Clinical trial results:
A multi-centre open label randomised phase III trial of the efficacy of sodium thiosulphate in reducing ototoxicity in patients receiving cisplatin chemotherapy for standard risk hepatoblastoma

Summary

EudraCT number	2007-002402-21
Trial protocol	GB BE FR IE ES DK
Global end of trial date	08 May 2018

Results information

Result version number	v1 (current)
This version publication date	13 March 2020
First version publication date	13 March 2020
Summary attachment (see zip file)	SIOPEL 6 - Clinical Trial Summary Report (SIOPEL6 - Clinical Trial Summary Report.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_09-205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00652132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham (Sponsor for UK ONLY)
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Trial Coordinator (for UK ONLY), University of Birmingham (for UK ONLY), 44 01214151061, siopel6@trials.bham.ac.uk
Scientific contact	Trial Coordinator, University of Birmingham, 44 01214151061, siopel6@trials.bham.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2018
Global end of trial reached?	Yes
Global end of trial date	08 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Sodium Thiosulphate to reduce the hearing impairment caused by Cisplatin chemotherapy.

Protection of trial subjects:

Early stopping may be warranted in case of convincing evidence that a reduction in hearing impairment by at least 25% is corroborated. Interim analyses were conducted at 1/3 and 2/3 of process time, i.e. after 34 and 68 patients were evaluable for the primary endpoint. If the nominal alpha levels for the test of the primary endpoint were <0.00069 (34 pts), <0.016 (68 pts), early stopping of the trial was to be considered. The final test was to be carried out at nominal alpha level of 0.045.

In case of concerns of an adverse effect of STS on the short-term efficacy of the Cisplatin chemotherapy, the trial may be stopped early as well. Interim efficacy results on response to chemotherapy were evaluated after every 20 patients and submitted immediately to the International Data Monitoring Committee (IDMC) and the trial committee. The IDMC and the trial committee independently reviewed the results. The IDMC was to formulate a recommendation to the trial committee.

If interim efficacy results observed in this trial were worse than observed in SIOPEL 2 and 3, or if the rate of early progressive disease after 2 cycles had raised concerns, early closure of the trial was to be considered.

After each 20 patients (10 per arm), the rates of progression in the two arms and their difference (rate of PD in CIS+STS arm minus (rate of PD in CIS arm) were to be calculated. If the 95% lower confidence limit (LCL) for the difference were above zero this meant that there was a higher rate of early progression in the CIS+STS arm, and the trial would be recommended for closure due to a negative effect of STS on response to chemotherapy.

Background therapy: -

Evidence for comparator:

N/A

Actual start date of recruitment	15 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 36

Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	113
EEA total number of subjects	96

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	83
Children (2-11 years)	30
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

129 patients were registered in the database. Registration was done prior to the eligibility check because SIOPEL's intent was to register all hepatoblastoma patients irrespective of their inclusion in a therapeutic trial.

Pre-assignment

Screening details:

Standard-risk hepatoblastoma patients are patients who are considered operable at time of diagnosis. The main eligibility criteria are:

- Histologically confirmed newly diagnosed hepatoblastoma
- Standard risk hepatoblastoma
- PRETEXT I, II or III
- Serum alpha-fetoprotein (AFP) > 100 µg/L
- No additional PRETEXT criteria
- Age ≤ 18 y

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cisplatin alone

Arm description:

Cisplatin alone

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	L01XA01
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For children > 10kg: 80 mg/m2 IV infusion over 6 hours
For infants and children 5-10kg: 2.7 mg/kg IV infusion over 6 hours
For infants < 5kg: 1.8 mg/kg IV infusion over 6 hours

Arm title	Cisplatin + STS

Arm description:

Cisplatin + STS

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	L01XA01
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For children > 10kg: 80 mg/m2 IV infusion over 6 hours
For infants and children 5-10kg: 2.7 mg/kg IV infusion over 6 hours
For infants < 5kg: 1.8 mg/kg IV infusion over 6 hours

Investigational medicinal product name	Sodium Thiosulphate
Investigational medicinal product code	
Other name	ADH300001
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For children > 10kg: 20 g/m2 IV infusion over 15 minutes
For infants and children 5-10kg: 15 g/m2 IV infusion over 15 minutes
For infants < 5kg: 10 g/m2 IV infusion over 15 minutes

Number of subjects in period 1	Cisplatin alone	Cisplatin + STS
Started	53	60
Completed	52	57
Not completed	1	3
Re classified as High Risk	1	-
reclassified as high risk	-	1
Consent withdrawn by subject	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cisplatin alone
Reporting group description: Cisplatin alone	
Reporting group title	Cisplatin + STS
Reporting group description: Cisplatin + STS	

Reporting group values	Cisplatin alone	Cisplatin + STS	Total
Number of subjects	53	60	113
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	43	43	86
Children (2-11 years)	10	17	27
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	1.08	1.05	
full range (min-max)	0.25 to 5.9	0.10 to 8.2	-
Gender categorical Units: Subjects			
Female	23	28	51
Male	30	32	62
PRETEXT			
PRE-Treatment EXTent of disease			
Units: Subjects			
I/II	31	42	73
III	22	18	40
weight class Units: Subjects			
less than 5 kg	1	1	2
5 - 10 kg	27	31	58
more than 10 kg	24	25	49
not recorded	1	3	4
alfa feto protein Units: ng/mL			
median	76439	152319	
full range (min-max)	187 to 2175690	273 to 4536500	-

Subject analysis sets

Subject analysis set title	randomized and treated (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

of 113 randomised patients, two received no trial treatment due to parental refusal, and two received no trial treatment because the diagnosis was revised to "high risk hepatoblastoma" shortly after randomisation.

Subject analysis set title	ITT evaluable for hearing loss
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

of the 109 randomized and treated patients, 101 have a centrally reviewed hearing assessment

Reporting group values	randomized and treated (ITT)	ITT evaluable for hearing loss	
Number of subjects	109	101	
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	83	76	
Children (2-11 years)	26	25	
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median	1.08	1.08	
full range (min-max)	0.10 to 8.2	0.10 to 8.2	
Gender categorical Units: Subjects			
Female	50	46	
Male	59	55	
PRETEXT			
PRE-Treatment EXTent of disease			
Units: Subjects			
I/II	72		
III	37		
weight class Units: Subjects			
less than 5 kg	2		
5 - 10 kg	58		
more than 10 kg	49		
not recorded	4		
alfa feto protein Units: ng/mL			
median	130995		
full range (min-max)	187 to 4536500		

End points

End points reporting groups

Reporting group title	Cisplatin alone
Reporting group description:	
Cisplatin alone	
Reporting group title	Cisplatin + STS
Reporting group description:	
Cisplatin + STS	
Subject analysis set title	randomized and treated (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
of 113 randomised patients, two received no trial treatment due to parental refusal, and two received no trial treatment because the diagnosis was revised to "high risk hepatoblastoma" shortly after randomisation.	
Subject analysis set title	ITT evaluable for hearing loss
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
of the 109 randomized and treated patients, 101 have a centrally reviewed hearing assessment	

Primary: Brock grade ≥ 1 hearing loss

End point title	Brock grade ≥ 1 hearing loss
End point description:	
End point type	Primary
End point timeframe:	
after end of trial treatment or at an age of at least 3.5 years, whichever is later (Brock 1991)	

End point values	Cisplatin alone	Cisplatin + STS	ITT evaluable for hearing loss	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	46	55	101	
Units: yes vs no				
hearing loss	29	18	47	
no hearing loss	17	37	54	

Statistical analyses

Statistical analysis title	comparison of rates of hearing loss
Statistical analysis description:	
Chisquare test with significance level of 0.05	
Comparison groups	Cisplatin alone v Cisplatin + STS

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024 [1]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.81

Notes:

[1] - To account for the stratification used at randomization, a stratified Cochran-Mantel-Haenzel test was also done (strat: age, PRETEXT, groups of countries). With a p = 0.0021, and a CMH relative risk of 0.52 the results are virtually the same.

Secondary: Response to preoperative chemotherapy

End point title	Response to preoperative chemotherapy

End point description:

End point type	Secondary

End point timeframe:

at end of pre-operative chemotherapy

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
partial response	39	38	77	
stable disease	5	5	10	
progressive disease	5	11	16	
not evaluable	3	3	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete resection

End point title	Complete resection

End point description:

End point type	Secondary

End point timeframe:

surgery was performed after pre-operative chemotherapy

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
partial hepatectomy	48	53	101	
total hep & liver transplant	4	4	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete remission

End point title	Complete remission

End point description:

End point type	Secondary

End point timeframe:

at end of all trial treatment

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
died at surgery	1	0	1	
complete remission	44	52	96	
partial remission	4	5	9	
progressive disease	2	0	2	
not evaluable	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Event free survival (EFS)

End point title	Event free survival (EFS)

End point description:

Event free survival is calculated as difference from date of randomization to first date of an EFS event

(progression, relapse or death from any cause)

End point type	Secondary

End point timeframe:

event free survival at time of last follow-up

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
event free	41	46	87	
experienced an event	11	11	22	

Statistical analyses

Statistical analysis title	Kaplan-Meier estimation of event free survival
Comparison groups	Cisplatin alone v Cisplatin + STS
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	2.06

Notes:

[2] - event-free survival is presented in a descriptive manner only and not formally compared between the two arms

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival is calculated as difference from date of randomization to date of death from any cause.

End point type	Secondary

End point timeframe:

overall survival at a median follow-up of 52 months

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
alive	48	55	103	
dead	4	2	6	

Statistical analyses

Statistical analysis title	Kaplan-Meier estimation of overall survival
Comparison groups	Cisplatin + STS v Cisplatin alone
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	2.41

Secondary: Toxicity as graded by CTCAE v 3.0

End point title	Toxicity as graded by CTCAE v 3.0

End point description:

only grade 3, 4 and 5 adverse events were to be reported. CTCAE v 3.0 was to be used for grading adverse events.

End point type	Secondary

End point timeframe:

adverse events observed during pre- and post-operative chemotherapy

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
allergy	1	0	1	
febrile neutropenia	10	8	18	
infection	16	13	29	
hypomagnesemia	1	1	2	
hypernatremia	0	1	1	
vomiting	2	4	6	

nausea	3	2	5	
left ventricular systolic dysfunction	0	0	0	
renal event	0	0	0	
anemia	8	11	19	
leukopenia	2	2	4	
neutropenia	6	10	16	
thrombocytopenia	2	2	4	
gastrointestinal event	2	3	5	
elevated liver-enzyme level	6	4	10	
elevated serum glucose level	2	1	3	
hypermagnesemia	2	5	7	
hypophosphatemia	0	5	5	
hyperkalemia	2	0	2	
hypokalemia	0	5	5	
dyspnea	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Feasibility of central audiology review

End point title	Feasibility of central audiology review

End point description:

All audiology evaluations had to be based on pure tone audiometry at 8, 6, 4, 2, 1 and 0.5 kHz. The investigator had to submit results by uploading the audiogram into the database. The central reviewer then evaluated the uploaded material, decided whether the investigation had been done according to protocol and fulfilled the criteria to be accepted as final result, and if yes, adjudicated the Brock Grade. Several sites submitted partial audiograms or simple descriptions only which meant that the evaluation was not acceptable and had to be repeated at the next scheduled visit. Other audiograms were judged by the central reviewer as not having been done in a reliable fashion; these had to be repeated as well. Definitive audiology was available for 101 patients, 46 in the Cis alone arm and 55 in the Cis+STS arm. Five patients died before a reliable hearing assessment could be done; two could not be assessed due to their condition (one syndromic, one autistic); one was lost to followup

End point type	Secondary

End point timeframe:

central review of submitted audiograms was done during the conduct of the trial

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	57	109	
Units: subjects				
central review feasible	46	55	101	
died before audiometry	4	1	5	
not assessable (syndromic/autistic)	1	1	2	
lost to follow-up	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: long-term renal clearance

End point title	long-term renal clearance

End point description:

Long term development of renal function is of interest since cisplatin may affect renal function permanently. Renal monitoring was done during chemotherapy, at the end of treatment and at follow-up. Glomerular filtration rate was determined through the Cr51 EDTA method, Iohexol, isotope GFR, or calculated from serum creatinine.
For many patients, no GFR was recorded in follow-up. For such cases, a serum creatinine value was therefore collected retrospectively.

For the calculation of GFR in ml/min/1.73m2 from serum creatinine (Scr), the Schwartz equation (Schwartz 1976) was used:
CrCl (ml/min/1.73m2) = [length (cm) × k] / Scr in mg/dL
where
k = 0.45 for infants 1 to 52 weeks old
k = 0.55 for children 1 to 13 years old
k = 0.55 for adolescent females 13-18 years old
k = 0.7 for adolescent males 13-18 years old

the results are reported as *change in GFR* from pre-treatment to last follow-up

End point type	Secondary

End point timeframe:

change in renal clearance from baseline (time of diagnosis or early in treatment) to last follow-up with documented clearance

End point values	Cisplatin alone	Cisplatin + STS	randomized and treated (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49[3]	57	106[4]	
Units: change in clearance (ml/min/1.73m2)				
median (inter-quartile range (Q1-Q3))	-6 (-35.2 to 5.0)	-12 (-39.0 to 21.7)	-7.5 (-37.2 to 15.9)	

Notes:

[3] - one patient had no baseline value, and two patients had no value in the follow-up period

[4] - one patient had no baseline value, and two patients had no values recorded in follow-up

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of commencement protocol defined treatment until 30 days after the administration of the last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Cisplatin alone

Reporting group description:

Cisplatin alone

Reporting group title	Cisplatin + STS

Reporting group description:

Cisplatin + STS

Serious adverse events	Cisplatin alone	Cisplatin + STS	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 52 (30.77%)	13 / 57 (22.81%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombosis	Additional description: Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Intraoperative Injury	Additional description: Primary repair of injured organ/structure indicated		
subjects affected / exposed	0 / 52 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever	Additional description: Fever (in the absence of neutropenia, where neutropenia is defined as ANC<1.0 x 10e9/L)		
subjects affected / exposed	4 / 52 (7.69%)	5 / 57 (8.77%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Allergy to chemicals			
subjects affected / exposed	1 / 52 (1.92%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: Dyspnea with ADL		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pain	Additional description: Moderate pain; pain or analgesics interfering with function, but not interfering with ADL		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Neutrophil count	Additional description: <1000 - 500/mm(3) <1.0 - 0.5 x 10e9 /L		
subjects affected / exposed	0 / 52 (0.00%)	8 / 57 (14.04%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin	Additional description: <8.0 - 6.5 g/dL <4.9 - 4.0 mmol/L <80 - 65 g/L		
subjects affected / exposed	1 / 52 (1.92%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PTT (Partial Thromboplastin Time)	Additional description: >2 x ULN		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic disorder			

subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation time			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Wound			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	8 / 52 (15.38%)	8 / 57 (14.04%)	
occurrences causally related to treatment / all	2 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cisplatin alone	Cisplatin + STS	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 52 (84.62%)	52 / 57 (91.23%)	
Investigations			

PTT	Additional description: >2xULN		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	0 / 52 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	8 / 52 (15.38%)	11 / 57 (19.30%)	
occurrences (all)	8	11	
Leukopenia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Neutropenia			
subjects affected / exposed	6 / 52 (11.54%)	10 / 57 (17.54%)	
occurrences (all)	6	10	
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	2 / 52 (3.85%)	3 / 57 (5.26%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Weight loss	Additional description: >20%		
subjects affected / exposed	1 / 52 (1.92%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Elevated liver enzymes			
subjects affected / exposed	6 / 52 (11.54%)	3 / 57 (5.26%)	
occurrences (all)	6	3	
Hyper HDL cholesterolaemia			

subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hyperglycemia			
subjects affected / exposed	2 / 52 (3.85%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Hypermagnesemia	Additional description: The protocol specified the addition of magnesium to the cisplatin hydration fluid.		
subjects affected / exposed	2 / 52 (3.85%)	5 / 57 (8.77%)	
occurrences (all)	2	5	
Hypophosphatemia			
subjects affected / exposed	0 / 52 (0.00%)	5 / 57 (8.77%)	
occurrences (all)	0	5	
Hyperkalemia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 57 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2010	SA-04 Protocol v3.0 vd19-Aug-2010 Change of Sponsor (UK Only). With associated documents, Participant Consent Forms, Participant Information Sheets, GP/Consultant Information Letter, IMP labels and Data Transfer letters.
10 August 2012	SA-09 Protocol v4.0 vd18-Jul-2012 (UK Only). With associated documents, Participant Consent Forms, Participant Information Sheets and GP/Consultant Information Sheet.
01 February 2015	SA-11 Protocol v5.0 vd01-Feb-2015, change of sampling procedures and hydration requirements (UK Only). With associated documents, Addendum A Informed Consent Form and Patient Information Sheet,

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29924955