Study Protocol

Randomised Controlled Trial of 6-Mercaptopurine Versus Placebo to Prevent Recurrence of Crohn’s Disease Following Surgical Resection

MRC G060329

Co-Sponsors
University of Edinburgh
Lothian Health Board

Sponsor Contact
Marise Bucukoglu
Clinical Trials & Research Governance Manager
College of Medicine & Veterinary Medicine
The Queen's Medical Research Institute
The University of Edinburgh
47 Little France Crescent, Edinburgh EH16 4TJ

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MRC Contact
Jane Sinclair
Programme Manager
NETSCC - Efficacy and Mechanism Evaluation
Alpha House, University of Southampton Science Park
Southampton
SO16 7NS

Email: j.sinclair@southampton.ac.uk
Tel: 023 8059 7504

Trial Manager
Holly Ennis
Edinburgh Clinical Trials Unit
University of Edinburgh
Room D36, 2nd Floor, Outpatients Building
Western General Hospital, Crewe Road
Edinburgh, EH4 2XU

Tel: 0131 537 3845
Fax: 0131 537 3851

Email: Toppic@ed.ac.uk

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Host Institutions

University of Edinburgh and Lothian Health Board - ACCORD

Chief Investigator

Professor J Satsangi
Professor of Gastroenterology
Gastrointestinal Unit
Centre for Molecular Medicine
Western General Hospital
Crewe Road South, Edinburgh EH4 2XU
Tel: 0131 651 1807
Email: J.Satsangi@ed.ac.uk
PA: Colette McColl, Tel: 0131 651 1807

Statistician

Dr Steff Lewis
Edinburgh MRC Clinical Trials Methodology Hub, Centre for Population Health Sciences, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU.
Email: steff.lewis@ed.ac.uk
Tel: 0131 650 3198, Fax: 0131 650 3224

Site Addresses

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PROTOCOL APPROVAL

Randomised Controlled Trial of 6-Mercaptopurine Versus Placebo to Prevent Recurrence of Crohn's Disease Following Surgical Resection

MRC G060329
EudraCT number 2006-005800-15

Signatures

Professor Jack Satsangi
Chief Investigator

Signature

Date

Dr Marise Bucukoglu
Sponsor Representative

Signature

Date

Dr Holly Ennis
Trial Manager

Signature

Date

Dr Steff Lewis
Trial Statistician

Signature

Date
INVESTIGATOR STATEMENT

Randomised Controlled Trial of 6-Mercaptopurine Versus Placebo to Prevent Recurrence of Crohn's Disease Following Surgical Resection

MRC G060329
EudraCT number 2006-005800-15

I agree to conduct the study according to this protocol, the principles of International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice (ICH GCP) and the applicable regulatory requirements. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the patients.

I agree to take responsibility for the conduct of the study and ensure that all other staff involved are adequately informed about the protocol and amendments, the IMP and their study related duties and functions.

I have read and understood the information in the Summary of Product Characteristics, including the potential risk and adverse event profile of the IMP.

Signatures

________________________  ____________
Signature of Investigator    Date

__________________________
Name of Investigator (please print)
LAY SUMMARY

Crohn’s disease is a serious disease in which there is swelling and ulceration of the gut wall. Although now a common illness, the cause is unknown. Symptoms may include pain, tiredness and the feeling of being generally unwell. Most patients are treated with medicines. But after ten years, 2 out 3 people with Crohn’s disease will need an operation. Crohn’s disease can often come back after an operation, and almost half those who had an operation will need another one.

Several medicines have been tested to see if they help stop Crohn’s disease coming back after an operation. The 5ASA medicines are not very good at stopping Crohn’s coming back. Antibiotics have some effect but cannot be taken for very long because of side effects. Azathioprine and 6-Mercaptopurine are medicines that alter the way the immune system works. Over the last 10 years, they have become widely used for Crohn’s disease when it is not easily treated with other medicines but is not serious enough to need an operation. They have also been tested to see if they can stop Crohn’s disease coming back after an operation, but those studies have been flawed and the results have been unhelpful for doctors.

We have been very fortunate to receive money from the Medical Research Council, to carry out a new, better study of the treatment of Crohn’s disease after an operation. It is called the TOPPIC trial, and will answer an important question. Does 6-mercaptopurine stop (or slow down) Crohn’s disease coming back after an operation?

In order for this study to be a success, we need 234 patients with Crohn’s disease from across the UK to take part. Patients who have recently had an operation to remove a section of bowel will be invited to take part, and if they agree they will receive either 6-mercaptopurine or a placebo. Patients will be followed up for 3 years.

The main thing we want to find out is whether Crohn’s disease comes back or not. We will assess this in 3 ways.
(1) By recording symptoms of Crohn’s disease,
(2) By recording the need for more medicines, and
(3) By looking at the operation site using a flexible telescope (endoscopy).

There are several other important questions that this study will be able to answer.
- Can we measure gut swelling by measuring a chemical in a patient’s stool (calprotectin) instead of using a flexible telescope (endoscopy)?
- Can we use blood tests to guide doctors as to the best dose of medicine for individual patients?
- Can we use genetic and other blood tests to tell which patients are more likely to have the disease come back after an operation?

Importantly we will also be able to provide economic data about the treatment of Crohn’s disease, and this will help policymakers decide which treatments doctors should use in the future.

The study started in 2007 and will continue for 7.5 years. It is being led by experts in Crohn’s disease from Edinburgh, and also involves experts from centres throughout the UK.
PROFESSIONAL SUMMARY

Background
Crohn’s disease is a common debilitating condition of unknown cause in which there is inflammation of the wall of the gut. This may result in diarrhoea, abdominal pain, weight loss, tiredness and feeling generally unwell. The disease commonly affects young people, affecting education, employment, and family life. Most patients are first treated medically but over the first ten years of the condition up to 65% of patients will need an operation to control the disease. Recurrence of Crohn’s disease following surgery is universal, most commonly occurring at the anastomosis (join) between the two sections of bowel. In excess of 40% of these individuals will need further surgery to again control of the disease within 10 years. A number of medicines have been tested previously to prevent or delay the recurrence of Crohn’s disease. The 5ASA medicines are ineffective and nitroimidazole antibiotics have some effect but cannot be taken in the long term due to side effects. Azathioprine and 6-Mercaptopurine (collectively termed thiopurines) are drugs that alter the way the immune system responds. They have become, especially over the last 10 years, established and widely used treatments for Crohn’s disease that has been unresponsive to other treatments but has not required surgery. They have been tested to prevent the recurrence postoperatively but the studies have been flawed and results mixed.

Methods
The TOPPIC trial is an adequately powered and robustly designed randomised controlled trial that will address the question of whether 6-mercaptopurine is able to prevent or delay postoperative recurrence in Crohn’s disease. We aim to recruit 234 patients from centres throughout the UK. This will give an 80% power to detect a 20% difference between the study groups. Patients who have recently had an operation to remove an affected section of bowel will be approached for consent, and then randomised to receive 6-mercaptopurine at a dose of 1-1.5mg/kg body weight or an identical placebo. Patients will be followed up for 3 years. The primary endpoint of the study is the recurrence of Crohn’s disease. We will assess this in two ways, firstly by the clinical recurrence of Crohn’s disease (evidenced by symptoms and the need for further medicines to treat these) and secondly a direct examination of the join between the 2 segments of bowel by flexible telescope (endoscopy).

We will also be able to answer the following research questions:
- Will a non-invasive marker of gastrointestinal inflammation (calprotectin) reliably identify recurrence and replace the need for endoscopy?
- Will the analysis of the breakdown products of 6MP in the blood help direct treatment?
- Will we be able to predict those individuals at high risk of rapid recurrence by testing a panel of genetic markers and antibodies in a blood test taken at the start of treatment?
- Importantly we will also be able to provide health economic data about the cost effectiveness of the treatment.

This is an important study that may result in tangible benefits for the many patients with Crohn’s disease for whom surgery is a necessity. The study started in 2007 and will continue for 7.5 years. It is led by Prof Jack Satsangi and colleagues at the University of Edinburgh and Western General Hospital, Edinburgh, and involves leading GI consultants from centres throughout the UK.
1. Introduction

Prevalence of Crohn’s Disease
Crohn’s disease (CD) is a common, chronic, relapsing inflammatory illness which can involve any part of the gastrointestinal tract, but most commonly involves the terminal ileum. The prevalence in Northern England has recently been estimated to be 144/100,000 population\(^1\). The incidence amongst young people in Scotland is the highest in the UK, and continues to rise\(^2\). Although the mortality associated with CD is low, there is significant morbidity with serious effects on growth, development, education and employment potential.

Medical Treatment of Crohn’s Disease
Corticosteroids remain the first line medical treatment for the induction of remission in CD. In patients failing steroids, immunosuppression with azathioprine (Aza) or 6-Mercaptopurine (6MP) (6MP: the active metabolite of azathioprine) or methotrexate is now regarded as the standard of care. Azathioprine and 6-Mercaptopurine are of proven efficacy in this setting and are also used for the induction of remission (odds ratio 2.36, NNT=5) and have a potent steroid sparing effect (odds ratio 3.86, NNT=3)\(^3\). For patients entering a medically induced remission, immunosuppression with Azathioprine or 6MP is the most effective maintenance strategy (odds ratio 3.17, NNT=3.3 favouring azathioprine 2mgs/kg over placebo)\(^4\), offering an acceptable balance of efficacy, tolerability and cost.

Biological therapies, specifically monoclonal antibodies against tumour necrosis factors alpha (Infliximab) are increasingly used in resistant disease. Infliximab has a duration of action of 8-12 weeks with relapse frequently occurring after that. Maintenance of remission with Infliximab is possible in a small number of patients but cost, efficacy, immunogenicity, tolerability and the uncertain long-term safety profile are all limiting factors\(^5\).

Despite current medical therapy, up to 50% of patients have aggressive disease and require surgery within 5 years of diagnosis\(^6\). Unfortunately, disease relapse rates are high within 2 years of surgery for both endoscopic (72 - 98%) and clinical recurrence (37 to 70%)\(^7\). Re-operation rates cumulate at 5% of patients per year\(^8\).

Preventing post-operative recurrence
No medical therapy has a license to prevent post-operative recurrence. 5-Aminosalicylic acid, corticosteroids and Metronidazole have all been suggested but the evidence in favour of these drugs is weak and none are widely used\(^7\). Post-operative maintenance therapy with Aza or 6MP is more widely used and is included in a number of clinical algorithms\(^7\) but trial data from controlled trials available thus far have failed to demonstrate whether this is an effective therapy or not. Existing studies have been underpowered, poorly designed or used an inappropriate drug dose\(^9-14\).

6MP for preventing post-operative recurrence
For these reasons, we consider that identification of evidence-based strategies to prevent post-operative recurrence is both an un-met clinical need and a research priority.

6MP has been shown to be better tolerated with less minor toxicity than Azathioprine. (GUT 2007; 56 (Supl II: A24)
Other trials of 6MP for the prevention of post-operative recurrence to date have been subject to design problems such as power, eligibility criteria and critically, a lack of flexibility of 6MP dose. The largest trial published\(^{13}\) was unsuccessful in addressing these research questions due to the use of a fixed single dose used (50 mg).

**Health Economics**

The economic burden of disease recurrence has not yet been fully assessed. EQ-5D will be used as a measure of health outcome and for cost-effectiveness analyses following the advice of a Health Economist.
2. Study Objectives

2.1 Objectives

2.1.1 Primary Objective

Does 6MP prevent or delay post-operative recurrence of Crohn’s disease?

2.1.2 Secondary Objectives

1. Can faecal calprotectin be used as a non-invasive marker of disease recurrence that may remove the need for colonoscopy in some patients? Calprotectin is a stable neutrophil derived faecal protein, that correlates with disease activity\textsuperscript{15}. Elevated calprotectin predicts relapse in patients in a medically induced remission but has not been assessed in the postoperative setting.

2. Do drug metabolite levels relate to clinical efficacy of 6MP?

3. Can we predict postoperative recurrence using clinical, genetic or serological data? The recent Montreal classification of Crohn’s disease\textsuperscript{16} has identified the need to integrate clinical, genetic and serological data. This study provides the opportunity to perform exploratory analyses of this data in a prospective, rigorously phenotyped cohort.

4. Does 6MP prevent or delay endoscopic evidence of recurrence?

5. Does endoscopic recurrence predict clinical recurrence?

2.2 Outcome Measures

2.2.1 Primary Outcome

Clinical recurrence of Crohn’s disease (defined by a CDAI value of greater than 150 together with a 100 point rise in the CDAI score from baseline), together with the need for anti-inflammatory rescue therapy or primary surgical intervention.

2.2.2 Secondary Outcome

1. The need for a second operation to remove recurrent Crohn’s disease from the anastomotic site.


3. Endoscopic recurrence using the Rutgeerts scoring system.

4. Clinical recurrence of Crohn’s disease (defined by a CDAI value of greater than 150 together with a 100 point rise in the CDAI score from baseline), OR the need for anti-inflammatory rescue therapy or primary surgical intervention.

3. Regulatory Requirements

This protocol is subject to Medicines and Healthcare products Regulatory Agency (MHRA) approval and the study must not commence until Clinical Trial Application approval is obtained. The protocol and study conduct will comply with the UK law on trials (The Medicines for Human Use (Clinical Trials) Regulations 2004, and
Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006) and will be submitted to an MREC for ethical approval. Local R&D approval will also be obtained before the first patient is recruited.

4. Study Design

This was initially a 3 year multi-site, randomised double-blind, placebo controlled trial of 6MP in patients with Crohn's disease undergoing ileocolonic or small bowel resection. Additional funding was obtained in September 2010 to extend the recruitment period of the trial by 18 months. Patients undergoing an ileocolonic or small bowel resection will be approached during their hospital admission. Eligible patients will complete a screening procedure following their operation and be randomised to either 6MP or placebo during a randomisation visit following discharge from hospital after surgery. Patients will receive 6MP or placebo for up to 3 years (156 weeks) and attend 12 study visits during this time.

The assessments to be performed at each study visit are detailed in Table 4, Section 8.14.

5. Study Population

5.1 Number of Patients

A total of 234 patients with Crohn's disease, undergoing ileocolonic or small bowel resection, will be randomised across UK sites during an anticipated recruitment period of 4.5 years.

5.2 Inclusion Criteria

A patient will be considered eligible for inclusion in the study if all of the following criteria apply:

1. At least 16 years of age in Scotland and 18 years of age in England and Wales.
2. Established diagnosis of Crohn's disease confirmed at recent resection.
3. Ileocolonic or small bowel resection within 3 months before screening.
4. No more than 100 cm of fixed small bowel resected in total. Previous ileocolonic resection is acceptable.
5. Able to start oral nutrition within the first 2 postoperative weeks.
6. Normal or heterozygous TPMT (activity present or reduced consistent with carrier status).
7. Able to provide written informed consent prior to screening and to comply with the requirements of the study protocol.
8. Off antibiotics 2 weeks prior to randomisation.

5.3 Exclusion Criteria

A patient will not be eligible for inclusion in the study if any of the following criteria apply:

1. Pregnancy at baseline or breast feeding.
2. A known hypersensitivity or intolerance to 6MP.
3. Pancreatitis associated with azathioprine.
4. Receiving an experimental treatment for Crohn’s disease in the 4 weeks prior to study entry.
5. Known to require further surgery at study entry i.e. for the removal of an abscess developing from the primary surgery.
6. Strictureplasty procedure alone
   (Please note that strictureplasty and resection procedure together will not be considered an exclusion.)
7. Presence of stoma.
8. Significant haematological, renal or hepatic dysfunction or clinically important lung disease (i.e. liver function tests (except GGT) >x2 upper limit of normal, Haemoglobin ≤10, total white blood cell count <3.5, Neutrophils <1.5, Platelets <100x10⁹/l).
9. Systemic infection including hepatitis B, hepatitis C, HIV and active TB.
10. A diagnosis of indeterminate colitis or ulcerative colitis.
11. A history of illicit drug or alcohol abuse in the 1 year prior to study entry.
12. Active or untreated malignancy (excluding basal cell carcinoma and in situ tumours). (Patients who have had successful treatment for malignancy and have been in remission for more than 5 years may be considered for inclusion only after detailed discussion with, and written approval, from the patient's medical oncologist.)
13. Presence of a medical or psychiatric condition, disease or laboratory abnormality that in the opinion of the PI may place the subject at unacceptable risk during the study.
14. Homozygous deficient for TPMT (absent activity)
15. Evidence of untreated post-operative infection e.g. clostridium difficile, urinary tract infection or chest infection. If these have been appropriately treated in the opinion of the PI, and inclusion criteria 8 is met, this will not be considered an exclusion.

6. Participant Selection and Enrolment

6.1 Identifying Potential Participants

The research nurse responsible for each site will receive weekly operating lists via the Waiting List Manager and will attend the appropriate multidisciplinary meetings to enable the identification of all potential patients. The research nurse will conduct an initial screening process and will only approach those patients who appear to be eligible.

Clinicians (collaborators) at local District General Hospitals (Participant Identification Centres) will also identify patients. A pack will be provided for the Clinician which will include an Inclusion/Exclusion criteria checklist, a letter for the patient with a contact telephone number for the Co-ordinating Research Nurse, along with the Patient Information Leaflet. If the patient is interested in taking part then the Co-ordinating Research Nurse will arrange for the patient to be seen at the nearest local site for all of the study visits. The Research Nurse will contact the Clinician again at the DGH for any relevant data.

Travel expenses will be offered to participants for additional visits to the research site.
6.2 Approaching Potential Participants

The research nurse will approach identified patients in the peri-operative period. Patients will be given the Patient Information Leaflet on the study and allowed adequate time to read this.

6.3 Screening for Eligibility

Prior to discharge from hospital, patients will be approached again by the Investigator and be given an opportunity to ask questions and discuss the study.

If patients wish to be screened for eligibility to participate in the study, they will be asked to read the Patient Information Leaflet and sign the Screening Consent Form. They will be allocated a subject number at this stage. The following screening procedures will then be carried out during an inpatient screening assessment (Visit -1).

TPMT
A blood sample will be obtained to check TPMT activity, unless a test has already been carried out within the last 6 months.

Stool Sample
A post-operative stool sample will be obtained from all patients to exclude enteric infection, including clostridium difficile toxin. Where treatment is required with e.g. oral vancomycin, the patient should be off antibiotics for 2 weeks prior to randomisation.

Safety Bloods will be taken at Visit 1.

6.4 Consenting Participants

If the results of the screening assessment are satisfactory (in the absence of surgical complications, compatible TPMT, and acceptable stool results), patients will be invited to Visit 1 (1-7 days prior to randomisation) and safety bloods will be collected. Patients will be given the opportunity to discuss the study and to ask any questions.

A provisional appointment for Visit 2 should be made within 7 days, whilst awaiting safety blood results.

At Visit 2, the Investigator and/or research nurse will fully explain the nature of the study and the risks involved to each patient and will also explain that the patient would be free to withdraw from the trial at any time without consequences.

Patients will be informed that they could be asked to change their dose of study drug at any time and that their results will not be disclosed to them in order to maintain the study blind, unless required for safety reasons.

As part of the consent process patients can opt out of blood sampling for genetic studies.

When the Investigator is assured that the patient understands the implications of participating in the trial and the genetic studies, patients wishing to take part will be asked to sign and date the Study Consent Form.
The patient and Investigator will sign one original of each Informed Consent Form. The forms will be printed on carbonless copy paper, with 3 sheets. The top original signed form will be retained in the site file, the second copy will be given to the participant and the third copy will be kept in the hospital notes.

**Pregnancy Test**

A urinary pregnancy test will be carried out for female patients of childbearing age.

A negative pregnancy test must be obtained before the start of study medication.

**6.5. Patient Identification (Pre-Screening)**

The research nurse for each site will screen potentially eligible patients and enter anonymised patient details on to the study database for those who fail the inclusion criteria or decline to be screened. The details to be added will be gender and date of birth.

**6.6. Non-Recruited Patients**

For eligible patients who were screened and not subsequently randomised a reason should be entered on to the database and will become ‘non-recruits’.

**6.7. Randomisation and Treatment Allocation**

**6.7.1 Randomisation**

At Visit 2, following completion of the consenting procedures and baseline assessments, patients will be randomly assigned (1:1) to active treatment with 6MP or matching placebo using a web based randomisation system.

Patients will be stratified at randomisation according to smoking status and trial site. Active smoking is an independent variable which is associated with increased rates of post-operative recurrence’. Smokers will be defined as those smoking >1 cigarette/day.

Names and addresses, mobile phone numbers and email addresses (if agreed) will be held locally with the nurse at each site.

Patients will be asked if they wish to be sent notification and reminders eg for appointments and for CDAI diary completion, by text to their mobile phone or by email.

**6.7.2 Treatment Allocation**

Following randomisation to 6MP or matching placebo, patients will be given a prescription by the research nurse. This prescription will provide details of the bottle codes and number of tablets. The patient will be instructed to take this prescription to the site Pharmacy where they will receive their allocated blinded treatment.

Patients will be instructed to take the appropriate number of tablets orally, once daily.
6.7.3 Emergency Unblinding Procedures

The study will be performed double blind, so neither the patient nor the Investigator will know which treatment has been allocated.

Breaking of the study blind should only be performed where knowledge of the treatment is absolutely necessary for further management of the patient. Breaking of the blind can only be performed by contacting the Edinburgh Clinical Trials Unit (ECTU). The relevant contact names, telephone and fax number will be provided by the ECTU to the local site in a working practice document.

Unless there is a clinical requirement, the blind will not be broken until after data entry is complete, the validity of the data is checked, all queries resolved and the patient populations agreed.

6.7.4 Premature Discontinuation

Participation in the study is voluntary. A patient has the right to discontinue drug or completely withdraw from the study at any time for any reason. The Investigator has the right to discontinue a patient taking drug at any time if it is deemed to be in the patient’s best interest. The reason and circumstances for premature discontinuation will be documented in the CRF.

6.7.4.1 Reasons for Discontinuing Drug

Reasons for discontinuation may include
- Disease progression – such patients may fulfil the primary endpoint of the study but would continue to have study visits regardless of treatment to assess secondary outcomes
- Occurrence of a concomitant disease that may interfere with the objectives of the study
- Intolerable adverse event
- Prohibited medications (refer to Section 7.9.2)
- Significant non-compliance with the protocol

6.7.4.2 Discontinuation Procedures

For patients who discontinue drug, the assessments scheduled for that study visit will be performed and the patient will continue to attend further study visits.

If a patient chooses to withdraw completely from the trial and all study assessments, a withdrawal visit will be performed to address any concerns the patient may have.

7. Investigational Medicinal Product and Placebo

7.1 6MP

6-Mercaptopurine (Mercaptopurine) 50 mg tablets

Drug Manufacturer
EXCELLA GmbH
Nürnberger Strasse 12
90537 Feucht
Germany
Marketing Authorisation Holder
Aspen Pharma Trading Limited
12/13 Exchange Place
I.F.S.C
Dublin 1, Ireland

MA No: PL 39699/0047

Labelling and Packaging will be carried out by:
Catalent Pharma Solutions
Inchwood
Bathgate
West Lothian
EH48 2EH
UK

Catalent Pharma Solutions will provide QP release.

Storage
6-MP will be stored at controlled room temperature (15 C to 25 C) in a secure, temperature controlled, limited access area.

Mode of Administration
Oral

Summary of Product Characteristics (SmPC)

SmPC is given in Appendix 1.
Licensed indications are for the treatment of acute leukaemia. It may be utilised in remission induction and it is particularly indicated for maintenance therapy in acute lymphoblastic leukaemia and acute myelogenous leukaemia. Mercaptopurine may be used in the treatment of chronic granulocytic leukaemia.

6-MP will be used in this study outwith its licensed indications. Contraindications are hypersensitivity to any component of the preparation, but this is detailed in the exclusion criteria (see Section 5.3).

6MP is known to cause bone marrow suppression and frequent safety monitoring is built into this protocol (see Section 8.2, and also see section on dose reductions 7.7, Table 2).

Hepatic and liver problems will also be frequently monitored and if >x2 upper limit of normal the dose will be reduced (see Section 8.2, and also see section on dose reductions 7.7, Table 2).

Known side effects

See SmPC in Appendix 1 but also listed below:

<table>
<thead>
<tr>
<th>Known Side Effects</th>
<th>Special Warnings/ Precautions for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow suppression</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Hyperuricaemia and/or hyperuricosuria</td>
</tr>
<tr>
<td>Hepatic necrosis</td>
<td>Uric acid nephropathy</td>
</tr>
<tr>
<td>Biliary stasis</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Side effect</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Increases in chromosomal aberrations</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>Carcinogenesis</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Acute nonlymphatic leukaemia</td>
</tr>
<tr>
<td>Nausea</td>
<td>Pyoderma gangrenosum</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Acute myelogenous leukaemia</td>
</tr>
<tr>
<td>Oral ulceration</td>
<td>Chronic myeloid leukaemia</td>
</tr>
<tr>
<td>Intestinal ulceration</td>
<td>Bone marrow aplasia</td>
</tr>
<tr>
<td>Drug Fever and skin rash</td>
<td>Fall in leucocyte and platelet counts</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Infection from live organism vaccination</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Secondary Leukaemia/ myelodysplasia (in combination with other cytotoxics)</td>
</tr>
<tr>
<td>Transient oligospermia</td>
<td>Hepatosplenic T-cell lymphoma (when used in combination with anti-TNF agents)</td>
</tr>
<tr>
<td>Facial oedema</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
</tr>
</tbody>
</table>

7.2 Placebo
Matching placebo tablets will be manufactured by GSK containing Lactose, Microcrystalline cellulose, Povidone, Croscarmellose Sodium, Quinoline yellow, Orange yellow, Magnesium stearate.

7.3 Packaging and Labels
6-MP and placebo will be bottled by GSK, each bottle will contain 70 tablets.

The number of tablets/bottles prescribed to each patient at each visit is dictated by a regime based upon body weight.

The bottle will have a white, single panel coded English label along with a white double panel coded English label (with tear off).

Label text will be in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004.

The allocation of active/placebo to patients within a dose level will be blinded.

7.4 Handling and Storage
6-MP will be handled and stored according to the Material Safety Data Sheet.

7.5 Overdose
Please see Section 4.9 of SmPC in Appendix 1.

7.6 Dosing Regime
6MP will be given at a dose of 1-1.5 mg per/kg body weight, rounded to the nearest 25 mg, to be taken as a single daily dose in the morning. Treatment is on a maintenance basis for 3 years or until study drug is discontinued.

At Visit 2, patients will be randomised to 6MP or matching placebo and will be instructed to take the appropriate number of tablets by mouth, once daily.
The appropriate number of tablets will be based on body weight, as detailed below in Table 1.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Initial dose 6MP (mg)</th>
<th>mg/kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33*</td>
<td>50 alternate days</td>
<td>1-1.5</td>
</tr>
<tr>
<td>33-49.9</td>
<td>50 daily</td>
<td>1-1.5</td>
</tr>
<tr>
<td>50-74.9</td>
<td>50/100 alternate days</td>
<td>1-1.5</td>
</tr>
<tr>
<td>75-99.9</td>
<td>100 daily</td>
<td>1-1.33</td>
</tr>
<tr>
<td>100-150</td>
<td>150 daily</td>
<td>1-1.5</td>
</tr>
<tr>
<td>&gt;150*</td>
<td>200 daily</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

*There are unlikely to be many patients in these groups

NB: Patients heterozygous for TPMT mutations should be prescribed 6MP at half normal dose; those homozygous deficient are not eligible for the trial.

7.7 Dose Changes

Dose will be adjusted up or down for weight changes during the study according to Table 1.

The blinded treatment dose of 6MP or placebo may be reduced or temporarily stopped following patient intolerance (profound nausea or persistent flu like symptoms) or abnormal blood safety results as detailed in Section 8.2, Safety Assessments. The dose will be reduced according to the schedule in Table 2, and will not be increased again.

If symptoms or blood safety test result abnormalities persist and in the view of the Investigator are of sufficient severity, drug may be stopped. Where a patient will discontinue drug, refer to Section 6.7.4.2, Discontinuation Procedures.

<table>
<thead>
<tr>
<th>Initial dose 6MP (mg)</th>
<th>Reduced dose 6MP (mg)</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 alternate days*</td>
<td>Stop</td>
<td>100</td>
</tr>
<tr>
<td>50 daily</td>
<td>50 alternate days</td>
<td>50</td>
</tr>
<tr>
<td>50/100 alternate days</td>
<td>50 daily</td>
<td>33</td>
</tr>
<tr>
<td>100 daily</td>
<td>50 daily</td>
<td>50</td>
</tr>
<tr>
<td>150 daily</td>
<td>50/100 alternate days</td>
<td>50</td>
</tr>
<tr>
<td>200 daily*</td>
<td>100 daily</td>
<td>50</td>
</tr>
</tbody>
</table>

*There are unlikely to be many patients in these groups

The Investigator will not know if a patient is randomised to 6MP or placebo, therefore doses should be reduced regardless.

7.8 Patient Compliance

Patients will be asked to bring all used and unused study medication to the site at each study visit. For each patient, the number of tablets dispensed and returned or wasted/lost will be counted by the pharmacy, the nurse will be informed of the number and will record on the drug accountability log and on the eCRF.

7.9 Other Medications
7.9.1 Permitted Medications

Patients will be advised that they will be taken off all Crohn’s medication at time of consent. In routine clinical practice many patients will have already stopped these drugs at the time of their surgery, at the discretion of their surgeon.

Patients will be advised not to take any medication without approval from the Investigator.

Symptomatic treatment with antacids, anti-diarrhoeal agents, or spasmodic agents (e.g. loperamide and codeine phosphate) is allowed but must be carefully recorded for calculation of the Crohn’s Disease Activity Index.

It is anticipated that many patients will have had medium/long-term exposure to corticosteroids pre-operatively. If a patient is receiving prednisolone or equivalent at the time of study entry, the dose will be tapered at 5 mgs/week unless long term therapy necessitates a more gradual dose reduction to avoid adrenal suppression.

All permitted medications prescribed will have a marketing authorisation (MA) valid in the UK. Details of any permitted medications given will be recorded on the electronic CRF to ensure appropriate traceability of all medications prescribed.

7.9.2 Prohibited Medications

Initiation of the following drugs during the study is not allowed. Initiation of some of these medications will be defined as clinical recurrence of Crohn’s disease and the appropriate steps should be taken at this stage (refer to Section 6.7.4.2, Discontinuation Procedures). For further guidance please see Appendix 8.

All prohibited medications taken during the study will be recorded in the CRF with dose information and dates of administration.

- 5 ASAs
- corticosteroids (it is expected that patients may be on corticosteroids at entry. Doses will be tapered according to local protocols)
- anti-tumour necrosis factor
- azathioprine
- methotrexate
- allopurinol
- antibiotics for Crohn’s disease (for a duration of >10 days)
- oral non-steroidal anti-inflammatory drugs (for a duration of >7 days)

8. Study Assessments

8.1 Outcome Measures

Disease activity will be assessed by the Crohn’s Disease Activity Index (CDAI)\textsuperscript{30}. Disease recurrence will be defined as a CDAI value of greater than 150 together with a 100 point rise in the CDAI score (from baseline), together with the need for anti-inflammatory rescue therapy or primary surgical intervention.

The number of repeat ileocolonic resections to remove recurrent disease from the initial ileocolonic anastomosis will measure the frequency of further surgery.
Quality of life will be assessed by the validated indices IBDQ and SF-36\textsuperscript{31}.

Endoscopic recurrence has been seen to precede clinical recurrence\textsuperscript{7}. The endoscopic scoring system of Rutgeerts et al\textsuperscript{32} will be used to classify macroscopic changes seen at the ileocolonic anastomosis. Abnormal mucosa will be photographed. A histological index will be used to document the presence and activity of Crohn’s disease in mucosal biopsies.

### 8.2 Safety Assessments

Consistent with clinical practice across the study sites for treatment with 6MP, safety blood monitoring comprising a full blood count, liver function tests and urea and electrolytes will be performed regularly. Blood tests will be performed every week for the first 6 weeks followed by every 6 weeks (+/- 1 week) thereafter until the treatment period is completed or discontinued.

It may be impractical for many patients to visit study sites for all of these tests, therefore patients can attend their local GP practice for blood sampling – under shared care protocol.

Bloods will be sent to local Laboratories at each site. Results will be recorded according to local practice and SOPs at each site. A system will be set up at each site to ensure results are faxed direct to the Central Trial Office. In Lothian the Central Trial Office will have access to results via the hospital web based reporting system. The eCRF will be set up to alert the Central Trial Office of when results are expected and will flag up any that are overdue.

The procedure for safety blood monitoring is detailed below:

- Patients will be given pre-prepared blood forms for sampling at their local GP practice. This will cover all samples required between study visits and include an extra form in the event of a drug reaction.
- Bloods will be sent to local Laboratories at each site.
- Blood results will then be sent directly to the Edinburgh Clinical Trials Unit, Fax 0131 537 3851) from participating laboratories via designated person from each site.
- The Central Trial Office will load these results on to a database. The MCV will not be available to Investigators on this database to avoid unblinding.
- A nominated physician (Investigator) for the week will check these results three times a week (with patients being identified by a number only). A rota will identify the responsible physician each week during the study. Results outside the reference range will trigger an electronic reminder.
- The nominated physician will log onto the database and review each anonymised abnormal result. Outlying results will be highlighted and the appropriate action will be taken according to the 4 options as detailed below.

#### Option 1
No action required as not deemed to be a safety issue (Some abnormal results will be at the discretion of the Investigators as to whether they require any action.)

#### Option 2
Hb<10.0: E-mail local nurse to telephone patient and arrange for review and assessment by Investigator as would be done in routine clinical practice. Anaemia could be caused by a number of reasons so this should not affect the study blind.
Option 3
Total White Cell Count 2.5-3.5, or Neutrophil count between 1.0 and 2.0 or any LFT (except GGT) between >2 and 5 times the upper limit of normal or Platelet count between 50-100x10^9/l:
Email local nurse who will telephone patient to reduce dose. Ensure safety bloods are done within 1 week at local site. This should not affect the study blind.

Option 4
Total White Cell Count <2.5 or Neutrophil count <1.0 or Any LFT >x5 upper limit of normal or platelet count <50x10^6/l: Email and telephone local nurse who will telephone patient to discontinue the study drug, arrange for immediate patient review by Investigator and repeat bloods, at weekly intervals, until resolved. At the duty clinicians' discretion drug could be recommenced or the dose reduced [see Para 7.7 of Protocol Dose Reduction Schedule (Table 2)], if out of range values improve above the lower limits designated. Patient will continue as per protocol. Otherwise study drug would be stopped and patient should continue with scheduled visits but not take any more IMP. (The breaking of the study blind will only be performed where knowledge of the treatment is absolutely necessary for further management of the patient).

The Central Trial Office will track when blood results are planned for patients and will make contact with the patient if the results are not received as planned.

In the event of the following adverse events:

Abdominal pain
If the patient reports abdominal pain the Investigator can temporarily stop study drug and they should be reviewed as in normal clinical practice. If the Investigator suspects pancreatitis Amylase should be checked. If pancreatitis is diagnosed then study drug will be stopped permanently although patient can continue with the study visits. If not pancreatitis then study drug can be re-started. Study blind will only be broken if patient has pancreatitis.

Nausea, malaise, arthralgia, flu like illness
If patient reports nausea, malaise, arthralgia or flu like illness/symptoms then they should be reviewed by Investigator and assessed as they would be in normal routine clinical practice.

8.2.1 Clinical Chemistry
The following clinical chemistry assessments will be performed for safety blood monitoring:

- ALT
- Alkaline Phosphatase
- Gamma GT
- Albumin
- CRP
8.2.2 Haematology

The following haematological assessments will be performed for safety blood monitoring:
- Haemoglobin
- Total White Cell Count
- Neutrophil count
- Platelets
- Erythrocyte Sedimentation Rate
- Urea and electrolytes

8.3 Additional Blood Tests

8.3.1 Serological Studies

Blood will be obtained at Visit 2 (Week 0, Randomisation) for serological studies related to Crohn’s disease. These tests include ASCA, ANCA, anti-OmpC, anti-12 and anti-flagellin antibodies.

8.3.2 Genetic Studies

Blood will also be taken at Visit 2 (if consented) (Week 0) for DNA extraction to assess genetic determinants that may be important in Crohn’s disease and the recurrence of disease post-operatively.

8.3.3 6MP Metabolite Levels

Blood samples for assay of drug metabolite levels will be obtained at Visits 2, 4, 6, 9, and 12.

8.4 Stool Samples for Faecal Calprotectin

Stool samples will be collected for faecal calprotectin at Visits 2, 4, 6, 9 and 12 (Weeks 13, 49, 103 and 157).

8.5 Bowel Prep

Bowel Prep will be provided to the patient Prior to Visits 6 and 12. Each centre will use their normal standard prep but Fleet is not to be used.

8.6 Colonoscopy

At Visits 6 and 12 (Weeks 49 and 157), patients (other than patients who had small bowel operation) will undergo colonoscopic examination of the colon, anastomosis and neo-terminal ileum.

Potential complications from colonoscopy are bleeding (1 in 1000), perforation (1 in 1000), death (1 in 10,000), drug reaction, haematoma at site of IV cannulation, nausea and vomiting, abdominal distension and discomfort following the procedure and post procedure infection.

Consent will be obtained specifically for this procedure in accordance with NHS guidelines. The anastomosis will be examined and macroscopic changes assessed
according to the criteria of Rutgeerts et al (refer to Section 8.10.2). The rest of the colonic mucosa will also be assessed and scored according to the Crohn's disease endoscopic index of severity (CDEIS, refer to Section 8.10.3). Biopsies will also be taken for histological examination (refer to Section 8.10).

Laminated photographs of Rutgeert's scoring have been produced to standardise scoring and to minimise site variability. In addition procedures will be performed by nominated investigators at each site and images will be recorded, if possible, so that they can then be scored independently.

8.7 Patient Diaries

Patients will be asked to record stool frequency, abdominal pain and general well being in a trial diary for 7 days prior to each study visit to allow calculation of the CDAI. Patients will also be asked to begin to record this data if they notice a deterioration in their symptoms.

To prompt patients during study visits, the diaries will also contain a section to note concomitant medications and adverse events.

8.8 Physical Examination

A general physical examination will be performed at each study visit by the Investigator.

8.9 Medical History

A medical history and Crohn's history will be obtained at randomisation, paying particular attention to the time since diagnosis of Crohn's disease, duration, location, type, surgical history, medication history.

8.10 Activity Indices

8.10.1 Crohn's Disease Activity Index

The Crohn's disease activity index (CDAI) will be used to assess clinical disease activity at each study visit. A relapse is defined as a value of greater than 150 together with a 100-point rise in the score (from baseline). To satisfy the primary endpoint of the study this should be coupled with the need for anti-inflammatory therapy. The CDAI used in this study is shown below:

1. No. of liquid or very soft stools \[ \text{sum of seven days} \times 2 = \]

2. Abdominal pain rating \[ \text{sum of seven days} \times 5 = \]
   (0=none, 1=mild, 2=moderate, 3=severe)

3. General well being \[ \text{sum of seven days} \times 7 = \]
   (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)

4. Complications
   - Arthritis or arthralgia
   - Iritis or uveitis
   - Erythema nodosum or pyoderma gangrenosum
   - Anal fissure, fistula or abscess
   - Fever >37.8 in the last week
5. Use of loperamide, codeine or other anti-diarrhoeals
   No=0, yes=1  \( \times 30 = \)

6. Abdominal mass
   None=0, questionable=2, definite=5  \( \times 10 = \)

7. Haematocrit
   Males 47-crit, females 42-crit  \%  \( \times 6 = \)

8. Body weight = Standard weight = 1-BW/SW x100  \( \times 1 = \)

TOTAL SCORE =

8.10.2 Rutgeert’s Endoscopic Score of Post-Operative Recurrence

The Rutgeert’s criteria divide the macroscopic appearances of the ileocolonic anastomosis into 4 categories. Recurrence is defined as the presence of typical endoscopic features of Crohn’s disease in the neoterminal ileum and/or anastomosis. It is graded as follows:

- 0 – no lesions;
- 1 – less than five aphthous ulcers;
- 2 – more than five aphthous ulcers with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileo-colonic anastomatic lining (< 1 cm);
- 3 – diffuse aphthous ileitis with diffusely inflamed mucosa;
- 4 – diffuse ileal inflammation with larger ulcers, nodules or narrowing. Hyperaemia and oedema alone were not considered as signs of recurrence.

8.10.3 Crohn’s Disease Endoscopic Index of Severity

Appearances of the colonic mucosa will also be assessed using the Crohn’s disease endoscopic index of severity (CDEIS). This is shown in Table 3 below as described by Mary JY et al, Gut 1989;30:983-989.
For partially explored segments and for the ileum, the Ilocum linear scale represents the surface effectively explored.

<table>
<thead>
<tr>
<th>CDEIS</th>
<th>=</th>
<th>Total B + C + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total D</td>
<td>+</td>
<td>Quote 3 if non-ulcerated stenosis anywhere, 0 if not</td>
</tr>
<tr>
<td>Total C</td>
<td>+</td>
<td>Quote 3 if ulcerated stenosis anywhere, 0 if not</td>
</tr>
<tr>
<td>Total B</td>
<td>=</td>
<td>Total A divided by n</td>
</tr>
<tr>
<td>n</td>
<td>=</td>
<td>Number (n) of segments totally or partially explored (1-5)</td>
</tr>
<tr>
<td>Total A</td>
<td>=</td>
<td>Total 1 + Total 2 + Total 3 + Total 4</td>
</tr>
</tbody>
</table>

| Total 4 | = | + + + + |
| Surface involved by the disease measured in cm |
| Total 3 | = | + + + + |
| Surface involved by the disease measured in cm |
| Total 2 | = | + + + + |
| Absent |
| Total 1 | = | + + + + |
| Absent |
| Ileum | Right colon | Transverse and sigmoid |
| Right colon | Left colon |

Table 3: Crohn's Disease Endoscopic Index of Severity
Study assessments to be performed at each study visit are detailed in Table 4. Study visits to be carried out +/- 10 days.

8.14 Study Visits

8.13 EQ-5D

The Informational Bowel Disease Quality of Life Questionnaire (IBD-Q), Full versions of the IBD-Q are given in Appendix 2.

At visits 2, 4, 6, 9 and 12 (weeks 0, 13, 49, 103 and 157). EQ-5D will be used to measure health outcome and for cost-effectiveness.

8.12 Quality of Life Scores

For blinded assessment.

Histopathologies (as would be done in normal clinical practice) subsequent to the end of the trial, they will be sent to a central laboratory for histopathology (as would be done in normal clinical practice). Subsequently (at the end of the trial) they will be sent to a central laboratory. They will be stored and examined by the local histopathologist. Biopsies will be taken at the time of colonoscopy at visits 6 and 12 (weeks 49 and 157). At least two samples will be taken from the area of

8.11 Histological Assessment

03 October 2013

Page 28
<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Specimen Selected</th>
<th>Laboratory</th>
<th>Investigator</th>
<th>Consent Form</th>
<th>Study Visit</th>
<th>Contact Information</th>
<th>Randomization</th>
<th>Visit Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>6</td>
<td>6</td>
<td>0</td>
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</tr>
<tr>
<td>11</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>10</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>9</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>3</td>
<td>4</td>
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<td>8</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>3</td>
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<td>-1</td>
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<tr>
<td>7</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>6</td>
<td>5</td>
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<td>-1</td>
</tr>
<tr>
<td>6</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>6</td>
<td>6</td>
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<td>0</td>
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<td>5</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>-1</td>
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<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>3</td>
<td>2</td>
<td>-1</td>
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<td>2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>6</td>
<td>5</td>
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<td>1</td>
<td>x</td>
<td>x</td>
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<td>0</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>-1</td>
</tr>
</tbody>
</table>

Table 4: Study Assessments
8.14.1 Baseline Assessments

Inpatient pre-assessment (Visit -1)
Following signature of the Screening consent form, the following screening procedures will be carried out:

- TPMT
- Stool Sample

Safety Visit (Visit 1)

Patients will be invited for Visit 1 (1-7 days prior to randomisation) when safety bloods will be collected. Patients will be given the opportunity to discuss the study and to ask any questions.

Randomisation and drug prescription (Visit 2)

Following discharge, patients will return to a designated clinic run by the Investigator and research nurse. In the absence of surgical complications, a negative pregnancy test or fulfilment of exclusion criteria, patients will be randomised to 6MP or placebo.

Prior to randomisation and drug prescription, the following assessments will be performed:

- Pregnancy Test
- Medical history, including history of Crohn’s disease (duration, location, type, surgical history, medication history)
- CDAI (Diary to be completed by patient 7 days prior to this visit)
- Height and weight
- Physical examination including vital signs
- 6MP metabolite levels
- Concomitant medications
- Patient to complete IBDQ, SF36 and EQ-5D Questionnaires
- Genetic studies
- Serological studies
- Faecal Calprotectin

Following randomisation, blinded study drug will be dispensed by the site pharmacy.

Appropriate safety blood monitoring will be arranged via the patient’s general practitioner every week for the first 6 weeks and a follow up clinic appointment will be arranged. Or the patient can attend clinic and the Research Nurse will take the safety bloods.

8.14.2 Treatment Period Assessments

Interim safety assessment (Visit 3, Week 6)

Patients will return 6 weeks following drug commencement for Visit 3. The following assessments will be performed:

- CDAI (Diary to be completed by patient 7 days prior to this visit)
- Weight
- Physical examination including vital signs
- Review and record adverse events
- Blood safety monitoring
- Concomitant medications

**Study visit 4, Week 13**

Patients will then return 7 weeks later for the first full study visit where the study endpoints will be formally assessed. The following assessments will be performed:

- CDAI (Diary to be completed by patient 7 days prior to this visit)
- Weight
- Physical examination including vital signs
- Review and record adverse events
- Blood safety monitoring
- 6MP metabolite levels
- Faecal calprotectin
- Patient to complete IBDQ, SF36 and EQ-5D Questionnaires
- Concomitant medications

**Study visits 5-12, Weeks 31-157**

Patients will then be assessed 3 times a year for safety and efficacy.

When the visit includes a colonoscopy, it will take place at the same time and the CDAI will be calculated for the 7 days prior to starting the bowel preparation. Faecal calprotectin sample will be obtained prior to commencing bowel prep.

The following assessments will be performed at each visit:

- CDAI (Diary to be completed by patient 7 days prior to this visit)
- Weight
- Physical examination including vital signs
- Review and record adverse events
- Blood safety monitoring

- Concomitant medications
- Faecal calprotectin at Visits 6, 9 and 12 (Weeks 49, 103 and 157)
- Patient to complete IBDQ, SF36 and EQ-5D Questionnaires at Visits 6, 9 and 12 (Weeks 49, 103 and 157)
- Colonoscopy at Visits 6 and 12 (Weeks 49 and 157)
- 6-MP Metabolite Levels at Visits 6, 9 and 12 (Weeks 49, 103 and 157)

**8.14.3 Additional Visits**

Additional visits will be arranged following an adverse event or safety blood message as detailed in Paragraph 8.2.

In the event of a clinical relapse the patient will contact the study nurse, complete a CDAI diary card and be reviewed in the clinic within the next 7 days.

At this visit the following procedures will be undertaken

- CDAI
- Weight
- Physical examination including vital signs
- Review and record adverse events
- Blood safety monitoring
- 6MP metabolite levels
- Faecal calprotectin
- Concomitant medications
- Colonoscopy arranged, if appropriate
- Treatment instigated as thought appropriate by the Investigator.

8.14.4 Early Withdrawal

An early withdrawal visit should be carried out and recorded in the hospital notes and on the eCRF if the subject does not wish to or cannot continue to participate in the trial.

It should be undertaken after any of the following occurs at a scheduled or additional visit.

1. Primary Endpoint is reached, study drug has been stopped and the patient no longer wishes to continue the scheduled visits.
2. Study Drug has been stopped due to a clinical decision by the Investigator e.g., prohibited med or rescue therapy has been commenced and the patient no longer wishes to continue the scheduled visits.
3. Study Drug has been stopped due to an adverse event and the patient no longer wishes to continue the scheduled visits.
4. Study Drug has been stopped due to blood results and the patient no longer wishes to continue the scheduled visits.
5. Declines to continue with any further visits and wishes no further participation in the TOPPIC trial.
6. Any other reason that patient cannot or does not wish to attend.

If the subject has been lost to follow up and has not completed the trial an early withdrawal visit should be completed wherever possible but may be carried out on the scheduled visit 12 date.

Please see Section 11.3 (Pharmacovigilance) with regard to Adverse Events following early withdrawal.

At the early withdrawal visit the following procedures should be undertaken (if appropriate).

- CDAI
- Pregnancy record
- Weight
- Physical examination including vital signs
- Review and record adverse events
- Blood safety monitoring
- 6MP metabolite level
- Faecal calprotectin
- Concomitant medications
- Final drug accountability
- Colonoscopy arranged, if appropriate

Future treatment instigated as thought appropriate by the Investigator
9. Statistical Analysis

9.1 Proposed analyses

The primary outcome variable is postoperative recurrence of Crohn's Disease and it's timing if it recurs. Analysis will be by intention-to-treat and will be based on the application of Cox proportional hazards model. The primary analysis will include terms for the treatment and the variables on which the randomisation was stratified.

The quality of life variables will be analysed using a repeated measures analysis of covariance to evaluate treatment and treatment by time interactions.

The use of faecal calprotectin as a non-invasive marker of disease recurrence will be examined in two ways. It will be firstly considered as a time dependent covariate in the Cox proportional hazards model described above. Secondly, levels will be compared descriptively between those with negative or positive colonoscopies at 12 and 36 months. Similarly, 6MP drug metabolite levels will be also considered as a time dependant covariate in the Cox proportional hazards model.

Exploratory analyses will investigate the inclusion of the clinical, genetic and serological markers in the model. The models will be used to develop a simple scoring system to predict the risk of recurrence. The sample size will be too small to use a split sample approach to validate the prediction, but the use of a simple scoring system will mitigate to some degree the more extreme effects of using observed regression coefficients to define the risk. During the period after trial recruitment, data from new patients will provide limited short-term validation of the predictions.

The ways in which these data will be displayed in the final report are illustrated in Appendix 3.

9.2 Sample Size Calculation

A study population of 182 evaluable patients has an 80% power to detect a reduction in the frequency of recurrence from 50% in the placebo group to 30% in the treatment arm by 3 years at the 5% level of significance. Accurate data from surgical and pathology databases at the recruiting sites have demonstrated that this is an achievable target. A total of 130 ileocolonic resections are performed each year at the recruiting sites. We estimate that we could recruit 60% of the potential patients giving a sample population of 234 patients. In order to be conservative we have allowed for a 15% dropout rate. This would leave an evaluable population of 200 patients over 3 years.

These figures are based on an intention to treat analysis, with the number needed to treat in order to prevent one recurrence predicted to be five. It is notable that the treatment effect of 20% is lower than previously conducted studies (Hanauer et al 40% and 75%), (Ardizzzone et al 25%). We also judge a treatment effect of 20% appropriate because given the side effect profile of 6MP, it is arguable that a treatment effect of significantly less than 20% is of limited clinical significance.
10. **Trial Management and Oversight Arrangements**

10.1 **The Project Management Group**

The trial will be coordinated by a Project Management Group, consisting of the grantholders (Chief Investigator and Principal Investigator in Edinburgh), the Trial Manager (located in the Edinburgh Clinical Trials Unit) and coordinating nurse (based in Edinburgh).

10.2 **Trial Management**

The Trial Manager will oversee the study and will be accountable to the Chief Investigator and MRC. Following completion of the study, the Trial Manager and coordinating nurse will check the CRFs for completeness, plausibility and consistency, queries will be resolved by the Investigator.

Each site will have a Principal Investigator and research nurse time. The central coordinating nurse will support the local research nurses.

A List of Trial Related Duties will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

10.3 **Central Trial Office**

The Central Trial Office is based in the Edinburgh Clinical Trials Unit and will provide support to each site. The office will be responsible for randomisation, collection of data in collaboration with the research nurses, data processing and analysis.

Publication and dissemination of the study results will be coordinated by the Central Trial Office in collaboration with the Chief Investigator and Investigators.

10.4 **Trial Steering Committee**

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in Appendix 4.

10.5 **Data Monitoring Committee**

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of subjects in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in Appendix 5.

10.6 **Inspection of Records**

Principal Investigators and institutions involved in the study will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation.

10.7. **Study Monitoring and Audit**

An ACCORD Clinical Trials Monitor or designee will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring
plan if required. Investigator sites will be risk assessed by the ACCORD QA Manager, or designee, in order to determine if audit by the ACCORD QA group is required.

10.8 Risk Assessment

An independent risk assessment has been performed by an ACCORD Clinical Trials Monitor to determine the monitoring plan which will be followed by an ACCORD Clinical Trials Monitor or designee. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

10.8.1 Potential Risks

10.8.2 6MP

See Summary of Product Characteristics in Appendix 1.

10.8.3 Colonoscopy

There is a risk of perforation needing surgery (1/1000), gastrointestinal haemorrhage, patient discomfort and AEs related to the sedative given for the procedure.

10.8.4 Crohn’s Disease

Complications of Crohn’s disease may lead to further surgery, hospitalisation, infection and death.

10.8.5 Minimising Risk

The pre-treatment assessment of TPMT will identify if any individuals are TPMT deficient. Drug will not be given to these individuals. If there are low levels of TPMT activity then a lower starting dose will be used (the same for placebo and active treatment). The comprehensive monitoring of therapy will identify any adverse events and treatment will be altered accordingly.

Experienced endoscopists who are accredited to perform the procedures will perform all colonoscopies hence minimising the risk of procedural complications.
11. Good Clinical Practice Module

11.1 Ethical Conduct of the Study

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

11.2 Investigator Responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on the List of Trial Related Duties and signed by all those named on the list.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a patient to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Patients must receive adequate oral and written information – appropriate Patient Information and Informed Consent Forms will be provided. The oral explanation to the patient will be performed by the Investigator or designated person, and will cover all the elements specified in the Patient Information Sheet/Informed Consent.

The patient must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The patient must be given sufficient time to consider the information provided. It must be emphasised that the patient may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The patient should be informed and agree to their medical records being inspected by regulatory authorities but understand that their name will not be disclosed outside the hospital.

The Investigator (or authorised delegate) and the patient will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The patient will receive a copy of this document.

11.2.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and its requirements. It is the Investigator’s responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

11.2.3 Data Recording

The Investigator is ultimately responsible for the quality of the data recorded in the CRF.
11.2.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the Clinical Trial Office, including but not limited to:

- An original signed Investigator’s Statement page of the protocol;
- Curriculum vitae (CV), signed and dated by the Investigator indicating that it is accurate and current.

The Clinical Trial Office will ensure all other documents required by ICH GCP are retained in a Trial Master File and that appropriate documentation is available in local Site Files.

11.2.5 GCP Training

All study staff will undergo GCP training which will be updated every two years throughout the trial.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. The Principal Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. Access to collated patient data will be restricted to those clinicians treating the patients.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual patients.

12. Pharmacovigilance

12.1 Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. This responsibility may be delegated to a member of the research team. Assessment of events may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting adverse events (AEs).
Investigational Medicinal Product (IMP) is defined as any active substance or placebo being studied or used as a reference in the trial. This section also applies to medicinal products that are not the active substance or placebo, but are used as a concomitant medication to the IMP or as a rescue/escape medicine for preventative, diagnostic or therapeutic reasons. These are referred to as non Investigational Medicinal Products (NIMPs).

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC) in Appendix 1. For updated version of the Summary of Product Characteristics please see the electronic Medicines Compendium (eMC) website:

http://www.medicines.org.uk/EMC/medicine/24688/SPC/MERCAPTOPURINE+50+mg+Tablets/

Participants should be instructed to contact their Investigator or local nurse at any time after consenting to join the trial if any symptoms develop. All AEs that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

Participants with AEs present once the primary endpoint has been reached or the study drug has been stopped will be followed up at 30 days following the withdrawal visit.

12.2 Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An adverse reaction (AR) is any untoward or unintended response to an IMP which is related to any dose administered to that participant.

An unexpected adverse reaction (UR) is an adverse reaction that is not consistent with the applicable product information for the IMP, e.g. the Investigator Brochure (IB) for a non licensed IMP or the SmPC for a licensed product.

A serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is any AE, AR or UR that at any dose:

- results in death;
- is life threatening (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs.
12.3 Detecting AEs and SAEs

All AEs and SAEs must be recorded from the time a participant is consented to participate in the trial until the last study visit.

The Investigator or local nurse should ask about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant should be used to enquire about AE/SAE occurrence. Participants should also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded. Symptoms of Crohn's disease will not be classified as AEs if they are within the normal day-to-day fluctuations or expected progression of the disease. Significant worsening of the symptoms should be recorded as an AE.

AEs and SAEs may also be identified by support departments e.g. laboratories.

Symptoms of Crohn's disease will not be classified as AEs if they are within the normal day-to-day fluctuations or expected progression of the disease. Significant worsening of the symptoms should be recorded as an AE.

12.4 Recording AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The nurse should then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

12.5 Assessment of AEs and SAEs

Seriousness, causality, severity and expectedness should be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) should be unblinded.

The Investigator is responsible for assessing each AE. This may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

12.5.1 Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 12.2.

12.5.2 Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.
All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the IMP will be considered as related to the IMP (ARs/SARs).

Where non Investigational Medicinal Products (NIMPs) e.g. concomitant or rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR/SAR.

Unrelated: where an event is not considered to be related to the IMP.

Possibly: although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.

Definitely: The known effects of the IMP or its therapeutic class, or based on challenge testing, suggest that the IMP is the most likely cause.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

### 12.5.3 Assessment of Severity

The Investigator should make an assessment of severity for each AE/SAE and record this on the CRF or AE form according to one of the following categories:

**Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

**Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe**: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

### 12.5.4 Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event should be classed as either:

**Expected**: the AR is consistent with the toxicity of the IMP listed in the SmPC or IB.

**Unexpected**: the AR is not consistent with the toxicity in the SmPC or the IB.

### 12.6 Reporting SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the ACCORD Research Governance & QA Office within 24 hours. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator or designee. If the Investigator does not have all information
regarding an SAE, they should not wait for this additional information before notifying ACCORD. The form can be updated when the additional information is received.

The SAE report must provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

The SAE form should be transmitted by fax to ACCORD on +44 (0)131 242 9447 or may be transmitted by hand to the office.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information until this is supplied.

All SAE, SAR and SUSAR reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

12.7 Regulatory Reporting Requirements

The ACCORD Research Governance & QA Office is responsible for Pharmacovigilance reporting on behalf of the Co-Sponsors (Edinburgh University and Lothian Health Board).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (main Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report will be submitted to the regulatory competent authority and main REC listing all SARs and SUSARs.

12.8 Reporting SAEs/SARs/SUSARs to Trial Steering Committee and Data Monitoring Committee

SUSARs will be reported to the Trial Steering Committee and Data Monitoring Committee within the same timelines as for Regulatory reporting (see section 12.7).

SAEs/SARs

A copy of each report will be sent to the Data Monitoring Committee, and a list will be sent annually to the Trial Steering Committee.

12.9 Follow up Procedures

After initially recording an AE or recording and reporting an SAE, the Investigator is required to follow each participant until resolution or death of the participant. Follow up information on an SAE should be reported to ACCORD.

AEs still present in participants at the last study visit should be monitored until resolution of the event or until no longer medically indicated.
13. Pregnancy

13.1 Background

At the present time it is regarded as standard practice in the United Kingdom, Europe and North America to continue Azathioprine or Mercaptopurine use in patients of child bearing age, and indeed in pregnancy, following discussion with the patients involved. In any individual patient, the risks of under treated Crohn’s disease and its complications are weighed up against the concerns regarding Azathioprine or Mercaptopurine.

The guidelines for the management of inflammatory bowel disease in adults were published by the British Society of Gastroenterology in 2004 (Carter MJ et al. Gut 2004;53 Suppl V:V1-16.). These state “Azathioprine should in general be continued during pregnancy as the risks to the foetus from disease activity appear to be greater than continued therapy. Babies born to mothers on Azathioprine may be lighter than normal and the risk benefit ratio should be discussed with patients (grade B)”.

The European Crohn’s Colitis Organisation (ECCO) published guidelines in 2006 (Gut 2006;55;Suppl 1:i16-i35;doi:10.1136/gut.2005.081950b. The ECCO guidelines state that Thiopurines can reasonably continue during pregnancy if CD has been refractory. The guidelines highlight as a pivotal study the data from the Mount Sinai Hospital Medical Centre in New York Francellia A, Gastroenterology 2003;124:9-17). In this study the records of 485 patients who received Thiopurines were reviewed. Of these 155 patients had conceived at least one pregnancy after developing inflammatory bowel disease. In detailed analysis there was no statistical difference in conception failures, congenital abnormalities, neoplasia or infection rates.

The University of Toronto group have also presented data (American Journal of Gastroenterology 2005;100:1897-8). In 113 female patients with 207 conceptions, none of the drugs used to treat inflammatory bowel disease was reported associated with poor pregnancy outcomes.

Therefore there does appear to be a general consensus in Europe, and in North America that there is a strong rationale to continue these drugs during pregnancy, to avoid severe relapse of Crohn’s disease and associated complications.

In the only contradictory studies in the current literature, Danish investigators have suggested an increased risk of pre-term and anomalies (Nørgård B, Am J Gastroenterol. 2007;102:1406-13). However, the authors themselves concede that the precision of risk estimates is contentious in their own study. Most importantly the authors express the view that it is impossible to differentiate between the effect of the drug and of poorly controlled disease (requiring immunosuppression) in these outcomes. The accompanying editorial also strongly makes the point that the Danish data are difficult, if not impossible to interpret, as disease activity was not appropriately assessed in the study (Friedman S. Am J Gastroenterol 2007 Jul;102(7):1414-6).

In clinical practice in the United Kingdom, North America, and in Europe, a consensus supports the continuing use of these drugs in patients of childbearing age, without the need for contraception. The data also support the fact that the drug may be used in women during pregnancy, after informed discussion between the patient and physician of risks and benefits.
At consent all patients will be informed that:
i) According to the Summary of Product Characteristics 6-MP is potentially teratogenic but in any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.
ii) Current standard clinical practice in the UK, Europe and North America is now to continue 6-MP use in patients of child bearing age, and indeed during pregnancy.

Safety of Patients of Childbearing Age

Options for Patients and Investigators:
a) Not enter trial;
b) Adequate contraceptive precautions should be advised if either patient or their partner is receiving 6-MP or placebo;
c) Should they or their partners become pregnant, counselling will be provided.

Safety of Patients During Pregnancy

Patients who do become or whose partners become pregnant during the trial will be counselled on the risks of under treated Crohn’s disease and its complications will be weighed up against the concerns regarding 6-MP and the unborn foetus.

Options:
a) Continue in the trial, if they wish, with steps taken to ensure patient remains closely monitored, but would be unable to breastfeed;
b) Withdraw from the trial.

The rights, safety and well-being of the patients are paramount.

13.2 Pregnancy Reporting

Pregnancy is not considered an AE or SAE, however, the Investigator must collect pregnancy information for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator should record the information on a Pregnancy Notification Form and submit this to ACCORD within 14 days of being made aware of the pregnancy.

All pregnant female participants and partners of male participants should be followed up until following the birth or otherwise (i.e. spontaneous termination) to allow information on the status of the mother and child to be reported to ACCORD.

14. Study Conduct Responsibilities

14.1 Protocol Amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Chief Investigator. Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authorities and local R&D for approval prior to patients being enrolled into an amended protocol.

14.2 Protocol Violations and Deviations

The Investigator or designee must document and explain in the patient’s medical record any deviation from the approved protocol or GCP.
Deviations
A deviation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial that does not result in harm to the trial participants or significantly affect the scientific value of the trial data.

Violations
A violation is any departure from the approved protocol, trial documents or any other information relating to the conduct of the trial which may affect the safety or physical or mental integrity of the trial participants or the scientific value of the trial data.

A log of deviations, violations and urgent safety measures must be maintained and reported as necessary. A Deviation/Violation Form must be completed to assess if the departure is a deviation or a violation. If a departure is assessed as a violation, a copy of the Deviation/Violation Form must be submitted to the sponsor within 3 days of becoming aware of the violation.

Urgent Safety Measure
The Investigator may implement a deviation from, or a change to the protocol to eliminate an immediate hazard to trial patients without prior approval from the REC, Regulatory Authority or local R&D departments. This is defined as an urgent safety measure and must be reported to the sponsor, REC, Regulatory Authority and local NHS R&D department(s) immediately after implementing the measure.

The Investigator must then notify the sponsor, REC, Regulatory Authority and local NHS R&D department(s) in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

14.3 Study Record Retention
All study documentation will be kept for 20 years according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

14.4 End of Study
The end of study is defined as the last patient last visit.

The Investigators and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and MHRA within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform patients and ensure that the appropriate follow up is arranged for all involved.

A summary report of the study will be provided to the REC and MHRA within 1 year of the end of the study.

A final report will be submitted to the MRC at the end of the grant.

14.5 Continuation of Drug Following End of Study
Recruitment is over a 4.5 year period, followed by up to a 3 year treatment period for each patient. Patients will be informed that a summary of results will be published on the Edinburgh Clinical Trials Unit website and patients can find out if they were taking 6-MP or the placebo.

A previous study has shown that the effects of the drug wear off after 4 years, suggesting that there is little point in taking it for longer than 4 years. However, patients can discuss the possibility of continuing with active treatment with the Investigator if they wish.

15. Reporting, Publications and Notification of Results

15.1 Authorship Policy

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion) and will be published on the Edinburgh Clinical Trials Unit website.

15.3 Peer Review

The MRC procedures for peer-review of the trial are detailed in the MRC Guidelines for Good Clinical Practice in Clinical Trials 1998 (currently under review).

The results of the study will be disseminated by peer review publication and presentation at national and international meetings.

16. References

(12) Korelitz BI. Gastroenterology 1990;A1011.
APPENDIX 1: SUMMARY OF PRODUCT CHARACTERISTICS

For updated version of the Summary of Product Characteristics please see the electronic Medicines Compendium (eMC) website:

http://www.medicines.org.uk/EMC/medicine/24688/SPC/MERCAPTOPURINE+50+mg+Tablets/

Mercaptopurine 50 mg tablets

1. Name of Medicinal Product

Mercaptopurine® 50 mg tablets

2. Qualitative and Quantitative Composition

Each tablet contains 50 mg of 6-mercaptopurine.
For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Tablets

Pale yellow, round tablets, biconvex, scored on one side, engraved GX above the score and EX2 below the score and plain on the other side

4. Clinical Particulars

4.1 Therapeutic indications

Cytotoxic agent

Mercaptopurine is indicated for the treatment of acute leukaemia. It may be utilised in remission induction and it is particularly indicated for maintenance therapy in: acute lymphoblastic leukaemia; acute myelogenous leukaemia. Mercaptopurine may be used in the treatment of chronic granulocytic leukaemia

4.2 Posology and method of administration

For oral administration

Dosage in adults and children:

For adults and children the usual starting dose is 2.5 mg/kg bodyweight per day, or 50-75 mg/m² body surface area per day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with Mercaptopurine.

The dosage should be carefully adjusted to suit the individual patient.

Mercaptopurine has been used in various combination therapy schedules for acute leukaemia and the literature should be consulted for details.

Dosage in the elderly:
No specific studies have been carried out in the elderly. However, it is advisable to monitor renal and hepatic function in these patients, and if there is any impairment, consideration should be given to reducing the Mercaptopurine dosage.

**Dosage in renal impairment:**

Consideration should be given to reducing the dosage in patients with impaired renal function.

**Dosage in hepatic function:**

Consideration should be given to reducing the dosage in patients with impaired hepatic function.

**In general:**

When Zyloric (allopurinol) and 6-mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of 6-mercaptopurine is given since Zyloric (allopurinol) decreases the rate of catabolism of 6-mercaptopurine.

4.3 Contraindications

Hypersensitivity to any component of the preparation.

In view of the seriousness of the indications there are no other absolute contraindications.

4.4 Special warnings and precautions for use

Mercaptopurine is an active cytotoxic agent for use only under the direction of physicians experienced in the administration of such agents.

**Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.**

Safe handling of Mercaptopurine Tablets:

See section 6.6 Instructions for Use/Handling

Monitoring:

Treatment with Mercaptopurine causes bone marrow suppression leading to leucopenia and thrombocytopenia and, less frequently, to anaemia. Full blood counts must be taken daily during remission induction and careful monitoring of haematological parameters should be conducted during maintenance therapy.

The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in the counts, treatment should be interrupted immediately.

Bone marrow suppression is reversible if Mercaptopurine is withdrawn early enough.
During remission induction in acute myelogenous leukaemia the patient may frequently have to survive a period of relative bone marrow aplasia and it is important that adequate supportive facilities are available.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of 6-mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with Mercaptopurine. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfazalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine in combination with other cytotoxics (see Section 4.8 Undesirable Effects). Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.

Mercaptopurine is hepatotoxic and liver function tests should be monitored weekly during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. The patient should be instructed to discontinue Mercaptopurine immediately if jaundice becomes apparent.

During remission induction when rapid cell lysis is occurring, uric acid levels in blood and urine should be monitored as hyperuricaemia and/or hyperuricosuria may develop, with the risk of uric acid nephropathy.

Cross resistance usually exists between 6-mercaptopurine and 6-tioguanine.

The dosage of 6-mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression.

Mutagenicity and carcinogenicity:

Increases in chromosomal aberrations were observed in the peripheral lymphocytes of leukaemic patients, in a hypernephroma patient who received an unstated dose of 6-mercaptopurine and in patients with chronic renal disease treated at doses of 0.4 – 1.0 mg/kg/day.

In view of its action on cellular deoxyribonucleic acid (DNA) 6-mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

Two cases have been documented of the occurrence of acute nonlymphatic leukaemia in patients who received 6-mercaptopurine, in combination with other drugs, for non-neoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with 6-mercaptopurine and later developed acute nonlymphatic leukaemia, but it is not clear whether this was part of the natural history of the disease or if the 6-mercaptopurine played a causative role.

A patient with Hodgkins Disease treated with 6-mercaptopurine and multiple additional cytotoxic agents developed acute myelogenous leukaemia.
Twelve and a half years after 6-mercaptopurine treatment for myasthenia gravis a female patient developed chronic myeloid leukaemia.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease (IBD) population have been received when 6-mercaptopurine is used (an unlicensed indication) in combination with anti-TNF agents (see section 4.8 Undesirable Effects).

4.5 Interaction with other medicinal products and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see Section 4.4 Special Warnings and Precautions for Use).

When Zyloprim (allopurinol) and Mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of Mercaptopurine is given since Zyloprim decreases the rate of catabolism of Mercaptopurine.

Inhibition of the anticoagulant effect of warfarin, when given with Mercaptopurine, has been reported.

As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent Mercaptopurine therapy (see Section 4.4 Special Warnings and Precautions for Use).

4.6 Pregnancy and lactation

Pregnancy:

6-mercaptopurine is potentially teratogenic. The use of Mercaptopurineshould be avoided whenever possible during pregnancy. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving Mercaptopurinetablets.

Maternal Exposure:

Studies of 6-mercaptopurine in animals have shown reproductive toxicity (see Section 5.3 Preclinical Safety Data). The potential risk for humans is unclear.

Normal offspring have been born after mercaptopurine therapy administered as a single chemotherapy agent during human pregnancy. Abortions and prematurity have been reported after maternal exposure. Multiple congenital abnormalities have been reported following maternal 6-mercaptopurine treatment in combination with other chemotherapy agents.

Paternal Exposure:

Congenital abnormalities and spontaneous abortion have been reported after paternal exposure to 6-mercaptopurine.

Effects on fertility:
The effect of Mercaptopurinetherapy on human fertility is largely unknown but there are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence. Transient profound oligospermia was observed in a young man who received 6-mercaptopurine 150 mg/day plus prednisone 80 mg/day for acute leukaemia. Two years after cessation of the chemotherapy, he had a normal sperm count and he fathered a normal child.

Lactation:
6-Mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with azathioprine, a pro-drug of 6-mercaptopurine and thus mothers receiving Mercaptopurineshould not breast-feed.

4.7 Effects on ability to drive and use machines

There are no data on the effect of 6-mercaptopurine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

4.8 Undesirable effects

For mercaptopurine there is a lack of modern clinical documentation which can serve as support for accurately determining the frequency of undesirable effects.

The following convention has been utilised for the classification of undesirable effects:- Very common ≥1/10, common ≥1/100, < 1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

**Neoplasms benign, malignant and unspecified (including cysts and polyps)**

Very Rare; secondary leukaemia and myelodysplasia (see Section 4.4 Special Warnings and Precautions for Use); hepatosplenic T-cell lymphoma in patients with IBD (an unlicensed indication) when used in combination with anti-TNF agents (see Section 4.4 Special Warnings and Precautions for Use).

**Blood and lymphatic system disorders**

Very common  Bone marrow suppression; leucopenia and thrombocytopenia.

The main side effect of treatment with 6-mercaptopurine is bone marrow suppression leading to leucopenia and thrombocytopenia.

Uncommon  anaemia

**Immune system disorders**

Hypersensitivity reactions with the following manifestations have been reported:

Rare:  Arthralgia; skin rash; drug fever

Very Rare:  Facial oedema

**Metabolism and nutrition disorders**

Uncommon  Anorexia

**Gastrointestinal disorders**
Common  Nausea; vomiting; pancreatitis in the IBD population* (an unlicenced indication)
Rare    Oral ulceration; pancreatitis (in the licensed indications)
Very rare    Intestinal ulceration

**Hepato-biliary disorders**
Common    Biliary stasis; hepatotoxicity
Rare    Hepatic necrosis

6-mercaptopurine is hepatotoxic in animals and man. The histological findings in man have shown hepatic necrosis and biliary stasis.

The incidence of hepatotoxicity varies considerably and can occur with any dose but more frequently when the recommended dose of 2.5 mg/kg bodyweight daily or 75 mg/m² body surface area per day is exceeded.

Monitoring of liver function tests may allow early detection of hepatotoxicity. This is usually reversible if 6-mercaptopurine therapy is stopped soon enough but fatal liver damage has occurred.

**Skin and subcutaneous tissue disorders**
Rare    Alopecia

**Reproductive system and breast disorders**
Very Rare    Transient oligospermia

4.9 Overdose

**Symptoms and signs:**

Gastrointestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of overdosage having occurred. The principal toxic effect is on the bone marrow, resulting in myelosuppression. Haematological toxicity is likely to be more profound with chronic overdosage than with a single ingestion of Mercaptopurine. Liver dysfunction and gastroenteritis may also occur.

The risk of overdosage is also increased when Zyloric is being given concomitantly with Mercaptopurine (see Section 4.5 Interactions with other Medicaments and other forms of Interaction).

**Management:**

As there is no known antidote the blood picture should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of 6-mercaptopurine overdose unless the procedure can be undertaken within 60 minutes of ingestion.

Further management should be as clinically indicated or as recommended by the national poisons centre.
5. Pharmacological Properties

5.1 Pharmacodynamic properties

ATC Code: L01BB02

Pharmacotherapeutic group:

6-Mercaptopurine is sulphhydryl analogue of the purine base hypoxanthine and acts as a cytotoxic antimetabolite.

Mode of Action:

6-Mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thio guanine nucleotides for cytotoxicity. The 6-mercaptopurine metabolites inhibit de novo purine synthesis and purine nucleotide interconversions. The thio guanine nucleotides are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the drug.

5.2 Pharmacokinetic properties

The bioavailability of oral 6-mercaptopurine shows considerable inter-individual variability, which probably results from its first-pass metabolism (when administered orally at a dosage of 75 mg/m² to 7 paediatric patients, the bioavailability averaged 16% of the administered dose, with a range of 5 to 37%).

The elimination half-life of 6-mercaptopurine is 90 ± 30 minutes, but the active metabolites have a longer half-life (approximately 5 hours) than the parent drug. The apparent body clearance is 4832 ± 2562 ml/min/m². There is low entry of 6-mercaptopurine into the cerebrospinal fluid.

The main method of elimination for 6-mercaptopurine is by metabolic alteration. The kidneys eliminate approximately 7% of 6-mercaptopurine unaltered within 12 hours of the drug being administered. Xanthine oxidase is the main catabolic enzyme of 6-mercaptopurine and it converts the drug into the inactive metabolite, 6-thiouric acid. This is excreted in the urine.

5.3 Preclinical safety data

6-Mercaptopurine, in common with other antimetabolites, is potentially mutagenic in man and chromosome damage has been reported in mice, rats and man.

Teratogenicity

6-Mercaptopurine causes embryolethality and severe teratogenic effects in the mouse, rat, hamster and rabbit at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and the type of malformations are dependent on the dose and stage of the gestation at the time of administration.

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose
Maize Starch
Hydrolysed Starch
Stearic Acid
Magnesium Stearate
Purified Water

6.2 Incompatibilities
None known

6.3 Shelf life
60 months

6.4 Special precautions for storage
Store below 25°C. Keep the bottle tightly closed.

6.5 Nature and contents of container
Amber glass bottles with child resistant high density polyethylene closures with induction heat seal liners.
Pack size: 25 tablets

6.6 Special precautions for disposal and other handling
Safe handling and disposal:
It is recommended that 6-mercaptopurine tablets should be handled following the prevailing local recommendations and/or regulations for the handling and disposal of cytotoxic drugs.

Administrative Data

7. Marketing Authorisation Holder
Aspen Pharma Trading Limited
12/13 Exchange Place
I.F.S.C
Dublin 1, Ireland

8. Marketing authorisation number(s)
PL 39699/0047

9. Date of first authorisation/renewal of the Authorisation
29 August 2006

10. Date of revision of the text
October 2012
11. Legal Status
POM

APPENDIX 2: QUALITY OF LIFE ASSESSMENTS, SF-36, EQ-5D
APPENDIX 4: TRIAL STEERING COMMITTEE
APPENDIX 5: DATA MONITORING COMMITTEE
APPENDIX 8: PROHIBITED MEDICATIONS TABLE

PROCEDURE FOR THE USE OF PROHIBITED MEDICATIONS
(as per Protocol)

- 5 ASAs
- Corticosteroids (it is expected that patients may be on corticosteroids at entry. Doses will be tapered according to local protocols)
- anti–tumour necrosis factor
- azathioprine
- methotrexate
- allopurinol
- antibiotics for Crohn’s disease, in particular Metronidazole and Ciprofloxacin (for a duration of >10 days)
- oral non-steroidal anti-inflammatory drugs (for a duration of >7 days)

<table>
<thead>
<tr>
<th>Used as Rescue Therapy for Crohn’s</th>
<th>Other clinical Indication BUT contraindicated</th>
<th>Drug Interactions</th>
<th>Other clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prohibited Medication used because of exacerbation of Crohn’s Together with $\uparrow$CDAI $\Rightarrow$ Primary endpoint e.g. Anti-TNF, Prednisolone</td>
<td>Prohibited Medication used for another clinical reason e.g. arthritis. Prohibited Med is contraindicated for e.g. Methotrexate Azathioprine or Allopurinol</td>
<td>Warfarin Reduced anti-coagulant effect (Monitor INR closely) Trimethoprim Avoid extended courses as there is an increased risk of myelosuppression</td>
<td>Prohibited Medication used for another clinical reason e.g. Asthma. Prohibited Med may affect the response of 6-MP or confuse effect of 6-MP e.g. Steroid, SASAs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stop Study Drug (treat as investigator deems necessary)</th>
<th>Stop Study Drug (as contraindication)</th>
<th>Increase blood monitoring if required</th>
<th>Continue Study Drug (as we can still analyse effect of 6-MP)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Continue follow-up for intention to treat analysis</th>
<th>Continue follow-up for intention to treat analysis</th>
<th>Continue follow-up for intention to treat analysis</th>
</tr>
</thead>
</table>

Continue all assessments
Statistician will ensure analysis is separated.