Clinical trial results:
GLiSten: Next generation intraoperative lymph node staging for stratified colon cancer surgery- Development Phase

Summary

EudraCT number	2012-002623-15
Trial protocol	IE GB
Global end of trial date	07 August 2015

Results information

Result version number	v1 (current)
This version publication date	22 May 2020
First version publication date	22 May 2020
Summary attachment (see zip file)	GLiSten (2020.03.09_GLiSten final report.pdf)

Trial information

Trial identification

Sponsor protocol code	GS11/9681

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Worsley Building, Leeds, United Kingdom, LS2 9JT
Public contact	Catherine Lowe, Clinical Trials Research Unit, 0113 3431494, c.m.lowe@leeds.ac.uk
Scientific contact	Catherine Lowe, Clinical Trials Research Unit, 0113 3431494, c.m.lowe@leeds.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 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2015
Global end of trial reached?	Yes
Global end of trial date	07 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To optimise the dose of oral 5-ALA administration for intra-operative fluorescence diagnosis of metastatic lymph nodes in colon cancer.

Protection of trial subjects:

Participants for this study will be selected on the basis that they have a diagnosis of colon cancer that requires surgical resection, and are suitable for segmental colectomy with D3 lymphadenectomy. There will be the normal risk of surgical complications associated with general anaesthesia and surgical resection. There is a small risk of photosensitivity reactions related to 5-ALA administration. This includes transient derangement of liver function tests (returning to baseline at 24 – 72 hours post-administration) and skin hypersensitivity reactions due to exposure to UV-light. Other mild and transient side effects associated with 5-ALA administration include nausea, vomiting, tachycardia, and hypotension. When 5-ALA is administered in conjunction with surgical resection of malignant brain tumours, a potential side effect is brain oedema. In response to these potential adverse effects, all patients will be kept out of direct sunlight for at least the first 48 hours following surgery and monitored for changes in vital signs and liver function (this is normal postoperative care). During the operation patient’s eyes and skin will be protected from the operating lights, using standard methods such as sterile drapes and tape to keep their eyes closed.

Background therapy:

Colorectal cancer is the third most common cancer in the UK with an incidence of over 41,142 new cases per annum with over two thirds occurring in the colon (26,330 cases)(1); as such it represents a substantial burden on healthcare resources. In comparison to rectal cancer, which has seen improvement in survival over the past decade, the survival from colon cancer has remained largely unchanged with 5-year overall survival around 50%. In terms of segmental distribution, the right colon is the most common site harbouring ~25% of colorectal cancers, followed by the sigmoid colon with ~20%. Curative resection involves segmental colectomy to resect the primary cancer and the draining lymphatic field. Emerging evidence suggests that the standard of segmental colectomy as performed in the UK is of variable quality and that improvement in technique may help to improve survival outcomes with a survival advantage of up to 27% in patients with lymph node involvement (2). If this is correct, then a change in surgical technique to complete mesocolic resection and extended D3 lymphadenectomy would make a substantial contribution to improving the prognosis of patients with colon cancer (3-5). The corollary is that only ~25% of patients have lymph node involvement, meaning that in the other 75% of patients extended D3 lymphadenopathy potentially represents overtreatment. Such surgical changes can be quickly and cheaply introduced into practice and even very modest improvements in outcome, way below the potential that could be achieved, would be highly cost effective.

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
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: 37
Country: Number of subjects enrolled	Ireland: 7
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	9
From 65 to 84 years	33
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 44 patients were recruited to the trial with no participants withdrawing during the study period. A total of 37 patients were recruited at St James's University Hospital, Leeds, UK, and seven were recruited from The Mater Misericordiae University Hospital, Dublin, Ireland.

Pre-assignment

Screening details:

Patients will be identified via cancer multidisciplinary team meetings and approached in outpatient clinics for participation in the study. Patients will be approached during standard clinic visits for management of their disease and will be provided with verbal and written details about the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1- 20mg/kg of 5-ALA

Arm description:

Cohort 1 patients were recruited between
October 2013 and October 2014 and received an oral dose of 20 mg/kg of 5-ALA. Eighteen patients were required to achieve the target of 10 patients with metastatic LN disease as detected on standard histopathology.

Arm type	Experimental
Investigational medicinal product name	5-ALA 20mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Cohort 1 patients received an oral dose of 20 mg/kg of 5-ALA.

Arm title	Cohort 2- 30mg/kg of 5-ALA

Arm description:

Cohort 2 patients were recruited between October 2014 and June 2015 and received an oral dose of 30 mg/kg of 5-ALA, in line with the dose escalation defined in the trial protocol.

Arm type	Experimental
Investigational medicinal product name	5-ALA 30mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Cohort 2 patients received an oral dose of 30 mg/kg of 5-ALA.

Number of subjects in period 1	Cohort 1- 20mg/kg of 5-ALA	Cohort 2- 30mg/kg of 5-ALA
Started	18	26
Completed	18	26

Baseline characteristics

Reporting groups	
Reporting group title	Main Trial Period

Reporting group description: -

Reporting group values	Main Trial Period	Total	
Number of subjects	44	44	
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)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	71		
full range (min-max)	52 to 88	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	26	26	

End points

End points reporting groups

Reporting group title	Cohort 1- 20mg/kg of 5-ALA

Reporting group description:

Cohort 1 patients were recruited between
October 2013 and October 2014 and received an oral dose of 20 mg/kg of 5-ALA. Eighteen patients were required to achieve the target of 10 patients with metastatic LN disease as detected on standard histopathology.

Reporting group title	Cohort 2- 30mg/kg of 5-ALA

Reporting group description:

Cohort 2 patients were recruited between October 2014 and June 2015 and received an oral dose of 30 mg/kg of 5-ALA, in line with the dose escalation defined in the trial protocol.

Primary: Patients with fluorescent LNs

End point title	Patients with fluorescent LNs[1]

End point description:

End point type	Primary

End point timeframe:

N

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: Please see the attached results paper for all details regarding statistical analysis's performed.

End point values	Cohort 1- 20mg/kg of 5-ALA	Cohort 2- 30mg/kg of 5-ALA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	24		
Units: percentage	3	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events /reactions will be collected for all participants from the time of registration into the trial until 30 days post-operatively and will be evaluated for duration and intensity. Information will be recorded on the relevant CRF

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No Drug Related Serious Adverse events occured on the trial, only minor 5-ALA side effects. Details of all adverse events can be found in the attached publication.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	Changes made to the Protocol and PIS for the trial in light of comments from the MHRA and Irish Medicines Board. Protocol & PIS amended to v3.0. This amendment was approved by the REC on 29/4/2013, and by the MHRA on 22/5/2013
19 November 2013	Amendment submitted to temporarily halt the trial, so the research team could work with the manufacturer to address the issue of non-fluorescence in the trial IMP. No patients were adversely affected by this failure of the IMP to fluoresce.
19 December 2013	This amendment was submitted to restart the trial following the previous temporary halt amendment. the trial was approved to restart by the MHRA on 6/2/2014
14 March 2014	Protocol & PIS amended to bring it in line with the changes to the IB for the trial IMP, recommended by the EMA. minor changes also made to the protocol to change the definition of normal renal function within eligibility criteria.
23 July 2014	Amendment submitted in Ireland to add and remove Irish trial sites from the study, as the Irish Chief Investigator moved place of employment. This amendment was submitted alongside the changes requested by the EMA in the previous amendment listed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 November 2013	trial was temporarily halted so the research team could work with the manufacturer to address the issue of non-fluorescence in the trial IMP. No patients were adversely affected by this failure of the IMP to fluoresce. It appeared that the IMP's fluorescent properties were not stable as in three of a total of five patients treated no fluoresce was detected. As the lack of fluorescence occurred in a higher than anticipated proportion of patients this suggested that the fluorescent properties of the IMP may have degraded. The company supplying the IMP confirmed that, by using chromatography, the drug was stable. The research team also checked the process for drug supply, storage, preparation and administration at site, and this was as recommended practice. The MHRA approved the trial to restart on 06/02/2014	06 February 2014

Notes:

Limitations and caveats

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

N/A

Notes: