Trial Information Form	*EMA*

Title of Trial

Full title of the trial	Randomised Controlled Trial of 6-Mercaptopurine Versus Placebo to Prevent Recurrence of Crohn's Disease Following Surgical Resection (TOPPIC)

Trial Identifiers

EudraCT number C	2006-005800-15		**Sponsor protocol code**		MRC G060329	
Other Trial Identifiers						
Other identifier name	ISRCTN number	NCT number	WHO trial number	Universal reference (UTRN)		
Other identifier	ISRCTN89489788					

Sponsor

Organisation name	ACCORD (University of Edinburgh & NHS Lothian)		
Street address	47 Little France Crescent	**Town/city**	Edinburgh
Post code	EH16 4TJ	**Country**	United Kingdom

Contact Points – Scientific Contact Point

Functional name of contact point	Professor Jack Satsangi	**Name of organisation**	University of Edinburgh
Telephone number	0131 651 1807		

Email address	J.Satsangi@ed.ac.uk

Contact Points – Public Contact Point ②

Functional name of contact point	Dr Holly Ennis	**Name of organisation**	University of Edinburgh
Telephone number	0131 537 3845		
Email address	holly.ennis@ed.ac.uk		

Paediatric Regulatory Details

Is trial part of a Paediatric Investigation Plan?	*[Circle one]* Yes / No				
EMA Paediatric Investigation Plans	N/A				
Does article 45 REGULATION (EC) No 1901/2006 apply to this trial?	*[Circle one]* Yes / No		**Does article 46 REGULATION (EC) No 1901/2006 apply to this trial?**	*[Circle one]* Yes / No	

Result Analysis Stage

Primary completion data reached?	*[Circle one]* Yes / No	**Primary completion date**	30/05/2015
Analysis stage	*[Circle one]* Interim / Final	**Date of interim/final analysis**	15/06/2015
Global end of trial reached?	*[Circle one]* Yes / No	**Date of global end of trial**	30/09/2015

General Information About Trial

Main objective of the trial	To assess whether Mercaptopurine can prevent or delay post-operative recurrence of Crohn's disease.
Actual date of start of recruitment to the	01/05/2008

protocol (in any country)			
Long term follow up planned	*[Circle one]* Yes / No	**Follow up planning rationale**	
Long term follow up duration	Value: _____ Unit: *[Select one]* Months / Years		

Independent Data-Monitoring Committee (DMC) involvement	*[Circle one]* Yes / No
Protection of subjects ③	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 ④	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(s)	N/A.

Actual Number of Subjects Included in the Trial

Actual number of subjects included in each country concerned

Country	UK									
Number of subjects	240									

For multinational trials

Actual number of subjects included in the EEA	N/A
Actual number of subjects included worldwide	N/A

Age group breakdown for the whole trial

Age of subjects	Number of subjects
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
From 18 and 64 years	232
From 65 years to 84 years	5
85 years and over	0

ㄷ The EudraCT number cannot be amended

② The public contact and scientific contact points may be the same as each other.

③ A description of the actual measures taken to protect subjects.

④ Details such as the dosage and frequency plus any other relevant information should be captured here.

Subject Disposition Form *EMA*

Recruitment details ①	Between May 2008 and June 2012 (a period of 49 months), patients with a histologically confirmed diagnosis of Crohn's disease undergoing ileocolonic or small bowel resection were recruited from 29 hospitals across the UK. Patients were 16 years or older in Scotland and 18 years or older in England and Wales. Patients were excluded if they had a known intolerance or hypersensitivity to thiopurines, were known to require further surgery; underwent strictureplasty alone; presence of stoma; active or untreated malignancy or absent thiopurine s-methyltransferase (TPMT) activity. Prior to randomisation any post-operative infections were fully treated and existing treatments for Crohn's disease were stopped prior to randomisation.
Screening details ②	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.

Pre-Assignment Period **Title: Pre-Assignment Period**

		Number of subjects
STARTED		A total of 329 patients were screened for recruitment of whom 89 were excluded leavinng 240 patients to undergo randomization.
Milestone Title ③		
Milestone Title ③		
COMPLETED		The primary analysis included all randomized patients on an intention-to-treat analysis regardless of compliance with allocated treatment and post-randomization events.
Reason not completed		136 did not complete the full three year treatment period.
Adverse event, not serious		**80**
Adverse event, serious fatal		**1**
Adverse event, serious non-fatal		**0**
Consent withdrawn by subject		**0**
Physician decision		**0**

Pregnancy		**0**
Protocol violation		**0**
Other reason ④	**Abnormal blood test result**	**18**
Other reason ④	**Early withdrawal**	**21**
Other reason ④	**Lost to follow-up**	**16**

① Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and types of location (e.g. medical clinic), to provide context.

② Screening details are required if the results will not contain a pre-assignment period.

③ Add as many Milestone Title. A descriptive title for each row is required.

④ Add as many other reason not completed rows as needed. A descriptive title for each row is required.

Period ① **Title: Title Name:** _____ **Baseline Period:** *[Circle one]* Yes / No

Blinding	*[Circle one]* Double blind / Single blind / N/A	**Roles blinded** ②	*[Circle any]* Subject / Investigator / Monitor / Data analyst / Carer / 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 the patients care.All patients underwent regular safety blood monitoring every week for the initial 6 weeks and thereafter at 6 weekly intervals as long as the patient remained on study drug. Blood samples were processed at participating site laboratories. Results were reviewed by an independent central clinician who was blinded to the treatment allocation. Pre-specified dose reduction or cessation then occurred in the event of abnormal monitoring parameters. In the event of patient intolerance (profound nausea or persistent flu-like symptoms) protocol driven dose reduction was also undertaken. If abnormal parameters improved after a temporary stop, treatment was started again at a lower level. All of the decisions were made by experienced clinicians who were blinded to the treatment allocation. To protect blinding a programme of sham dose reductions was planned for patients on placebo. On the advice of the Data Monitoring Committee these were not undertaken, however the investigators were not informed of this decision, hence protecting the study blind.		
Allocation method	*[Circle one]* Randomised – controlled / Non-randomised - controlled / N/A		

Arm title ③	Active	Placebo		**TOTAL**
Arm description ④	6MP	Placebo		
	Number of Subjects	**Number of Subjects**	**Number of Subjects**	**Number of Subjects**
STARTED	128	112		240
Milestone title ⑤				
Milestone title ⑤				
COMPLETED	62	42		104 (Trial medication taken for 3 years)
Reason not completed ⑥				
Adverse event, not serious	39	41		80
Adverse event, serious fatal	0	1		1
Adverse event, serious non-fatal	0	0		0

Consent withdrawn by subject		0	0		0
Lack of efficacy		0	0		0
Lost to follow up		7	9		16
Physician decision		0	0		0
Pregnancy		0	0		0
Protocol violation		0	0		0
Transferred to other arm / group		0	0		0
Other reason ⑦	**Abnormal blood test result**	12	6		18
Other reason ⑦	**Early withdrawal**	8	13		21
Reasons for joining					
Transferred in from other arm / group					[Derived: total for reason]
Late recruitment					[Derived: total for reason]
Other reason ⑧					[Derived: total for reason]
Other reason ⑧					[Derived: total for reason]

① Complete a period table for each period you wish to report. Provide a descriptive title for each reported period.

② If blinding is single or double, then the roles blinded must be specified.

③ Arms are created on the next form. Only the Arm title and description will be displayed on the Subject disposition form

④ Arm Description provides more details about the Arm.

⑤ Add as many Milestone Titles as necessary. A descriptive title for each row is required.

⑥ Use only the most appropriate reason for not completing in each case and do not double count.

⑦ Add as many other reason not completed rows as needed. A descriptive title for each row is required.

⑧ Add as many other reasons for joining the Arm as needed. A descriptive title for each row is required.

Subject Disposition Arm Form ① *EMA*

Arm title	Active
Arm description ②	Mercaptopurine 50mg tablets
Arm type	*[Circle one]* Experimental / Active comparator / Placebo comparator / No IMP / Other (specify):_____

Products used ③

IMP name	Mercaptopurine
IMP code	ATC Code: L01BB02 CAS Code: 50-44-2
Other names (separated by commas)	6-Mercaptopurine
Route of administration ④	*[Select any number of terms from the human domain of the EUTCT list]* Oral
Pharmaceutical form ⑤	*[Select any number of terms from the human domain of the EUTCT list]* Tablets
Dosage and administration details ⑥	6-Mercaptopurine (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 title	Placebo
Arm description ②	Matching placebo tablets containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate
Arm type	*[Circle one]* Experimental / Active comparator / Placebo comparator / No IMP / Other (specify):_____

Products used ③

IMP name	Placebo
IMP code	N/A
Other names (separated by commas)	N/A

Route of administration ④	*[Select any number of terms from the human domain of the EUTCT list]* Oral
Pharmaceutical form ⑤	*[Select any number of terms from the human domain of the EUTCT list]* Tablets
Dosage and administration details ⑥	Matching placebo 50mg tablets containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate. Prepared by Glaxo Wellcome GmbH (batch 1) & Co or Aspen Pharma Trading Limited (batch 2) and packaged by Catalent (later Aptuit).

① This form is used to create the Arms used as reference information in the Subject disposition details (see previous)

② Arm Description describes details about the arms evaluated.

③ Details of the products used. There may be multiple products created.

④ A product may have any number of Routes of Administration

⑤ A product may have any number of Pharmaceutical Forms

⑥ Provide any or all of the following details: the dosage and frequency of administration.

Subject Analysis Sets Form *EMA*

Subject analysis set ①

Subject analysis set title	Intention-to-treat
Subject analysis set type	*[Circle one]* Intent to treat / Per protocol / Full analysis set / Safety population / Sub-group analysis set
Subject analysis set description ②	All patients randomised to the group to which they were allocated.
Number of subjects ③	240

① Complete a subject analysis set table for additional groups of subjects you wish to report on.

② Subject analysis set description that defines the population type.

③ Provide the number of subjects that constitute this subject analysis set.

Baseline Characteristics Form - Age *EMA*

Reporting group title	Active	Placebo		**TOTAL**
Reporting group description ①	6MP	Placebo		
Overall number of baseline subjects	128	112		240
Age Categorical ②	**Number of Subjects**	**Number of Subjects**	**Number of Subjects**	**Number of Subjects**
Unit of measure Subjects				
In utero	0	0		0
Preterm newborn – gestational age <37 wk	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
From 18 to 64 years	126	106		232
From 65 to 84 years	1	4		5
Over 85 years	0	0		0

Age, continuous	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**		
	[Circle one] arithmetic mean, geometric mean, least squares mean,	*[Circle one]* Standard deviation, interquartile range, range, sample	*[Circle one]* arithmetic mean, geometric mean, least squares mean,	*[Circle one]* Standard deviation, interquartile range, range, sample	*[Circle one]* arithmetic mean, geometric mean, least squares mean,	*[Circle one]* Standard deviation, interquartile range, range, sample		

		log mean, median	min/max	log mean, median	min/max	log mean, median	min/max		
Unit of measure	**Years**	**Mean = 39.2 years**	**SD = 12.8**	**Mean = 38.2 years**	**SD = 13.1**				

① Reporting group description contains details about the group of subjects receiving treatment.

②The age categories above are the default categories that match the protocol details in the clinical trial application. However, any age categorisation can be used.

Baseline Characteristics Form – Gender *EMA*

Reporting group title	Active	Placebo		**TOTAL**
Reporting group description ①	6MP	Placebo		
Overall number of baseline subjects	128	112		240
Gender, male, female ②	**Number of Subjects**	**Number of Subjects**	**Number of Subjects**	**Number of Subjects**
Unit of measure Subjects				
Female	79	67		146
Male	49	45		94

① Reporting group description contains details about the group of subjects receiving treatment.

② At least one Gender baseline measure (female, male or Customised) is required

Baseline Characteristics Form – Study Specific Measure *EMA*

Study specific characteristic title	Baseline characteristics
Baseline measure description	Key baseline measurements – contributing to pre-specified subgroup analyses

Reporting group title		Active		Placebo				**TOTAL** ④	
Reporting group description ①		6MP		Placebo					
Overall number of baseline subjects		128		112				[Derived: total]	
Unit of measure	**Number of subjects**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**		
		[Circle one] arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max	*[Circle one]* arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max	*[Circle one]* arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max		
		Number of Subjects		**Number of Subjects**		**Number of Subjects**		**Number of Subjects**	
Category title ③	**Previous treatment with 6MP**	**Yes 14 No 114 Missing 0**		**Yes 5 No 106 Missing 1**				**Yes 19 No 220 Missing 1**	
Category title ③	**Previous treatment with Azathioprine**	**Yes 80 No 48 Missing 0**		**Yes 47 No 64 Missing 1**				**Yes 127 No 112 Missing 1**	
Category title ③	**Previous treatment with Infliximab**	**Yes 21 No 104 Missing 3**		**Yes 15 No 96 Missing 1**				**Yes 36 No 200 Missing 4**	
Category title ③	**Previous treatment with Methotrexate**	**Yes 8 No 120 Missing 0**		**Yes 7 No 104 Missing 1**				**Yes 15 No 224 Missing 1**	

Category title ③	**Previous surgery**	**Yes 46** **No 82** **Missing 0**	**Yes 28** **No 83** **Missing 1**		**Yes 74** **No 165** **Missing 1**
Category title ③	**Smoking status**	**Yes 29** **No 99**	**Yes 26** **No 86**		**Yes 55** **No 185**
Category title ③	**Duration of disease**	**≤ 1 year 37** **> 1 year 91** **Unknown 0**	**≤ 1 year 41** **> 1 year 69** **Unknown 2**		**≤ 1 year 78** **> 1 year 160** **Unknown 2**
Category title ③	**Age at diagnosis**	**≤ 40 years 103** **> 40 years 25** **Unknown 0**	**≤ 40 years 87** **> 40 years 23** **Unknown 2**		**≤ 40 years 190** **> 40 years 48** **Unknown 2**

① Reporting group description contains details about the group of subjects receiving treatment.

② A single number should be entered for all dispersion types in this table.

③ Add as many Categories as needed if the data can be categorised.

④ The total group is only relevant to categorical data.

Baseline Characteristics Form – Study Specific Measure *EMA*

Study specific characteristic title	CDAI score
Baseline measure description	Crohn's Disease Activity Index score

Reporting group title		Active		Placebo				**TOTAL** ④	
Reporting group description ①		6MP		Placebo					
Overall number of baseline subjects		128		112				240	
Unit of measure	**Score (no units)**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**		
		[Circle one] arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max	*[Circle one]* arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max	*[Circle one]* arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max		
		Number of Subjects		**Number of Subjects**		**Number of Subjects**		**Number of Subjects**	
Category title ③		**Mean = 130, SD = 86**		**Mean = 121, SD = 72**				Mean = 125, SD = 80	

① Reporting group description contains details about the group of subjects receiving treatment.

② A single number should be entered for all dispersion types in this table.

③ Add as many Categories as needed if the data can be categorised.

④ The total group is only relevant to categorical data.

Baseline Characteristics Form – Study Specific Measure *EMA*

Study specific characteristic title	Weight (kg)
Baseline measure description	Characteristics at randomisation/Visit 2

Reporting group title		Active		Placebo				**TOTAL** ④	
Reporting group description ①		6MP		Placebo					
Overall number of baseline subjects		128		112				240	
Unit of measure	**kg**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**		
		[Circle one] arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max	*[Circle one]* arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max	*[Circle one]* arithmetic mean, geometric mean, least squares mean, log mean, median	*[Circle one]* ② Standard deviation, interquartile range, range, sample min/max		
		Number of Subjects		**Number of Subjects**		**Number of Subjects**		**Number of Subjects**	
Category title ③		**Mean = 70.7, SD = 14.4**		**Mean = 70.7, SD = 13.7**				Mean = 70.7, SD = 14.0	

① Reporting group description contains details about the group of subjects receiving treatment.

② A single number should be entered for all dispersion types in this table.

③ Add as many Categories as needed if the data can be categorised.

④ The total group is only relevant to categorical data.

End Points Form *EMA*

End point type	*[Circle one]* Primary / Secondary / Other pre-specified / Post-hoc
End point title	Primary outcome - postoperative clinical recurrence of Crohn's disease
End point description (max 999 characters)	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 timeframe (max 255 characters)	Up to the end of the trial (3 years)
Arms / subjects analysis sets	ITT population

Reporting group title		Active				Placebo					
Reporting group description ①		6MP				Placebo					
Overall number of baseline subjects		128	**Comment** ②			112	**Comment** ②				**Comment** ②
		Measure type	**Dispersion/ Precision type**			**Measure type**	**Dispersion/ Precision type**			**Measure type**	**Dispersion/ Precision type**
Unit of measure	**Number of patients experiencing postoperative clinical recurrence of Crohn's disease (primary outcome)**	*[Circle one]* Number, Arithmetic mean, Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)			*[Circle one]* Number, Arithmetic mean, Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)			*[Circle one]* Number, Arithmetic mean, Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)
Category title ⑤	**Reached primary endpoint?**	**Yes 16** **No 112**	④**NA**			**Yes 26** **No 86**	④**NA**				④
Category title ⑤			④				④				④

Graphical Representation

Upload images containing the graphical representation relevant to the End point.

① Reporting group description contains details about the group of subjects receiving treatment.

② A comment explaining why the number of subjects for the variable differs to the number of subjects in the selected arm.

③ “Not applicable” Dispersion/Precision type should not be used only when Measure type is not “number”.

④ Numeric lower and upper values should be entered when precision type is a “confidence interval”. A single number should be entered for all other Dispersion/Precision types.

⑤ Add as many categories as needed if the end point can be categorised.

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Statistical analysis of the primary outcome	**Analysis type**	*[Circle one]* Non-inferiority / Equivalence / Superiority / Other
		Comment	
Statistical analysis description	Cox's proportional hazards model		
Comparison group	**Omnibus analysis:** *[Circle one]* all reporting groups / all subject analysis sets	**Selection of reporting groups:** _____ ②	
Number of subjects	240		
Analysis specification	*[Circle one]* pre-specified / post-hoc		
Statistical hypothesis test			
P-value	*[Cicle one]* = < ≤ > ≥ ③	Value: 0.073 _	**Comment** ④ Adjusted for randomisation stratification variables (centre and smoking status), also adjusted for previous treatment with 6MP or Azathioprine.
Method [required if P-value provided]	*[Circle one]* ANCOVA / ANOVA / Chi-squared / Chi squared corrected / Cochran-Mantel-Haenszel / Fisher Exact / Kruskal-Wallis / Logrank / Mantel-Haenszel / McNemar / Mixed Models Analysis / Regression, Cox / Regression, Linear / Logistic / Sign Test / t-Test 1-sided / t-Test 2-sided / Wilcoxon (Mann-Whitney / Other method name: (specify) _____		
Parameter Estimate			
Point estimate	0.535		
Confidence interval	Level: 95% / 90% / Other: _____%	Sides: *[Circle one]* 1 / 2	Lower limit: 0.27 / Upper limit: 1.96
Parameter type	*[Circle one]* Cox Proportional Hazard / Hazard Ratio(HR) / Hazard Ratio Log, Mean Difference (final values) / Mean Difference (net) / Median Difference (final values) / Median Difference (net) / Odds Ratio(OR) / Odds Ratio log / Risk Difference (RD) / Risk Ratio (RR) / Risk Ratio log / Slope		

	Other effect estimate: (specify) _____		
Variability estimate	*[Circle one]* Standard Deviation / Standard Error of the Mean	**Dispersion value**	0.349

① Add any number of statistical analyses for each end point as required.

② Select the reporting groups from those included in the end point that are relevant to this statistical analysis if an omnibus analysis is not being performed.

③ Prefix the P-value with a comparison operator.

④ This field contains additional information about the P-value such as whether it is adjusted for multiple comparisons and a priori threshold for statistical significance.

End Points Form *EMA*

End point type	*[Circle one]* Primary / Secondary / Other pre-specified / Post-hoc
End point title	Secondary outcome - postoperative clinical recurrence of Crohn's disease
End point description (max 999 characters)	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 timeframe (max 255 characters)	Up to the end of the trial (3 years)
Arms / subjects analysis sets	ITT population

Reporting group title		Active				Placebo					
Reporting group description ①		6MP				Placebo					
Overall number of baseline subjects		128	**Comment** ②			112	**Comment** ②			**Comment** ②	
		Measure type		**Dispersion/ Precision type**		**Measure type**		**Dispersion/ Precision type**		**Measure type**	**Dispersion/ Precision type**
Unit of measure	**Number of patients experiencing postoperative clinical recurrence of Crohn's disease (secondary outcome)**	*[Circle one]* Number, Arithmetic mean, Least squares mean, Geometric mean, Log mean, median		*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)		*[Circle one]* Number, Arithmetic mean, Least squares mean, Geometric mean, Log mean, median		*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)		*[Circle one]* Number, Arithmetic mean, Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)
Category title ⑤	**Reached secondary endpoint?**	**Yes 34** **No 94**		**④NA**		**Yes 40** **No 72**		**④NA**			④

Category title ⑤			④		④		④

Graphical Representation

Upload images containing the graphical representation relevant to the End point.

① Reporting group description contains details about the group of subjects receiving treatment.

② A comment explaining why the number of subjects for the variable differs to the number of subjects in the selected arm.

③ “Not applicable” Dispersion/Precision type should not be used only when Measure type is not “number”.

④ Numeric lower and upper values should be entered when precision type is a “confidence interval”. A single number should be entered for all other Dispersion/Precision types.

⑤ Add as many categories as needed if the end point can be categorised.

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Statistical analysis of the secondary outcome	**Analysis type**	*[Circle one]* Non-inferiority / Equivalence / Superiority / Other
		Comment	
Statistical analysis description	Cox's proportional hazards model		
Comparison group	**Omnibus analysis:** *[Circle one]* all reporting groups / all subject analysis sets	**Selection of reporting groups:** _____ ②	
Number of subjects	240		
Analysis specification	*[Circle one]* pre-specified / post-hoc		
Statistical hypothesis test			
P-value	*[Cicle one]* = < ≤ > ≥ ③	Value: 0.243 _	**Comment** ④ Adjusted for randomisation stratification variables (centre and smoking status), also adjusted for previous treatment with 6MP or Azathioprine.
Method [required if P-value provided]	*[Circle one]* ANCOVA / ANOVA / Chi-squared / Chi squared corrected / Cochran-Mantel-Haenszel / Fisher Exact / Kruskal-Wallis / Logrank / Mantel-Haenszel / McNemar / Mixed Models Analysis / Regression, Cox / Regression, Linear / Logistic / Sign Test / t-Test 1-sided / t-Test 2-sided / Wilcoxon (Mann-Whitney / Other method name: (specify) __		
Parameter Estimate			
Point estimate	0.737		

Confidence interval	Level	95% / 90% / Other: _____%	Sides	*[Circle one]* 1 / 2	Lower limit	0.44	Upper limit	1.23
Parameter type	*[Circle one]* Cox Proportional Hazard / Hazard Ratio(HR) / Hazard Ratio Log, Mean Difference (final values) / Mean Difference (net) / Median Difference (final values) / Median Difference (net) / Odds Ratio(OR) / Odds Ratio log / Risk Difference (RD) / Risk Ratio (RR) / Risk Ratio log / Slope						

	Other effect estimate: (specify) _____		
Variability estimate	*[Circle one]* Standard Deviation / Standard Error of the Mean	**Dispersion value**	0.262

① Add any number of statistical analyses for each end point as required.

② Select the reporting groups from those included in the end point that are relevant to this statistical analysis if an omnibus analysis is not being performed.

③ Prefix the P-value with a comparison operator.

④ This field contains additional information about the P-value such as whether it is adjusted for multiple comparisons and a priori threshold for statistical significance

End Points Form *EMA*

End point type	*[Circle one]* Primary / Secondary / Other pre-specified / Post-hoc
End point title	Subgroup analyses – Smoking status Primary outcome - postoperative clinical recurrence of Crohn's disease
End point description (max 999 characters)	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. Subgroup analysis of smoking status.
End point timeframe (max 255 characters)	Up to the end of the trial (3 years)
Arms / subjects analysis sets	ITT population

Reporting group title		Active			Placebo				
Reporting group description ①		6MP			Placebo				
Overall number of baseline subjects		128	**Comment** ②		112	**Comment** ②			**Comment** ②
		Measure type	**Dispersion/ Precision type**		**Measure type**	**Dispersion/ Precision type**		**Measure type**	**Dispersion/ Precision type**
Unit of measure	**Number of patients experiencing postoperative clinical recurrence of Crohn's disease (primary outcome)**	*[Circle one]* Number, Arithmetic mean Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)		*[Circle one]* Number, Arithmetic mean Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)		*[Circle one]* Number, Arithmetic mean Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)
Category title ⑤	**Smokers**	**Yes 3**	④**NA**		**Yes 12**	④**NA**			④

		No 26		**No 14**			
Category title ⑤	**Non-smokers**	**Yes 13** **No 86**	④	**Yes 14** **No 72**	④		④

Graphical Representation

Upload images containing the graphical representation relevant to the End point.

① Reporting group description contains details about the group of subjects receiving treatment.

② A comment explaining why the number of subjects for the variable differs to the number of subjects in the selected arm.

③ “Not applicable” Dispersion/Precision type should not be used only when Measure type is not “number”.

④ Numeric lower and upper values should be entered when precision type is a “confidence interval”. A single number should be entered for all other Dispersion/Precision types.

⑤ Add as many categories as needed if the end point can be categorised.

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Subgroup analysis of the primary outcome – Smoking status	**Analysis type**	*[Circle one]* Non-inferiority / Equivalence / Superiority / Other
		Comment	
Statistical analysis description	Cox's proportional hazards model		
Comparison group	**Omnibus analysis:** *[Circle one]* all reporting groups / all subject analysis sets	**Selection of reporting groups:** _____ ②	
Number of subjects	240		
Analysis specification	*[Circle one]* pre-specified / post-hoc		

Statistical hypothesis test

P-value	*[Cicle one]* = < ≤ > ≥ ③	Value: 0.018 _	**Comment** ④	Unadjusted results presented only for all subgroup analyses. This is the subgroup p-value, testing for an interaction between treatment and smoking status.
Method [required if P-value provided]	*[Circle one]* ANCOVA / ANOVA / Chi-squared / Chi squared corrected / Cochran-Mantel-Haenszel / Fisher Exact / Kruskal-Wallis / Logrank / Mantel-Haenszel / McNemar / Mixed Models Analysis / Regression, Cox / Regression, Linear / Logistic / Sign Test / t-Test 1-sided / t-Test 2-sided / Wilcoxon (Mann-Whitney / Other method name: (specify) _____			

Parameter Estimate

Point estimate	Smokers: 0127 Non-smokers: 0.898							
Confidence interval	Level	95% / 90% / Other: _____%	Sides	*[Circle one]* 1 / 2	Lower limit	Smokers 0.04 Non-smokers 0.42	Upper limit	Smokers 0.46 Non-smokers 1.94
Parameter type	*[Circle one]* Cox Proportional Hazard / Hazard Ratio(HR) / Hazard Ratio Log, Mean Difference (final values) / Mean Difference (net) / Median Difference (final values) / Median Difference (net) / Odds Ratio(OR) / Odds Ratio log / Risk Difference (RD) / Risk Ratio (RR) / Risk Ratio log / Slope							

	Other effect estimate: (specify) _____		
Variability estimate	*[Circle one]* Standard Deviation / Standard Error of the Mean	**Dispersion value**	NA

① Add any number of statistical analyses for each end point as required.

② Select the reporting groups from those included in the end point that are relevant to this statistical analysis if an omnibus analysis is not being performed.

③ Prefix the P-value with a comparison operator.

④ This field contains additional information about the P-value such as whether it is adjusted for multiple comparisons and a priori threshold for statistical significance.

End Points Form	***EMA***

End point type	*[Circle one]* Primary / Secondary / Other pre-specified / Post-hoc
End point title	Subgroup analyses – Smoking status Secondary outcome - postoperative clinical recurrence of Crohn's disease
End point description (max 999 characters)	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 Subgroup analysis of smoking status.
End point timeframe (max 255 characters)	Up to the end of the trial (3 years)
Arms / subjects analysis sets	ITT population

Reporting group title		Active				Placebo					
Reporting group description ①		6MP				Placebo					
Overall number of baseline subjects		128	**Comment** ②			112	**Comment** ②				**Comment** ②
		Measure type		**Dispersion/ Precision type**		**Measure type**		**Dispersion/ Precision type**		**Measure type**	**Dispersion/ Precision type**
Unit of measure	**Number of patients experiencing postoperative clinical recurrence of Crohn's disease (primary outcome)**	*[Circle one]* Number, Arithmetic mean Least squares mean, Geometric mean, Log mean, median		*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)		*[Circle one]* Number, Arithmetic mean Least squares mean, Geometric mean, Log mean, median		*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)		*[Circle one]* Number, Arithmetic mean Least squares mean, Geometric mean, Log mean, median	*[Circle one]* ③ Not applicable, Standard deviation, Interquartile range, Range, Sample min/max, Standard error, Confidence interval (%)
Category title ⑤	**Smokers**	**Yes**	**6**	④**NA**		**Yes**	**13**	④**NA**			④

		No 23		**No 13**			
Category title ⑤	**Non-smokers**	**Yes 28** **No 71**	④	**Yes 27** **No 59**	④		④

Graphical Representation

Upload images containing the graphical representation relevant to the End point.

① Reporting group description contains details about the group of subjects receiving treatment.

② A comment explaining why the number of subjects for the variable differs to the number of subjects in the selected arm.

③ “Not applicable” Dispersion/Precision type should not be used only when Measure type is not “number”.

④ Numeric lower and upper values should be entered when precision type is a “confidence interval”. A single number should be entered for all other Dispersion/Precision types.

⑤ Add as many categories as needed if the end point can be categorised.

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Subgroup analysis of the secondary outcome – Smoking status	**Analysis type**	*[Circle one]* Non-inferiority / Equivalence / Superiority / Other
		Comment	
Statistical analysis description	Cox's proportional hazards model		
Comparison group	**Omnibus analysis:** *[Circle one]* all reporting groups / all subject analysis sets	**Selection of reporting groups:** _____ ②	
Number of subjects	240		
Analysis specification	*[Circle one]* pre-specified / post-hoc		

Statistical hypothesis test

P-value	*[Cicle one]* = < ≤ > ≥ ③	Value: 0.033	**Comment** ④	Unadjusted results presented only for all subgroup analyses. This is the subgroup p-value, testing for an interaction between treatment and smoking status.
Method **[required if P-value provided]**	*[Circle one]* ANCOVA / ANOVA / Chi-squared / Chi squared corrected / Cochran-Mantel-Haenszel / Fisher Exact / Kruskal-Wallis / Logrank / Mantel-Haenszel / McNemar / Mixed Models Analysis / Regression, Cox / Regression, Linear / Logistic / Sign Test / t-Test 1-sided / t-Test 2-sided / Wilcoxon (Mann-Whitney / Other method name: (specify) _____			

Parameter Estimate

Point estimate	Smokers: 0127 Non-smokers: 0.898							
Confidence interval	Level	95% / 90% / Other: _____%	Sides	*[Circle one]* 1 / 2	Lower limit	Smokers 0.10 Non-smokers 0.58	Upper limit	Smokers 0.72 Non-smokers 1.70
Parameter type	*[Circle one]* Cox Proportional Hazard / Hazard Ratio(HR) / Hazard Ratio Log, Mean Difference (final values) / Mean							

	Difference (net) / Median Difference (final values) / Median Difference (net) / Odds Ratio(OR) / Odds Ratio log / Risk Difference (RD) / Risk Ratio (RR) / Risk Ratio log / Slope Other effect estimate: (specify) _____		
Variability estimate	*[Circle one]* Standard Deviation / Standard Error of the Mean	**Dispersion value**	NA

① Add any number of statistical analyses for each end point as required.

② Select the reporting groups from those included in the end point that are relevant to this statistical analysis if an omnibus analysis is not being performed.

③ Prefix the P-value with a comparison operator.

④ This field contains additional information about the P-value such as whether it is adjusted for multiple comparisons and a priori threshold for statistical significance.

Adverse Events Form *EMA*

Time frame for adverse event reporting (max 255 characters)	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 (max 350 characters)	As above.			
Dictionary used ①	**Dictionary name**	*[Circle one]* MedDRA / SNOMED CT / Other: (specify) AEs coded by trial management team	**Dictionary version**	N/A
Method	*[Circle one]* Systematic / Non-systematic		**Frequency threshold for reporting non-serious adverse events** ②	_____% No set thresholds and all AEs reported

Serious Adverse Events

Reporting group title	Active	Placebo	Total
Reporting group description ③	6MP	Placebo	All patients
Number of subjects exposed	128	112	240
Number of subjects affected by serious adverse events	51	49	100
Number of subjects affected by non-adverse events	121	105	226
Number of deaths (all causes)	0	1	1
Number of deaths resulting from adverse events	0	0	0

Serious Adverse Events															
System organ class	**Eve**	**Additional**	**Diction**	*Number of subjects affected*	*Number of subjects exposed*	*Event term occurrence – all*	*Event term occurrence – causally*	*Number of subjects affected*	*Number of subjects exposed*	*Event term occurrenc*	*Event term occurren*	*Number of subjects affected*	*Number of subject*	*Event term occurrence – all*	*Event term occurrence – causally*

	nt term	description	ary				*related to the treatment*			*e – all*	*ce – causally related to the treatment*		*s exposed*		*related to the treatment*
Cardiac disorders				3	④	3	0	2	④	2	0	5	④	5	0
Congenital, familial and genetic disorders				0	④	0	0	1	④	1	1	1	④	1	1
Eye disorders				0	④	0	0	1	④	1	1	1	④	1	1
Gastrointestinal disorders				23	④	26	2	29	④	33	4	52	④	59	6
General disorders and administration site conditions				1		1	0	1		1	0	2		2	0
Hepatobiliary disorders				1		1	1	1		1	0	2		2	1
Infections and infestations				4		7	0	3		3	1	7		10	1
Injury, poisoning and procedural complications				1		1	0	1		1	0	2		2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				1		1	0	1		1	0	2		2	0
Nervous system disorders				0		0	0	1		1	0	1		1	0
Renal and urinary disorders				4		6	0	2		2	0	6		8	0
Reproductive system and breast disorders				2		2	0	0		0	0	2		2	0
Skin and subcutaneous tissue disorders				1		1	0	1		2	1	2		3	1
Surgical and medical procedures				9		9	0	5		5	0	14		14	0
Vascular disorders				1		1	0	0		0	0	1		1	0

Fatalities									
System organ	**Event term**		*Fatalities - all*	*Fatalities – causally related to the treatment*	*Fatalities - all*	*Fatalities – causally related to the treatment*	*Fatalities - all*	*Fatalities – causally related to the treatment*

class								
General disorders and administration site conditions	Death ⑤	Coronary heart disease	0	N/A	1	N/A		
	⑤							
	⑤							

Non-Serious Adverse Events

Reporting group title	Active	Placebo	Total
Reporting group description	6MP	Placebo	All patients
Number of subjects affected by non-adverse events	121	105	226

Non-Serious Adverse Events

System organ class	**Event term**	**Additional description**	**Dictionary**	*Number of subjects affected*	*Number of subjects exposed*	*Event term occurrence – all*	*Event term occurrence – causally related to the treatment*	*Number of subjects affected*	*Number of subjects exposed*	*Event term occurrence – all*	*Event term occurrence – causally related to the treatment*	*Number of subjects affected*	*Number of subjects exposed*	*Event term occurrence – all*	*Event term occurrence – causally related to the treatment*
Uncoded				1	④	1	0	1	④	1	0	2	④	2	0
GI Symptoms - Other				34	④	53	10	28	④	40	6	62	④	93	16
Infections				81	④	171	82	68	④	184	81	149	④	355	163
Pain				18	④	30	3	17	④	19	1	35	④	49	4

Other				85		212	30	62		153	21	147		365	51
Cancers				2		3	0	1		1	0	3		4	0
Deranged LFTs				4		4	2	5		5	4	9		9	6
Pancreatitis				1		1	1	1		1	0	2		2	1
GI Symptoms - nausea/vomiting				45		78	41	30		41	16	75		119	57
GI Symptoms - abdominal pain				66		132	35	67		141	21	133		273	56
GI Symptoms - Constipation/diarrhoea				37		54	14	37		56	4	74		110	18
Joint pain/arthralgia				40		72	11	36		65	14	76		137	25
Worsening Crohn's				24		41	1	29		37	4	53		78	5
Rash				24		35	13	14		17	7	38		52	20
Headache				26		61	18	20		38	12	46		99	30

① The table defaults provide a short-cut for entering the dictionary used for recording all Adverse events in a study. If entered, the table default values respectively apply to any Adverse Event with a blank Dictionary name.

② The frequency of non-serious adverse events that, when exceeded within any arm or comparison group, are reported in the results database for all arms or comparison groups. The number must be less than or equal to the allowed maximum expressed as a percentage. For example, a threshold of 5 per cent indicates that all non-serious adverse events with a frequency greater than 5 per cent within at least one arm or comparison group are reported.

③ Reporting group description contains details about subjects in this group.

④ Number of subjects exposed for a single Adverse event in a reporting group is only required when the value differs from the Total number of subjects at exposed in the reporting group.

⑤ The event terms used for reporting fatalities must also appear in the serious adverse events table.

More Information	*EMA*

Global Substantial Protocol Amendments ①

Amendment date	Description
16/12/2007	**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.
18/11/2008	**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.
15/06/2009	**Substantial Amendment 5:** Reduce number of colonoscopies and clarification in PIL/Consent the types of sample and how they are handled and stored.
07/07/2008	**Substantial Amendment 6:** Decision to stop study drug if subjects prescribed Allopurinol.
15/12/2009	**Substantial Amendment 7:** Amendment to safety assessments in protocol, prohibited medications added as appendix.
03/03/2010	**Substantial Amendment 8:** Isolated elevation of GGT do not represent exclusion to recruitment or withdrawal.
28/09/2010	**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.
10/02/2011	**Substantial Amendment 13:** Clarifications to the protocol
15/03/2012	**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.
03/10/2013	**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.
07/05/2015	**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.

Global Interruptions and Restarts ②

Interruption date	Description	Restart Date
N/A	N/A	N/A

Limitations and Caveats ③

Limitations and caveats that apply to the results
N/A

① Provide details of the substantial amendments to the protocol that affected the trial globally. There may not have been any global substantial protocol amendments, so their presence is optional. However if a global substantial protocol amendment is created, then both the date and the description are necessary. There is sufficient provision to support the presence of any number of global substantial protocol amendments to the trial.

② Provide details of the interruptions that affected the trial globally. There may not have been any global interruptions, so their presence is optional. If a global amendment is created it must have an interruption date and a description. The restart date is provided only if the trial was restarted globally after the interruption. There is sufficient provision to support the presence of any number of global interruptions and restarts to the trial.

③ Based on the conduct of the trial provide any limitations or caveats to the results of the trial.