# Clinical trial results:
# Prevention of post-operative complications by using HMG-CoA Reductase Inhibitor in patients undergoing oesophagectomy - A multicentre, randomised, double blind, placebo controlled trial

## Summary

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|---|---|
| EudraCT number | 2015-004424-65 |
| Trial protocol | GB |
| Global end of trial date | 28 September 2022 |

**Results information**

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

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 15085MS-AS |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | ISRCTN48095567 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Belfast Health and Social Care Trust |
| Sponsor organisation address | 2nd Floor King Edward Building, RVH, Belfast, United Kingdom, BT12 6BA |
| Public contact | Dr Murali Shyamsundar, The Queen's University of Belfast, 0044 2890976381, murali.shyamsundar@qub.ac.uk |
| Scientific contact | Dr Murali Shyamsundar, The Queen's University of Belfast, 0044 2890976381, murali.shyamsundar@qub.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 | 28 September 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 September 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The aim of the study was to test the hypothesis that treatment with enteral simvastatin 80mg once daily for four days pre-surgery and up to 7 days post-surgery will prevent cardiac and respiratory complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

Primary objective:
To conduct a prospective randomised, double-blind, placebo-controlled phase II multi-centre trial of simvastatin for the prevention of cardiac and pulmonary complications in patients undergoing elective oesophagectomy, lobectomy or pneumonectomy.

Protection of trial subjects:

A risk assessment to ensure patient safety and integrity of the data was carried out prior to opening of the trial and at regular intervals during the course of the study. The assessment was approved by the Sponsor/Associate Medical Director. Areas of risk assessed included Informed Consent, Patient Withdrawal, Patient privacy, Safety of the intervention IMP, Assessment of Adverse Events, Research Staff training and qualifications, recruitment, adherence to regulatory and GCP requirements. Trial Oversight was conducted through regular reporting and meetings with the Trial Management Group, Trial Steering Committee and Data Monitoring and Ethics Committee.

Background therapy:

One lung ventilation (OLV) is an anaesthetic technique used in common surgeries like oesophagectomy, lobectomy and pneumonectomy and is associated with postoperative pulmonary complications (PPC) including acute respiratory distress syndrome (ARDS)and cardiac complications. Development of these complications is associated with a significantly worse outcome including increased mortality, readmission to ICU, increased ICU and hospital stay.
Postoperative pulmonary complications PPC and ARDS are common and devastating clinical conditions with high morbidity and mortality secondary to respiratory failure and multi-organ failure . PPC and ARDS have a high incidence as well as a high mortality rate of up to 65%. Cardiac and respiratory complications have both immediate and long standing resource implications which include an increase in ventilator usage, critical care support and on-going rehabilitation needs in the community post discharge . There is a significant reduction in health related quality of life and economic loss as up to 46% of survivors are still unable to work for 12 months after discharge.
The precise incidence of PPC and ARDS post OLV is less well defined but studies have shown a high incidence ranging from 13 - 43% and a mortality rate of up to 50% has been reported. One-lung ventilation (OLV) is implicated in the aetiology of ARDS following surgery using this technique and lung injury and inflammation is detectable after OLV even in the absence of clinical ARDS. There is no specific pharmacological therapy for cardiac or respiratory complications post elective surgeries utilising one lung ventilation technique. Statins have been shown to modulate various inflammatory processes underlying cardiac and respiratory complications. This trial studied statins as a specific pharmacotherapy to prevent these complications post-surgery.

Evidence for comparator:

There is no proven pharmacotherapy to prevent cardiac and respiratory complications after oesophagectomy, lobectomy or pneumonectomy. A placebo arm was used as a comparator to study the benefits of the active drug, simvastatin, in the absence of an established standard treatment to prevent these complications. A placebo arm was essential to ensure adequate blinding of participants and the research team involved in this study. Blinding post-operatively was maintained by drug administration by the clinical team that were not involved in data collection and analysis.

| | |
|---|---|
| Actual start date of recruitment | 22 November 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: 251 |
| Worldwide total number of subjects | 251 |
| 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) | 144 |
| From 65 to 84 years | 104 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

A  total of 251 patients were recruited to the trial at 13 participating sites across the UK.

### Pre-assignment

Screening details:

Potential participants were identified at the local cancer multi-disciplinary meeting (MDM) or from pre-op assessment waiting lists. Patients were screened by the research team to assess whether they met the inclusion criteria and none of the exclusion criteria.
Across the participating sites 1882 potential participants were screened.

### 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 |

Blinding implementation details:

A placebo arm was essential to ensure adequate blinding of participants and the research team involved in this study. Blinding post-operatively was maintained by drug administration by the clinical team that were not involved in data collection and analysis.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Intervention |

Arm description:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days
The total duration of the course was 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Simvastation 80mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Enteral use , Oral use |

Dosage and administration details:

80mg once daily
Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsulesadministered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days. Patients would record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient would stop the study drug and start it again once a date for surgery had been confirmed again. The total duration of the course was 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days. Patients would record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient would stop the study drug and start it again once a date for surgery had been confirmed again. The total duration of the course would be 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo tablets to match Simvastation 40mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Enteral use , Oral use |

Dosage and administration details:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days. Patients would record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient would stop the study drug and start it again once a date for surgery had been confirmed again. The total duration of the course will be 11 days if there was no postponement of surgery and up to 14 days if surgery is postponed.

| **Number of subjects in period 1** | Intervention | Placebo |
|---|---|---|
| Started | 126 | 125 |
| Completed | 108 | 100 |
| Not completed | 18 | 25 |
| Consent withdrawn by subject | 1 | - |
| Adverse event, non-fatal | - | 2 |
| Death | 3 | 2 |
| lost to follow up | 14 | 20 |
| Protocol deviation | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Intervention |
| Reporting group description: | |
| Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days<br>The total duration of the course was 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days. Patients would record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient would stop the study drug and start it again once a date for surgery had been confirmed again. The total duration of the course would be 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed. | |

| Reporting group values | Intervention | Placebo | Total |
|---|---|---|---|
| Number of subjects | 126 | 125 | 251 |
| Age categorical<br>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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.4 | 63.2 | |
| standard deviation | ± 11.0 | ± 10.5 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 41 | 46 | 87 |
| Male | 84 | 79 | 163 |
| Smoking Status | | | |
| Data was available for 125 participants in the intervention group and 124 participants in the placebo group. | | | |
| Units: Subjects | | | |
| Current Smoker | 16 | 21 | 37 |
| Previous Smoker | 71 | 69 | 140 |
| Never Smoked | 38 | 34 | 72 |
| Pre-surgery Chemotherapy | | | |
| Data was available for 125 participants in the intervention group and 124 participants in the placebo | | | |

| | | | |
|---|---|---|---|
| group. | | | |
| Units: Subjects | | | |
| Yes | 61 | 54 | 115 |
| No | 64 | 70 | 134 |
| Reason for Surgery | | | |
| Data was available for 125 participants in the intervention group and 124 participants in the placebo group. | | | |
| Units: Subjects | | | |
| Barrett's oesophagus | 6 | 6 | 12 |
| Squamous cell | 14 | 19 | 33 |
| Adenocarcinoma | 82 | 65 | 147 |
| Small cell carcinoma | 0 | 1 | 1 |
| Other | 23 | 33 | 56 |
| Type of surgery | | | |
| Data was available for 113 participants in the intervention group and 103 participants in the placebo group. | | | |
| Units: Subjects | | | |
| Oesophagostomy | 63 | 56 | 119 |
| Lobectomy | 44 | 43 | 87 |
| Pneumonectomy | 3 | 2 | 5 |
| Other | 3 | 2 | 3 |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 171.5 | 170.9 | |
| standard deviation | ± 9.9 | ± 10.1 | - |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 77.7 | 78.7 | |
| standard deviation | ± 15.5 | ± 18.3 | - |
| Systolic Blood Pressure | | | |
| Data was available for 124 participants in the intervention group and 124 participants in the placebo group. | | | |
| Units: mmHg | | | |
| arithmetic mean | 134.9 | 133.8 | |
| standard deviation | ± 18.8 | ± 18.9 | - |
| Diastolic Blood Pressure | | | |
| Data was available for 124 participants in the intervention group and 124 participants in the placebo group. | | | |
| Units: mmHg | | | |
| arithmetic mean | 79.2 | 80.0 | |
| standard deviation | ± 10.9 | ± 10.0 | - |
| FEV1/FVC ratio | | | |
| This was an optional test. Completed for 98 participants in the intervention arm and 105 participants in the placebo arm | | | |
| Units: litres | | | |
| arithmetic mean | 0.7 | 0.7 | |
| standard deviation | ± 0.1 | ± 0.1 | - |
| Number of chemotherapy cycles | | | |
| This was an optional field based off those participants that had received pre-surgery chemotherapy (if chemotherapy, number of cycles). This field was completed for 61 participants in the intervention arm and 54 in the placebo arm | | | |
| Units: chemotherapy cycles | | | |
| arithmetic mean | 3.4 | 3.4 | |
| standard deviation | ± 1.0 | ± 0.9 | - |

## End points

### End points reporting groups

| Reporting group title | Intervention |
|---|---|

Reporting group description:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days
The total duration of the course was 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed.

| Reporting group title | Placebo |
|---|---|

Reporting group description:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days. Patients would record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient would stop the study drug and start it again once a date for surgery had been confirmed again. The total duration of the course would be 11 days if there was no postponement of surgery and up to 14 days if surgery was postponed.

### Primary: Primary Outcome Composite End point

| End point title | Primary Outcome Composite End point |
|---|---|

End point description:

The modified intention to treat population is defined as all participants randomised who proceeded with the planned surgery and had at least one pre-operative dose of study drug regardless of further protocol adherence. Primary outcome measure was a composite endpoint of the incidence of ARDS defined according to the Berlin definition, post-operative pulmonary complications (PPC) as defined by Melbourne group scale and myocardial infarction as defined by ischaemic chest pain, ECG changes and a raise in plasma troponin and also by myocardial ischaemia post non-cardiac surgery (MINS) criteria during the first seven days post operatively or hospital discharge if earlier. These end points were chosen based on their effect on short term and long term outcomes and a biological rationale for statin in modulating these endpoints. Units are the number of patients who met the composite endpoint

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

End point timeframe:

7 days post operatively or until hospital discharge if earlier

| End point values | Intervention | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 102 | | |
| Units: participants | 45 | 39 | | |

### Statistical analyses

| Statistical analysis title | Primary Outcome Modified Intention to Treat |
|---|---|
| Comparison groups | Intervention v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.536 |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 2.08 |

| **Statistical analysis title** | Primary Outcome Modified Intention to Treat |
|---|---|
| Comparison groups | Intervention v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.536 |
| Method | Chi-squared |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.55 |

| **Statistical analysis title** | Primary Outcome Modified Intention to Treat |
|---|---|
| Comparison groups | Intervention v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.536 |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.18 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

upon informed consent for the trial and ends 28 days post-surgery or until discharge from hospital if <28 days following the administration of the study drug

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

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.03 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Intervention |

Reporting group description:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days
The total duration of the course was be 11 days if there is no postponement of surgery and up to 14 days if surgery was postponed.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Patients were randomised to receive once daily simvastatin 80mg (as two 40mgcapsules) or 2 matched placebo capsules administered enterally. Patients would self-administer the medication orally for 4 days pre-operatively and postoperatively the study drug was administered by the clinical team via a feeding tube for up to 7 days. Patients would record self-administration of the drug in a patient diary pre-surgery. In the event of postponement of the date of surgery, the patient would stop the study drug and start it again once a date for surgery had been confirmed again. The total duration of the course was 11 days if there was no postponement of surgery and up to 14 days if surgery is postponed.

| Serious adverse events | Intervention | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 2 / 125 (1.60%) | |
| number of deaths (all causes) | 3 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 1 / 125 (0.80%) | |
| 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 %

| **Non-serious adverse events** | Intervention | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 23 / 125 (18.40%) | 25 / 125 (20.00%) | |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 125 (0.80%)<br>1 | 0 / 125 (0.00%)<br>0 | |
| Cardiac disorders<br>Acute coronary syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 125 (0.00%)<br>0 | 1 / 125 (0.80%)<br>1 | |
| Surgical and medical procedures<br>N/A<br>subjects affected / exposed<br>occurrences (all) | 0 / 125 (0.00%)<br>0 | 1 / 125 (0.80%)<br>1 | |
| Blood and lymphatic system disorders<br>Elevated CK<br>subjects affected / exposed<br>occurrences (all) | 6 / 125 (4.80%)<br>6 | 8 / 125 (6.40%)<br>8 | |
| Autoimmune thrombocytopenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 125 (0.00%)<br>0 | 1 / 125 (0.80%)<br>1 | |
| Social circumstances<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 0 / 125 (0.00%)<br>0 | 1 / 125 (0.80%)<br>1 | |
| Gastrointestinal disorders<br>Flatulence<br>subjects affected / exposed<br>occurrences (all) | 0 / 125 (0.00%)<br>0 | 1 / 125 (0.80%)<br>1 | |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 125 (1.60%) | 0 / 125 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Hepatobiliary disorders | | | |
| Elevated ALT | | | |
| subjects affected / exposed | 9 / 125 (7.20%) | 5 / 125 (4.00%) | |
| occurrences (all) | 9 | 5 | |
| Elevated AST | | | |
| subjects affected / exposed | 3 / 125 (2.40%) | 1 / 125 (0.80%) | |
| occurrences (all) | 3 | 1 | |
| Elevated LFT | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Elevated ALK | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Elevated Bilirubin | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial Fistula | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory Disorders | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Chest infection | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoxia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 125 (1.60%) | 0 / 125 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash acneiform | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Hot elbows | | | |
| subjects affected / exposed | 0 / 125 (0.00%) | 1 / 125 (0.80%) | |
| occurrences (all) | 0 | 1 | |
| Post-operative surgical discomfort | | | |
| subjects affected / exposed | 1 / 125 (0.80%) | 0 / 125 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 December 2015 | Amendment 1<br>Was not submitted to REC. Protocol was approved as version 2.0 25.04.2016 by MHRA |
| 04 April 2016 | Amendment 2<br>Update to :<br>Protocol V3.0_06.07.2016<br>GP Letter v1.0_06.07.2016<br>90 Day Follow up letter v1.0_06.07.2016<br>GP Response Letter v1.0_06.07.2016 |
| 20 July 2016 | Amendment 3<br>Addition of new site BHSCT |
| 17 February 2017 | Amendment 6<br>Addition of new site Queen Elizabeth Birmingham |
| 23 February 2017 | Amendment 7<br>Change of PI at Queen Elizabeth Birmingham |
| 06 April 2017 | Amendment 8<br>Protocol and supporting documents amended to include other surgeries where one lung ventilation (which is the main driving factor as an inflammatory insult) is used, which are lobectomy and pneumonectomy.<br>Protocol v5.0 14.03.2017<br>PIS v6.0 16.05.2017<br>ICF v4.0 16.05.2017<br>GP Letter v3.0 14.03.2017<br>90day Follow Up GP Letter v2.0 14.03.2017<br>Patient Survival Status Response GP Letter v2.0 14.03.2017<br>Patient Information Letter v3.0 06.02.2017<br>Poster v2.0 14.03.2017<br>90 Day Patient Follow Up Letter V2.0 21.02.2017<br>Health Service Use Questionnaire V2.0 21.02.2017<br>Patient Diary v2.0 14.03.2017<br>Patient Study Card v2.0 14.03.2017 |

| | |
|---|---|
| 21 August 2017 | Amendment 10<br>Following on from amendment 8 the study title was changed to include other surgeries where one lung ventilation is used, which are lobectomy and pneumonectomy as per the outlined below:<br><br>Old Title:<br>Prevention Of Post-operative Complications By Using HMG-CoA Reductase Inhibitor In Patients Undergoing Oesophagectomy – A multicentre, randomised, double blind, placebo controlled<br>New Title:<br>Prevention Of Post-operative Complications By Using HMG-CoA Reductase Inhibitor In Patients Undergoing One Lung Ventilation For Surgery – A multicentre, randomised, double blind, placebo controlled trial<br><br>Protocol and supporting documents approved:<br>Protocol v6.0 18.08.2017<br>GP Letter v 4.0 18.08.2017<br>90 Day Follow Up GP Letter v 3.0 18.08.2017<br>90 Day Follow GP Response 2nd Letter v3.0 18.08.2017<br>Patient Information Letterv 4.0 18.08.2017<br>Prescription For Clinical Trial Medication v3.0 18.08.2017<br>Product Specification (PSF) Prevention Harp2 Version B 17 Aug 2017 |
| 21 November 2017 | Amendment 11<br>Updated PIS and new sites added:<br>Site added - Leeds (St James)<br>Site added - Southampton (General)<br>Site added - Bristol (Royal Infirmary)<br>Site added - North Midlands (Royal Stoke)<br>PIS updated to v8.0 (15.01.2018) |
| 07 December 2017 | Amendment 12:<br>SmPC (Simvastatin) 13.07.2017<br>Protocol v7.0 07.12.2017<br>Site Letter to GP v5.0 07.12.2017<br>Product Specification (PSF) vC 22.01.2018 |
| 25 January 2018 | Amendment 13<br>Update to the placebo dossier Revision C 24.01.2018 |
| 28 March 2018 | Amendment 14<br>Addition of 2 new sites |
| 16 November 2018 | Amendment 16<br>Update to protocol to v8 09.11.2018<br>Includes removal Exclusion criteria for screening included creatinine kinase (CK) > 5 ULN for the local laboratory and update to supporting documentation |
| 31 December 2018 | Amendment 17<br>Change of PI at Wythenshaw Site |
| 27 April 2020 | Amendment 19<br>Addition of new site |
| 09 October 2020 | Amendment 22<br>Change of PI at Salford site |
| 25 January 2021 | Amendment 24<br>Study Pause (Due to no drug available) |

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| 22 April 2021 | Amendment 25<br>Study re-opened.<br>Update to protocol v10.0 15.03.2021.<br>Includes changes to supporting documentation and updates to study drug production |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 25 January 2021 | Changes in the production of the study drug (Simvastatin)affected the duration of treatment and necessitated the exclusion of participants requiring drug administration via feeding tube. A new placebo was required to match the updated Simvastatin tablet. The trial was paused until protocol updates were approved and a suitable placebo was sourced. | 22 April 2021 |
| 28 September 2022 | The Prevention HARP-2 trial was terminated early. A total of 251 patients out of the planned 452 patients were recruited. Recruitment to the trial was terminated early on 28/09/2022. This decision was based on recommendations from the Data Monitoring and Ethics Committee and the and Trial Steering Committee. The decision was based primarily on the view that further recruitment would not materially alter the scientific findings of the trial, and also took into account the amount of additional work required by the trial team to recruit a further 200 patients during the ongoing pandemic, and the burden of trial participation on those patients (albeit modest). | - |

Notes:

## Limitations and caveats

None reported