Clinical trial results:
An Evaluation of the Tolerability and Feasibility of combining 5-Amino-Levulinic Acid (5-ALA) with Carmustine Wafers (Gliadel) in the Surgical Management of Primary Glioblastoma (GALA-5 Trial)

Summary

EudraCT number	2010-022496-66
Trial protocol	GB
Global end of trial date	07 March 2014

Results information

Result version number	v1 (current)
This version publication date	26 October 2016
First version publication date	26 October 2016
Summary attachment (see zip file)	End of trial report submitted to REC. Publication is being drafted at the time of EMA submission (GALA5 end of trial report.pdf)

Trial information

Trial identification

Sponsor protocol code	UCL/09/0398

Additional study identifiers

ISRCTN number	ISRCTN77105850
ClinicalTrials.gov id (NCT number)	NCT01310868
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E6BT
Public contact	Public contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.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	19 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Treatments for patients with glioblastoma are limited. It accounts for around 60% of brain tumours and life expectancy in optimally managed patients is 12-14 months. Treatment options for patients with glioblastoma represents a major unmet need.

To establish that the combined use of 5-ALA and Carmustine wafers is safe and does not compromise a patient from receiving or completing standard chemo-radiotherapy.

Protection of trial subjects:

Patients were closely monitored for site effects following surgery/treatment so they could be treated quickly.

There was a chance patients may have died after surgery following 5-ALA administration and therefore all surgeons using 5-ALA in this trial had to receive training by Medac to minimise this risk.

Treatment for cancer is inherently toxic and like all medication can cause side effects. Many of the anticipated side effects of the two trial drugs were no different to those of other chemotherapy drugs that might be offered to patients off-trial but patients were closely monitored for side effects (including monitoring blood pressure, blood results etc.).

Because 5-ALA should be used in caution in patients with low blood pressure/ cardiac/renal impairment patients with active liver disease, or significant comorbidity precluding radical aggressive therapy were not eligible for the trial. Patients were kept away from UV light sources (e.g windows) for 24 hours after surgery to prevent photosensitivity reactions.

Stopping criteria were in place so that the trial would be recommended to stop if >5% patients failed to start chemoRT due to surgical complications.

Background therapy:

Treatment with temozolomide and RT was to continue as normal based on standard clinical protocols determined by the neuro-oncologist.

For patients which the neuro-oncologists judged to be fit enough, the standard Stupp chemoRT regimen was followed:

- Radiotherapy: 60Gy in 30 fractions (2Gy per fraction given once daily, five days per week (Monday-Friday) over 6 weeks. Radiotherapy delivered to gross tumour volume with 2-3cm margin
- Concomitant chemotherapy: temozolomide given alongside the radiotherapy at 75mg/m2 daily from the first day of radiotherapy, until the last day of radiotherapy, but for no longer than 49 days
- 4 week break
- Adjuvant chemotherapy: temozolomide given 150-200mg/m2 TMZ 5/28* days for 6 cycles (dosage increase to 200mg/m2 on second and subsequent cycles dependent on haematological toxicity. Sites should follow local guidelines if different.). *TMZ to be given on 5 consecutive days followed by 23 days with no TMZ, per cycle.

Evidence for comparator:

not applicable - no comparitor used

Actual start date of recruitment	07 July 2011
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: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	54
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date first site open: 22/06/2011
Date first patient entered: 08/07/2011
Date final patient entered: 05/05/2013
72 patients were recruited across 10 sites in the UK.

Pre-assignment

Screening details:

Screening was performed to confirm eligibility - see reporting group description

Period 1

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

Blinding implementation details:

Single arm trial. Blinding not required.

Arms

Arm title	5-ALA and Carmustine wafers

Arm description:

Patients drank up to 20mg/kg of 5-aminolevulinic acid hydrochloride 3-5 hours prior to the beginning of anesthesia.

Carmustine wafers (Gliadel implants) are small discs containing carmustine 7.7mgs (a cytotoxic chemotherapeutic agent) and an inactive ingredient, proliferosan 20. Carmustine implants were inserted (as a single episode) into the cavity left on completion of brain tumour resection. During surgery up to eight discs may have been used to line the resection cavity.

Arm type	Experimental
Investigational medicinal product name	Carmustine Wafers
Investigational medicinal product code	L01AD0I
Other name	Gliadel
Pharmaceutical forms	Implant
Routes of administration	Intracerebral use

Dosage and administration details:

Max 61.6 mg carmustine - i.e. max 8 wafers each containing 7.7mg carmustine plus 192.3mg polifeprosan 20 (exipient) may have been placed in the resection cavity. The number of wafers dispensed depended on clinical judgement.

Oxidised regenerated cellulose (Surgicel) may have been placed over the implants to secure them to the cavity surface. After placement of the implants, the resection cavity should have been irrigated and the dura closed in a water-tight fashion.

Investigational medicinal product name	5-ALA
Investigational medicinal product code	
Other name	5-aminolevulinic acid hydrochloride or Gliolan
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The patient drank up to 20mg/kg* of 5-aminolevulinic acid hydrochloride 3-5 hours prior to the beginning of anesthesia - with 5% dose rounding permitted.

Number of subjects in period 1	5-ALA and Carmustine wafers
Started	72
Completed	59
Not completed	13
Glioblastoma not diagnosed post-operatively	4
simultaneous diagnosis of unrelated carcinoma	1
Carmustine wafers not inserted	8

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Inclusion criteria
Patient reviewed by MDT and judged fit for treatment
Stealth MRI (neuronavigation) prior to surgery and judged to have typical appearances of a primary GBM
WHO performance status 0 or 1
Age ≥18

Exclusion criteria
GBM thought to be transformed low grade or secondary disease
There is uncertainty about the radiological diagnosis
5-ALA or Carmustine wafers is contra-indicated
Pregnant or lactating women
Known or suspected HIV or other significant infection or comorbidity that would preclude radical aggressive therapy for GBM
Active liver disease (ALT or AST ≥5 x ULRR)
Concomitant anti-cancer therapy except steroids
History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within 5 years
Previous brain surgery (including biopsy) or cranial radiotherapy
Platelets <100 x109/L
Mini mental status score <15

Reporting group values	Overall trial	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	54	54	
From 65-84 years	18	18	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	23	23	
Male	49	49	

End points

End points reporting groups

Reporting group title	5-ALA and Carmustine wafers

Reporting group description:

Patients drank up to 20mg/kg of 5-aminolevulinic acid hydrochloride 3-5 hours prior to the beginning of anesthesia.

Carmustine wafers (Gliadel implants) are small discs containing carmustine 7.7mgs (a cytotoxic chemotherapeutic agent) and an inactive ingredient, proliferosan 20. Carmustine implants were inserted (as a single episode) into the cavity left on completion of brain tumour resection. During surgery up to eight discs may have been used to line the resection cavity.

Primary: Proportion of 5-ALA resected patients receiving Carmustine wafers

End point title	Proportion of 5-ALA resected patients receiving Carmustine wafers[1]

End point description:

End point type	Primary

End point timeframe:

% 5-ALA resected patients receiving Carmustine wafers

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

End point values	5-ALA and Carmustine wafers			
Subject group type	Reporting group			
Number of subjects analysed	72[2]			
Units: Patients				
5-ALA resected patients receiving Carmustine wafer	62			

Notes:

[2] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with post operative complication

End point title	Number of patients with post operative complication[3]

End point description:

Number of patients with a new post-operative deficit or surgical complication (wound infection, CSF leakage, intracranial hypertension)

End point type	Primary

End point timeframe:

post-surgery

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

End point values	5-ALA and Carmustine wafers			
Subject group type	Reporting group			
Number of subjects analysed	59[4]			
Units: patients				
wound infections	5			
cerebrospinal fluid leakage	4			

Notes:

[4] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with chemoRT delay

End point title	Number of patients with chemoRT delay[5]

End point description:

Number of patients with chemoRT delay (i.e number who do not begin chemoRT 6 weeks after surgery) due to surgical complications.

Standard chemoRT refers to the Stupp regimen as described earlier.

End point type	Primary

End point timeframe:

Following surgery until the beginning of chemoRT

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

End point values	5-ALA and Carmustine wafers			
Subject group type	Reporting group			
Number of subjects analysed	59[6]			
Units: patients				
wound infections (did not begin chemoRT)	1			
cerebrospinal fluid leakage (did not begin chemoRT	1			
cerebrospinal fluid leakage (6 week+ delay)	1			
wound infections (6week+ delay)	3			

Notes:

[6] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients failing to complete chemoRT without interruption

End point title	Number of patients failing to complete chemoRT without interruption[7]

End point description:

Number of patients failing to complete chemoRT without interruption (RT with concomitant chemotherapy, and RT with concomitant plus adjuvant chemotherapy)

Standard chemoRT refers to the Stupp regimen as described earlier.

End point type	Primary

End point timeframe:

Duration of chemoRT

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

End point values	5-ALA and Carmustine wafers			
Subject group type	Reporting group			
Number of subjects analysed	59[8]			
Units: patients				
concomitant chemo interrupted - toxicity	13			
concomitant RT interrupted - logistical	9			
concomitant RT interrupted - toxicity	4			
adjuvant chemo interrupted - toxicity	11			
adjuvant chemo interrupted - progression	5			
adjuvant chemo interrupted - admin failure	2			
adjuvant chemo interrupted - unknown	1			

Notes:

[8] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of patients with a lower WHO performance status after surgery with Carmustine wafers

End point title	Proportion of patients with a lower WHO performance status after surgery with Carmustine wafers[9]

End point description:

Proportion of patients with a lower WHO performance status after surgery with Carmustine wafers (at first post-operative clinic visit)

End point type	Primary

End point timeframe:

Measured at first post-operative clinic visit

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

End point values	5-ALA and Carmustine wafers			
Subject group type	Reporting group			
Number of subjects analysed	59[10]			
Units: patients				
same or improved WHO performance status category	31			
lower WHO status post-surgery - 1 category	21			
lower WHO status post-surgery- at least 1 category	6			
not known	2			

Notes:

[10] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients failing to start chemoRT due to surgical complications

End point title	Number of patients failing to start chemoRT due to surgical complications[11]

End point description:

Number of patients failing to start chemoRT due to surgical complications.

Standard chemoRT refers to the Stupp regimen as described earlier.

End point type	Primary

End point timeframe:

Post-surgery until decision to not administer chemoRT

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm descriptive study. As advised by chersoni raffaella on 23/06/2016 for another study, we cannot post the results without entering the details of the statistical analysis as the system cannot accommodate one arm studies.

End point values	5-ALA and Carmustine wafers			
Subject group type	Reporting group			
Number of subjects analysed	59[12]			
Units: patients				
cerebrospinal fluid leakage	1			
wound infection	1			

Notes:

[12] - 59 patients eligible (glioblastoma confirmed peri/post-op, received 5-ALA and carmustine wafers)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred between informed consent and 8 weeks post surgery or the end of all radiotherapy and concomitant and adjuvant chemotherapy, whichever is later (or after this date if the site investigator felt the event was trial treatment related)

Adverse event reporting additional description:

As per publication, AEs have only been reported for the 59 eligible patients. SAEs are listed in full. Non-serious adverse events includes all events (including SAEs) of grade 3 or higher with a 5% threshold frequency.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	All eligible patients (59)

Reporting group description:

Patients received up to 20mg/kg 5-ALA prior to surgery and up to 8 carmustine wafers inserted into the resected cavity.

Serious adverse events	All eligible patients (59)		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 59 (44.07%)		
number of deaths (all causes)	49		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Wound dehiscence			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 59 (5.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerbrospinal Fluid Leak			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 59 (13.56%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
Stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vasovagal Reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal detachment				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colonic Perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
other - bowel perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal hemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Edema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychiatric Disorders- other	Additional description: steroid induced aggression		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle weakness left sided			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection - Cerebral Abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections - other	Additional description: not otherwise specified		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All eligible patients (59)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 59 (38.98%)		
Investigations			
Neutrophil Count Decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Platelet count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
White blood cell decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Injury, poisoning and procedural			

complications Wound infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3		
Vascular disorders Thrombolytic event alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4		
Nervous system disorders Seizure alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Lethargy alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 5 3 / 59 (5.08%) 3		
Gastrointestinal disorders Nausea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vomiting alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4 3 / 59 (5.08%) 3		
Musculoskeletal and connective tissue disorders Muscle weakness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2011	Response to REC comments: Protocol v2.0 with minor amendments & statistics section updated, Amended PIS v2.0 and consent form v2.0 as per RECs comments, IRAS form questions regarding loss of capacity answered
22 February 2011	Amendment to site IMP labelling requirements to meet Annex 13 clause 32
25 May 2011	Change to IRAS filter question 7 (capacity to consent) in response to change to the IRAS wording.
24 June 2011	Protocol v3.0. Amendment to Pregnant Partner Information Sheet & ICF. New document: Pregnant Patient Information Sheet & ICF.
14 February 2012	5.1 MRI no longer ideally to be conducted on either no or stable steroids 5.1. MRI registration assessment date extended from 2 to 4 weeks. The MRI scan date given must correspond to the scan discussed at a recent MDT meeting from which a provisional diagnosis has been made. 5.3.1. Clarification that Stealth MRI (neuronavigation) will be performed prior to surgery.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

-non-serious AEs: 'occurrences all number' cannot be provided as only highest grade experienced by patients collected on CRF; subjects affected number is entered instead
-serious AEs & non-serious AEs are listed under non-serious adverse event.

Notes: