



Clinical trial results:

Coversin in Paroxysmal Nocturnal Haemoglobinuria (PNH) in patients with resistance to Eculizumab due to complement C5 Polymorphisms

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-003778-34 |
| Trial protocol | NL |
| Global end of trial date | 20 March 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 18 November 2021 |
| First version publication date | 18 November 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | AK578 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|----------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02591862 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Coversin VIP578: Coversin VIP578 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Akari Therapeutics plc |
| Sponsor organisation address | 75-76 Wimpole Street, London, United Kingdom, W1G 9RT |
| Public contact | Chief Scientific Officer, Akari Therapeutics Plc, +44 (0)2080040261, miles.nunn@akaritx.com |
| Scientific contact | Chief Scientific Officer, Akari Therapeutics Plc, +44 (0)2080040261, miles.nunn@akaritx.com |

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 | 20 March 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 March 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 March 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: Safety and tolerability of Nomacopan

Protection of trial subjects:

The study was performed in accordance with the current version of the declaration of Helsinki. The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) E6(R1) which were current at the time of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 1 |
| Worldwide total number of subjects | 1 |
| EEA total number of subjects | 1 |

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) | 1 |
| From 65 to 84 years | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were screened up to 14 days prior to study treatment to confirm eligibility for the study. A total of 1 patient was screened and enrolled onto the study.

Period 1

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

Arms

| | |
|--|---|
| Arm title | Nomacopan (Coversin) |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Nomacopan |
| Investigational medicinal product code | rVA576 |
| Other name | Coversin, rEV576 |
| Pharmaceutical forms | Powder for solution for injection, Solution for injection in vial |
| Routes of administration | Solution for injection , Subcutaneous use |

Dosage and administration details:

Patient will be given a single ablating dose of 0.57mg/kg per subject followed by daily repeat maintenance doses. The initial repeat dose will be 25% of the ablating dose. If this is insufficient to maintain complement inhibition at $\leq 10\%$ of baseline (pre-treatment) level after 5 days of treatment the daily dose will be increased by doubling until that level of inhibition is achieved. In the event of 100% inhibition being achieved the dose may be titrated downwards at the PI's discretion until a satisfactory clinical result is obtained. If at any point in treatment complement inhibition falls to less than 50% of baseline a further ablating dose of 0.57mg/kg should be given. Nomacopan lyophilised powder in each vial was diluted with 0.6 mL water for injection prior to use.

| Number of subjects in period 1 | Nomacopan (Coversin) |
|---------------------------------------|----------------------|
| Started | 1 |
| Completed | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description:

Results from 1 enrolled patient.

| Reporting group values | Overall Trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 1 | 1 | |
| 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) | 1 | 1 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 1 | 1 | |
| Race | | | |
| Units: Subjects | | | |
| white | 1 | 1 | |
| Region of enrolment | | | |
| Units: Subjects | | | |
| Netherlands | 1 | 1 | |
| Dependency on blood transfusion | | | |
| Units: Subjects | | | |
| Dependent on blood transfusion | 0 | 0 | |
| Not dependent on blood transfusion | 1 | 1 | |
| Weight | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 67.8 | | |
| standard deviation | ± 0 | - | |
| Height | | | |
| Units: centimeter | | | |
| arithmetic mean | 172 | | |
| standard deviation | ± 0 | - | |
| Serum Lactate Dehydrogenase | | | |
| Units: U/L | | | |
| arithmetic mean | 1391 | | |
| standard deviation | ± 0 | - | |
| Haemoglobin concentration (Hb) | | | |

| | | | |
|--------------------------------|-----|---|--|
| Units: Millimole(s)/litre | | | |
| arithmetic mean | 8.2 | | |
| standard deviation | ± 0 | - | |
| Haptoglobin (Hp) concentration | | | |
| Units: grams(s)/litre | | | |
| arithmetic mean | 0.0 | | |
| standard deviation | ± 0 | - | |

End points

End points reporting groups

| | |
|------------------------------|----------------------|
| Reporting group title | Nomacopan (Coversin) |
| Reporting group description: | - |

Primary: Measurement of Serum lactate dehydrogenase (LDH) from Day 0 (pre-dose) to Day 28 (AUC) compared with 28 days pre-treatment

| | |
|-----------------|---|
| End point title | Measurement of Serum lactate dehydrogenase (LDH) from Day 0 (pre-dose) to Day 28 (AUC) compared with 28 days pre-treatment ^[1] |
|-----------------|---|

End point description:

LDH is an indicator of disease progression in patients with PNH and is expected to fall to within 2x upper limit of normal (ULN) within 28 days in successfully treated patients. Units are measured in ratio of LDH:ULN, where the ULN is 250 U/L.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 and Day 28

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: This was an open-label study in which just one patient was recruited. Simple descriptive statistics were therefore used.

| End point values | Nomacopan (Coversin) | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: ratio of LDH:ULN (250 U/L) | | | | |
| number (not applicable) | | | | |
| Day 0 | 5.6 | | | |
| Day 28 | 1.9 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number and Type of Adverse Events (AE)

| | |
|-----------------|---|
| End point title | Number and Type of Adverse Events (AE) ^[2] |
|-----------------|---|

End point description:

The number and type of reported AEs will be recorded as well as the opinion of the Principle Investigator (PI) as to their possible relationship to the study drug.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

2 years

Notes:

[2] - 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: This was an open-label study in which just one patient was recruited. Simple descriptive

statistics were therefore used.

| End point values | Nomacopan (Coverstin) | | | |
|--|--------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: Events | | | | |
| Serious Adverse Events (SAE) | 2 | | | |
| Adverse Event (AE) (Total) | 20 | | | |
| Treatment Emergent Adverse Event (TAEA) | 13 | | | |
| AE- moderate | 1 | | | |
| AE- severe | 1 | | | |
| AE- mild | 18 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Haemoglobin (Hb) at Days 28, 90 and 180, absolute and change from baseline

| | |
|------------------------|---|
| End point title | Measurement of Haemoglobin (Hb) at Days 28, 90 and 180, absolute and change from baseline |
| End point description: | Measuring change in mean Hb from Day 28, Day 90 and Day 180 (absolute and change from baseline) |
| End point type | Secondary |
| End point timeframe: | Baseline, Day 28, Day 90 and 180 |

| End point values | Nomacopan (Coverstin) | | | |
|--------------------------------|--------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: millimole(s)/litre | | | | |
| number (not applicable) | | | | |
| Baseline | 8.2 | | | |
| Day 28 (absolute) | 7.8 | | | |
| Day 28 (change from baseline) | -0.7 | | | |
| Day 90 (absolute) | 7.8 | | | |
| Day 90 (change from baseline) | -0.4 | | | |
| Day 180 (absolute) | 8.0 | | | |
| Day 180 (change from baseline) | -0.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Lactate Dehydrogenase (LDH) at Baseline, day 90 and 180

| | |
|-----------------|--|
| End point title | Measurement of Lactate Dehydrogenase (LDH) at Baseline, day 90 and 180 |
|-----------------|--|

End point description:

Measuring the change in LDH at Baseline, Day 90 and Day 180. LDH is an indicator of disease progression in patients with PNH and is expected to fall to within 2x upper limit of normal (ULN) within 28 days in successfully treated patients. Units are measured in ratio of LDH:ULN, where the ULN is 250 U/L.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 90 and Day 180

| End point values | Nomacopan (Coversin) | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: ratio of LDH:ULN (250 U/L) | | | | |
| number (not applicable) | | | | |
| Day 0 | 5.6 | | | |
| Day 90 | 1.6 | | | |
| Day 180 | 1.5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of Haptoglobin (Hp) at Days 28, 90 and 180, Absolute and Change From Baseline

| | |
|-----------------|---|
| End point title | Measurement of Haptoglobin (Hp) at Days 28, 90 and 180, Absolute and Change From Baseline |
|-----------------|---|

End point description:

Measuring change in mean Hp from Day 28, Day 90 and Day 180 (absolute and change from baseline)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 28, Day 90 and Day 180

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | Nomacopan (Coversin) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: gram(s)/litre | | | | |
| number (not applicable) | | | | |
| Baseline | 0.0 | | | |
| Day 28 | 0.0 | | | |
| Day 90 | 0.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dependency on blood transfusion

| | |
|---|---------------------------------|
| End point title | Dependency on blood transfusion |
| End point description: Number of participants depending on blood transfusion prior to starting the study compared to during the study. | |
| End point type | Secondary |
| End point timeframe: Day 0 through to study completion (2 years) | |

| | | | | |
|---|----------------------|--|--|--|
| End point values | Nomacopan (Coversin) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: Participants | | | | |
| Transfusion dependent prior to starting trial | 0 | | | |
| Transfusion dependent during trial | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Functional Assessment of Chronic Illness Therapy (FACIT) Score at Days 0, 28, 90 and 180

| | |
|--|--|
| End point title | Change in Functional Assessment of Chronic Illness Therapy (FACIT) Score at Days 0, 28, 90 and 180 |
| End point description: Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-F) is a 13 item instrument designed to assess fatigue/tiredness and its impact on daily activities and functioning in a chronic disease setting. The scale for each question in relation to quality of life ranges from 0-4 where 0= not at all, 1= a little bit, 2= somewhat, 3 = quite a bit and 4= very much. An increase in the scale score indicates an improvement in quality of life (less fatigue). A maximum score of 52 is interpreted as no fatigue . Baseline is assumed as 0.0 to demonstrate the change in units. The subscale score (as presented) is | |

determined as per FACIT-f guidance, by multiplying the sum of the item scores by the number of items in the subscale, then divide by the number of items answered.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 28, 90 and 180

| End point values | Nomacopan (Coversin) | | | |
|---|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: FACIT-f scale (Change from Baseline) | | | | |
| number (not applicable) | | | | |
| Day 28 | 13.0 | | | |
| Day 90 | 13.3 | | | |
| Day 180 | 11.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Quality Of Life Questionnaire (QQQ) Score at Days 0, 28, 90 and 180

| | |
|-----------------|---|
| End point title | Change in Quality Of Life Questionnaire (QQQ) Score at Days 0, 28, 90 and 180 |
|-----------------|---|

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) QQQ C30 instrument measures the change in the quality of life of patients in the trial. Quality of Life Questionnaire (QLQ)-C30 comprises 30 questions on daily quality of life and incorporates a global health status, five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, nausea/vomiting, pain), and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). Higher score for the functioning scales and global health status denote a better level of functioning (i.e. a better state of the patient), while higher scores on the symptom and single-item scales indicate a higher level of symptoms (i.e. a worse state of the patient). Baseline is assumed as 0.0 to demonstrate the change in units.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 28, 90 and 180

| End point values | Nomacopan (Coversin) | | | |
|---|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: QLQ-C30 scale (Change from baseline) | | | | |
| number (not applicable) | | | | |
| Global Health Status/ QOL (day 28) | 16.7 | | | |

| | | | | |
|---|-------|--|--|--|
| Global Health Status/ QOL (day 90) | 16.7 | | | |
| Global Health Status/ QOL (day 180) | 16.7 | | | |
| Physical Functioning (day 28) | 6.6 | | | |
| Physical Functioning (day 90) | 0.0 | | | |
| Physical Functioning (day 180) | 6.6 | | | |
| Role functioning (day 28) | 33.4 | | | |
| Role functioning (day 90) | 33.4 | | | |
| Role functioning (day 180) | 16.7 | | | |
| Emotional functioning (day 28) | 16.6 | | | |
| Emotional functioning (day 90) | 8.3 | | | |
| Emotional functioning (day 180) | 8.3 | | | |
| Cognitive functioning (day 28) | 33.3 | | | |
| Cognitive functioning (day 90) | 16.7 | | | |
| Cognitive functioning (day 180) | 16.7 | | | |
| Social functioning (day 28) | 0.0 | | | |
| Social functioning (day 90) | 0.0 | | | |
| Social functioning (day 180) | 0.0 | | | |
| Fatigue symptom scale (day 28) | -11.1 | | | |
| Fatigue symptom scale (day 90) | 0.0 | | | |
| Fatigue symptom scale (day 180) | 0.0 | | | |
| Nausea and vomiting symptom scale (day 28) | 0.0 | | | |
| Nausea and vomiting symptom scale (day 90) | 0.0 | | | |
| Nausea and vomiting symptom scale (day 180) | 0.0 | | | |
| Pain symptom scale (day 28) | 0.0 | | | |
| Pain symptom scale (day 90) | 16.7 | | | |
| Pain symptom scale (day 180) | 0.0 | | | |
| Symptom: Dyspnoea (day 28) | 0.0 | | | |
| Symptom: Dyspnoea (day 90) | 0.0 | | | |
| Symptom: Dyspnoea (day 180) | 0.0 | | | |
| Symptom: Insomnia (day 28) | -33.3 | | | |
| Symptom: Insomnia (day 90) | 0.0 | | | |
| Symptom: Insomnia (day 180) | 0.0 | | | |
| Symptom: Appetite loss (day 28) | 0.0 | | | |
| Symptom: Appetite loss (day 90) | 0.0 | | | |
| Symptom: Appetite loss (day 180) | 0.0 | | | |
| Symptom: constipation (day 28) | 0.0 | | | |
| Symptom: constipation (day 90) | 0.0 | | | |
| Symptom: constipation (day 180) | 0.0 | | | |
| Symptom: diarrhoea (day 28) | -33.3 | | | |
| Symptom: diarrhoea (day 90) | -33.3 | | | |
| Symptom: diarrhoea (day 180) | -33.3 | | | |
| Symptom: financial difficulties (day 28) | 0.0 | | | |
| Symptom: financial difficulties (day 90) | 0.0 | | | |
| Symptom: financial difficulties (day 180) | 0.0 | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of the study (2 years)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | nomacopan (coversin) |
|-----------------------|----------------------|

Reporting group description: -

| Serious adverse events | nomacopan (coversin) | | |
|---|-------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Blood and lymphatic system disorders | | | |
| Breakthrough haemolysis | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | nomacopan (coversin) | | |
|---|-------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| Vascular disorders | | | |
| Cold fingers and toes | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 6 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Flu like symptoms | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 5 | | |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 13 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 2 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|--|--|
| Coughing subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Sore throat subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 2 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |
| | | | |
| Haemoglobinuria subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |
| Infections and infestations Papulopustular rash subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 November 2015 | <ul style="list-style-type: none">- Volution Immuno Pharmaceuticals changes to Akari Therapeutics Plc- primary efficacy endpoint - Significant Reduction in serum LDH from day 0 – Day 28 (AUC) compared with 28 days pre treatment- secondary endpoint change of timepoints, and wording clarification- clarity over patient discharge before day 7- addition of prohibited drugs- addition to clarity over patient comparisons- change to concentration of drug product for first treatment (8.9 mg/ml to 7.2 mg/ml)- addition to have vaccination against meningococci type ACW135Y as a requirement for the study- addition of patients being required to be admitted to hospital for a minimum of 2 days at the start of treatment- If an ablating dose is repeated , PK/PD and other assessment will be performed as indicated in Appendix 1 at 1hr, day 2 and day 5- Extra samples for PK/PD may be taken at the discretion of the investigators during illness or infection- clarification over statistical approach- clarity over storage of biological samples |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported