A Pilot Study of Allopurinol As A Modifier of 6-MP Metabolism in Pediatric ALL and Lymphoblastic Lymphoma

JHU Protocol #: J1357

Study Products: Allopurinol, 6-Mercaptopurine, Methotrexate

IND # N/A

Principal Investigators

Stacy Cooper, MD
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
1650 Orleans Street, CRBI, 2M49
Baltimore, MD 21287
Phone (410) 502-7364, Fax (410) 955-0028
Email scoope30@jhmi.edu

Edward Allan R. Sison, MD
Texas Children’s Cancer and Hematology Centers
Texas Children’s Hospital, Baylor College of Medicine
6701 Fannin Street, Suite 1510,
Houston, TX 77030
Phone (617) 223-7609
Email ersison@txch.org

Co-Investigators and Administrative Staff

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
Senior Co-Investigator: Patrick Brown, MD
Phone (410) 614-4915
Email pbrown2@jhmi.edu

Seattle Children’s Hospital
Site Principal Investigator: Colleen Annesley, MD
Phone (206) 987-7122
Email colleen.annesley@seattlechildrens.org

Co-Investigators: Alan Friedman, Donald Small, Heather Symons
Statistician: Gary Rosner
Primary Research Nurse: Genevieve Corpuaas

Texas Children’s Cancer and Hematology Centers
Site Principal Investigator: Julienne Brackett, MD
Phone (832) 824-1511
Email jxbracke@txch.org

Research Facilities

Coordinating Center:
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
550 North Broadway Suite 409
Baltimore, MD 21205
Phone: 443-287-9377

Seattle Children’s Hospital
Cancer and Blood Disorders Center
4800 Sand Point Way NE
Seattle, WA 98105
Outpatient Clinic: (206) 987-2106

IRB: Institutional Review Board
Johns Hopkins School of Medicine
1620 McElriddy Street
Reed Hall, Suite B-130
Baltimore, MD 21205-1911

Texas Children’s Cancer and Hematology Centers
Texas Children’s Hospital,
Baylor College of Medicine
6701 Fannin Street, 14th Floor, Houston, TX 77030
Outpatient Clinic: (832) 822-4242

Participating Centers:
Confidential Information

Protocol Revision Record

Original Version: August 22, 2013
  Version #1: August 22, 2013
  Version #2: July 1, 2014
  Version #3: September 15, 2014
  Version #4: May 16, 2016
  Version #5: September 12, 2016
  Version #6: December 12, 2016
  Version #7: June 1, 2017
  Version #8: July 14, 2017
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Tables</td>
<td>6</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>7</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>8</td>
</tr>
<tr>
<td>1.1. Study Disease</td>
<td>8</td>
</tr>
<tr>
<td>1.2. Clinical Agent: Allopurinol</td>
<td>8</td>
</tr>
<tr>
<td>1.2.1. Relevant Prior Clinical and Non-clinical Information</td>
<td>8</td>
</tr>
<tr>
<td>1.2.2. Safety/Adverse Events</td>
<td>8</td>
</tr>
<tr>
<td>1.3. Rationale</td>
<td>9</td>
</tr>
<tr>
<td>2. Study Objectives and Endpoints</td>
<td>10</td>
</tr>
<tr>
<td>2.1. Objectives</td>
<td>10</td>
</tr>
<tr>
<td>2.2. Endpoints</td>
<td>11</td>
</tr>
<tr>
<td>3. Subject Selection</td>
<td>11</td>
</tr>
<tr>
<td>3.1. Inclusion Criteria</td>
<td>11</td>
</tr>
<tr>
<td>3.2. Exclusion Criteria</td>
<td>12</td>
</tr>
<tr>
<td>3.3. Inclusion of Women and Minorities</td>
<td>12</td>
</tr>
<tr>
<td>4. Subject Registration Procedures</td>
<td>13</td>
</tr>
<tr>
<td>4.1. General Guidelines</td>
<td>13</td>
</tr>
<tr>
<td>4.2. Registration Process</td>
<td>13</td>
</tr>
<tr>
<td>4.3. Screening Assessments</td>
<td>144</td>
</tr>
<tr>
<td>5. Multicenter Guidelines</td>
<td>15</td>
</tr>
<tr>
<td>6. Study Design/Investigational Plan</td>
<td>16</td>
</tr>
<tr>
<td>6.1. Overall Design</td>
<td>166</td>
</tr>
<tr>
<td>6.2. Agent Administration</td>
<td>177</td>
</tr>
<tr>
<td>6.2.1. Regimen Description</td>
<td>177</td>
</tr>
<tr>
<td>6.2.2. Dose Escalations</td>
<td>177</td>
</tr>
<tr>
<td>6.2.3. Dose Reductions</td>
<td>188</td>
</tr>
<tr>
<td>6.2.4. Criteria for Continued Treatment</td>
<td>188</td>
</tr>
<tr>
<td>6.3. Visit Schedule and Study Evaluations</td>
<td>189</td>
</tr>
<tr>
<td>6.4. Duration of Therapy</td>
<td>222</td>
</tr>
</tbody>
</table>
6.5. Duration of Follow-up

6.6. Concomitant Therapy and Supportive Care Guidelines

6.7. Criteria for Removal from Study

7. Dosing Delays/Dose Modifications

8. Adverse Event Collection and Reporting Requirements

8.1. Definitions

8.1.1. Adverse Event (AE)

8.1.2. Serious Adverse Event (SAE)

8.1.3. Non-serious Adverse Event

8.2. Adverse Event Coding

8.3. Adverse Event Capture and Reporting

8.3.1. Routine Adverse Event Capture and Reporting

8.3.2. Serious Adverse Event Capture and Reporting

8.3.2.1. SAE Reporting to the Coordinating Center

8.3.2.2. SAE Reporting to the IRB

8.3.3. Other Potential Adverse Events

8.3.3.1. Laboratory Test Abnormalities

8.3.3.2. Overdose

8.3.3.3. Pregnancy

9. Study Drug Information

9.1. Allopurinol

10. Statistical Methods

10.1. Analysis Plan

10.1.1. Overview

10.1.2. Feasibility

10.1.3. Safety

10.1.4. Pharmacodynamics

10.1.5. Clinical Effect

10.2. Sample Size

10.3. Statistical Analysis

10.4. Early Stopping Rules

11. Regulatory Considerations

11.1. Clinical Trial Monitoring

11.2. Records to be Kept
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.2.1.</td>
<td>Case Report Forms (CRFs)</td>
<td>299</td>
</tr>
<tr>
<td>11.2.2.</td>
<td>Record Retention</td>
<td>30</td>
</tr>
<tr>
<td>12.</td>
<td>Ethics</td>
<td>30</td>
</tr>
<tr>
<td>12.1.</td>
<td>Institutional Review Board (IRB)</td>
<td>30</td>
</tr>
<tr>
<td>12.2.</td>
<td>Ethical Conduct of the Study</td>
<td>30</td>
</tr>
<tr>
<td>12.3.</td>
<td>Subject Information and Consent</td>
<td>30</td>
</tr>
<tr>
<td>13.</td>
<td>References</td>
<td>321</td>
</tr>
<tr>
<td>14.</td>
<td>Appendix</td>
<td>332</td>
</tr>
</tbody>
</table>
List of Tables

Table 1. Study Calendar .......................................................................................................................... 20

Table 2. Optional Follow-up Phase: Observations for Subjects Continuing Allopurinol Beyond Week 9 ........................................................................................................................................ 21
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-MP</td>
<td>6-Mercaptopurine</td>
</tr>
<tr>
<td>6-MMP</td>
<td>6-Methylmercaptopurine</td>
</tr>
<tr>
<td>6-TGN</td>
<td>6-thioguanine</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALL</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood cell count</td>
</tr>
<tr>
<td>CMP</td>
<td>Comprehensive metabolic panel</td>
</tr>
<tr>
<td>COG</td>
<td>Children’s Oncology Group</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>TPMT</td>
<td>Thiopurine methyltransferase</td>
</tr>
</tbody>
</table>
1. **Introduction**

1.1. Study Disease

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Children and young adults with ALL undergo years of therapy in order to achieve cure, including up to 2 1/2 years of “maintenance” therapy. Maintenance therapy is also an important part of therapy for lymphoblastic lymphoma. Oral chemotherapeutic agents, including methotrexate and 6-mercaptopurine (6-MP), are the backbone of maintenance therapy. Compliance, gastrointestinal absorption, and variations in drug metabolism are some of the many challenges associated with oral chemotherapy. Therefore, careful monitoring of laboratory studies, including absolute neutrophil count (ANC), platelet count, and liver function tests, is critical to ensure that methotrexate and 6-MP are being administered at effective and non-toxic doses. Doses of methotrexate and 6-MP are titrated to effect by keeping the ANC within a goal range (500 to 1500/µL). While most children with ALL and lymphoblastic lymphoma are able to maintain an ANC within the goal range, a significant proportion of patients have persistently elevated ANCs despite dose escalations of 6-MP and methotrexate. It is thought that elevated ANCs despite increased doses of 6-MP are due to skewed 6-MP metabolism. Further, some patients also experience hepatotoxicity and/or gastrointestinal (GI) toxicity due to abnormal 6-MP metabolism. We propose that administration of allopurinol during maintenance therapy will correct skewed 6-MP metabolism, resulting in improved ANCs and 6-MP-related toxicity.

1.2. Clinical Agent: Allopurinol

1.2.1. Relevant Prior Clinical and Non-clinical Information

Allopurinol is a xanthine oxidase inhibitor that is FDA-approved for use in the treatment of tumor lysis syndrome. Through inhibition of xanthine oxidase, allopurinol preferentially increases metabolism of 6-MP to its active metabolite, 6-thioguanine (6-TGN). This strategy has been effective and well-tolerated in children and adults with inflammatory bowel disease who do not respond to treatment with a thiopurine alone.2-5

1.2.2. Safety/Adverse Events

Common adverse effects of allopurinol include maculopapular eruption and pruritus (less than 1 percent). Serious adverse effects of allopurinol include rash (less than 1 percent), Stevens-Johnson syndrome (less than 1 percent), toxic epidermal necrolysis (less than 1 percent), agranulocytosis, aplastic anemia, eosinophilia, myelosuppression, thrombocytopenia (0.6 percent), granulomatous hepatitis (less than 1 percent), hepatic necrosis (less than 1 percent), hepatotoxicity, immune hypersensitivity reaction, and renal failure (less than 1 percent).
1.3. Rationale

1.3.1. Rationale for co-administration of allopurinol with 6-MP

Research has suggested that low systemic exposure to 6-MP may predispose children with ALL to relapse. Doses of methotrexate and 6-MP are often increased during maintenance therapy because of patient growth or because the ANC is above the goal range. However, a significant proportion of patients are unable to achieve goal ANC despite increasing oral chemotherapy doses to greater than 150 percent of the starting dose. The current recommendations of Children’s Oncology Group (COG) for management of persistently elevated ANC despite documented good medication compliance are to continue to increase the doses of 6-MP and methotrexate. However, high doses of methotrexate and 6-MP can cause GI discomfort and pain, nausea, vomiting, and hepatotoxicity, and dose escalations are often limited by these adverse effects. Further, there are no recommendations from COG for the management of persistently elevated ANC with evidence of hepatotoxicity. It is clear that alterations in 6-MP metabolism play a significant role in the development of adverse effects and drug efficacy and we propose that altering 6-MP metabolism with allopurinol will decrease hepatotoxicity, decrease GI toxicity, and increase the production of anti-leukemic 6-MP metabolites. 6-MP is converted into three metabolites: 6-methyl mercaptopurine (6-MMP), a hepatotoxic metabolite with no anti-leukemic activity; 6-thiouracil, which also has no anti-leukemic activity; and 6-TGN, which is the active, anti-leukemic metabolite. An inability to achieve adequate levels of the active metabolites of 6-MP and methotrexate may contribute to ALL relapse. Interestingly, allopurinol, an inhibitor of xanthine oxidase that is routinely used in ALL to prevent or treat tumor lysis syndrome, has long been known to increase levels of 6-MP when given concurrently. In addition, concurrent use of allopurinol and 6-MP decreases the production of 6-MMP and 6-thiouracil and increases production of 6-TGN. Combining allopurinol with a reduced dose of 6-MP has shown tolerability and efficacy in children with inflammatory bowel disease (IBD) who do not respond to 6-MP alone. Further, allopurinol reverses thiopurine-induced hepatotoxicity and increases 6-TGN in children with IBD.

In a recently published case series from Texas Children’s Hospital, three children with ALL were given allopurinol in an effort to reduce skewed 6-MP metabolism. In all three patients, 6-MMP levels were significantly elevated (>12,000/8x10^8 RBC). After 2 to 8 weeks of treatment with allopurinol, 6-MMP levels were significantly reduced. Further, one patient achieved an ANC within the desired range after allopurinol. Experience with allopurinol at Johns Hopkins Hospital includes four children with ALL and hepatotoxicity during maintenance therapy; all four patients had 6-MMP levels >12,000/8x10^8 RBC. After 2 to 8 weeks of allopurinol treatment, 6-MMP levels were significantly decreased in all four patients (unpublished data, 2015). In addition, all four patients had improvement or resolution of hepatotoxicity and two patients achieved an ANC near goal range (1500-1750/µL).
Gastrointestinal complaints and pancreatitis have previously been reported as thiopurine-related toxicities in patients with IBD. As such, a patient with ALL who had experienced GI toxicity secondary to an increased dose of 6-MP was treated with allopurinol at Johns Hopkins Hospital. Notably, this patient had an elevated 6-MMP level but did not have hepatotoxicity. After 4 weeks of allopurinol, this patient saw a striking reduction in the 6-MMP level, complete resolution of GI symptoms (which included nausea, anorexia, and weight loss), and an ANC within goal range (unpublished data, 2015). This suggests that patients with non-hepatic GI toxicity with an elevated 6-MMP level may also benefit from allopurinol.

1.3.2. Rationale for using 6-MMP:6-TGN ratio in determining eligibility and response

While elevated 6-MMP levels seem to identify patients susceptible to toxicity while receiving thiopurine therapy, low 6-TGN levels identify patients at risk of suboptimal therapeutic response. We therefore propose that the calculation of a 6-MMP:6-TGN ratio will aid in identifying those patients most likely to benefit from altering 6-MP metabolism with allopurinol. In a cohort of 363 patients with IBD receiving azathioprine or 6-MP, compliance to therapy, therapeutic efficacy, treatment-related adverse effects, and 6-MMP:6-TGN ratios were measured. Though not statistically significant, the median 6-MMP:6-TGN ratio in patients continuing thiopurine therapy (40% of patients) was 9.4, compared to a median ratio of 31.8 in patients that discontinued thiopurine therapy (57% of patients). Common reasons for discontinuing therapy in this cohort were toxicity (39%) and refractoriness to therapy (16%); these patients had median 6-MMP:6-TGN ratios of 26.1 and 45.3, respectively. Univariate regression analysis also demonstrated that 6-MMP concentrations were significantly higher in the discontinuation group compared to those continuing therapy (p <0.001), suggesting that both 6-MMP levels and the 6-MMP:6-TGN ratio may distinguish those patients likely to experience toxicity or refractoriness. Interestingly, all of the patients with ALL who were treated with allopurinol at Johns Hopkins Hospital and Texas Children’s Hospital and described above had 6-MMP:6-TGN ratios >40 (range 42 to 160), and had a significant reduction in the ratio after starting allopurinol (range 64% to 98% reduction).

1.3.3. Summary of rationale

We propose performing a pilot study of the addition of allopurinol to ALL and lymphoblastic lymphoma maintenance therapy for patients with laboratory and clinical evidence of skewed 6-MP metabolism. We hypothesize that the addition of allopurinol to maintenance therapy will be tolerable, improve the 6-MMP:6-TGN ratio, safely decrease ANC, decrease 6-MMP levels, and improve hepatotoxicity and other GI toxicity in children with ALL and lymphoblastic lymphoma. We anticipate that this strategy will increase tolerability and efficacy of 6-MP and thereby contribute to improved outcomes in pediatric ALL and lymphoblastic lymphoma.

2. Study Objectives and Endpoints

2.1. Objectives
2.1.1 To assess the feasibility of adding allopurinol to standard maintenance therapy that includes 6-MP for pediatric ALL and lymphoblastic lymphoma

2.1.2 To assess the safety of adding allopurinol to standard maintenance therapy that includes 6-MP for pediatric ALL and lymphoblastic lymphoma

2.1.3 To gather preliminary data about the pharmacodynamics of adding allopurinol to standard maintenance therapy for pediatric ALL and lymphoblastic lymphoma

2.1.4 To gather preliminary data about the clinical benefits of adding allopurinol to standard maintenance therapy for pediatric ALL and lymphoblastic lymphoma

2.2. Endpoints

2.2.1. Feasibility: We will assess feasibility according to the definition in Section 10.1.2

2.2.2. Safety: Incidence of adverse events possibly, probably, or definitely attributable to allopurinol.

2.2.3. Pharmacodynamics: Change in 6-MMP levels, 6-TGN levels, and the ratio of 6-MMP:6-TGN measured after 8 weeks of protocol therapy (i.e., study week 9).

2.2.4. Clinical benefits: For patients who meet feasibility endpoint, proportion of patients who receive at least 70% of the planned doses of protocol therapy and whose ANC begins above 1500/µL and falls into the range 500-1500/µL at study week 9; Proportion of patients with elevated ALT, AST, and/or direct bilirubin that falls into normal range at study week 9; Proportion of patients with non-hepatic GI toxicity that resolves at study week 9.

3. Subject Selection

3.1. Inclusion Criteria

3.1.1. Currently being treated in the maintenance phase of therapy for pediatric ALL or lymphoblastic lymphoma

3.1.2. Age ≤30 years

3.1.3. 6-MMP:6-TGN ratio ≥40 \textit{within 21 days prior to enrollment}

3.1.4. 6-MMP ≥12,000/8x10^8 RBC \textit{within 21 days prior to enrollment}

3.1.5. \textit{One} of the following \textit{within 21 days prior to enrollment}:

3.1.5.1. ANC persistently ≥1500/mm³ (as measured by 3 CBCs done over 6 weeks or 2 successive monthly CBCs) despite 6-MP ≥150% of COG dosing
3.1.5.2. Evidence of ≥ Grade 3 hepatotoxicity with one of the following:

- ALT ≥5x upper limit of normal (based on institutional standards)
- AST ≥5x upper limit of normal (based on institutional standards)
- Direct bilirubin ≥5x upper limit of normal (based on institutional standards)

3.1.5.3. Evidence of ≥ Grade 2 gastrointestinal toxicity (including, but not limited to: nausea, vomiting, anorexia, gastrointestinal pain)

3.2. Exclusion Criteria

3.2.1. Allergy to allopurinol

3.2.2. Active relapse of ALL or lymphoblastic lymphoma

3.2.3. Currently enrolled on any therapeutic research study for the treatment of ALL or lymphoblastic lymphoma

3.2.4. Known history of chronic liver disease (other than Gilbert’s syndrome)

3.2.5. Pregnant or breastfeeding females

3.3. Inclusion of Women and Minorities

3.3.1. This study will be open to women and minorities.
4.0 Subject Registration Procedures

4.1 General Guidelines

Eligible subjects will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Coordinating Center.

Following registration, subjects should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the site principal investigator. If a subject does not receive protocol therapy following registration, the subject’s registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an IRB-approved consent form. To initiate registration, study sites/institutions should forward copies of the signed informed consent form, the research authorization/HIPAA form, the institutional registration form, plus any required laboratory tests to the coordinating center or sponsor by fax or email. Upon receipt of these forms, research personnel at the coordinating center will confirm patient eligibility with study personnel, assign a unique patient study identification number, and complete patient registration. Treatment must not commence until the site has received their patient’s identification number. All patients must be registered centrally at SKCCC.

To register a subject participating sites must send the documents by email to (crocc@jhmi.edu) and CC the Lead Study Coordinator to the Coordinating Center (hschne12@jhmi.edu). The Coordinating Center fax (410-502-9933) may be used if email is not available.

- Signed subject consent form
- Registration form
- Eligibility Screening Checklist
- Copies of all source documentation of all clinical studies confirming eligibility

The Coordinating Center will review the documents to confirm eligibility. To complete the registration process the Coordinating Center will:
• Assign a patient study number

• Register the patient on the study with SKCCC’s CRO Coordinating Center

• Fax or e-mail the patient study number to the participating site

The Johns Hopkins Pediatric Oncology Research Team will not register their patients through the SKCCC’s CRO Coordinating Center. Eligibility for Hopkins subjects will be reviewed and confirmed internally by the Pediatric Oncology Research Team and verified by the Study PI. A subject number, however, must be requested upon consent and prior to enrollment from the SKCCC’s CRO Coordinating Center via email or telephone. The SKCCC CRO Coordinating Center Lead Study Coordinator will provide this number to the study team.

4.3 Screening Assessments

Potentially eligible subjects will be identified by physicians, nurses, physician assistants, and nurse practitioners practicing in the Division of Pediatric Oncology at Johns Hopkins, the Division of Pediatric Hematology/Oncology at Seattle Children’s Hospital, and the Section of Pediatric Hematology/Oncology at Texas Children’s Hospital. During scheduled clinic visits, Pediatric Oncology providers will routinely review medication dosage and laboratory studies in order to determine if subjects may be eligible for this study.
5. Multicenter Guidelines

**Protocol Chair**

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Reviewing data from all sites.

**Coordinating Center**

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE’s and SAE’s to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

**Participating Sites**

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
J1357 Study Protocol

- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.

- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.

- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

- Collecting and submitting data according to the schedule specified by the protocol.

6 Study Design/Investigational Plan

6.1 Overall Design

This study is a multi-center, single-arm, non-blinded study of the addition of allopurinol to maintenance therapy in pediatric ALL and lymphoblastic lymphoma. Study procedures will include physical examinations and laboratory evaluations as part of routine care for children and young adults with ALL and lymphoblastic lymphoma.

Subjects will have a baseline physical examination and baseline laboratory studies performed (week 0) that will include a complete blood cell count (CBC) with differential, comprehensive metabolic panel (CMP), direct bilirubin, thiopurine methyltransferase (TPMT) enzyme activity, and TPMT metabolites (6-TGN and 6-MMP). At this visit, subjects will also stop taking their current doses of 6-MP and methotrexate.

One week later (week 1), subjects will follow up with their oncology provider and will be prescribed allopurinol once daily (100 mg for weight >30 kg, 50 mg for weight ≤30 kg) and will restart 6-MP at 50 percent of the most recent dose. Methotrexate will also be restarted at week 1 according to the following: 1) if the methotrexate dose at study entry is ≤100% of the recommended dose, methotrexate should be restarted at the study entry dose; 2) if the methotrexate dose at study entry is >100% of the recommended dose, methotrexate should be restarted at 100% of the recommended dose.

Subjects will return for follow up laboratory evaluation weekly through study end (week 9), including CBC with differential, CMP, direct bilirubin, TPMT enzyme activity (weeks 3 and 9 only), and TPMT metabolites (weeks 3, 5, and 9 only). During weeks 4-8, TPMT metabolites and/or TPMT enzyme activity will be sent if clinically indicated. Grading of any non-hepatic GI toxicity will be recorded at weeks 0, 3 and 9 at a minimum. All of the proposed laboratory studies are standard of care for children with ALL and lymphoblastic lymphoma according to the current COG recommendations for the evaluation of patients with high ANC despite high doses of 6-MP. Required observations are listed in Table 1.
6.2 Agent Administration

6.2.1 Regimen Description

As stated in section 5.1, subjects will stop taking their 6-MP and methotrexate at week 0. One week later (week 1), subjects will begin allopurinol daily (100 mg for weight >30 kg, 50 mg for weight ≤30 kg), will restart 6-MP at 50 percent of the most recent dose, and will restart methotrexate based on dose at study entry. Dose adjustments of 6-MP and methotrexate will be directed by the guidelines outlined in sections 6.2.2 and 6.2.3.

6.2.2 Dose Escalations

These dose escalation guidelines apply to subjects being treated during the study period (weeks 0 to 9) as well as subjects who continue the study treatment after completion of their individual study period (i.e., after week 9).

- Doses of 6-MP and methotrexate should not be increased until week 5 or later.

- Doses should be escalated for persistent ANC ≥1500/µL (ANC ≥1500/µL on 3 CBCs performed over 6 weeks or 2 successive monthly CBCs). Notably, if a subject met criteria for persistent ANC ≥1500/µL at study entry and the week 5 ANC continues to be ≥1500/µL, that subject is eligible for dose escalation at week 5. Dose escalations in 6-MP and methotrexate should not be made more frequently than every 4 weeks.

- When a subject meets criteria for a dose escalation, noncompliance should be assessed by history and measurement of TPMT metabolites. 6-TGN ≤100 pmol/8x10^8 RBC suggests noncompliance.

- After a dose escalation, subjects should be evaluated every 2 to 4 weeks with CBC with differential and CMP until a stable ANC nadir is reached. TPMT metabolites should be measured 2 to 4 weeks after a dose increase.

Dose escalation guidelines:

- First occurrence of persistent ANC ≥1500/µL: Allopurinol and methotrexate should be continued at the same doses and 6-MP should be increased by 12.5 percent of the week 1 dose. Therefore, allopurinol and methotrexate will be at 100 percent of the week 1 dose, and 6-MP will be at 112.5 percent of the week 1 dose.

- Second occurrence: Allopurinol and 6-MP should be continued at the same doses and methotrexate should be increased by 12.5 percent of the week 1 dose. Therefore, allopurinol will be at 100 percent of the week 1 dose, 6-MP will
be at 112.5 percent of the week 1 dose, and methotrexate will be at 112.5 percent of the week 1 dose.

- Recommendations for subsequent occurrences after study week 9: Allopurinol should be continued at the same dose. Doses of 6-MP and methotrexate should be increased by 12.5 percent of the week 1 dose in an alternating fashion.

6.2.3 Dose Reductions

These dose reduction guidelines apply to subjects being treated during the study period (weeks 0 to 9) as well as subjects who continue the study treatment after completion of their individual study period (i.e., after week 9).

If the ANC falls below 500/µL or the platelet count falls below 50,000/µL while being treated on this study, and this is the first time the counts have fallen, then allopurinol, 6-MP, and methotrexate should be stopped. Subjects should be evaluated weekly with CBC with differential and CMP until the ANC recovers to ≥500/µL and the platelet count recovers to ≥50,000/µL. Once the ANC and platelet count recover, allopurinol should be restarted at the same dose and 6-MP and methotrexate should be restarted at 50 percent of the most recent doses. Doses of 6-MP and methotrexate may be escalated according to the guidelines in section 6.2.2.

If the ANC falls below 500/µL or the platelet count falls below 50,000/µL for a second or greater time while being treated on this study, allopurinol, 6-MP, and methotrexate should be stopped. Subjects should be evaluated at least every 2 weeks with CBC with differential and CMP until the ANC recovers to ≥750/µL and the platelet count recovers to ≥75,000/µL. Once the ANC and platelet count recover, allopurinol should be restarted at the same dose and 6-MP and methotrexate should be restarted at 50 percent of the most recent doses. Doses of 6-MP and methotrexate may be escalated according to the guidelines in section 6.2.2.

6.2.4 Criteria for Continued Treatment

Subjects who tolerate the treatment may continue taking the study treatment after week 9. These subjects will be eligible for participation in the optional follow-up phase (please see Section 5.5 and Table 2).

For subjects continuing on allopurinol beyond week 9, it is highly recommended, but not required, that patients be followed with physical examination, CBC, and CMP at least every 4 weeks; TPMT metabolites should be checked when clinically indicated. Dose escalation and dose reduction guidelines are listed in sections 6.2.2 and 6.2.3.

6.3 Visit Schedule and Study Evaluations

Please see the below Study Calendar table. The observations in Table 1 are required.
For subjects who consent to participation in the optional follow-up phase, the observations in Table 2 are required.
Table 1. Study Calendar

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0 *(+/- 3 days)</th>
<th>Week 1 **(+/- 3 days)</th>
<th>Week 2 *(+/- 3 days)</th>
<th>Week 3 *(+/- 3 days)</th>
<th>Week 4 *(+/- 3 days)</th>
<th>Week 5 *(+/- 3 days)</th>
<th>Week 6 *(+/- 3 days)</th>
<th>Week 7 *(+/- 3 days)</th>
<th>Week 8 *(+/- 3 days)</th>
<th>Week 9 *(+/- 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination (including height and weight)</td>
<td>X</td>
<td>X</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TPMT enzyme activity</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>TPMT metabolites (6-MMP, 6-TGN)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Grading of any non-hepatic GI toxicity (CTCAE v4.0)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*+, stop 6-MP and methotrexate; **, start allopurinol and restart 6-MP at 50% of previous dose; see Section 5.1 for methotrexate dosing.

(X), if clinically indicated or 2 weeks after 6-MP dose change; 6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine; CBC, complete blood cell count; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; TPMT, thiopurine methyltransferase.
Table 2. Optional Follow-up Phase: Observations for Subjects Continuing Allopurinol Beyond Week 9

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 11 (+/- 3 days)</th>
<th>Week 13 (+/- 3 days)</th>
<th>Week 17 (+/- 3 days)</th>
<th>Week 21 (+/- 3 days)</th>
<th>Week 25 (+/- 3 days)</th>
<th>Week 29 (+/- 3 days)</th>
<th>Week 33 (+/- 3 days)</th>
<th>Week 37 (+/- 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>TPMT metabolites (6-MMP, 6-TGN)</td>
<td>(X)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Grading of any non-hepatic GI toxicity (CTCAE v4.0)</td>
<td>(X)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
</tr>
<tr>
<td>TPMT enzyme activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

(X), if clinically indicated or 2 weeks after 6-MP or methotrexate dose change; 6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine; CBC, complete blood cell count; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; TPMT, thiopurine methyltransferase.
6.4 Duration of Therapy

Duration of therapy will be 8 weeks (study weeks 1 through 9). Subjects who are tolerating therapy and would like to continue therapy after week 9 may do so at the discretion of the treating physician.

6.5 Duration of Follow-up

Duration of follow-up will be 9 weeks. Subjects who continue to be cared for by the Division of Pediatric Oncology at Johns Hopkins, the Division of Pediatric Hematology/Oncology at Seattle Children’s Hospital, and the Section of Pediatric Hematology-Oncology at Texas Children’s will continue to be followed through the course of their treatment.

Subjects who are interested in continuing protocol therapy beyond week 9 may participate in the optional follow-up phase. The follow-up phase, which will continue through week 37, will consist of continuing protocol therapy and the required observations listed in Table 2.

For subjects who have not consented to the optional follow-up phase but who continue protocol therapy, the observations in Table 2 are highly recommended.

6.6 Concomitant Therapy and Supportive Care Guidelines

Subjects will be allowed to continue or start supportive care medications as guided by standard of care or institutional preference (eg, trimethoprim-sulfamethoxazole for Pneumocystis jirovecii prophylaxis, ondansetron for nausea prophylaxis, etc.).

6.7 Criteria for Removal from Study

Criteria to remove participants from the trial include consent withdrawal, intolerable adverse effects, if it is in best interest of the subject to remove the participant from the trial (as determined by the subject, family, or treating physician), relapse, or the development of another malignancy.

7 Dosing Delays/Dose Modifications

Details regarding dose modifications are listed in sections 6.2.2 and 6.2.3.

8 Adverse Event Collection and Reporting Requirements

8.1 Definitions

8.1.1 Adverse Event (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including
abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product (refer to ICH E6 GCP Guidance – section 1.2).

8.1.2 Serious Adverse Event (SAE)

A Serious AE (SAE) is any untoward medical occurrence that at any dose produces any of the following outcomes (refer to ICH E6 GCP Guidance – section 1.50):

- Results in death;
- Is life threatening (defined as an event in which the subject 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 inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below for exceptions);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form);
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

**NOTE:**

The following hospitalizations are not considered SAEs:

- Admissions as per protocol for a planned medical/surgical procedure;
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative);
- Admission due to poor recovery after anesthesia for scheduled procedure (e.g., bone marrow aspirate, lumbar puncture).

8.1.3 Non-serious Adverse Event

A non-serious adverse event is any adverse events not classified as serious (as described in previous section).
8.2 Adverse Event Coding

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

- **Attribution of the AE:**
  - **Definite** – The AE is clearly related to the study treatment.
  - **Probable** – The AE is likely related to the study treatment.
  - **Possible** – The AE may be related to the study treatment.
  - **Unlikely** – The AE is doubtfully related to the study treatment.
  - **Unrelated** – The AE is clearly NOT related to the study treatment.

8.3 Adverse Event Capture and Reporting

8.3.1 Routine Adverse Event Capture and Reporting

All unexpected grade 4 AEs that are possibly, probably, or definitely attributable to allopurinol will be collected and reported. All grade 5 AEs will be collected and reported.

All identified AEs must be recorded and described on the appropriate AE page of the Case Report Form (CRF).

8.3.2 Serious Adverse Event Capture and Reporting

ALL serious adverse events, regardless of causality must be reported to the following entities:

- Principal Investigator
- IRB
- Local Institutional Biosafety Committee

8.3.2.1 SAE Reporting to the Coordinating Center

All SAEs must be reported to the Coordinating Center within 24 hours of becoming aware of the event occurrence. SAEs should be recorded on the Serious Adverse Event Reporting Form. This form along with any relevant medical documentation must be completed and submitted to the Site Principal Investigator for review and signature.

Report serious adverse events by email or facsimile to:

CRO Coordinating Center

Email: crocc@jhmi.edu, hschne12@jhmi.edu

Fax: 410-502-9933
8.3.2.2 SAE Reporting to the IRB

All SAEs that meet the definition of an unanticipated event per local institutional review requirements must be reported to each site’s IRB of record.

8.3.3 Other Potential Adverse Events

8.3.3.1 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a central laboratory. In addition, the following laboratory abnormalities should also be captured on the non-serious AE CRF page or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE;
- Any laboratory abnormality that is grade 4 or higher with the attribution of possible, probable or definitely related to allopurinol and requires the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

8.3.3.2 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

8.3.3.3 Pregnancy

Sexually active women of child bearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy.

9 Study Drug Information

9.1 Allopurinol

Other names: Zyloprim

Classification: Xanthine oxidase inhibitor

Mode of action: Allopurinol sodium and its metabolite, oxypurinol (alloxanthine), decrease the production of uric acid by inhibiting the action of xanthine oxidase, the enzyme that converts hypoxanthine to xanthine and xanthine to uric acid. Allopurinol sodium also increases
reutilization of hypoxanthine and xanthine for nucleotide and nucleic acid synthesis; the resultant increase in nucleotide concentration leads to feedback inhibition of de novo purine synthesis. Allopurinol thereby decreases uric acid concentrations in both serum and urine by inhibiting uric acid formation.

**Storage and stability:** Store at room temperature.

**Dose specifics and preparation:** 100 mg daily for weight >30 kg, 50 mg daily for weight ≤30 kg. Supplied as scored 100 mg and 300 mg tablets.

**Administration:** Oral.

**Availability:** Generic, available at commercial pharmacies.

**Side effects:** Common adverse effects of allopurinol include maculopapular eruption and pruritus (less than 1 percent). Serious adverse effects of allopurinol include rash (less than 1 percent), Stevens-Johnson syndrome (less than 1 percent), toxic epidermal necrolysis (less than 1 percent), agranulocytosis, aplastic anemia, eosinophilia, myelosuppression, thrombocytopenia (0.6 percent), granulomatous hepatitis (less than 1 percent), hepatic necrosis (less than 1 percent), hepatotoxicity, immune hypersensitivity reaction, and renal failure (less than 1 percent).

**Nursing implications:** None.
10 Statistical Methods

10.1 Analysis Plan

10.1.1 Overview

The goals of this pilot study are to assess the feasibility and safety of adding allopurinol to maintenance therapy that includes 6-MP, and to gather preliminary data about the pharmacodynamic changes in 6-MMP and 6-TGN and associated clinical benefits after adding allopurinol. Determining the variability of these measures of allopurinol effect will allow us to plan a future clinical study to evaluate the clinical benefit of this combination.

10.1.2 Feasibility

We will characterize feasibility by the ability to administer each patient’s maintenance therapy combined with allopurinol and to measure its effects over 8 weeks. Measures that characterize feasibility or lack thereof include: 1) for each patient, the percentage of total planned doses of study medication administered (we will call a patient “adherent to protocol therapy” if the patient has taken at least 70% of planned doses correctly); and 2) the fraction of patients who fail to complete the study evaluations through week 9.

10.1.3 Safety

We will describe adverse events, including the toxicity grades based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. We will also characterize and report all unexpected grade 4 (and 5) adverse events as possibly, probably, or definitely attributable to allopurinol. We will report any grade 5 adverse events. We will examine within-patient changes in laboratory measures (e.g., ANC, ALT, AST, and direct bilirubin) collected weekly from study week 0 through week 9 (see the Study Calendar in Section 6.3). We will report the grades of non-hepatic GI toxicities at weeks 0, 3, and 9, and describe the proportions of patients who experience these GI toxicities at each of those time points.

10.1.4 Pharmacodynamics

We will characterize the pharmacodynamics and the clinical effects of adding allopurinol after 8 weeks of daily allopurinol added to each patient’s maintenance regimens. The major measures we will analyze and report include levels of 6-MMP, 6-TGN, the ratio of 6-MMP to 6-TGN, and ANC, all of which we will measure weekly over the study’s 8 weeks (see the Study Calendar in Section 6.3). We will compare the measures after 8 weeks (i.e., study week 9) to the levels just prior to adding allopurinol (i.e., study week 0). We will also examine longitudinal changes over the course of the 8 weeks of study treatment based on values measures made periodically over the course of treatment, as specified in the study calendar (Section 6.3). Of particular interest is the change in the ratio 6-MMP:6-TGN after 8 weeks of allopurinol combined with maintenance therapy. One way to characterize the distribution of this change is via a histogram. The histogram would show the fraction of patients whose 6-MMP:6-TGN ratios decline by 20%, 30%, etc. after 8
weeks of protocol therapy. We consider a 70-percent reduction in a patient’s 6-MMP:6-TGN ratio to be particularly meaningful.

10.1.5 Clinical effect

The clinical effect of protocol therapy will be characterized in patients that meet the feasibility criteria (We will assess feasibility according to the definition in Section 10.1.2) by: 1) the proportion of patients whose ANC begins above 1500/µL and falls into the range 500-1500/µL at study week 9; 2) the proportion of patients with elevated ALT, AST, and/or direct bilirubin that falls into normal range at study week 9; and 3) the proportion of patients with non-hepatic GI toxicity that resolves at study week 9.

10.2 Sample Size

This protocol describes a pilot study that will generate preliminary data that can inform a future study. Therefore, it is difficult to provide a firm sample size calculation. We can, however, provide an example of a power calculation for a statistical hypothesis test. We would consider a 70-percent reduction in the 6-MMP:6-TGN ratio as clinically meaningful, based on our experience described earlier in the protocol. Assume we can evaluate this change in 14 patients and consider the null hypothesis that at most 21% (3 of 14) of the patients will achieve a 70-percent reduction in the 6-MMP:6-TGN ratio after 8 weeks of protocol therapy versus the alternative hypothesis that 57% (8 of 14) or more of the patients achieve a 70-percent reduction in the 6-MMP:6-TGN ratio. The study will have 91% power to reject the null hypothesis at a significance level of around 5% with 14 patients. We are willing to enroll up to 35 patients to allow for 30% of the patients to drop out or be non-adherent to the study protocol (i.e., not take at least 70% of prescribed doses correctly) and an additional 30% of patients not to provide evaluable data for this analysis (i.e., not provide the required study data through week 9). In addition, 14 patients will allow an exact 95% confidence interval to have width at most 0.54. For example, if 7 of 14 patients experience an adverse event, the 95% exact confidence interval will be (0.23, 0.77). Additionally, 14 patients provide 77% probability that we will see at least one adverse event if the risk is just 10%, with greater probability for events with higher risk. Every year, approximately 24 patients at Johns Hopkins Children’s Center, 40 patients at Seattle Children’s Hospital, and 90 patients at Texas Children’s Hospital are diagnosed with ALL or lymphoblastic lymphoma. Because the treatment lasts 2 to 3 years, we will have approximately 400 patients in active ALL/LL treatment at any time. Based on our clinical experience, we anticipate an accrual rate of 3 subjects every 4 months. Therefore, we expect 19 to 47 months of accrual.

10.3 Statistical Analysis

Given the small sample size, any statistical tests will be hypothesis generating. We will produce summary statistics and include 95% confidence intervals. We acknowledge that there may be missing data in our cohort of 14 patients, as well as the fact that these 14 patients may be a biased sample, since these 14 patients will have completed all study visits and procedures and adhered to protocol therapy. Since this is an initial pilot study collecting data for planning future
studies, we accept this limitation. Furthermore, by focusing on patients who have adhered to the study treatment, we are able to get an idea of the best we might see in terms of allopurinol’s pharmacodynamic and clinical effect.

10.4 Early Stopping Rules

After 5 subjects are enrolled, if the percentage of subjects experiencing grade 4 or greater non-hematologic adverse events that may be attributed to allopurinol, 6-MP, or methotrexate is higher than 20%, the study will be suspended for safety consultation. We will continue to monitor patients for safety, using 20% as an allowable upper bound. At that time, the adverse events of all enrolled subjects will be reviewed. If it is determined that the study may be continued safely, subject enrollment will resume. In addition, the study will be closed early if any deaths occur that may be attributed to allopurinol, 6-MP, or methotrexate. Accrual will be stopped when 14 evaluable subjects have completed the study. If there are subjects currently enrolled in the study at that time, those subjects will be allowed to complete the study and the study will be closed early once those subjects have either completed or withdrawn from the study.

11 Regulatory Considerations

11.1 Clinical Trial Monitoring

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study.

Authorized representatives of the Coordinating Center will periodically audit data from participating satellite sites depending on the rate of accrual and prior audit results (this satellite site auditing will be accomplished remotely or via on-site visits as applicable).

11.2 Records to be Kept

11.2.1 Case Report Forms (CRFs)

As used in this protocol, the term case report form (CRF) refers to either a paper form or an electronic data record or both, depending on the data collection method used in this study. A CRF is required and should be completed for each included subject.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection
and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. All CRFs must be signed by the investigator to verify that the data contained on the CRFs is accurate. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

Usually, source documents are the hospital's or the physician's subject medical chart. In these instances the data collected on the CRFs must match the data in the corresponding charts. A CRF, or part of the CRF, may also serve as a source document. The de-identified source documentation for each CRF should be uploaded into the CRMS system for each patient.

An electronic or paper CRF will be created and will contain demographic information, point in treatment, 6-MP and methotrexate doses, weight, and laboratory values as described in Table 1 and Table 2 (if applicable). CRF’s will should be completed prior to the patient’s next scheduled visit.

11.2.2 Record Retention

To enable inspections and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (i.e. information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the IRB’s policies, FDA’s regulations, or as specified in the Clinical Study Agreement, whichever is longer.

12 Ethics

12.1 Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All IRB correspondence should be retained in the Investigator File.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws.
The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Principal Investigator before implementation.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject’s signed consent form.
13 References


14 Appendix

A – JHU SKCCC Data Safety Monitoring Plan