Clinical trial results:
Proof-of-concept study of AZD 4547 in patients with FGFR1 or FGFR2 amplified tumours

Summary

EudraCT number	2011-003718-18
Trial protocol	GB
Global end of trial date	21 December 2018

Results information

Result version number	v1 (current)
This version publication date	29 June 2019
First version publication date	29 June 2019

Trial information

Trial identification

Sponsor protocol code	CCR3689

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01795768
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ROYAL MARSDEN NHS FOUNDATION TRUST
Sponsor organisation address	FULHAM ROAD , LONDON, United Kingdom, SW3 6JJ
Public contact	Angela Gillbanks, The Royal Marsden Hospital NHS Foundation Trust, 44 0208 642 6011 X 4448, angela.gillbanks@rmh.nhs.uk
Scientific contact	Angela Gillbanks, The Royal Marsden Hospital NHS Foundation Trust, 44 0208642 6011 X 4448 , angela.gillbanks@rmh.nhs.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	21 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2018
Global end of trial reached?	Yes
Global end of trial date	21 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To correlate the anti-tumour activity of AZD4547 with molecular changes on treatment in the FGFR pathway in serial biopsies.

Protection of trial subjects:

The investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Act of 1998. On the case report forms or other documents submitted to the sponsor, patients should be identified by their initials and a patient study number only. Documents that are not for submission to the sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the investigator.

Background therapy:

There are about 1.5 million new cases and over 1.1 million deaths from gastro-oesophageal cancer per year worldwide (Jemal, Bray et al. 2011). The incidence in most Western countries lies between 10 and 15 new cases per 100,000 population per year, with great geographic differences. Worldwide, Japan, Korea and China now lead with up to 80 new cases per 100,000 population per year. Currently, gastric cancer and oesophageal cancers are the 2nd and 6th most common cause of cancer mortality worldwide. There is a male preponderance, with an approximate male: female ratio of 2:1 (Kreps 2010). Globally, the majority (60% to 70%) of gastric cancer cases present with locally advanced or metastatic disease that is unresectable. In addition, sixty percent of those initially treated with curative intent will develop loco regional or metastatic disease (Wagner, Grote et al. 2005; Field, Michael et al. 2008).Globally, there is no agreed standard first-line regimen for the treatment of advanced gastric cancer, though most patients would receive a platinum based doublet or triplet chemotherapy regimen. The choice of treatment is based on a variety of factors, including clinical study results, availability and cost of drugs, therapy-related toxicity, and the patient's physical status. Limited therapeutic options exist upon progression in second line treatment settings for advanced gastro-oesophageal cancer. Although a statistically significant benefit in survival has been shown from second-line chemotherapy in patients with advanced gastric cancer (Park, Lim et al. 2011), the benefit is relatively modest and outcomes or most patients who have progressed following treatment with first-line chemotherapy remain generally poor. Current ESMO guidelines recommend clinical trials as the most appropriate option for treatment of these patients and there are no NICE approved second-line treatments for patients with advanced gastro-oesophageal cancers.

Evidence for comparator:

FGFR2 amplifications have been described in 10% of gastric cancers, usually associated with the poor prognosis diffuse-type histology (Kunii, Davis et al. 2008). Gastric cancer cell lines with FGFR2-amplification are dependent on the over-expressed and activated FGFR2 kinase for continued growth. Loss of FGFR2 signalling can cause potent growth inhibition and apoptosis in FGFR2 amplified gastric cancer cell lines. Anti-tumour activity of AZD4547 (FGFR 1-3 inhibitor) has also been shown in xenograft models of FGFR2 amplified (SNU 16) gastric cancer cell lines (Xie, Su et al.). Thus, there is strong preclinical evidence for using FGFR2 inhibition as a therapeutic target in FGFR2 amplified gastric cancers.

Actual start date of recruitment	28 September 2012
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	12
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study will be run in two independent tumour cohorts – advancedFGFR2 amplified upper GI cancer, other FGFR dysregulated tumours. Recruitment in each cohorts will be independent of each other.

The primary endpoint of the study is to assess the response rate to AZD4547 across each tumour group. Assuming AZD4547 is active with a true underly

Pre-assignment

Screening details:

Stage 1 (pre-screening): Patients who the investigator considers may be eligible for the study, or may become eligible within the recruitment period (e.g. patients who are currently being treated with first line or adjuvant therapy who may relapse during the recruitment period), will be pre-screened for their FGFR status.

Period 1

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

Arms

Arm title	Registered

Arm description:

AZD4547 administered 80 mg twice daily continuously

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	4547
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AZD4547 20mg tablets are beige film coated tablets, with a 6mm diameter and normal round concave shape, each is 3.1mm thick, with an approximate weight of 98mg.

Number of subjects in period 1	Registered
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	REGISTERED

Reporting group description: -

Reporting group values	REGISTERED	Total	
Number of subjects	20	20	
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)	12	12	
From 65-84 years	8	8	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	11	11	
Male	9	9	

Subject analysis sets

Subject analysis set title	REGISTERED
Subject analysis set type	Full analysis

Subject analysis set description:

For the analysis of response rate all consented and treated patients will be included and any patient without an imaging assessment will be counted as a non-responder

Subject analysis set title	ANALYSED (End of Study)
Subject analysis set type	Full analysis

Subject analysis set description:

For the analysis of response rate all consented and treated patients will be included and any patient without an imaging assessment will be counted as a non-responder
(Set up to allow a single arm study to be entered)

Reporting group values	REGISTERED	ANALYSED (End of Study)	
Number of subjects	20	20	
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)	12		
From 65-84 years	8		
85 years and over	0		
Gender categorical Units: Subjects			
Female	11		
Male	9		

End points

End points reporting groups

Reporting group title	Registered
Reporting group description:	
AZD4547 administered 80 mg twice daily continuously	
Subject analysis set title	REGISTERED
Subject analysis set type	Full analysis
Subject analysis set description:	
For the analysis of response rate all consented and treated patients will be included and any patient without an imaging assessment will be counted as a non-responder	
Subject analysis set title	ANALYSED (End of Study)
Subject analysis set type	Full analysis
Subject analysis set description:	
For the analysis of response rate all consented and treated patients will be included and any patient without an imaging assessment will be counted as a non-responder (Set up to allow a single arm study to be entered)	

Primary: Response Rate

End point title	Response Rate
End point description:	
Primary endpoint • To assess the objective response rate to AZD4547	

End point type	Primary
End point timeframe:	
8 Weeks	

End point values	Registered	REGISTERED	ANALYSED (End of Study)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: proportion				
CR / PR	4	4	4	
SD / PD	16	16	16	

Statistical analyses

Statistical analysis title	Objective Response Rate
Statistical analysis description:	
Objective response rate at 8 weeks defined as confirmed CR and PR (assessed according to RECIST 1.1) to AZD4547. All responses will be assessed centrally using RECIST 1.1 criteria The proportion of patients with disease control (CR, PR or SD) at 8 weeks is also be presented with a 95% confidence interval.	
Comparison groups	Registered v REGISTERED v ANALYSED (End of Study)

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Proportion
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	43.7

Notes:

[1] - No formal Comparison

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Investigator is responsible for ensuring that all AE's observed by the investigator or reported by patients from signing the informed consent until 30 days after last study treatment is administered are properly captured in the patients medical records.

Adverse event reporting additional description:

Investigator is responsible for recording all AE's in source data and on study specific CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	REGISTERED

Reporting group description: -

Serious adverse events	REGISTERED		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Postoperative hemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
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	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Pain			
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	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Esophageal hemmorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

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: 0 %

Non-serious adverse events	REGISTERED		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Mucositis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin rash			
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
16 November 2011	V1 to v 2: Protocol version number and date updated to Version 2 date 08/11/2011 in the document header, title page and protocol signature page; Change study acronym from FGF-R to FGFR in the header and page 2;Change study acronym from FGFR to FGFR; Page numbers updated in the table of contents; Addition of heading Appendix B – Summary of protocol changes to the table of contents; Removal of abstinence as an acceptable method of contraception for this study; Change Echo/MUGA scan to Echo/MUGA Scan;Correction of schedule of assessment for MUGA/Echo scan in Table 2 – change to C2D1 from C1D1;Addition of details regarding MUGA/Echo scan: A MUGA scan or echocardiogram to assess left ventricular ejection fraction (LVEF) will be conducted at screening and on day 1 of Cycle 2 (± 1 week) and 3-monthly thereafter until discontinuation of study treatment;Replace 'Table 1' with 'Table 2'; Addition of Appendix B, Summary of Protocol changes. PISCF changes: Removal of abstinence as a method of contraception, clarification of the ECHO/MUGA scanning schedule and correction of typo errors.
22 November 2013	Prot v2 - v3: Removed 'effective date' 'review date' & protocol reference; Change of Trial Physician to Dr E Smyth;Insertion of 'site name' for protocol sign. page & changed date of protocol version; changed RMH to RM Trust;Change of Trial Stat to C Peckitt; Amended fax no: Addition of exploratory cell culture objective; Addition of data regarding levels of FGFR amplification & relationship to response to FGFR inhibition; Clarification of results of mutagenicity testing; Data regarding safety of AZD4547 safety & tolerability at 80 mg BD cont. dosing schedule; Removal of genotoxicity as risk due to negative Ames test result; Addition of requirement for 10/16 patients per cohort to have amplification ratio of >=2.8, Removal of limited field radiation within 2 weeks of study entry as exclusion criteria; Change in inclusion criteria to reflect both FGFR amplification and ratio of >=2.0; Stability of brain metastases to be confirmed radiologically prior to study entry; Change in eligibility criteria 5 to allow patients with grade 2 neuropathy; Change in eligibility criteria 15 to allow patients with a history of varicella zoster; Description of 20mg tablets; Change to dosing schedule from 80 mg BD two weeks on one week off to continuous dosing; Update on RPED events referred to investigators brochure; Change in time allowed for resolution of ocular toxicity from 14 to 21 days; Change to dose levels – dose level – 1 now 60mg bd, dose level -2 now 40mg bd; Change toxicity management algorithm to reference figure 4; Changes to guidelines for management of ocular toxicity (Figure 3) provision of separate algorithm (figure 4) for management of asymptomatic RPED; Change eligibility criteria to study, patients must demonstrate FGFR amplification & FGFR ratio of >=2.0; Clarification that PET-CT, biopsy, bone & blood borne biomarker testing is due to eligibility criteria met; Confirmation that data is password protected & data transfer agreement with Quintiles.

17 July 2014	Protocol v3 - 4: Version number and date updated throughout; Study period updated; Emerging safety data removed (IB used as reference – see p 57); clinical experience updated. Typos amended. insertion of…. Three of the 34 patients had on treatment SAE's …..in the same patient the investigator also listed morphine as a suspected medication; Insertion to confirm IB is reference safety source. Addition of ….average tumour size change with AZD 4547 was at BEST comparable with paclitaxel; Study duration updated; Exclusion criteria amended;;Added text "The above toxicity management refers to non-haematological toxicity only. Specifically, at the beginning of each cycle of treatment absolute neutrophil count must be ≥1.5 and Plt≥100 in order to initiate treatment." Determination of the expectedness of an SAE will be based on the contents of the IB. (amended); Section 12.1 reference to the use of CRF's as source data; Removal of 'both' arms – is a single arm study; Confirmation that CRF's will be used as source data
06 July 2015	Protocol v4 -5: Title corrected to insert CYP3A4 and the word NOT into the following title: Drugs affecting CYP3A4 or CYP2D6 Metabolism that are strongly NOT recommended to be combined with AZD4547; Removed text referring to FISH6 score as this was Quintiles specific; Change in primary endpoint to objective response; Change in eligbility of NSCLC specific cohort, establishment of "basket" cohort for patients with FGFR dysregulated tumours; Each cohort will recruit 9-17 patients dependent on response observed; Addition of copy number variation assessment at prescreening; Change in provision of second biopsy from mandatory to optional but encouraged;Minor formatting changes;Addition of publication of arms separately; Update of clinical data on other AZD4547 studies; Addition of CT one month following response to confirm response; Addition of cholangiocarcinoma translational protocol: Main study PISCF v7, 23.2.15 Pre screening PISCF v4, 23.2.15 GP letter v5, 23.2.15 IB updated v 8 & 9
02 February 2016	Protocol v5 - 6 : Removal of breast cohort; includes updated lcinial results from part B of study D2610C00003, alopecia removed from list of expected toxicities; change in age of eligibility from age 25 to age 16 plus for oesteosarcoma pts, clarification of management of ocular toxicity; removal of blood borne biomarker testing for FGFR 23 and BFGF. removed as replaced by lab manual.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2017	THE MHRA REQUESTED THE STUDY BE HALTED DUE TO THE NEED FOR A SCHEDULE 1 LICENCE TO BE IN PLACE, FOR THE STUDY IMP AZD4547	26 May 2017

Notes:

Limitations and caveats

None reported