



## Clinical trial results:

### Pilot study to investigate the feasibility of 13-cis-Retinoic acid pharmacokinetic monitoring in high-risk neuroblastoma

#### Summary

EudraCT number	2008-003606-33
Trial protocol	GB
Global end of trial date	19 May 2015

#### Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019
Summary attachment (see zip file)	Adaptive dosing approaches to the individualization of 13-cis-retinoic acid (isotretinoin) treatment for children with high-risk neuroblastoma (Clin_Cancer_Res-2013-Veal.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	PK 2008 03
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##### Additional study identifiers

ISRCTN number	ISRCTN37126758
ClinicalTrials.gov id (NCT number)	NCT00939965
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Newcastle Upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1, Regent Point, Regent Farm Road, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Prof. Gareth J Veal, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, NE2 4HH, 44 01912084332, g.j.veal@newcastle.ac.uk
Scientific contact	Prof. Gareth J Veal, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, NE2 4HH, 44 01912084332, g.j.veal@newcastle.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	01 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2014
Global end of trial reached?	Yes
Global end of trial date	19 May 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The study is designed as a pilot study to:

- Investigate the feasibility of implementing 13-cis-Retinoic acid dose modification following course 1 of treatment, based on targeted 13-cis-Retinoic acid plasma concentrations and observed toxicity.
- Minimize the large inter-patient variation in plasma concentrations of 13-cis-Retinoic acid observed following standard treatment for high-risk neuroblastoma. This will ensure that patients are not exposed to potentially sub-optimal plasma concentrations of 13-cis-RA during long-term treatment, particularly for those children who are not able to swallow 13-cis-RA capsules.
- Obtain preliminary data investigating the potential impact of 13-cis-RA therapeutic monitoring on clinical response and toxicity in children with high-risk neuroblastoma

Protection of trial subjects:

Patients receiving the IMP were doing so as part of their standard clinical treatment. Blood volumes for samples taken as part of this trial were kept to a minimum and were taken from the patients central line to minimise pain and distress. Where possible PK samples were taken at the same time as clinical samples to keep discard volumes to a minimum. Participants received age specific participant information sheets so they understood what taking part in the trial involved.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2009
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: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

Notes:

### Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	9
Children (2-11 years)	65
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment period 17/07/2009 to 05/03/2012 UK wide (NHS Sites only).

### Pre-assignment

Screening details:

Patients screened by their treating clinician/research nurses as they reach their 13-cis-retinoic acid treatment period (standard care) against the inclusion criteria stated in the protocol. Patients only excluded during screening if they fail to meet the study inclusion criteria.

### Period 1

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

### Arms

<b>Arm title</b>	Overall trial
Arm description:	
Overall trial	
Arm type	Experimental
Investigational medicinal product name	Roaccutane
Investigational medicinal product code	
Other name	13-cis-retinoic acid, Isotretinoin
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Maximum dose 240mg/m<sup>2</sup>/day.

Start dose 160mg/m<sup>2</sup>/day given over 2 divided doses for 14 days followed by 14 days drug free (1 cycle), typically 6 cycles of treatment.

Dose adjustments were carried out on cycle 2 with dose increases of 25% and 50% in patients with peak plasma concentrations of <2.0µM and <1.0µM respectively.

Children less than 12kg received a reduced starting dose of 5.33mg/kg/day.

<b>Number of subjects in period 1</b>	Overall trial
Started	75
Completed	75

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	75	75	
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)	9	9	
Children (2-11 years)	65	65	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	26	26	
Male	49	49	

## End points

### End points reporting groups

Reporting group title	Overall trial
Reporting group description:	
Overall trial	

### Primary: Quantification of Roaccutane plasma levels

End point title	Quantification of Roaccutane plasma levels <sup>[1]</sup>
End point description:	

End point type	Primary
End point timeframe:	
Drug levels measured on multiple courses of treatment for each patient until target level reached	

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: End point was determined by a defined cut off point which patients fell either above or below. No statistical analysis directly related to the primary endpoint required.

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	75 <sup>[2]</sup>			
Units: µM				
number (not applicable)	75			

Notes:

[2] - Values obtained for all patients

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

Per patient - from start of recruitment to 1 month after final cycle of treatment for which PK monitoring is carried out.

Adverse event reporting additional description:

Only adverse events directly related to PK sampling were collected for this trial.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI CTC
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Dictionary version	4
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Frequency threshold for reporting non-serious adverse events: 5 %

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### 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: There were no reported non serious adverse events recorded. Only adverse events related to PK sampling from the central line are required to be reported. All other AE's are reported via the main clinical trial the patient is being treated on.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2009	Change of sponsor from University Hospitals of Leicester NHS Trust to Newcastle upon Tyne Hospitals NHS Foundation Trust. Change in study sponsor accompanied by change in study management to the Northern Institute for Cancer Research, Newcastle University from the CCLG Data Centre in Leicester. Protocol changes relate to change of sponsor and study management only (New protocol version 2.0).
29 June 2010	Change of Principal Investigator at Birmingham Children's Hospital. No changes to protocol.
26 July 2010	Change of Principal Investigator at Nottingham University Hospitals. No changes to protocol.
15 August 2011	Addition of a new site, the Royal Hospital for Sick Children, Edinburgh and new Principal Investigator. No changes to protocol.
15 March 2012	Change of Principal Investigator at Southampton University Hospital NHS Foundation Trust. No changes to protocol.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23087409>