element-1, *LINE-1*) in blood in monkeys. SGI-110 re-sensitized ovarian cancer cells and xenografts to cisplatin treatment.

Pharmacokinetics of SGI-110 after SC administration in humans show efficient, gradual conversion to decitabine, resulting in more prolonged decitabine exposure due to continuous appearance of decitabine and extending the apparent $t_{1/2}$ several fold, compared to IV infusion. SGI-110 doses of 60 and 90 mg/m^2 deliver decitabine exposures by area under the curve (AUC) in the range seen after 1 hour IV infusion at a dose of 20 mg/m^2 with C_{max} levels less than half those of IV decitabine.

Drug-drug interaction studies have not been conducted with SGI-110 or decitabine. In vitro studies suggest SGI-110 is unlikely to inhibit or induce human cytochrome p450 enzymes.

No studies have been conducted in specific patient populations.

SGI-110 for SC injection is supplied in a two-vial system of 100 mg SGI-110 and diluent for reconstitution, which is available in 1.2ml or 3ml.

1.6 SGI-110 CLINICAL DATA

Information in this section summarises information from the current version of the SGI-110 IB. Investigators should consult the IB for more detailed information.

As of 30th June 2018, 3 clinical trials of SGI-110 sponsored by Astex Pharmaceuticals, Inc. are completed and 5 ongoing, 7 as monotherapy and 1 in combination, with 1227 participants having received the drug.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.7 RATIONALE FOR CURRENT TRIAL

SGI-110 is a DNA methyltransferase inhibitor developed for SC administration that may provide for optimised delivery of the active metabolite decitabine. Pre-clinical data support a mechanism of action consistent with reversal of gene silencing associated with promoter methylation. Clinical data in the development program to date support its anticipated clinical activity with provisional evidence for efficacy and a biologically effective dose that can be achieved within acceptable levels of toxicity. Toxicity data to date, irrespective of causality, is dominated by myelosuppression, gastrointestinal effects and fatigue.

Pre-clinical data support that cisplatin resistance in bladder and other cancers, either as a primary or acquired phenomenon is derived, at last in part, through promotor methylation of silenced genes relevant to a cisplatin resistance phenotype. Experimentally this is reversible through co-administration of DNA hypomethylating agents, including decitabine, with resultant synergy for anti-cancer effect.

The central hypothesis to be tested in this clinical trial is that SGI-110 can be safely combined with GC in bladder cancer at doses able to induce demethylation of genes including those associated with cisplatin resistance. If confirmed this would allow subsequent investigation at the recommended phase II dose (RP2D) to test the impact on clinical efficacy and potentially also provide the basis for a selection strategy hypothesis for the targeted use of SGI-110 in this combination to be tested.

This protocol is for a phase Ib/IIa clinical trial to develop a combination of SGI-110 with GC. It incorporates an initial Dose Escalation Phase (which has now completed recruitment) in advanced solid tumours (including advanced/metastatic bladder cancer). This will be followed by a randomised Dose Expansion Phase in bladder cancer patients receiving neoadjuvant chemotherapy. An expansion phase in neoadjuvant bladder cancer was selected to allow early investigation of this strategy as a part of radical therapy for this disease ultimately aimed at improvement in cure rates. If successful it is hoped that this would reduce emergence of cisplatin-resistant advanced disease, which remains swiftly lethal. This approach will also allow for access to pre- and post-chemotherapy translational samples for investigation of pharmacodynamic read-outs of demethylation. Data also support that this combination might be relevant for testing in other tumour sites (e.g., lung, biliary tract, and ovarian cancers) where gemcitabine and platinum combinations are utilised.

2 TRIAL OBJECTIVES

Primary:

- To establish a safe and biologically effective dose and schedule for SGI-110 in combination with GC chemotherapy for future phase II/III investigation as a neoadjuvant therapy in bladder cancer

Secondary:

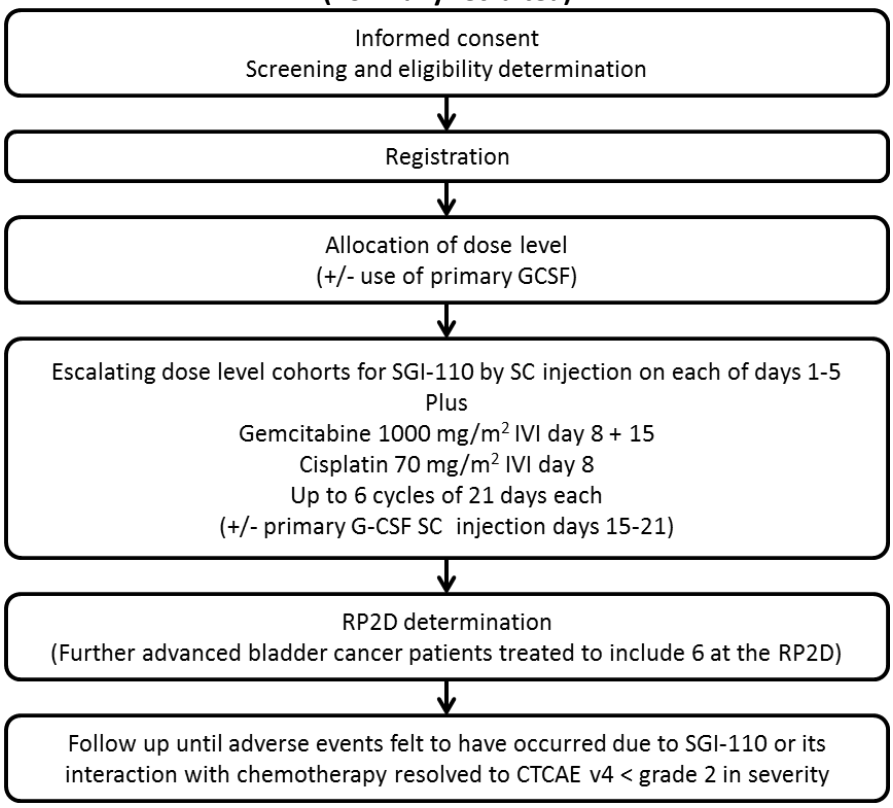
- To evaluate the safety and toxicity profile of SGI-110 when combined with GC
- To provide evidence of the pharmacodynamic effect of SGI-110 in combination with GC in blood and bladder cancer tissue
- To provide pharmacokinetic data for SGI-110 exposure
- To evaluate the safety and deliverability of SGI-110 when combined with GC as a neoadjuvant treatment for muscle invasive bladder cancer prior to radical local therapy

3 TRIAL DESIGN

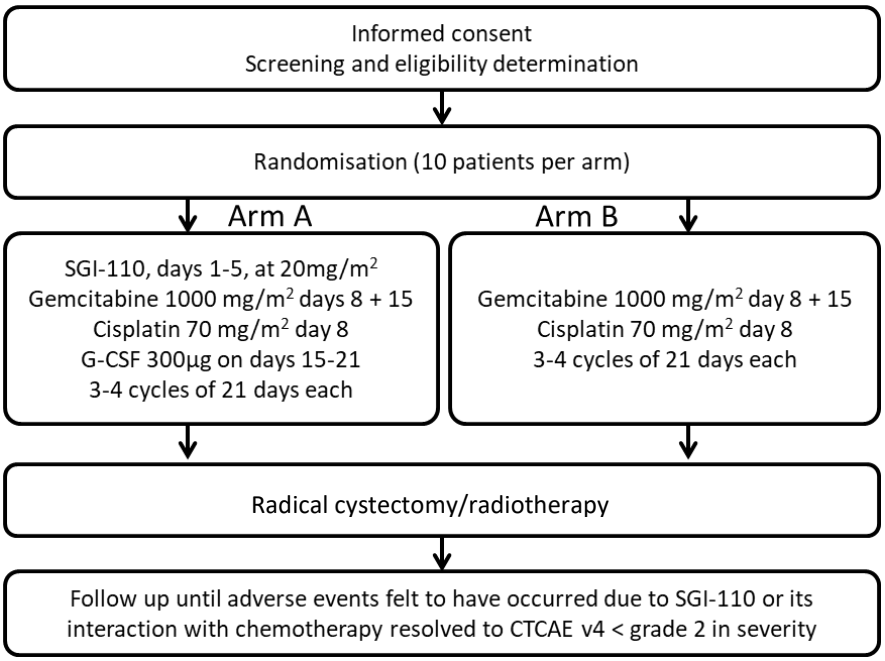
3.1 TRIAL DESIGN OVERVIEW

SPIRE comprises an initial phase Ib Dose Escalation Phase (**now fully recruited**) in advanced solid tumours to establish a RP2D. This will be followed by a phase IIa open label randomised Dose Expansion Phase in the neoadjuvant setting for bladder cancer.

DOSE ESCALATION PHASE (locally advanced or metastatic solid cancers, inc. bladder) **(now fully recruited)**



DOSE EXPANSION PHASE (T2-4a N0 M0 bladder cancer)



3.2 TRIAL OUTCOME MEASURES

Primary endpoint: To establish a RP2D for SGI-110 when combined with GC chemotherapy from both

- the MTD based on defined criteria for dose limiting toxicity (DLT) assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and
- the Maximally Biologically Effective Dose (MBED) based on plasma/serum DNA *LINE-1* methylation and haemoglobin F (HbF) re-expression status

Secondary endpoints:

- The toxicity profile using CTCAE v4.03 of SGI-110 in combination with GC, including a randomised comparison to GC alone at the RP2D
- Pharmacokinetics of SGI-110 when combined with GC
- The pathological complete response rate of bladder cancer patients enrolled in the dose expansion phase of the trial (not formally statistically powered for this)
- Investigation of other potential PD biomarkers for SGI-110 target effect in plasma/serum DNA and/or PBMCs and/or in archival pre- and post-treatment tissue samples, potentially including but not limited to:
    - promoter methylation of *MAGE-A1* and other cancer testis antigens
    - 5-methylcytosine levels
    - biomarkers of Nrf2 activation including Nrf2, KEAP1, Nrf2 transcriptional targets (e.g., glutathione reductase-1, metallothioneins, NQO-1)

3.3 DEFINITION OF AN EVALUABLE PATIENT FOR THE DOSE ESCALATION PHASE

(The Dose Escalation Phase, which this subsection relates to, is now fully recruited)

An evaluable patient is defined as one that, during Cycle 1 (between first dose of administration of SGI-110 and day 1 of the second cycle of treatment), has completed all relevant safety evaluation requirements and:

- has received the full doses of SGI-110 on days 1-5, and
- full doses of cisplatin and gemcitabine on day 8, and
- where applicable, has received at least one dose of G-CSF i.e. patients that have been registered to a cohort with G-CSF prophylaxis

AND/OR

- has experienced a DLT as defined below

3.4 DEFINITION OF DOSE LIMITING TOXICITY

(The Dose Escalation Phase, which this subsection relates to, is now fully recruited)

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 ≥ 7 days duration
- Grade 3 – 4 neutropenia associated with a temperature ≥ 38.5°C
- Grade 3 – 4 neutropenia associated with bacteriologically proven sepsis
- Any grade 4 thrombocytopenia ≥ 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.

In all cases of suspected DLT, clinical judgement will be the final arbiter as to whether the event should be categorised as such. National Cancer Institute CTCAE version 4.03 will be used to characterise DLTs.

3.5 DOSE ESCALATION COHORT RULES AND DETERMINATION OF MTD

(The Dose Escalation Phase, which this subsection relates to, is now fully recruited)

Patients with advanced or metastatic solid cancers will be treated in one of four sequentially enrolled Dose Escalation cohorts according to treatment details described in Section 5 and according to a modified rolling 6 phase I design.[33]

Up to six evaluable patients will be entered at each dose level for the determination of MTD and safety and toxicity profile. After the first patient has been entered into the trial an observation period of 21 days from them starting treatment until subsequent patients may start will occur. Ongoing recruitment of patients will occur without staggering but this will be assessed and confirmed on an ongoing basis by the Sponsor based on emerging data from the study.

The dose level of SGI-110 will be assigned according to the number of patients already enrolled at the current dose level, the number of DLTs (and any other drug related AEs) observed at the current dose level and the number of patients enrolled who are at risk of developing a DLT (see Section 3.4: Definition of dose limiting toxicity). When sufficient data, as deemed by the Sponsor and Chief Investigator (CI), are available to assess these, the SGI-110 dose level will be assigned according to the following:

- If data are available from a minimum of three evaluable patients who have been treated in a cohort and no DLTs in cycle 1 have been observed at that dose level, then dose escalation can be considered (or if this is the maximum dose level, then it is established as the MTD).
- If data are available from a minimum of three evaluable patients who have been treated in a cohort and one DLT in cycle 1 has been observed at that dose level, then the cohort may be expanded to include up to six patients.
- If data are available from six evaluable patients who have been treated in a cohort and one DLT in cycle 1 has been observed at that dose level then dose escalation can be considered (or if this is the maximum dose level, then it is established as the MTD).
- If two DLTs have been observed at any dose level, the dose will be de-escalated and the previous dose level will be expanded (if needed) to include up to six patients. Once the previous dose level comprises a cohort of six evaluable patients, with 0 or 1 DLTs in cycle 1 seen, then this will be identified as the MTD.
- If not all data are available from at least three evaluable patients in order to take a decision on dose escalation but an eligible patient is ready to begin treatment, the

dose level will remain the same. Up to six patients may be enrolled at that dose level.

- An intermediate dose level between the previous and current dose level may be explored following full discussion between the Sponsor and CI.

Decisions for dose escalation and designation of MTD will occur according to the following rules and table:

- Non-evaluable patients will be replaced so there are at least 3 evaluable in each cohort (and at least 6 patients to determine RP2D) (see Section 3.3)
- Tolerability and chemotherapy dose intensity over multiple dosing cycles may also be considered in determining the MTD
- Clinical judgment will be the final arbiter in dose escalation decisions
- Schedule may also be explored (in addition to dose) to optimise hypomethylation (based on plasma/serum DNA *LINE-1* methylation and HbF re-expression status) with respect to timing of cisplatin administration based on emergent data
- No intra-patient dose escalation will occur and GC dose changes will not be explored

Cohort size (evaluable patients)	DLTs in cycle 1	Actions
3-6	0	Cohorts 1 - 3: dose escalate to the next cohort Cohort 4: MTD is established at this dose level
< 6	1	Expand cohort to include up to 6 evaluable patients and re-evaluate
6	1	Cohorts 1 - 3: dose escalate to the next cohort Cohort 4: MTD is established at this dose
≥ 2	≥ 2	Dose level will be considered a non-tolerated dose (NTD). No further recruitment to this cohort and dose escalation will cease. Cohort 1: The combination will be considered non-viable (<u>but see below regarding incorporation of G-CSF</u>) Cohorts 2-4: The previous dose level will be expanded to incorporate 6 evaluable patients (<u>but see below regarding incorporation of G-CSF</u>)

Incorporation of G-CSF Prophylaxis: if ≥2 of 2 to 6 evaluable patients experience a DLT in cycle 1, at a particular dose level, and at least one of these DLTs is due to neutropenia and/or its complications then a further 3-6 patients will be enrolled to repeat the same dose level but with the addition of G-CSF primary prophylaxis. Other rules regarding dose level decisions and designation of MTD will remain the same. Any subsequent dose levels would then incorporate G-CSF.

3.6 DETERMINATION OF MBED AND RP2D

(The Dose Escalation Phase, which this subsection relates to, is now fully recruited)

MBED will be based on plasma/serum DNA *LINE-1* demethylation and HbF re-expression at day 8 of the chemotherapy cycle.[34-36] If (as has been seen in AML/MDS for SGI-110) we can define a dose beyond which no further increase in demethylation of plasma/serum DNA *LINE-1* or re-expression of HbF is seen, then this will be defined as the MBED. (If the MBED is above the NTD then no further dose escalation would occur and the MBED would remain undefined.)

The MTD and MBED will then be considered in establishing the RP2D according to the following principles:

- If the MBED is clearly demonstrated to be below the MTD then it will be utilised as the RP2D
- If the MBED and MTD are established to be equivalent then this would be the RP2D
- If the MTD occurs at a dose at which at least a degree of plasma/serum DNA *LINE-1* demethylation and/or HbF re-expression occurs (but not necessarily maximal) then the MTD would be used as the RP2D
- If the MTD occurs at a dose at which no plasma/serum DNA *LINE-1* demethylation or HbF re-expression is demonstrated then this would result in discontinuation of development of this combination

3.7 ADDITION OF ADVANCED BLADDER CANCER PATIENTS AT THE RP2D

(The Dose Escalation Phase, which this subsection relates to, is now fully recruited)

Once the RP2D is determined according to the rules in section 3.6, additional bladder cancer patients with incurable advanced/metastatic disease (N1-3 and/or M1 staging) will be recruited at the RP2D dose/schedule until a total of six (including any already treated at this dose level) have been treated. This will be done to further establish tolerability and chemotherapy dose delivery over multiple cycles prior to proceeding to the Dose Expansion Phase for neoadjuvant treatment of curable T2-4a N0 M0 bladder cancer.

3.8 SAFETY REVIEW COMMITTEE (SRC)

(The Dose Escalation Phase, which this subsection relates to, is now fully recruited)

The SRC will consist of:

- Chief Investigator
- Principal Investigator or delegate from each investigational site
- Non-voting representative from Astex Pharmaceuticals
- SCTU Statistician
- Senior Trial Manager and Trial Manager

The SRC Charter for this study will define the exact membership and who should be present for decisions to be made. Further experts may be consulted by the SRC as necessary. The Southampton CTU Head of Quality Management and Sponsor

representative should always be present at the SRC if there are safety issues for discussion.

For the first patient entered into the trial, a delay of at least 21 days will be mandatory between administration of first patient first dose (of SGI-110) to administration of first dose for any subsequent patient. Providing there are no serious or unexplained safety issues during this period, as determined by the SRC, then dosing of subsequent patients will continue as they are identified. Should toxicity findings of concern occur, the SRC may choose to stagger the start of dosing for subsequent patients and/or cohorts.

Once at least 3 evaluable patients at a dose level have completed cycle 1, the SRC will review and assess the safety, tolerability and pharmacokinetics of SGI-110 in combination with GC from the cohort to make a decision as detailed below. The decision may be to:

- Proceed with dose escalation to the next cohort level
- Repeat the cohort with the addition of primary G-CSF prophylaxis and then potentially utilise G-CSF in all future patients
- Expand the cohort to a maximum of 6 evaluable patients
- Reduce the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
- Define the RP2D (and MTD and MBED where applicable)
- Stop the Dose Escalation Phase of the study

The safety review committee will review safety data from cycle 1 from evaluable patients in order to make dose escalation decisions for future patients. However, the remit of the safety review committee is also to review safety data from all patients from all cycles to decide whether anything that is being observed from other patients and other cycles would cause them to want to stop the trial early or over-rule the dose escalation decision suggested from the cycle 1 data for the patients at the current dose level (i.e. their role is also to act as an overall data monitoring committee). Therefore, the SRC retains the option to overrule the decision suggested by the table above regarding dose escalation when taking into account the wider picture regarding safety of patients treated so far. This overruling ability does not allow the SRC to escalate the dose above that suggested by the table above (i.e. the SRC will be able to maintain the current dose, de-escalate the dose but not escalate it unless the criteria in the table above are met).

3.9 DOSE EXPANSION PHASE

Once the Dose Escalation Phase is complete, including addition of further advanced bladder cancer patients at the RP2D if required (see section 3.7), an open label randomised Dose Expansion Phase will be undertaken. This will test SGI-110/GC at the RP2D alongside GC alone in 20 bladder cancer patients (10 patients per arm) undergoing neoadjuvant chemotherapy for T2-4a N0 M0 disease prior to radical cystectomy or radiotherapy. This will not be powered for formal statistical comparisons of efficacy however the locally assessed pathological complete response rates will be recorded. The intention is to develop further safety and activity data for this combination and provide translational data to further investigate a potential translational readout and potentially a patient selection strategy that can be tested subsequently in phase II/III evaluation. In addition to plasma samples, tissue samples at pre-treatment biopsy/transurethral resection of a bladder tumour (TURBT) and post-treatment radical cystectomy will be collected. Any patient not proceeding to cystectomy will instead have tissue sampling undertaken at cystoscopy where possible.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 SCREENING AND PRE-REGISTRATION / RANDOMISATION PROCEDURES

Please also refer to the tabulated study schedules on pages 13 and 14.

Patients must have provided written informed consent before any trial specific procedures are undertaken. Informed consent may be obtained up to 42 days prior to registration/randomisation.

Patients will have a minimum of 24 hours after their initial invitation to participate, and having been provided with the Patient Information Sheet, before being asked to sign the Trial Consent Form. Consent may be obtained up to 42 days prior to registration/randomisation.

The SCTU should be notified of all patients who sign a consent form (see section 4.5).

The screening assessments described below will then be carried out within 28 days prior to commencing treatment within the SPIRE trial for both the Dose Escalation Phase and Dose Expansion Phase (unless otherwise stated).

1. Eligibility criteria determination
2. Medical history including all prior medical conditions
3. Height (cm)
4. Weight (kg)
5. Physical examination including all relevant organ systems
6. Vital signs (pulse, blood pressure)
7. ECOG performance status
8. Full blood count and differential
9. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
10. Glomerular filtration rate (GFR) assessment calculated by the Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice
11. Translational tissue sample (archival sample) from the most recent available archival TURBT, biopsy or surgical sample, see section 8
12. Pregnancy test. Women of child-bearing potential will have a pregnancy test performed within 7 days prior to the start of trial treatment

Disease evaluation will be undertaken only at the discretion of the investigator according to local policy and routine practice for the relevant disease site. The exact timing and method to undertake it is not mandated but results will be recorded where it is done.

4.2 INCLUSION CRITERIA

Queries regarding eligibility should be addressed to the Southampton CTU. Patients will be required to fully meet all eligibility criteria to be registered/randomised within the trial.

All Patients:

1. Eastern Cooperative Oncology Group (ECOG, see Appendix I) performance status of 0 or 1
2. Glomerular filtration rate estimation of ≥ 60 ml/min according to either the Cockcroft and Gault formula (see Appendix II) or by Cr-51 EDTA or Tc-99m DTPA clearance
3. Adequate haematological parameters
   - Haemoglobin ≥ 90 g/L
   - Neutrophil count ≥ 1.5 $x10^9$/L
   - Platelets ≥ 100 $x10^9$/L
4. Adequate biochemical parameters
   - Bilirubin ≤ 1.5 x ULN
   - ALT and ALP ≤ 2.5 x ULN (ALP ≤ 5 x ULN if caused by liver or bone metastases)
5. Aged 16 years or over
6. Life expectancy > 3 months
7. Provision of written informed consent

Patients In The Dose Expansion Phase:

8. Bladder cancer with a pure or a predominant component of transitional cell carcinoma
9. Clinical stage T2-4a N0 M0
10. Planned to commence GC for 3 or 4 cycles.

4.3 EXCLUSION CRITERIA

All Patients:

1. Unresolved toxicities from prior therapy greater than CTCAE v4.03 grade 1 (with the exception of alopecia) at the time of registration
2. Prior radiotherapy to > 30% of bone marrow
3. Major surgery within 30 days of registration/randomisation
4. Any investigational medicinal product within 30 days registration/ randomisation
5. Allergy or other known intolerance to any of the proposed study drugs including supportive agents and inclusive of G-CSF and locally utilised anti-emetics
6. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable angina pectoris or congestive cardiac failure (New York Heart Association ≥ grade 2) within the last 6 months
7. Women who are pregnant or breast feeding. (Women of child-bearing potential must have a negative pregnancy test performed within 7 days prior to the start of trial treatment)
8. Patients of child-bearing potential who are not using a highly effective method of contraception as detailed in section 4.7
9. Any patient who, in the judgment of the local investigator, is unlikely to comply with trial procedures, restrictions or requirements
10. Any patient who has received a live vaccine within 4 weeks of initiation of their treatment.

Patients In The Dose Expansion Phase:

11. Current separate other malignancy. Current non-melanoma skin cancer, cervical carcinoma in situ or incidental localised prostate cancer is permissible. Other

prior malignancy is acceptable if the treatment within the SPIRE trial would be given with curative intent.

4.4 PRIOR USE OF PLATINUM AGENTS

Patients with prior use of platinum agents, including cisplatin, carboplatin and oxaliplatin, are eligible for inclusion into this trial if retreatment with a cisplatin based chemotherapy regimen is consistent with the local institutional policy for the relevant treatment setting. Investigators should however consider the potential for hypersensitivity reactions on re-exposure to platinum agents and have undertaken suitable discussion with the patient about the potential risks from further retreatment and platinum re-exposure. As with all other patients in this trial, access to suitable emergency and critical care support, again according to local institutional policies, should be available at all relevant times.

4.5 REGISTRATION / RANDOMISATION PROCEDURE

For the Dose Escalation Phase of the study, patient screening information should be recorded in the study eCRF. Each screening entry will automatically generate a screening number. If a patient is eligible and proceeds to full enrolment on to the study, the screening number will become their patient ID number. This patient ID number should be used to identify the patient on all study-related communications.

For the randomised Dose Expansion Phase of the study, randomisation of eligible patients will be via a web-based system. Please ensure that patient eligibility has been confirmed by a SPIRE clinician (delegated 'decide on patient eligibility' on the SDL) prior to the patient being randomised. The Principal Investigator or designee will log into the randomisation system, randomise the patient and be informed of the randomisation allocation (full instructions will be given) along with the patient ID.

4.6 WITHDRAWAL CRITERIA

Patients can decide to withdraw from the study at any time without providing a reason.

Investigators should explain to patients the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, patients who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If patients additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect standard follow-up data and unless the patient explicitly states otherwise, follow-up data will continue to be collected.

The PI has the right to withdraw patients from study treatment if he/she feels that it is in the best interests of the patient. Full details of the reasons for withdrawal should be recorded in the eCRF and medical records.

Should any patient become pregnant during participation in the trial then they will discontinue treatment.

Dose Escalation Phase: Patients that are withdrawn from the study but are evaluable will not be replaced. Any patient that is withdrawn and is not evaluable (see section 3.3) will be replaced.

Dose Expansion Phase: Patients that commence study treatment will not be replaced. If study treatment has not commenced then patients will be treated in the same manner as screening failures and replaced.

4.7 CONTRACEPTION

Requirements for adequate contraception in patients of child-bearing potential are as follows:

- Female patients who have a negative serum or urine pregnancy test during screening (within 7 days prior to the start of trial treatment) and agree to use two highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom; an intra-uterine device and condom; diaphragm with spermicidal gel and condom) effective from the first administration of all study drugs, throughout the trial and for six months afterwards are considered eligible.

- Male patients with partners of child-bearing potential who agree to take measures not to father children by using one form of highly effective contraception (oral, injected or implanted hormonal contraception and condom; an intra-uterine device and condom; diaphragm with spermicidal gel and condom) effective from the first administration of all study drugs, throughout the trial and for six months afterwards are considered eligible. Male participants must also refrain from donating sperm during this period.

- Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the fetus or neonate

Where appropriate, and according to local policy, investigators should discuss with and advise patients on the need for cryopreservation of sperm or oocytes for future fertility.

5 TREATMENTS

5.1 TREATMENT

Treatment will be administered over a 21 day cycle (see diagram)

Arm A (SGI-110 + GC + GCSF) – All cycles

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
SGI-110	X	X	X	X	X																
Cisplatin								X													
Gemcitabine								X							X						
GCSF															X	X	X	X	X	X	X

Arm B (GC Alone) - Cycle 1 Only (patients in arm B proceed direct from screening to cycle 1 day 8 without any pause)

Day	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cisplatin	X													
Gemcitabine	X							X						

Arm B (GC Alone) - Cycle 2 Onwards

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cisplatin								X													
Gemcitabine								X							X						

According to local practice, patients will receive either 3 or 4 cycles of treatment in the Dose Expansion Phase

Body Surface Area (BSA) should be used to calculate SGI-110, cisplatin and gemcitabine doses according to the formula (according to local preference). Actual body weight should be used to calculate BSA.
Weight should be monitored with each cycle of treatment and if there is a change of greater than 10% from baseline then BSA should be recalculated and doses adjusted accordingly.
Dose banding (to +/- 5% or as per national dose banding schedule) for gemcitabine and cisplatin is permitted where it is local practice to do so.

GC chemotherapy will be administered in all patients throughout as follows:

- Cisplatin 70 mg/m^2 on day 8 of each cycle by IV infusion over 2-4 hours
- Gemcitabine 1000 mg/m^2 on days 8 and 15 of each cycle by IV infusion over 30-60 minutes (and prior to cisplatin on day 8)
- Supportive treatment including both anti-emetics and a suitable intravenous hydration schedule pre- and post-cisplatin will be administered according to local institutional policy (to be reviewed and confirmed as adequate as part of site selection).

SGI-110 and GCSF administration (in Arm A patients only):

The RP2D of SGI-110 has been established as 20 mg/m^2, daily, on days 1-5 + 300µg GCSF, daily, on days 15-21.

- SGI-110 administration, will be 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, pre-treatment with topical or systemic analgesics can be considered.
- In the Dose Expansion Phase, patients will be randomised 1:1 in a non-blinded manner to receive either:
    - Arm A: GC combined with SGI-110 at 20 mg/m^2, daily, on days 1-5 + 300µg GCSF, by subcutaneous injection, 300 µg daily, on days 15-21 (RP2D)
    - Arm B: GC alone

5.2 DOSE MODIFICATIONS FOR HAEMATOLOGICAL TOXICITY

Modifications of drug timings and doses will be made as follows. Once dose reductions have been made then doses will not be re-escalated during subsequent cycles.

The required assessments prior to treatment are outlined in section 6.1 of the protocol.

Criteria For Treatment To Occur On Day 1 and 8

At the point of treatment on day 1, for patients in the SGI-110 arm (Arm A, i.e. for administration of SGI-110 for days 1-5) and on day 8, for all patients (for the administration of cisplatin and gemcitabine), of each cycle, haematological and non–haematological toxicities must have resolved to within the following limits for further treatment to occur. If these parameters are not met then treatment will be deferred up to a maximum of 14 days. During such a period of deferred treatment the patient should undergo weekly review (or more frequent if clinically appropriate) and the relevant parameter, and any others that are deemed important, should be reassessed. If a delay of > 14 days occurs then SGI-110 will be discontinued permanently and further use of cisplatin/gemcitabine will at the discretion of the local investigator.

Criteria For Treatment To Occur On:

Day 1 of a cycle

- absolute neutrophil count ≥ 0.5 x 10^9/L;
- and platelet count ≥ 50 x 10^9/L;
- and non-haematological toxicities have resolved to ≤ grade 2

Day 8 of a cycle

- absolute neutrophil count ≥ 1.0 x 10^9/L;
- and platelet count ≥ 100 x 10^9/L;

- and non-haematological toxicities have resolved to ≤ grade 2

Day 15 of a cycle

Treatment on day 15 (gemcitabine alone) will be according to the following table

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Gemcitabine
≥ 1.0	and	≥ 75	Continue current existing dose
0.5 to <1.0	and/or	50-74	Reduce by 25% the dose on this and future cycles
<0.5	or	<50	Omit on this cycle

Haematological Criteria For Subsequent Dose Reductions

In the dose expansion phase, if during the preceding treatment cycle any of the following occur:

- Grade 3 – 4 neutropenia associated with a temperature ≥ 38.5°C or bacteriologically proven sepsis
- Grade 3 thrombocytopenia associated with non-traumatic bleeding
- Any grade 4 thrombocytopenia

Then:

- In Arm A, SGI-110 should be reduced by one dose level to 10 mg/m^2, daily, on days 1-5, for all subsequent cycles, and
- In all patients, gemcitabine should be reduced by 25% on day 8 and day 15 for all subsequent cycles

If a patient meets the criteria above on a subsequent cycle (and after the relevant dose reduction) or requires a greater than 14 day delay in starting a treatment cycle then SGI-110 will be discontinued permanently and further use of cisplatin/gemcitabine will at the discretion of the local investigator.

5.3 DOSE MODIFICATIONS FOR NON-HAEMATOLOGICAL TOXICITY

The required assessments prior to treatment are outlined in section 6.1 of the protocol.

Neurotoxicity: is a recognised complication of cisplatin. Dose modifications for cisplatin should not be routinely made on the basis of grade 1 or 2 neurotoxicity. If participants experience grade 3 or 4 neurotoxicity then protocol treatment, including SGI-110, should be permanently stopped. Further off-trial chemotherapy will be at the discretion of the local investigator.

Renal toxicity: is a recognised complication of cisplatin. Serum creatinine should be measured prior to cisplatin on cycle 2 onwards and used to calculate GFR (ml/min) according to the Cockcroft and Gault formula. Dose adjustments for renal function should be made according to the following table.

Calculated GFR	Dose (cycles 2 onwards)
≥ 60ml/min and ≥ 80% of base-line (pre-cycle 1)	Full dose
< 60ml/min or < 80% of base-line value	Consider hydration, avoidance of other nephrotoxic drugs and correct if possible. Continue treatment only if an uncorrected isotopic GFR is > 60ml/min. If GFR remains <60ml/min, the participant should discontinue trial therapy. Further off-trial chemotherapy will be at the discretion of the local investigator

Liver toxicity: Liver transaminitis (elevated alanine or aspartate transaminase) may occur following gemcitabine chemotherapy. Day 8 treatment will be delayed and day 15 gemcitabine doses will be omitted in case of grade 3 or 4 transaminitis (i.e. ALT or AST > 5 x upper limit of normal). Further gemcitabine should not be given until toxicity has resolved to grade 2 or less and gemcitabine doses should be reduced by 25% with subsequent cycles of treatment. If a greater than 14 day delay in day 8 treatment occurs then trial treatment will be discontinued permanently and further use of cisplatin/gemcitabine will at the discretion of the local investigator. Careful monitoring of liver function should be performed if alanine or aspartate transaminase become elevated during treatment.

Other non-haematological toxicities not previously specified:

Grade 1 or 2:

- Begin appropriate symptomatic care, e.g. anti-emetics, anti-diarrhoeals, laxatives, emollient creams, etc. as clinically indicated
- Delay of up to 14 days may be undertaken at the discretion of the local investigator to allow reduction of toxicity to ≤ grade 1 severity
- Maintain dose level

Grade 3 or 4:

With the exception of any non-haematological toxicity previously specified, treatment dose modifications should be made according to the following criteria.

- Begin appropriate symptomatic care
- Interrupt trial treatment until toxicity is resolved to grade 1 or less
- Decrease dose of SGI-110 by one dose level with subsequent cycles. Reduction of cisplatin and gemcitabine or both may also be reduced (by 25% each) at the discretion of the local investigator and with respect to the perceived likely causative agent.

If any grade non-haematological toxicity has not resolved to grade 1 or less within 14 days, then treatment within the SPIRE trial should be discontinued. Further treatment off-trial will remain at the discretion of the responsible clinician.

5.4 DOSE DELAY/OMISSION DUE TO PUBLIC HOLIDAYS

Cisplatin and gemcitabine

If a patient's chemotherapy administration falls on a Public Holiday, the administration can be moved forward by 1 day or moved back by 1 day.

SGI-110

If a patient's SGI-110 injection falls on a Public Holiday, the injection should be omitted (eg. patient has 4 SGI-110 injections for that cycle rather than 5).

5.5 INTERACTION WITH OTHER DRUGS

Drug-drug interaction studies have not been conducted with SGI-110 or decitabine. In vitro studies in human hepatocytes suggest that SGI-110 is unlikely to inhibit or induce cytochrome p450 enzymes.

5.6 SGI-110 SUPPLY, FORMULATION AND RECONSTITUTION

SGI-110 is considered an investigational medicinal product (IMP) for the purpose of this protocol. IMP (SGI-110) will be provided free of charge by [redacted] to sites for use by patients in the SPIRE trial and will be study-specific investigational medicinal product clinical trial stock. Only those supplies intended for use in the study should be dispensed to study participants and clinical trial supplies must be dispensed in accordance with the study protocol.

To request resupply of IMP (SGI-110), an 'IMP Shipment Request Form' should be completed and sent to [redacted] (contact details will be supplied by SCTU).

Further information can be found in the SGI-110 Pharmacy Manual.

5.7 GEMCITABINE AND CISPLATIN SUPPLY

Gemcitabine and cisplatin are standard of care and will be from local supplies.

5.8 GCSF

GCSF is considered a non-investigational medicinal product for the purpose of this protocol.

5.9 CONCOMITANT MEDICATION

Information on any treatment received by the patient, along with dose, frequency and therapeutic indication, from 4 weeks prior to starting study treatment up to the end of treatment visit or discontinuation of follow-up for residual toxicities, whichever is the latest, will be recorded, in the electronic case report form (eCRF). No other investigational medicinal products should be received whilst on study.

Live vaccines are prohibited during treatment and for 4 weeks following the end of treatment.

In accordance with the cisplatin SmPC, nephrotoxic and ototoxic drugs are contraindicated during the course of the trial.

6 ASSESSMENT AND FOLLOW UP OF PARTICIPANTS

6.1 PROCEDURES DURING TRIAL PARTICIPATION

Please also refer to the tabulated study schedules on pages 13 and 14.

The procedures and assessments described below will then be carried out within the SPIRE trial for both the Dose Escalation Phase and Dose Expansion Phase (unless otherwise stated).

Disease evaluation will be undertaken only at the discretion of the investigator according to local policy and routine practice for the relevant disease site. The exact timing and method to undertake it is not mandated but results will be recorded where it is done.

Standard pathology blood tests can be undertaken at any NHS accredited laboratory.

Within 3 days prior to Cycle 1, Day 1 (Arm A patients only)

Patients randomised to Arm B (GC alone) should proceed directly to C1D8 after randomisation to ensure no delay in administration of chemotherapy.

(If undertaken within the last 7 days during screening then weight, physical exam, performance status, full blood count, serum biochemistry and pregnancy test do not need to be repeated within 3 days prior to C1D1)

1. Weight
2. Physical examination
3. Vital signs including pulse and blood pressure
4. ECOG performance status
5. Full blood count and differential
6. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
7. PK samples according to the schedule in section 7 (Dose Escalation Phase patients only)
8. Translational blood samples taken prior to administration of SGI-110
9. Haemoglobin electrophoresis sample
10. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
11. Documentation of all concomitant medications including name, doses and duration
12. Administration of SGI-110 (Cycle 1 Day 1)
13. Pregnancy Test

All treatment cycles, Days 2-5 (Arm A (SGI-110 + GC + GCSF) only)

1. Vital signs including pulse and blood pressure (only when required to attend for administration of SGI-110)
2. Administration of SGI-110 (only in Dose Escalation Phase patients and in those randomised to receive it in the Dose Expansion Phase)

Within 3 days prior to Cycle 1, Day 8
(For patients randomised to Arm B (GC alone) weight, physical exam, performance status, full blood count, serum biochemistry and pregnancy test do not need to be repeated within 3 days prior to C1D8 if they were undertaken within the last 7 days during screening)

1. Physical examination
2. Vital signs including pulse and blood pressure
3. ECOG performance status
4. Full blood count and differential
5. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
6. Glomerular filtration rate (GFR) assessment calculated by the Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice
7. Translational blood samples taken prior to administration of chemotherapy
8. Haemoglobin electrophoresis sample
9. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
10. Administration of cisplatin and gemcitabine (Cycle 1 Day 8)
11. Documentation of all concomitant medications including name, doses and duration *
12. Pregnancy Test*

*Patients randomised to Arm B (GC Alone) only

Within 3 days prior to Cycle 1, Day 15

1. Physical examination
2. Vital signs including pulse and blood pressure
3. ECOG performance status
4. Full blood count and differential
5. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
6. Translational blood samples taken prior to administration of chemotherapy (Dose Escalation Phase patients only)
7. Haemoglobin electrophoresis sample taken prior to administration of chemotherapy (Dose Escalation Phase patients only)
8. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
9. Administration of gemcitabine
10. Administration of G-CSF on days 15 to 21 only for Arm A patients.

Within 3 days prior to Cycle 2, Day 1

1. Weight
2. Physical examination
3. Vital signs including pulse and blood pressure
4. ECOG performance status
5. Full blood count and differential
6. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles

7. Translational blood samples
8. Haemoglobin electrophoresis sample
9. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
10. Documentation of all concomitant medications including name, doses and duration
11. Administration of SGI-110 (Patients randomised to Arm A only) (Cycle 2 Day 1)
12. Pregnancy Test

Within 3 days prior to Cycle 2, Day 8

1. Physical examination (Dose Escalation Phase patients only)
2. Vital signs including pulse and blood pressure (Dose Escalation Phase patients only)
3. ECOG performance status (Dose Escalation Phase patients only)
4. Full blood count and differential
5. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
6. Glomerular filtration rate (GFR) assessment calculated by the Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice
7. Translational blood samples
8. Haemoglobin electrophoresis sample
9. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
10. Administration of cisplatin and gemcitabine (Cycle 2 Day 8)

Within 3 days prior to Cycle 2, Day 15

1. Physical examination (Dose Escalation Phase patients only)
2. Vital signs including pulse and blood pressure (Dose Escalation Phase patients only)
3. ECOG performance status (Dose Escalation Phase patients only)
4. Full blood count and differential
5. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
6. Translational blood samples taken prior to administration of chemotherapy (Dose Escalation Phase patients only)
7. Haemoglobin electrophoresis sample taken prior to administration of chemotherapy (Dose Escalation Phase patients only)
8. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
9. Administration of gemcitabine (Cycle 2 Day 15)
10. Administration of G-CSF on days 15 to 21 (in Arm A patients only for the dose expansion phase)

Within 3 days prior to Cycle 3 onwards, Day 1

1. Weight
2. Physical examination

3. Vital signs including pulse and blood pressure
4. ECOG performance status
5. Full blood count and differential
6. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
7. Translational blood samples
8. Haemoglobin electrophoresis sample
9. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
10. Documentation of all concomitant medications including name, doses and duration
11. Administration of SGI-110 (Cycle 3 onwards, Day 1) Patients randomised to Arm A only)
12. Pregnancy Test

Within 3 days prior to Cycle 3 onwards, Day 8

1. Full blood count and differential
2. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
3. Glomerular filtration rate (GFR) assessment calculated by the Cockcroft and Gault formula or by alternative methods (e.g., Cr-51 EDTA or Tc-99m DTPA clearance) according to local routine practice
4. Translational blood samples
5. Haemoglobin electrophoresis sample
6. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
7. Administration of cisplatin and gemcitabine (Cycle 3 onwards, Day 8)

Within 3 days prior to Cycle 3 onwards, Day 15

1. Full blood count and differential
2. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
3. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
4. Administration of gemcitabine (Cycle 3 onwards, Day 15)
5. Administration of G-CSF on days 15 to 21 (patients in Arm A only)

Visits when treatment is delayed

If a patient is delayed in starting a new cycle of treatment due, for example, to myelosuppression or other toxicity, then they should be reviewed at weekly intervals (e.g. at day 22, 29 and 36 of the extended cycle). The assessments listed below should be carried out (please note that this information must be entered in to an 'unscheduled visit' folder in the study eCRF):

1. Weight
2. Physical examination
3. Vital signs including pulse and blood pressure
4. ECOG performance status

5. Full blood count and differential
6. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
7. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration

End of Treatment (EOT) Visit

An end of treatment visit should occur 28 ± 7 days after the last doses of SGI-110 or chemotherapy, and the following should be undertaken:

1. Weight
2. Physical examination
3. Vital signs including pulse and blood pressure
4. ECOG performance status
5. Full blood count and differential
6. Serum biochemistry including renal (including sodium, potassium, magnesium, urea and creatinine), liver (including ALT, AST, ALP and bilirubin) and bone (including serum albumin and calcium) profiles
7. Translational blood samples
8. Haemoglobin electrophoresis sample
9. Post chemotherapy translational tissue sample collection (archival sample) in the Dose Expansion Phase will be from the cystectomy sample (or if cystectomy is not performed then from the next cystoscopy sample). Translational tissue samples will not be routinely taken after chemotherapy in to the Dose Escalation Phase of the trial but will be collected if they have been undertaken as part of routine practice. See section 8
10. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
11. Documentation of all concomitant medications including name, doses and duration
12. Pregnancy Test

Follow-Up Visits After EOT Visit

Patients will continue to be followed-up beyond the EOT visit until they meet the criteria for ending trial participation as defined in section 6.2. Until that point, they should be assessed at intervals judged as appropriate by the local Principal Investigator, and guided by the clinical significance of any residual AEs under review. At these visits the following should be undertaken:

1. Collection of tissue samples for central collection if not already undertaken. See section 8
2. Toxicity assessment with documentation of all AEs with grading according to CTCAE v4.03 and duration
3. Documentation of all concomitant medications including name, doses and duration
4. Mortality/morbidity review. To be assessed at 30 days (+/- 2 weeks) after:
    - bladder cystectomy (using Clavien Dindo Grading (see Appendix IV))

    or

    - radiotherapy

    or

    - last trial treatment (if no bladder cystectomy or radiotherapy).

6.2 END OF STUDY (EOS)

Patients will be followed-up and remain participants in the trial until:

- Completion of the EOT visit

and until

- Resolution to CTCAE v4.03 < grade 2 in severity of treatment related toxicities, that are felt to be clinically significant and to have occurred due to SGI-110 or its interaction with chemotherapy.
  - If the patient has a cystectomy or radiotherapy, this assessment and confirmation of meeting this must be after the cystectomy or radiotherapy.
- Central collection of translational tissue (archival sample) and blood samples where these exist or are planned.

Patients who meet these criteria will be deemed to have completed study participation and further follow up within the SPIRE trial will cease.

7 PHARMACOKINECTICS (PK) ANALYSIS

(PK sampling is not included for dose expansion phase patients.)

All patients in the Dose Escalation Phase of the study will undergo PK profiling for SGI-110 in cycle 1 only on day 1 at the time points shown below.

Sample number	Sampling time point following SGI-110 dose
1	Pre-dose
2	15 minutes +/- 5 minutes
3	30 minutes +/- 5 minutes
4	60 minutes +/- 5 minutes
5	90 minutes +/- 5 minutes
6	2 hours +/- 5 minutes
7	4 hours +/- 10 minutes
8	6 hours +/- 10 minutes
9	8 hours +/- 10 minutes

Samples will be collected, processed, labelled, stored and shipped centrally as detailed in the PK laboratory manual. The exact date and time taken of each PK sample must be recorded in the eCRF.

8 TRANSLATIONAL RESEARCH SAMPLES

Plasma and serum samples will be collected prior to treatment administration according to the schedule below, unless the patient declines to participate in the translational aspect of the study.

Blood:

- Dose Escalation Phase
  - Screening
  - Cycles 1 and 2: days 1, 8 and 15
  - Cycle 3 onwards: day 1 and 8
  - End of Treatment visit

- Dose Expansion Phase (Arm A (SGI-110 + GC alone))
  - Cycle 1 onwards: within 3 days prior to days 1 and 8
  - End of Treatment visit

- Dose Expansion Phase (Arm B (GC alone))
  - Cycle 1: within 3 days prior to day 8
  - Cycle 2 onwards: within 3 days prior to day 1 and day 8
  - End of Treatment visit

Tissue

- Dose Escalation Phase
  - Screening (the most recent available archival biopsy or surgical sample)
  - Subsequent samples will not be routinely taken after entry on to the Dose Escalation Phase of the trial but will be collected if they have been undertaken subsequently as part of routine practice
- Dose Expansion Phase
  - Screening (the most recent available archival biopsy or TURBT sample)
  - Cystectomy sample (or if cystectomy is not performed from the next cystoscopy sample)

Full details for sample collection, processing, storage and shipping are detailed in the separate laboratory manual. All centres will participate in the translational research, but patients may consent or decline to participate without restricting entry into the main study. Samples will be stored at the [redacted]

9 SAFETY

9.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. the IB for an unapproved investigational product or SmPC for an authorised product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** – refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Important medical events***.

***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

9.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this trial, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this trial. A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists the local investigator should inform the Southampton Clinical Trials Unit (SCTU) who will notify the Chief Investigator. Pharmaceutical companies and/or other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description	
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	SAR/SUSAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/SUSAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/SUSAR

9.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the SCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

Pre-existing Conditions

A pre-existing condition should not be reported as an AE unless the condition worsens by at least one CTCAE v4.03 grade during the trial. The condition, however, must be reported in the pre-treatment section of the eCRF, if symptomatic at the time of entry, or under concurrent medical conditions if asymptomatic.

Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the relevant eCRF and submitted to SCTU.

Serious Adverse Events (SAEs) and Reactions

SAEs, SARs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE/SUSAR form asks for nature of event, date of onset, severity, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should assign the causality and expectedness of the event with reference to the current approved IMP IB/SmPC and use medical terms, with grades given in the NCI CTCAE v4.03. Additional information should be provided as soon as possible if the event/reaction has not resolved at the time of reporting.

The most recent SGI-110 IB and the SmPC for cisplatin and gemcitabine will be circulated to participating centres by the SCTU and are to be stored in the local site file.

Expectedness assessments are made against the approved Reference Safety Information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product (IMP)	IB/SMPC	Section/Table No.	Manufacturer	Date of text revision	Last updated on EMC
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patients experiencing isolated, uncomplicated grade 4 neutropenia or thrombocytopenia will not need to be reported as a SAE. However, if the local investigator believes neutropenia is life-threatening for any patient, a SAE should still be submitted.

As per standard practice, for the nIMPs (GCSF) in this trial please assess expectedness against the most up to date SmPC in place at the time of the event.

Relapse and death due to the cancer for which protocol treatment was initiated, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

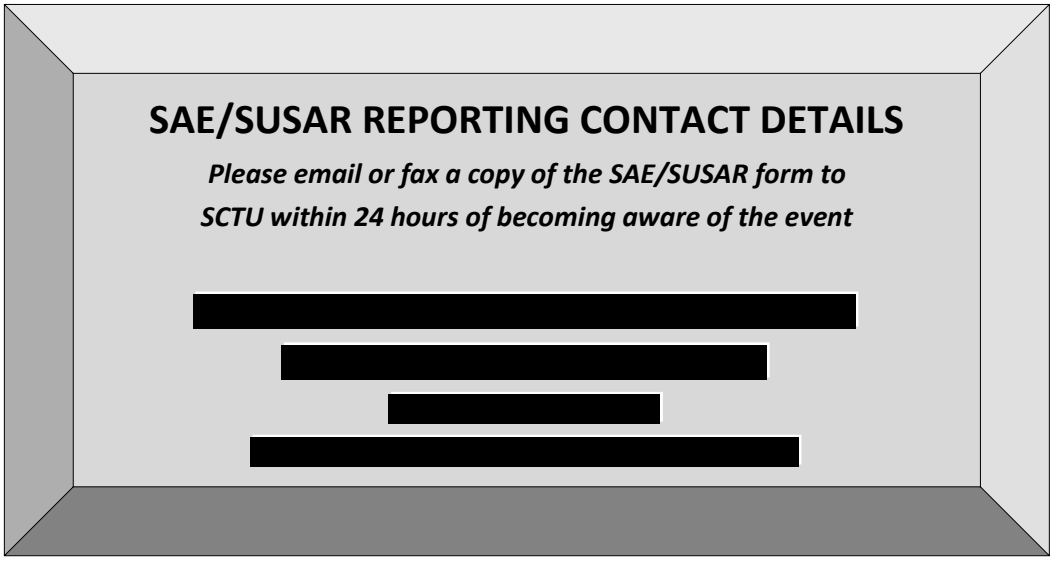
Reporting Details

An SAE/SUSAR form should be completed for all SAEs, SARs and SUSARS and faxed or emailed to the SCTU immediately but at least within 24 hours of site becoming aware of the event.

Complete the SAE/SUSAR form and fax or email a scanned copy of the form with as many details as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

Or

Contact the SCTU by phone for advice and then fax or email a scanned copy of the completed SAE/SUSAR form.



The SAE report form asks for nature of event, date of onset, severity, outcome, causality and expectedness. The responsible investigator (or delegate) should assign the seriousness, causality and expectedness of the event with reference to the approved IMP IB/SmPC and provide version used for the assessment. The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the NCI CTCAE v4.03.

Additional information should be provided as soon as possible if all information was not included at the time of reporting, but no more than 7 days after initial report.

Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the necessary REC of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit all safety information to the REC in annual progress report and in the annual Development Safety Update Report.

SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit the Developmental Safety Update Reports to MHRA annually.

Follow-Up and Post-study SAEs

The reporting requirement for SAEs affecting participants applies for all events occurring up to 4 weeks after the last administration of study drugs. All unresolved adverse events should be followed by the investigator until one of the end of study criteria is met (i.e. lost to follow up, withdrawal etc.) At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse

event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study.

Pregnancy
If a participant or a participant's partner becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP, the investigator must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy. If the participant leaves the area, their new healthcare professional should also be informed. A pregnancy notification form should be completed.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE

10.1.1 DOSE ESCALATION PHASE

The phase Ib part of the trial will be a rolling 6 dose escalation design looking at four potential dose levels. An additional 3-6 patients may be recruited if the addition of G-CSF is required (see section 3.5). Once the R2PD has been determined, up to 6 additional patients will be recruited to assess the R2PD in patients with incurable advanced/metastatic bladder cancer (see section 3.7).

Depending on SGI-110 tolerability when combined with GC, the number of patients recruited in this phase will range from 3-36.

10.1.2 DOSE EXPANSION PHASE

The phase II part of the trial will include 20 patients, half will be randomly allocated to receive RP2D of SGI-110 in combination with GC and the other half will receive GC alone, to further explore the RP2D.

10.2 STATISTICAL PLAN

10.2.1 DOSE ESCALATION PHASE

All patients entered into the phase Ib part of the trial will be accounted for. The phase Ib analysis will focus on the incidence of dose limiting toxicities, which will be summarised by dose cohort.

In addition, worst recorded toxicity grade for each patient on the NCI-CTCAE toxicity scale (version 4.03) during GC/SGI-110 treatment will be summarised by dose cohort with classification by the latest version of MedDRA. Details of dose delivery will also be summarised.

10.2.2 DOSE EXPANSION PHASE

The analysis will be conducted in the intent to treat population, which includes all randomisation patients who have commenced study treatment. The analysis will not be powered for formal statistical comparisons of efficacy.

Worst toxicity grade for each patient experienced during chemotherapy will be summarised by treatment arm and compared using the Mann-Whitney U test.

Relative dose intensity of GC will be summarised by treatment arm.

Pathological complete response rate according to local assessment will be summarised by treatment arm (the trial is not statistically powered for this).

11 REGULATORY ISSUES

11.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

11.2 ETHICS APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee.

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs, participants will not be identified by their names, but by an identification code. The investigator should keep a participant enrolment log showing codes, names and addresses.

11.3 CONSENT

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Patient Information Sheet provided and a minimum of 24 hours allowed for consideration. Signed participant consent should be obtained. Consent forms should also be signed by the person undertaking the consent procedure at site, who must be detailed on the site delegation log as having this authorisation. The Principal Investigator is responsible for ensuring designees for this task are suitably qualified by training and experience to take informed consent.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. All patients must be given a patient information sheet and a photocopy of the signed consent form for their records. A copy of the consent form should be sent to the SCTU. The SCTU copy should be emailed to [redacted] using a secure nhs.net email address to allow for central monitoring. In the event that new patient information sheets/consent forms are produced during the study, it maybe that patients already participating in the study should be re-consented to the updated version of the patient information sheet. However, if the Principal Investigator decides that this is not in the best interests of the patient re-consent is not required. Decisions to not re-consent patients must be documented in the patient's medical records.

11.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

11.5 INDEMNITY

[redacted] public and professional indemnity insurance policy provides an indemnity to [redacted] for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff.

11.6 SPONSOR

University Hospital Southampton NHS Foundation Trust is acting as the sponsor for this trial. The SCTU, Chief Investigator and other appropriate organisations have been delegated duties by the Sponsor relating to: submissions to regulatory authorities, GCP and pharmacovigilance.

The duties assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

11.7 FUNDING

Cancer Research UK and Astex Pharmaceuticals Incorporated are providing funding for this trial.

SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

This study is adopted onto the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

Participants will not be paid for participation in this study. However, participants in Arm A (SGI-110) can claim the following travel costs due to having to attend Days 1-5 of each cycle for SGI-110 administration:

- [redacted] Receipts and mileage required.

11.8 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. The SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations defined as serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

11.9 AUDITS AND INSPECTIONS

The trial may be subject to inspection and audit by University Hospital Southampton NHS Foundation Trust, under their remit as sponsor, the SCTU as the Sponsor's delegate and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

11.10 DEFINITION OF END OF TRIAL

The End of Trial is the date when all planned data points are received following last patient last visit.

12 TRIAL MANAGEMENT

12.1 TRIAL MANAGEMENT STRUCTURE

The Trial Management Group (TMG) is responsible for overseeing progress of this trial. The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by a Trial Steering Committee (TSC), Safety Review Committee (SRC) and the Data Monitoring and Ethics Committee (DMEC).

The TSC will provide overall supervision for the trial and will be responsible for monitoring the progress towards its interim and overall objectives, focusing on adherence to the protocol, GCP, and patient safety. The TSC will include independent members who are not directly involved in other aspects of the trial.

In the Dose Escalation Phase the SRC will meet when there are at least 3 evaluable patients at a dose level. The SRC will review and assess the safety, tolerability and pharmacokinetics from the cohort to make a decision as detailed.

- Proceed with dose escalation to the next cohort
- Expand the cohort to a maximum of 6 evaluable patients
- Reduce the dose either to a previous lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
- Define the RD (and NTD/MTD where applicable)
- Stop the dose escalation part of the study

Once the Dose Escalation Phase is complete a DMEC will be convened on behalf of, and with input from, the TMG. The DMEC will meet at regular intervals during the Dose Expansion Phase to review safety listings, recruitment and to make a recommendation on whether to continue, modify or stop the trial. DMEC reviews will focus on safety data and determine whether it is safe to continue recruitment to completion of the trial. Study recruitment will not be suspended to permit these reviews. The DMEC will meet at intervals set by itself, but at least annually.

12.2 TRIAL PERFORMANCE AND MONITORING

The PI must ensure that all staff participating in the trial are trained regarding their involvement and that the entire trial information is passed on continuously to all those who are involved in the conduct of the trial. The trial will be monitored and audited in accordance with SCTU procedures. All trial related documents will be made available on request for monitoring and audit by SCTU staff, UHS, REC and for inspection by the MHRA or other relevant bodies. Prior to the trial start, the PI will be advised of the anticipated frequency of the monitoring visits. The PI will receive reasonable notification prior to each monitoring visit.

The study may be subject to inspection and audit by University Hospital Southampton NHS Foundation Trust (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

12.3 SOURCE DOCUMENT VERIFICATION

The PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRFs taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the results will be documented in the monitoring report form. Access should also be given to trial staff and departments (e.g. pharmacy).

The patients' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, and by regulatory authorities.

12.4 SITE CORE DOCUMENTS

These consist of:

- Clinical Study Agreement
- Site Contact Details
- Site delegation log
- Confirmation of favorable Site Specific Assessment (SSA)/ Trust R&D Approval letter/ HRA approval
- Local versions of Patient Information Sheets, Consent Forms and GP Letters on hospital headed paper
- Biochemistry and haematology normal ranges and laboratory accreditation certificates
- Up-to-date, signed and dated CV for the Principal Investigator must be provided to SCTU. The CV should detail the qualifications, experience and training (including GCP training) and should be updated every 3 years
- At site, the PI is responsible for ensuring that an up-to-date signed and dated CV and GCP certificate is held for all staff on the site delegation log when they are first involved in the study. Any further GCP training certificates or updates to staff CVs should also be retained in the Investigator Site File (ISF).

12.5 ECRF COMPLETION

Data will be collected and retained in accordance with current Data Protection Regulations. eCRFs will be used to collect the data. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data reported in the eCRFs. Trial documents will be retained in a secure location during and after the trial has finished.

Only the PI and those personnel authorised by them on the delegation log should enter or change data in the eCRFs. All laboratory data and investigator observations must be transcribed into the eCRF. The original laboratory reports must be retained by the Investigator for future reference. Queries will either be automatically generated within the eCRF or raised by the trials team. Any alterations made to the eCRF will be visible via an audit trail which will identify the person who has made the change. The date and time of the change will also be visible.

After all the queries have been resolved at the end of the trial, the PI will confirm this by electronically signing off the eCRFs. The eCRFs will subsequently be archived according to SCTU procedures.

12.6 DATA COLLECTION

All data submitted on eCRFs must be verifiable in the source documentation. If a patient withdraws from the study during the treatment phase, the reason must be noted on the eCRF and in the patient's medical record, the patient must be followed-up as per protocol. If the patient withdraws their consent to any further participation in the study (treatment and follow-up) this must be documented in the eCRF and patient's medical record. eCRFs from the study will be archived in line with current regulatory requirements. Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required. The data custodian for the trial will be the Director of the SCTU.

12.7 RECORD RETENTION

The PI or designee must maintain adequate and accurate records to enable the conduct of the trial to be fully documented, and the trial data to be subsequently verified. After trial closure, the PI will maintain all source documents and trial related documents. The SCTU will maintain specific trial related documents. All source documents will be retained for a period of 25 years following the end of the trial. Sites will be required to archive either on site or in a suitable and secure off-site facility. Data and all appropriate documentation will be stored for a minimum of 25 years after the completion of the trial, including the follow-up period.

13 PUBLICATION POLICY

All publications and presentations relating to this trial will be authorised by the TMG. Authorship will be decided according to active participation in the study and accrual of eligible patients and will be agreed between the CI and the Director of the SCTU. Contributing centres and participating Investigators will be acknowledged in the final manuscript. No participant will present data from his/her centre separately from the rest of the study results unless approved by the TMG and the Sponsor.

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APPENDICES

APPENDIX I

ECOG Performance status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

APPENDIX II

Cockcroft and Gault Formula for Creatinine Clearance

$$\text{CrCl (mL/min)} = \frac{N \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{Serum creatinine (micromol/L)}}$$

Where N = 1.23 for males or 1.04 for females

APPENDIX III

Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03)

Please go to the following website to access the CTCAE Version 4.03

[redacted]

APPENDIX IV

Clavien Dindo Grading

Grades	Definition
Grade I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
Grade II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
Grade III	Complications requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthetic
- IIIb	Intervention under general anaesthetic
Grade IV	Life-threatening complications; this includes CNS complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs)
- IVa	Single-organ dysfunction (including dialysis)
- IVb	Multi-organ dysfunction
Grade V	Death of a patient

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-213.

Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250(2):187-196.

APPENDIX V

SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]