Clinical trial results:
Trial of afatinib (BIBW 2992) in suspected or confirmed mutant EGFR lung cancer patients unfit for chemotherapy

Summary

EudraCT number	2011-003608-19
Trial protocol	GB
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	UCL/09/0426

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01415011
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	TIMELY Trial Co-ordinator, CR UK & UCL Cancer Trials Centre, +44 02076799284, ctc.timely@ucl.ac.uk
Scientific contact	TIMELY Trial Co-ordinator, University College London, +44 02076799284, ctc.timely@ucl.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	15 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2018
Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine the efficacy and safety of afatinib (BIBW 2992) in non-small cell lung cancer patients who had either suspected or confirmed EGFR mutation and were considered unfit for chemotherapy. The primary outcome measure is progression free survival at 6 months.

Protection of trial subjects:

Regular Trial Management Group meetings and Independent Data Monitoring Committee meetings were held throughout the trial to monitor overall safety in the patient group. Pharmacovigilance requirements and safety compliance rules were detailed in the trial protocol with overall risk assessment, on-site monitoring and central monitoring conducted by the trial teams.

Patient data is stored in a secure manner and the trial is registered in accordance with the Data Protection Act.

Background therapy:

In the TIMELY trial, loperamide was a named NIMP. At the time of initiation of treatment with afatinib (BIBW 2992), patients were given a supply of loperamide to keep with them at all times, and were counselled on the appropriate use. Loperamide was administered to the patients for management of diarrhoea adverse events associated with afatinib.

Evidence for comparator:

No comparators where applicable in the trial design.

Actual start date of recruitment	01 March 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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	27
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 39 eligible patients were recruited to the study between 12th March 2013 and 13th August 2015.
Patients were recruited from 13 different UK NHS hospital sites.

Pre-assignment

Screening details:

Patient enrolled were non-small cell lung cancer patients with comorbidities precluding chemotherapy, with either (i) EGFR-mutation, PS 0-3, or (ii) suspected EGFR-mutation (tissue unavailable/failed genotyping), never/former-light smoker, adenocarcinoma, and performance status 0-2.

Period 1

Period 1 title	Overall trial
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Arm title	Single arm - 40mg daily oral afatinib

Arm description:

All patients were given daily oral afatinib (BIBW 2992) (40mg) until disease progression, toxicity, or physician/patient decision. Afatinib (BIBW 2992) was provided to all patients in cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient started afatinib at a dose of 40mg, once daily, orally, in the form of tablet. Each cycle of afatinib was administered every 28 days. Daily dosing continued until progression, unacceptable adverse events or other reason necessitating withdrawal.

30mg and 20mg doses were provided for patients who required protocol dose modifications due to adverse events.

Number of subjects in period 1	Single arm - 40mg daily oral afatinib
Started	39
Completed	39

Period 2

Period 2 title	1 month
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Single arm - 40mg daily oral afatinib

Arm description:

All patients were given daily oral afatinib (BIBW 2992) (40mg) until disease progression, toxicity, or physician/patient decision. Afatinib (BIBW 2992) was provided to all patients in cycles of 28 days.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each patient started afatinib at a dose of 40mg, once daily, orally, in the form of tablet. Each cycle of afatinib was administered every 28 days. Daily dosing continued until progression, unacceptable adverse events or other reason necessitating withdrawal.

30mg and 20mg doses were provided for patients who required protocol dose modifications due to adverse events.

Number of subjects in period 2	Single arm - 40mg daily oral afatinib
Started	39
Completed	39

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Patients had any stage non-small cell lung cancer with either suspected or confirmed EGFR status and were unable to receive chemotherapy due to co-morbidity. At trial entry, patients were age 18 or over, were required to have adequate organ function and have no existing conditions that would exclude them from treatment with afatinib, such as interstitial lung disease, and cardiac abnormalities.

Patients assessments were fortnightly for the first two cycles, then monthly for twelve months and two-monthly thereafter. After discontinuing afatinib (BIBW 2992), all patients were followed-up two-monthly during the first twelve months.

Tumour response was evaluated by CT scan of the chest and abdomen (4 calendar weeks after the start date for treatment and then every 8 calendar weeks until disease progression). If after 1 year the patient was still on afatinib (BIBW 2992) CT scans were planned every 12 calendar weeks.

Reporting group values	Overall trial	Total	
Number of subjects	39	39	
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)	9	9	
From 65-84 years	27	27	
85 years and over	3	3	
Age continuous Units: years			
median	72		
full range (min-max)	36 to 90	-	
Gender categorical Units: Subjects			
Female	30	30	
Male	9	9	
WHO performance status Units: Subjects			
PS 0 - Fully Active	6	6	
PS 1 - Ambulatory (work able)	21	21	
PS 2 - Ambulatory (not work able)	11	11	
PS 3 - Limited Selfcare	1	1	
EGFR mutation Units: Subjects			
Confirmed EGFR	21	21	
Suspected EGFR	18	18	
Non-Small Cell Lung Cancer (NSCLC)			

Stage Units: Subjects			
Stage 1 NSCLC	1	1	
Stage II NSCLC	0	0	
Stage III NSCLC	8	8	
Stage IV NSCLC	30	30	

End points

End points reporting groups

Reporting group title	Single arm - 40mg daily oral afatinib

Reporting group description:

All patients were given daily oral afatinib (BIBW 2992) (40mg) until disease progression, toxicity, or physician/patient decision. Afatinib (BIBW 2992) was provided to all patients in cycles of 28 days.

Reporting group title	Single arm - 40mg daily oral afatinib

Reporting group description:

All patients were given daily oral afatinib (BIBW 2992) (40mg) until disease progression, toxicity, or physician/patient decision. Afatinib (BIBW 2992) was provided to all patients in cycles of 28 days.

Primary: Progression-free survival at 6 months

End point title	Progression-free survival at 6 months[1]

End point description:

The end point value reported is the proportion of patients alive and progression free at 6 months with corresponding exact binomial 80% confidence interval.

End point type	Primary

End point timeframe:

Progression-free survival at 6 months; calculated as the time between the date of registration and date of first progression or death (from any cause), whichever occured first. Patients who have not died or progressed were censored at the date last seen.

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: TIMELY was a single arm study; the system is unable to accommodate the details required for statistical analysis for a single arm trial, therefore the analysis details have not been added.

End point values	Single arm - 40mg daily oral afatinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Proportion alive and progression free				
number (confidence interval 80%)	0.590 (0.474 to 0.698)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response

End point title	Overall Response

End point description:

End point type	Secondary

End point timeframe:

Best response from initial response assessment for the whole duration of the trial.

End point values	Single arm - 40mg daily oral afatinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Number of responders				
Partial Response	21			
Stable Disease	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Overall survival is defined as the time from start of treatment to death from any cause. The median follow up time censoring for deaths was 42 months (range for survivors 32 to 65).

End point values	Single arm - 40mg daily oral afatinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Months				
median (confidence interval 95%)	15.5 (10.0 to 27.5)			

Attachments (see zip file)	OS all patients/OS (all).tif

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival in patients aged 70 and over

End point title	Progression free survival in patients aged 70 and over

End point description:

End point type	Secondary

End point timeframe:

Defined as the time from start of treatment to progression or death from any cause in patient aged 70 and over.

End point values	Single arm - 40mg daily oral afatinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Months				
median (confidence interval 95%)				
Aged 70 or over Under 70 years old	6.7 (3.0 to 10.2) 8.2 (4.6 to 27.5)			

Attachments (see zip file)	PFS by age/PFS (by age).tif

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance

End point title	Treatment Compliance

End point description:

End point type	Secondary

End point timeframe:

Calculated from date of first dose to date of last known dose. Patients who were still on treatment at the time of analysis were censored at the date last seen.

End point values	Single arm - 40mg daily oral afatinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Months				
median (confidence interval 95%)	4.4 (3.0 to 10.2)			

Attachments (see zip file)	Time on treatment/Time on treatment.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Change in performance status at 1 month

End point title	Change in performance status at 1 month

End point description:

End point type	Secondary

End point timeframe:

Baseline assessment at registration and one month after registration (+/- 1 week).

End point values	Single arm - 40mg daily oral afatinib	Single arm - 40mg daily oral afatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Number of patients				
Fully Active - WHO PS 0	6	3		
Ambulatory (work able) - WHO PS 1	21	24		
Ambulatory (not work able) - WHO PS 2	11	5		
Limited Selfcare - WHO PS 3	1	0		
Dead - WHO PS 5	0	2		
Unknown	0	5		

Statistical analyses

Statistical analysis title	Wilcoxon signed-rank test
Comparison groups	Single arm - 40mg daily oral afatinib v Single arm - 40mg daily oral afatinib
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.5
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Wilcoxon signed-rank test to determine whether there is evidence of a change in performance status from registration to 1 month.

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

Progression-free survival is defined as the time from registration to the date of first progression or death (from any cause), whichever occurs first. Patients who have not died or progressed were censored at the date last seen.

End point values	Single arm - 40mg daily oral afatinib			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Months				
median (confidence interval 95%)	7.9 (4.6 to 10.5)			

Attachments (see zip file)	PFS all patients/PFS (all).tif

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occured between informed consent and 30 days post last administration of afatinib.

Adverse event reporting additional description:

Adverse events were collected from patients through clinical assessment and review of self-reported patient diaries. For each type of adverse event, the maximum toxicity grade was obtained for each patient. Focus is on those with a grade 3 or 4 event. The proportion of patients with any grade 3 or 4 event are examined.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	All trial subjects

Reporting group description:

For each type of adverse event, the maximum toxicity grade was obtained for each patient.

Serious adverse events	All trial subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 39 (51.28%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	2		
Investigations			
Creatinine increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Food poisoning			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Atrial fibrillation				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	4 / 39 (10.26%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Mucositis oral				

subjects affected / exposed	3 / 39 (7.69%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia coli infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Lower respiratory tract infection				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	3 / 39 (7.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Nail infection				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Norovirus				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Anorexia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest wall pain				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	1 / 39 (2.56%)		
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	All trial subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Surgical and medical procedures			
Toe nail surgery			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Toe nail surgery			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		

Nail infection subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1 1 / 39 (2.56%) 1 2 / 39 (5.13%) 2		
Investigations Creatinine increased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1 1 / 39 (2.56%) 1		
Injury, poisoning and procedural complications Food poisoning subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1		
Cardiac disorders Left ventricular failure subjects affected / exposed occurrences (all)	 1 / 39 (2.56%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea	 12 / 39 (30.77%) 12 		

subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Mouth ulceration			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Left loin pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Escherichia Coli			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Norovirus			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		

Paronychia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Sepsis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Hypercalcemia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Hypomagnesemia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Hyponatremia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2013	Protocol version 2.0 dated 15th March 2013: 1. Updated Investigator's Brochure (IB)for afatinib implemented - version 13, dated 11th July 2012. 2. The IMP name BIBW 2992 was amended to afatinib (BIBW 2992) on all trial documents following generic name approval. 3. Participant Information sheet and Protocol updated to include new safety information described in the updated IB. 4. Reference Safety Information updated; all serious adverse reactions were evaluated, in order to determine whether they are suspected unexpected serious adverse reactions, using information contained in the current investigator brochure for Afatinib (BIBW 2992).
05 November 2013	Protocol version 3 dated 12th November 2013: 1. Updated Afatinib Investigator's Brochure implemented - version 14 dated 4th July 2013. 2. Reference Safety Information; all serious adverse reactions were evaluated, in order to determine whether they are suspected unexpected serious adverse reactions, using information contained in the updated investigator brochure for afatinib (BIBW 2992) version 14 dated 04/07/2013 using the list of expected AEs under section 7. 3. The main change was to include patients with a known EGFR mutation. As a result the trial title has been amended on all trial documents to reflect the inclusion of this group of patients. 4. The Participant Information Sheet was updated to include an additional side effect referenced in the updated safety information. 5. Protocol updated to include confirmed EGFR patients and the safety profile of afatinib was updated with information from ongoing phase I and II trials.
02 July 2014	Protocol version 4.0 dated 24th June 2014: Clarification regarding eligibility of patients with WHO performance status (PS) 3 added. Patients with a confirmed activating EGFR mutation and WHO PS 0-3 were eligible, whereas patients who had suspected EGFR mutation were only eligible if WHO PS was 0-2.
12 December 2016	Protocol version 5 dated 9th August 2016: 1. End of trial definition updated. 2. Inclusion of central review of progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

1. SAEs and non-serious grade 3+ AEs are listed under non-serious AE section.
2. Under non-serious AEs, only the highest grade experienced by patients was collected and therefore the 'subjects affected' number has been entered for 'occurrences'.

Notes: