Clinical trial results:
A Phase IIa trial of 177 Lutetium Dotatate in Children with Primary Refractory or Relapsed High-Risk Neuroblastoma

Summary

EudraCT number	2012-000510-10
Trial protocol	GB
Global end of trial date	16 February 2018

Results information

Result version number	v1 (current)
This version publication date	07 October 2018
First version publication date	07 October 2018

Trial information

Trial identification

Sponsor protocol code	RG_11-141

Additional study identifiers

ISRCTN number	ISRCTN98918118
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, Birmingham, United Kingdom, B15 2TT
Public contact	Emmanouela Gbandi, University of Birmingham, 0044 01214143799, ludo@trials.bham.ac.uk
Scientific contact	Emmanouela Gbandi, University of Birmingham, 0044 01214143799, ludo@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	17 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2018
Global end of trial reached?	Yes
Global end of trial date	16 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial will evaluate how effective 177Lutetium DOTATATE is in children with high-risk relapsed or refractory neuroblastoma and determine the safety and adverse events of the treatment experienced by patients on the study.

Protection of trial subjects:

Not applicable

Background therapy:

None mandated in the protocol

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	1
Children (2-11 years)	19
Adolescents (12-17 years)	1
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One site was activated in the UK in March 2013 and first patient was recruited on 19 September 2013. The last patient was recruited on 28 July 2017. The trial was closed to recruitment on 16 February 2018. 21 patients in total were recruited.

Pre-assignment

Screening details:

No screening assessments involved. Please refer to the protocol for the eligibility criteria.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	LuDO Treatment

Arm description:

177 Lutetium DOTATATE

Arm type	Experimental
Investigational medicinal product name	177 Lutetium DOTATATE
Investigational medicinal product code	Not applicable
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The first administered activity of 177Lutetium DOTATATE = 75MBq/kg . The administered activity for the subsequent administrations will depend on the whole body dose received and the haematological toxicity from the previous administration (detailed instructions included in the trial protocol)

Number of subjects in period 1	LuDO Treatment
Started	21
Completed	8
Not completed	13
Progression and Death	1
Adverse event, non-fatal	1
Death	1
Progression	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial baseline
Reporting group description:	
This group contains the full number of patients that took part in stage 1 of this phase IIa study.	

Reporting group values	Overall trial baseline	Total	
Number of subjects	21	21	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	19	19	
Adolescents (12-17 years)	1	1	
Age continuous Units: years			
median	5.4		
inter-quartile range (Q1-Q3)	4.4 to 8.0	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	10	10	
MYCN status at diagnosis Units: Subjects			
Amplified	1	1	
Not amplified	20	20	
INSS Stage at diagnosis Units: Subjects			
Stage 3	3	3	
Stage 4	18	18	
Number of relapses prior to registration in the LuDO trial Units: Subjects			
Zero relapses	6	6	
One relapse	11	11	
Two relapses	1	1	
Three relapses	1	1	
Four relapses	2	2	
Disease type Units: Subjects			
Not responsive	2	2	
Persistent	3	3	
Progressive	1	1	
Progressive; Persistent; Not responsive	2	2	
Relapsed	11	11	
Relapsed; Progressive	1	1	
Relapsed; Progressive; Persistent; Not responsive	1	1	

End points

End points reporting groups

Reporting group title	LuDO Treatment

Reporting group description:

177 Lutetium DOTATATE

Subject analysis set title	Primary endpoint population
Subject analysis set type	Full analysis

Subject analysis set description:

The analysis of the primary outcome measure was carried out on an eligible and evaluable patient basis, i.e. patients who were ineligible and for whom primary outcome data was unavailable were excluded from the analysis (note: any patients who progressed or died prior to their 1 month end of treatment (EOT)
assessment were treated as non responders). Patients who did not start treatment and those who died due to any cause within 3 months from registration (i.e. time between death date and registration date is less than 92 days) were excluded from this analysis.

Primary: Response at 1 month after EOT measured by INRC

End point title	Response at 1 month after EOT measured by INRC

End point description:

- Response at 1 month after EOT measured by INRC. Complete, very good partial and partial response were count as responses for the purpose of the primary outcome.
- EOT was defined as the last administration of 177Lutetium DOTATATE.

Note: if there is no response assessment at 1 or 4 months post last administered course of 177Lutetium DOTATATE, the patient would be considered a non-responder.

End point type	Primary

End point timeframe:

Measured at 1 month after end of treatment (EOT).

End point values	LuDO Treatment	Primary endpoint population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	14		
Units: Response				
Responder	0	0		
Non responder	21	14		

Statistical analyses

Statistical analysis title	Proportion of responders at 1 month by INRC

Statistical analysis description:

Proportion of responders at 1 month by INRC with confidence intervals for eligible and evaluable patient population

Comparison groups	LuDO Treatment v Primary endpoint population

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Proportion - analysis on 14 patients
Point estimate	0
Confidence interval	
level	95 %
sides	1-sided
lower limit	0

Notes:

[1] - Proportion of responders at 1 month with confidence intervals. Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed separately on two patient groups of 21 and 14 patients respectively.

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression-free Survival is defined as the time from registration until objective tumour progression or death or to date of censoring for patients who do not experience the event during trial follow up.

End point type	Secondary

End point timeframe:

Patients were followed up from registration until progression or death or last assessment date from patients who did not experience an event.

End point values	LuDO Treatment	Primary endpoint population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	14[2]		
Units: Months	21	0		

Notes:

[2] - This group was not analysed for Progression Free Survival

Statistical analyses

Statistical analysis title	Median Progression-free Survival (PFS)
Comparison groups	LuDO Treatment v Primary endpoint population
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Median PFS - analysis on 21 patients
Point estimate	2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.71
upper limit	7.66

Notes:

[3] - Median Progression-free Survival (PFS). Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed on 21 patients (overall trial population patients).

Secondary: Overall Surivival

End point title	Overall Surivival

End point description:

Overall Survival is defined as the time from registration into the trial until date of death (death from any cause) or to date of censoring for patients who do not experience the event during trial follow-up.

End point type	Secondary

End point timeframe:

Patients were followed up from registration until death or last assessment date from patients who did not experience an event.

End point values	LuDO Treatment	Primary endpoint population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	14[4]		
Units: Months	21	0		

Notes:

[4] - This group was not analysed for Overall Survival

Statistical analyses

Statistical analysis title	Median Overall Survival
Comparison groups	LuDO Treatment v Primary endpoint population
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Median OS - analysis on 21 patients
Point estimate	13.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.99
upper limit	21.52

Notes:

[5] - Median Overall Survival (OS). Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed on 21 patients (overall trial population patients).

Secondary: Response at 4 month after EOT measured by INRC

End point title	Response at 4 month after EOT measured by INRC

End point description:

End point type	Secondary

End point timeframe:

Response by International Neuroblastoma Response Criteria at 4 months after completion of therapy.

End point values	LuDO Treatment	Primary endpoint population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	14[6]		
Units: Response at 4 months				
Responder	0	0		
Non responder	21	0		

Notes:

[6] - This group was not analysed for Response at 4 months post EoT

Statistical analyses

Statistical analysis title	Proportion of responders at 4 months
Statistical analysis description:	
Proportion of responders at 4 months with confidence intervals	
Comparison groups	LuDO Treatment v Primary endpoint population
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Proportion - analysis on 21 patients
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.155

Notes:

[7] - Proportion - Please note "Number of patients included in the analysis" is INCORRECT. Analysis performed separately on 21 patients (overall trial population patients).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events should be reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
vascular access complication			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomach pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Other, specify: vesicular rush			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		

Alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 11		
Neutrophil count decreased subjects affected / exposed occurrences (all)	7 / 20 (35.00%) 10		
Platelet count decreased subjects affected / exposed occurrences (all)	7 / 20 (35.00%) 8		
White blood cell decreased subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 10		
Injury, poisoning and procedural complications Vascular access complication subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 6		
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
General disorders and administration site conditions Fever subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 7		
General disorders and administration site conditions - Other, specify			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Diarrhea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Enterocolitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mucositis oral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Stomach pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Vomiting			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Periorbital edema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Infections and infestations - Other, specify			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Skin infection			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypoalbuminemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2014	Amendment of protocol to v 2.0 03-Sep-2014 and age adapted Patient Information Sheets v3.0 12-May-2014 Summary of changes: • Adaptation of time schedule of investigations and IMP handling instructions due to IMP supply changes • Change in SAE reporting due to new contract with manufacturer • Amendment of follow up investigations

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 March 2016	Temporary halt due to IMP supply issues	08 September 2016

Notes:

Limitations and caveats

None reported