# EU Clinical Trials Register

## 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 | | | |

| | Single | | |
|---|---|---|---|
| **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):<br>- IRAS SA Form<br>- Cover Letter<br>- Kate Fife (CV & GCP) |
| 19 June 2018 | Addition of a new site:<br>Broomfield Hospital<br>Mid Essex NHS Trust<br>-IRAS SA Form<br>-Cover Letter<br>-Dr Srinivasan (CV & GCP) |
| 26 June 2018 | Protocol amendment (V1.2 to V2.0)<br>- IRAS SA Form<br>- Cover Letter<br>- V2.0 Protocol (clean and tracked)<br>- Main PIS/ICF V2.1 (REC & HRA only) |
| 20 September 2018 | Addition to new site: Royal Free London NHS Foundation Trust<br>- IRAS SA Form<br>- Cover letter<br>- Dr Boleti (CV and GCP) |
| 05 December 2018 | Change of PI at Broomfield<br>- IRAS SA Form<br>- Cover Letter<br>- Abdel Hamid (CV & GCP) |
| 22 May 2020 | Updated SmPC<br>-Inlyta 5mg SmPC with changes highlighted<br>-Inlyta 7mg SmPC with changes highlighted<br><br>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:

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### 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: