Clinical trial results:
Tyrosine kinase Inhibitors in DysplAsia of Lung epithelium Study 1

Summary

EudraCT number	2010-023355-29
Trial protocol	GB
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	21 March 2019
First version publication date	21 March 2019
Summary attachment (see zip file)	summary results (Working version TIDAL manuscript.pdf)

Trial information

Trial identification

Sponsor protocol code	PO1425

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01405846
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal Papworth Hospital NHS Foundation Trust
Sponsor organisation address	Ermine Street, Papworth Everard, United Kingdom, CB23 3RE
Public contact	Vikki Hughes, Royal Papworth Hospital NHS Foundation Trust, 01480 830541, victoria.hughes1@nhs.net
Scientific contact	Dr Robert Rintoul, Royal Papworth Hospital NHS Foundation Trust, 01480 830541, robert.rintoul@nhs.net

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	Interim
Date of interim/final analysis	11 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to identify a group of patients who have a high incidence of abnormal, pre-cancerous areas in the lining of their airways which put them at high risk of developing lung cancer.

Protection of trial subjects:

Independent Chair of the Trial Steering Committee

Background therapy:

No background therapy, these patients are standardly clinically managed by routine follow-up to assess if there has been disease progression

Evidence for comparator:

The study also aimed to provide an early indication as to whether the EGFR inhibitor gefitinib can resolve the dysplastic process.. The development of dysplasia is characterised by EGFR overexpression (Merrick et al., Clin Cancer Res 2006;12(7)). Gefitinib (ZD1839, Gefitinib, AstraZeneca Pharmaceuticals, Wilmington, Del.) is an oral inhibitor of EGFR tyrosine kinases. There are extensive in vitro and in vivo data demonstrating that Gefitinib blocks proliferation in cell culture induced by activation of EGFR and causes regression of human tumour xenografts with EGFR over-expression. If such a signal was demonstrated then future randomized trials of EGFR inhibition in this setting would be warranted.

Actual start date of recruitment	02 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	7

From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was from 01/01/2012 to 12/11/2015 at Royal Papworth Hospital NHS Foundation Trust

Pre-assignment

Screening details:

Patients underwent a contrast-enhanced staging CT of chest and abdomen and if this did not show any evidence of new or recurrent malignant disease or interstitial lung disease, a flexible bronchoscopy with autofluorescence was performed. Patients found at bronchoscopy to have areas of high-grade dysplasia were consented to the treatment arm

Pre-assignment period milestones

Number of subjects started	32
Number of subjects completed	2

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 7
Reason: Number of subjects	no high grade dysplasia: 21
Reason: Number of subjects	study terminated: 2

Period 1

Period 1 title	Stage 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

all pts eligible for stage 2 to receive study drug

Arms

Arm title	Treatment

Arm description:

Gefitinib 250mg daily for 26 weeks

Arm type	Experimental
Investigational medicinal product name	gefitinib
Investigational medicinal product code	zd1839
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250mg od

Number of subjects in period 1[1]	Treatment
Started	2
Completed	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Patients were enrolled for screening and only those with high grade dysplasia were eligible for the study.

Baseline characteristics

Reporting groups	
Reporting group title	Stage 2
Reporting group description:	
Patients receive 250mg dailing gefitinib for 26 weeks	

Reporting group values	Stage 2	Total	
Number of subjects	2	2	
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)	0	0	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
age range			
Units: years			
median	70		
full range (min-max)	67 to 73	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	1	1	

Subject analysis sets	
Subject analysis set title	response to treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Response to treatment	

Reporting group values	response to treatment		
Number of subjects	2		
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	2		
85 years and over	0		
Age continuous			
age range			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: Gefitinib 250mg daily for 26 weeks	
Subject analysis set title	response to treatment
Subject analysis set type	Per protocol
Subject analysis set description: Response to treatment	

Primary: Response to treatment

End point title	Response to treatment
End point description: 1 = no high grade dyplasia on biopsy and 0 = presence of high grade dysplasia	
End point type	Primary
End point timeframe: Post treatment and 6 months post treatment	

End point values	Treatment	response to treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	2	2		
Units: biopsy				
number (not applicable)	0.5	0.5		

Attachments (see zip file)	consort diagram/TIDAL1 CONSORT manuscript version.docx

Statistical analyses

Statistical analysis title	TIDAL study

Statistical analysis description:

The primary aim of this study was to estimate the proportion of patients in the risk population who are diagnosed as having high-grade dysplasia of the bronchial epithelium on autofluorescence bronchoscopy. There was little information on the true value of this proportion and the aim of this study was to reduce this uncertainty.

Comparison groups	Treatment v response to treatment
Number of subjects included in analysis	4
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05 [2]
Method	Bayesian Posterior Probability

Notes:

[1] - The statistical analysis is a likelihood-based Bayesian approach to estimation of the proportion using a Beta-Binomial conjugate analysis with a minimally informative Beta(1,1) prior. The analysis will estimate a posterior probability distribution with 80% and 95% credible intervals and estimate the probability that the true proportion is less than 10% which is the level at which further research of this

condition in this population would be deemed infeasible.

[2] - The Bayesian posterior probability distribution for the true incidence rate of high dysplasia had mean of 12% and median of 11%. Credible intervals showed that there is a 95% chance that the true incidence rate falls between 2.7% to 27.0%

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12/01/2012 - 09/08/2016	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	Treatment Group

Reporting group description: -

Serious adverse events	Treatment Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory deterioration post-bronchoscopy	Additional description: Acute respiratory deterioration post-bronchoscopy		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Investigations			
nodule detected on CT	Additional description: new benign nodule detected on CT		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Eye disorders			
sore eyes			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	4		
dry cough			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
increase in liver enzymes			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	5		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
increase in creatinine	Additional description: increase to above ULN		
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Infections and infestations			

chest infection subjects affected / exposed occurrences (all)	2 / 2 (100.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2011	Addition of another site
19 July 2012	Change from low dose to contract enhanced CT scan in the screening phase

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 February 2015	In November 2014 a temporary halt was made to the study to allow for futility analysis. The study was restarted in May 2015 but with clear target for recruiting eligible patients. The Trial Management Group (TMG) was held on the 9th February 2016 and no further eligible patients have been identified despite the very best efforts of the research team. The Independent Chair of the requested that the study be stopped due to futility and this was accepted by the study team. The proposed management of patients receiving treatment at time of the halt: No patients are currently receiving treatment. There were 2 patients who had been given patient information sheets to read, these will be told of the closure of the study. Early termination will not have any consequences on the overall risk benefit assessment of the IMP as the study was primarily designed to assess the rate of high grade dysplasia, which was significantly lower than expected.	14 May 2015

Notes:

Limitations and caveats

None reported