Janssen Research & Development *

Clinical Protocol

A Research Study to Bank Samples for Future Evaluation to Identify Biomarkers that Predispose Patients with Crohn's Disease and Ulcerative Colitis to Develop Hepatosplenic T-Cell Lymphoma (HSTCL)

Protocol REMICADELYM4001; Phase 4
Amendment 3

REMICADE® (infliximab)
SIMPONI® (golimumab)

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Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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SYNOPSIS

TITLE

A Research Study to Bank Samples for Future Evaluation to Identify Biomarkers that Predispose Patients with Crohn's Disease and Ulcerative Colitis to Develop Hepatosplenic T-Cell Lymphoma (HSTCL)

PURPOSE

This study is being conducted to address 2 postmarketing requirements by the United States (US) Food and Drug Administration (FDA) to bank HSTCL tumor tissue as well as blood, buccal swab, and/or other tissue samples for future evaluation to identify genetic mutations and other biomarkers that may predispose inflammatory bowel disease (IBD) patients to develop hepatosplenic T-cell lymphoma (HSTCL). No medical or scientific benefit will be provided to patients who participate in the study; however, future patients at risk for developing HSTCL may benefit from the results of this research.

OBJECTIVE, ENDPOINTS, AND HYPOTHESIS

The objective of this study is to collect samples from IBD patients diagnosed with HSTCL to identify biomarkers that may allow earlier evaluation of a patient's risk of developing HSTCL.

There are no formal endpoints or hypothesis for this study.

OVERVIEW OF STUDY DESIGN

This study is designed to collect tissue samples from the biopsy specimen used to diagnose HSTCL in patients with IBD. Additional patient information, and if possible, additional blood, buccal swab, and/or tissue samples will be collected as described below in Evaluations. This study will be conducted in North America and the planned duration is 8 years. This study will not restrict or introduce any therapeutic interventions, including medications. All patients will continue to be managed by their personal physicians.

PATIENT SELECTION

Patients eligible for enrollment include males or females with IBD of any age who have a confirmed diagnosis of HSTCL. No healthy subjects will be enrolled in this study.

Patients will be identified through the sponsor's adverse event reporting systems. Cases reported to the sponsor's Medical Information Center will be queried to ascertain if the reporter is interested in participating in the study. Where appropriate, cases may also be identified through the sponsor's new or on-going clinical trials and registries. Samples may be collected from living patients or from stored tissue of deceased patients.

EVALUATIONS

After obtaining informed consent as described in Section 8.1.2 in the body of the protocol, physicians of participating patients will be asked to provide the following:

- Sample(s) of the biopsy specimen used to confirm the diagnosis of HSTCL (tumor tissue and adjacent healthy tissue if possible)

- Additional samples, if possible, including the following:
  - A single blood and/or a buccal swab sample (for genomic DNA analysis), and/or
  - A bowel tissue sample previously collected as part of the patient's IBD diagnosis or treatment (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).

In addition, the following information will be collected:

- HSTCL diagnosis and related information
- Demographic data
- Diseases and medical/surgical conditions prior to or at the time of diagnosis
- Medical history including family history of cancer, if available
- Cytogenetic and flow cytometric data, if available

Samples collected will be banked for future testing by the sponsor or its delegate. Potential test methods include, but are not limited to, the following:

- Deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequencing
- Messenger ribonucleic acid (mRNA) gene expression
- Protein expression or functional tests on cells isolated from peripheral blood

STATISTICAL METHODS

A Scientific Advisory Committee has been established for this study that includes an independent panel of experts who will review the emerging science related to HSTCL and latest available test methods and make recommendations to the sponsor. When the types of analyses to be performed on the tissue samples collected have been determined by the sponsor in consultation with the Scientific Advisory Committee, the sample analysis plan will be developed.

Descriptive statistics of demographic information, information on medical/surgical (including treatment) history, and baseline characteristics at the time of HSTCL diagnosis will be summarized for all patients enrolled in this study. Protein assay data will be summarized when available, using descriptive statistics. Gene expression in tumor cells may be compared with expression levels observed in cells isolated from whole blood with moderated t-statistics or other appropriate statistical methods.

Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with DNA from the same patient from the following:

- The normal adjacent tissue from the same biopsy specimen, or
- The bowel tissue sample, or
- Cells isolated from the buccal swab, or
- Peripheral blood mononuclear cells.

Individual mutations will be tabulated within and between patients and cross-referenced with human variation databases (eg, COSMIC, dbSNP, etc.). To identify cancer driver genes or pathways, somatic mutation frequencies will be evaluated per gene or pathway across all patients with HSTCL and compared with empirical background mutation frequencies by mutation type (Wendl, 2011; Youn, 2011).

ABBREVIATIONS

CRF	case report form (paper)
DCFs	Data Correction/Clarification Forms
DNA	deoxyribonucleic acid
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HSTCL	hepatosplenic T-cell lymphoma
HPRT	hypoxanthine-guanine phosphoribosyltransferase
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
mRNA	messenger ribonucleic acid
RNA	ribonucleic acid
US	United States
TNF	tumor necrosis factor
USP	United States Pharmacopeia

1. INTRODUCTION

1.1. Purpose

The United States (US) Food and Drug Administration (FDA) has requested that the sponsor conduct a postmarketing study to collect samples from inflammatory bowel disease patients (IBD) treated with Remicade® (infliximab) and/or Simponi® (golimumab) to learn more about hepatosplenic T-cell lymphoma (HSTCL). Specifically, samples will be collected to identify genetic mutations and other biomarkers that may allow earlier evaluation of a patient's risk of developing HSTCL. Samples to be requested from each patient include the biopsy used to diagnose HSTCL, and if possible, additional samples including a single blood sample, buccal swab sample, and/or a bowel tissue sample previously collected as part of the patient's IBD diagnosis or treatment. In addition, patient information will be collected including, but not limited to, patient demographics and medical history. Samples will be stored by the sponsor or its delegate for future testing. The study will be conducted in North America and the planned duration of the study is 8 years.

A Scientific Advisory Committee has been established for this study and includes an independent panel of experts who will review the emerging science related to HSTCL and latest available test methods and make recommendations to the sponsor (see Section 5.3, Scientific Advisory Committee). When the types of analyses to be performed on the tissue samples collected have been determined by the sponsor in consultation with the Scientific Advisory Committee, the sample analysis plan will be developed. The test methods that may be used include deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequencing, messenger ribonucleic acid (mRNA) gene expression, protein expression, or functional tests on cells isolated from peripheral blood. No medical or scientific benefit will be provided to patients who participate in the study; however, future patients at risk for developing HSTCL may benefit from the results of this research.

1.2. Hepatosplenic T-cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive subtype of peripheral T-cell lymphoma with a poor prognosis (Herrinton, 2011; de Leval, 2011). HSTCL generally shows T-cell proliferation, particularly in the sinusoids of the liver or spleen, without lymph node enlargement. It is also occasionally diagnosed through bone marrow aspirate and, later in its course, malignant T-cells can be found in peripheral blood. In the US, the incidence is approximately 0.3 cases per million person-years in the general population. However, in patients with immune mediated conditions such as IBD or acquired immune deficiency syndrome, the incidence increases as much as 100-fold. HSTCL has also been reported in organ transplant patients (Tey, 2008). DNA, RNA, or protein biomarkers may provide a method to identify patients predisposed to develop HSTCL.

Specific risk factors that contribute to HSTCL in patients with IBD have been reviewed (Kotylar, 2010; Kotylar, 2011), and include gender (> 90% male); age (90% under 35 years of age); treatment with thiopurines such as 6-mercaptopurine or azathioprine (100%); treatment with a tumor necrosis factor (TNF) inhibitor such as infliximab (REMICADE®; 56%, all with concomitant thiopurine treatment); and duration of thiopurine treatment (97% >2 years). HSTCL has also been reported in patients treated with other TNF inhibitors such as adalimumab (Ochenrider, 2010), and other monoclonal antibodies with other mechanisms of action such as natalizumab (Kotylar, 2010). Although most published cases of HSTCL have occurred in immunocompromised individuals, a recent study describes some patients with no history of immune-related comorbidities or immunosuppressive therapy (Voss, 2013).

Literature describing the clinical and presenting features of patients with HSTCL has been reviewed (Tripido, 2009). Diagnosis is typically confirmed by bone marrow, liver, or spleen biopsy using histologic, flow cytometric, and cytogenetic analyses. The tumor cells are generally γ/δ T cells with a Vδ1 variable region, positive for CD3 and occasionally positive for CD8 or CD56 but negative for CD4. The chromosomal abnormality isochromosome 7q has been reported in many cases (Alonsozana, 1997; Kotylar, 2010). Recently, in an analysis of HSTCL cases, some of which included paired germline DNA, mutations were commonly found in the genes SETD2, INO80, STAT5B, SMARCA2, TET3, and PIK3CD (McKinney, 2017).

1.3. Overall Rationale for the Study

While there is no formal hypothesis to be tested in this study, the samples collected during this study will be used to explore several possible hypotheses for the development of HSTCL reported in IBD patients. Methods such as genome sequencing (Chapman, 2011; Ng, 2010), mRNA gene expression microarray profiles (Miyazaki, 2009), and multiplex analysis of serum proteins may be used to identify these biomarkers.

1. *Genes that increase susceptibility for developing inflammatory bowel disease.* The incidence of HSTCL is approximately 100-fold greater in IBD patients compared with the general population (Herrington, 2011). Therefore, IBD susceptibility genes identified through genome-wide association studies (Franke, 2010; McGovern, 2010) may also be susceptibility genes for HSTCL.
2. *Genes that are part of the TNF signaling pathway.* Although HSTCL is generally observed in infliximab-treated IBD patients who received infliximab in combination with a thiopurine, TNF blockade may also increase susceptibility for developing HSTCL independent of thiopurine exposure. Therefore, genes that are part of the TNF signaling pathway may also influence susceptibility for HSTCL.

3. *Genes whose expression is significantly different than other T-cell lymphomas.* The majority of HSTCL in infliximab-treated IBD patients are known to be γ/Vδ1 T-cell clones, although α/β T-cell clones have also been reported (Mackey, 2009). One group (Miyazaki, 2009) studied the gene expression profile of peripheral T-cell lymphomas and identified a distinctive profile for 5 cases of HSTCL, including 4 cases that were γ/δ lymphomas and 1 case that was α/β T-cell lymphoma. Others have found that mutations that occur frequently in other T cell lymphomas in genes such as *RHOA*, *CD28* and *CCR4* were either absent or occurred at a much lower frequency in HSTCLs (McKinney, 2017). Recognizing HSTCL tumor cell genes with significantly different expression compared with other types of T-cell lymphomas suggests these genes might influence susceptibility for development of HSTCL.
4. *Genes that are part of the DNA mismatch repair pathway.* Thiopurines are mutagens that cause base pair mismatches when incorporated into replicating DNA; these are corrected by the DNA mismatch repair pathway (Hsieh, 2008). One group (Nyugen, 2009) investigated the frequency and spectra of somatic mutation events at the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus in T-cells from IBD patients. Thiopurine treatment resulted in a total dose-dependent ($p<0.001$) and duration of treatment-dependent ($p<0.001$) increase in the frequency of somatic mutations. Mutations in genes from the DNA mismatch repair pathway might increase the mutation rate due to thiopurine treatment and thereby increase the risk of HSTCL.
5. *Cytogenetic abnormalities.* Chromosomal abnormalities often associated with HSTCL include isochromosome 7q and trisomy 8 (Jonveaux, 1996); these abnormalities were also reported in IBD patients who developed HSTCL (Kotylar, 2010). The copy number or expression level of genes influenced by these abnormalities might also be linked to susceptibility to the development or progression of HSTCL.

2. OBJECTIVE, ENDPOINTS, AND HYPOTHESIS

The objective of this study is to collect samples from IBD patients diagnosed with HSTCL to identify biomarkers that may allow earlier evaluation of a patient's risk of developing HSTCL.

There are no formal endpoints or hypothesis for this study.

3. STUDY DESIGN

This study is designed to collect tissue samples from the biopsy specimen used to diagnose HSTCL, additional patient information, and if possible, to obtain additional samples including a single blood sample, a buccal swab sample, and/or a bowel tissue sample as described in further detail below. Samples obtained will be stored by the sponsor or its delegate for future testing. The study will be conducted in North America and the planned duration of the study is 8 years.

Patients eligible for enrollment include males or females with IBD of any age who have a confirmed diagnosis of HSTCL. Patients will be identified through the sponsor's adverse event reporting systems. Cases reported to the sponsor's Medical Information Center will be queried to ascertain if the reporter is interested in participating in the study. Where appropriate, cases may also be identified through the sponsor's new or on-going clinical trials and registries. Samples may be collected from living patients or from stored tissue of deceased patients.

This study will not restrict or introduce any therapeutic interventions, including medications. All patients will continue to be managed by their personal physicians. No healthy subjects will be enrolled in this study.

After obtaining informed consent as described in Section 8.1.2, physicians of participating patients will be asked to provide the following:

- Sample(s) of the biopsy specimen used to confirm the diagnosis of HSTCL (tumor tissue and adjacent healthy tissue if possible)
- Additional samples, if possible, including the following:
  - A single blood and/or a buccal swab sample (for genomic DNA analysis), and/or
  - A bowel tissue sample previously collected as part of the patient's IBD diagnosis or treatment (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).

In addition, the following information will be collected:

- HSTCL diagnosis and related information
- Demographic data
- Diseases and medical/surgical conditions prior to or at the time of diagnosis
- Medical history including family history of cancer, if available
- Cytogenetic and flow cytometric data if available

Samples collected will be banked for future testing by the sponsor or its delegate. Potential test methods include, but are not limited to, the following:

- Deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequencing
- Messenger ribonucleic acid (mRNA) gene expression
- Protein expression or functional tests on cells isolated from peripheral blood

A Scientific Advisory Committee has been established for this study as described in Section 5.3, Scientific Advisory Committee. When the types of analyses to be performed on the tissue samples collected have been determined by the sponsor in consultation with the Scientific Advisory Committee, the sample analysis plan will be developed.

It is important to note that participation in this study provides no direct medical or scientific benefit to the patient; however, future patients at risk for developing HSTCL may benefit from the results of this research.

4. PATIENT SELECTION

The inclusion and exclusion criteria for enrolling patients in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a patient in the study.

4.1. Inclusion Criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study. Each patient must:

1. Be a male or female of any age

2. Have a confirmed diagnosis of IBD

3. Have a confirmed diagnosis of HSTCL

4. Modified per Protocol Amendment 3

4.1 Provide written informed consent (either by the patient or his/her legal representative) as described in Section 8.1.2. Consent from a legally acceptable representative of a deceased patient will be obtained for enrollment into the study and sample collection.

5. Be willing to provide a tumor biopsy sample for the study

4.2. Exclusion Criteria

Any potential patient who meets one or both of the following criteria will be excluded from participating in the study. The patient will be excluded if he or she:

1. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the patient or that could prevent, limit, or confound the protocol-specified assessments

2. Is unable to provide critical clinical and/or demographic patient and/or sample information

5. STUDY EVALUATIONS/PROCEDURES

The sponsor (or delegate) will identify cases of HSTCL through the sponsor's adverse event reporting system. Cases reported to the sponsor's Medical Information Center will be queried to ascertain if the reporter is interested in participating in the study. Where appropriate, cases may also be identified through the sponsor's new or ongoing clinical trials and registries.

Once a patient with HSTCL has been identified, the treating physician will be contacted and invited to participate in the study. When the physician agrees to participate, study related information will be provided to the physician for submission to the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Each patient (or their legal representative) must give written informed consent as described in Section 8.1.2.

The collection and processing of personal data from patients enrolled in this study will be limited to data necessary to fulfill the objectives of the study. Sample data and corresponding relevant demographic and clinical data will be made non-identifiable by the removal of personal identifiers and are to be sent to the sponsor in coded form, in which the patient is identified by means of a study number. The code should be retained at the study site of the treating physician(s). Samples collected will be shipped under protocol-defined conditions as described in the laboratory reference manual to the sponsor's (or delegate's) bioanalytical facility for storage and future analysis. Samples will be shipped with a unique identifier to maintain confidentiality. Samples may be kept and used for up to 15 years after the study is completed; see also Section 8.1.2, Informed Consent, for sample handling if a patient withdraws consent. Detailed instructions for sample collection/processing and shipments will be defined in a laboratory reference manual.

5.1. Sample Collection

A tissue sample from the biopsy specimen used to diagnose HSTCL is required for this study. In addition, although not required for entry into the study, every effort is to be made to obtain a single blood sample, a buccal swab sample, and/or a bowel tissue sample as described in further detail in the following subsections.

5.1.1. Tumor Biopsy Tissue Sample

A sample of the tumor biopsy tissue, including adjacent non-tumor tissue if available, originally used for the diagnosis of HSTCL must be provided to the sponsor (or delegate). Approximately ten, 6-micron sections of the formalin-fixed, paraffin-embedded tumor are required (approximately 50 milligrams of the tumor biopsy).

5.1.2. Additional Samples

5.1.2.1. Blood and/or Buccal Swab Samples

A single blood and/or buccal swab sample is requested (each optional) for genomic DNA analysis.

The estimated total blood volume to be collected from each patient will be based on patient weight as per the table below.

Table 1: Blood sample and volume collected

Blood Sample Type	Blood Volume (total volume approximately 20 - 37 mL) *
Serum	5 mL (2 x 2.5 mL)
Whole blood for RNA	5 mL (2 x 2.5 mL)
Whole blood for DNA	10 mL (2 x 5 mL)
Whole blood for cellular analysis	17 mL (2 x 8.5 mL) *

* Obtain whole blood sample for cellular analysis only if patient weight is ≥ 45 kg

Buccal swabs will be used to collect cells from the cheek area inside the mouth of the patient.

5.1.2.2. Bowel Tissue Sample

If possible, a sample of bowel tissue previously collected as part of the patient's IBD diagnosis or treatment is requested (optional) if a specimen is already available. The sample will be used for mutation analysis of IBD to tumor. Approximately ten, 6-micron sections of the formalin-fixed, paraffin-embedded tissue are required (approximately 50 milligrams of the bowel tissue biopsy).

5.1.3. Sample Collection and Handling

Collection tubes for the blood samples, the buccal swab collection kit, and the slides for tumor biopsy tissue and bowel tissue samples will be provided to the patient's physician with specific instructions for collection, labeling, storing, and shipping to the sponsor or delegate.

The actual dates and times of sample collection must be recorded in the case report form (CRF) or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Please refer to the laboratory reference manual for detailed instructions for the collection, handling, and shipment of blood, tissue, and buccal swab samples.

5.2. Additional Patient Information

For each identified case of HSTCL for which the treating physician(s) agreed to participate, the investigator or an authorized member of the investigational staff will collect data from the

patient's medical records and transfer this information to the CRF at a data collection visit at the treating physician(s) site.

The data elements to be collected from patient's medical records include:

1. HSTCL diagnosis

    a. Diagnosis confirmation and date. Tumor stage and findings that support staging including system used.

    b. Clinical course

    c. Type, dose, and duration of treatment with corticosteroids and any immunomodulator therapies (including biologics) prior to and at time of diagnosis of lymphoma

2. Demographic data including age at diagnosis of HSTCL, gender, race, and nationality

3. Diseases and medical/surgical conditions prior to or at the time of diagnosis (including date of diagnosis, treatment and medications, and outcome) including but not limited to the following:

    a. Autoimmune disease

    b. Cancer

    c. Organ transplant

    d. Infection with human immunodeficiency virus (HIV)

4. Medical history including family history of cancer, if available

5. Cytogenetic and flow cytometric data, if available

Care must be taken to safeguard the privacy of patients and ensure that all applicable privacy guidelines are met. Collected data entered on the CRF are to be sent to the sponsor in coded form, in which the patient was identified by means of numbers. The code should be retained at the study site of the treating physician(s).

5.3. Scientific Advisory Committee

A Scientific Advisory Committee has been established and includes representatives from the sponsor and global medical experts in the disease under study. Meetings will be held as needed to review the emerging science related to HSTCL, the latest available test methods, and to determine the types of analyses to be performed on the tissue samples collected. Details will be provided in a separate Scientific Advisory Committee Charter.

5.4. Withdrawal from the Study

If a patient withdraws from the study or withdraws consent, refer to Section 8.1.2, Informed Consent, for further details on handling of samples.

6. TEST METHODS AND DATA ANALYSIS

In consultation with the Scientific Advisory Committee (see Section 5.3), a detailed analysis plan will be written and statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used is outlined below. Specific details will be provided in the Statistical Analysis Plan.

Descriptive statistics of demographic information, information on medical/surgical (including treatment) history, and baseline characteristics at the time of HSTCL diagnosis will be summarized for all patients enrolled in this study. Protein assay data will be summarized using descriptive statistics. Gene expression in tumor cells may be compared with expression levels observed in normal tissue surrounding the tumor or in bowel tissue sample, or with cells isolated from whole blood or from buccal swabs with moderated t-statistics or other appropriate statistical methods.

Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA from the same patient from the following:

- The normal adjacent tissue from the same biopsy specimen, or
- The bowel tissue sample, or
- Cells isolated from the buccal swab, or
- Peripheral blood mononuclear cells.

Individual mutations will be tabulated within and between patients and cross-referenced with human variation databases (eg, COSMIC, dbSNP, etc.). To identify cancer driver genes or pathways, somatic mutation frequencies will be evaluated per gene or pathway across all patients with HSTCL and compared with empirical background mutation frequencies by mutation type (Wendl, 2011; Youn, 2011).

7. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

During the conduct of this study, adverse events may be reported that are related to venipuncture for blood sample collection or buccal swab collection as described in Section 7.2.

7.1. Definitions

For the purposes of this study, and in accordance with ICH and the sponsor's safety reporting guidelines, the following definitions will apply.

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study 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 ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form.

Serious Adverse Event

A serious adverse event based on ICH and European Union (EU) Guidance on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence 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 expedited reporting is also appropriate in other situations, 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. These should usually be considered serious.

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.

7.2. Reporting and Follow-up of Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The investigator (or sponsor where required) must report these events to the appropriate IRB/IEC that approved the protocol unless otherwise required and documented by the IRB/IEC.

Adverse events that are associated with study interventions (eg, bruising or infection at venipuncture site, fainting, irritation, and bleeding at the inside of the cheek from the buccal swab) will be captured within the study database. All other adverse events/serious adverse events that are identified through the study data collection processes and not associated with study interventions (eg, blood draw, buccal swabbing) will be reported as solicited reports.

All serious adverse events that are considered as related to study intervention (eg, venipuncture) will be followed until resolution, stabilization, or follow-up is no longer possible.

7.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

8. ETHICAL ASPECTS

This study is being conducted to address 2 postmarketing requirements by the US FDA to bank blood, buccal cells, and/or tissue samples for future evaluation to identify genetic mutations and other biomarkers that may predispose IBD patients to develop HSTCL. No medical or scientific benefit will be provided to patients who participate in the study; however, future patients at risk for developing HSTCL may benefit from the results of this research.

8.1. Regulatory Ethics Compliance

This research study is to be performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

8.1.1. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IRB/IEC with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the patients)

- Information on compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IRB/IEC)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for patients
- Any other documents that the IRB/IEC requests to fulfill its obligation

This study will be undertaken only after the IRB/IEC has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IRB/IEC and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IRB/IEC for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to patients
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Summaries of the status of the study at intervals stipulated in guidelines of the IRB/IEC (at least annually)
- New information that may adversely affect the safety of the patients or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients
- Report of deaths of patients under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IRB/IEC

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or trial conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IRB/IEC for review and approval before implementation of the change(s). If applicable, at least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IRB/IEC about the study completion.

8.1.2. Informed Consent

Each patient (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form and assent form that is used must be approved by both the sponsor and by the reviewing IRB/IEC and be in a language that the patient can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential patients or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Patients will be told that the investigator will maintain a patient identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the patient or legally acceptable representative is authorizing such access, and agrees to allow his or her study physician to recontact the patient for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her health status.

The patient or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the patient's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

If the patient or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the patient or legally acceptable representative is obtained.

Children (minors) or patients who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically patients 6 years of age and older, depending on the institutional policies. Written assent should be obtained from patients who are able to write. A separate assent form written in language the patient can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the patient, and to the patient's parent and/or legally acceptable representative.

Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time by contacting the sponsor through the contact information given on the ICF. They will be informed that choosing not to participate will not affect the care he/she will receive for the treatment of his/her disease. The sponsor will destroy any remaining samples upon receipt of such a request. However, sample testing that has already taken place will be retained by the sponsor to avoid compromising data analysis.

Consent from a legally acceptable representative of a deceased patient will be obtained for enrollment into the study and sample collection.

8.1.3. Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study patients confidential.

The informed consent obtained from the patient (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, pharmacodynamic, biomarker, pharmacokinetic, and immunogenicity research is not conducted under standards appropriate for the return of data to patients. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to patients or investigators, unless required by law. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

8.1.4. Long-Term Storage of Samples for Future Research

Samples may be kept and used for up to 15 years after the study is completed; see also Section 8.1.2, Informed Consent, for sample handling if a patient withdraws consent.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IRB/IEC approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IRB/IEC and relevant competent authority. Documentation of amendment approval by the investigator and IRB/IEC must be provided to the sponsor or its delegate. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

9.2. Regulatory Documentation

9.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities. A study may not be initiated until all local regulatory requirements are met.

9.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study-related materials (eg, sample collection kit) to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed, written IRB/IEC approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IRB/IEC, including a current list of the IRB/IEC members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IRB/IEC, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IRB/IEC, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Any other documentation required by local regulations

9.3. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: patient identification, eligibility, and study identification; study discussion and date of informed consent; results of safety parameters as required by the protocol; record of all adverse events and follow-up of adverse events, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study patient should be consistent with that commonly recorded at the site as a basis for standard medical care and recorded in the CRF (see Section 5.2).

9.4. Case Report Form Completion

Case report forms are provided for each patient in printed format.

All printed forms must be filled out legibly in black ballpoint pen or typed. The appropriate pages of the CRF must be signed and dated by the investigator.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the patient's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete the CRF as soon as possible.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query.

Corrections to paper CRFs must be made in such a way that the original entry is not obscured. Correction fluid or tape must NOT be used. The correct data must be inserted, dated, and initialed by the investigator or an authorized member of the investigational staff. If multi-part pressure-sensitive CRFs are used, the investigational staff must not write on separated parts of the CRFs left at the investigational site once the original has been sent to the sponsor. Completed CRFs will be continuously submitted according to the sponsor's instructions and reviewed by the sponsor to determine their acceptability. If necessary, Data Correction/Clarification Forms (DCFs) will be generated and transmitted to the study site. The investigator or an authorized member of the investigational staff must complete, sign, and date the DCFs.

If corrections to a CRF are needed after removal of the original CRF copy from the investigational site, a DCF will be used.

9.5. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the review of protocol procedures with the investigator and associated personnel before the study. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor or delegate will review CRFs for accuracy and completeness; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

9.6. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

For CRFs completed on pressure-sensitive paper, a copy is to be retained in the archives of the sponsor. A second copy must be archived by the investigator.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

The study will be considered complete upon submission of the final clinical study reports to the FDA for the two postmarketing requirements for which this study is being conducted.

9.7. Use of Information and Publication

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Study subject identifiers will not be used in 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 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 such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data 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 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 study 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.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1 Protocol History

Original Protocol: 25 June 2012

Amendment 1: 26 March 2013

Amendment 2: 17 February 2014

Amendment 3: 02 August 2017

Amendment 3 – 02 August 2017

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study and therefore have not been included in the following table. Note that in the following table, unless otherwise noted, the new text is shown in a bold, black font with italicized text, and deleted text is shown in a black font with strikethrough.

1. Description/Rationale: The protocol has been updated to:

- **Provide more details on how patients will be identified for participation in the study,**
- **Provide clarification on potential sample collection from deceased patients,**
- **Update information on HSTCL,**
- **Update information on the Scientific Advisory Committee,**
- **Update the protocol text to be consistent with the most recent version of the sponsor's protocol template, and**
- **Revise text for clarity and to correct inadvertent errors or omissions.**

Sections Affected	Original Content	Amended/New Content
Synopsis, Purpose	… to bank blood and/or tissue samples for future…	… to bank ***HSTCL tumor tissue as well as*** blood***, buccal swab,*** and/or ***other*** tissue samples for future…
Synopsis and Section 2, Objective, Endpoints, and Hypothesis (previously Objective)	OBJECTIVE The objective of this study is to collect samples from IBD patients diagnosed with HSTCL for the purpose of identifying biomarkers that may allow earlier evaluation of a patient's risk of developing HSTCL.	OBJECTIVE, ***ENDPOINTS, AND HYPOTHESIS*** The objective of this study is to collect samples from IBD patients diagnosed with HSTCL ~~for the purpose of identifying~~ ***to identify*** biomarkers that may allow earlier evaluation of a patient's risk of developing HSTCL. ***There are no formal endpoints or hypothesis for this study.***
Synopsis, Overview of Study Design (Note that the entire section was revised; however, most changes entailed deleting text and moving it as appropriate to other sections in the synopsis.)	This study is designed to collect tissue samples from the biopsy specimen used to diagnose HSTCL, and if possible, to obtain a single blood sample, a buccal swab sample (to determine the patient tissue type and establish non-mutated deoxyribonucleic acid [DNA] baseline), and a bowel tissue sample (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone). Samples obtained will be stored by the sponsor or its delegate for future testing. In addition, demographic and clinical patient information will be collected. The study will be conducted in North America.	This study is designed to collect tissue samples from the biopsy specimen used to diagnose HSTCL in patients with IBD. Additional patient information, and if possible, additional blood, buccal swab, and/or tissue samples will be collected as described below in Evaluations. This study will be conducted in North America and ***the planned duration is 8 years***. This study will not restrict or introduce any therapeutic interventions, including medications. All patients will continue to be managed by their personal physicians.

Sections Affected	Original Content	Amended/New Content
	The study population will include IBD patients with HSTCL who are identified through the sponsor's adverse event reporting systems. Cases of HSTCL will be identified through the sponsor's postmarketing adverse event reporting system (eg, spontaneous reports, reports from late phase clinical trials, reports from patient registries), from parties seeking participation in the study through reporting of cases directly to the sponsor's Medical Information Center, or from the sponsor's new or ongoing clinical trials. Eligible for enrollment are male or female patients of any age who have a confirmed diagnosis of HSTCL. There is no study-related therapeutic intervention and this protocol will not restrict or introduce any therapeutic interventions, including medications. All patients will continue to be managed by their personal physicians. No healthy subjects will be enrolled in this study. Informed consent/assent will be obtained by the investigator (ie, patient's physician or designee), from all adult patients or parents/legally acceptable representative(s), and pediatric patients prior to collection of any information or samples.	
Synopsis, Patient Selection (Note that the section was revised to include information from the overview section of the synopsis and to add new information.)	Eligible are male or female patients of any age with IBD who also have a confirmed diagnosis of HSTCL.	Patients eligible for enrollment include males or females ***with IBD*** of any age with IBD who have a confirmed diagnosis of HSTCL. No healthy subjects will be enrolled in this study. Patients will be identified through the sponsor's adverse event reporting systems. ***Cases reported to the sponsor's Medical Information Center will be queried to ascertain if the reporter is interested in participating in the study. Where appropriate, cases may also be identified through the sponsor's new or on-going clinical trials and registries. Samples may be collected from living patients or from stored tissue of deceased patients.***
Synopsis, Evaluations (Note that this section was primarily revised for clarity and consistency with the body of the protocol.)	Physicians of participating patients will be asked to provide information on the following: • demographics • medical and surgical history • treatment history and medications	***After obtaining informed consent as described in Section 8.1.2 in the body of the protocol,*** physicians of participating patients will be asked to provide the following: – Sample(s) of the biopsy specimen used to confirm the diagnosis of HSTCL (tumor tissue and adjacent healthy

Sections Affected	Original Content	Amended/New Content
	• samples of the biopsy specimen that was used to confirm the diagnosis of HSTCL (tumor tissue and adjacent healthy tissue if possible) In addition, if possible, every effort is to be made to obtain other specimens including a single blood sample, a buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline), and a bowel tissue sample (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone). Samples collected will be banked for future testing. Potential test methods include the following: …	tissue if possible) – Additional samples, if possible, including the following: – A single blood and/or a buccal swab sample ***(for genomic DNA analysis****), and/or* – A bowel tissue sample ***previously collected as part of the patient's IBD diagnosis or treatment*** (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone). In addition, the following information will be collected: – ***HSTCL diagnosis and related information*** – ***Demographic data*** – ***Diseases and medical/surgical conditions prior to or at the time of diagnosis*** – ***Medical history including family history of cancer, if available*** – ***Cytogenetic and flow cytometric data, if available*** Samples collected will be banked for future testing ***by the sponsor or its delegate.*** Potential test methods include, ***but are not limited to,*** the following: …
Synopsis, Statistical Methods 1st paragraph, 1st sentence. Similar changes were made throughout the protocol as appropriate.	A Scientific Advisory Committee will be established for this study that will include an independent panel of experts who will …	A Scientific Advisory Committee ~~will be~~***has been*** established for this study that ~~will include an~~***includes an*** independent panel of experts who will…
3rd paragraph, 1st through 3rd sentences	Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with normal lining tissue DNA from the same biopsy specimen, or DNA from a bowel tissue sample, or DNA from cells isolated from the buccal swabs, or DNA isolated from peripheral blood mononuclear cells obtained from the same patient. Buccal swab sample analysis will help to determine the patient's genetic makeup and the bowel tissue sample analysis will help	Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with ~~normal lining tissue~~ DNA from the same ***patient from the following:*** • ***The normal adjacent tissue from the same*** biopsy specimen, or ~~DNA from a~~ • ***The*** bowel tissue sample, or ~~DNA from~~ • Cells isolated from the buccal ~~swabs~~***swab***, or ~~DNA isolated from~~

Sections Affected	Original Content	Amended/New Content
	to perform mutation analysis of IBD to the tumor.	• Peripheral blood mononuclear cells ~~obtained from the same patient. Buccal swab sample analysis will help to determine the patient's genetic makeup and the bowel tissue sample analysis will help to perform mutation analysis of IBD to the tumor.~~.
Section 1.1. Purpose, 1st paragraph revised	The United States (US) Food and Drug Administration (FDA) has requested that the sponsor collect samples for the purpose of identifying biomarkers that may allow earlier evaluation of a patient's risk of developing hepatosplenic T-cell lymphoma (HSTCL). Medical and surgical information, samples from the biopsy used to diagnose HSTCL, and if possible, additional samples (a single blood sample, a buccal swab sample, and a bowel tissue sample), will be requested from each patient and stored by the sponsor or its delegate for future testing. The planned duration for sample collection is 6 years.	The United States (US) Food and Drug Administration (FDA) has requested that the sponsor ***conduct a postmarketing study to*** collect samples ~~for the purpose of identifying~~ ***from inflammatory bowel disease patients (IBD) treated with Remicade® (infliximab) and/or Simponi® (golimumab) to learn more about hepatosplenic T-cell lymphoma (HSTCL). Specifically, samples will be collected to identify genetic mutations and other*** biomarkers that may allow earlier evaluation of a patient's risk of developing ~~hepatosplenic T-cell lymphoma (HSTCL). Medical and surgical information, samples from~~ ***HSTCL. Samples to be requested from each patient include*** the biopsy used to diagnose HSTCL, and if possible, additional samples ***including*** a single blood sample, ~~a~~ buccal swab sample, and***/or*** a bowel tissue sample~~), will be requested from each patient and~~***previously collected as part of the patient's IBD diagnosis or treatment. In addition, patient information will be collected including, but not limited to, patient demographics and medical history. Samples will be*** stored by the sponsor or its delegate for future testing. ***The study will be conducted in North America and*** the planned duration ~~for sample collection~~***of the study*** is ~~6~~***8*** years.
Section 1.3. Overall Rationale for the Study, No. 3 under first paragraph (new 4th sentence and corresponding new reference)	3. …T-cell lymphoma. Recognizing HSTCL tumor…	*3.* ...T-cell lymphoma. ***Others have found that mutations that occur frequently in other T cell lymphomas in genes such as RHOA, CD28 and CCR4 were either absent or occurred at a much lower frequency in HSTCLs (McKinney, 2017).*** Recognizing HSTCL tumor … Corresponding New Reference: ***McKinney M, Moffitt AB, Gaulard P. The Genetic Basis of Hepatosplenic T Cell Lymphoma. Cancer Discovery. 2017;7:369-79.***
Section 3. Study Design (Note that the entire section	This study is designed to collect tissue samples from the biopsy specimen used to diagnose HSTCL, and if	This study is designed to collect tissue samples from the biopsy specimen used to diagnose HSTCL, additional patient

Sections Affected	Original Content	Amended/New Content
was revised for clarity and to add new information.)	possible, to obtain a single blood sample, a buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline), and a bowel tissue sample (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone). In addition, demographic and clinical patient information will be collected and samples obtained will be stored by the sponsor or its delegate for future testing. The study will be conducted in North America. The study population will include IBD patients with HSTCL who are identified through the sponsor's adverse event reporting systems. Cases of HSTCL will be identified through the sponsor's postmarketing adverse event reporting system (eg, spontaneous reports, reports from late phase clinical trials, reports from patient registries), from parties seeking participation in the study through reporting of cases directly to the sponsor's Medical Information Center, or from the sponsor's new or ongoing clinical trials. Eligible for enrollment are male or female patients of any age who have a confirmed diagnosis of HSTCL. There is no study-related therapeutic intervention and this protocol will not restrict or introduce any therapeutic interventions, including medications. All patients will continue to be managed by their personal physicians. No healthy subjects will be enrolled in this study. Informed consent/assent will be obtained by the investigator (ie, patient's physician or designee), from all adult patients or parents/legal guardians, and pediatric patients prior to collection of any information or samples. When referring to the signing of the informed consent form, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child. For each pediatric patient, his or her parent(s) (preferably both parents, if available) or a legally	information, and if possible, to obtain additional samples including a single blood sample, a buccal swab sample, and/or a bowel tissue sample as described in further detail below. Samples obtained will be stored by the sponsor or its delegate for future testing. The study will be conducted in North America and the ***planned duration of the study is 8 years.*** Patients eligible for enrollment include males or females with IBD of any age who have a confirmed diagnosis of HSTCL. Patients will be identified through the sponsor's adverse event reporting systems. ***Cases reported to the sponsor's Medical Information Center will be queried to ascertain if the reporter is interested in participating in the study. Where appropriate, cases may also be identified through the sponsor's new or on-going clinical trials and registries. Samples may be collected from living patients or from stored tissue of deceased patients.*** This study will not restrict or introduce any therapeutic interventions, including medications. All patients will continue to be managed by their personal physicians. No healthy subjects will be enrolled in this study. ***After obtaining informed consent as described in Section 8.1.2.,*** physicians of participating patients will be asked to provide the following: • Sample(s) of the biopsy specimen used to confirm the diagnosis of HSTCL *(tumor tissue and **adjacent healthy tissue*** if possible) • *Additional samples, if possible, including the following:* - A single blood and/or a buccal swab *sample (**for genomic DNA analysis**), and/or* - A bowel tissue sample ***previously collected as part of the patient's IBD diagnosis or treatment*** (if available, for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone). In addition, the following information will be collected: • HSTCL diagnosis and related information • Demographic data • ***Diseases and medical/surgical conditions prior to or at the***

Sections Affected	Original Content	Amended/New Content
	acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically patients 7 years of age and older, depending on the institutional policies. For the purpose of this study, all references to patients who have provided consent/assent refer to the patient (assent as applicable) and his or her parent(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate. If applicable, consent/assent will include permission to obtain a copy of the patient's autopsy report or death certificate if available. Physicians of participating patients will be asked to provide information on the following: • demographics • medical and surgical history • treatment history and medications • samples of the biopsy specimen that was used to confirm the diagnosis of HSTCL (tumor tissue and adjacent healthy tissue if possible) In addition, if possible, every effort is to be made to obtain additional samples including a single blood sample, a buccal swab sample, and a bowel tissue sample if available (discretionary) to be used for the test procedures that are part of this study. The planned duration for sample collection is 6 years. A Scientific Advisory Committee will be established for this study that will include an independent panel of experts who will review the emerging science related to HSTCL and latest available test methods and make recommendations to the sponsor (see Section 5.4,	***time of diagnosis*** • Medical history including family history of cancer**, *if* available** • Cytogenetic and flow cytometric data if available Samples collected will be banked for future testing by the sponsor or its delegate. Potential test methods include, ***but are not limited to,*** the following: • Deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequencing • Messenger ribonucleic acid (mRNA) gene expression • Protein expression or functional tests on cells isolated from peripheral blood A Scientific Advisory Committee ***has been*** established for this study as described in Section 5.3, Scientific Advisory Committee. When the types of analyses to be performed on the tissue samples collected have been determined by the sponsor in consultation with the Scientific Advisory Committee, the sample analysis plan will be developed. It is important to note that participation in this study provides no direct medical or scientific benefit to the patient; however, future patients at risk for developing HSTCL may benefit from the results of this research.

Sections Affected	Original Content	Amended/New Content
	Scientific Advisory Committee). When the types of analyses to be performed on the tissue samples collected have been determined by the sponsor in consultation with the Scientific Advisory Committee, the sample analysis plan will be developed. Samples collected will be banked for future testing. The test methods that may be used include the following: • DNA or RNA sequencing • mRNA gene expression • protein expression or functional tests on cells isolated from peripheral blood It is important to note that participation in this study provides no direct medical or scientific benefit to the patient; however, future patients at risk for developing HSTCL may benefit from the results of this research.	
Section 4.1. Inclusion Criterion #4	4. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Section 8.1.2, Informed Consent.	***4. Modified per Protocol Amendment 3*** ***4.1*** ~~*Sign (*~~***Provide written informed consent (either by the patient or his/her legal representative) as described in Section 8.1.2. Consent from a legally acceptable representative of a deceased patient will be obtained for enrollment into the study and sample collection.***
Section 5. Study Evaluations/Procedures (This section was previously titled Study Evaluations. Note that the entire section was revised for clarity and to add new information.)	**STUDY EVALUATIONS** The sponsor (or delegate) will identify cases of HSTCL through the postmarketing adverse event reporting system (eg, spontaneous reports, reports from late phase clinical trials, reports from patient registries), from parties seeking participation in the trial through reporting of cases directly to the sponsor's Medical Information Center, or from the sponsor's new or ongoing clinical trials. Once a patient with HSTCL has been identified, the treating physician will be contacted and invited to participate in the study. When the physician agrees to participate, study related information will be provided to the physician for submission to the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Each	**STUDY EVALUATIONS*/PROCEDURES*** The sponsor (or delegate) will identify cases of HSTCL through the ***sponsor's*** adverse event reporting system. ***Cases reported to the sponsor's Medical Information Center will be queried to ascertain if the reporter is interested in participating in the study. Where appropriate, cases may also be identified through the sponsor's new or ongoing clinical trials and registries.*** Once a patient with HSTCL has been identified, the treating physician will be contacted and invited to participate in the study. When the physician agrees to participate, study related information will be provided to the physician for submission to the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC). ***Each patient (or their legal representative) must give written informed consent as***

Sections Affected	Original Content	Amended/New Content
	patient must give written consent according to local requirements after the nature of this research study has been fully explained. The informed consent form (ICF) must be signed before any study-related activity is performed. The ICF used must be approved by both the sponsor and the reviewing IRB/IEC and acceptable to the investigator. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, current International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and the sponsor's policy. The collection and processing of personal data from patients enrolled in this study will be limited to data necessary to fulfill the objectives of the study. Sample data and corresponding relevant demographic and clinical data will be made non-identifiable by the removal of personal identifiers and are to be sent to the sponsor in coded form, in which the patient is identified by means of a study number. The code should be retained at the study site of the treating physician(s). Samples collected will be shipped under protocol-defined conditions as described in the laboratory reference manual to the sponsor's (or delegate's) bioanalytical facility for storage and future analysis. Samples will be shipped with a unique identifier to maintain confidentiality. A patient may withdraw their consent for this research study at any time by contacting the sponsor through the contact information given on the ICF. The sponsor will destroy any remaining samples upon receipt of such a request. However, sample testing that has already taken place will be retained by the sponsor to avoid compromising data analysis. Detailed instructions for sample collection/processing and shipments will be defined in a laboratory reference manual.	***described in Section 8.1.2***. The collection and processing of personal data from patients enrolled in this study will be limited to data necessary to fulfill the objectives of the study. Sample data and corresponding relevant demographic and clinical data will be made non-identifiable by the removal of personal identifiers and are to be sent to the sponsor in coded form, in which the patient is identified by means of a study number. The code should be retained at the study site of the treating physician(s). Samples collected will be shipped under protocol-defined conditions as described in the laboratory reference manual to the sponsor's (or delegate's) bioanalytical facility for storage and future analysis. Samples will be shipped with a unique identifier to maintain confidentiality. ***Samples may be kept and used for up to 15 years after the study is completed; see also Section 8.1.2, Informed Consent, for sample handling if a patient withdraws consent.*** Detailed instructions for sample collection/processing and shipments will be defined in a laboratory reference manual.
Section 5.1. Sample Collection, entire section revised beginning with 2nd sentence in	5.1. Study Procedures … every effort is to be made to obtain a single blood sample, a buccal swab sample, and a bowel tissue	5.1. ***Sample Collection*** … every effort is to be made to obtain a single blood sample, a buccal swab sample, and/**or** a bowel tissue sample as described

<table>
<tr><th>Sections Affected</th><th>Original Content</th><th>Amended/New Content</th></tr>
<tr>
<td>Section 5.1
(This section was previously titled Study Procedures. Note that the section was revised for clarity.)</td>
<td>sample as described in further detail in the following subsections.
5.1.1. Tumor Biopsy Tissue Sample
A sample of the tumor biopsy tissue, including lining tissue if available, originally used for the diagnosis of HSTCL …

5.1.2. Blood Sample
A single blood sample is requested. The estimated total blood volume to be collected from each patient will be based on patient weight as per the table below.

Table 1: Blood sample and volume collected
<table>
<tr><th>Blood Sample Type</th><th>Blood Volume (total volume approximately 37 mL)</th></tr>
<tr><td>Serum</td><td>5 mL (2 x 2.5 mL)</td></tr>
<tr><td>Whole blood for RNA</td><td>5 mL (2 x 2.5 mL)</td></tr>
<tr><td>Whole blood for DNA</td><td>‘10 mL (2 x 5 mL)</td></tr>
<tr><td>Whole blood for cellular analysis*</td><td>17 mL (2 x 8.5 mL)*</td></tr>
</table>
*obtain sample only if patient weight is ≥ 45 kg</td>
<td>in further detail in the following subsections.
5.1.1 Tumor Biopsy Tissue Sample
A sample of the tumor biopsy tissue, including adjacent non-tumor tissue if available, originally used for the diagnosis of HSTCL …
5.1.2 Additional Samples
5.1.2.1 Blood and/or Buccal Swab Samples
A single blood and/or buccal swab sample is requested (each optional) for genomic DNA analysis.
The estimated total blood volume to be collected from each patient will be based on patient weight as per the table below.

Table 1: Blood sample and volume collected
<table>
<tr><th>Blood Sample Type</th><th>Blood Volume (total volume approximately 20 - 37 mL) *</th></tr>
<tr><td>Serum</td><td>5 mL (2 x 2.5 mL)</td></tr>
<tr><td>Whole blood for RNA</td><td>5 mL (2 x 2.5 mL)</td></tr>
<tr><td>Whole blood for DNA</td><td>10 mL (2 x 5 mL)</td></tr>
<tr><td>Whole blood for cellular analysis</td><td>17 mL (2 x 8.5 mL)*</td></tr>
</table>
* Obtain whole blood sample for cellular analysis only if patient weight is ≥ 45 kg</td>
</tr>
</table>

Sections Affected	Original Content	Amended/New Content
	5.1.3. Buccal Swab Sample A buccal swab sample is requested to determine the patient tissue type, and a sample collection kit will be provided. Buccal swabs will be used to collect cells from the cheek area inside the mouth of the patient. 5.1.4. Bowel Tissue Sample If possible, a sample of bowel tissue is requested … 5.2 Sample Collection and Handling	Buccal swabs will be used to collect cells from the cheek area inside the mouth of the patient. ***5.1.2.2*** Bowel Tissue Sample If possible, a sample of bowel tissue ***previously collected as part of the patient's IBD diagnosis or treatment*** is requested … 5.1.3. Sample Collection and Handling *(Note that the only change to this section was heading numbering)*
Section 5.2. Additional Patient Information (Previously Section 5.3. Data Collection 2nd paragraph, order of information in numbers 1 through 5 changed and "if available" was added to new number 4	5.3. Data Collection The data elements that are collected from patient's medical records include: 1. HSTCL diagnosis 2. Medical history including family history of cancer. 3. Diseases and medical/surgical conditions prior to or at the time of diagnosis (including date of diagnosis, treatment and medications, and outcome) including but not limited to the following: 4. Cytogenetic and flow cytometric data if available 5. Demographic data including age at diagnosis of HSTCL, gender, race, and nationality	***5.2***. ~~Data Collection~~***Additional Patient Information*** The data elements ~~that are~~ ***to be*** collected from patient's medical records include: 1. HSTCL diagnosis 2. ***Demographic data including age at diagnosis of HSTCL, gender, race, and nationality*** 3. Diseases and medical/surgical conditions prior to or at the time of diagnosis (including date of diagnosis, treatment and medications, and outcome) including but not limited to the following: ***4. Medical history including family history of cancer, if available*** ***5. Cytogenetic and flow cytometric data, if available***
Section 5.3. Scientific Advisory Committee, 1st paragraph	A Scientific Advisory Committee will be established and will include representatives from the sponsor and global medical experts in the disease under study. Meetings will be held at regular intervals (eg, yearly) to review the emerging science related to HSTCL and latest available test methods and determine the types of analyses to be performed on the tissue samples collected. Details will be provided in a separate Scientific Advisory Committee Charter.	A Scientific Advisory Committee ~~will be~~***has been*** established and ~~will include~~***includes*** representatives from the sponsor and global medical experts in the disease under study. Meetings will be held ~~at regular intervals (eg, yearly)~~ ***as needed*** to review the emerging science related to HSTC ~~and~~, ***the*** latest available test methods, and ***to*** determine the types of analyses to be performed on the tissue samples collected. Details will be provided in a separate Scientific Advisory Committee Charter.

Sections Affected	Original Content	Amended/New Content
Section 5.4. Withdrawal from the Study (New Section)	*(No prior text)*	***5.4 Withdrawal from the Study*** ***If a patient withdraws from the study or withdraws consent, refer to Section 8.1.2, Informed Consent, for further details on handling of samples.***
Section 6. Test Methods and Data Analysis, 1st paragraph	In consultation with the Scientific Advisory Committee, a detailed analysis plan will be written (see Section 5.4).	In consultation with the Scientific Advisory Committee ***(see Section 5.3),*** a detailed analysis plan will be written ~~(see Section).~~ ***and statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used is outlined below. Specific details will be provided in the Statistical Analysis Plan.***
2nd paragraph, 3rd sentence	Protein assay data will be summarized using descriptive statistics. Gene expression in tumor cells may be compared with expression levels observed in normal tissue lining or in bowel tissue sample…	Protein assay data will be summarized using descriptive statistics. Gene expression in tumor cells may be compared with expression levels observed in normal tissue ~~lining~~***surrounding the tumor*** or in bowel tissue sample…
3rd paragraph revised	Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with normal lining tissue DNA from the same biopsy specimen, or DNA from a bowel tissue sample, or DNA from Cells isolated from the buccal swabs, or DNA isolated from Peripheral blood mononuclear cells obtained from the same patient. Buccal swab sample analysis will help to determine the patient's genetic makeup and the bowel tissue sample analysis will help to perform mutation analysis of IBD to the tumor.	Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA ~~with~~***from the same patient from the following:*** • ***The*** normal ~~lining~~***adjacent*** tissue ~~DNA~~from the same biopsy specimen, or ~~DNA from a~~ • **The** bowel tissue sample, or ~~DNA from~~ • Cells isolated from the buccal ***swab***, or ~~DNA isolated from~~ • Peripheral blood mononuclear cells. ~~obtained from the same patient. Buccal swab sample analysis will help to determine the patient's genetic makeup and the bowel tissue sample analysis will help to perform mutation analysis of IBD to the tumor.~~
Section 7. Adverse Event Reporting, new last paragraph	*(No prior text)*	***During the conduct of this study, adverse events may be reported that are related to venipuncture for blood sample collection or buccal swab collection as described in Section 7.2.***
7.1.1. Adverse Event Definitions and Classifications	7.1.1. Adverse Event Definitions and Classifications	*(Section heading and text deleted, no new text)*
Section 7.1, 2nd paragraph under	*Medical and scientific judgment should be exercised in	*Medical and scientific judgment should be exercised in

Sections Affected	Original Content	Amended/New Content
Serious Adverse Event	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.	deciding whether ***expedited reporting is also appropriate in*** 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. ***These should usually be considered serious***.
Section 7.2. Reporting and Follow-up of Serious Adverse Events, 1st paragraph	There is no administration of study drug. This study is designed to collect a tissue sample from the biopsy specimen that was used to diagnose HSTCL, and if possible, to obtain a single blood sample, a buccal swab sample, and a bowel tissue sample. Samples obtained will be stored by the sponsor or delegate for future testing.	*(Text deleted)*
Section 7.2. Reporting and Follow-up of Serious Adverse Events 2nd paragraph, 1st sentence	The only potential adverse event related to this study would be secondary to the venipuncture that is performed to obtain a blood sample. This may cause bruising at the venipuncture site. Fainting, and in rare cases infection, may occur. Adverse events that are associated with these study interventions will be captured within the study database.	~~The only potential adverse events related to this study would be secondary to the venipuncture that is performed to obtain a blood sample. This or buccal swab. Venipuncture may cause bruising at the venipuncture site. Fainting, and in rare cases infection, may occur. The buccal swab, which will be done against the inside of a patient's cheek, may cause irritation and bleeding.~~ Adverse events that are associated with ~~these~~ study interventions ***(eg, bruising or infection at venipuncture site, fainting, irritation, and bleeding at the inside of the cheek from the buccal swab)*** will be captured within the study database.
3rd paragraph	All serious adverse events that are considered as related to study intervention (ie, venipuncture) will be followed until resolution, stabilization, or follow-up is no longer possible.	All serious adverse events that are considered as related to study intervention (~~ie~~***eg***, venipuncture) will be followed until resolution, stabilization, or follow-up is no longer possible.
Section 8.1.1. IEC/IRB, 4th paragraph	… for review and approval before implementation of the change(s).	… for review and approval before implementation of the change(s). ***If applicable, at least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.***
Section 8.1.2. Informed Consent, 1st paragraph 2nd sentence deleted	Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that	~~Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not~~

Sections Affected	Original Content	Amended/New Content
	choosing not to participate will not affect the care the patient will receive for the treatment of his or her disease. Finally, they will ….	~~affect the care the patient will receive for the treatment of his or her disease. Finally, they will~~ ….
5th paragraph, 2nd sentence revised	…typically patients 7 years of age and older…	… typically patients ~~7~~ ***6*** years of age and older…
6th paragraph revised and 7th paragraph added	A patient may withdraw their consent for this research study at any time by contacting the sponsor through the contact information given on the ICF. The sponsor will destroy any remaining samples upon receipt of such a request. However, sample testing that has already taken place will be retained by the sponsor to avoid compromising data analysis. Detailed instructions for sample collection/processing and shipments will be defined in a laboratory reference manual.	***Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time by contacting the sponsor*** through the contact information given on the ICF***. They will be informed that choosing not to participate will not affect the care he/she will receive for the treatment of his/her disease.*** The sponsor will destroy any remaining samples upon receipt of such a request***.*** However, sample testing that has already taken place will be retained by the sponsor to avoid compromising data analysis. ***Consent from a legally acceptable representative of a deceased patient will be obtained for enrollment into the study and sample collection.***
Section 8.1.4. Long-Term Storage of Samples for Future Research	Samples will be stored for an indefinite period of time by sponsor or delegate, until an expert panel (ie, Scientific Advisory Committee) decides on the appropriate analyses of the samples (see Section 5.4)	***Samples may be kept and used for up to 15 years after the study is completed; see also Section 8.1.2, Informed Consent, for sample handling if a patient withdraws consent.***
Section 9.2.2. Required Prestudy Documentation, 1st paragraph, new last bullet	*(no prior text)*	• ***Any other documentation required by local regulations***
Section 9.3. Source Documentation, last paragraph	At a minimum, the type and level of detail of source data available for a study patient should be consistent with that commonly recorded at the site as a basis for standard medical care.	At a minimum, the type and level of detail of source data available for a study patient should be consistent with that commonly recorded at the site as a basis for standard medical care ***and recorded in the CRF (see Section 5.2).***
Section 9.6. Record Retention, 2nd paragraph	Essential documents must be retained until at least formal discontinuation of the study. These documents …	Essential documents must be retained until at least ~~formal discontinuation of the study~~***2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.*** These documents …

Sections Affected	Original Content	Amended/New Content
New last paragraph	*(No prior text)*	***The study will be considered complete upon submission of the final clinical study reports to the FDA for the two postmarketing requirements for which this study is being conducted.***
Section 9.7. Use of Information and Publication (Note that the entire section was revised; only the revised text is shown in the Amended/New Content column.)	Results of this study will be presented in a final study report. The sponsor shall have the right to publish such data and information without approval from any participating investigator. Study patient identifiers will not be used in publication of results. For any publications or presentations that may contain patentable patient matter which, at the sponsor's discretion, warrants intellectual property protection, the sponsor may delay any publication or presentation for up to 60 days for the purpose of pursuing such protection. Contributions to the study by investigators will be recognized by an acknowledgment or authorship based on guidelines described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.	***The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Study subject identifiers will not be used in 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 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 such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data 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 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 study 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***

Sections Affected	Original Content	Amended/New Content
		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. ***Registration of Clinical Studies and Disclosure of Results*** ***The sponsor will register and disclose the existence of and the results of clinical studies as required by law.***

Amendment 2 – 17 February 2014

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. **Description/Rationale: Janssen Research & Development is a global organization that operates through different legal entities; therefore, references to specific legal entities have been updated as appropriate on the Title Page and, within the body of the protocol, references to specific legal entities have been removed and replaced with the term "sponsor."**

Sections Affected	Original Content	Amended/New Content
Title Page	No original content or Janssen Biotech Inc.	***Janssen Scientific Affairs, LLC***
Throughout the protocol as appropriate	Reference to specific legal entities, eg, Janssen Biotech, Inc.; JBI	***Sponsor***

2. **Description/Rationale: The protocol has been expanded to include SIMPONI® (golimumab) in order to fulfill a postmarketing commitment to the Food and Drug Administration (FDA).**

Sections Affected	Original Content	Amended/New Content
Title Page	REMICADE® (infliximab)	REMICADE® (infliximab) ***SIMPONI® (golimumab)***
Synopsis, Purpose (sentence 1) 8. Ethical Aspects (sentence 1)	This study is being conducted to address a postmarketing requirement…..	This study is being conducted to address ~~a~~ ***2*** postmarketing requirement***s***…..

3. **Description/Rationale: The protocol has been expanded to include Canada in addition to the United States.**

Sections Affected	Original Content	Amended/New Content
Throughout the document as appropriate	US	~~US~~ ***North America***
3. Study Design (paragraph 6)	For each pediatric patient, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by US regulations, must give written consent (permission) according to US requirements after the nature of the study has been fully explained and before the performance of any study-related assessments.	For each pediatric patient, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by ~~US~~ ***local*** regulations, must give written consent (permission) according to ~~US~~ ***local*** requirements after the nature of the study has been fully explained and before the performance of any study-related assessments.
Throughout the document as appropriate	Institutional Review Board (IRB)	Institutional Review Board (IRB)/***Independent Ethics Committee (IEC)***

4. Description/Rationale: The objective and protocol content were modified to clarify that the objective of the study is to identify markers that may predispose patients to HSTCL, not to identify biomarkers that may allow for an earlier diagnosis.

Sections Affected	Original Content	Amended/New Content
Synopsis, Objective 2. Objective	The objective of this study is to collect samples from IBD patients diagnosed with HSTCL for the purpose of identifying biomarkers that may allow either earlier evaluation of a patient's risk of developing HSTCL or possibly earlier diagnosis.	The objective of this study is to collect samples from IBD patients diagnosed with HSTCL for the purpose of identifying biomarkers that may allow ~~either~~ earlier evaluation of a patient's risk of developing HSTCL~~ or possibly earlier diagnosis~~.
1.1. Purpose (sentence 1)	The United States (US) Food and Drug Administration (FDA) has requested that Janssen Biotech, Inc. (referred to hereafter as JBI or the sponsor) collect samples for the purpose of identifying biomarkers that may allow either earlier evaluation of a patient's risk of developing hepatosplenic T-cell lymphoma (HSTCL) or possibly earlier diagnosis.	The United States (US) Food and Drug Administration (FDA) has requested that ***the sponsor*** collect samples for the purpose of identifying biomarkers that may allow ~~either~~ earlier evaluation of a patient's risk of developing hepatosplenic T-cell lymphoma (HSTCL)~~ or possibly earlier diagnosis~~.
1.2. Hepatosplenic T-cell Lymphoma (paragraph 1, last sentence)	DNA, RNA, or protein biomarkers may provide a method to identify patients predisposed to develop HSTCL or may allow earlier diagnosis of HSTCL in these patient populations.	DNA, RNA, or protein biomarkers may provide a method to identify patients predisposed to develop HSTCL~~ or may allow earlier diagnosis of HSTCL in these patient populations~~.

5. Description/Rationale: The content of the protocol was modified to clarify that a sample of the biopsy specimen used to confirm the diagnosis of HSTCL is required; moreover, while not required, every effort is to be made to obtain additional samples including a single blood sample, a buccal swab sample, and if already available, a bowel tissue sample.

Sections Affected	Original Content	Amended/New Content
Synopsis, Overview of Study Design (paragraph 1, sentence 1) 3. Study Design (paragraph 1, sentence 1)	This study is designed to collect a single blood sample, if possible, and obtain tissue samples from the biopsy specimen that was used to diagnose HSTCL. Other specimens requested may include a buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline) and a bowel tissue sample (if available for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).	This study is designed to collect ~~a single blood sample, if possible, and obtain~~ tissue samples from the biopsy specimen ~~that was~~ used to diagnose HSTCL***, and if possible, to obtain a single blood sample,***~~. Other specimens requested may include~~ a buccal swab sample (to determine the patient tissue type and establish non-mutated deoxyribonucleic acid [DNA] baseline)**,** and a bowel tissue sample (if available for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).

Synopsis, Evaluations (original paragraph 2 removed, new paragraph 2 revised)	Patients will be asked to provide a single blood sample that will be used for the test procedures that are part of this study. Other specimens requested may include a buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline) and a bowel tissue sample (if available for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).	~~Patients will be asked to provide a single blood sample that will be used for the test procedures that are part of this study.~~ ***In addition, if possible, every effort is to be made to obtain o***ther specimens ~~requested may~~ ***including*** a ***single blood sample, a*** buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline) and a bowel tissue sample (if available for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).
1.1. Purpose (sentence 2)	Medical and surgical information, samples from the biopsy used to diagnose HSTCL, and a blood sample will be requested from each patient and stored by the sponsor for future testing.	Medical and surgical information, samples from the biopsy used to diagnose HSTCL, and ***if possible, additional samples (a single blood sample, a buccal swab sample, and a bowel tissue sample)*** will be requested from each patient and stored by the sponsor ***or its delegate*** for future testing.
3. Study Design (paragraph 8)	Patients will be asked to provide a single blood sample, a buccal swab sample, and a bowel tissue sample if available (discretionary) to be used for the test procedures that are part of this study.	***In addition, if possible, every effort is to be made to obtain additional samples including,*** ~~Patients will be asked to provide~~ a single blood sample, a buccal swab sample, and a bowel tissue sample if available (discretionary) to be used for the test procedures that are part of this study.
5.1. Study Procedures (new paragraph 1)	*No previous content*	***A tissue sample from the biopsy specimen used to diagnose HSTCL is required for this study. In addition, although not required for entry into the study, every effort is to be made to obtain a single blood sample, a buccal swab sample, and a bowel tissue sample as described in further detail in the following subsections.***
7.2. Reporting and Follow-up of Serious Adverse Events (paragraph 1, sentence 2)	This study is designed to collect a single blood sample, if possible, and obtain tissue samples from the biopsy specimen that was used to diagnose HSTCL. Samples obtained will be stored by the sponsor for future testing.	This study is designed to collect a ~~single blood sample, if possible, and obtain~~ tissue sample ***from the biopsy specimen that was used to diagnose HSTCL, and if possible, to obtain a single blood sample, a buccal swab sample, and a bowel tissue sample***.

6. Description/Rationale: The content of the protocol was modified to clarify that the planned duration of sample collection for this study is 6 years.

Sections Affected	Original Content	Amended/New Content
1.1. Purpose (sentence 3)	Because HSTCL is rare, it is expected that samples will be collected over approximately 6 years.	***The planned duration for sample collection is*** 6 years.
3. Study Design (paragraph 9)	It is anticipated that it will take approximately 6 years to collect samples for analyses because of the rare occurrence of HSTCL.	***The planned duration for sample collection is*** 6 years.

7. Description/Rationale: Text was reorganized in Section 1.2 Hepatosplenic T-cell Lymphoma for clarity. No substantive changes were made with the exception of additional information that provides context for the addition of golimumab to the protocol, and to remove the statement that no cases of HSTCL have been reported in rheumatoid arthritis patients as one such case has been identified in the sponsor database. Note that references were updated accordingly.

Sections Affected	Original Content	Amended/New Content
1.2. Hepatosplenic T-cell Lymphoma (revised paragraphs 1 through 3)	Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive subtype of peripheral T-cell lymphoma with a poor prognosis (Herrinton, 2011; de Leval, 2011). HSTCL generally shows T cell proliferation, particularly in the sinusoids of the liver or spleen, without lymph node enlargement. It is also occasionally diagnosed through bone marrow aspirate and, later in its course, malignant T-cells can be found in peripheral blood. In the US, the incidence is approximately 0.3 cases per million person-years in the general population. However, in patients with immune mediated conditions such as inflammatory bowel disease (IBD) or acquired immune deficiency syndrome, the incidence increases as much as 100-fold. HSTCL has also been reported in organ transplant patients (Tey, 2008). DNA, RNA, or protein biomarkers may provide a method to identify patients predisposed to develop HSTCL or may allow earlier diagnosis of HSTCL in these patient populations. Literature describing the clinical and presenting features of patients with HSTCL has recently been reviewed (Tripido, 2009). Diagnosis is typically confirmed by bone marrow, liver, or spleen biopsy using histologic, flow cytometric and cytogenetic analyses. The tumor cells are generally γ/δ T cells with a Vδ1 variable region, positive for CD3 and occasionally positive for CD8 or	Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive subtype of peripheral T-cell lymphoma with a poor prognosis (Herrinton, 2011; de Leval, 2011). HSTCL generally shows T cell proliferation, particularly in the sinusoids of the liver or spleen, without lymph node enlargement. It is also occasionally diagnosed through bone marrow aspirate and, later in its course, malignant T-cells can be found in peripheral blood. In the US, the incidence is approximately 0.3 cases per million person-years in the general population. However, in patients with immune mediated conditions such as inflammatory bowel disease (IBD) or acquired immune deficiency syndrome, the incidence increases as much as 100-fold. HSTCL has also been reported in organ transplant patients (Tey, 2008). DNA, RNA, or protein biomarkers may provide a method to identify patients predisposed to develop HSTCL~~. or may allow earlier diagnosis of HSTCL in these patient population.~~. ***Specific risk factors that contribute to HSTCL in patients with IBD have been reviewed (Kotylar, 2010; Kotylar, 2011), and include gender (> 90% male); age (90% under 35 years of age); treatment with thiopurines such as 6-mercaptopurine or azathioprine (100%); treatment with a tumor necrosis factor (TNF) inhibitor such as infliximab (REMICADE®; 56%, all with concomitant thiopurine treatment); and duration of thiopurine treatment (97% >2***

	CD56 but negative for CD4. The chromosomal abnormality isochromosome 7q has been reported in many cases (Alonsozana, 1997; Kotlyar, 2010). Specific risk factors that contribute to HSTCL in patients with IBD have been reviewed (Koltyar, 2010; Koltyar, 2011). These specific risk factors in IBD include gender (>90% male); age (90% under 35 years of age); treatment with thiopurines such as 6-mercaptopurine or azathioprine (100%); and treatment with a tumor necrosis factor (TNF) inhibitor such as infliximab (REMICADE®; 56%, all with concomitant thiopurine treatment); and duration of thiopurine treatment (97% >2 years). Of note, no cases of HSTCL have been reported in rheumatoid arthritis patients treated with infliximab (Koltyar, 2010; Herrinton, 2011).	***years). HSTCL has also been reported in patients treated with other TNF inhibitors such as adalimumab (Ochenrider, 2010), and other monoclonal antibodies with other mechanisms of action such as natalizumab (Kotylar, 2010). Although most published cases of HSTCL have occurred in immunocompromised individuals, a recent study describes some patients with no history of immune-related comorbidities or immunosuppressive therapy (Voss, 2013).*** ***Literature describing the clinical and presenting features of patients with HSTCL has recently been reviewed (Tripido, 2009). Diagnosis is typically confirmed by bone marrow, liver, or spleen biopsy using histologic, flow cytometric, and cytogenetic analyses. The tumor cells are generally γ/δ T cells with a Vδ1 variable region, positive for CD3 and occasionally positive for CD8 or CD56 but negative for CD4. The chromosomal abnormality isochromosome 7q has been reported in many cases (Alonsozana, 1997; Kotylar, 2010).***
1.3. Overall Rationale for the Study (Number 2)	Although HSTCL is only observed in infliximab-treated IBD patients who received infliximab in combination with a thiopurine, TNF blockade may also increase susceptibility for developing HSTCL. Therefore, genes that are part of the TNF signaling pathway may also influence susceptibility for HSTCL.	Although HSTCL is ***generally*** observed in infliximab-treated IBD patients who received infliximab in combination with a thiopurine, TNF blockade may also increase susceptibility for developing HSTCL ***independent of thiopurine exposure***. Therefore, genes that are part of the TNF signaling pathway may also influence susceptibility for HSTCL.

8. Description/Rationale: Instructions were modified such that the sponsor may use a delegate during the study.

Sections Affected	Original Content	Amended/New Content
Throughout the document as appropriate	sponsor	sponsor ***or its delegate*** sponsor ***(or delegate)***

9. Description/Rationale: Content was corrected in Section 5.1.4 to clarify that a bowel tissue sample is to be collected.

Sections Affected	Original Content	Amended/New Content
5.1.4. Bowel Tissue Sample (paragraph 1)	A sample of bowel tissue is requested (optional) if a specimen is already available. The sample will be used for mutation analysis of IBD to tumor. Approximately ten 6-micron sections of the formalin-fixed, paraffin-embedded tumor are required (approximately 50 milligrams of the tumor biopsy).	***If possible***, a sample of bowel tissue is requested (optional) if a specimen is already available. The sample will be used for mutation analysis of IBD to tumor. Approximately ten, 6-micron sections of the formalin-fixed, paraffin-embedded ~~tumor~~ ***tissue*** are required (approximately 50 milligrams of the ~~tumor~~ ***bowel tissue*** biopsy).

10. Description/Rationale: Content in Section 5.1.4 Bowel Tissue Sample was moved to Section 5.2 Sample Collection and Handling for clarity.

Sections Affected	Original Content	Amended/New Content
5.2 Sample Collection and Handling (previously last paragraph in Section 5.1.4; now first paragraph in Section 5.2)	Tubes for the blood samples, the buccal swab collection kit, and the slides for tumor biopsy tissue and bowel tissue samples will be provided to the patient's physician with specific instructions for collection, labeling, storing, and shipping to the sponsor or delegate.	***Collection t***ubes for the blood samples, the buccal swab collection kit, and the slides for tumor biopsy tissue and bowel tissue samples will be provided to the patient's physician with specific instructions for collection, labeling, storing, and shipping to the sponsor or delegate.

11. Description/Rationale: Content in Section 5.3 Data Collection instructions were modified for clarity.

5.3 Data Collection (paragraph 1)	For each identified case of HSTCL for which the treating physician(s) agreed to participate, the investigator or an authorized member of the investigational staff will collect data from the patient's medical records to a CRF at a data collection visit at the treating physician(s) site.	For each identified case of HSTCL for which the treating physician(s) agreed to participate, the investigator or an authorized member of the investigational staff will collect data from the patient's medical records ***and transfer this information to the*** ~~to a~~ ***CRF*** at a data collection visit at the treating physician(s) site.

12. Description/Rationale: The Steering Committee was relabeled as the Scientific Advisory Committee for consistency across sponsor documents. In addition, the description of the members of the Scientific Advisory Committee was modified for accuracy in Section 5.4.

Sections Affected	Original Content	Amended/New Content
Throughout the document as appropriate	Steering Committee	~~Steering~~ ***Scientific Advisory*** Committee
5.4 Scientific Advisory Committee (paragraph 1, sentence 1)	A Scientific Advisory Committee will be established and include representatives from the sponsor, appropriate expert health authority representatives, and global medical experts in the disease under study.	A Scientific Advisory Committee will be established and ***will*** include representatives from the sponsor~~, appropriate expert health authority representatives,~~ and global medical experts in the disease under study.

13. Description/Rationale: Section 7.1.1 Adverse Event Definitions and Classifications were updated to reflect the most recent guidance recommendations.

Sections Affected	Original Content	Amended/New Content
7.1.1. Adverse Event Definitions and Classifications, Serious Adverse Event (paragraphs 1, 2, and 3)	A serious adverse event based on ICH is any untoward medical occurrence 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 expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.	A serious adverse event based on ICH ***and European Union (EU) Guidance on Pharmacovigilance for Medicinal Products for Human Use*** is any untoward medical occurrence 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.***

14. Description/Rationale: Content was clarified that while adverse events will be reported as solicited reports, these reports will not necessarily be reported via postmarketing routes only.

Sections Affected	Original Content	Amended/New Content
7.2. Reporting and Follow-up of Serious Adverse Events (paragraph 3, last sentence)	All other adverse events/serious adverse events that are identified through the study data collection processes and not associated with study interventions (ie, blood draw, buccal swabbing) will be reported as solicited reports via the postmarketing routes.	All other adverse events/serious adverse events that are identified through the study data collection processes and not associated with study interventions (~~ie~~***eg***, blood draw, buccal swabbing) will be reported as solicited reports~~ via the postmarketing routes~~.

Amendment 1 – 26 March 2013

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. Description/Rationale: Revisions were made to allow for the collection of additional specimens (ie, buccal swab sample, and bowel tissue sample, if available). In additional to a single blood sample (if possible) and tissue samples from the biopsy specimen used to diagnose HSTCL, other specimens requested may now include a buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline) and a bowel tissue sample (if available for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).

Sections Affected	Original Content	Amended/New Content
Synopsis (Overview of Study Design, paragraph 1; Evaluations, new paragraph 3 added; 3 Study Design (paragraph 1)	This study is designed to collect a single blood sample, if possible, and obtain tissue samples from the biopsy specimen that was used to diagnose HSTCL. Samples obtained will be stored by the sponsor for future testing. In addition, demographic and clinical patient information will be collected. The study will be conducted in the US only.	This study is designed to collect a single blood sample, if possible, and obtain tissue samples from the biopsy specimen that was used to diagnose HSTCL. **Other specimens requested may include a buccal swab sample (to determine the patient tissue type and establish non-mutated DNA baseline) and a bowel tissue sample (if available for mutation analysis between the tumor and T cells residing in the bowel to attempt to determine the origin of the tumor clone).** Samples obtained will be stored by the sponsor for future testing. In addition, demographic and clinical patient information will be collected. The study will be conducted in the US only.
3 Study Design (paragraph 8)	Patients will be asked to provide a single blood sample that will be used for the test procedures that are part of this study.	Patients will be asked to provide a single blood sample**, a buccal swab sample, and a bowel tissue sample if available (discretionary) to** be used for the test procedures that are part of this study.
Synopsis (Statistical Methods, paragraph 3)	Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with normal tissue lining DNA from the same biopsy specimen or DNA isolated from peripheral blood mononuclear cells obtained from the	Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with normal **lining** tissue DNA from the same biopsy specimen **, or DNA from a**

<table>
<tr>
<td></td>
<td>same patient. Individual mutations will be tabulated within and between patients and cross-referenced with human variation databases (eg, COSMIC, dbSNP, etc.). To identify cancer driver genes or pathways, somatic mutation frequencies will be evaluated per gene or pathway across all patients with HSTCL and compared with empirical background mutation rates by mutation type (Wendl, 2011; Youn, 2011).</td>
<td>bowel tissue sample, or DNA from cells isolated from the buccal swabs, or DNA isolated from peripheral blood mononuclear cells obtained from the same patient. Buccal swab sample analysis will help to determine the patient’s genetic makeup and the bowel tissue sample analysis will help to perform mutation analysis of IBD to the tumor. Individual mutations will be tabulated within and between patients and cross-referenced with human variation databases (eg, COSMIC, dbSNP, etc.). To identify cancer driver genes or pathways, somatic mutation frequencies will be evaluated per gene or pathway across all patients with HSTCL and compared with empirical background mutation frequencies by mutation type (Wendl, 2011; Youn, 2011).</td>
</tr>
<tr>
<td>5.1 Study Procedures
(new subsection headings added; table header added, table row 1 edited title, table row 5 deleted)</td>
<td>5.1 Study Procedures
A sample of the tumor biopsy tissue, including lining tissue if available, originally used for the diagnosis of HSTCL must be provided to JBI. Approximately ten 6-micron sections of the formalin-fixed, paraffin-embedded tumor are required (approximately 50 milligrams of the tumor biopsy).

A single blood sample is required. The estimated total blood volume to be collected from each patient will be based on patient weight as per the table below.

Tubes for the blood samples and the slides for tumor samples will be provided to the patient’s physician with specific instructions for collection, labeling, storing, and shipping to the sponsor.</td>
<td>5.1.1 Tumor Biopsy Tissue Sample
A sample of the tumor biopsy tissue, including lining tissue if available, originally used for the diagnosis of HSTCL must be provided to JBI or designee. Approximately ten 6-micron sections of the formalin-fixed, paraffin-embedded tumor are required (approximately 50 milligrams of the tumor biopsy).

5.1.2 Blood Sample
A single blood sample is requested. The estimated total blood volume to be collected from each patient will be based on patient weight as per the table below.

<table>
<tr><th colspan="2">Table: Blood sample and volume collected</th></tr>
<tr><td>Blood Sample Type</td><td>Blood Volume (total volume approximately 37 mL)</td></tr>
</table>

5.1.3 Buccal Swab Sample
A buccal swab sample is requested to determine the patient tissue type, and a sample collection kit will be provided. Buccal swabs will be used to collect cells from the cheek area inside the mouth of the patient.</td>
</tr>
</table>

		5.1.4 Bowel Tissue Sample **A sample of bowel tissue is requested (optional) if a specimen is already available. The sample will be used for mutation analysis of IBD to tumor. Approximately ten 6-micron sections of the formalin-fixed, paraffin-embedded tumor are required (approximately 50 milligrams of the tumor biopsy).** Tubes for the blood samples, **the buccal swab collection kit,** and the slides for tumor **biopsy tissue and bowel tissue** samples will be provided to the patient's physician with specific instructions for collection, labeling, storing, and shipping to the sponsor.
5.2 Sample Collection and Handling (paragraph 2)	Instructions for the collection, handling, and shipment of samples are found in the laboratory reference manual.	**Please refer to the laboratory reference manual for detailed instructions for the collection, handling, and shipment of blood, tissue, and buccal swab samples.**
6 Test Methods and Data Analysis (paragraph 2 and paragraph 3)	Descriptive statistics of demographic information, information on medical/surgical (including treatment) history, and baseline characteristics at the time of HSTCL diagnosis will be summarized for all patients enrolled in this study. Protein assay data will be summarized using descriptive statistics. Gene expression in tumor cells may be compared with expression levels observed in normal tissue lining or with cells isolated from whole blood with moderated t-statistics or other appropriate statistical methods. Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with normal tissue lining DNA from the same biopsy specimen or DNA isolated from peripheral blood mononuclear cells obtained from the same patient. Individual mutations will be tabulated within and between patients and cross-referenced with human variation databases (eg, COSMIC, dbSNP, etc.). To	Descriptive statistics of demographic information, information on medical/surgical (including treatment) history, and baseline characteristics at the time of HSTCL diagnosis will be summarized for all patients enrolled in this study. Protein assay data will be summarized using descriptive statistics. Gene expression in tumor cells may be compared with expression levels observed in normal tissue lining **or in bowel tissue sample,** or with cells isolated from whole blood **or from buccal swabs** with moderated t-statistics or other appropriate statistical methods. Full genome or targeted sequencing may also be used to reveal patterns of mutations responsible for development of HSTCL. Somatic mutations will be identified by comparing HSTCL tumor DNA with normal **lining** tissue DNA from the same biopsy specimen**, or DNA from a bowel tissue sample, or DNA from cells isolated from the buccal swabs,** or DNA isolated from peripheral blood

	identify cancer driver genes or pathways, somatic mutation frequencies will be evaluated per gene or pathway across all patients with HSTCL and compared with empirical background mutation rates by mutation type (Wendl, 2011; Youn, 2011).	mononuclear cells obtained from the same patient. **Buccal swab sample analysis will help to determine the patient's genetic makeup and the bowel tissue sample analysis will help to perform mutation analysis of IBD to the tumor.** Individual mutations will be tabulated within and between patients and cross-referenced with human variation databases (eg, COSMIC, dbSNP, etc.). To identify cancer driver genes or pathways, somatic mutation frequencies will be evaluated per gene or pathway across all patients with HSTCL and compared with empirical background mutation **frequencies** by mutation type (Wendl, 2011; Youn, 2011).
7.2 Reporting and Follow-up of Serious Adverse Events (paragraph 3, last sentence)	All other adverse events/serious adverse events that are identified through the study data collection processes and not associated with study interventions (ie, blood draw) will be reported as solicited reports via the postmarketing routes.	All other adverse events/serious adverse events that are identified through the study data collection processes and not associated with study interventions (ie, blood draw, **buccal swabbing**) will be reported as solicited reports via the postmarketing routes.
8. Ethical Aspects	This study is being conducted to address a postmarketing requirement by the US FDA to bank blood and/or tissue samples for future evaluation aiming at identifying genetic mutations and other biomarkers that predispose IBD patients to develop HSTCL. No medical or scientific benefit will be provided to patients who participate in the study; however, future patients at risk for developing HSTCL may benefit from the results of this research.	This study is being conducted to address a postmarketing requirement by the US FDA to bank blood**, buccal cells,** and/or tissue samples for future evaluation **to identify** genetic mutations and other biomarkers that **may** predispose IBD patients to develop HSTCL. No medical or scientific benefit will be provided to patients who participate in the study; however, future patients at risk for developing HSTCL may benefit from the results of this research.

2. Description/Rationale: Revisions were made to include identification of HSTCL cases that may have been reported directly through the sponsor's Medical Information Center. This change may provide an increase in sample size.

Sections Affected	Original Content	Amended/New Content
Synopsis (Overview of Study Design, paragraph 2) 3 Study Design (paragraph 2) 5 Study Evaluations (paragraph 1)	The study population will include IBD patients in the US with HSTCL who are identified through the sponsor's adverse event reporting systems. Cases of HSTCL will be identified through postmarketing adverse event reporting (eg, spontaneous reports, reports from late phase clinical trials, reports from patient registries) or from the sponsor's new or ongoing clinical trials. Eligible for enrollment are male or female patients of any age who have a confirmed diagnosis of HSTCL.	The study population will include IBD patients in the US with HSTCL who are identified through the sponsor's adverse event reporting systems. Cases of HSTCL will be identified through **the sponsor's** postmarketing adverse event reporting **system** (eg, spontaneous reports, reports from late phase clinical trials, reports from patient registries), **from parties seeking participation in the trial through reporting of cases directly to the sponsor's Medical Information Center,** or from the sponsor's new or ongoing clinical trials. Eligible for enrollment are male or female patients of any age who have a confirmed diagnosis of HSTCL.

3. Description/Rationale: An exclusion criterion was added for any who are unable to provide critical clinical and/or demographic patient and/or sample information.

Sections Affected	Original Content	Amended/New Content
4.2 Exclusion Criteria (criterion 2 added)		**2. Unable to provide critical clinical and/or demographic patient and/or sample information.**

4. **Description/Rationale: Data collected were revised with clarifications and to include collection of information on medical history including family history of cancer.**

Sections Affected	Original Content	Amended/New Content
5.3 Data Collection (paragraph 2 numbered items)	The data elements that are collected from patient's medical records include: 1. HSCTL diagnosis a. Diagnosis confirmation b. Clinical course c. Type and duration of treatment with corticosteroids and any immunomodulator therapies (including biologics) prior to and at time of diagnosis of lymphoma	The data elements that are collected from patient's medical records include: 1. HSCTL diagnosis a. Diagnosis confirmation **and date. Tumor stage and findings that support staging including system used.** b. Clinical course c. Type**, dose,** and duration of treatment with corticosteroids and any immunomodulator therapies (including biologics) prior to and at time

	2. Diseases and medical/surgical conditions prior to or at the time of diagnosis (including date of diagnosis, treatment and medications, and outcome) including but not limited to the following: a. Autoimmune disease b. Cancer c. Organ transplant d. Infection with human immunodeficiency virus (HIV) 3. Cytogenetic and flow cytometric data if available 4. Demographic data including age at diagnosis, gender, race, and nationality	of diagnosis of lymphoma **2. Medical history including family history of cancer.** **3**. Diseases and medical/surgical conditions prior to or at the time of diagnosis (including date of diagnosis, treatment and medications, and outcome) including but not limited to the following: a. Autoimmune disease b. Cancer c. Organ transplant d. Infection with human immunodeficiency virus (HIV) **4**. Cytogenetic and flow cytometric data if available **5**. Demographic data including age at diagnosis **of HSTCL**, gender, race, and nationality

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 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): Andrew Greenspan, MD

Institution: Janssen Research & Development

Signature: PPD Date: 15 August 2017
(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.

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Approved 11 August 2017 CONFIDENTIAL