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 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 Units: Subjects			
Female	79	67	146
Male	49	45	94
Previous treatment with Mercaptopurine Units: Subjects			
Yes	14	5	19
No	114	107	221
Previous treatment with Azathioprine Units: Subjects			
Yes	80	48	128
No	48	64	112
Missing	0	0	0
Previous treatment with Infliximab Units: Subjects			
Yes	21	15	36
No	104	96	200
Missing	3	1	4
Previous treatment with Methotrexate Units: Subjects			
Yes	8	7	15
No	120	104	224

Missing	0	1	1
Previous surgery Units: Subjects			
Yes	46	28	74
No	82	83	165
Missing	0	1	1
Smoking status Units: Subjects			
Yes	29	26	55
No	99	86	185
Missing	0	0	0
Duration of disease Units: Subjects			
40 years or less	37	41	78
> 40 years	91	69	160
Unknown	0	2	2
Age at diagnosis 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 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