Clinical trial results:
Gefitinib and methotrexate to resolve tubal ectopic pregnancy: the GEM3 RCT

Summary

EudraCT number	2015-005013-76
Trial protocol	GB
Global end of trial date	06 October 2021

Results information

Result version number	v1 (current)
This version publication date	29 March 2023
First version publication date	29 March 2023

Trial information

Trial identification

Sponsor protocol code	AC15004

Additional study identifiers

ISRCTN number	ISRCTN67795930
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Ethics number: 16/SS/0014

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh and NHS Lothian
Sponsor organisation address	Queen's Medical Research Institute, 47 Little France Crescent Edinburgh, United Kingdom, EH16 4TJ
Public contact	Ann Doust, University of Edinburgh, 0044 1312422963, ann.doust@ed.ac.uk
Scientific contact	Ann Doust, University of Edinburgh, 0044 1312422963, ann.doust@ed.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	02 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2021
Global end of trial reached?	Yes
Global end of trial date	06 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomised controlled trial.

To see if taking methotrexate (MTX) in combination with gefitinib is better at reducing the need for surgery against methotrexate alone in the treatment of stable tubal ectopic pregnancy.

Protection of trial subjects:

Patient safety was monitored closely at each clinical care visit where adverse events were recorded.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
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: 328
Worldwide total number of subjects	328
EEA total number of subjects	0

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)	328
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

GEM3 participants were recruited from early pregnancy units (EPU) in 50 of the 74 NHS participating sites across the UK. First participant was consented on 9th November 2016 and the last participant was consented on 6th October 2021.

Pre-assignment

Screening details:

Participants were screening clinically to ensure that they fulfilled the inclusion criteria

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Gefitinib

Arm type	Active comparator
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	Iressa
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg for seven days

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

One tablet taken for 7 days

Number of subjects in period 1	Active	Placebo
Started	165	163
Completed	165	160
Not completed	0	3
Consent withdrawn by subject	-	1
Pregnancy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	328	328	
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)	328	328	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	31.7		
standard deviation	± 5.5	-	
Gender categorical Units: Subjects			
Female	328	328	
Male	0	0	

End points

End points reporting groups	
Reporting group title	Active
Reporting group description: Gefitinib	
Reporting group title	Placebo
Reporting group description: Placebo	

Primary: Surgical intervention	
End point title	Surgical intervention
End point description:	
End point type	Primary
End point timeframe: Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	160		
Units: Number of women				
Yes	50	47		
No	115	113		

Statistical analyses

Statistical analysis title	Full
Comparison groups	Active v Placebo
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.58

Secondary: Additional MTX

End point title	Additional MTX

End point description:

End point type	Secondary

End point timeframe:

Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: Number of women				
Yes	20	23		
No	145	139		

Statistical analyses

Statistical analysis title	Additional MTX Analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.28

Secondary: Time to hCG Resolution

End point title	Time to hCG Resolution

End point description:

End point type	Secondary

End point timeframe:

Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165[1]	162[2]		
Units: Days				
median (inter-quartile range (Q1-Q3))	28.0 (23.5 to 36.0)	28.0 (21.0 to 36.5)		

Notes:

[1] - Median presented for 108 women whose pregnancy resolved.

[2] - Median presented in 108 women whose pregnancy resolved

Statistical analyses

Statistical analysis title	Time to hCG resolution-Cause specific hazard ratio
Comparison groups	Active v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.33

Statistical analysis title	Time to hCG resolution-Subdistribution hazard rati
Comparison groups	Active v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
Method	Fine and Grey competing risk model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.4

Secondary: Number of hospital visits

End point title	Number of hospital visits

End point description:

End point type	Secondary

End point timeframe:

Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	162		
Units: Number of hospital visits				
median (inter-quartile range (Q1-Q3))	5.0 (4.0 to 7.0)	5.0 (3.0 to 6.0)		

Statistical analyses

Statistical analysis title	Number of hospital visits analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Incidence rate ratio
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.12

Secondary: Acceptability-satisfaction with treatment

End point title	Acceptability-satisfaction with treatment

End point description:

End point type	Secondary

End point timeframe:

3 months post pregnancy resolution (hCG <15 IU/L or surgical resolution).

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	138		
Units: Number of women				
Very satisfied	59	72		
Mostly satisfied	44	33		
Neither satisfied or dissatisfied	24	23		
Mostly dissatisfied	3	4		
Very dissatisfied	4	6		

Statistical analyses

Statistical analysis title	Acceptability-Satisfaction with treatment analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.12

Secondary: Acceptability-acceptability of treatment

End point title	Acceptability-acceptability of treatment

End point description:

End point type	Secondary

End point timeframe:

Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	138		
Units: Number of women				
Very acceptable	78	87		
Mostly acceptable	32	32		
Neither acceptable nor unacceptable	19	13		
Mostly unacceptable	3	4		
Very unacceptable	2	2		

Statistical analyses

Statistical analysis title	Acceptability-acceptability of treatment analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.28

Secondary: Acceptability-recommend treatment

End point title	Acceptability-recommend treatment

End point description:

End point type	Secondary

End point timeframe:

Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	139		
Units: Number of women				
Very likely to recommend	78	93		
Fairly likely to recommend	32	33		
Neither likely to recommend or recommend against	15	4		
Fairly likely to recommend against	4	6		
Very likely to recommend against	5	3		

Statistical analyses

Statistical analysis title	Acceptability-recommend treatment analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.01

Secondary: Return to menses	
End point title	Return to menses
End point description:	
End point type	Secondary
End point timeframe:	
Up to pregnancy resolution (hCG <15 IU/L or surgical resolution).	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	134		
Units: days				
median (inter-quartile range (Q1-Q3))	24.0 (24.0 to 38.0)	24.0 (24.0 to 38.0)		

Statistical analyses

Statistical analysis title	Return to menses analysis
Comparison groups	Active v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from time of consent to resolution of ectopic pregnancy (hCG <15 IU/L or surgical resolution).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	2.4

Reporting groups

Reporting group title	Active
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 165 (3.03%)	6 / 162 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Scan	Additional description: For renal calculi - none seen		
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ultrasound scan			
subjects affected / exposed	1 / 165 (0.61%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised CRP			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparoscopy	Additional description: Ruptured ovarian cyst		
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hyperventilation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pelvic inflammatory disease			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 165 (22.42%)	38 / 162 (23.46%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Laparoscopy	Additional description: Only reported at the beginning of the trial. Protocol amended.		
subjects affected / exposed	3 / 165 (1.82%)	1 / 162 (0.62%)	
occurrences (all)	4	4	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy	Additional description: Presenting with pain/rupture - reported in the beginning of the trial before a protocol amendment which meant this no longer had to be reported.		
subjects affected / exposed	8 / 165 (4.85%)	6 / 162 (3.70%)	
occurrences (all)	14	14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Pain			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Cough			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Sore throat			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Psychiatric disorders			
Hyperventilation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Low mood			
subjects affected / exposed	1 / 165 (0.61%)	1 / 162 (0.62%)	
occurrences (all)	2	2	
Investigations			
Low haemoglobin			
subjects affected / exposed	2 / 165 (1.21%)	2 / 162 (1.23%)	
occurrences (all)	4	4	
Low lymphocytes			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	0	
Low white cell count			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Raised CRP			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Raised alanine aminotransferase level			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Low haematocrit			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 165 (3.03%)	4 / 162 (2.47%)	
occurrences (all)	9	9	
Feeling shaky			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Numbness			
subjects affected / exposed	2 / 165 (1.21%)	0 / 162 (0.00%)	
occurrences (all)	2	2	
Paresthesia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Deranged LFTs			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Reduced lymphocytes			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Reduced neutrophils			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Hearing loss	Additional description: This was due to a cold		
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Tinnitus			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Eye disorders			
Painful eyes			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	

Conjunctivitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Rectal pain			
subjects affected / exposed	0 / 165 (0.00%)	3 / 162 (1.85%)	
occurrences (all)	3	3	
Bleeding gums			
subjects affected / exposed	1 / 165 (0.61%)	1 / 162 (0.62%)	
occurrences (all)	2	2	
Toothache			
subjects affected / exposed	0 / 165 (0.00%)	2 / 162 (1.23%)	
occurrences (all)	2	2	
Constipation			
subjects affected / exposed	1 / 165 (0.61%)	2 / 162 (1.23%)	
occurrences (all)	3	3	
Rectal bleeding			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Dry mouth			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Tongue feeling burnt	Additional description: Not due to eating or drinking. Happened spontaneously.		
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 165 (2.42%)	4 / 162 (2.47%)	
occurrences (all)	8	8	
Dry skin			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Nails breaking			

subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Candida infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Urinary urgency			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	3 / 165 (1.82%)	4 / 162 (2.47%)	
occurrences (all)	7	7	
Feeling weak			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 165 (0.61%)	3 / 162 (1.85%)	
occurrences (all)	4	4	
Chlamydial infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
Vaginal discharge			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Insect bites			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Wound infection bacterial			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Rhinitis			

subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	
COVID-19			
subjects affected / exposed	2 / 165 (1.21%)	0 / 162 (0.00%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Loss of appetite			
subjects affected / exposed	0 / 165 (0.00%)	1 / 162 (0.62%)	
occurrences (all)	1	1	
Raised potassium level			
subjects affected / exposed	1 / 165 (0.61%)	0 / 162 (0.00%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2016	Protocol v4_Clarification of documents after ethical review
10 October 2016	Protocol v5_ clarificiation of terms following co-investigators, TSC and DMEC meetings
12 April 2017	Protocol v 6_clarification of processes, update of SmPC. Update to reflect TSC change of Chair and DMC change of statistician, contacts details of trial team.
17 April 2017	Protocol v7_Change to SmPC gefitinib. Change in contact details. Clarification of terms.
26 July 2019	Protocol v8_Change of address for Sharp Clinical UK. Removal of mechanistic study. Addition of information re long term follow up. Change of staff information. Addition of data management details.
19 February 2021	Protocol v9_Change to SmPC gefitinib and methotrexate. Minor changes to analysis section for clarification. Minor administrative changes for clarification of terms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 March 2020	Recruitment stopped due to the COVID-19 pandemic.	09 June 2021

Notes:

Limitations and caveats

None reported