Janssen Research & Development*

Exposure Registry Protocol

An Observational Prospective Long-term Exposure Registry of Adult Patients with Moderate-to-Severe Ulcerative Colitis

OPAL Registry

Protocol CNTO148UCO4001; Phase 4
AMENDMENT 1

CNTO148 (SIMPONI®, golimumab)

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Status: Approved
Date: 22 February 2016
Prepared by: Janssen Scientific Affairs, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Approved, Date: 22 February 2016
Amendment INT-1 (22 February 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it may significantly impact the safety or physical/mental integrity of patients, or the scientific value of the study. No patient was enrolled at the time of this amendment.

The overall reason for the amendment: The overall reason for the amendment is to harmonize the data to be collected, between this registry and one being conducted by another sponsor in the same population (Study number NCT01848561 on www.clinicaltrials.gov). Since both registries include a thiopurine-treated cohort, this registry protocol is being modified to reflect that data from the thiopurine-treated group of the other registry will be shared, and analyzed as OPAL data. This amendment also decreases the sample size of the OPAL protocol due to an error in the sample size calculation that was identified during the development of the SAP.

Applicable Section(s) | Description of Changes
--- | ---
Rationale: The adverse events to be collected in this registry have been aligned with those being collected in the other sponsor’s registry; rather than collecting all adverse events, all serious adverse events and adverse events of interest will be collected and analyzed for both cohorts, to align with the data being collected, shared, and analyzed from the thiopurine-treated patients in the other sponsor’s registry. | Throughout the protocol as appropriate: Original Text: ....adverse events.... Modified Text: .... adverse events of interest and serious adverse events....

Approved, Date: 22 February 2016
Rationale: The sample size was decreased since the previous sample size of 7,000 patients was incorrectly based on a calculation using absolute dropout rate, rather than exponential parameter of the dropout rate; the corrected calculation allows the registry to achieve ≥86% power with a sample size of 6000 patients.

Synopsis, Number of Patients

Original Text: Approximately 7,000 patients are planned for enrollment, with 3,500 patients in the Simponi-exposed cohort and 3,500 patients in the comparator cohort….The remainder of the comparator cohort (approximately 750 additional patients receiving thiopurines) and the Simponi-exposed cohort will be enrolled by the sponsor of the OPAL registry.

Modified Text: Approximately 6,000 patients are planned for enrollment, with 3,000 patients in the Simponi-exposed cohort and 3,000 patients in the comparator cohort….The remainder of the comparator cohort and the Simponi-exposed cohort will be enrolled by the sponsor of the OPAL registry.

Synopsis, Sample Size

Original Text: Approximately 7,000 patients will be enrolled, with 3,500 patients in each cohort. Assuming a 25% exponential dropout rate during the 10-year follow-up period, with 3,500 per group, the total patient years per group over the 10-year period would be 30,410.

The estimation precision of lymphoma event rate, using the 2-sided 95% confidence interval (CI) and based on 30,410 patient years, will be between 0.043 and 0.048 per 100 patient-years. The corresponding upper limits of the 2-sided 95% CIs of event rate will be between 0.193 and 0.228 per 100 patient-years. The sample size provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.

In addition, a sample size of 7,000 patients (3,500 per cohort), with 39 to 46 events observed during 10 years of follow-up, will provide 57% to 65% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort.

Modified Text: Approximately 6,000 patients will be enrolled, with 3,000 patients in each cohort. Assuming a 25% dropout rate during the 10-year follow-up period (exponential parameter $\lambda_{df} = 0.0288$), with 3,000 per group, the total patient years per group over the 10-year period would be 26,066.

The estimation precision of lymphoma event rate, using the 2-sided 95% confidence interval (CI) and based on 26,066 patient-years, will be between 0.047 and 0.051 per 100 patient-years. The corresponding upper limits of the 2-sided 95% CIs of event rate will be between 0.197 and 0.231 per 100 patient-years. The sample size provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.

In addition, a sample size of 6,000 patients (3,000 per cohort), with 78 to 93 expected events observed during 10 years of follow-up, will provide 86% to 91% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort.

3.1 Overview of Registry Design

Original Text: Approximately 7,000 patients are planned for enrollment, with 3,500 patients in the Simponi-exposed cohort and 3,500 patients in the comparator cohort.

Modified Text: Approximately 6,000 patients are planned for enrollment, with 3,000 patients in the Simponi-exposed cohort and 3,000 patients in the comparator cohort.

3.2 Registry Design

Original Text: The sample size of 7,000 patients (3,500 per cohort), provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.

Modified Text: The sample size of 6,000 patients (3,000 per cohort), provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.
## Rationale

Risk for lymphoma. In addition, this sample size will provide 57% to 65% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort.

### Modified Text:

The sample size of 6,000 patients (3,000 per cohort), provides sufficient estimation precision to rule out doubling of the thiopurine background risk for lymphoma. In addition, this sample size will provide 86% to 91% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort.

### 7.2 Sample Size Determination

**Original Text:**
Approximately 7,000 patients will be enrolled, with 3,500 patients in each cohort. Assuming a 25% exponential dropout rate during the 10 year follow-up period, with 3,500 per group, the total patient years per group over the 10-year period would be 30,410, as shown in the calculation below.

\[
\text{Patient years of follow up} = 3500 \int_{0}^{10} e^{-0.0288t} \, dt = 30,410
\]

The estimation precision of the lymphoma event rate, using the 2-sided 95% CI and based on 30,410 patient-years, will be between 0.043 and 0.048 per 100 patient-years. The corresponding upper limits of the 2-sided 95% CIs of event rate will be between 0.193 and 0.228 per 100 patient-years. The sample size provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.

In addition, a sample size of 7,000 patients (3,500 per cohort), with 39 to 46 events observed during 10 years of follow-up, will provide 57% to 65% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort.

**Modified Text:**

Approximately 6,000 patients will be enrolled, with 3,000 patients in each cohort. Assuming a 25% dropout rate during the 10-year follow-up period (exponential parameter \( \lambda_{\text{dif}} = 0.0288 \)), with 3,000 per group, the total patient years per group over the 10-year period would be 26,066, as shown in the calculation below.

\[
\text{Patient years of follow up} = 3000 \int_{0}^{10} e^{-0.0288t} \, dt = 26,066
\]

The estimation precision of the lymphoma event rate, using the 2-sided 95% CI and based on 26,066 patient-years, will be between 0.047 and 0.051 per 100 patient-years. The corresponding upper limits of the 2-sided 95% CIs of event rate will be between 0.197 and 0.231 per 100 patient-years. The sample size provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.

In addition, a sample size of 6,000 patients (3,000 per cohort), with 78 to 93 expected events observed during 10 years of follow-up, will provide 86% to 91% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort.

Table 2, now entitled **Scenarios for ruling out hazard ratios of 2.0 with a sample size of 6,000 patients with 10 years of follow up, alpha**

Approved, Date: 22 February 2016
= 0.025 (1-sided) was changed according to the corrected calculations, and 2 rows pertaining to the percent of patients with a lymphoma event through 10 years were deleted.

**Rationale:** Three secondary objectives were deleted so that the secondary objectives match those in the other sponsor’s registry. In accordance with this change, corresponding text for these objectives was updated or deleted as appropriate from Objectives (Section 2.1), as well as the registry design (Section 3.2), secondary endpoints (Section 6), and statistical methods (Sections 7.4.3, 7.4.4 and Section 7.4.5).

<table>
<thead>
<tr>
<th>2.1 Secondary Objectives</th>
<th>Original Text:</th>
<th>Modified Text:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The relative risk of lymphoma following exposure to Simponi compared with exposure to thiopurines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term safety, including malignancies other than lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical status, quality of life, and health care utilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease features and concomitant medications for ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The incidence of colectomy and frequency of abdominal and anorectal procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The incidence of colonic dysplasia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rationale:** To align with the other sponsor’s registry, the cohort receiving thiopurines must now have been receiving them for at least 12 weeks prior to registry entry.

<table>
<thead>
<tr>
<th>3.1 Overview of Registry Design</th>
<th>Original Text:</th>
<th>Modified Text:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The comparator cohort will include the following: Patients currently receiving thiopurines or patients scheduled to receive thiopurines within 30 days after enrollment.</td>
<td>The comparator cohort will include the following: Patients currently receiving thiopurines, having received at least 12 consecutive weeks of therapy prior to registry entry. Patients in this cohort must not be receiving approved biologic agents, including Simponi, or investigational agents at enrollment. These patients may have received biologics other than Simponi or investigational agents prior to enrollment.</td>
<td></td>
</tr>
</tbody>
</table>

**Rationale:** The protocols for the 2 registries are being harmonized, in order for the sponsor of this registry to include data from the thiopurine group from the other sponsor’s registry. Text was added to explain the planned data sharing for the thiopurine group.

<table>
<thead>
<tr>
<th>3.1 Overview of Registry Design</th>
<th>Added Text:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Another sponsor is performing a similar ulcerative colitis registry (Study number NCT01848561 on <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>). In that registry, it is anticipated that 2,750 thiopurine patients will be enrolled. For the thiopurine-treated patients in the other registry who give consent for their data to be shared, data will be shared and analyzed with the data from the OPAL registry. The remainder of the thiopurine-exposed cohort and the Simponi-exposed cohort will be enrolled by the sponsor of the OPAL registry.</td>
<td></td>
</tr>
</tbody>
</table>
**Rationale:** The quality of life instruments were aligned with those being used in the other sponsor’s registry; accordingly, SF-12 was replaced with the EuroQoL-5Dimensions-5Levels (EQ-5D-5L) and the Treatment Satisfaction Questionnaire for Medication (TSQM). The Work Productivity Activity Impairment (WPAI) instrument for inflammatory bowel disease (IBD) was changed to the WPAI for ulcerative colitis (UC) instrument, to match the one being used in the other sponsor’s registry.

Text was updated throughout the protocol to remove all references to the SF-12 and to add information as appropriate for the EQ-5D-5L and TSQM, including adding these evaluations to the Data Collection Schedule and references in text; detailed descriptions of each questionnaire; updated endpoints and statistical methods; and citations (Sections 3.2, 5.7, 6, and 7.4.2).

WPAI-IBD was replaced with WPAI-UC.

**Rationale:** Two inclusion criteria were aligned with criteria in the other sponsor’s registry, changed as shown below; and an inclusion criterion regarding the initiation of Simponi was clarified.

<table>
<thead>
<tr>
<th><strong>Inclusion criterion #3a</strong></th>
<th>Note added</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Text:</td>
<td>Note: a patient who does not receive Simponi within 30 days after enrollment should be withdrawn from registry participation as this will be a protocol deviation. The patient may re-enroll in the registry when the patient starts Simponi.</td>
</tr>
<tr>
<td>Modified Text:</td>
<td>Comparator cohort:</td>
</tr>
<tr>
<td></td>
<td>The patient is currently receiving thiopurines</td>
</tr>
</tbody>
</table>

**Inclusion criterion #3b**

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>Comparator cohort:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Text:</td>
<td>The patient is currently receiving thiopurines, having received at least 12 consecutive weeks of therapy prior to registry entry</td>
</tr>
</tbody>
</table>

**Added Note (after #3b):**

1. At sites that are participating in both registries, no thiopurine patients will be enrolled in the OPAL registry until enrollment in the other sponsor’s thiopurine group is complete.
2. At sites that are participating in the OPAL registry only, patients in the thiopurine group will be enrolled in the OPAL registry.

**Inclusion criterion #6**

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>Be able to participate in regular follow-up visits.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Text:</td>
<td>Deleted</td>
</tr>
</tbody>
</table>
### Rationale: Participation in this registry does not need to be interrupted if a patient desires to participate in another clinical study of an investigational agent. This is to align with the other sponsor’s registry.

#### 4.3 Participation in Other Clinical Studies

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>In order to allow patients to seek alternative therapies while still allowing for the long-term follow-up required in this registry, participation in this registry must be interrupted for patients who subsequently enroll in the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>· Any interventional clinical study with an investigational agent (ie, non-marketed agent)</td>
</tr>
<tr>
<td></td>
<td>· Any interventional clinical study with inclusion/exclusion criteria that prohibit concurrent enrollment in other studies</td>
</tr>
<tr>
<td></td>
<td>Patients may participate in other observational studies and/or registries as permitted by inclusion/exclusion criteria of this registry.</td>
</tr>
</tbody>
</table>

| Modified Text: | In order to allow patients to seek alternative therapies while still allowing for the long-term follow-up required in this registry, participation in this registry must be interrupted for patients who subsequently enroll in any interventional clinical study with inclusion/exclusion criteria that prohibit concurrent enrollment in other studies. |
|                | Patients may participate in other studies and/or registries as permitted by inclusion/exclusion criteria of this registry. |

**Rationale:** Text pertaining to data being collected at baseline was clarified to note all the data being collected and refer to local practice.

#### 5.1 Demographics and Medical History

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>Demographic and medical history will include, but are not limited to age, gender, race/ethnicity, smoking status, duration of disease, and extent/location of disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Text:</td>
<td>Demographic and medical history will include, but are not limited to age, gender, race/ethnicity (where allowed by local laws), smoking and alcohol status, duration of disease, extent/location of disease, and surgical history.</td>
</tr>
</tbody>
</table>
**Rationale:** A section was added to describe treatment and dosing changes with registry drug, to align with the other sponsor’s registry.

### 5.3 Registry Drug Treatment and Dosing Changes (new section)

**Original Text:**

(Prior to enrollment into the registry, the participating physician should have prescribed the registry drug, along with instructions for appropriate use. At subsequent protocol-defined visits the physician will collect the start and stop dates, any dose interruptions, and reason for the dose interruption that may have occurred since the last visit. The dose, dates of administration, dose interruptions, and the reason for the interruption will be captured in the source documents and case report forms (CRFs).

Dose interruptions of Simponi treatment will be defined as missing >1 dose.

Patients being treated with a thiopurine (AZA or 6-MP) without a concurrent biologic at enrollment may add biologic therapy with or without concurrent thiopurine therapy during the registry. For these patients the 10-year follow-up period will start at the time of enrollment into the registry.

All patients will be followed for 10 years upon entry into the registry unless they withdraw their consent from the scheduled portion of the registry and also decline participation in the direct to Health Care Provider (HCP) process or direct to patient follow-up (described in Section 5.10).

**Modified Text:**

Prior to enrollment into the registry, the participating physician should have prescribed the registry drug, along with instructions for appropriate use. At subsequent protocol-defined visits the physician will collect the start and stop dates, any dose interruptions, and reason for the dose interruption that may have occurred since the last visit. The dose, dates of administration, dose interruptions, and the reason for the interruption will be captured in the source documents and case report forms (CRFs).

Dose interruptions of Simponi treatment will be defined as missing >1 dose.

Patients being treated with a thiopurine (AZA or 6-MP) without a concurrent biologic at enrollment may add biologic therapy with or without concurrent thiopurine therapy during the registry. For these patients the 10-year follow-up period will start at the time of enrollment into the registry.

All patients will be followed for 10 years upon entry into the registry unless they withdraw their consent from the scheduled portion of the registry and also decline participation in the direct to Health Care Provider (HCP) process or direct to patient follow-up (described in Section 5.10).

**Rationale:** Text clarifying that safety events are to be collected any time they occur was added.

### 5.5 Long-term Safety

**Original Text:**

Long-term safety will be evaluated by physical examinations and reporting of other adverse events in addition to lymphoma, including, but not limited to, collection of information on malignancy other than lymphoma, colectomies, abdominal procedures, anorectal procedures, and colonic dysplasia. Any abnormality noted on physical examination should be reported as an adverse event.

**Modified Text:**

Long-term safety will be evaluated by physical examinations and reporting of lymphoma, other adverse events of interest, and serious adverse events. Any abnormality noted on physical examination that indicates an adverse event of interest or a serious adverse event should be reported as such. Adverse events of interest and serious adverse events, including any events leading to discontinuation of registry drug, will be recorded throughout the patient's participation in the registry. All adverse events of interest and serious adverse events will be followed by the investigator as specified in Section 8.

Approved, Date: 22 February 2016
**Rationale:** Text regarding partial Mayo score and Physician Global Assessment was aligned with the other sponsor’s registry.

<table>
<thead>
<tr>
<th>5.6 Clinical Status – Partial Mayo Score and Physician Global Assessment</th>
<th>Original Text: The stool frequency and rectal bleeding components will be obtained from the most recent consecutive 3-day period prior to the visit, excluding the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The day(s) that medications for constipation, diarrhea, or irregularity were taken. (For patients maintained on a stable dose of bulking or stool softening agents throughout the registry, the days on which these agents are taken should not be excluded from consideration in calculating the Mayo score.)</td>
</tr>
<tr>
<td></td>
<td>• The day(s) of a procedure or preparation for a procedure (eg, enemas, other laxatives, a clear liquid diet) that would affect bowel frequency and/or blood content of the stool.</td>
</tr>
<tr>
<td></td>
<td>• The 48-hour period after the use of antimotility agents (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide).</td>
</tr>
<tr>
<td></td>
<td>• The 72-hour period immediately following a colonoscopy.</td>
</tr>
<tr>
<td></td>
<td>While endoscopy is not required per protocol, if a patient undergoes a colonoscopy, the investigator should obtain the results and provide this information to the company. At a minimum, the date and reason for colonoscopy should be collected.</td>
</tr>
<tr>
<td></td>
<td>The PGA portion of the Mayo Score will be used independently of the partial Mayo Score as an additional measure of clinical status.</td>
</tr>
</tbody>
</table>

**Modified Text:** All patients will be provided with a Patient Diary at the Enrollment Visit to record ulcerative colitis-related symptoms. If the patient forgets to complete the diary, patient recall will be used. The patient diary will provide information on the patient-reported subscores for calculating the Partial Mayo Score at each visit. Patients should record the total number of stools each day from the 3 days prior to each visit. Patients should record normal stool frequency as the number of stools when not experiencing a flare of their ulcerative colitis. The average score of the diary entries from the 3 days prior to each visit will be used for each patient-reported subscore. In addition to the physical examination, the investigator should use the patient-reported subscores of abdominal discomfort and functional assessment to determine the physician's global assessment subscore. An estimate of the Partial Mayo or the Mayo score using data from the patient's ulcerative colitis medical history (if available) at the time of the patient's first dose of Simponi or thiopurine will be completed at the time of enrollment. If the site completes an endoscopy up to 21 days prior to or at the visit, then a full Mayo score is calculated.

Approved, Date: 22 February 2016
Rationale: Text was corrected to note that data pertaining to surgical procedures will not specify whether they are inpatient or outpatient procedures. Further, duration of hospitalizations was removed to align with the other registry’s data collection.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Modified Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.7.5 Surgical Procedures and Hospitalizations</td>
<td>The number of, duration of, and reasons for hospitalizations as well as the number of and reasons for inpatient and outpatient surgical procedures, including colectomy, will be collected…</td>
<td>The number of and reasons for hospitalizations as well as the number of and reasons for surgical procedures, including colectomy, will be collected…</td>
</tr>
<tr>
<td>6. Secondary Endpoints</td>
<td>Clinical disease status (partial Mayo score and PGA, a component of the partial Mayo score); quality of life (SIBDQ, EQ-5D-5L, TSQM, and WPAI-UC), and healthcare utilization (ie, the number of, duration of, and reasons for hospitalizations as well as the number of and reasons for inpatient and outpatient surgical procedures)</td>
<td>Clinical disease status (partial Mayo score and PGA, a component of the partial Mayo score); quality of life (SIBDQ, EQ-5D-5L, TSQM, and WPAI-UC), and healthcare utilization (ie, the number of and reasons for hospitalizations as well as the number of and reasons for surgical procedures)</td>
</tr>
<tr>
<td>7.4.2 Clinical Status, Quality of Life, and Health Care Utilization</td>
<td>The number of, duration of, and reasons for hospitalizations as well as the number of and reasons for in patient and outpatient surgical procedures, including colectomy, will be summarized for each exposure cohort.</td>
<td>The number of and reasons for hospitalizations as well as the number of and reasons for surgical procedures, including colectomy, will be summarized for each exposure cohort.</td>
</tr>
</tbody>
</table>
### Rationale:
Text describing disease features was aligned with the other sponsor’s registry (in 2 sections); Section 7.4.3 was renumbered to 7.5 (since Disease Features and Concomitant Medications is no longer a secondary outcome measure).

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Modified Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8 Disease Features – Epidemiological Evaluations (retitled to Disease Features)</td>
<td>The patient’s ulcerative colitis disease features will be collected for each cohort and recorded on the CRF. Disease features include the following: disease duration, disease location, change in diagnosis over time (eg, ulcerative colitis to Crohn’s disease), disease extension (eg, proctitis to pancolitis), and/or extra-intestinal manifestations of ulcerative colitis (ie, the most common manifestations involve the musculoskeletal and dermatologic systems), and any comorbidities.</td>
<td>The patient’s ulcerative colitis disease features will be collected for each cohort and recorded on the CRF. Disease features include the following: disease duration, disease location, and/or extra-intestinal manifestations of ulcerative colitis (ie, the most common manifestations involve the musculoskeletal and dermatologic systems), and any comorbidities.</td>
</tr>
<tr>
<td>7.5 Disease Features and Concomitant Medications</td>
<td>Disease features, such as disease duration, disease location, change in diagnosis over time (eg, ulcerative colitis changed to Crohn’s disease), disease extension (eg, proctitis to pancolitis), extra-intestinal manifestations of ulcerative colitis, and/or comorbidities will be summarized using descriptive statistics for the treatment cohorts.</td>
<td>Disease features, such as disease duration, disease location, extra-intestinal manifestations of ulcerative colitis, and/or comorbidities will be summarized using descriptive statistics for the treatment cohorts.</td>
</tr>
</tbody>
</table>

### Rationale:
Text for Laboratory Evaluations was added to align with the other sponsor’s registry.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Added text</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9 Laboratory Evaluations (new section)</td>
<td>(None)</td>
<td>Laboratory tests including C-reactive protein, hemoglobin, and fecal calprotectin may be performed at a local laboratory if deemed part of routine patient care. If such tests are conducted, results are to be recorded in the CRF.</td>
</tr>
</tbody>
</table>
Rationale: Text for a Direct to Healthcare Provider process was added to align with the other sponsor’s registry and instructions for direct to patient follow-up by the sponsor designee were added.

5.10 Direct to Healthcare Provider/Patient Process (new section)

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>Added text:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(None)</td>
<td>Due to the duration of the study and the length of time between the follow-up visits, the proportion of patients lost to follow-up might be significant. The frequency of loss to follow-up should be minimized by use of the retention strategies described below to ensure collection of data of interest and vital status until study end.</td>
</tr>
</tbody>
</table>

5.10.1 Direct to Healthcare Provider Process

For patients who discontinue from the scheduled portion of the registry before Year 10 of follow-up, every effort will be made to continue to collect data. For example, the patient may be offered the possibility to release data from a simplified HCP questionnaire on an annual basis through 10 years from the patient's enrollment in the registry. In order to participate in the direct to HCP process, the patient will be asked to provide consent (either at study entry or during the study).

The first data collection period will capture data from the date of the patient's discontinuation visit or last contact while still enrolled in the registry through the completion of the first annual HCP questionnaire for the patient. The questionnaire focuses on the collection of surgeries (eg, especially colectomies), hospitalizations, deaths, adverse events of interest, and ulcerative colitis related medication use since registry discontinuation. The questionnaire may be completed by a registry physician or the patient's current HCP (if the patient is no longer under the care of a registry physician). Any other serious adverse events experienced by the patient should be reported according to standard spontaneous reporting procedures, and they are not subject to the requirements of this protocol.

5.10.2 Direct to Patient Process

Patients may also be followed by a CRO designated by the sponsor. The sponsor’s designee is responsible for follow-up on patients who move away from the investigative site or leave the registry for other reasons but consent to continue their participation in the registry (either at study entry or during the study). The patient will be contacted by this designee of the sponsor to follow-up with him/her directly and to obtain subsequent interval registry data through 10 years from the patient’s enrollment in the registry.

Patients who have affirmatively withdrawn authorization to have their personal health information used or disclosed in connection with the registry will not be asked to continue in the registry or asked to participate in the direct to HCP/patient process.

Approved, Date: 22 February 2016
### Rationale:

Text was clarified regarding prior and concomitant treatment at time of registry enrollment, and a clarifying edit was made.

#### 7.1 Patient Information

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>Modified Text:</th>
</tr>
</thead>
</table>
| Patients will be classified into 2 cohorts based on their medication exposure prior to and during registry follow up.  
- The Simponi-exposed cohort includes those exposed to Simponi prior to or during registry participation, with or without exposure to thiopurines. Subgroup analyses will allow for the evaluation of Simponi-exposed patients who were not exposed to thiopurines, and the exposure definitions below.  
- The thiopurine-exposed cohort includes those exposed to thiopurines but not Simponi or other biologics.  
  
  …For example, if patients in the thiopurine-exposed cohort are exposed to biologics other than Simponi after or concurrent with thiopurine exposure, they may be included in a ‘thiopurines plus other biologic’ cohort…. |
| Patients will be classified into 2 cohorts based on their medication exposure prior to and during registry follow up.  
- The Simponi-exposed cohort includes those exposed to Simponi at enrollment or during registry participation, with or without exposure to thiopurines. Subgroup analyses will allow for the evaluation of Simponi-exposed patients who were not exposed to thiopurines, and the exposure definitions below. These patients must not be receiving other approved biologics or investigational agents at enrollment.  
- The thiopurine-exposed cohort includes those exposed to thiopurines but not receiving Simponi or other biologics at enrollment. These patients may have received biologics other than Simponi or investigational agents prior to enrollment.  
  
  …For example, if patients in the thiopurine-exposed cohort are exposed to biologics other than Simponi after or concurrent with thiopurine exposure, they may be included in a ‘thiopurines plus other biologic’ group…. |

#### Synopsis, Primary Outcome Analysis; 7.3 Primary and Secondary Outcome Analyses

<table>
<thead>
<tr>
<th>Original Text:</th>
<th>Modified Text:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The incidence of lymphoma and rates per 10,000 patient years and the corresponding 2-sided 95% CIs will be summarized and compared between the Simponi cohort and the thiopurines cohort.</td>
<td></td>
</tr>
<tr>
<td>The incidence of lymphoma and rates per 100 patient-years and the corresponding 2-sided 95% CIs will be summarized and compared between the Simponi cohort and the thiopurines cohort.</td>
<td></td>
</tr>
</tbody>
</table>
Rationale: Reasons for medication discontinuation will not be collected and this has been corrected.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Modified Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 Disease Features and Concomitant Medications</td>
<td>Changes in ulcerative colitis medications and other relevant medications over time and reasons for medication discontinuation will be summarized using descriptive statistics.</td>
<td>Changes in ulcerative colitis medications and other relevant medications over time will be summarized using descriptive statistics.</td>
</tr>
</tbody>
</table>

Rationale: Introductory text was added for Section 8, noting that the timing of collection of adverse events was aligned with that in the other sponsor’s registry.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>New Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Adverse Event Reporting and Follow-up</td>
<td>(None)</td>
<td>Timely, accurate, and complete reporting and analysis of safety information from studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the sponsor or its affiliates will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information. Systematic collection of safety events provides a unique resource of consistent and contemporaneously collected information. Ideally, the practice for handling safety events should be applied to all treatments under study, so that appropriate comparisons can be made. In fact, a strong advantage of registries with systematic data collection is that they provide both numerators and denominators for safety events. The contrast with comparators helps promote clarity about whether the observed effects are unique to the product or common to the condition being treated.31 In this protocol, to minimize loss to follow-up of safety events and to increase the quality and the completeness of the data for the important events and risks as previously identified in the European (EU) Risk Management Plans (RMPs) for the class, safety data collection will be restricted to serious adverse events and adverse events of interest. In addition, as described above (see Section 3.1), most patients in the comparator cohort will be enrolled in the other sponsor’s registry. In order to allow for comparison between the cohorts in this registry, all safety information collected for Simponi-exposed patients and for thiopurine-exposed patients in this registry (after the other sponsor’s registry completes its thiopurine cohort enrollment), has been fully aligned between this protocol and the other sponsor’s previously approved protocol in which the majority of the thiopurine cohort will be enrolled. Briefly, in this registry, safety events consist of serious adverse events, pregnancies, non-serious malignancies in patients &lt; 30 years old, and adverse events of interest. For these events, data will be collected through Year 6. From Years 7 to 10, data will be collected only for selected adverse events of interest (ie, those related to malignancy, infection, colonic dysplasia, and any event that leads to discontinuation of Simponi or thiopurines), and serious adverse events.</td>
</tr>
</tbody>
</table>

Approved, Date: 22 February 2016
Adverse events on Simponi not predefined for collection in this program/protocol design, or adverse events on Janssen products not included in the program/protocol design, should be reported to the identified contact or manufacturer, as necessary per local regulations but may not be included in study reports.

**Rationale:** Adverse events of interest were aligned with those in the other sponsor’s registry. The list of adverse events of interest was moved to this section.

<table>
<thead>
<tr>
<th>8.1.1 Previously Adverse Event, now Adverse Events and Adverse Events of Interest (new title)</th>
<th>Original Text</th>
<th>In this registry, adverse events of special interest will include the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma and malignancies other than lymphoma, including melanoma and leukemia:</td>
<td>Any diagnosis of a malignancy in patients participating in the registry must be reported by the investigator. After the initial report of a malignancy (including during the enrollment visit, with the exception of lymphoma or hematologic malignancy, which are exclusion criteria for this registry [see Section 4.2]), only new malignancies (defined as a malignancy that was not diagnosed prior to the time of the last contact in the registry) should be reported thereafter.</td>
<td></td>
</tr>
<tr>
<td>These include lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, intraclavicular, epitrochlear, or periaortic areas), or splenomegaly. Although not considered an adverse event of special interest, investigators should report any occurrence of a premalignant condition.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infections:</td>
<td>A serious infection is an infection diagnosed by an investigator based on results of culture, microscopy, serology, biopsy, or imaging, or based on clinical judgment, and that meets one or more of the criteria for a serious adverse event.</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis (TB):</td>
<td>Any diagnosis of active or latent TB occurring in a patient participating in the registry must be reported by the investigator. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of a serious adverse event.</td>
<td></td>
</tr>
<tr>
<td>Opportunistic infections:</td>
<td>Whether an infection should be considered opportunistic (e.g. cytomegalovirus, <em>Pneumocystis carinii</em>, aspergillosis) will be determined by the company. These events are to be considered serious only if they meet the definition of a serious adverse event (see Section 8.1.3).</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure:</td>
<td>Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including Simponi. Simponi has not been studied in subjects with CHF. Simponi should be discontinued if new or worsening symptoms of CHF appear. Any case of CHF must be reported by the investigator.</td>
<td></td>
</tr>
</tbody>
</table>
• **Serious systemic hypersensitivity reactions:** In postmarketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following Simponi administration. Some of these reactions were reported after the first administration of Simponi. If an anaphylactic or other serious allergic reaction occurs, administration of Simponi should be discontinued immediately and appropriate therapy instituted. Any case of serious systemic hypersensitivity reaction must be reported by the investigator.

• **Demyelinating events:** Use of TNF-blocking agents, including Simponi, has been associated in rare cases with onset or exacerbation of clinical symptoms and/or radiographic evidence of central or peripheral nervous system demyelinating disorders. Any case of a demyelinating event must be reported by the investigator.

• **Dysplasia of the colon:** The presence of dysplasia in the colon will be determined on the basis of biopsies obtained by colonoscopy and interpreted by a local pathologist. The determination of the need to conduct a colonoscopy or obtain biopsies will be made by the investigator. If a patient undergoes a colonoscopy, the investigator should obtain the results and provide this information to the company. At a minimum, the date and reason for the colonoscopy should be collected.

### Adverse events of interest for this registry include the following:

- Lymphoma
- Hepatosplenic T-cell lymphoma (HSTCL)
- Leukemia
- Non-melanoma skin cancer (NMSC)
- Other malignancies (except lymphoma, leukemia, and NMSC)
- Colonic dysplasia
- Opportunistic infections (both serious and non-serious), including the following bacterial, fungal, viral and parasitic infections: Aspergillus, Blastomyces, Candida, Coccidioides, Cryptococcal, Cryptosporidium, Histoplasma, Legionella, Listeria, Nocardia, Paracoccidioides, Pneumocystis, Toxoplasma, Herpes, Bacillary angiomatosis, Mucormycosis, Progressive Vaccinia, Zygomycesosis, BK virus, and JC virus
- Immune reactions including lupus, lupus-like reactions, and severe allergic reactions
- Congestive heart failure
- Cerebrovascular accident
- Myocardial infarction
- Central nervous system demyelinating disorders (including Multiple Sclerosis and Guillain-Barré syndrome)
- Hepatic events that are serious or lead to permanent discontinuation of registry drug (eg, persistent liver function test abnormalities, acute liver failure, and other serious hepatic events)
- Hematologic events that are serious or lead to permanent discontinuation of registry drug (eg, aplastic anemia, granulocytopenia, granulocytes maturation arrest, leukopenia, neutropenia, pancytopenia, and thrombocytopenia)
- Worsening or new onset of psoriasis
- Vasculitis
- Diverticulitis
- Amyotrophic lateral sclerosis
- Interstitial lung disease

Approved, Date: 22 February 2016
• Intestinal perforation
• Melanoma
• Pancreatitis
• Progressive multifocal leukoencephalopathy
• Pulmonary embolism
• Reactivation of hepatitis B
• Reversible posterior leukoencephalopathy syndrome
• Sarcoidosis
• Stevens-Johnson Syndrome and erythema multiforme
• Tuberculosis, Tuberculosis re-activation, Tuberculosis test conversion positive
• Events leading to premature discontinuation of registry treatment
  (Note: During the Direct to HCP/patient process: Of the events leading to discontinuation, only the adverse events of interest leading to premature discontinuation of registry drug will be collected)

During the course of the registry additional adverse events of interest may be identified. Updates to the adverse events of interest will be maintained and collected through the electronic data capture (EDC) system. Sites will be trained on all updates to the EDC system.

The physician will assess and record any additional information on the adverse event of interest in detail on the adverse events of interest CRF.

The physician will assess all reported adverse events of interest for seriousness and follow the requirements/timelines for reporting any adverse events of interest that fulfills the criteria of a serious adverse event, as defined in Section 8.1.3.

**Rationale:** The section was updated to reflect the sponsor’s current practice.

<table>
<thead>
<tr>
<th>Rationale: The section was updated to reflect the sponsor’s current practice.</th>
<th>Original Text:</th>
<th>Modified Text:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Previously) 8.1.2, now 8.1.4 Unlisted (Unexpected) Adverse Event/Reference Safety Information</td>
<td>Unlisted (unexpected) serious adverse reactions generated from the sponsor’s interventional trials will not be distributed to registry sites or their associated Institutional Review Board/Independent Ethics Committee (IRBs/IECs). Line listings and Annual Safety Reports for these events will be sent to Health Authorities where indicated, per local regulations.</td>
<td>NOTE: Unlistedness of an event is only relevant for the sponsor’s reporting obligations, but is not determining reporting requirements of the participating physician to the sponsor or Marketing Authorization Holder.</td>
</tr>
</tbody>
</table>
Rationale: The section and instructions for reporting of Special Situations were deleted to align with the other sponsor’s registry.

<table>
<thead>
<tr>
<th>(Previously) 8.1.3</th>
<th>Original Text:</th>
<th>Safety events of interest for a product under study that require reporting and/or safety evaluation include, but are not limited to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Drug exposure during pregnancy for all products under study (maternal and paternal; see also Section 8.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Overdose of a sponsor product under study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exposure to a sponsor product under study from breastfeeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Suspected abuse/misuse of a sponsor product under study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inadvertent or accidental exposure to a sponsor product under study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Any failure of expected pharmacological action (i.e., lack of effect) of a sponsor product under study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Medication error involving a sponsor product (with or without patient exposure to the sponsor product under study, e.g., name confusion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Suspected transmission of any infectious agent via administration of a medicinal product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unexpected therapeutic or clinical benefit from use of a sponsor product under study</td>
</tr>
</tbody>
</table>

These safety events may not meet the definition of an adverse event of interest or serious adverse event; however, from a policy perspective, they are treated in the same manner as adverse events of interest or serious adverse events. Special situations should be recorded on the Adverse Event page of the CRF. Any special situation that meets the criteria of a serious adverse event or pregnancy should be recorded on a Serious Adverse Event Report Form and be reported to the local sponsor within 24 hours of them becoming aware of the event.
Rationale: Reporting of all adverse events was changed to reporting of adverse events of interest and serious adverse events, to align with the other sponsor’s registry. Further, the timing of adverse events to be reported throughout the 10-year study period was changed to be the same as that in the other sponsor’s registry. The change in timing is reflected in the specific changes shown below, for Sections 3.1 and 8.2.1. Specific details for reporting non-serious events of malignancy in patients 30 years of age and younger, whether related to registry treatment or not, were added. Adverse events of interest no longer need to be reported to the sponsor within 24 hours.

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Text</th>
<th>Modified Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Overview of Registry Design</td>
<td>Demographics and medical history will be obtained at the time of enrollment. In addition, at the time of enrollment and every 6 months thereafter, evaluations will be conducted and information will be collected to assess the following: the incidence of lymphoma; other safety data including malignancies other than lymphoma; medications and changes in medications; clinical status; quality of life; health care utilization; and disease features. An expert panel of oncologists with extensive experience in lymphoma will be convened to validate cases of lymphoma.</td>
<td>Demographics and medical history will be obtained at the time of enrollment. The incidence of lymphoma and serious adverse events will be collected through the 10-year registry follow-up. Events of interest and serious adverse events will be collected through Year 6 and selected events of interest and serious adverse events will be collected through Year 10. In addition, at the time of enrollment and every 6 months through Year 6 and annually thereafter, evaluations will be conducted and information will be collected to assess the following: medications and changes in medications; clinical status; quality of life; and health care utilization. An expert panel of oncologists with extensive experience in lymphoma will be convened to validate cases of lymphoma.</td>
</tr>
</tbody>
</table>
| 8.2.1 During Registry Participation | Information on adverse events and special situations will be collected by site personnel on an ongoing basis in the patient’s source data and at each 6-month visit, and recorded every 6 months in the electronic data capture (EDC) system. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a product under study….. The following categories of adverse events must be reported by the investigator to the local company or designee within 24 hours of becoming aware of the event using an electronic or paper Serious Adverse Event Form (or local equivalent) or a pregnancy notification form, where appropriate:  
• Serious adverse events or serious adverse drug reactions  
• Serious and unexpected (unlisted) adverse events  
• Adverse events of special interest  
• Special situations that meet the definition of a serious adverse event  
• Pregnancy (refer to Section 8.4 for reporting requirement for exposure during pregnancy) | Information on adverse events of interest and serious adverse events will be collected by site personnel on an ongoing basis in the patient’s source data and at each 6-month visit, and recorded every 6 months in |
the electronic data capture (EDC) system for the first 6 years of the patients’ participation in the registry. In Years 7, 8, 9, and 10, data will be collected on an ongoing basis and at annual visits only for selected adverse events of interest (ie, those related to malignancy, infection, colonic dysplasia, and any event that leads to discontinuation of Simponi or thiopurines) and serious adverse events. Safety data that meets the criteria for collection should be collected regardless of protocol-defined visits.

Investigators must record in the CRF their opinion concerning the relationship of the adverse event of interest and/or serious adverse event to a product under study. Data collection should start with the first use of a product under study within the registry and will apply to all adverse events of interest, whether serious or non-serious, serious adverse events, and pregnancy exposures for the duration of a patient’s participation in the registry.

The following categories of adverse events must be reported by the investigator to the local sponsor or designee within 24 hours of becoming aware of the event using the appropriate electronic or paper form:

- Serious adverse events or serious adverse drug reactions
- Non-serious event of malignancy in patients 30 years of age and younger, whether related to registry treatment or not
- Serious and unexpected (unlisted) adverse events
- Pregnancy (refer to Section 8.4 for reporting requirement for exposure during pregnancy)

**Rationale:** Details for the Direct to Healthcare Provider/patient process were added here, for completeness.

<p>| Added Text: If treatment with registry drug is permanently discontinued for any reason, patients should be encouraged to continue in the registry or the direct to HCP/patient process (Section 5.10) for a full 10-year observation period irrespective of future treatment decisions so important safety information can be obtained. | 8.2.2 Reporting Requirements for Patients Who Temporarily Interrupt Registry Participation |</p>
<table>
<thead>
<tr>
<th>Rationale:</th>
<th>Details for the follow-up of adverse events were aligned with the other sponsor’s registry, and reference to the direct to patient follow-up were added.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8.3 Follow-up of Adverse Events</strong></td>
<td><strong>Original text:</strong> All (serious and non-serious) adverse events should be followed-up in accordance with clinical practice. This follow-up should be recorded in the patients’ source records and documented according to company instructions.</td>
</tr>
<tr>
<td></td>
<td>All reported serious adverse events and adverse events of special interest will be followed until resolution unless the patient withdraws informed consent, or no additional information can be obtained despite due diligence in obtaining follow-up information (e.g., patient or healthcare provider refuses to provide additional information; patient is lost to follow-up).</td>
</tr>
<tr>
<td></td>
<td>All reported adverse events of interest and serious adverse events will be followed until resolution unless the patient withdraws informed consent, or no additional information can be obtained despite due diligence in obtaining follow-up information (e.g., patient or healthcare provider refuses to provide additional information; patient is lost to follow-up).</td>
</tr>
<tr>
<td></td>
<td>The physician will monitor each patient for serious adverse events and adverse events of interest throughout the patient's participation in the registry or direct to HCP process, and/or until 70 days following discontinuation of registry drug administration have elapsed (whichever period is longer).</td>
</tr>
<tr>
<td></td>
<td>If the direct to HCP process is not possible, patients may be followed by the sponsor’s designee for follow-up if they move away or leave the registry for other reasons but agree to continue their participation. Efforts will be made to identify a registry site for the patient, and if none is available, the patient will be asked to provide consent for a designee of the sponsor to follow-up with him/her directly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rationale:</th>
<th>Instructions for cases of pregnancy were aligned with the other sponsor’s registry.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8.4 Pregnancy</strong></td>
<td><strong>Original text:</strong> All reports of pregnancy occurring in temporal association with the administration of a product under study must be reported to the company by the participating study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.</td>
</tr>
<tr>
<td></td>
<td>All reports of pregnancy with an abnormal outcome (e.g., spontaneous abortion, stillbirth, and congenital anomaly) occurring in temporal association with the administration of a product under study are considered serious adverse events and must be reported to the company by the participating site personnel within 24 hours of their knowledge of the event using the Serious Adverse Event Form.</td>
</tr>
<tr>
<td></td>
<td>As this is an observational study, investigators should follow the guidance in the approved local labels for medications the patient is receiving regarding discontinuation of therapy in patients who become...</td>
</tr>
</tbody>
</table>
pregnant during the study. If a patient becomes pregnant during the study, data specified in the Data Collection Schedule that is collected as part of the patient’s standard-of-care will continue to be recorded in the CRF for the applicable time points.

Because the effect of the company product under study on sperm is unknown, pregnancies in partners of male patients exposed to a company product under study will be reported by the participating site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be obtained where possible.

Modified text:

All reports of pregnancy occurring from the date of the first dose through 150 days following the last dose of registry drug (or end of registry, whichever is longer) must be reported to the sponsor by the participating study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

All reports of pregnancy with an abnormal outcome (eg, elective or spontaneous abortion, stillbirth, and congenital anomaly) from the date of the first dose through 150 days following the last dose of registry drug (or end of registry, whichever is longer) are considered serious adverse events and must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using the Serious Adverse Event Form.

As this is an observational study, investigators should follow the guidance in the approved local labels for medications the patient is receiving regarding discontinuation of therapy in patients who become pregnant during the study. If a patient becomes pregnant during the study, data specified in the Data Collection Schedule that is collected as part of the patient’s standard-of-care will continue to be recorded in the CRF for the applicable time points. Patients who become pregnant and interrupt their registry drug should remain in the registry and should continue to be monitored for new adverse events of interest or serious adverse events.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be obtained where possible.

Note: All of the changes noted above have been incorporated in the Data Collection Schedule and the Synopsis, as appropriate and the Data Collection Schedule has been edited to reflect this amended protocol.

Approved, Date: 22 February 2016
## DATA COLLECTION SCHEDULE

<table>
<thead>
<tr>
<th>Assessment</th>
<th>At Enrollment</th>
<th>Month 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72; Month 84, 96, 108, and 120</th>
<th>Or Upon Premature Termination</th>
<th>At Time of Reported Event</th>
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<tr>
<td>Informed consent &lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Medical and surgical history (including UC medical and surgical history)</td>
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<td></td>
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<tr>
<td>Tobacco and alcohol use history</td>
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<tr>
<td>Previous medications (including UC medications)</td>
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</tr>
<tr>
<td>Concomitant medications (including UC medications)</td>
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<td>Physical examination</td>
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<tr>
<td>Incidence of lymphoma &lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Safety events &lt;sup&gt;e&lt;/sup&gt;</td>
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<td>SIBDQ</td>
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<td>EQ-5D-5L</td>
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<tr>
<td>WPAI-UC</td>
<td>X</td>
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<tr>
<td>Disease features &lt;sup&gt;g&lt;/sup&gt;</td>
<td>X</td>
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<td>CRP, hemoglobin, fecal calprotectin &lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Discontinuation status</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Before enrollment in this registry, all patients must sign an informed consent form. Patients will be reconsented if they withdraw to participate in another study but then return to the registry.

<sup>b</sup> Includes all ulcerative colitis medications (eg, 5-ASAs; corticosteroids; immunomodulators, including thiopurines; biologics) and other relevant medications taken at any time in the past and at enrollment.

<sup>c</sup> Includes all ulcerative colitis medications (eg, 5-ASAs; corticosteroids; immunomodulators, including thiopurines; biologics) and other relevant medications currently being taken and any changes in these medications during participation in the registry.

<sup>d</sup> Information on cases of lymphoma will be collected using a lymphoma questionnaire through Year 10.
e. Long-term safety data will be collected including malignancies other than lymphoma. Safety events consist of serious adverse events (to be reported within 24 hours of site awareness), pregnancies (to be reported within 24 hours of site awareness), non-serious malignancies in patients < 30 years old (to be reported within 24 hours of site awareness), and adverse events of interest. At Years 7 through 10, selected adverse events of interest will be collected (related to malignancy, infection, colonic dysplasia, and adverse events causing discontinuation of Simponi or thiopurine). For safety events, data will be collected on an ongoing basis and at study visits every 6 months through Year 6, and on an ongoing basis and at annual study visits from Years 7 to 10. Refer to Section 8.1.1 for a list of adverse events of interest.

f. A full Mayo score will be calculated if an endoscopy is performed up to 21 days prior to the study visit.

g. Disease features include the following: disease duration, disease location, and/or extra-intestinal manifestations of ulcerative colitis, and any comorbidity.

h. Laboratory studies including CRP, hemoglobin, and fecal calprotectin may be performed at a local laboratory if deemed part of routine patient care. If such tests are conducted, results are to be recorded in the CRF.

i. At the time of discontinuation.

Key: ASA = aminosalicylic acid; EQ-5D-5L = EuroQoL-5 Dimensions-5 Levels; CRF = case report form; CRP = c-reactive protein; SIBDQ = Short Inflammatory Bowel Disease Questionnaire; TSQM = Treatment Satisfaction Questionnaire for Medication; UC = ulcerative colitis; WPAI-UC = Work Productivity Activity Impairment-Ulcerative Colitis
PROTOCOL SYNOPSIS

Product: SIMPONI® (golimumab)

Protocol Number: CNTO148UCO4001

Protocol Title: An Observational Prospective Long-term Exposure Registry of Adult Patients with Moderate-to-Severe Ulcerative Colitis

Protocol Name: OPAL

Target Disease: Moderate-to-severe ulcerative colitis

Patients: Men and women at least 18 years of age with moderate-to-severe ulcerative colitis for at least 3 months prior to enrollment are eligible to participate in this registry. Refer to the protocol for a complete description of inclusion and exclusion criteria.

Objectives and Hypothesis:

Primary Objective:
The primary objective of this registry is to compare the incidence of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi versus those treated with thiopurines.

Secondary Objectives:
Secondary objectives of this registry are to evaluate the following in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi or thiopurines:

- The relative risk of lymphoma following exposure to Simponi compared with exposure to thiopurines
- Long-term safety, including malignancies other than lymphoma
- Clinical status, quality of life, and health care utilization

Hypothesis:
There is no clinically meaningful increased risk of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi when compared with the risk in a similar patient population treated with thiopurines.

Registry Design: This is a global, observational, prospective, long-term, exposure registry of adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi or thiopurines in a routine clinical setting. Two cohorts, a Simponi-exposed cohort and a comparator cohort, will be enrolled as described below:

- The Simponi-exposed cohort will include the following: Patients currently receiving Simponi, patients who are still receiving Simponi after participation in an ulcerative colitis study supported by the sponsor, or patients scheduled to receive Simponi within 30 days after enrollment. Patients in this cohort may be receiving Simponi alone or in combination with thiopurines but must not be receiving other approved biologics or investigational agents at enrollment.

- The comparator cohort will include the following: Patients currently receiving thiopurines, having received at least 12 consecutive weeks of therapy prior to registry entry. Patients in this cohort must not be receiving approved biologic agents, including Simponi, or investigational agents at enrollment. These patients may have received biologics other than Simponi or investigational agents prior to enrollment.

Demographics and medical history will be obtained at the time of enrollment. The incidence of lymphoma will be collected through the 10-year registry follow-up. Events of interest and serious adverse events
will be collected through Year 6 and selected events of interest and serious adverse events will be collected through Year 10. In addition, at the time of enrollment and every 6 months through Year 6 and annually thereafter, evaluations will be conducted and information will be collected to assess the following: medications and changes in medications; clinical status; quality of life; and health care utilization. An expert panel of oncologists with extensive experience in lymphoma will be convened to validate cases of lymphoma.

**Treatment:** Patients are to receive treatments in a routine clinical setting as prescribed by their physician. Medications will not be supplied by the sponsor during patient participation in the registry.

**Duration of Registry Participation:** The planned duration of participation in the registry will be 10 years for each patient. It is anticipated that the enrollment period will be 5 years, and that the registry will be closed after the last patient has completed his or her last visit.

**Number of Patients:** Approximately 6,000 patients are planned for enrollment, with 3,000 patients in the Simponi-exposed cohort and 3,000 patients in the comparator cohort. Another sponsor is performing a similar ulcerative colitis registry (Study number NCT01848561 on www.clinicaltrials.gov). In that registry, it is anticipated that 2,750 thiopurine patients will be enrolled. For the thiopurine-exposed patients in the other registry who give consent for their data to be shared, data will be shared and analyzed with the data from the OPAL registry. The remainder of the comparator cohort and the Simponi-exposed cohort will be enrolled by the sponsor of the OPAL registry.

**Data Evaluation:**

**Sample Size**

Approximately 6,000 patients will be enrolled, with 3,000 patients in each cohort. Assuming a 25% dropout rate during the 10-year follow-up period (exponential parameter \( \lambda_{\text{_dropout}} = 0.0288 \)), with 3,000 per group, the total patient years per group over the 10-year period would be 26,066.

The estimation precision of lymphoma event rate, using the 2-sided 95% confidence interval (CI) and based on 26,066 patient-years, will be between 0.047 and 0.051 per 100 patient-years. The corresponding upper limits of the 2-sided 95% CIs of event rate will be between 0.197 and 0.231 per 100 patient-years. The sample size provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.

In addition, a sample size of 6,000 patients (3,000 per cohort), with 78 to 93 expected events observed during 10 years of follow-up, will provide 86% to 91% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort. These estimations were based on \( \alpha = 0.025 \) (1-sided), and an expected 25% dropout rate, resulting from loss to follow-up during the course of the registry.

**Primary Outcome Analysis – Lymphoma Incidence**

The incidence of validated outcomes of lymphoma, rates per 100 patient-years, and the corresponding 95% CIs will be summarized and compared between the Simponi-exposed cohort and the comparator cohort. To rule out a clinically meaningful increase in the lymphoma rate in the Simponi-exposed cohort that exceeds the lymphoma rate in the thiopurine-exposed cohort, hazard ratios and 95% CIs for lymphoma will be estimated using the Cox proportional hazards regression analysis, adjusting for potential confounding variables.

**Interim Reports:** Progress updates of registry patient accrual and a demographic summary will be provided annually. In addition, a summary of registry safety data will be included in periodic safety reports.
ABBREVIATIONS

5-ASA  5-aminosalicylic acid
6-MP   6-mercaptopurine
AZA    azathioprine
CESAME Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France
CI     confidence interval
CRF    case report form (paper or electronic as appropriate for this registry)
CRP    c-reactive protein
EDC    electronic data capture
EQ-5D-5L EuroQoL-5 Dimensions-5 Levels
EU     European Union
FDA    Food and Drug Administration
GCP    Good Clinical Practice
GPPPA  Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
HCP    healthcare provider
HSTCL  hepatosplenic T-cell lymphoma
IBD    inflammatory bowel disease
ICF    informed consent form
ICH    International Conference on Harmonisation
IEC    Independent Ethics Committee
IRB    Institutional Review Board
MedDRA Medical Dictionary for Regulatory Activities
NCC    nested case-control
NMSC   non-melanoma skin cancer
PGA    Physician’s Global Assessment
PQC    Product Quality Complaint
RMP    risk management plan
SIBDQ  Short Inflammatory Bowel Disease Questionnaire
TNF    tumor necrosis factor
TSQM   Treatment Satisfaction Questionnaire for Medication
US     United States
VA     Veterans Affairs
WPAI-UC Work Productivity and Activity Impairment – Ulcerative Colitis

Approved, Date: 22 February 2016
1. INTRODUCTION

This registry is being established to fulfill a postmarketing requirement from the United States (US) Food and Drug Administration (FDA) to rule out a clinically meaningful increase in lymphoma risk in patients with moderate-to-severe ulcerative colitis treated with Simponi, above an estimated background risk in a suitable comparator patient population. Patients will be recruited from a routine clinical setting. According to the postmarketing requirement, each patient will be followed for a period of 10 years from the time of his or her enrollment. An overview of the registry design and a detailed discussion of the rationale for the design of the registry and choice of comparator cohort are provided in Section 3.

The assessment of the incidence of lymphoma following long-term treatment with Simponi versus thiopurines in patients with moderate-to-severe ulcerative colitis will be the primary objective of this registry. The risk of lymphoma, as well as malignancies in general, has not been well characterized in patients with ulcerative colitis who receive long-term treatment with immunomodulator and/or biologic therapies such as Simponi; therefore, long-term safety, including review of other adverse events of interest and serious adverse events, will also be conducted in this registry. Additional outcome measures such as clinical status and quality of life will be included in this registry and may provide further details on the overall risk-benefit profile of Simponi in routine clinical practice.

Investigators are advised to refer to the latest version of the approved Simponi prescribing information for the most accurate and current information regarding the efficacy and safety of Simponi.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective:
The primary objective of this study is to compare the incidence of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi versus those treated with thiopurines.

Secondary Objectives:
Secondary objectives of this registry are to evaluate the following in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi or thiopurines:

- The relative risk of lymphoma following exposure to Simponi compared with exposure to thiopurines
- Long-term safety, including malignancies other than lymphoma
- Clinical status, quality of life, and health care utilization
2.2. Hypothesis

There is no clinically meaningful increased risk of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi when compared with the risk in a similar patient population treated with thiopurines.

3. REGISTRY DESIGN AND RATIONALE

3.1. Overview of Registry Design

This is a global, observational, prospective, long-term, exposure registry of adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi or thiopurines in a routine clinical setting. Two cohorts, a Simponi-exposed cohort and a comparator cohort, will be enrolled as described below:

- **The Simponi-exposed cohort will include the following:** Patients currently receiving Simponi or patients who are still receiving Simponi after participation in an ulcerative colitis study supported by the sponsor, or patients scheduled to receive Simponi within 30 days after enrollment. Patients in this cohort may be receiving Simponi alone or in combination with thiopurines but must not be receiving other approved biologics or investigational agents at enrollment.

- **The comparator cohort will include the following:** Patients currently receiving thiopurines, having received at least 12 consecutive weeks of therapy prior to registry entry. Patients in this cohort must not be receiving approved biologic agents, including Simponi, or investigational agents at enrollment. These patients may have received biologics other than Simponi or investigational agents prior to enrollment.

Approximately 6,000 patients are planned for enrollment, with 3,000 patients in the Simponi-exposed cohort and 3,000 patients in the comparator cohort. Another sponsor is performing a similar ulcerative colitis registry (Study number NCT01848561 on www.clinicaltrials.gov). In that registry, it is anticipated that 2,750 thiopurine patients will be enrolled. For the thiopurine-treated patients in the other registry who give consent for their data to be shared, data will be shared and analyzed with the data from the OPAL registry. The remainder of the thiopurine-exposed cohort and the Simponi-exposed cohort will be enrolled by the sponsor of the OPAL registry.

Patients are to receive treatments as prescribed by their physician. After enrollment, during the 10-year follow-up period, a patient may stop his or her ulcerative colitis treatment regimen and switch to a new treatment regimen. Medications will not be supplied by the sponsor during patient participation in the registry.

Demographics and medical history will be obtained at the time of enrollment. The incidence of lymphoma and serious adverse events will be collected through the 10-year registry follow-up. Events of interest and serious adverse events will be collected through Year 6 and selected events of interest and serious adverse events will be collected through Year 10. In addition, at the time of enrollment and every 6 months through Year 6 and annually thereafter, evaluations will be conducted and information will be collected to assess the following: medications and changes in medications; clinical status; quality of life; and health care utilization. An expert panel of
oncologists with extensive experience in lymphoma will be convened to validate cases of lymphoma.

The planned duration of participation in the registry will be 10 years for each patient. It is anticipated that the enrollment period will be 5 years, and that the registry will be closed after the last patient has completed his or her last visit.

3.2. Registry Design Rationale

This registry is being established to fulfill a postmarketing requirement from the US FDA to compare the incidence of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi versus those treated with thiopurines and to rule out a clinically meaningful increase in lymphoma risk in patients with moderate-to-severe ulcerative colitis treated with Simponi, above an estimated background risk in a suitable comparator patient population.

Ulcerative colitis is characterized by chronic colonic inflammation, leading to mucosal damage, tissue destruction, and significant disease burden. With a global prevalence of 37 to 246 cases per 100,000 in adults, ulcerative colitis currently affects approximately 700,000 individuals in the US.\(^1\)\(^2\) Although corticosteroids are used for induction of remission in ulcerative colitis, chronic steroid use is associated with significant morbidity and mortality.\(^3\)\(^4\) Immunosuppressive agents, including azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP), in addition to anti-tumor necrosis factor (TNF) agents such as Simponi, are more commonly used for induction and maintenance of remission in ulcerative colitis and also have the benefit of minimizing patient exposure to the side effects associated with long-term corticosteroid therapy.\(^5\)\(^6\) Indeed, medical management of ulcerative colitis as well as Crohn’s disease has emphasized earlier use of immunosuppressive and biologic agents.\(^7\)

Large population-based studies of patients with ulcerative colitis have identified no increased risk of lymphoproliferative disorders; however, these studies were conducted prior to the widespread use of immunomodulator and biologic therapies.\(^8\)\(^9\) The use of thiopurines is standard in the treatment of patients with steroid-dependent or steroid-refractory ulcerative colitis, and the association between thiopurine use and an increased risk of lymphoma has been well documented.\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) A recent population-based database study from the Veterans Affairs (VA) health care system in the US (Khan et al, 2013), reported an age-adjusted incidence rate of 15 cases of lymphoma per 10,000 patient years for patients with ulcerative colitis exposed to thiopurines, roughly a 4-fold increase in risk compared to ulcerative colitis patients not exposed to thiopurines.\(^17\) The authors in this study identified a relative risk of lymphoma of 1.7 in patients treated with infliximab and thiopurines compared to patients treated with thiopurines alone, acknowledging that their study had a limited number of patients with exposure to infliximab. These findings are consistent with data reported from the earlier CESAME prospective cohort study,\(^18\) which followed patients with Crohn’s disease and ulcerative colitis and identified a standardized incidence ratio for lymphoma of 10.2 (95% confidence interval [CI]: 1.24 – 36.9) for patients with Crohn’s disease and ulcerative colitis on combination thiopurine and anti-TNF therapy, roughly twice that of patients exposed to thiopurines alone.\(^18\)
Determination of the risk of lymphoma in patients treated with biologics such as Simponi is complicated by multiple factors, including confounding by indication; patients with more severe disease are at highest risk of lymphoma due to ongoing inflammation, but are also more likely to receive biologic therapies due to the severity of their disease. Furthermore, as the majority of patients receiving biologics has had past or concomitant exposure to immunomodulators during biologic therapy, the evaluation of the isolated risk of lymphoma conferred by biologics becomes difficult. Serial or combination therapy involving thiopurines and biologics may have additive or synergistic risks. Further complicating matters is the uncertainty in terms of the impact of duration of thiopurine exposure or cumulative dose of thiopurine exposure on lymphoma risk in ulcerative colitis, and whether or not this risk decreases after thiopurine discontinuation. The studies by Khan and Beaugerie discussed above, suggest that the risk of lymphoma decreases after discontinuation of thiopurines; however, it is not clear when this risk diminishes.

The above challenges in the ascertainment of lymphoma risk in patients with ulcerative colitis notwithstanding, the sponsor considers that the most appropriate comparator group for this registry is a cohort of patients with moderate-to-severe ulcerative colitis treated with thiopurines. Despite the confounding effects of differences in disease characteristics and activity as well as prior medication use in patients exposed to thiopurines compared with those exposed to Simponi with or without thiopurines, the thiopurine-exposed cohort will provide the most accurate estimate of the background risk of lymphoma in patients with moderate-to-severe ulcerative colitis. Regression analyses will be able to adjust for some but not all of these confounding effects and these will be elaborated upon in Section 7, as well as the Statistical Analysis Plan.

Other outcomes chosen for evaluation in this registry include clinical status, quality of life, and health care utilization assessments. The indices chosen to evaluate clinical status (the partial Mayo score and Physician’s Global Assessment [PGA]), quality of life or health status (Short Inflammatory Bowel Disease Questionnaire [SIBDQ], the EuroQoL-5 Dimensions-5 Levels [EQ-5D-5L Questionnaire], Work Productivity and Activity Impairment Questionnaire for Ulcerative Colitis [WPAI-UC], Treatment Satisfaction Questionnaire for Medication [TSQM]) are established instruments that are commonly employed in controlled clinical trials to evaluate disease status and the impact of the patient’s disease on quality of life. Health care utilization, in addition to quality of life parameters, will be further evaluated by collecting information on hospitalizations and/or surgical procedures (collected as serious adverse events). Overall, evaluation of these outcomes may allow for additional assessment of potential unknown risks, such as colonic dysplasia, as well as potential benefits associated with the long-term use of Simponi in this patient population.

For the primary outcome, an independent expert panel with extensive experience in the diagnosis of lymphoma will be convened to validate reported cases of lymphoma. In order to minimize bias, these experts will be blinded to all personal identifiers, medical treatment, and information on antecedent illness.

The sample size of 6,000 patients (3,000 per cohort), provides sufficient estimation precision to rule out doubling of the thiopurine background risk for lymphoma. In addition, this sample size will provide 86% to 91% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort.
compared with the thiopurine-exposed cohort. Refer to Section 7 for further details on the sample size calculations and rationale for the statistical analyses.

4. **PATIENT POPULATION**

To be eligible to participate in this registry, a patient must meet all of the inclusion and none of the exclusion criteria.

4.1. **Inclusion Criteria**

Each potential patient must:

1. Be a man or woman at least 18 years of age

2. Have moderate-to-severe ulcerative colitis of at least 3 months’ duration prior to enrollment, confirmed by endoscopy at any time in the past.

3. Be eligible for enrollment into the Simponi-exposed cohort or the comparator cohort according to the following:

   a. **Simponi-exposed cohort:**
      
      • The patient is currently receiving Simponi, or
      
      • The patient is continuing to receive Simponi after participation in an ulcerative colitis study supported by the sponsor, or
      
      • The patient is scheduled to receive Simponi within 30 days after enrollment.

      Note: a patient who does not receive Simponi within 30 days after enrollment should be withdrawn from registry participation as this will be a protocol deviation. The patient may re-enroll in the registry when the patient starts Simponi.

      Patients in this cohort:
      
      - may be receiving Simponi alone or in combination with thiopurines
      
      - must not be receiving other approved biologics or investigational agents at enrollment
      
      - may have received other approved biologics or investigational agents prior to enrollment

   b. **Comparator cohort:**
      
      • The patient is currently receiving thiopurines, having received at least 12 consecutive weeks of therapy prior to registry entry

      Patients in this cohort:
      
      - must not be receiving other approved biologic agents, including Simponi, or any investigational agents at enrollment.
      
      - may have received biologics other than Simponi or investigational agents prior to enrollment.
Note:  
(1) At sites that are participating in both registries, no thiopurine patients will be enrolled in the OPAL registry until enrollment in the other sponsor’s thiopurine group is complete.

(2) At sites that are participating in the OPAL registry only, patients in the thiopurine group will be enrolled in the OPAL registry.

4. Sign an informed consent form (ICF) indicating that he or she understands the purpose of the registry procedures and is willing to participate in the registry.

5. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participating in the registry:

1. Patients who cannot be treated with Simponi or thiopurines

2. Patients with a previous diagnosis of lymphoma or hematologic malignancy at any time prior to enrollment.

3. Patients currently receiving an investigational or biologic agent other than Simponi

4. Patients with any condition for which, in the opinion of the investigator, participation in the registry would not be in the best interest of the patient (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all registry enrollment criteria have been met.

4.3. Participation in Other Clinical Studies

In order to allow patients to seek alternative therapies while still allowing for the long-term follow-up required in this registry, participation in this registry must be interrupted for patients who subsequently enroll in any interventional clinical study with inclusion/exclusion criteria that prohibit concurrent enrollment in other studies.

Patients may participate in other studies and/or registries as permitted by inclusion/exclusion criteria of this registry.

Patients may be re-enrolled in this registry after ending their participation in other clinical studies. For patients who are re-enrolled in the registry, study visits will continue at scheduled time points and will be determined from the initial date of registry enrollment. Such patients should retain their original registry identification number and provide written informed consent again. Exposure to agents in other clinical studies will be considered in the analyses of lymphoma risk. Safety information will be collected as described in Section 8.2.1.
5. **REGISTRY EVALUATIONS**

The Data Collection Schedule summarizes the frequency and timing of information to be obtained and assessments to be performed at enrollment and every 6 months through Year 6 and annually thereafter.

5.1. **Demographics and Medical History**

Demographic and medical history will include, but are not limited to age, gender, race/ethnicity (where allowed by local laws), smoking and alcohol status, duration of disease, extent/location of disease, and surgical history.

5.2. **Medications**

5.2.1. **Medications Prior to Enrollment in the Registry**

All ulcerative colitis medications (eg, 5-aminosalicylic acid [5-ASA]; corticosteroids; immunomodulators, including thiopurines; biologics) and other relevant medications taken at any time in the past and at enrollment will be recorded at enrollment. Recorded information will include the name, dose, frequency, route of administration, the start and stop dates, and duration of therapy. For biologics, brand (trade) names will be recorded. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a patient into the registry.

5.2.2. **Medications During Participation in the Registry**

Once patients are enrolled in the registry, they may receive other commercially available medications (both over-the-counter or by prescription) in accordance with routine clinical practice. No medication will be prohibited except as specified in Section 4.3. During the 10-year follow-up period, a patient may stop his or her ulcerative colitis treatment regimen and switch to a new treatment regimen.

All cohort-defined treatments, all other therapies for ulcerative colitis, and other relevant medications taken during participation in the registry must be recorded throughout the registry. Recorded information will include the name, dose, frequency, route of administration, the start and stop dates, and duration of therapy. If a patient discontinues a cohort-defined treatment, the reason for discontinuation will be collected.

For patients who interrupt registry participation because of participation in a clinical study (see Section 4.3), all medications for ulcerative colitis or other relevant medications taken in the interval since the patient exited the registry should be collected at the first visit after the patient re-enrolls. The sponsor will attempt to obtain treatment assignments for patients who participate in blinded clinical studies.

5.3. **Registry Drug Treatment and Dosing Changes**

Prior to enrollment into the registry, the participating physician should have prescribed the registry drug, along with instructions for appropriate use. At subsequent protocol-defined visits the physician will collect the start and stop dates, any dose interruptions, and reason for the dose
interruption that may have occurred since the last visit. The dose, dates of administration, dose interruptions, and the reason for the interruption will be captured in the source documents and case report forms (CRFs).

Dose interruptions of Simponi treatment will be defined as missing >1 dose.

Patients being treated with a thiopurine (AZA or 6-MP) without a concurrent biologic at enrollment may add biologic therapy with or without concurrent thiopurine therapy during the registry. For these patients the 10-year follow-up period will start at the time of enrollment into the registry.

All patients will be followed for 10 years upon entry into the registry unless they withdraw their consent from the scheduled portion of the registry and also decline participation in the direct to Healthcare Provider (HCP) process or direct to patient follow-up (described in Section 5.10).

5.4. Primary Outcome Evaluation – Lymphoma Incidence

For all cases of lymphoma, a questionnaire will be sent to the investigator to obtain complete medical information about each case.

An Adjudication Committee will validate cases of lymphoma. Information will be obtained from the CRF, the lymphoma questionnaire, and other source data such as hospitalization summary, histological analysis results, and laboratory values, as specified in the Trial Center File.

The Adjudication Committee will not be informed of the patient’s exposure status for Simponi or thiopurines during case evaluation to eliminate potential bias. If the patient is under the care of an Adjudication Committee member, that member will be excused from the evaluation of the case.

For any validated case of hepatosplenic T-cell lymphoma (HSTCL), investigators will be approached to participate in the interventional sponsor protocol REMICADELYM4001 in which HSTCL tumor biopsy specimens from patients exposed to either Remicade or Simponi are collected for further analysis.

5.5. Long-term Safety

Long-term safety will be evaluated by physical examinations and reporting of lymphoma, other adverse events of interest, and serious adverse events. Any abnormality noted on physical examination that indicates an adverse event of interest or a serious adverse event should be reported as such. Adverse events of interest and serious adverse events, including any events leading to discontinuation of registry drug, will be recorded throughout the patient's participation in the registry. All adverse events of interest and serious adverse events will be followed by the investigator as specified in Section 8.
5.6. Clinical Status – Partial Mayo Score and Physician Global Assessment

The partial Mayo score, a validated tool used to assess disease status in patients with ulcerative colitis, will be utilized to assess clinical status in this registry. Information will be obtained using 3 of the individual components of the full Mayo score, including stool frequency, rectal bleeding, and PGA as shown in Table 1. Endoscopy is not required for calculation of the partial Mayo score. A higher score indicates more severe disease.

Table 1: Mayo Scoring System for Assessment of Ulcerative Colitis Activity

<table>
<thead>
<tr>
<th>Stool frequency a</th>
<th>0 = Normal number of stools for this patient</th>
<th>1 = 1 to 2 stools more than normal</th>
<th>2 = 3 to 4 stools more than normal</th>
<th>3 = 5 or more stools more than normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscore: 0 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rectal bleeding b</th>
<th>0 = No blood seen</th>
<th>1 = Streaks of blood with stool less than half the time</th>
<th>2 = Obvious blood with stool most of the time</th>
<th>3 = Blood alone passes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscore: 0 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings on endoscopy c</th>
<th>0 = Normal or inactive disease</th>
<th>1 = Mild disease (erythema, decreased vascular pattern, mild friability)</th>
<th>2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)</th>
<th>3 = Severe disease (spontaneous bleeding, ulceration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscore: 0 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician’s Global Assessment d</th>
<th>0 = Quiescent, normal</th>
<th>1 = Mild disease</th>
<th>2 = Moderate disease</th>
<th>3 = Severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscore: 0 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
b. The daily bleeding score represents the most severe bleeding of the day.
c. Endoscopy is not required for calculation of the partial Mayo score.
d. The Physician’s Global Assessment acknowledges the three other criteria, the patient’s daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient’s performance status.

All patients will be provided with a Patient Diary at the Enrollment Visit to record ulcerative colitis-related symptoms. If the patient forgets to complete the diary, patient recall will be used. The patient diary will provide information on the patient-reported subscores for calculating the Partial Mayo Score at each visit. Patients should record the total number of stools each day from the 3 days prior to each visit. Patients should record normal stool frequency as the number of stools when not experiencing a flare of their ulcerative colitis. The average score of the diary entries from the 3 days prior to each visit will be used for each patient-reported subscore. In addition to the physical examination, the investigator should use the patient-reported subscores of abdominal discomfort and functional assessment to determine the physician's global assessment subscore. An estimate of the Partial Mayo or the Mayo score using data from the patient's ulcerative colitis medical history (if available) at the time of the patient's first dose of

Approved, Date: 22 February 2016
5.7. Quality of Life Evaluations and Health Care Utilization

The following subsections describe each of the quality of life evaluations and health care utilization tools to be utilized in this registry.

5.7.1. Short Inflammatory Bowel Disease Questionnaire

The SIBDQ measures health related quality of life over the preceding 2 weeks of the patient’s treatment. The questionnaire consists of 10 items about issues of the patient’s disease symptoms, as well as social and emotional domains, ie, the questions are about symptoms the patient has been experiencing as a result of the disease, how the patient has been feeling in general, and how the patient’s mood has been. The answers range from ‘always’ through 7 levels to ‘never.’ The total score ranges from 10 (worst health) to 70 (best health). The SIBDQ can be administered and scored quickly and easily and therefore is of potential value to physicians in the clinical setting; although, the use of the SIBDQ in this setting has not been well documented.

5.7.2. EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L is a standardized non-disease specific instrument for describing and assessing health-related quality of life. This instrument evaluates 5 areas including mobility, ability for self-care, ability in usual activities, pain/discomfort and anxiety/depression. There also is a self-evaluated 100-point health assessment.

5.7.3. Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis (WPAI-UC)

The WPAI-UC is a validated instrument that measures the effect of ulcerative colitis (UC) symptoms on a patient’s life (eg, diarrhea, loss of appetite, weight loss, abdominal pain, fever, joint pain, skin sores, rectal bleeding) and on his or her ability to work and perform regular activities. The recall period for the WPAI-UC is the previous 7 days.

5.7.4. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a 14-question instrument that gauges a patient’s experience with his or her medication. The questionnaire was designed to evaluate the effectiveness, side effects, and convenience of the medication over a period of 2- to 3-weeks or since the last time it was taken.

5.7.5. Surgical Procedures and Hospitalizations

The number of and reasons for hospitalizations as well as the number of and reasons for surgical procedures, including colectomy, will be collected for each patient in the CRF.
5.8. **Disease Features**

The patient’s ulcerative colitis disease features will be collected for each cohort and recorded on the CRF. Disease features include the following: disease duration, disease location, and/or extra-intestinal manifestations of ulcerative colitis (ie, the most common manifestations involve the musculoskeletal and dermatologic systems), and any comorbidities.

5.9. **Laboratory Evaluations**

Laboratory tests including C-reactive protein, hemoglobin, and fecal calprotectin may be performed at a local laboratory if deemed part of routine patient care. If such tests are conducted, results are to be recorded in the CRF.

5.10. **Direct to Healthcare Provider/Patient Process**

Due to the duration of the study and the length of time between the follow-up visits, the proportion of patients lost to follow-up might be significant. The frequency of loss to follow-up should be minimized by use of the retention strategies described below to ensure collection of data of interest and vital status until study end.

5.10.1 **Direct to Healthcare Provider Process**

For patients who discontinue from the scheduled portion of the registry before Year 10 of follow-up, every effort will be made to continue to collect data. For example, the patient may be offered the possibility to release data from a simplified HCP questionnaire on an annual basis through 10 years from the patient's enrollment in the registry. In order to participate in the direct to HCP process, the patient will be asked to provide consent (either at study entry or during the study).

The first data collection period will capture data from the date of the patient's discontinuation visit or last contact while still enrolled in the registry through the completion of the first annual HCP questionnaire for the patient. The questionnaire focuses on the collection of surgeries (eg, especially colectomies), hospitalizations, deaths, adverse events of interest, and ulcerative colitis related medication use since registry discontinuation. The questionnaire may be completed by a registry physician or the patient's current HCP (if the patient is no longer under the care of a registry physician). Any other serious adverse events experienced by the patient should be reported according to standard spontaneous reporting procedures, and they are not subject to the requirements of this protocol.

5.10.2 **Direct to Patient Process**

Patients may also be followed by a CRO designated by the sponsor. The sponsor’s designee is responsible for follow-up on patients who move away from the investigative site or leave the registry for other reasons but consent to continue their participation in the registry (either at study entry or during the study). The patient will be contacted by this designee of the sponsor to follow-up with him/her directly and to obtain subsequent interval registry data through 10 years from the patient’s enrollment in the registry.
Patients who have affirmatively withdrawn authorization to have their personal health information used or disclosed in connection with the registry will not be asked to continue in the registry or asked to participate in the direct to HCP/patient process.

6. **REGISTRY ENDPOINTS**

**Primary Endpoint**

The primary endpoint of this registry is the incidence of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi versus thiopurines.

**Secondary Endpoint(s)**

The major secondary endpoints of this registry in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi or thiopurines are:

- The relative risk of lymphoma
- Long-term safety, including malignancies other than lymphoma, based on safety data
- Clinical disease status (partial Mayo score and PGA, a component of the partial Mayo score); quality of life (SIBDQ, EQ-5D-5L, TSQM, and WPAI-UC), and healthcare utilization (ie, the number of and reasons for hospitalizations as well as the number of and reasons for surgical procedures)

7. **STATISTICAL METHODS**

Statistical analysis will be conducted by the sponsor or under the authority of the sponsor. A general description of the statistical methods is provided in this section. Specific details will be provided in the Statistical Analysis Plan.

7.1. **Patient Information**

All ulcerative colitis patients who sign an ICF and have a baseline visit will be included in the analyses.

Patients will be classified into 2 cohorts based on their medication exposure prior to and during registry follow up.

- The Simponi-exposed cohort includes those exposed to Simponi at enrollment or during registry participation, with or without exposure to thiopurines. Subgroup analyses will allow for the evaluation of Simponi-exposed patients who were not exposed to thiopurines, and the exposure definitions below. These patients must not be receiving other approved biologics or investigational agents at enrollment.

- The thiopurine-exposed cohort includes those exposed to thiopurines but not receiving Simponi or other biologics at enrollment. These patients may have received biologics other than Simponi or investigational agents prior to enrollment.

During the 10-year follow-up period, a patient may discontinue and/or change therapies. Therefore, other potential medication exposure cohorts may be evaluated. For example, if patients in the thiopurine-exposed cohort are exposed to biologics other than Simponi after or
concurrent with thiopurine exposure, they may be included in a ‘thiopurines plus other biologic’ group. Patients in the thiopurine-exposed cohort who initiate Simponi during participation in the registry will cross over to the Simponi-exposed cohort.

On-treatment analyses will allow assessment of actual exposure to drug (Simponi or thiopurines) in patient-years during participation in the registry for each cohort. The possible varying latency periods of drug effects will also be considered. Sensitivity analyses will evaluate these exposure groups in the absence of concomitant use of other biologics or investigational products initiated after registry enrollment. Adverse events of interest and serious adverse events will be classified in the appropriate cohorts based on history of drug exposure prior to the event.

Patients’ baseline data, demographics, and baseline disease characteristics will be summarized. The baseline measurement is defined as the measurement collected at the baseline visit. The medical and medication history data collected at the baseline visit will also be summarized for the 2 cohorts. Disease characteristics at baseline will also be summarized.

### 7.2. Sample Size Determination

The primary endpoint of this registry is the incidence of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi versus thiopurines. Based on a recent retrospective nationwide cohort study from the VA health care system, the incidence of lymphoma for patients less than 40 years old was 0.15 per 100 patient-years,\(^1\) for patients from 40 to 65 years old was 0.18 per 100 patient-years and for patients older than 65 years was 0.39 per 100 patient-years. In the Phase 3 Simponi UC program, the mean baseline age of subjects was 40.0 years. It is assumed that the mean age in the registry will be similar to that in the Phase 3 UC program, not anticipating a significant number of patients older than 65 will be enrolled. Therefore, the expected background lymphoma event rate for the thiopurine-exposed cohort is between 0.15 to 0.18 per 100 patient-years. The doubling of event risk would be between 0.30 and 0.36 events per 100 patient-years.

Approximately 6,000 patients will be enrolled, with 3,000 patients in each cohort. Assuming a 25% dropout rate during the 10-year follow-up period (exponential parameter \(\lambda_{\text{drot}} = 0.0288\)), with 3,000 per group, the total patient years per group over the 10-year period would be 26,066, as shown in the calculation below.

\[
\text{Patient years of follow up} = 3000 \int_{0}^{10} e^{-0.0288t} dt = 26,066
\]

The estimation precision of the lymphoma event rate, using the 2-sided 95% CI and based on 26,066 patient-years, will be between 0.047 and 0.051 per 100 patient-years. The corresponding upper limits of the 2-sided 95% CIs of event rate will be between 0.197 and 0.231 per 100 patient-years. The sample size provides sufficient estimation precision to rule out doubling of the thiopurine background risk between 0.30 and 0.36 events per 100 patient-years.
In addition, a sample size of 6,000 patients (3,000 per cohort), with 78 to 93 expected events observed during 10 years of follow-up, will provide 86% to 91% power to rule out a hazard ratio of 2.0 for the Simponi-exposed cohort compared with the thiopurine-exposed cohort. These estimations were based on \(\alpha = 0.025\) (1-sided), and an expected 25% dropout rate, resulting from loss to follow-up during the course of the registry (Table 2).

Table 2: Scenarios for ruling out hazard ratios of 2.0 with a sample size of 6,000 patients with 10 years of follow up, alpha = 0.025 (1-sided)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>2.0</th>
<th>2.0</th>
<th>2.0</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule out: X-fold or greater hazard ratio ((\lambda_{\text{simp}} / \lambda_{\text{thio}})) Simponi exposed vs. thiopurines exposed in the absence of a biologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential parameter ((\lambda_{\text{thio}})) thiopurines exposed in the absence of a biologic</td>
<td>0.0015</td>
<td>0.0016</td>
<td>0.0017</td>
<td>0.0018</td>
</tr>
<tr>
<td>Upper limit of exponential parameter ((\lambda_{\text{simp}})) Simponi exposed (with or without thiopurines)</td>
<td>0.0030</td>
<td>0.0032</td>
<td>0.0034</td>
<td>0.0036</td>
</tr>
<tr>
<td>Loss of follow up rate in 10 years</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Exponential parameter ((\lambda_{\text{lof}})) for loss of follow up rate</td>
<td>0.0288</td>
<td>0.0288</td>
<td>0.0288</td>
<td>0.0288</td>
</tr>
<tr>
<td>Number of events expected</td>
<td>78</td>
<td>83</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>Sample size per group</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Power</td>
<td>86%</td>
<td>88%</td>
<td>90%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Note: The sample size calculation was based on the non-inferiority test for two exponential survival curves using nQuery® software.30,31

7.3. Primary and Key Secondary Outcome Analyses

The primary endpoint of this registry is to determine the incidence of lymphoma in adult patients with moderate-to-severe ulcerative colitis who are treated with Simponi versus thiopurines.

The incidence of lymphoma and rates per 100 patient-years and the corresponding 2-sided 95% CIs will be summarized and compared between the Simponi cohort and the thiopurines cohort.

The key secondary endpoint of this registry is to evaluate the relative risk of lymphoma following exposure of Simponi compared with exposure to thiopurines without exposure to biologics.

The Cox proportional hazards model will be used to compare time to first lymphoma event between Simponi and thiopurines exposed cohorts, adjusting for the key prognostic variables, including demographics, baseline disease characteristics, disease duration, and other ulcerative colitis medication exposure. The hazard ratio and 95% CI will be estimated. The upper bound of the 95% CI of the hazard ratio for the Simponi cohort compared with the thiopurines cohort will provide an estimation to rule out the increased risk of lymphoma. For example, the upper bound of the 95% CI for the hazard ratio of < 2.0 indicates a \(\geq 2.0\)-fold risk of lymphoma can be ruled out, comparing the Simponi-exposed cohort with the thiopurine-exposed cohort. Additional Cox
proportional hazard model analyses, using medication exposure as time varying covariates, will also be performed.

The effect of Simponi or thiopurines exposure duration on the incidence of lymphoma will also be investigated. Exposure duration for the Simponi cohort and thiopurines cohort may be classified into intervals (eg, <1 year, 1 − 2 years, >2 − 4 years, >4 − 7 years, >7 years). The lymphoma rates by exposure duration interval for the Simponi and thiopurines cohorts will be summarized.

The nested case-control (NCC) analysis may be performed at the end of the registry based on the amount of missing information on important risk factors. If performed, the NCC analysis will be used to compare lymphoma cases with controls matched by appropriate factors to further evaluate the relative risk of Simponi and thiopurines exposure on lymphoma.

7.4. Other Secondary Outcome Analyses

7.4.1. Long-term Safety

The adverse event verbatim terms reported by investigators in the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The adverse event rate per 100 patient-years of exposure with 95% CIs will be estimated by treatment cohorts for both adverse events of interest and serious adverse events.

The Cox proportional hazards model may be used to further evaluate the impact of Simponi exposure on adverse events of interest and serious adverse events. Propensity score adjustments may be performed.

7.4.2. Clinical Status, Quality of Life, and Health Care Utilization

Partial Mayo Scores for patients in the Simponi and thiopurines cohorts will be summarized using descriptive statistics. Graphic methods, such as box-whisker plots, will be used to display the distributions of partial Mayo scores for the 2 cohorts. The proportion of patients who achieve a partial Mayo score ≤ 2, with no individual sub-score > 1 will be summarized by exposure cohorts over time. PGA scores will also be summarized using descriptive statistics.

Quality of life, health status measurements, treatment satisfaction, and work productivity including SIBDQ, EQ-5D-5L, TSQM, and WPAI-UC will be summarized for the 2 cohorts using descriptive statistics, including number, mean, standard deviation, median, interquartile range, minimum, and maximum values for continuous variables and frequency and percentage for categorical variables.

The number of and reasons for hospitalizations as well as the number of and reasons for surgical procedures, including colectomy, will be summarized for each exposure cohort.
7.5. Disease Features and Concomitant Medications

Disease features, such as disease duration, disease location, extra-intestinal manifestations of ulcerative colitis, and/or comorbidities will be summarized using descriptive statistics for the treatment cohorts.

Other medications for ulcerative colitis (such as 5-ASA; corticosteroids; immunomodulators other than thiopurines; and other biologics) and other relevant medications prior to enrollment in the registry and during participation in the registry will be summarized using descriptive statistics.

Changes in ulcerative colitis medications and other relevant medications over time will be summarized using descriptive statistics. The Kaplan-Meier method may be used to estimate time on medication.

7.6. Missing Data

All efforts will be made to enhance data collection procedures and minimize missing data. Imputation rules may be applied when appropriate, such as using the first day of the month and the first month of the year to impute missing dates, and using median and mode to impute baseline parameters. Sensitivity analyses, comparing results obtained with and without missing data imputation, will be performed.

8. Adverse Event Reporting and Follow-up

Timely, accurate, and complete reporting and analysis of safety information from studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. All studies conducted by the sponsor or its affiliates will be conducted in accordance with established procedures and regulatory requirements worldwide to ensure appropriate reporting of safety information.

Systematic collection of safety events provides a unique resource of consistent and contemporaneously collected information. Ideally, the practice for handling safety events should be applied to all treatments under study, so that appropriate comparisons can be made. In fact, a strong advantage of registries with systematic data collection is that they provide both numerators and denominators for safety events. The contrast with comparators helps promote clarity about whether the observed effects are unique to the product or common to the condition being treated.

In this protocol, to minimize loss to follow-up of safety events and to increase the quality and the completeness of the data for the important events and risks as previously identified in the European (EU) Risk Management plans (RMPs) for the class, safety data collection will be restricted to serious adverse events and adverse events of interest. In addition, as described above (see Section 3.1), most patients in the comparator cohort will be enrolled in the other sponsor’s registry. In order to allow for comparison between the cohorts in this registry, all safety information collected for Simponi-exposed patients and for thiopurine-exposed patients in this registry (after the other sponsor’s registry completes its thiopurine cohort enrollment), has been
fully aligned between this protocol and the other sponsor’s previously approved protocol in which the majority of the thiopurine cohort will be enrolled.

Briefly, in this registry, safety events consist of serious adverse events, pregnancies, non-serious malignancies in patients < 30 years old, and adverse events of interest. For these events, data will be collected through Year 6. From Years 7 to 10, data will be collected only for selected adverse events of interest (ie, those related to malignancy, infection, colonic dysplasia, and any event that leads to discontinuation of Simponi or thiopurines), and serious adverse events.

Adverse events on Simponi not predefined for collection in this program/protocol design, or adverse events on Janssen products not included in the program/protocol design, should be reported to the identified contact or manufacturer, as necessary per local regulations but may not be included in study reports.

8.1. Definitions

8.1.1. Adverse Events and Adverse Events of Interest

An adverse event is any untoward medical occurrence in a registry patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the time of enrollment, or abnormal results of diagnostic procedures conducted outside of the scope of this observational registry, including laboratory test abnormalities.

Adverse events of interest for this registry include the following:

- Lymphoma
- Hepatosplenic T-cell lymphoma (HSTCL)
- Leukemia
- Non-melanoma skin cancer (NMSC)
- Other malignancies (except lymphoma, leukemia, and NMSC)
- Colonic dysplasia
- Opportunistic infections (both serious and non-serious), including the following bacterial, fungal, viral and parasitic infections: Aspergillus, Blastomyces, Candida, Coccidioides, Cryptococcal, Cytomegalovirus, Histoplasma, Legionella, Listeria, Nocardia, Paracoccidiodes, Pneumocystis, Toxoplasma, Herpes, Bacillary angiomatosis, Mucormycosis, Progressive Vaccinia, Zygomycosis, BK virus, and JC virus
- Immune reactions including lupus, lupus-like reactions, and severe allergic reactions
• Congestive heart failure
• Cerebrovascular accident
• Myocardial infarction
• Central nervous system demyelinating disorders (including Multiple Sclerosis and Guillain-Barré syndrome)
• Hepatic events that are serious or lead to permanent discontinuation of registry drug (eg, persistent liver function test abnormalities, acute liver failure, and other serious hepatic events)
• Hematologic events that are serious or lead to permanent discontinuation of registry drug (eg, aplastic anemia, granulocytopenia, granulocytes maturation arrest, leukopenia, neutropenia, pancytopenia, and thrombocytopenia)
• Worsening or new onset of psoriasis
• Vasculitis
• Diverticulitis
• Amyotrophic lateral sclerosis
• Interstitial lung disease
• Intestinal perforation
• Melanoma
• Pancreatitis
• Progressive multifocal leukoencephalopathy
• Pulmonary embolism
• Reactivation of hepatitis B
• Reversible posterior leukoencephalopathy syndrome
• Sarcoidosis
• Stevens-Johnson Syndrome and erythema multiforme
• Tuberculosis, Tuberculosis re-activation, Tuberculosis test conversion positive
• Events leading to premature discontinuation of registry treatment (Note: During the Direct to HCP/patient process: Of the events leading to discontinuation, only the adverse events of interest leading to premature discontinuation of registry drug will be collected)

During the course of the registry additional adverse events of interest may be identified. Updates to the adverse events of interest will be maintained and collected through the electronic data capture (EDC) system. Sites will be trained on all updates to the EDC system.

The physician will assess and record any additional information on the adverse event of interest in detail on the adverse events of interest CRF.
The physician will assess all reported adverse events of interest for seriousness and follow the requirements/timelines for reporting any adverse events of interest that fulfills the criteria of a serious adverse event, as defined in Section 8.1.3.

8.1.1.1. Attribution Definitions

An adverse event is considered not associated with the use of the treatment if the attribution is not related or doubtful according to the definitions listed below:

**Not Related:** An adverse event that is not related to the use of the treatment.

**Doubtful:** An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

An adverse event is considered associated with the use of the treatment if the attribution is possible, probable, or very likely according to the definitions listed below:

**Possible:** An adverse event that might be due to the use of the treatment. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

**Probable:** An adverse event that might be due to the use of the treatment. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

**Very Likely:** An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

8.1.1.2. Severity Definitions

Where applicable, an assessment of severity grade will be made using the following general categorical descriptors:

**Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

**Moderate:** Sufficient discomfort is present to cause interference with normal activity.

**Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (eg, laboratory abnormalities).
8.1.2. Adverse Drug Reaction

An adverse drug reaction is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended. The phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a possibility; ie, the relationship cannot be ruled out.

An adverse drug reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions.

8.1.3. Serious Adverse Event or Serious Adverse Drug Reaction

A serious adverse event or serious adverse drug reaction based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence (or a “response to a medicinal product” as defined above) that at any dose:

- Results in death
- Is life-threatening
  (The patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
• Surgery or procedure planned before entry into the study. Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a patient in a study, whether or not the event is expected or associated with the product under study, is considered a serious adverse event.

Hospitalizations not reported as serious adverse events will be recorded for the purposes of evaluation of health care utilization.

8.1.4 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information, such as the locally approved prescribing information at the time of the event.

NOTE: Unlistedness of an event is only relevant for the sponsor’s reporting obligations, but is not determining reporting requirements of the participating physician to the sponsor or Marketing Authorization Holder.

8.2. Pharmacovigilance and Reporting Procedures

The sponsor will provide appropriate pharmacovigilance training to the participating study-site personnel.

8.2.1. During Registry Participation

Information on adverse events of interest and serious adverse events will be collected by site personnel on an ongoing basis in the patient’s source data and at each 6-month visit, and recorded every 6 months in the EDC system for the first 6 years of the patients’ participation in the registry. In Years 7, 8, 9, and 10, data will be collected on an ongoing basis and at annual visits only for selected adverse events of interest (ie, those related to malignancy, infection, colonic dysplasia, and any event that leads to discontinuation of Simponi or thiopurines) and serious adverse events. Safety data that meets the criteria for collection should be collected regardless of protocol-defined visits.

Investigators must record in the CRF their opinion concerning the relationship of the adverse event of interest and/or serious adverse event to a product under study. Data collection should start with the first use of a product under study within the registry and will apply to all adverse events of interest, whether serious or non-serious, serious adverse events, and pregnancy exposures for the duration of a patient’s participation in the registry.
The following categories of adverse events must be reported by the investigator to the local sponsor or designee within 24 hours of becoming aware of the event using the appropriate electronic or paper form:

- Serious adverse events or serious adverse drug reactions
- Non-serious event of malignancy in patients 30 years of age and younger, whether related to registry treatment or not
- Serious and unexpected (unlisted) adverse events
- Pregnancy (refer to Section 8.4 for reporting requirement for exposure during pregnancy)

For serious adverse events and pregnancy exposures following exposure to a non-sponsor medicinal product under study (ie, a product under study that is not marketed by the sponsor), the investigator should notify the appropriate Competent Authority (or the manufacturer of that medicinal product in the absence of appropriate local legislation) as soon as possible.

The sponsor or their designee assumes responsibility for appropriate reporting of serious adverse events that occur in patients exposed to Simponi to regulatory authorities. The investigator must also report these events to the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that approved the registry protocol unless otherwise required by local regulations and documented by the IRB/IEC.

**8.2.2. Reporting Requirements for Patients Who Temporarily Interrupt Registry Participation**

For patients who interrupt registry participation because of participation in an interventional clinical trial supported by the sponsor or its designee (see Section 4.3 for further details), adverse events of interest and serious adverse events that occurred since the patient completed the interventional trial should be collected at the first visit after re-enrollment in this registry. This will ensure that all safety events are captured appropriately when a patient participates in more than one study supported by the sponsor or its designee over time.

For patients who interrupt registry participation because of participation in a non-sponsor clinical study, adverse events of interest and serious adverse events that occurred since the patient exited the registry should be collected at the first visit after re-enrollment in this registry.

If treatment with registry drug is permanently discontinued for any reason, patients should be encouraged to continue in the registry or the direct to HCP/patient process (Section 5.10) for a full 10-year observation period irrespective of future treatment decisions so important safety information can be obtained.

**8.3. Follow-up of Adverse Events**

All adverse events of interest and serious adverse events should be followed-up in accordance with clinical practice. This follow-up should be recorded in the patients’ source records and documented according to sponsor instructions.
All reported adverse events of interest and serious adverse events will be followed until resolution unless the patient withdraws informed consent, or no additional information can be obtained despite due diligence in obtaining follow-up information (e.g., patient or healthcare provider refuses to provide additional information; patient is lost to follow-up).

The physician will monitor each patient for serious adverse events and adverse events of interest throughout the patient's participation in the registry or direct to HCP process, and/or until 70 days following discontinuation of registry drug administration have elapsed (whichever period is longer).

If the direct to HCP process is not possible, patients may be followed by the sponsor’s designee for follow-up if they move away or leave the registry for other reasons but agree to continue their participation. Efforts will be made to identify a registry site for the patient, and if none is available, the patient will be asked to provide consent for a designee of the sponsor to follow-up with him/her directly.

All follow-up information for serious adverse events that are not resolved at the end of the registry or by the time a patient withdraws from the registry must be reported directly by the investigator, within 24 hours of them becoming aware, to the local sponsor (see country-specific information in the Trial Center File) by using an electronic or paper Serious Adverse Event Report Form (or local equivalent).

When necessary, the sponsor will inform the local authorities following applicable requirements for expedited and aggregated reporting.

8.4. Pregnancy

All reports of pregnancy occurring from the date of the first dose through 150 days following the last dose of registry drug (or end of registry, whichever is longer) must be reported to the sponsor by the participating study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

All reports of pregnancy with an abnormal outcome (e.g., elective or spontaneous abortion, stillbirth, and congenital anomaly) from the date of the first dose through 150 days following the last dose of registry drug (or end of registry, whichever is longer) are considered serious adverse events and must be reported to the sponsor by the participating site personnel within 24 hours of their knowledge of the event using the Serious Adverse Event Form.

As this is an observational study, investigators should follow the guidance in the approved local labels for medications the patient is receiving regarding discontinuation of therapy in patients who become pregnant during the study. If a patient becomes pregnant during the study, data specified in the Data Collection Schedule that is collected as part of the patient’s standard-of-care will continue to be recorded in the CRF for the applicable time points. Patients who become pregnant and interrupt their registry drug should remain in the registry and should continue to be monitored for new adverse events of interest or serious adverse events.

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Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be obtained where possible.

9. PRODUCT QUALITY COMPLAINT HANDLING

9.1. Product Quality Complaint Handling

9.1.1. Definition
A Product Quality Complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labelling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labelling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

9.1.2. Reporting Requirements for Product Quality Complaints for Sponsor Products Under Study
All initial PQCs involving a sponsor product under study must be reported to the sponsor by the participating site personnel within 24 hours after being made aware of the event. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding PQCs for a sponsor product are listed on the Contact Information page(s), which are provided separately.

If the defect for a sponsor product under study is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (see Section 8.2.1). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

9.1.3. Reporting Requirements for Product Quality Complaints for Non-sponsor Products Under Study
Product quality complaints involving a non-sponsor medicinal product under study should be reported to the identified contact or manufacturer, as necessary per local regulations.

10. DATA COLLECTION, HANDLING, QUALITY ASSURANCE, AND RECORD KEEPING
Information needed during the data collection periods should be obtained by the investigator or designee via review of the patient’s source data and direct contact at each visit. If a patient is not available for a visit, then data collection may include information from the patient’s medical records during the specified period of the data collection interval and direct communication with the patient (eg, telephone call).
The investigator, or designee, at each participating registry site will complete the CRF and provide information every 6 months through Year 6 and annually thereafter unless it meets the requirement for expedited reporting as detailed in Section 8.2. Detailed instructions for completion of the CRF pages are provided in the EDC system.

All CRFs will be tracked and archived following ICH-Good Clinical Practice (GCP) guidelines. Quality assurance procedures will be established prior to the start of the registry to ensure that data integrity is maintained. Appropriate edit checks, electronic queries, and audit trails will be implemented to ensure accurate and complete data collection and processing.

Investigators will be required to maintain the records of all protocol-specified source documents (eg, pathology reports) and registry-related documentation until notified by the sponsor that records may be disposed or transferred. The sponsor should be contacted if the investigator plans to leave the institution so that arrangements can be made for transfer of records.

The Trial Center File will delineate the procedures for training investigators and personnel and the quality control and assurance measures that will be implemented for ensuring data accuracy, protocol adherence, and compliance with applicable regulations pertaining to the conduct of registries.

11. SITE MONITORING AND TRAINING

All sites will be trained on the protocol, registry logistics, and the EDC system. As part of the educational sessions, investigators will be reminded of the processes and importance of reporting adverse events of interest and serious adverse events.

The sponsor or its designee will perform onsite monitoring/remote monitoring contacts (eg, via telephone follow-up) consistent with the Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (GPPPA). Additional site monitoring and site education may be performed as needed.

12. PATIENT FOLLOW-UP AND RETENTION

The investigator is responsible for the follow-up and retention of patients enrolled at their investigative site. If a patient moves away from an investigative site every effort will be made to identify a registry investigative site in the geographic area where the patient is moving.

13. INVESTIGATOR’S STATEMENT OF AGREEMENT

All responsible parties have provided a written statement agreeing to the content of the proposal and the confidential nature of the documentation made as part of this registry, and acknowledging that the sponsor has the right to discontinue this registry at any time and/or amend this registry as appropriate.

By signing the Statement of Agreement, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, the sponsor, its designee, or responsible government agencies (as required by law) may, at any time, review or copy source
documents (eg, laboratory reports, electrocardiograms, x-rays, workbooks and patients’ medical records) in order to verify CRF data.

14. ETHICAL CONSIDERATIONS AND PRIVACY OF PERSONAL DATA

The sponsor, or its designee, is responsible for assuring that IRB/IEC approval is obtained, developing the informed consent necessary to conduct research, procuring additional informed consent of patients for any additional required patient-specific data, and providing any additional documentation that is required. Observational studies solely using existing medical records generally do not require the same oversight as clinical trials since protocol-specified experimental therapy, invasive procedures, or treatment interventions are not involved.

Patient information collected in this registry will comply with the standards for protection of privacy of individually identifiable health information as required by each region in which this registry will be conducted.

15. USE OF INFORMATION AND PUBLICATION

All information, including but not limited to information regarding Simponi or the sponsor's operations (eg, patent applications, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information obtained in the study will be used by the sponsor in connection with the continued development of Simponi, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information obtained to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish the primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish data specific to the associated participating site after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have

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the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

16. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in interval reports generated by the sponsor, which will contain data collected from all study sites that participated in the study. The sponsor will register and/or disclose the existence of and the results as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator) shall be the property of the sponsor as author and owner of copyright in such work.

17. REGISTRATION OF REGISTRY AND DISCLOSURE OF RESULTS

The sponsor will register and/or disclose the existence of and the results of the registry as required by law.
REFERENCES


16. PURINETHOL [product information]. Sellersville, PA: Teva Pharmaceuticals; April 2011.


INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): ______________________________________________________
Institution and Address: ______________________________________________________

Signature: ____________________________ Date: ____________________________
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): ______________________________________________________
Institution and Address: ______________________________________________________

Telephone Number: ______________________________________________________

Signature: ____________________________ Date: ____________________________
(Day Month Year)

Sponsor’s Responsible Medical Officer:

Name (typed or printed): ____________________________
Institution and Address: ____________________________

Signature: ____________________________ Date: ____________________________
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE

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