MULTI-SITE TRIAL OF AZATHIOPRINE DOSING IN CROHN’S DISEASE
IND# 67, 402

Manual of Operations and Procedures (MOOP)

Version 8
23 August 04
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STUDY OVERVIEW

Study Synopsis
This multi-center, double blind, randomized clinical trial will compare two 52-week-long azathioprine (AZA) dosing regimens in the induction and maintenance of remission of steroid-dependent and steroid-refractory Crohn’s disease (CD). During the induction phase (weeks #0-28), subjects in the fixed-dose, control arm, will receive an AZA dose based on body weight. In the individualized dose arm, subjects will begin treatment at a dose determined by the levels of thiopurine methyl transferase (TPMT) enzyme activity, and the dose will subsequently be adjusted to maintain the 6-thioguanine nucleotide (6-TGN) levels within the target therapeutic range. During the maintenance phase (weeks #29-52), subjects from both groups who have entered remission between weeks 16-28 will continue on an AZA maintenance dose equal to their dose at the end of the induction phase. In the individualized dose arm, dosing will continue to be adjusted according to 6-TGN levels. The trial is designed to enroll 262 subjects in participating adult and pediatric centers. The participants will be evaluated using standardized instruments of disease activity (Crohn's Disease Activity Index (CDAI), for adults; modified CDAI (mCDAI), for children), health-related quality of life (HRQOL), and perianal disease activity. Frequency of adverse events and corticosteroid use will be compared in the two treatment arms.

Assuming a 25% dropout rate, the proposed sample size will provide 80% power (2-tailed $\alpha=0.05$) to detect a 20% increase in the frequency of remission, from 55% in the fixed dose arm, to 75% in the individualized dose arm.

Type of trial
• Randomized, multicenter, double-blinded
• Two parallel treatment groups
• In order to achieve the expected enrollment of 262 total participants, each site is expected to enroll 10-15 participants in a three year period.

Objective
To evaluate the efficacy of individualized dose AZA as compared to fixed dose AZA in the induction of clinical remission of steroid-dependent and steroid-refractory CD.

Treatments
• Fixed dose group: 1.0 mg/kg/day on weeks #1 and #2, 1.75 mg/kg/day on weeks #3 and #4, and 2.5 mg/kg/day on weeks #5-52
• Individualized dose group: Subjects with intermediate and high TPMT activity begin at doses of 1.0 mg/kg/day and 2.5 mg/kg/day respectively, and doses are subsequently adjusted to achieve the target 6-TGN RBC concentrations
Outcomes

Primary Outcome measure:
The primary outcome measure will be the proportion of subjects achieving clinical remission at week #16.

- For steroid-dependent subjects, clinical remission is defined as complete withdrawal of corticosteroids, and Crohn's Disease Activity Index (CDAI) score <150 in adults, or modified Crohn's Disease Activity Index (mCDAI) score <150 in children.
- For steroid-refractory subjects, clinical remission is defined as CDAI score <150 (or mCDAI <150 in children), and a reduction of at least 70 points from the baseline score (CDAI or mCDAI), and complete withdrawal of corticosteroids.

Secondary Outcome measures:

- Proportion of subjects maintaining clinical remission at week #28
- Proportion of subjects maintaining clinical remission at week #52
- Frequency of Adverse Events (AE)
  - Frequency of AEs requiring dose reduction.
  - Frequency of AEs requiring drug cessation.
- Corticosteroid use in the two treatment arms
- Adult and Pediatric Health related quality of life (HRQOL) index scores in the two treatment arms, calculated using the Inflammatory Bowel Disease Questionnaire (IBDQ) in Adults and IMPACT in children.
- Levels of TPMT at 28 weeks compared to baseline to determine if TPMT activity is induced during therapy.
- Evaluate TPMT activity and 6-TGN levels as predictors of AZA response in both groups and will correlate 6-TGN levels with WBC, neutrophil and lymphocyte counts, and clinical remissions. Finally, we will attempt to develop a predictive model of AZA dosing according to baseline weight, TPMT activity, week #4 and #8 6-TGN levels, post dose escalation 6-TGN levels or change in 6-TGN levels and other exploratory parameters.
# Schedule of Procedures

## Induction Phase (weeks 0-28)

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| Visit forms checklist / Comments page | X | X | X | X | X | X | X | X | X | X |
| Subject Demographics | X |
| Crohn's Medical History | X |
| Comprehensive Physical Exam | X |
| Medical History | X |
| Inclusion/Exclusion Criteria | X |
| Informed Consent | X |
| Smoking Use | X |
| Brief Physical Exam | X | X | X | X | X | X | X | X | X | X |
| Disease Activity Index (CDAI or mCDAI) | X² | X | X | X | X | X | X | X | X | X |
| Quality of Life Index (IBDQ or IMPACT) | X | X | X | X | X | X | X | X | X | X |
| Drug Accountability | X | X | X | X | X | X | X | X | X | X |
| PDAI³ | X | X | X | X | X | X | X | X | X | X |
| Prednisone/Budesonide use | X | X | X | X | X | X | X | X | X | X |
| Hematology⁴ | X | X | X | X | X | X | X | X | X | X |
| Liver Profile⁴ | X | X | X | X | X | X | X | X | X | X |
| Serum Chemistry | X |
| Urine Pregnancy test | X |
| Urinalysis | X |
| Remission Assessment⁵ | X |
| Lab review | X | X | X | X | X | X | X | X | X | X |
| Adverse/Serious Adverse events | X | X | X | X | X | X | X | X | X | X |
| Study termination form (source document) | X | X | X | X | X | X | X | X | X | X |
| Prohibited Medications Checklist | X | X | X | X | X | X | X | X |
| Subject Diary | X | X | X | X | X | X | X | X | X | X |
| TPMT | X | X | X | X |
| RBC 6-TGN, 6-MMPR | X | X | X | X |
| Tanner Staging (Pediatric Subjects only) | X |
| Drug Dispensing | X | X | X | X | X | X | X |
| Pharmacy Instruction checklist⁶ | X | X | X | X | X | X | X |

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1. Non physician /phone call with coordinator/ blood work
2. Calculated based on recall
3. In adult subjects with perianal disease
4. Additional blood draws may be required for dose adjustments and toxicity
5. If Subject does not meet remission criteria at Week 28, Subject is withdrawn from study. Complete termination form
6. One week after each 6TGN draw
### Schedule of Procedures

#### Maintenance Phase (weeks 29-52)

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Visit forms checklist / Comments page: X X X X X X

- **Subject Demographics**
- **Crohn's Medical History**
- **Comprehensive Physical Exam**
- **Medical History**
- **Inclusion/Exclusion Criteria**
- **Informed Consent**
- **Smoking Use**
- **Brief Physical Exam**
- **Disease Activity Index (CDAI or mCDAI)**
- **Quality of Life Index (IBDQ or IMPACT)**
- **Drug Accountability**
- **PDAI**
- **Prednisone/Budesonide use**
- **Hematology**
- **Liver Profile**
- **Serum Chemistry**
- **Urine Pregnancy test**
- **Urinalysis**
- **Remission Assessment**
- **Lab review**
- **Adverse/Serious Adverse events**
- **Study termination form (source document)**
- **Prohibited Medications Checklist**
- **Subject Diary**
- **TPMT**
- **RBC 6-TGN, 6-MMPR**
- **Tanner Staging (Pediatric Subjects only)**
- **Drug Dispensing**
- **Pharmacy Instruction checklist**

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1. Non physician /phone call with coordinator/ blood work
2. Calculated based on recall
3. In adult subjects with perianal disease
4. Additional blood draws may be required for dose adjustments and toxicity
5. If Subject does not meet remission criteria at Week 28, Subject is withdrawn from study. Complete termination form
6. One week after each 6TGN draw
Data Collection Schedule

Scheduled visits
This section describes the procedures and assessments to be done at every study visit.

Visit 0: Screening Evaluation (week # -2)
Subjects will be screened for eligibility to the study 2 weeks before baseline at which time the following procedures will be performed:

1. Review and signing of the informed consent form by the subject, the investigator, and the study coordinator.

2. Visit Forms Checklist and CRF completion

3. Determination of the inclusion and exclusion criteria.

4. Medical history and demographic characteristics. All elements of the medical history will be obtained. All medications will be reviewed.

5. Comprehensive physical examination, including blood pressure (mm Hg, seated, after a 5 minute rest), heart rate (beats/minute, seated, after a 5 minute rest), temperature, height, and weight (kg).

6. Laboratory assessment. Blood will be drawn for the following tests (Adults: 24cc or 2 tablespoons, Children: 12cc or 2 teaspoons)
   - CBC and differential, platelet count
   - Serum chemistry: Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase.
   - TPMT activity. The sample will be express mailed to Prometheus, Inc. for analysis.

7. Urinalysis

8. Urine pregnancy test

9. The study coordinator will calculate the subject CDAI/mCDAI score based on the subject’s recall of the most recent consecutive seven-day period in which the subject was not taking laxatives or enemas in preparation for tests. This estimated CDAI/mCDAI score will be used to determine if the subject meets the inclusion criteria for the study.

10. Potentially eligible subjects will be asked to stop oral and topical 5-ASA preparations, antibiotics and topical steroids in order to be eligible for the study at the time of the baseline evaluation two weeks later.

11. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed in the use of the diary card and will be asked to complete the diary card for the week preceding the next visit.

12. The subject will be instructed which drugs are allowed and which drugs are forbidden during the study.
13. A screening log will be maintained in which the initials date of birth, and results of screening procedures for each subject screened will be recorded.

14. Smoking use to be recorded

15. Study termination form to be completed if subject withdraws or does not qualify.

16. Once all data concerning subject eligibility is collected and recorded, this information will be entered on study website as either a request for randomization, or as a screen failure.
Visit 1: Baseline Evaluation (week # 0)
Visit Window: Must be within 14 days of Screening
At the time of the baseline evaluation, the following procedures will be performed:

1. Visit Forms Checklist and CRF completion

2. Review of the inclusion and exclusion criteria. The subject will be excluded if the screening evaluation reveals that the subject has absent/low TPMT activity (<6.7 EU/mL RBC).

3. Review and completion of the medical history and demographic characteristics.


5. Laboratory assessments. Blood will be drawn (Adults: 8cc or 1.5 teaspoons or Children: 4cc or 1 teaspoon) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).

6. Calculation by the study coordinator of the CDAI/mCDAI.

7. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

8. Subject will complete the IBDQ/IMPACT.

9. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

10. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

11. For Pediatric subjects, the investigator will record Tanner Staging.

12. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

13. The first 8 weeks of study drug blister packs will be given to the subject. The coordinator will instruct the subject how to take the pills, using the subject dosing instruction sheet.

14. Coordinator will instruct subject on directions and schedule of steroid taper

15. Study termination form to be completed if Subject withdraws or no longer qualifies.
Visit 2: Week 2
Visit Window: -5 days / + 1 day (Days 11-15)
At this visit the following procedures will be done:

1. Subjects have the option to have a phone visit with the coordinator, and have the labs drawn at a local laboratory if more convenient. If they come to the clinic, they will only see the study coordinator; this is not a physician visit.

2. Visit Forms Checklist and CRF completion


4. Laboratory assessments. Blood will be drawn (Adults: 8cc or 1.5 teaspoons or Children: 4cc or 1 teaspoon) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).

5. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

6. Study termination form to be completed if Subject withdraws or no longer qualifies.

7. The subject will be instructed to complete the diary card for the week preceding the next visit.
Visit 3: Week 4
Visit Window: -5 days / + 1 day (Days 23-29)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. Blood will be drawn (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

7. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

8. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

9. Study drug accountability will be assessed by counting unused blisters.

10. Study termination form to be completed if Subject withdraws or no longer qualifies.


12. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.
Visit 4: Week 8
Visit Window: -5 days / + 1 day (Days 51-57)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. Blood will be drawn (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Subject will complete the IBDQ/IMPACT.

7. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

8. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

9. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

10. Study drug accountability will be assessed by counting unused blisters.

11. Study termination form to be completed if Subject withdraws or no longer qualifies.

12. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.

13. Prednisone/Budesonide Medication Log

14. Study drug dispensing of next 4 weeks of blister packs.
Visit 5: Week 12
Visit Window: -5 days / + 1 day (Days 79-85)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

7. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

8. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

9. Study drug accountability will be assessed by counting unused blisters.

10. Study termination form to be completed if Subject withdraws or no longer qualifies.

11. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.

12. Prednisone/Budesonide Medication Log

13. Study drug dispensing of next 4 weeks of blister packs.
Visit 6: Week 16
Visit Window: -5 days / + 1 day (Days 107-113)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. Blood will be drawn (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   c. Hematology (CBC with differential, platelet count)
   d. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   e. 6 TGN, and 6MMPR

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Subject will complete the IBDQ/IMPACT.

7. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

8. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

9. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

10. Study drug accountability will be assessed by counting unused blisters.

11. Study termination form to be completed if Subject withdraws or no longer qualifies.

12. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.

13. Prednisone/Budesonide Medication Log

14. Study drug dispensing of next 4 weeks of blister packs.
Visit 7: Week 20
Visit Window: -5 days / + 1 day (Days 135-141)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

7. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

8. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

9. Study drug accountability will be assessed by counting unused blisters.

10. Study termination form to be completed if Subject withdraws or no longer qualifies.

11. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.

12. Prednisone/Budesonide Medication Log

13. Study drug dispensing of next 4 weeks of blister packs.
Visit 8: Week 24
Visit Window: -5 days / + 1 day (Days 163-169)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Subject will complete the IBDQ/IMPACT.

7. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

8. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

9. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

10. Study drug accountability will be assessed by counting unused blisters.

11. Study termination form to be completed if Subject withdraws or no longer qualifies.

12. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.

13. Prednisone/Budesonide Medication Log

14. Study drug dispensing of next 4 weeks of blister packs.
Visit 9: Week 28
Visit Window: -5 days / + 1 day (Days 191-197)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR, TPMT

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Subject will complete the IBDQ/IMPACT.

7. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

8. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

9. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

10. Study drug accountability will be assessed by counting unused blisters.

11. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.
12. Prednisone/Budesonide Medication Log

13. Study drug dispensing of next 4 weeks of blister packs.

14. Remission Assessment: ONLY Subjects in clinical remission (CDAI <150 and off steroids) at week 28 will continue in the Maintenance Phase. If after week 28 the subjects has a CDAI greater that 200, but less that 300, he/she will be scheduled for an unscheduled visit 4 weeks later. If at any time after week 28, a subjects who develops an increase in CDAI of >100 points from Maintenance Baseline (week 28), or have scores greater that 200 for two consecutive visits will be considered treatment failures.

15. Study termination form to be completed if Subject withdraws or no longer qualifies (see above).
Visit 10: Week 36
Visit Window: -5 days / + 1 day (Days 247-253)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion
2. Brief Physical examination.
3. Laboratory assessments. (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR
4. Calculation by the study coordinator of the CDAI/mCDAI.
5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).
6. Subject will complete the IBDQ/IMPACT.
7. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.
8. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.
9. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.
10. Study drug accountability will be assessed by counting unused blisters.
11. Study termination form to be completed if Subject withdraws or no longer qualifies.
12. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.
13. Prednisone/Budesonide Medication Log
14. Remission Assessment: If after week 28 the subjects has a CDAI greater that 200, but less that 300, he/she will be scheduled for an unscheduled visit 4 weeks later. If at any time after week 28, a subjects who develops an increase in CDAI of >100 points from Maintenance Baseline (week 28), or have scores greater that 200 for two consecutive visits will be considered treatment failures.
15. Study drug dispensing of next 8 weeks of blister packs.
Visit 11: Week 44
Visit Window: -5 days / + 1 day (Days 303-309)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. (13cc or 2.5 teaspoons or Children: 9cc or almost 2 teaspoons) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).
   c. 6 TGN, and 6MMPR

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Subject will complete the IBDQ/IMPACT.

7. Dispensation of the CDAI/mCDAI diary card. The subject will be instructed to complete the diary card for the week preceding the next visit.

8. The subject will be reminded which drugs are allowed and which drugs are forbidden during the study.

9. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

10. Study drug accountability will be assessed by counting unused blisters.

11. Study termination form to be completed if Subject withdraws or no longer qualifies.

12. One week after 6 TGN draw the coordinator will call subject with new dosing instruction.

13. Prednisone/Budesonide Medication Log

14. Remission Assessment: If after week 28 the subject has a CDAI greater than 200, but less than 300, he/she will be scheduled for an unscheduled visit 4 weeks later. If at any time after week 28, a subjects who develops an increase in CDAI of >100 points from Maintenance Baseline (week 28), or have scores greater than 200 for two consecutive visits will be considered treatment failures.

15. Study drug dispensing of last 8 weeks of blister packs.
Visit 12: Week 52
Visit Window: -5 days / + 1 day (Days 359-365)
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Brief Physical examination.

3. Laboratory assessments. Blood will be drawn (Adults: 8cc or 1.5 teaspoons or Children: 4cc or 1 teaspoon) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).

4. Calculation by the study coordinator of the CDAI/mCDAI.

5. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

6. Subject will complete the IBDQ/IMPACT.

7. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

8. Study drug accountability will be assessed by counting unused blisters.

9. Study termination form to be completed for subject’s reaching end of study.

10. Prednisone/Budesonide Medication Log

11. Tanner staging will be recorded for pediatric subjects
SAFETY VISITS
Laboratory evaluations will be done at 1-2 and 3-4 weeks after dose changes, and weekly for toxicity, until it resolves.
At this visit the following procedures will be done:

1. Visit Forms Checklist and CRF completion

2. Laboratory assessments. Blood will be drawn (Adults: 8cc or 1.5 teaspoons or Children: 4cc or 1 teaspoon) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).

3. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

4. Study termination form to be completed if Subject withdraws or no longer qualifies.

UN SCHEDULED/EARLY TERMINATION VISIT
At this visit the following procedures will be done:

1. Brief Physical examination.

2. Laboratory assessments. Blood will be drawn (Adults: 8cc or 1.5 teaspoons or Children: 4cc or 1 teaspoon) for:
   a. Hematology (CBC with differential, platelet count)
   b. Liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin).

3. Calculation by the study coordinator of the CDAI/mCDAI.

4. Subject will complete the IBDQ/IMPACT.

5. Collection of CDAI/mCDAI diary card.

6. Calculation by the study coordinator of the PDAI (in adult subjects with perianal disease).

7. The study coordinator will review previous lab data with subject and ask the subject about any adverse or serious adverse events since the last visit.

8. Study drug accountability will be assessed by counting unused blisters.

9. Study termination form to be completed if Subject withdraws or no longer qualifies.

10. Prednisone/Budesonide Medication Log
**Inclusion criteria**

Male and female patients will be recruited for the study from the participating outpatient gastroenterology clinics. For inclusion in the study subjects must:

1. Be 10-70 years-old.
2. Weigh 20-100 kg (44-220 lbs).
3. Intermediate or High Functional TPMT level at screening visit (≥ 6.7 EU/ml RBC).
4. Have a diagnosis of CD of the ileum, colon or ileocolon, verified by colonoscopy, barium enema, or small bowel series performed within the 36 months prior to randomization. Subjects with perianal fistulae will be eligible provided that the perianal disease does not account for the preponderance of symptoms.
5. Have steroid-dependent or steroid-refractory CD.
   - Subjects with steroid-dependent CD are defined as subjects in clinical remission (CDAI or mCDAI < 150) while receiving prednisone 10-40 mg/day or budesonide 3-9 mg/day for at least 12 weeks prior to screening, but unable to taper prednisone below 10 mg/day or budesonide below 3 mg/day without experiencing a flare within the previous 6 months. Steroids must be at a stable dose for 2 weeks prior to screening (week #2), prednisone at a dose of 10-40 mg/day and budesonide at a dose of 3-9 mg/day.
   - Subjects with steroid-refractory CD are defined as subjects with currently moderately active CD (CDAI or mCDAI 200 – 450) despite treatment with prednisone ≥20 mg/day (if weighing ≥40 kg) or 0.5 mg/kg/day (if weighing <40 kg), or budesonide ≥9 mg/day for the previous 4 weeks prior to the screening evaluation. Prednisone or budesonide must be at a stable dose for 2 weeks prior to screening (week #2).
6. Provide written informed consent to participate in the study and to comply with the protocol requirements. For pediatric subjects, consent will be obtained from the legal guardian.
7. If sexually active, females either have no childbearing potential (i.e. post-menopausal or surgically sterile), or, consent to one acceptable contraceptive method throughout the duration of the study and for 6 weeks after the end of the study. Acceptable methods of contraception include:
   - Double Barrier method (spermicide + condom, diaphragm, cervical cap or sponge)
   - Oral birth control pills administered for at least 1 monthly cycle prior to screening visit
   - Progesterone implanted rods (Norplant®) inserted for at least 1 month prior to the screening visit, but not beyond the 3rd successive year following insertion.
   - Intrauterine devices inserted by a qualified physician.
   - Injectable contraceptives: Medroxyprogesterone acetate (Depo-Provera®) or Lunelle (administered for at least 1 month prior to screening visit).
   - Contraceptive patch (OthoEvra) administered for at least 1 month prior to screening visit
   - Vaginal Ring (Nuvaring) administered for at least 1 month prior to screening visit
8. Females with childbearing potential must also commit not to undergo fertilization procedures or any other procedure intended to result in pregnancy for at least 4 weeks before the trial, during the trial, and for at least 6 weeks after the end of the trial.

9. If the subject is receiving oral or topical 5-Aminosalicylic acid (5-ASA) therapies, topical steroids, ciprofloxacin and metronidazole, then these agents must be discontinued at the screening visit.
Exclusion Criteria

Patients with the following characteristics are ineligible for participation in the study:

1. Active CD isolated to the stomach, duodenum, jejunum, or perianal region, without ileal or colonic involvement (in whom the CDAI has not been evaluated as an outcome measure).

2. CD requiring immediate surgical, endoscopic or radiologic interventions, i.e. those subjects with massive hemorrhage, perforation and sepsis, suppurative complications (intra-abdominal or perianal abscesses), fulminant colitis or toxic megacolon, obstructing stenoses secondary to high grade fibrotic strictures or adhesive processes, and subjects who have failed inpatient management.

3. Severe CD with a CDAI > 450

4. CD requiring hospitalization and intravenous corticosteroids, intravenous antibiotics or total parenteral nutrition (TPN).

5. Nutritional requirement of TPN or enteral nutrition of >1000 Calories/day (both TPN and elemental diets impact the CDAI).

6. History of resection of more than 100 cm of small bowel, total proctocolectomy, or subtotal colectomy with ileorectal anastomosis (interfere with the CDAI).

7. Presence of an ileostomy or colostomy (unevaluable by CDAI).

8. Presence of a known severe fixed symptomatic stenosis of the small or large intestine.

9. Low TPMT activity (<6.7 U/mL RBC) at screening visit.

10. History of a blood transfusion within 3 months before screening (transfusions interfere with the determination of TPMT activity).

11. Any history of past treatment with 6-MP or AZA.

12. Treatment with immunosuppressants or biologic therapies in the 3 months before screening. These therapies have long half-lives and/or prolonged effects. To minimize the risk that of measuring the effects of such prior therapies, subjects who have received the following agents in the 3 months before screening will be excluded:
   - Any investigational drug in the context of a trial.
   - Anti-TNF monoclonal antibody therapies (Infliximab or CDP-571), Interleukin-10, or ISIS 2302 ICAM-1 Antisense
   - Methotrexate, cyclosporin, mycophenolate, tacrolimus, thalidomide

13. Treatment with any of the following medications in the 2 weeks before screening:
   - Allopurinol (inhibits xanthine oxidase and increases the risk of leukopenia).
   - Trimethoprim-sulfamethoxazole (inhibits folate metabolism and may increase the risk of leukopenia).
   - Non-steroidal anti-inflammatory agents (NSAIDs) and aspirin (may cause flares of CD).
14. Treatment with any of the following medications after screening: Oral or topical 5-ASA, rectal steroids, antibiotics (ciprofloxacin, metronidazole).

15. Known malignancy, excluding a non-melanoma skin cancer, or precancerous dysplasia, past or present, excluding non-melanoma skin cancer.

16. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic or cerebral disease.

17. Presence of infections requiring systemic antimicrobial therapy within the last 3 months, or history of opportunistic infections, or HIV.

18. Presence of the following abnormal laboratory parameters:
   - Hemoglobin < 9.0 g/dl
   - WBC < 4,000 / mm³
   - ANC < 1,500 / mm³
   - Platelet count < 120,000 or > 800,000 / mm³
   - ALT/AST > 2 x ULN
   - Alkaline phosphatase or gamma GT > 1.5 x ULN
   - Amylase or lipase > 2 x ULN
   - Creatinine > 1.5 x ULN.

19. Known history of carriage of hepatitis B surface antigen or known history of positive hepatitis C antibody.

20. Presence of an enteric or non-enteric infection at the time of screening.

21. Pregnancy or lactation.

22. In sexually active women of child-bearing potential, lack of one acceptable form of contraception while receiving AZA, and unwillingness to continue such contraception for at least 6 weeks after AZA discontinuation.

23. History of alcohol or other abuse within one year, or any conditions associated with poor compliance.

24. Inability, on the part of the subject or guardian, to understand the nature and requirements of the study, or to report the development of adverse events, or to comply with the protocol procedures.
Criteria for Withdrawal from Study

- Withdrawal of consent
- Development of mild or severe myelosuppression or hepatotoxicity that does not resolve after the drug has been discontinued for 3 weeks
- Development of pancreatitis, defined as abdominal pain accompanied by hyperamylasemia and/or hyperlipasemia (values > 3 x ULN).
- Development of a severe allergic reaction (e.g. fever, hypotension)
- Development of an opportunistic infection with Cytomegalovirus, Varicella zoster virus, Pneumocystis carinii; pneumonia necessitating hospitalization; liver abscess; or any infection that in the judgment of the investigators was related to the use of AZA
- Development of a malignancy aside from non-melanoma skin cancer
- Development of intolerable adverse effects. Mild or tolerable adverse effects (fever, rash, arthralgias, malaise, nausea, diarrhea, abdominal pain not related to pancreatitis) will be handled on a case-by-case basis. Symptomatic therapy will be provided as necessary (i.e. anti-emetics, anti-histamines, acetaminophen, anti-diarrheals)
- Development of any disease that, in the investigators’ judgment, makes continued participation in the study ill advised
- Development of any laboratory abnormalities that, in the investigators’ judgment, make continued participation in the study ill advised
- Development of severe CD requiring parenteral steroids, hospitalization or surgery
- In the induction phase (weeks #1-28), persistent moderate or severe disease (defined by CDAI/mCDAI > 300) after 4 months of treatment
- In the induction phase (weeks #1-28), CDAI/mCDAI score that increases by more than 100 points or goes above 450 points AND does not improve with an increase in the prednisone dose to 40 mg/day
- In the maintenance phase (weeks #28-52), CDAI/mCDAI score greater than 200 for two consecutive visits
- In the maintenance phase (weeks #28-52), treatment with steroids or infliximab for worsening disease
- Worsening perianal disease that makes continued participation in the study ill advised
- After study enrollment, presence of exclusion criteria or failure to meet the inclusion criteria
- Noncompliance with the study drug or taking of forbidden medications
Procedure for Randomizing a Subject

Study ID Numbers
Each site will be provided a Screening and Recruitment Log containing the list of unique StudyIDs generated for that site. Each time a participant signs the informed consent, the site coordinator will assign that subject the next available Study ID from this Log. He/she will enter the initials of the subject and date of screening to indicate that the Study ID has been assigned. This assigned Study ID will be used on all study related documents and for the central labs sent to Prometheus Laboratories, Inc. (TPMT, 6-TGN and 6-MMPR). For other lab tests, follow your local lab’s instructions, as these are standard of care labs and are not blinded (CBC, LFT, Chemistry, UA, Urine β-HCG).

Eligibility
After completion of the screening visit, the site coordinator will review the eligibility criteria and make a determination of eligibility. The results of screening should be recorded on the provided source documents. When all information has been collected as required at screening (except TPMT results), the Coordinator will go to the study website: http://www.cgibd.med.unc.edu/gi and enter the subjects lab values for the screening procedures, as well as the request for randomization.

Randomization
The DMC will process the Request for Randomization, assign the subject to a treatment group, and calculate the initial AZA dose, based upon the weight entered, as well as the TPMT lab results. The Group assignment and dose will be sent to the Pharmacy, with email or fax confirmation of randomization to the Study Administrator and the site coordinator who submitted the request. The Pharmacy will then package and mail the study drug to the Study Coordinator. The coordinator will have the drug for the subject’s baseline visit in which the drug will be allocated.

All screening results (eligible or ineligible) are entered in the Screening and Recruitment Log for that Study ID. However, if the subject is found to be ineligible before labs are drawn you do not need to enter any information on the website. If the subject has blood drawn and the labs values received are exclusionary, you must enter that the subject does not qualify on the website, under the section of randomization.

The TPMT assay results from screening will be sent to the DMC by Prometheus Labs within 3-4 days of the screening visit. These results will be used for calculate the initial AZA dose for subjects randomized to the individualized dose group (Group 2). If TPMT activity is below the minimum required for eligibility, (approximately 1 in 300 subjects) the DMC will notify the site and the Study Administrator to immediately terminate the screening process due to ineligible TPMT activity.
Prohibited Medications

*Prohibited Medications*

*Loperamide, diphenoxylate and codeine are permitted.*

The following medications are not allowed during the study period:

- Any immunosuppressants (including parenteral steroids) other than the study medications
- Allopurinol
- Trimethoprim-sulfamethoxazole
- NSAIDs
- Aspirin >81mg/day
- Cholestyramine or other drugs that interfere with enterohepatic circulation
- Metronidazole or quinolones
- Topical corticosteroids
- Oral or topical 5-aminosalicylates
- Furosemide or thiazide diuretics
- Fish oil preparations

Any prohibited medications taken during the study must be recorded on the subject’s CRF and must be entered into the Protocol Deviation Log. The study administrator must be contacted to determine if the subject will be terminated.
Dose Adjustments

Dose adjustments will be made for 2 reasons:
- Toxicity
- 6-TGN activity as defined by blood levels sent to Prometheus Laboratories at weeks: 4, 8, 12, 16, 20, 24, 28, 36, and 44.

Mild Toxicity (Myelosuppression or Hepatotoxicity):
Mild myelosuppression
WBC ≤ 3,500 / mm³, > 3,000 / mm³
ANC ≤ 2,000 / mm³, > 1,500 / mm³
Platelet count ≤ 120,000 / mm³, > 100,000 / mm³

Mild hepatotoxicity
AST or ALT > 90 U/L - <180 U/L

For subjects developing mild myelosuppression or mild hepatotoxicity, the dose will be reduced by 50% (by taking study drug every other day). Laboratory assessments will be performed weekly. The 50% dose reduction will remain stable for as long as mild myelosuppression or mild hepatotoxicity persists. If these abnormalities resolve, the dose will be increased. If the dose is > 50mg, the dose will be increased by one 25 mg increment once every 4 weeks. If the dose is <50 mg, the dose will be increased by one 12.5 mg increment every 4 weeks. The dose maximum will be 75% of the dose at which the subject first developed myelosuppression or hepatotoxicity. This dose will remain the same for the length of the trial. No further dose-adjustments will be made for subjects in the individualized-dose group, regardless of metabolite levels. Laboratory assessments will be performed weekly during period of toxicity and then 1-2 weeks and 3-4 weeks after the change of dose when the toxicity resolves.

Individual sites will receive fax correspondence detailing instructions for dose modification due to toxicity. Study Coordinators will be responsible for notifying subjects of their dose change. Safety blood work will then need to be repeated weekly until the toxicity resolves. Once resolved, the un-blinded physician at the DMC will re-write the prescription and send it to the appropriate pharmacy gradually increasing the dose to 75% of the original dose. A new blister pack will be sent to the site with each dose change.

Severe Toxicity
Severe myelosuppression
WBC ≤ 3,000 / mm³
ANC ≤ 1,500 / mm³
Platelet count ≤ 100,000 / mm³

Severe hepatotoxicity
AST or ALT ≥ 180 U/L

For subjects developing severe myelosuppression or severe hepatotoxicity, the drug will be stopped and laboratory assessments will be performed weekly. Once the investigator or coordinator receives laboratory records showing the subject has severe toxicity, the investigator/coordinator is responsible for notifying the subject of the lab result, and instructing the subject to stop taking the drug. Within 24 hours of entering in lab data onto the website, the DMC will fax instructions to the coordinator detailing the instruction for dose modification. If the abnormalities do not resolve within 3 weeks, the drug will
be discontinued permanently and the subject will be considered a treatment failure. If the abnormalities resolve to parameters within the “mild” category, within 3 weeks, the drug will be restarted at a dose equal to 25% of the dose at which the subject developed myelosuppression or hepatotoxicity.

The 25% dose will remain stable for as long as mild abnormalities persist. If these abnormalities resolve, the dose will be increased by a 25 mg increment once every 4 weeks if the dose is \( \geq 50\text{mg} \). If the dose is <50 mg, the dose will be increased by a 12.5 mg increment once every 4 weeks. The maximum dose will be 50% of the dose at which the subject first developed myelosuppression or hepatotoxicity. The dose will then remain the same for the remainder of the trial. Laboratory assessments will be performed weekly during period of toxicity and then 1-2 weeks and 3-4 weeks after the change of dose when the toxicity resolves.

**6-TGN:**

If the subject is randomized to Group II, then based on 6-TGN levels, the dose may be adjusted based on the following 6-TGN levels (pmol/8 x 108 RBCs):

<table>
<thead>
<tr>
<th>6-TGN Levels (pmol/8 x 108 RBCs)</th>
<th>Increase Dose by 25 mg/d</th>
<th>No Dose Change</th>
<th>Decrease Dose by 25 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 250</td>
<td>(or 12.5 mg/d if total dose &lt; 50 mg/d)</td>
<td>No dose change</td>
<td>(or 12.5 mg/d if total dose &lt; 50 mg/d)</td>
</tr>
<tr>
<td>250-400</td>
<td>No dose change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 400</td>
<td>No dose change</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results of the 6-TGN metabolite levels will be received by the DMC approximately one week following the blood draw. If a dose modification is needed, the DMC will send the new dose prescription to the pharmacy and notify the Site Coordinator the new instructions for the subject. The study coordinator will be responsible for alerting the subject of new dosing instructions.
Definitions of Adverse Events

- **Adverse Event (AE)** - An AE is any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, whether or not related to the intervention.

- **Unexpected Adverse Event** - An unexpected adverse event is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product/device or package insert/summary of product characteristics for an approved product or device).

- **Serious Adverse Event (SAE)** - An SAE is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

  - **Death**: Report if the subject’s death is suspected as being a direct outcome of the adverse event
  - **Life Threatening**: Report if the subject was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the study drug would result in the subject’s death
  - **Hospitalization (initial or prolonged)**: Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event
  - **Disability**: An adverse event that results in a significant, persistent, or permanent change, impairment, damage or disruption in the subject’s body function/structure, physical activities or quality of life
  - **Congenital anomaly**: Report if there are suspicions that exposure to the study drug prior to conception or during pregnancy resulted in an adverse outcome in the child.
  - **Requires intervention to prevent permanent impairment or damage**: Report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent damage to a subject.
Adverse Event Recording

At each visit, the subject will be questioned about AEs. All adverse events experienced by the subject during administration of the study drug should be recorded in the subject’s study chart or source document. Include new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity. Subjects who develop AEs will be monitored until there is a return to normal or until the outcome is resolved. The subject will continue to be followed after completing the study if the AE has not resolved at the end of the study period. Adverse events will be monitored at scheduled monitoring visits and do not need to be faxed to the Study Administrator. The severity of myelosuppression and hepatotoxicity is defined below: These events are considered AE’s, unless the subject requires hospitalization or emergency medical intervention, which would qualify as an SAE.

Mild myelosuppression
WBC ≤ 3,500 / mm3, > 3,000 / mm3
ANC ≤ 2,000 / mm3, > 1,500 / mm3
Platelet count ≤ 120,000 / mm3, > 100,000 / mm3

Mild hepatotoxicity
AST or ALT ≥ x 2 ULN and < 4 x ULN

Severe myelosuppression
WBC ≤ 3,000 / mm3
ANC ≤ 1,500 / mm3
Platelet count ≤ 100,000 / mm3

Severe hepatotoxicity
AST or ALT ≥ x 4 ULN

Instructions for Recording AEs:
The Coordinator/Investigator will record the AEs believed to be possibly, probably or definitely related to AZA on the CRF AE form, and report them to their local IRB. Complete all cells in chart, except for date of resolution if an AE if unresolved. Adverse events will be monitored at scheduled monitoring visits and do not need to be faxed to the Study Administrator. (SAEs however, will be recorded and reported to the Study Administrator no later than 24 hours after knowledge of occurrence).

1. Subject Initials: Enter subject initials in spaces provided at the top of the page. Each subject will have a separate log.
2. CoStart coded #: LEAVE BLANK. This number is to be filled in by Study Administrator.
3. Adverse Event: enter diagnosis, sign or symptom, and use a separate line for multiple symptoms.
4. Date of Onset: Enter Month, Day and 2 digit Year that sign or symptom began.
5. Resolution: Enter 1 if AE is resolved, 2 if AE is Unresolved or Ongoing, and 3 if Fatal and subject has died.
6. Date of Resolution: Enter the date the AE was resolved.
7. **Duration:** Indicate how long the adverse event lasted if less than 24 hours. Approximate the length of time in hours, and/or minutes and/or seconds.

8. **Relationship to study drug:** In the opinion of the Investigator, enter the relationship between the adverse event and the study drug.
   - **Unrelated:** AE is definitely not related to the study drug
   - **Unlikely:** AE has little or no relationship to the study drug. More than likely an alternative etiology exists.
   - **Possible:** AE has a strong relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
   - **Probable:** AE has a strong relationship to the study drug and another etiology is unlikely.
   - **Definite:** AE is positively related.

9. **Action:** Enter appropriate action taken concerning the study drug.
   - Enter 0 if no action has been taken with the study drug.
   - Enter 1 if study drug has been reduced.
   - Enter 2 if study drug has been interrupted.
   - Enter 3 if study drug has been discontinued.

10. **Withdraw:** Indicate if the subject has been withdrawn from the study due to the AE.
    - Enter 1 if subject did not withdraw from the study due to the AE.
    - Enter 2 if subject has withdrawn from the study due to the AE.

11. **Serious:** Indicate whether or not the AE meets the definition of serious.
    - Enter 1 if the AE does not meet the definition of serious.
    - Enter 2 if the AE meets the definition of serious.
Serious Adverse Event Recording and Reporting

Investigators will document all Serious and/or Unexpected AEs on the CRF AE and SAE forms, which will assess the possible relationship to the study drug. The investigators will record the AEs believed to be possibly, probably or definitely related to AZA on the CRF AE form, and report them to their local IRB. AEs believed to be possibly, probably or definitely related to AZA, which are also both serious and unexpected, must be reported to both the IRB as well as the Study Administrator, who will then report to appropriate authorities, including the FDA, in accord with IND regulations. SAEs will be reported to both the Study Administrator and the site’s IRB within 24 hours of recognition. The Coordinating Center will notify all investigators, via MedWatch reports, of all SAEs that are considered unexpected and at least possibly associated with AZA per FDA regulations.

Instructions for Recording an SAE:
Fill out the both the AE and SAE forms as completely as possible. It is very important to capture how long the time interval was between taking the study drug and the onset of symptoms, as well as to answer the questions thoroughly. The reporting investigator must sign and date this form.

Serious Adverse Events Form

1. **Subject Initials:** Enter subject initials in spaces provided at the top of the page. Each subject will have a separate log.
2. **Initial or Follow up:** Indicate if report being completed is the initial report or the follow up report by checking the appropriate box.
3. **Sex:** Enter the subject’s sex by checking male or female.
4. **Date of Birth:** Enter the subject’s date of birth in the format mm/dd/yy.
5. **Weight:** Enter the subject’s weight in kilograms.
6. **Ethnicity and Race:** Enter the subject’s corresponding ethnic and race category, if the subject does not wish to answer, check refused.
7. **Time Interval:** Enter the time interval between taking the study drug (the last dose before the symptoms) and the subsequent onset of symptoms. Circle the corresponding units: either seconds, minutes hours or days.
8. **Study Drug:** Enter the name of the study drug (Azathioprine). Since the study is blinded, the dose is unknown.
9. **Frequency:** Enter the frequency (QD)
10. **Route:** Enter the route of administration (PO)
11. **Date Started:** Enter the date the SAE began in the mm/dd/yy format.
12. **Date Stopped:** Enter the date the SAE stopped in the mm/dd/yy format. If ongoing do not fill this section out.
13. **Indicate How the Event Met the Definition of Serious:**
   - Check 1 for a fatal event.
   - Check 2 for a life-threatening event.
   - Check 3 for inpatient hospitalization required.
   - Check 4 for prolonged hospitalization.
   - Check 5 if event was disabling or incapacitating.
   - Check 6 if event is a result of an overdose.
   - Check 7 event resulted in cancer.
   - Check 8 if event resulted in a congenital anomaly.
   - Check 9 if met the definition of serious is any other way. Enter the details in the brief description field.
14. **What Caused the SAE:** According to the Investigator, specify all possible causes of the event from the list:
   - Check 1 if the study drug cause the event
   - Check 2 if lack of study drug efficacy caused the event
   - Check 3 if withdrawal of the study drug caused the event
   - Check 4 if concurrent medications cause the event, and specify medication
   - Check 5 if a concurrent disorder cause the event, and specify disorder
   - Check 6 if the reason is not listed, or another concurrent reason exists

15. **Description of the SAE:** Give a description of the events that have occurred, and any relevant information that will help explain the event, including but not limited to: clinical presentation, treatments, laboratory test or procedures

16. **Relevant Medical History:** Describe any medical disorders (Crohn’s disease) as well as any relevant concurrent disorders, allergies, or surgeries that may help explain this event.

17. **Date of Onset:** Record the date of onset for the corresponding entry in the relevant medical history section. Record in the mm/dd/yy format.

18. **Condition still present:** Enter yes or no to the corresponding entry in the relevant medical history.

19. **Subject Died:** If the subject died, list cause of death

20. **Autopsy:** Check yes or no if an autopsy was performed. If yes, attach the autopsy report. If it is not yet available, include the report in the Follow-up SAE report as soon as it is available.

21. **Reporting Investigator and Signature:** This is very important!! You must have the investigator write and sign this report.

22. **Site and Address:** write in your site name and address

23. **Date:** Write in the date this report was filled out.

**SAE Reporting**

After the form has been filled out and signed, fax it to the Study Administrator, using the designated fax transmittal form to:

   Jennifer Bentsen        FAX: 773-834-4172
   Study Administrator     Phone: 773-834-4176

**You must fill out and FAX the form within 24 hours of the knowledge of the SAE**

The Study Administrator will confirm with the site and obtain any missing information, meanwhile notify the study PI, Dr. Hanauer as well as the independent safety officer. After the event has been assessed, a Med Watch form will be sent to all sites as well as the FDA, and the DSMB.

**Follow up Reports:**

Any additional information about an SAE should be reported within 24 hours of obtaining the additional information. Use the SAE form, and follow the same instructions, but check the box for Follow-up.
**ADVERSE EVENTS**

**Instructions:** Please record all adverse events. If an adverse event is serious (see definition below), a Serious Adverse Event Form should be completed for that event. All cells should be completed, except for Date of Resolution when resolution of an AE in unresolved.

<table>
<thead>
<tr>
<th>Line #</th>
<th>Coded #</th>
<th>ADVERSE EVENT</th>
<th>DATE OF ONSET</th>
<th>Resolution</th>
<th>Date of Resolution</th>
<th>Duration</th>
<th>Relationship to study drug</th>
<th>Action</th>
<th>Withdraw</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Diagnosis, Sign or Symptom</td>
<td>MONTH/DAY/YEAR</td>
<td>1 = Resolved 2 = Unresolved 3 = Fatal</td>
<td>Month/day/year</td>
<td>1=Unrelated 2=Unlikely 3=Possible 4=Probable 5=Definite</td>
<td>Action taken with study drug. 0=None 1=Reduced 2=Interrupted 3=Discontinued</td>
<td>Did the subject withdraw from study due to AE? 1=No 2=Yes</td>
<td>Does the AE meet the definition of serious? 1=No 2=Yes</td>
<td></td>
</tr>
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<td>2</td>
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</tr>
</tbody>
</table>

**EXAMPLE ONLY**
# SERIOUS ADVERSE EVENTS

**Sex:** ___ Male  
___ Female  

**Ethnic:**  
□ Hispanic or Latino  
□ Not Hispanic or Latino  
□ Unknown  
□ Black or African American  
□ White  
□ Other  
□ More than one race  
□ Refused  

**Race:**  
□ American Indian / Alaska Native  
□ Asian  
□ Native Hawaiian / Other Pacific Islander  
□ American Indian / Alaska Native  
□ Asian  
□ Native Hawaiian / Other Pacific Islander  
□ Refused  

**DOB:** ____ / ____ / _________  
□ Refused  

**Weight:** _____ . ___ kg  

**Study Drug**  
(If study is blinded, complete only route, therapy dates)  

<table>
<thead>
<tr>
<th>Dose</th>
<th>Units</th>
<th>Freq.</th>
<th>Route</th>
<th>Date Started</th>
<th>Date Stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Time interval between taking the study drug (the last dose before the symptoms) and the subsequent onset of symptoms:**  
Circle units: secs mins hours days  

**Why was the event serious?**  
(Please check all that apply)  
___ 1. Fatal event  
___ 2. Life-threatening event  
___ 3. Inpatient hospitalization required  
___ 4. Hospitalization prolonged  
___ 5. Disabling or incapacitating  
___ 6. Result of an overdose  

**What, in your opinion caused the event?**  
(Please check all that apply)  
___ 1. Study drug  
___ 2. Lack of efficacy  
___ 3. Withdrawal of study drug  
___ 4. Concurrent medication, specify__________________  
___ 5. Concurrent disorder, specify ____________________  
___ 6. Other, specify________________________________  

**Brief description of clinical presentation, treatment and evolution of the event and any other assessments (e.g. laboratory data) which help explain the event and have not been recorded elsewhere on these forms:**  
_______________________________________________________________________________________________________________________________  
____________________________________________________________________________________________________________________________________________________

**Relevant Medical History**  
(please specify below any medical disorders, allergies, surgeries which help explain the event):  

<table>
<thead>
<tr>
<th>Date of Onset</th>
<th>Condition Still Present? (No/Yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>Day</td>
</tr>
<tr>
<td>1. _______ / _______ / _______</td>
<td>__ Yes _ No</td>
</tr>
<tr>
<td>2. _______ / _______ / _______</td>
<td>__ Yes _ No</td>
</tr>
<tr>
<td>3. _______ / _______ / _______</td>
<td>__ Yes _ No</td>
</tr>
<tr>
<td>4. _______ / _______ / _______</td>
<td>__ Yes _ No</td>
</tr>
</tbody>
</table>

**If patient died, cause of death:**  
_______________________________________________________________________________________________________________________________  

**Was an autopsy done?**  
____ Yes  ____ No  
If YES, attach report or send as soon as possible

**Reporting Investigator:**  
__________________________________________________________________________  
**Address:**  
__________________________________________________________________________  
**Date:** ____ / _____ / ________  
Month      Day          Year
Emergency Unblinding Procedure

A subject’s blinded dosing information is available if an emergency occurs, and the dose of AZA is required.

In order for the blind to be broken, you must contact the Data Coordinating Center. During regular business hours of 9am-6pm (central time) call the Study Administrator, at 773-834-4176. The study administrator will contact Dr. Hanauer to receive permission to break the blind. Dr. Hanauer will then contact Dr. Sandler at the Data Monitoring Center, who will call the Site Investigator with the blinded information.

If the blind needs to be broken after business hours, or on the weekend, page Dr. Hanauer at: 773-702-6800, pager # 3046.

If the blind needs to be broken, the following information will be needed to break the blind:

1. Site #
2. Subject ID #
3. Reason for Unblinding

After the blind has been broken, the person’s who are no longer blinded need be recorded on the source documentation.
Participating Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Local P.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Chicago Hospitals, Chicago, IL</td>
<td>Stephen B. Hanauer, MD (Adults)</td>
</tr>
<tr>
<td></td>
<td>Barbara S. Kirschner, MD (Peds)</td>
</tr>
<tr>
<td>Johns Hopkins University, Baltimore, MD</td>
<td>Themistocles Dassopoulos, M.D.</td>
</tr>
<tr>
<td>Hospital for Sick Children, Toronto</td>
<td>Ann M. Griffiths, M.D. (Peds)</td>
</tr>
<tr>
<td>University of North Carolina, Chapel Hill, NC</td>
<td>Kim L. Isaacs, M.D., Ph.D.</td>
</tr>
<tr>
<td>Atlanta Gastroenterology Associates, Atlanta, GA</td>
<td>Douglas C. Wolf, M.D.</td>
</tr>
<tr>
<td>Cedars-Sinai Medical Center, Los Angeles, CA</td>
<td>Eric A. Vasiliauskas, M.D. (Adults)</td>
</tr>
<tr>
<td>Sainte-Justine Hospital, Montreal, Quebec</td>
<td>Marla Dubinsky, M.D. (Peds)</td>
</tr>
<tr>
<td>Mount Sinai Hospital, New York, NY</td>
<td>Ernest G. Seidman, M.D. (Peds)</td>
</tr>
<tr>
<td>University of Pittsburgh Medical Center, Pittsburgh, PA</td>
<td>Daniel H. Present, M.D.</td>
</tr>
<tr>
<td>University of Western Ontario, London, Ontario</td>
<td>Miguel Regueiro, M.D.</td>
</tr>
<tr>
<td>University of Alberta, Edmonton, Alberta</td>
<td>Brian Feagan, M.D.</td>
</tr>
<tr>
<td>Cincinnati Children’s Hospital Medical Center</td>
<td>Richard N. Fedorak, M.D.</td>
</tr>
<tr>
<td>University of Toronto, Toronto, Ontario</td>
<td>M. Susan Moyer, M.D. (Peds)</td>
</tr>
<tr>
<td>North Shore University Hospital, Manhasset, NY</td>
<td>Gordon R. Greenberg, M.D.</td>
</tr>
<tr>
<td>Mayo Clinic, Rochester, MN</td>
<td>James Markowitz, M.D. (Peds)</td>
</tr>
<tr>
<td></td>
<td>William J. Sandborn, M.D.</td>
</tr>
</tbody>
</table>

Responsibilities of the sites include:

- **In order to achieve the expected enrollment of 262 total participants, each site is expected to enroll 10-15 participants in a three year period.**
- Assuring that the study is conducted according to the most current IRB/EC approved Protocol and Manual of Operations and Procedures
- Identifying, recruiting, screening and enrolling participants in this trial.
- Protecting participants' rights
- Obtaining informed consent from each participant
- Collecting study data and following participants through study completion
• Retaining specific records, (e.g., Case report forms, laboratory results, drug distribution records, source documentation)
• Preparing and sending required forms reports to coordinating center in a timely manner (e.g., screening and enrollment log, eligibility and enrollment log, Case Report Forms, adverse event reporting and follow up)
• Assuring IRB review and approval of Protocol, Consent form and Manual of Operations and Procedures, including all subsequent amendments
• Communicating questions, concerns, and/or observations to the Principal Investigator and/or Coordinating Center
• Compliance with all regulation as indicated on signed FORM FDA 1572, or equivalent
Data Coordinating Center (DCC)

The Data Coordinating Center is located at the University of Chicago, and is responsible for the management and administration of the trial. Specific responsibilities of the DCC include:

- Correspond with the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Health Canada and the Data and Safety Monitoring Board (DSMB) to obtain approval and guidelines for conducting this trial
- Collection and approval of all site Regulatory Documents
- Development of Clinical site agreements and budgets in compliance with NIH guidelines
- Collection and approval of site Enrollment /Randomization log and Case Report Forms
- Confirmation to site of approved and enrolled subjects
- Review CRF data prior to submission to DMC to ensure completeness
- Organize and implement site initiation teleconference
- Ensure site’s understanding of Protocol and Manual of Operations and Procedures
- Account for all shipments of study drug
- Report and confirm change of dosing as specified in the protocol to clinical sites
- Reporting of Serious Adverse Events to the FDA, and participating sites
- Communication with clinical sites
- Periodic site monitoring visits to ensure adherence to the protocol and procedures
- Issue reports of study progress to clinical sites and the NIH
- Distribution of any changes or updates in pertinent study documents to the NIH as well as all participating clinical sites
- Coordinate with Prometheus Laboratories for blood samples, active drug and placebo shipments
Data Management Center (DMC)

The Data Management Center is responsible for creating and implementing tools to capture and analyze study data, as well as provide troubleshooting and statistical analysis. The DMC is located at the University of North Carolina, Chapel Hill and is also the data management center for the Clinical Alliance of the CCFA as well as a number of epidemiological studies and clinical trials. Robert Sandler, MD, MPH will be responsible for overseeing all aspects of the operation of the DMC. The specific responsibilities of the DMC include:

- Developing Case Report Forms, and Case Report Form Guidelines
- Developing computer algorithms to monitor laboratory values and adjust drug doses
- Developing the website for sites to enter laboratory data
- Developing interface between DCC and DMC to ensure data is collected and correct, and all dose changes and drug shipments have been completed
- Data entry of CRFs, as well as any other relevant data collected
- Communication with Prometheus Laboratory for results of blood work
- Communication with the Investigational Pharmacy to implement dose change
- Developing and performing data analysis, as well as preparing reports of analysis

Address: (Mail Case Report Forms to this address, Attn: Ella Akin)
The University of North Carolina
CGIBD
CB# 7555, 4160-Q Bioinformatics Building
130 Mason Farm Road
University of North Carolina
Chapel Hill, NC  27599-7555

Phone: 919-966-9340
Steering Committee

The Steering Committee will consist of Dr. Hanauer as chairman, and Drs. Ernest Seidman, Themistocles Dassopoulos, Marla Dubinsky and Robert Sandler as members. The committee will meet quarterly to assess enrollment and to address any issues regarding recruitment and trial operations. The committee will address any questions related to eligibility, protocol violations or study inquiries. The Steering Committee and the P.I. will communicate with the NIH-assigned Data and Safety Monitoring Board (DSMB) and provide case-reports of all adverse events occurring during the trial on a quarterly basis. Any serious, unexpected, or life-threatening adverse events will be communicated to the DSMB as they accrue. The Steering Committee is responsible for the following areas:

- The general design and conduct of the trial
- Review of data collection practices and procedures
- Change study procedures as appropriate
- Appointments to and disbanding of study implementation subcommittees
- Review of study progress in achieving goals and taking necessary steps to enhance the likelihood of achieving these goals
- Review and implementation of recommendations from the DSMB for protocol treatment amendments (e.g., termination of treatment due to lack of efficacy)
- Review and respond to other general advice and/or recommendations from the DSMB
Investigational Pharmacy Service (IPS)

The Investigational Pharmacy is located at the University of Chicago and is responsible for the storage, dispensing and accountability of the investigational agent. The pharmacist at the IPS will accept drug shipments from Prometheus Laboratories, package and allocate the drug to the study sites according to instructions from the DMC. The un-blinded physician at the DMC will be responsible for writing the prescription for the subjects as doses change. All dosing changes will be blinded to the subject, coordinator and treating physician. The only un-blinded study personnel include the central pharmacist and the un-blinded physician at the DMC. Specific Responsibilities of the IPS are:

- Receive and store Azathioprine and placebo tablets from Prometheus Laboratories, Inc.
- Develop dosing regimen based on DMC prescription
- Package drug into blister card
- Record and store all subject dosing regimen information and prescriptions
- Communicate with DCC that new drug or new dosing instruction needs to be allocated to site’s study coordinator
The Data and Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) will monitor the safety of the trial and will recommend possible termination in the event of early significant findings, whether these findings are favorable or unfavorable for the experimental intervention. The DSMB will remain a neutral body, communicating advice or concerns to the P.I of the study through the NIDDK Program Director, Patricia Robuck, Ph.D. Likewise, the NIDDK will act as the liaison between the P.I. and DSMB. Meetings of the DSMB will be held twice per year, and will alternate between in-person meeting and conference call. The DSMB responsibilities include:

- Approve the initiation of the trial
- Review protocol, informed consent documents, plans for data safety and monitoring
- Evaluate study progress, including periodic assessments of data quality, participant recruitment and retention, participant risk versus benefit, site performance, and other factors that may affect study outcome
- Consider external factors such as scientific or therapeutic developments that may impact on the safety of the participants or the ethics of the trial
- Protect the safety and scientific progress of the trial
- Make recommendations to the Principal Investigator, and, if required, to the FDA regarding continuation, termination, or other modifications to the study based on observed beneficial or adverse effects of the treatment under study; Recommendations should be in accordance with stopping rules, which are clearly defined prior to data analysis and have the approval of the DSMB
- Ensure data integrity
- Ensure the confidentiality of the trial data and the monitoring results
- Provide recommendations on any problems with study conduct, enrollment, sample size, and/or data collection.

DSMB Members

The DSMB has been appointed by the NIDDK and consists of 5 individuals with relevant clinical and statistical experience. Three members constitute a quorum. The members are persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Written attestation to absence of conflict of interest is required. The DSMB includes experts or representatives in the fields of relevant clinical expertise, clinical trial methodology and biostatistics. The members are:

- Gary Lichtenstein, MD, University of Pennsylvania
- John Singleton, MD, University of Colorado
- Hillary Steinhart, MD, Mount Sinai Hospital/University Health Network (Toronto)
- Harland Winter, MD, MassGeneral Hospital for Children
- Kevin Kip, PhD (statistician), University of Pittsburgh School of Public Health

Dr. Gary Lichtenstein has been selected as the Chairperson of the DSMB. The Chair will oversee the meetings, as well as develop the agenda in conjunction with the NIDDK Program Official and the Primary Investigator. The Chair is the contact person for the DSMB. The University of Chicago will provide the logistical management and support of the DSMB.
Michael Becker, M.D, Professor of Medicine at the University of Chicago has been appointed by Dr. Hanauer as the Safety Officer for this trial. Dr. Becker will be the contact for severe adverse event (SAE) reporting, and will review and assess all safety reports. He will also evaluate whether the number and type of events are reasonable.

**DSMB Process**

A face to face meeting will be scheduled, and include all DSMB members, to take place before subject enrollment. The issues to be discussed at this meeting will be the protocol, any modifications of the trial, guidelines to monitor the study, procedures for reporting adverse events and statistical considerations.

Thereafter, meetings of the DSMB will be held twice per year, and will alternate between a conference call and an in-person meeting. Emergency meetings may be called at any time by the chairperson or the NIH/NIDDK should questions of subject safety arise. Meetings shall be closed to the public because discussions may address confidential patient data.

**Reports**

**Interim Reports:** Interim reports will be prepared by the Data Coordinating Center, located at the University of Chicago, in conjunction with the statistician at The Data Monitoring Center (DMC), an independent entity from the U of C which will collect and analyze the study data. The reports will be distributed 10 days prior to the scheduled meeting and provided in a confidential manner preferred by the members (either secure e-mail, or express mailed in a sealed envelope). The reports will contain information specified by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports will be in two parts:

Part 1: This will be an open session report and provide information on study accrual, and other general information on study status. The PI, and appointed study staff, as well as the statistician, will be present in this session. The reports contained in this section will include:

- Comparison of Target Enrollment to Actual Enrollment by Month
- Comparison of Target Enrollment to Actual Enrollment by Site
- Overall Subject Status by Site, including: Subjects screened, Enrolled, Active, Completed and Terminated
- Demographic and Key Baseline Characteristics by Group
- Treatment Duration for all Subjects
- Treatment Duration for Subjects who Discontinue Therapy
- Adverse Events/ Serious Adverse Events by Site and Subject

Part 2: This will be a closed session involving only the DSMB members and the study statistician. The session will provide data concerning safety, including serious adverse events or termination. While unlikely, due to the well-recognized safety profile of azathioprine, the study statistician may distribute interim reports to the DSMB between meetings to allow members to call special sessions when appropriate. The safety reports will be in aggregate fashion and by blinded treatment groups. The DSMB may request that the treatment groups be unblinded to ensure that there are no untoward treatment effects. The Closed Session Report is confidential information and will be destroyed at the conclusion of the meeting.
**Post Meeting Report:** A formal report containing the recommendations for continuation or modification of the study will be prepared by the NIDDK with the concurrence of the DSMB Chairman and sent to the other Board members within 4 weeks of the meeting. Once approved by the DSMB, the NIDDK will forward the formal DSMB recommendation report to the PI. The PI will respond in writing to the action items noted by the DSMB, and forward the report to the NIDDK Program Director. The DSMB report will conclude with a recommendation to either continue or to terminate the study. The recommendation will be made by a formal majority vote.

**E. Stopping Rules and Interim Analysis:** Due to the well-recognized safety profile of azathioprine and the background studies in Crohn’s disease, it is not anticipated that unblinding will be necessary. No interim analysis for safety or efficacy is anticipated. No “stopping rules” will be specified due to the well-recognized safety profile of azathioprine.
Written Informed Consent Checklist

☐ The Informed Consent Process must take place prior to any study related screening.
   Comments:
   Date of consent process:
   Person conducting:

☐ Give the subject adequate information concerning the study
   *Subject should not be sedated
   *Use IRB approved informed consent to provide the written information and detailed description of the study
   Comments:

☐ Provide adequate opportunity for the subject to consider all options
   *Subject should not be moments away from a stressful/invasive procedure
   Comments:

☐ Respond to the subject's questions
   Comments:

☐ Ensure that the subject has comprehended this information
   *Document how information was comprehended
   Comments:

☐ Obtain the subject's voluntary agreement to participate by signing the consent
   *The subject needs to complete the time and date
   *The subject should initial all pages of the informed consent
   Comments:

☐ Provide copy of signed and dated consent and HIPAA authorization if applicable to the subject
   Comments:

☐ Continue to provide information as the subject as situation requires
   *Re-consent as needed (see IRB policy)
   Comments:

*To be effective, the process should provide ample opportunity for the investigator and the subject to exchange information and ask questions.

Other Comments:

Signature with title: __________________________ Date: __________________________

Principal Investigator __________________________ Date: __________________________
SAMPLE CONSENT TEMPLATE
CONSENT BY SUBJECT FOR PARTICIPATION IN A RESEARCH PROTOCOL

Protocol Number: Name of Subject: _________________________________
Medical History Number: _________________________________

Title of Protocol: Multi-site Trial of Azathioprine Dosing in Crohn’s Disease

Doctor(s) Directing Research

Address:

Phone:

“You” refers to “you/ your child” throughout the consent form as minors may be enrolled in this study. You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form.

WHY IS THIS STUDY BEING DONE?
This is a medical research study for patients with Crohn’s disease who depend on steroids (anti-inflammatory medications like prednisone or budesonide) for control of their symptoms, or who are not responding to steroid treatment. This study will compare two different experimental treatments with a drug called azathioprine (Imuran®, manufactured by Prometheus, Inc.).

Azathioprine was originally developed for kidney transplant patients to prevent rejection of the transplanted kidney. It was then found to have effects in medical conditions where the immune system (the body system that protects a person against foreign substances or infections) is overactive. Azathioprine is an immunosuppressant drug. Immunosuppressant drugs suppress the immune system in conditions where the immune system is overactive. By bringing the overactive immune system down toward normal, immunosuppressant drugs decrease the tissue damage and patients improve. The FDA has approved azathioprine for use in kidney transplantation and rheumatoid arthritis. In gastroenterology (the diagnosis and treatment of diseases and disorders affecting the digestive system), the drug has now been demonstrated to be very useful in Crohn's disease. Azathioprine is experimental (not approved by the FDA) in treating Crohn’s Disease.

Crohn’s disease is a disease characterized by inflammation (swelling and redness) and ulceration (beginning formation of a hole) of the intestines and digestive tract. Physicians treat Crohn’s disease with medications for diarrhea and infection, immunosuppressant drugs, and surgery. Azathioprine, itself, does not fight inflammation. After azathioprine gets into the bloodstream and reaches the tissues, the tissues change azathioprine into the substances that actually fight inflammation. Scientists are able to measure these substances, called 6-TGN (short for “6-thioguanine nucleotides”), in the bloodstream. The more 6-TGN circulates in the blood, the more successful the body is in fighting inflammation. However, not everyone makes the same amount of 6-TGN. In fact, a protein in the tissues called TPMT turns azathioprine into substances that are not as powerful as 6-TGN in fighting inflammation. If a person has low levels of TPMT, he or she will make more 6-TGN. On the other hand, if a person has high levels of TPMT, he or she will
The purpose of this study is to determine if there is a difference between two different methods of deciding the dose of azathioprine. The usual method is to base the dose on the person’s weight. The experimental method is to base the dose on the body’s ability to make the 6-TGN compounds.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

You are asked to participate in this research study that will involve approximately 262 subjects in several different hospitals across the United States and Canada.

**WHAT IS INVOLVED IN THE STUDY?**

If you agree to participate in this study you must sign and date a consent form prior to the screening procedures. The screening procedures will help determine if you meet the study entrance requirements. They include: a review of your Crohn’s medical history (for example: number and types of surgical procedures, complications from Crohn’s disease, treatments used to fight the disease, etc.), a complete physical examination including vital signs (weight, height, temperature, pulse, blood pressure) and an evaluation of your Crohn’s symptoms as measured by the Crohn’s Disease Activity Index (CDAI). If you have perianal disease, the doctor will perform a fistula examination and ask you questions about your symptoms for measure on the Perianal Disease Activity Index (PDAI).

Blood will be collected for laboratory tests (Adults: 24cc or 2 tablespoons, Children: 12cc or 2 teaspoons), including hematology (blood counts), chemistry, and TPMT levels. A urine analysis will check to see if you have adequate kidney function. If you are female and of childbearing potential, you will also have a urine pregnancy test performed.

You will be asked to keep a diary card, for 7 days before each study visit, to record the number of liquid or soft stools, and to rate your abdominal pain and general well being.

If you are eligible and decide to continue, you will be assigned to one of two groups to receive azathioprine in tablet form to be taken every night. Your assignment will be chosen at random (by chance, like the toss of a coin). Your chance of being assigned to one of the two groups is the same. The two groups are the following:

- **Group 1 (standard):** 1 milligram (mg) per kilogram (2.2 lbs.) per day for weeks 0 and week 1, then 2.5 mg/kg/day for weeks 2 to 52.

- **Group 2 (individualized):** The dose will be determined by the levels of TPMT. If you have intermediate TPMT levels, you will be given 1.0 mg/kg/day for weeks 0 to 5. If you have high TPMT activity, you will be given 2.5 mg/kg/day for weeks 0 to 4. Starting at week 5, the dose will be adjusted according to the results from the laboratory tests.

The study will be “blinded”, meaning that you and your study doctor will not know the dose of azathioprine you receive until the completion of the study.

You will begin taking the study drug at week 0 (Baseline visit), as instructed by the study coordinator and study doctor. The instructions that your study coordinator provides you for taking this drug will change throughout the study, because of possible changes in dosing. You must follow your study coordinators
directions for taking the pills. Remember that you need to take the pills before bedtime with water (never milk) as directed.

At week 2, you can either come into the clinic to have your blood drawn, or get an order to go to a closer laboratory. If you come into the clinic, the coordinator will draw your blood, and ask you about any adverse events (side effects) and go over what medications you are taking, and should not take. You will not see the study doctor at this visit. If you go to an outside lab, the coordinator will schedule a phone call with you.

During the study, you will return to the study doctor’s office at weeks, 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52. During some of these visits you will be asked to complete a Quality of Life questionnaire about how Crohn’s disease affects your life, and you will be asked about any side effects you may have experienced; a physical examination will be performed including vital signs (weight, blood pressure, pulse, oral temperature). Blood will be collected (Adults: 2.5 teaspoons or Children: almost 2 teaspoons) for routine laboratory tests (blood counts and liver profile) and for measurement of the 6-TGN levels.

Additionally, if you have a dose adjustment, you will be asked to return to the clinic 1-2 and 3-4 weeks after the dose adjustment for safety blood tests (Adults: 1.5 teaspoons or Children: 1 teaspoon). You may also be randomly selected to have safety bloods tests (Adults: 1.5 teaspoons or Children: almost 1 teaspoon) in between clinic visits. If you have side effects while on treatment, your dose of drug may be reduced or stopped and your doctor may ask that you come in every week for safety blood tests (Adults: 1.5 teaspoons or Children: almost 1 teaspoon) or visits, until you get better. Your doctor may order additional routine laboratory tests at the visit.

At each scheduled study visit, you will return your used blister packs so that the study doctor/coordinator can determine how much of the medication you have used. It is important not to throw away your used blister packs.

While you participate in the study, you will continue to take anti-diarrheals (Imodium®, Lomotil®) at the same doses that have been previously prescribed by your regular doctor. There are several medications that you are not allowed to take while you participate in the study. (See risks section.)

Your study doctor and coordinator will tell you when and how much to reduce your dosage of prednisone or budesonide at a set schedule. If your symptoms worsen with the steroid taper, then the study doctor may increase the dose to counteract these symptoms.

During this study, Dr. (Principle Investigator) and his/her research team will collect information about you for the purposes of research, including your name and medical history number. This information will also include data from your medical record, including: your Crohn’s disease medical history, endoscopic records, surgical records, X-rays, medication history and laboratory results. This information will be used to confirm your diagnosis of Crohn’s disease and confirm your eligibility to be in this study.

HOW LONG WILL I BE IN THE STUDY?
Study participation will involve 12 scheduled clinic visits during the 52-week trial. However, if at week 28 of the study, your Crohn’s disease is not better, and/or you are not off steroids, you will be taken out of the study, due to lack of efficacy.

There may be a possibility of returning to the clinic for unscheduled clinic visits, if you are feeling sick in between regular study visits. These visits will be determined by the study doctor. You may also need to
come back to the clinic to have safety blood draws. You will be notified by the study coordinator when you need to come to the clinic for a safety blood draw.

WHAT ARE THE RISKS OF THE STUDY?

Side Effects of Azathioprine
Azathioprine can cause serious lowering of the white blood cell count, resulting in an increased risk of infections. This can reverse when the dose is reduced or temporarily discontinued. Azathioprine can also cause pancreatitis (inflammation of the pancreas), which resolves after the drug is stopped. The symptoms of pancreatitis include abdominal pain, nausea, and vomiting. Azathioprine can also cause liver toxicity, which reverses when the dose is reduced or temporarily discontinued. All subjects taking azathioprine require regular blood testing for blood counts and liver function tests for monitoring. Other side effects include nausea, vomiting, loss of appetite, fever, skin rashes, fatigue, hair loss, joint pains, abdominal pain and diarrhea.

Most medicines can be taken safely with azathioprine. However, there are certain medications that you cannot use during this study. These medications are any immunosuppressant drugs (other than the azathioprine and the prednisone or budesonide); allopurinol; trimethoprim-sulfamethoxazole; non-steroidal anti-inflammatory agents (ibuprofen, naproxen, celecoxib, refecoxib, etc.) or aspirin greater than 81mg/day; cholestyramine; metronidazole; quinolones; topical corticosteroids; oral or topical 5-aminosalicylates (such as Asacol®, Pentasa®, Colazal®, Rowasa enemas®); furosemide or thiazide diuretics; and fish oil preparations. You can use acetaminophen (Tylenol) during this study.

Azathioprine is known to cause severe birth defects in animal studies. Azathioprine is transferred to the human fetus (unborn baby). Although it has been used successfully through pregnancy, there are still some concerns about its effects in the fetus. It is essential to take extra precautions to avoid pregnancy and to monitor women who are capable of becoming pregnant. To participate in this study, women who are physically able to bear children must not be pregnant and must commit to do the following in order to participate:

1. Commit to use one highly effective method of birth control described below while you are taking the study drug, and for at least 6 weeks after the end of the study. Acceptable methods of birth control include:

   o Double Barrier method (spermicide + condom, diaphragm, cervical cap, or sponge)
   o Oral birth control pills administered for at least 1 monthly cycle prior to study drug administration.
   o Progesterone implanted rods (Norplant®) inserted for at least 1 month prior to the study drug administration but not beyond the 3rd successive year following insertion.
   o Intrauterine devices inserted by a qualified physician.
   o Injectable contraceptives: Medroxyprogesterone acetate (Depo-Provera®) or Lunelle (administered for at least 1 month prior to study drug administration).
   o Contraceptive patch (OthoEvra) administered for at least 1 month prior to study drug administration.
   o Vaginal Ring (Nuvaring) administered for at least 1 month prior to study drug administration.

2. Commit not to undergo fertilization procedures or any other procedure intended to result in pregnancy for at least 4 weeks before you start taking azathioprine, while you are taking azathioprine and for at least 6 weeks after you stop taking azathioprine.
If you have been surgically sterilized either by tubal ligation (you have had your tubes tied) or hysterectomy (your uterus has been removed), or if you are post-menopausal (no period for more than 12 months), you will not need to use contraception to avoid pregnancy.

You should discuss with your doctor what the best methods of birth controls are for you. If you require rifampin, rifabutin, barbiturates, phenytoin or carbamazepine you should also use a barrier method (such as diaphragm or condom) since these agents reduce the effectiveness of hormonal contraceptives. Remember, however, that no method of birth control, besides complete abstinence, provides 100% protection from pregnancy.

It is possible you may experience mild pain, bleeding, discoloration or bruising, and/or an infection at the place where the needle enters the vein for the drawing of blood for routine and study-specific samples. Of course, care will be taken to avoid these complications.

There may be other risks that are less common or unknown, including allergic reactions, which could be severe or life-threatening. Should you have a severe reaction, appropriate medical action will be taken.

You should immediately contact the study doctors should you experience any problems or have any worrisome symptoms during the study.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?
The symptoms of your Crohn’s disease may be lessened as a result of treatment with azathioprine. However, there is no guarantee that you will receive any direct benefit from participation in this study. Other patients in the future may benefit from the knowledge gained from this research study.

WHAT OTHER OPTIONS ARE THERE?
Your participation in this study is voluntary. You do not have to be in this study. The decision whether or not you wish to participate in this study will not affect your care at the (Study Site). Instead of being in this study, you have the option to receive treatment for your Crohn’s disease which may include: corticosteroids, mesalamine, methotrexate, 6-MP, cyclosporine, Imuran, Tacrolimus, antagonists of tumor necrosis factor (TNF), and other experimental drugs.

WHAT ARE THE COSTS?
The costs of the tests done just for the purposes of the study (TPMT, 6-TGN and 6MMPR) will be paid for by a grant from the National Institute of Health (NIH) and will not be your responsibility or the responsibility of your medical insurance carrier. The drug will be supplied free of charge by Prometheus Laboratories, the manufacturer. Medical examinations, procedures and tests performed by the study doctor are considered standard medical care and will remain the responsibility of you or your medical insurance carrier.

WILL I BE PAID FOR MY PARTICIPATION?
You will not be paid for your participation in this study.

WHAT ABOUT CONFIDENTIALITY?
Study records that identify you will be kept confidential. You will be identified on all study records, data forms and blood samples (sent to Prometheus Laboratories), as a code number. This code number is known only to study investigators. Records will be stored in a locked office, and kept at the (Study Site). The data collected in this study will be used for the purpose described in the form. By signing this form, you are allowing the research team access to your medical records, which include Protected Health Information. Protected Health Information (PHI) consists of any health information that is collected about you, which
could include your medical history and new information collected as a result of this study. The research team includes the individuals listed on this consent form and other personnel involved in this study at the (Study Site).

Your records may be reviewed by federal agencies whose responsibility is to protect human subjects in research including the Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP). In addition, representatives of the (Study Site), including the Institutional Review Board, a committee that oversees the research at the (Study Site), may also view the records of the research. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

As part of the study, Dr. (Principle Investigator) and his research team will report the results of the study related procedures and tests explained in this form to the National Institutes of Health (NIH). The information will not include your name, only your code. Information sent may include: laboratory tests (blood tests taken for this study, adverse event reports, hospitalization records, Crohn’s disease medical history, medication history, surgical records, endoscopic records, X-ray records). This information will be sent in order for the Data Safety Monitoring Board, a group of experts, appointed by the NIH, who have no ties to this study, can independently review the data to ensure study safety and data integrity. The study sponsor, or their representatives, including monitoring agencies, may also review your medical record. Please note that these individuals may share your information with someone else. If they do, the same laws that the (Study Site) must obey, may not protect your health information.

The results from tests and/or procedures performed as part of this study may become part of your medical record.

During your participation in this study, you will have access to your medical record. Dr. (Principle Investigator) is not required to release to you research information that is not part of your medical record.

The study results will be kept in your research record and be used by the research indefinitely. Any research information in your medical record will be kept indefinitely.

Data from this study may be used in medical publications or presentations. Your name and other identifying information will be removed before this data is used. If we wish to use identifying information in publications, we will ask for your approval at that time.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Taking part in this study is voluntary. If you choose not to participate in this study, your care at the (Study Site) will not be affected. You may choose not to participate at any time during the study. Leaving the study will not affect your care at the (Study Site).

We will tell you about significant new information that may affect your willingness to stay in this study.

If you choose to no longer be in the study and you do not want any of your future health information to be used, you must inform the study doctor in writing at the address on the first page. The study doctor may still use your information that was collected prior to your written notice.

You will be given a signed copy of this document.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
You have talked to the study coordinator about this study and you had the opportunity to ask questions concerning any and all aspects of the research. If you have further questions about the study, you may call the study doctor at___________.

If you have a research related injury, you should immediately contact the study doctor at

If you have any questions concerning your rights in this research study you may contact the Institutional Review Board, which is concerned with the protection of subjects in research projects. You may reach the Committee office (between am and pm, Monday through Friday), by calling or by writing: (Insert IRB phone number and address).

CONSENT

SUBJECT
The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I have received a signed copy of this consent form for my records.

I agree to participate in this study. I am aware that my participation is voluntary and that I do not have to sign this form if I do not want to be part of this research study.

Signature of Subject: ____________________________

Date: _________________ Time: _______ AM/PM (Circle)

OR

Assent of minor: _____________________________________________________________

Date: _________________ Time: _________________ am/pm (circle)

Signature of Mother: _________________________________________________________

Date: _________________ Time: _________________ am/pm (circle)

Signature of Father: _________________________________________________________

Date: _________________ Time: _________________ am/pm (circle)

PERSON OBTAINING CONSENT
I have explained to ______________________ the nature and purpose of the study and the risks involved. I have answered and will answer all questions to the best of my ability. I have given a signed copy of the consent form to the subject.

Signature of Person Obtaining Consent: ____________________________

Date: _________________ Time: _______ AM/PM (Circle)

INVESTIGATOR/PHYSICIAN:

Signature of Investigator/Physician ____________________________

Date: _________________ Time: _______ AM/PM (Circle)
Protocol Deviations

**Definition:** A protocol deviation is any action, visit or procedure that falls outside the parameters as stated in the protocol.

**If you are unsure a deviation has occurred, contact the study administrator for assistance at 773-834-4176.**

**Instructions for Recording:** To record a known deviation, use the Protocol Deviation Log found on the proceeding page. Enter in the deviation code from the list provided, subject initials and ID code as well as date of deviation and date deviation was entered on the log. If particular deviation is not found on the code list, enter the code as other, and in the comments section define the deviation. If additional information is known about the deviation, write the information in the comments section, and add the deviation to the subject’s source documentation and appropriate CRF.

**Instructions for Reporting a Deviation:**
Deviations involving the use, misuse or non-compliance with the study drug, or any other deviation that could potentially cause harm to the subject (examples are: Subject enrolled in concurrent research study, subject non-compliance with study drug, steroid taper, or prohibited medications) MUST be reported to your local IRB as soon as it is known.

In addition to reporting the deviation to your IRB, fax the deviation log to the Study Administrator at 773-834-4172. If the deviation is grounds for withdrawal of the subject, the Study Administrator will discuss the event with the study PI, Dr. Hanauer, and the site study coordinator.
## PROTOCOL DEVIATION LOG

<table>
<thead>
<tr>
<th>Protocol Deviation Code:</th>
<th>Subject Initials</th>
<th>Subject ID#</th>
<th>Date Deviation Occurred: mm/dd/yyyy</th>
<th>Date Protocol Deviation Form Completed: mm/dd/yyyy</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<td>10.</td>
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</tbody>
</table>

## PROTOCOL DEVIATION CODES:

1. Randomization of an ineligible subject
2. Failure to obtain informed consent
3. Subject enrolled in concurrent research study
4. Failure to keep IRB approval up to date
5. Subject receives wrong treatment
6. Subject seen outside visit window
7. Consent form missing
8. Consent form not signed and/ or dated by subject
9. Consent form does not contain all required signatures
10. Consent form used was not current IRB-approved version at time of participant
11. Consent form does not include updates or information required by IRB
12. Not reporting an SAE to the DCC within 24 hours of knowledge
13. Randomization occurring outside normal window
14. Subject non-compliance with study drug
15. Subject non-compliance with steroid taper
16. Subject non-compliance with prohibited medications
17. Study procedure not completed at visit (Explain)
18. Other (Explain)
Laboratory Assessments

Materials:

As a means to ensure efficient and convenient collection of laboratory specimens throughout the study, sites will be provided with materials needed to obtain (AZA Metabolites) TPMT, RBC 6–TGN, & 6-MMPR levels from Prometheus laboratories. It is important to remember that Hematology, Chemistry, Liver Function Panel, Pregnancy Test, and Urinalysis will be done by the site’s local laboratory.

Coolant Equipped Specimen Transportation Kit:
Prometheus Laboratories will prepare and distribute AZA metabolite kits. The kits will include the materials necessary for the collection and shipment of blood specimens. Keep cold packs in freezer until you are ready to use.

Pre- Addressed Courier Shipping Documents:
Each coolant equipped specimen transportation kit will contain a pre- addressed Airborne Express shipping document. **Call Airborne Express to pick up your specimens, at 1-800-247-2676.** Additional airway bills must be ordered in advance by contacting Jeff White, Special Testing Coordinator Prometheus Laboratories, Inc. (888) 423-5227 ext 4125.
Materials NOT provided by Prometheus:
5 mL EDTA (lavender top) tubes. All sites will provide their own 5mL EDTA (lavender top) tubes.

Instructions for Test Requisition:

Requisition Forms: Locate a Prometheus Specimen Transportation Kit and ensure that you have a requisition with a Special Testing Sticker called the Azathioprine Dose Escalation Study (see arrows above). The requisition is a multi part carbon-less form, located inside each kit. When writing on the form, align properly and press firmly with a black ballpoint pen. Send the Original form to Prometheus, and file the bottom forms.

Locate a Prometheus Specimen Transportation Kit and ensure that you have a requisition with a Special Testing Sticker called the Azathioprine Dose Escalation Study (see arrows above).

Complete the following fields ONLY:

Place a Subject ID# in the “Last Name” field for subject demographics.
Indicate which test(s) are to be performed and the visit number on the Special Testing Sticker.

**For TPMT Test (at Screening and Week #28 only):**
Choose: PRO-PredictRx TPMT and PRO-PredictRx Enzact

**For 6-TGN and 6-MMPR (visits 3-11):**
Choose: PRO-PredictRx Metabolites

Write the collection date and Subject ID# on all vacutainers along with the test name (either TPMT/Enzact or Metabolites). Specimen stability and requirements are on the back of the test requisition. Unlabeled specimens cannot be tested.

**Shipping Instructions:**

Follow the packaging instructions inside the transportation kits. Be sure to include the completed test requisition and a frozen cold pack. Prometheus test results will be forwarded to the DMC within 3 business days. Study coordinators will not receive the results of these tests. However, you can confirm your shipment by contacting Airborne Express at 1800-247-2676.

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*Packing Diagram*
Ready to Ship!

Call Airborne Express at (800) 247-2676 for specimen pick up.

For questions, reports, or for additional supplies on Metabolite kits ONLY, contact:

Jeff White, Special Testing Coordinator
Prometheus Laboratories, Inc.
(888) 423-5227 ext 4125
jwhite@prometheuslabs.com

Local Laboratories

For Hematology, CBC, Basic Chemistry and Liver Profile follow the directions of your local laboratory.
Drug Allocation

Instructions

Subjects will receive the drug and placebo in “blister-packed” cards with single daily dosing. At specified time points (see drug distribution schedule below), the Pharmacy at the University of Chicago will express mail to each site blister packs containing a 4-8 week supply of drug. The initial shipment of drug will include an 8 week supply. Subsequent shipments will contain 4 week supplies. Each week’s blister pack will contain 3 blisters per day, each blister labeled either A, B or C. Subjects will be instructed which columns to take, with each combination holding the day’s supply of AZA and placebo.

In order to maintain the blind, the Pharmacy at the University of Chicago will add placebo to daily dosing. The number of pills taken may change throughout the course of the dosing cycle. In addition, Group I subjects will receive dose change orders to help maintain the blind even though doses are not actually changed. Subjects will be given additional instructions via phone when additional changes should occur.

Evidence from a prospective maintenance study among children with leukemia suggests that evening administration of 6-MP is preferable. Furthermore, it has been shown that the administration of milk reduces the bioavailability of 6-MP, likely due to the high concentrations of xanthine oxidase in fluid milk. Therefore, instruct all subjects to take their AZA at night, never with milk.

Below is a sample of what the blister pack will look like:
Along with the Blister packs, the Study Coordinator will give subject detailed instructions on the Subject Dosing Instruction sheet, located on the next page. One sheet of instructions will be used for each week. Each time there is a dose change (see chart below for potential dose change), the Study Coordinator will be given instructions from the DMC. The Study Coordinator will then contact the subject with new instructions.

**Study Schedule of Potential Dose Change**

The AZA/placebo supply will be provided to the subjects according to the following schedule:

<table>
<thead>
<tr>
<th>Week</th>
<th>Event Details</th>
<th>Supply Allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>#0</td>
<td>(clinic visit)</td>
<td>8 week supply</td>
</tr>
<tr>
<td>#2</td>
<td>(non-physician visit + labs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Phone visit for subject with outside lab)</td>
<td></td>
</tr>
<tr>
<td>#4</td>
<td>(clinic visit)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-TGN drawn</td>
<td></td>
</tr>
<tr>
<td>#5</td>
<td>(6-TGN levels from week #4 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#8</td>
<td>(clinic visit)</td>
<td>4 week supply</td>
</tr>
<tr>
<td>#9</td>
<td>(6-TGN levels from week #8 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#12</td>
<td>(clinic visit)</td>
<td>4 week supply</td>
</tr>
<tr>
<td></td>
<td>(6-TGN levels from week #12 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#16</td>
<td>(clinic visit)</td>
<td>4 week supply</td>
</tr>
<tr>
<td>#17</td>
<td>(6-TGN levels from week #16 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#20</td>
<td>(clinic visit)</td>
<td>4 week supply</td>
</tr>
<tr>
<td>#21</td>
<td>(6-TGN levels from week #20 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#24</td>
<td>(clinic visit)</td>
<td>4 week supply</td>
</tr>
<tr>
<td>#25</td>
<td>(6-TGN levels from week #24 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#28</td>
<td>(clinic visit)</td>
<td>8 week supply</td>
</tr>
<tr>
<td>#39</td>
<td>(6-TGN levels from week #28 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#36</td>
<td>(clinic visit)</td>
<td>8 week supply</td>
</tr>
<tr>
<td>#37</td>
<td>(6-TGN levels from week #36 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#44</td>
<td>(clinic visit)</td>
<td>8 week supply</td>
</tr>
<tr>
<td>#45</td>
<td>(6-TGN levels from week #44 available)</td>
<td>Potential Dose change</td>
</tr>
<tr>
<td>#52</td>
<td>(final clinic visit)</td>
<td></td>
</tr>
</tbody>
</table>
Subject Dosing Instructions
Subject # _____________
WEEK # __________________________

You are instructed to take column(s):

☐ A  ☐ B  ☐ C  Day 1 _____________________________
☐ A  ☐ B  ☐ C  Day 2 _____________________________
☐ A  ☐ B  ☐ C  Day 3 _____________________________
☐ A  ☐ B  ☐ C  Day 4 _____________________________
☐ A  ☐ B  ☐ C  Day 5 _____________________________
☐ A  ☐ B  ☐ C  Day 6 _____________________________
☐ A  ☐ B  ☐ C  Day 7 _____________________________

• Fill in each date of dosing on blister pack.
• Take the dose on the corresponding date.
• Take your dose before bed with water only. (no milk)
• If you miss a dose, do not take the missed dose.

KEEP YOUR USED BLISTER PACKS AND BRING TO YOUR NEXT CLINIC VISIT
Quality Oversight and Monitoring

Subject Record Confidentiality
All records will be kept confidential and the patient’s name will not be released at any time. Patient records will not be released to anyone other than the investigators, the NIH, and national health regulatory agencies (the FDA, OHRP and Health Canada), if requested. In all cases, caution will be exercised to ensure the patient’s confidentiality. Data sets for each patient will only be identified by the patient randomization number. A list linking individual identities to respective data will be stored at the DMC in a separate, secure computer file. All computer files will require passwords, and all paper files at all study sites will be maintained in locked cabinets.

Informed Consent Process
All subjects need to voluntarily consent before any study related procedure has commenced. Informed consent is a process which involves providing patients with adequate information concerning the study procedures, duration and scope. The patient will be provided with adequate time and information to consider the risk to benefit ratio, other available options, as well as any other questions the patient may have. The informed consent document will be read with the patient, and explained step by step, so that the patient may have a full understanding of the commitment and responsibility, as well subjects rights and confidentiality before signing the document. In order to capture the scope of informed consent, the Study Coordinator (or whoever gains consent) will document the process on the Informed Consent Checklist located in the Source Documents. The Study Coordinator will be trained on documenting Informed Consent during the Initiation Teleconference.

Data Collection
Data Collection tools specific to this study have been created in order to assure that data integrity and uniformity. Case Report Forms have been developed by the Data Management Center in conjunction with the Data Coordinating Center and will be used in tandem with the Source Documents that also have been created for this study. Checklists and visit summaries are included in the Source documents for the coordinator to prepare for each visit. Coordinators will be trained in how to use the documents during the Initiation Teleconference.

Data will be collected on two-part NCR paper. Each center will fax the CRF to the Study administrator for approval. The Study Administrator will ascertain completion of the Case Report Form, and if complete approval will be granted. After approval, the center will mail one copy to the DMC, and will keep the original. Each site will have 14 days after the study visit to complete and fax the CRF to the Study Administrator at the DCC for approval. By receiving the CRFs in “real” time we can feed back problems to study sites more rapidly. This facilitates timely identification and resolution of problems in data collection and processing.

Data Entry and Analysis
Data from clinical centers will be keyed from the Case Report Forms. For each form, the DMC will develop a computerized data entry screen that will closely resemble the paper form. The system will be menu-driven with context-sensitive help available at any time. Each data field will be edited during entry. Values that fail a validation routine will cause a message to be displayed that will require the data entry staff member to correct the value, flag the value as questionable, or confirm that the value is
known to be correct thereby overriding the validation routine. The data entry system will flag each data value with a “status character” that will document the current validation status of the item (empty, skipped, questionable, clean, confirmed, etc). The DMC will generate periodic reports concerning data quality (missing or overdue forms, outstanding data queries, etc) to facilitate the timely review, correction and resolution of data quality issues.

Before analysis, the database will go through a series of closure checks to insure the completeness and correctness of the data collection and processing. These checks will be performed on a “frozen” version of the database. The checks will assure that the status of each subject is correct, that all expected forms have been received, that all received forms have been processed, and that all queries have been resolved.

All statistical computing will be done using the SAS system. All computing will be documented. The analysis specification, the resulting analysis program, and the output produced will all be catalogued and archived (in both paper and electronic format) to provide complete documentation of each computing task.

**Data Storage and Security**

The original paper data-collection forms will be retained at the clinical centers. Copies of the data collection forms will be mailed to the DMC. In all centers, access to office space containing data is controlled through staffed reception areas and all office space is locked after working hours.

Data transferred to the DMC will be stored, processed and analyzed within DMC office space. All access to office space containing data is controlled through staffed reception areas. All office space is locked after working hours. Access to computer data file is controlled by passwords released only to those personnel who use the files. In addition critical data files are encrypted.

A backup database will be made daily to a networked disk drive. Automated backups of the database will also be made daily. Once a month, the current backup will be removed from the cycle and permanently archived at an off-site facility.

Output mailed to clinical center staff will identify participants only by ID number. No individually identifiable information will be distributed to clinical centers. When printed material containing confidential information is to be discarded, it will be loaded, transported and stored under supervision (using a chain of custody control process) until the material can be recycled into paper pulp.

All DMC staff is required to complete a confidentiality certification procedure upon employment. Policies regarding the confidential nature of the data collected, processed and stored are explained to all personnel who sign a “confidentiality certification” before being allowed access to confidential information.

**Data Monitoring**

Quality assurance and data monitoring will be completed by the Data Coordinating Center on an annual basis. The purpose of the monitoring will be to verify the accuracy and integrity of data submitted to the Data Management Center by the Clinical Sites as well as to protect the rights and safety of human
subjects participating in this trial.

The Study Administrator from the DCC, or their designee will be responsible for the monitoring. The monitor will be knowledgeable about the protocol and have qualifications to support the review and correction of study data. During the course of the monitoring visit, individual records and other supporting documents will be compared with the records prepared by the Clinical Sites and submitted to the DMC. Sites will be notified of the requirements and expectations during a monitoring visit. Sites should prepare for the validation of:

- Information being recorded is accurate, complete and legible
- There are no omissions in specific data elements
- Proper recording and reporting of adverse events and protocol deviations/violations
- Subject status reports
- Documentation of the Informed Consent Process

A record of the findings and corrections will be completed by the monitor and be made available to the DMC as well as the Clinical Sites. The record will enable other auditors, including those from the FDA to ensure that the responsibilities of the DCC are being filled.