# Clinical trial results:
# Randomised controlled trial of 6-Mercaptopurine versus placebo to prevent recurrence of Crohn's disease following surgical resection (TOPPIC)

## Summary

| | |
|---|---|
| EudraCT number | 2006-005800-15 |
| Trial protocol | GB |
| Global end of trial date | 30 September 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 September 2017 |
| First version publication date | 08 September 2017 |
| Summary attachment (see zip file) | TOPPIC Report (TOPPIC Eudract Final.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | MRCG060329 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN89489788 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Edinburgh |
| Sponsor organisation address | Old College, South Bridge, Edinburgh , United Kingdom, EH8 9YL |
| Public contact | Marise Bucukoglu (ACCORD Office), University of Edinburgh, 00 44 01312429262, Marise.Bucukoglu@ed.ac.uk |
| Scientific contact | Marise Bucukoglu (ACCORD Office), University of Edinburgh, 00 44 01312429262, Marise.Bucukoglu@ed.ac.uk |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 15 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 May 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 September 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess whether Mercaptopurine can prevent or delay post-operative recurrence of Crohn’s disease

Protection of trial subjects:

This multicentre clinical trial was carried out with the approval of the national research ethics committee (ref: 07/MRE00/74), in accordance with the Declaration of Helsinki (2000), under a Clinical Trial Authorization (01384/0206/001-0002) from the Medicine and Healthcare Products Regulatory Authority (MHRA, United Kingdom), and the written informed consent of all participants.

Background therapy:

N/A. All eligible patients were required to be free of medication for Crohn’s disease and to have been off antibiotics for the two weeks prior to randomization.

Evidence for comparator:

N/A.

| | |
|---|---|
| Actual start date of recruitment | 01 May 2008 |
| 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: 240 |
| Worldwide total number of subjects | 240 |
| EEA total number of subjects | 240 |

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) | 3 |
| Adults (18-64 years) | 232 |
| From 65 to 84 years | 5 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients with a histologically confirmed diagnosis of Crohn's disease undergoing ileocolonic or small bowel resection were recruited from 29 UK hospitals. Patients were ≥ 16 years in Scotland and ≥18 years in England and Wales. Prior to randomisation any post-operative infections were fully treated and existing treatments for Crohn's stopped.

### Pre-assignment

Screening details:

A total of 329 patients were screened for recruitment of whom 89 were excluded as ineligible or who declined to participate, leaving 240 patients to undergo randomisation.

### Period 1

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

Blinding implementation details:

Treatment was blinded to both the research team and the subject, as well as to the central trials team. Study drugs were prepared by pharmacy staff independent of the study investigators or clinical team responsible for patient care. Safety blood test results were sent to the central trials team by independent members of staff and assessed by a blinded, independent panel of clinicians. Data Monitoring Reports were prepared by an unblinded statistician.

### Arms

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

Arm description:

Mercaptopurine tablets containing 50mg of the active substance 6-Mercaptopurine prepared by Glaxo Wellcome GmbH (batch 1) & Co or Aspen Pharma Trading Limited (batch 2) and packaged by Catalent (later Aptuit).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Mercaptopurine |
| Investigational medicinal product code | ATC Code: L01BB02 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50mg tablet taken once a day

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

Arm description:

Matching placebo tablets containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate

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

Dosage and administration details:

50mg oral tablet

| **Number of subjects in period 1** | Active Arm | Placebo |
|---|---|---|
| Started | 128 | 112 |
| Completed | 62 | 42 |
| Not completed | 66 | 70 |
| Adverse event, serious fatal | - | 1 |
| Withdrawn | 8 | 13 |
| Adverse event, non-fatal | 39 | 41 |
| Abnormal safety blood test | 12 | 6 |
| Lost to follow-up | 7 | 9 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Active Arm |
| Reporting group description: | |
| Mercaptopurine tablets containing 50mg of the active substance 6-Mercaptopurine prepared by Glaxo Wellcome GmbH (batch 1) & Co or Aspen Pharma Trading Limited (batch 2) and packaged by Catalent (later Aptuit). | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo tablets containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate | |

| Reporting group values | Active Arm | Placebo | Total |
|---|---|---|---|
| Number of subjects | 128 | 112 | 240 |
| Age categorical<br>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) | 1 | 2 | 3 |
| Adults (18-64 years) | 126 | 106 | 232 |
| From 65-84 years | 1 | 4 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 79 | 67 | 146 |
| Male | 49 | 45 | 94 |
| Previous treatment with Mercaptopurine<br>Units: Subjects | | | |
| Yes | 14 | 5 | 19 |
| No | 114 | 107 | 221 |
| Previous treatment with Azathioprine<br>Units: Subjects | | | |
| Yes | 80 | 48 | 128 |
| No | 48 | 64 | 112 |
| Missing | 0 | 0 | 0 |
| Previous treatment with Infliximab<br>Units: Subjects | | | |
| Yes | 21 | 15 | 36 |
| No | 104 | 96 | 200 |
| Missing | 3 | 1 | 4 |
| Previous treatment with Methotrexate<br>Units: Subjects | | | |
| Yes | 8 | 7 | 15 |
| No | 120 | 104 | 224 |

| | | | |
|---|---|---|---|
| Missing | 0 | 1 | 1 |
| Previous surgery<br>Units: Subjects | | | |
| Yes | 46 | 28 | 74 |
| No | 82 | 83 | 165 |
| Missing | 0 | 1 | 1 |
| Smoking status<br>Units: Subjects | | | |
| Yes | 29 | 26 | 55 |
| No | 99 | 86 | 185 |
| Missing | 0 | 0 | 0 |
| Duration of disease<br>Units: Subjects | | | |
| 40 years or less | 37 | 41 | 78 |
| > 40 years | 91 | 69 | 160 |
| Unknown | 0 | 2 | 2 |
| Age at diagnosis<br>Units: Subjects | | | |
| 40 years or less | 103 | 87 | 190 |
| > 40 years | 25 | 23 | 48 |
| Unknown | 0 | 2 | 2 |
| CDAI Score | | | |
| Crohn's Disease Activity Index Score | | | |
| Units: Points | | | |
| arithmetic mean | 130 | 121 | |
| standard deviation | ± 86 | ± 72 | - |
| Weight<br>Units: kg | | | |
| arithmetic mean | 70.7 | 70.7 | |
| standard deviation | ± 14.4 | ± 13.7 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Active Arm |
| Reporting group description: | |
| Mercaptopurine tablets containing 50mg of the active substance 6-Mercaptopurine prepared by Glaxo Wellcome GmbH (batch 1) & Co or Aspen Pharma Trading Limited (batch 2) and packaged by Catalent (later Aptuit). | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo tablets containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate | |

### Primary: Primary outcome - postoperative clinical recurrence of Crohn's disease

| | |
|---|---|
| End point title | Primary outcome - postoperative clinical recurrence of Crohn's disease |
| End point description: | |
| Crohn’s Disease Activity Index (CDAI) >150 with an increase from baseline of 100 points, together with the need for anti-inflammatory rescue therapy or primary surgical intervention. | |
| End point type | Primary |
| End point timeframe: | |
| Up to the end of the trial (3 years). | |

| End point values | Active Arm | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 112 | | |
| Units: Number of patients with recurrence | | | | |
| Yes | 16 | 26 | | |
| No | 112 | 86 | | |

### Statistical analyses

| Statistical analysis title | Statistical analysis of primary outcome |
|---|---|
| Statistical analysis description: | |
| Cox's proportional hazards model | |
| Comparison groups | Active Arm v Placebo |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.073 [1] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.535 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.27 |
| upper limit | 1.96 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.349 |

Notes:

[1] - Adjusted for randomisation stratification variables (centre and smoking status), also adjusted for previous treatment with 6MP or Azathioprine.

## Secondary: Secondary outcome - postoperative clinical recurrence of Crohn's disease

| | |
|---|---|
| End point title | Secondary outcome - postoperative clinical recurrence of Crohn's disease |

End point description:

Crohn’s Disease Activity Index (CDAI) >150 with an increase from baseline of 100 points OR the need for anti-inflammatory rescue therapy OR primary surgical intervention.

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

End point timeframe:

Up to the end of the trial (3 years)

| **End point values** | Active Arm | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 112 | | |
| Units: Number of patients | | | | |
| Yes | 34 | 40 | | |
| No | 94 | 72 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical analysis of secondary outcome |
|---|---|

Statistical analysis description:

Cox’s proportional hazards model

| | |
|---|---|
| Comparison groups | Active Arm v Placebo |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.243 [2] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.737 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 1.23 |

| Variability estimate | Standard error of the mean |
|---|---|
| Dispersion value | 0.262 |

Notes:

[2] - Adjusted for randomisation stratification variables (centre and smoking status), also adjusted for previous treatment with 6MP or Azathioprine.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) that occurred after signing consent for the trial must be reported within the case report form (CRF) and all reported AEs were followed up before the end of the trial.

Adverse event reporting additional description:

As above.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | Coded by trial team |
| Dictionary version | N/A |

### Reporting groups

| | |
|---|---|
| Reporting group title | Active Arm |

Reporting group description:

Mercaptopurine tablets containing 50mg of the active substance 6-Mercaptopurine prepared by Glaxo Wellcome GmbH (batch 1) & Co or Aspen Pharma Trading Limited (batch 2) and packaged by Catalent (later Aptuit).

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

Reporting group description:

Matching placebo tablets containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate

| Serious adverse events | Active Arm | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 51 / 128 (39.84%) | 49 / 112 (43.75%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignnant and unspecified | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Vascular disorders | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 112 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 128 (7.03%) | 5 / 112 (4.46%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General disorders | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Reproductive system and breast disorders | | | |
| subjects affected / exposed | 2 / 128 (1.56%) | 0 / 112 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Injury | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Congenital, familial and genetic disorders | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac disorders | | | |
| subjects affected / exposed | 3 / 128 (2.34%) | 2 / 112 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Nervous system disorders | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Ear and labyrinth disorders | | | |
| Ear and labyrinth disorders | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorders | | | |
| subjects affected / exposed | 23 / 128 (17.97%) | 29 / 112 (25.89%) | |
| occurrences causally related to treatment / all | 2 / 26 | 4 / 33 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatobiliary disorders | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin and subcutaneous tissue disorders | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 1 / 112 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal and urinary disorders | | | |
| subjects affected / exposed | 4 / 128 (3.13%) | 2 / 112 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infections and infestations | | | |
| subjects affected / exposed | 4 / 128 (3.13%) | 3 / 112 (2.68%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Active Arm | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 121 / 128 (94.53%) | 105 / 112 (93.75%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancers | | | |
| subjects affected / exposed | 2 / 128 (1.56%) | 1 / 112 (0.89%) | |
| occurrences (all) | 3 | 1 | |
| Nervous system disorders | | | |
| Pain | | | |
| subjects affected / exposed | 18 / 128 (14.06%) | 17 / 112 (15.18%) | |
| occurrences (all) | 30 | 19 | |
| Headache | | | |
| subjects affected / exposed | 26 / 128 (20.31%) | 20 / 112 (17.86%) | |
| occurrences (all) | 61 | 38 | |
| General disorders and administration site conditions | | | |
| Other | | | |
| subjects affected / exposed | 85 / 128 (66.41%) | 62 / 112 (55.36%) | |
| occurrences (all) | 212 | 153 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 1 / 112 (0.89%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |
| GI Symptoms Other | | | |
| subjects affected / exposed | 34 / 128 (26.56%) | 28 / 112 (25.00%) | |
| occurrences (all) | 53 | 40 | |
| Nausea | | | |
| subjects affected / exposed | 45 / 128 (35.16%) | 30 / 112 (26.79%) | |
| occurrences (all) | 78 | 41 | |
| Abdominal pain | | | |
| subjects affected / exposed | 66 / 128 (51.56%) | 67 / 112 (59.82%) | |
| occurrences (all) | 132 | 141 | |
| Constipation | | | |
| subjects affected / exposed | 37 / 128 (28.91%) | 37 / 112 (33.04%) | |
| occurrences (all) | 54 | 56 | |
| Worsening Crohn's | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 24 / 128 (18.75%) | 29 / 112 (25.89%) | |
| occurrences (all) | 41 | 37 | |
| Hepatobiliary disorders | | | |
| Deranged LFTs | | | |
| subjects affected / exposed | 4 / 128 (3.13%) | 5 / 112 (4.46%) | |
| occurrences (all) | 4 | 5 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 24 / 128 (18.75%) | 14 / 112 (12.50%) | |
| occurrences (all) | 35 | 17 | |
| Musculoskeletal and connective tissue disorders | | | |
| Joint pain | | | |
| subjects affected / exposed | 40 / 128 (31.25%) | 36 / 112 (32.14%) | |
| occurrences (all) | 72 | 65 | |
| Infections and infestations | | | |
| Infections | | | |
| subjects affected / exposed | 81 / 128 (63.28%) | 68 / 112 (60.71%) | |
| occurrences (all) | 171 | 184 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 December 2007 | Substantial Amendment 1: Amendment to protocol concerning use of 6MP in pregnancy/subjects of childbearing age, switch to matching placebo (rather than over-encapsulation) supplied by GSK and amendment to safety blood procedures. |
| 07 July 2008 | Substantial Amendment 6: Decision to stop study drug if subjects prescribed Allopurinol. |
| 18 November 2008 | Substantial Amendment 3: Use of all Scottish district hospitals for referrals, repeat safety bloods not required at V2, clarifications to protocol: V2 ≤7 days of V1; point 3 of inclusion criteria added. |
| 15 June 2009 | Substantial Amendment 5: Reduce number of colonoscopies and clarification in PIL/Consent the types of sample and how they are handled and stored. |
| 15 December 2009 | Substantial Amendment 7: Amendment to safety assessments in protocol, prohibited medications added as appendix. |
| 03 March 2010 | Substantial Amendment 8: Isolated elevation of GGT do not represent exclusion to recruitment or withdrawal. |
| 28 September 2010 | Substantial Amendment 12: Extension to study, clarifications to protocol including amendment to exclusion criteria, retention of original signed consent forms in site files, updated policy on pharmacovigilance and protocol deviations. |
| 10 February 2011 | Substantial Amendment 13: Clarifications to the protocol |
| 15 March 2012 | Substantial Amendment 17: Protocol modified to add a secondary outcome, amend exclusion criteria error, MA holder and SmPC change, amendments to appendices 3,4,6,7. |
| 03 October 2013 | Substantial Amendment 20: Protocol modified: change of MA holder name and address, SmPc update of drug brand name, trial manager and trial statistician change, clarification of Appendix 8 on prohibited medications. |
| 07 May 2015 | Substantial Amendment 21: Protocol modified: health economics analysis plan revised, revisions to planned analysis section to bring in line with Statistical Analysis Plan, minor change to MA Holder and SmPC, removal of blank Annexes. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/28404197