Clinical trial results:
Phase II neoadjuvant study of Axitinib for reducing extent of venous tumour thrombus in clear cell renal cell cancer with venous invasion.

Summary

EudraCT number	2017-000619-17
Trial protocol	GB
Global end of trial date	10 June 2020

Results information

Result version number	v1 (current)
This version publication date	23 May 2021
First version publication date	23 May 2021

Trial information

Trial identification

Sponsor protocol code	NAXIVA v2.0

Additional study identifiers

ISRCTN number	ISRCTN96273644
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Common Services Agency
Sponsor organisation address	CSA at Public Health Scotland, Edinburgh, United Kingdom, EH12 9EB
Public contact	Kathleen Riddle, Scottish Clinical Trials Research Unit, Public Health Scotland, 0131 2757074, Kathleen.Riddle@phs.scot
Scientific contact	Prof Grant Stewart, University of Cambridge, 01223 256211, gds35@cam.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	25 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2020
Global end of trial reached?	Yes
Global end of trial date	10 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research objective is to examine how effective axitinib is at reducing the extent of the cancer invasion into the large blood vessels draining the kidney with a view to reducing the extent of surgery required to then remove the cancerous tissue.

Protection of trial subjects:

No specific additional measures were implemented for this trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2017
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: 24
Worldwide total number of subjects	24
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)	7
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were no recurring themes identified from screening logs.

Period 1

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

Blinding implementation details:

N/A

Arms

Arm title	Single arm

Arm description:

Patients taking axitinib.

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

Dosage and administration details:

The starting dose of axitinib will be 5mg BID and escalated to 7mg BID and then 10mg BID. A dose modification assessment will take place every 2 weeks in clinic during the 8 week pre-surgical treatment period and will be dependent on tolerability of treatment. Patients will follow an aggressive axitinib dose escalation process within the 8 week period to a maximum of 10mg BID. Patients should stop axitinib a minimum of 36 hours and a maximum of 7 days prior to surgery in week 9.

Number of subjects in period 1	Single arm
Started	24
Completed	18
Not completed	6
Adverse event, serious fatal	1
Physician decision	2
Did not start trial treatment	1
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	24	24	
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)	7	7	
From 65-84 years	17	17	
85 years and over	0	0	
Age continuous Units: years			
median	69		
standard deviation	± 7.94	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	17	17	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all patients in the ITT population who have received at least one dose of the study drug (including any patients who were enrolled in error, received study drug and were subsequently found to be ineligible). In this study, this population is equivalent to the evaluable population.

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population includes all patients registered onto the study.

Subject analysis set title	Evaluable population
Subject analysis set type	Per protocol

Subject analysis set description:

The evaluable population includes all patients in the ITT population who have received at least one dose of the study drug (including any patients who were enrolled in error, received study drug and were subsequently found to be ineligible).

Subject analysis set title	Surgical population
Subject analysis set type	Sub-group analysis

Subject analysis set description:
The group of evaluable patients who had surgery.

Reporting group values	Safety population	Intention to treat	Evaluable population
Number of subjects	21	24	21
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	7	6
From 65-84 years	15	17	15
85 years and over	0	0	0
Age continuous			
Units: years			
median	69	69	69
standard deviation	± 8.16	± 7.94	± 8.16
Gender categorical			
Units: Subjects			
Female	6	7	6
Male	15	17	15

Reporting group values	Surgical population		
Number of subjects	17		
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)	6		
From 65-84 years	11		
85 years and over	0		
Age continuous			
Units: years			
median	66		
standard deviation	± 7.83		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description: Patients taking axitinib.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population includes all patients in the ITT population who have received at least one dose of the study drug (including any patients who were enrolled in error, received study drug and were subsequently found to be ineligible). In this study, this population is equivalent to the evaluable population.	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intention-to-treat (ITT) population includes all patients registered onto the study.	
Subject analysis set title	Evaluable population
Subject analysis set type	Per protocol
Subject analysis set description: The evaluable population includes all patients in the ITT population who have received at least one dose of the study drug (including any patients who were enrolled in error, received study drug and were subsequently found to be ineligible).	
Subject analysis set title	Surgical population
Subject analysis set type	Sub-group analysis
Subject analysis set description: The group of evaluable patients who had surgery.	

Primary: Percentage of evaluable patients with an improvement in disease as a result of taking the study drug

End point title	Percentage of evaluable patients with an improvement in disease as a result of taking the study drug
End point description: The primary end-point for this study is the percentage of evaluable patients with an improvement in disease as a result of taking the study drug. The definition of an improvement will vary according to the patient's Mayo Level as captured at screening: * For patients presenting at screening with a Mayo Classification of Level 1 or above, an improvement in disease will be represented by a reduction in their Mayo Classification at week 9. * For patients presenting at screening with a Mayo Classification of Level 0, an improvement in disease will be represented by either: (i) a change of tumor thrombus from main renal vein to branches of the renal vein (on the right); or (ii) a change of tumor thrombus from main renal vein to the renal vein lateral to the gonadal vein (on the left).	
End point type	Primary
End point timeframe: 9 weeks	

End point values	Single arm	Evaluable population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: Patients				
Responder	6	6		
Non-responder	15	15		

Statistical analyses

Statistical analysis title	Koyama & Chen (implementation of Simon's 2 stage)

Statistical analysis description:

The study employed a Simon two stage minimax design to distinguish a <5% from a >25% improvement in the Mayo classification (90% power, 10% 1-sided) requiring 20 patients; interim assessment to be made at 13 patients. Inferences calculatied using: Koyama & Chen, "Proper inference from Simon's two-stage designs." Statistics in medicine vol. 27,16 (2008): 3145-54.

Comparison groups	Single arm v Evaluable population
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.01 [1]
Method	Koyama & Chen
Parameter estimate	Response rate
Point estimate	26.58
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	15.76
upper limit	39.74

Notes:

[1] - The estimated response rate in this setting is 26.58%, with 80% confidence intervals of (15.76%, 39.74%). The exact p-value is 4.413 x10^-4.

Secondary: Percentage change in surgical approach

End point title	Percentage change in surgical approach

End point description:

End point type	Secondary

End point timeframe:

Post-surgical

End point values	Surgical population			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Patients				
Improvement in control of IVC/renal vein	6			

Deterioration in control of IVC/renal vein	0			
No change in control of IVC/renal vein	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in VTT length

End point title	Percentage change in VTT length

End point description:

End point type	Secondary

End point timeframe:

9 weeks

End point values	Evaluable population			
Subject group type	Subject analysis set			
Number of subjects analysed	17[2]			
Units: Percentage				
median (standard deviation)	21.49 (± 27.60)			

Notes:

[2] - 3 (no 9wk scan) + 1 (ineligible) pts were not included in the assessment of this timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: RECIST response

End point title	RECIST response

End point description:

End point type	Secondary

End point timeframe:

Week 9

End point values	Evaluable population			
Subject group type	Subject analysis set			
Number of subjects analysed	18[3]			
Units: Patients				
Complete response	0			
Partial response	3			
Stable disease	13			
Progressive disease	2			
Non-evaluable	0			

Notes:

[3] - 3 pts did not have the relevant data and were removed from the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of surgical morbidity assessed by Clavian-Dindo classification

End point title	Evaluation of surgical morbidity assessed by Clavian-Dindo classification

End point description:

End point type	Secondary

End point timeframe:

Post-surgery

End point values	Surgical population			
Subject group type	Subject analysis set			
Number of subjects analysed	6[4]			
Units: Patients				
Grade I	1			
Grade II	3			
Grade IIIa	0			
Grade IIIb	0			
Grade IVa	0			
Grade IVb	1			
Grade V	1			

Notes:

[4] - Only 6 patients had post-surgical complications within 30 days.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Single

Reporting group description: -

Serious adverse events	Single		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 24 (33.33%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: Injury, poisoning and procedural complications		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders	Additional description: Cardiac disorders		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Nervous system disorders	Additional description: Nervous system disorders		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Psychiatric disorders	Additional description: Psychiatric disorders		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: Renal and urinary disorders		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Endocrine disorders	Additional description: Endocrine disorders		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: Metabolism and nutrition disorders		
subjects affected / exposed	1 / 24 (4.17%)		
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	Single		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Vascular disorders			
Vascular disorders	Additional description: Vascular disorders		
subjects affected / exposed	19 / 24 (79.17%)		
occurrences (all)	89		
General disorders and administration site conditions			

General disorders and administration site conditions	Additional description: General disorders and administration site conditions		
subjects affected / exposed	20 / 24 (83.33%)		
occurrences (all)	83		
Reproductive system and breast disorders			
Reproductive system and breast disorders	Additional description: Reproductive system and breast disorders		
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: Respiratory, thoracic and mediastinal disorders		
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	16		
Psychiatric disorders			
Psychiatric disorders	Additional description: Psychiatric disorders		
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	51		
Investigations			
Investigations	Additional description: Investigations		
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	28		
Cardiac disorders			
Cardiac disorders	Additional description: Cardiac disorders		
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	13		
Nervous system disorders			
Nervous system disorders	Additional description: Nervous system disorders		
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	37		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: Blood and lymphatic system disorders		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: Ear and labyrinth disorders		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Eye disorders			

Eye disorders	Additional description: Eye disorders		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	7		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: Gastrointestinal disorders		
subjects affected / exposed	17 / 24 (70.83%)		
occurrences (all)	88		
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: Hepatobiliary disorders		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: Skin and subcutaneous tissue disorders		
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	33		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: Renal and urinary disorders		
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	35		
Endocrine disorders			
Endocrine disorders	Additional description: Endocrine disorders		
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders	Additional description: Musculoskeletal and connective tissue disorders		
subjects affected / exposed	12 / 24 (50.00%)		
occurrences (all)	34		
Infections and infestations			
Infections and infestations	Additional description: Infections and infestations		
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Metabolism and nutrition disorders	Additional description: Metabolism and nutrition disorders		
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2017	Change of PI at Addenbrooke's (Grant Stewart to Kate Fife): - IRAS SA Form - Cover Letter - Kate Fife (CV & GCP)
19 June 2018	Addition of a new site: Broomfield Hospital Mid Essex NHS Trust -IRAS SA Form -Cover Letter -Dr Srinivasan (CV & GCP)
26 June 2018	Protocol amendment (V1.2 to V2.0) - IRAS SA Form - Cover Letter - V2.0 Protocol (clean and tracked) - Main PIS/ICF V2.1 (REC & HRA only)
20 September 2018	Addition to new site: Royal Free London NHS Foundation Trust - IRAS SA Form - Cover letter - Dr Boleti (CV and GCP)
05 December 2018	Change of PI at Broomfield - IRAS SA Form - Cover Letter - Abdel Hamid (CV & GCP)
22 May 2020	Updated SmPC -Inlyta 5mg SmPC with changes highlighted -Inlyta 7mg SmPC with changes highlighted Please note that the date provided for this amendment is the date we sumitted the amendment. The system will not accept the date that the amendment was approved (17th June 2020) as this is beyond the global end of trial date.

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.

Note that this is a single arm trial and the primary endpoint is reported according to the work around reported in point #82 here https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf.

Notes: