Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Study Protocol and Statistical Analysis Plan

Study Title: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma

The manuscript in NEJM is reporting the phase 1b portion of the study and the statistics are descriptive. The remainder of the statistical analysis plan is providing guidance for the analysis of the phase 2 portion of the study, which has not yet been completed and does not apply to the analysis of the phase 1 part of the trial. It is possible that modifications in this plan will be needed in the course of the study. Modifications will be IRB approved and documented at the time the phase 2 study is reported.

The manuscript in NEJM is reporting the phase 1b portion of the study. The remainder of the protocol describes a phase 2 portion of the study, which has not yet been completed and does not apply to the analysis of the phase 1 part of the trial. It is possible that modifications in this plan will be needed in the course of the study. Modifications will be IRB approved and documented at the time the phase 2 study is reported.

In addition, the statistics reporting in the NEJM manuscript are also for the phase 1b portion and are descriptive. The remainder of the statistical analysis plan is providing guidance for the analysis of the phase 2 portion of the study, which has not yet been completed and does not apply to the analysis of the phase 1 part of the trial. It is possible that modifications in this plan will be needed in the course of the study. Modifications will be IRB approved and documented at the time the phase 2 study is reported.

The following items are included:

1. Final study protocol
2. Original study protocol
3. Summary of amendments
4. Statistical analysis (version 1 which is the original and final version)

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma
Protocol Number:	5F9003
Investigational Products:	Hu5F9-G4 and rituximab
Indication:	Non-Hodgkin's Lymphoma
Development Phase:	1b/2
US IND Number:	118300
EudraCT Number:	2016-003408-29
Sponsor:	Forty Seven Inc. 1490 O'Brien Drive, Suite A Menlo Park, CA 94025 [redacted]
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Investigator(s):	Ranjana Advani, MD Study Lead Principal Investigator Professor of Lymphoma, Stanford University 875 Blake Wilbur Drive Clinic C Stanford, CA 94305, USA Telephone: 1-650-498-6000 Professor John G. Gribben, MD DSc FMedSci United Kingdom Lead Principal Investigator Chair of Medical Oncology, Barts Cancer Institute Queen Mary University of London John Vane Science Centre, Third Floor Charterhouse Square, London EC1M 68Q Telephone: 020 7882 3804
Amendment 5 Date:	18 May 2017

Amendment 4 Date: 10 February 2017

Amendment 3 Date: 28 November 2016

Amendment 2 Date: 24 August 2016

Amendment 1 Date: 23 August 2016

Original Protocol Date: 14 July 2016

Confidentiality Statement:

Compliance Statement:

This study will be conducted in accordance with Protocol 5F9003, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL APPROVAL PAGE

I have read the document described above, and my signature below indicates my approval:

Chris H. Takimoto, M.D, Ph.D.
Chief Medical Officer
Forty Seven Inc.

15 May 2017
Date

PROTOCOL ACCEPTANCE PAGE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, my local and regional clinical trial regulatory requirements (including the Code of Federal Regulations [CFR] Title 21), and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 5

The main reasons for amending the 5F9003 protocol is to harmonize recent feedback from the Food and Drug Administration (FDA) and Medicines and Healthcare Regulatory Agency (MHRA). Amendment 5 brings together regulatory feedback received from the MHRA and, most recently, the FDA on Amendment 3. Amendment 4 was a region-specific document to respond to MHRA feedback. Additional changes by the Sponsor are also included in this document.

The following changes have been made to the protocol in response to FDA feedback:

- Added requirement for premedication prior to the first 2 doses of Hu5F9-G4. (Section 6.1, Study Drug Administration)
  Rationale: Infusion reactions due to rituximab are observed in non-Hodgkin's lymphoma patients and the theoretical risk of potentiating rituximab-related infusion reactions with Hu5F9-G4, a premedication regimen for Hu5F9-G4 will be instituted to mitigate this potential safety risk. Hu5F9-G4 infusion reactions, when they have occurred, have been experienced primarily with the first or second dose. Thus, premedication for Hu5F9-G4 will be required for the first 2 Hu5F9-G4 doses, where the potential infusion reaction risk is highest.
- Modified the Dose Limiting Toxicity Exclusion Criterion of Grade 3 infusion reactions attributed to rituximab to specifically state that such reactions can only be attributed to rituximab if the adverse event occurs during rituximab infusion but prior to Hu5F9-G4 infusion. (Section 3.3, Definition of Dose-limiting Toxicity)
  Rationale: Hu5F9-G4 and rituximab are administered on the same day. Once both treatments are administered, the attribution of any infusion reactions to either Hu5F9-G4 or rituximab is difficult.

The Sponsor has made the following additional changes to the protocol:

- Modified the Dose-limiting Toxicity Exclusion Criterion of Grade 3 indirect/unconjugated hyperbilirubinemia, electrolyte abnormalities, and alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to

≤ Grade 2 with supportive care within 1 week from 72 hours.

(Section 3.3, Definition of Dose-limiting Toxicity)

Rationale: Clarify DLT exclusions for specific lab abnormalities to align with other Hu5F9-G4 protocols. The extension of AE severity reduction from 72 hours to 7 days represents an adequate risk/benefit ratio, as these lab abnormalities, when observed in other Hu5F9-G4 trials, have resolved or were reduced in severity by 7 days.

- Added the ability to enroll a fourth subject in each cohort.

  (Section 3.2.2, Phase 1b Dose Escalation)

  Rationale: A fourth patient enrolled in the same cohort is to have an extra patient in case 1 of the 3 earlier patients is unevaluable, or a DLT is experienced by a patient in the cohort, requiring cohort expansion to 6 patients. Given the patient population being studied (particularly relapsed/refractory DLBCL), there is a reasonable possibility that patients may not be able to stay on study until completion of the DLT assessment due to clinical disease course.

- Addition of LYRIC criteria as Secondary Endpoint for immune response evaluation.

  (Section 2.1, Study Objectives; Section 2.2, Study Endpoints; Section 7.3.5, Section Diagnostic Imaging; Section 7.9, Efficacy Assessment; Section 10.1.1, Overall Response Rate; Section 10.2, Evaluation of Response; Appendix C)

  Rationale: The additional safety and now efficacy data of Hu5F9-G4 suggests a favorable risk/benefit profile for utilizing the LYRIC criteria as a secondary endpoint. Hu5F9-G4 is an immunotherapy that activates both the innate and adaptive immune system and thus immune-mediated response assessments may be important for characterizing Hu5F9-G4 efficacy. One of five patients receiving Hu5F9-G4 + rituximab in this study has achieved a complete response. Additionally, mixed responses (tumor reduction of several lesions with tumor size increase in 1 solitary lesion) have been observed in 2 patients with NHL who have been treated (1 with Hu5F9-G4 monotherapy and 1 with Hu5F9-G4 + rituximab). These patients had been classified as having progressive disease according to the Lugano classification (Cheson 2014). Adding LYRIC criteria enables evaluation of any additional clinical benefit for patients who can be treated beyond progression. Because the long-term safety profile has shown Hu5F9-G4 to have been generally well tolerated to date, it is anticipated that the safety

risk of treating patients beyond progression will be acceptable. The LYRIC Criteria for lymphomas will be used as a secondary endpoint in the assessment of response using immune-mediated response criteria. The Lugano classification will still be used as a the primary endpoint.

- Increase the dose level for cohort 3 to 20 or 30 mg/kg.
  (Section 1.6.1, Hu5F9-G4; Section 3.2.1, Phase 1b Dose Level).
  Rationale: To evaluate the safety profile of Hu5F9-G4 at 30 mg/kg dose level. Emerging pharmacokinetic, pharmacodynamics, and clinical data suggests that Hu5F9-G4 doses of 20 mg/kg or higher (e.g., 30 mg/kg) may enhance the possibility of patients receiving more benefit from treatment. An MTD has not been reached on any Hu5F9-G4 trial at a dose of 20 mg/kg. Based on emerging data, the risk-benefit ratio of exploring higher doses appears to be acceptable.
- Define the roles of the Clinical Trial Steering Committee (CTSC) to allow this body to:
  - recommend dose increases of up to 50% intervals from 30 mg/kg to be explored in additional cohorts
  - expand the number of patients from 6 to 10 per cohort
  - approve the exploration of alternate recommended Phase 2 dose and schedule (RP2DS) after the initiation of the Phase 2 part of the study, based on emerging clinical, PK, and PD data

  (Section 1.6.1, Hu5F9-G4; Section 3.1; Overall Study Design; Section 3.2.1, Phase 1b Dose Level)
  Rationale: To evaluate the safety profile of Hu5F9-G4 at different dose levels in an expanded group of patients, as well as to provide additional PK data to assist in the selection of a recommended Phase 2 dose (RP2D).
- Add Lymphocyte subset analysis for local labs on Day 1 of each cycle and at the Safety Follow-up Visit. (Section 7, Study Evaluation; Table 2; Table 3; Table 4)
  Rationale: To evaluate the role of Hu5F9-G4 and/or rituximab in inducing B-cell depletion in patients with NHL. This analysis will enable enhanced understanding of potential efficacy signals of the treatment combination.

- Add CD47 blood sample collection on Day 11 to evaluate receptor occupancy (RO) in patients in the Loading Dose Cohort. (Section 7, Study Evaluation; Table 8)
  Rationale: To obtain RO data pre and post dose for a loading dose to gather more accurate RO data to assist with Hu5F9-G4 dose refinement.
- Obtain tumor/lymph node biopsies during the Screening period.
  (Section 7.1, Schedules of Assessment for Phase 1b and Phase 2: Table 2 and Table 3; Section 7.10, Pharmacodynamic and Biomarker Assessments)
  Rationale: To expand the window of time during which the screening biopsy can be obtained in order to provide additional accommodation for patient scheduling.

Editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document. Changes in sections of the protocol body have also been made in the protocol synopsis, study design schema, tabular schedules of assessments, and elsewhere in the document, as applicable.

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 4

The main reasons for amending the 5F9003 protocol (Amendment 4) was to respond to Medicines and Healthcare products Regulatory Agency (MHRA) feedback on Amendment 3 of the protocol submitted as part of a clinical trial application to the MHRA.

The following is a list of changes that were made to the protocol in response to MHRA feedback:

- Issue 1, definition of qualifying event
  (Section 11.11, Interim Analysis)
  Protocol language defining a qualifying event has been modified in accordance with MHRA feedback.
- Issue 2, pregnancy testing
  (Section 4.1.1, Inclusion Criterion 10; Section 7.3.6 Pregnancy Test)
  The wording of Inclusion Criterion 10 has been aligned with Table 3 in accordance with MHRA feedback.
- Issue 3, indirect bilirubin
  (Section 7.8 Safety Assessments, Table 10 Analyte Listing)
  Indirect bilirubin has been added to Table 10, Analyte Listing, in the chemistry column.
- Issue 4, addition of prohibited medications section
  (Section 6.3, Prohibited Medications)
  A section has been added in accordance with MHRA feedback to specify prohibited medications based on current Hu5F9-G4 data and the MabThera Summary of Product Characteristics (SmPC) and Rituxan United States Prescribing Information (USPI).
- Nonclinical Point
  (Section 9.3.1.8, Other Reportable Events, Pregnancy; Section 4.1.1, Inclusion Criteria 11 and 12)
  Entry criteria and content describing contraception requirements have been aligned in accordance with MHRA feedback.

PROTOCOL SYNOPSIS

Concept and Rationale:

Non-Hodgkin's lymphoma (NHL) is among the most common cancers in the USA and Europe, with more than 70,000 and 93,000 new cases diagnosed every year, respectively (Ferlay 2015). Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of NHL with high relapse rate and poor long-term survival. In addition, few treatment options are available to patients with indolent lymphoma who have relapsed or are refractory to rituximab. Novel and effective therapies are needed to address these high unmet medical needs. Hu5F9-G4 is a monoclonal antibody that targets CD47, an anti-phagocytic cell surface protein. Nonclinical studies have demonstrated that blockade of CD47 signaling through this antibody eliminates human tumor cells including NHL, through facilitating phagocytosis by macrophages. Additional nonclinical studies demonstrate that anti-CD47 antibodies can synergize with Fc receptor-activating anti-cancer antibodies including rituximab. Combination therapy with Hu5F9-G4 and rituximab, an anti-CD20 monoclonal antibody, demonstrated a synergistic anti-cancer response compared to either agent alone in nonclinical models of NHL.

It is hypothesized that the combination of Hu5F9-G4 and rituximab will be safely tolerated in NHL.
This Phase 1b/2 trial will establish the safety and tolerability and optimal dosing strategy of Hu5F9-G4 in combination with rituximab in patients with relapsed/refractory B-cell NHL. Hu5F9-G4 and rituximab will both be administered intravenously. Initially, this trial will utilize a reduced starting dose of Hu5F9-G4 in combination with full doses of rituximab. Subsequent dose cohorts will escalate the dose of Hu5F9-G4.
In addition, preliminary anti-cancer activity will be investigated with this antibody combination.

Patient Eligibility:

Inclusion Criteria:

1. Adults ≥ 18 years
2. Phase 1b only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy
3. DLBCL Phase 2 cohort: Histologically confirmed de novo or transformed DLBCL expressing CD20 by IHC or flow cytometry, refractory to frontline therapy; or relapsed or refractory to second line salvage regimens or autologous hematopoietic cell transplantation
4. Indolent lymphoma Phase 2 cohort: Histologically confirmed marginal zone or follicular lymphoma (Grade 1-3a) expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy
5. Eastern Cooperative Oncology Group (ECOG) score 0-2
6. Disease that is measurable or assessable for response per Lugano Classification for lymphomas
7. Laboratory measurements, blood counts:
   - Hemoglobin ≥ 9.5 g/dL
   - Absolute neutrophil count (ANC) ≥ 1.0×10^9/mL
   - Platelets ≥ 50×10^9/mL
8. Laboratory measurements, hepatic function:
   - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN)
   - Bilirubin ≤ 1.5 × or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent
9. Laboratory measurements, renal function:
   - Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) > 40 mL/min/1.73 m2
10. Negative urine or serum pregnancy test within 30 days before enrollment and within 72 hours before the first administration of Hu5F9-G4 for women of childbearing potential.
11. Females of childbearing potential must be willing to use 1 highly effective method of contraception during the study and for 12 months after the last dose of rituximab or 4 months after the last dose of

Hu5F9-G4, whichever occurs later

12. Males must be willing to use 1 effective method of contraception during the study and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9-G4, whichever occurs later, if the partner is a female of childbearing potential
13. Subject has provided informed consent
14. Must be willing and able to comply with clinic visits and procedures outlined in the study protocol
15. Phase 2 only: Willing to consent to 1 mandatory pre-treatment and 1 on-treatment tumor biopsy, unless not feasible as determined by the Investigator (reasons include but are not limited to lack of accessible tumor tissue to biopsy and patient safety issues)

Exclusion Criteria:

1. Patients with active brain metastases. (Patients with stable treated central nervous system [CNS] lesions who are off corticosteroid therapy for at least 3 weeks are not considered active.)
2. Prior anti-cancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 4 half-lives prior to Hu5F9-G4 dosing (up to a maximum of 4 weeks), whichever is longer. In all situations, the maximum required washout period will not exceed 4 weeks prior to the day of first treatment with Hu5F9-G4. Low dose steroids (oral prednisone or equivalent ≤ 20 mg per day), localized non-CNS radiotherapy, pre-existing previous hormonal therapy with LHRH agonists for prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion.
3. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
4. Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening and prior to enrollment to meet the hemoglobin inclusion criteria.
5. History of hemolytic anemia or Evans syndrome in the last 3 months.
6. Positive Direct Antiglobulin Test (DAT).
7. Prior treatment with CD47 or signal regulatory protein alpha (SIRPα) targeting agents.
8. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancy for which patients are not on active anti-cancer therapy as defined in Exclusion Criterion 2.
9. Hypersensitivity to the active substance, to murine proteins, or to any of the other excipients of rituximab listed in Appendix A.
10. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor that would substantially increase the risk-benefit ratio of participating in the study. This includes but is not limited to acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, severely immunocompromised state, and congestive heart failure New York Heart Association (NYHA) Class II-IV.
11. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
12. Pregnancy or active breastfeeding.

Study Objectives:

Primary Objectives:

- To investigate the safety and tolerability, and to define the recommended Phase 2 dose for Hu5F9-G4 in combination with rituximab
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in patients with indolent lymphoma and DLBCL as measured by the overall response rate (ORR)

Secondary Objectives:

- In Phase 1b and 2, to evaluate the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with rituximab
- In Phase 1b and 2, to evaluate the immunogenicity of Hu5F9-G4 in combination with rituximab
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in indolent lymphoma and DLBCL as measured by the duration of response, best overall response, progression free survival, and overall survival
- To evaluate response rates according to LYRIC criteria for lymphomas

Exploratory Objective:

- To assess biomarkers of immune cell efficacy and tumor penetration of Hu5F9-G4 in combination with rituximab
- To assess efficacy in molecular subtypes of NHL

Study Endpoints:

Primary Endpoints:

- Dose-limiting toxicities (DLTs) (Phase 1b only) and adverse events (AEs) according to NCI CTCAE, Version 4.03.
- Phase 2: Objective response as defined by the Investigator according to the Lugano Classification for lymphomas.

Secondary Endpoints:

- Phase 1b and 2: Concentration versus time measurements for Hu5F9-G4 in combination with rituximab and PK parameters, including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), area under the curve (AUC), clearance (CL), and volume of distribution during the terminal phase (V_z).
- Phase 1b and 2: Anti-drug antibodies to Hu5F9-G4 and rituximab.
- Phase 2: Duration of response (DOR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS).
- Objective response as defined by the Investigator according to the LYRIC criteria for lymphomas.

Exploratory Endpoints:

- CD47 receptor occupancy on peripheral RBCs and white blood cells (WBCs), and lymphoma cells, where applicable.
- Pharmacodynamic markers of Hu5F9-G4 biological activity potentially including, but not limited to, circulating cytokine profiles, T-cell receptor sequencing on circulating T cells, mass cytometry (CyTOF)/flow cytometry of circulating leukocytes, and T-cell activation studies.
- In patients undergoing tumor biopsies, Hu5F9-G4 saturation of tumor cells and changes in the tumor microenvironment including, but not limited to, macrophage and T-cell tumor infiltration.
- In patients undergoing tumor biopsies, correlation of anti-cancer response to molecular subtypes of NHL including, but not limited to, cell-of-origin in DLBCL and BCL2, BCL6, and MYC mutation/expression status.

Intervention and Mode of Delivery:

Hu5F9-G4 is a humanized monoclonal antibody against CD47 and rituximab is a chimeric monoclonal antibody against CD20. Both drugs are administered intravenously. Hu5F9-G4 will be administered on Days 1, 8, 15, and 22 for all cycles while rituximab will be administered on Days 8, 15, and 22 for the first cycle followed by Day 1 for Cycles 2-6.

Duration of Intervention and Evaluation:

Phase 1b/2: For the Phase 1b part of the study, patients will be treated with Hu5F9-G4 and rituximab in a standard 3+3 dose escalation design. DLT safety evaluation used for determination of the maximum tolerated dose (MTD) will occur within the first 4 weeks. A response assessment will occur every 2 cycles (8 weeks) until disease progression. Rituximab will be administered for a total of 6 cycles, while Hu5F9-G4 treatment can extend beyond 6 cycles for those who do not have disease progression.

Number of Patients:

Phase 1b: 9 to 18 patients total

Per dose level:

Level 1: 3-6

Level 2: 3-6

Level 3: 3-6

Phase 2: 48 patients (24 patients for indolent lymphoma; 24 patients for DLBCL)

Study Total: 57-66 patients (assuming progression to Stage 2 of Phase 2)

Statistical Methods:

The Efficacy Analysis Set (EAS) will be used for the analysis of the primary efficacy endpoint in Phase 2. The DLT Analysis Set will be used in Phase 1b to determine the MTD. The Full Analysis Set (FAS) will be used for OS, PFS, and safety analysis in Phase 2. Per Protocol (PP) set and PK analysis set (PAS) will be used for additional analyses. The PAS will be used for summaries of PK concentration data and PK parameters. Data from Phase 1b and Phase 2 will be summarized separately. In Phase 2, data for indolent lymphoma and DLBCL will be summarized separately.

Sample Size Calculations

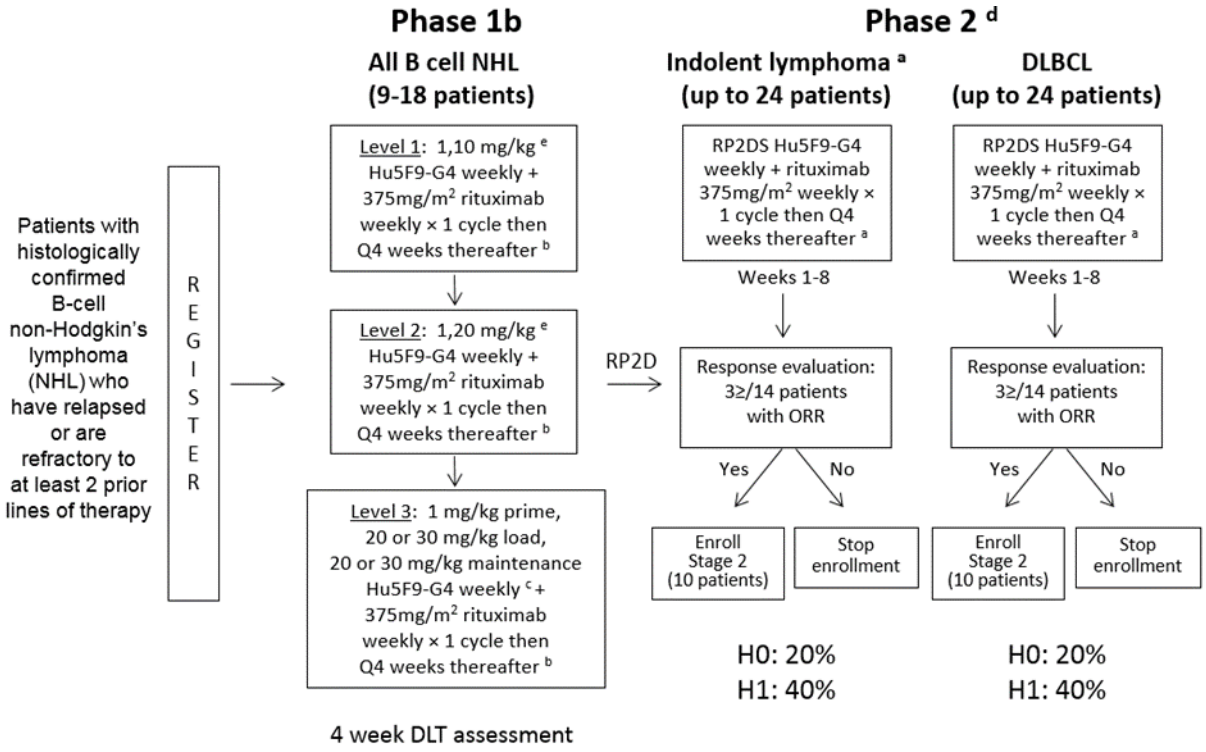
Phase 1b: The sample size will be determined based on the number of dose levels evaluated and the emerging study drug-related toxicities. This phase will consist of up to 18 patients.

Phase 2: Simon Two-Stage Minimax Design

- Indolent lymphoma: The null hypothesis that the true response rate is 20% will be tested against a one-sided alternative. The null hypothesis of 20% is based on single agent rituximab activity in patients previously treated and refractory to rituximab. The assumption is that Hu5F9-G4 in combination with rituximab will result in an overall response rate (ORR) of at least 40%. In the first stage, 14 patients will be accrued. If there are 2 or fewer responses in these 14 patients after at least 8 weeks of study participation, enrollment into this arm will be stopped. Otherwise, 10 additional patients will be accrued for a total of 28. The null hypothesis will be rejected if 8 or more responses are observed in 24 patients. This design yields a type I error rate of 0.10 and power of 0.80 when the true response rate is 40%.
- DLBCL: The null hypothesis that the true response rate is 20% will be tested against a one-sided alternative. The null hypothesis of 20% is based on single agent rituximab activity in patients receiving at least 2 prior lines of rituximab-containing therapies. The assumption is that Hu5F9-G4 in combination with rituximab will result in an ORR of at least 40%. In the first stage, 14 patients will be accrued. If there are 2 or fewer responses in these 14 patients after at least 8 weeks of study participation, enrollment into this arm will be stopped. Otherwise, 10 additional patients will be accrued for a total of 24. The null hypothesis will be rejected if 8 or more responses are observed in 24 patients. This design yields a type I error rate of 0.10 and power of 0.80 when the true response rate is 40%.

STUDY DESIGN SCHEMA

Study 5F9003: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma



[a] Indolent lymphoma includes follicular and marginal zone lymphoma.
[b] Treatment cycles are 4 weeks. Rituximab is given weekly at Weeks 2-4 in Cycle 1 only. Up to 6 cycles of rituximab will be given.
[c] Level 3 Hu5F9-G4 dosing regimen consists of 1 mg/kg priming dose on Day 1, then a loading dose of either 20 or 30 mg/kg twice weekly × 1 week, followed by weekly maintenance doses of 20 or 30 mg/kg. Dose concentration to be determined by the CTSC.
[d] Simon two-stage minimax design with an alpha of 0.1 and a power of 0.80. H0=null hypothesis; H1=alternative hypothesis.
[e] 1,10 mg/kg represents a first priming dose of 1 mg/kg followed by a maintenance dose of 10 mg/kg of Hu5F9-G4 one week after, similarly for 1,20 mg/kg.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITIONS

ADA	antidrug antibodies
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BOR	best overall response
BUN	blood urea nitrogen
CBCs	complete blood counts
CFR	Code of Federal Regulations
CHOP	alkylator combination of cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form (paper)
CT	computed tomography
CTSC	Clinical Trial Steering Committee
CyTOF	mass cytometry
DAT	direct antiglobulin test
DLBCL	diffuse large b-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EAS	Efficacy Analysis Set

ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H1	alternative hypothesis
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IWRS	interactive web response technology
kg	kilogram
KM	Kaplan-Meier
L	liters
LDH	lactate dehydrogenase
LDi	longest diameter
LISS	low ionic strength solution
LSC	leukemic stem cells
LSE	last subject enrolled
M1	macrophages that suppress tumor progression
M2	macrophages that promote tumor progression
mAb	monoclonal antibody
MedDRA	Medical Dictionary of Regulatory Activities

mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOA	mechanism of action
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PAS	Pharmacokinetic Analysis Set
PBMCs	peripheral blood mononuclear cells
PCD	programmed cell death
PD	progressive disease
PE	physical examination
PeG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	Per Protocol
PR	partial response
PrCR	programmed cell removal
PT	prothrombin time
RBCs	red blood cells
REC	research ethics committee
RP2DS	recommended Phase 2 dose and schedule
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease or standard deviation
SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha

SmPC	Summary of Product Characteristics
SOA	schedule of assessments
S-P	Ser-Pro
T_{max}	time to maximum concentration
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
V_z	volume of distribution during the terminal phase
WBCs	white blood cells

1. BACKGROUND

1.1. Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is among the most common cancers in the United States and Europe with more than 70,000 and 93,000 new cases diagnosed every year, respectively (Ferlay 2015). NHL is a heterogeneous group of malignancies with varying clinical characteristics that are optimally managed through a range of different treatment modalities. The spectrum of NHL includes more indolent variants such as follicular and marginal zone lymphomas, to more aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL). While systemic chemotherapy is a mainstay of treatment for most NHL variants, antitumor directed monoclonal antibodies (mAb) have an important role in the treatment of this disease (Oflazoglu 2010). Antibodies such as rituximab, which targets the B-cell antigen CD20, are now part of the standard treatment regimens for many B-cell non-Hodgkin's lymphomas (Keating 2010). However, once NHL becomes refractory to standard chemotherapy and antibody-based therapies, the overall prognosis is poor, with limited long-term survival. Thus, novel and effective therapies are needed to address this high unmet medical need.

1.1.1. Indolent Lymphoma

Indolent lymphomas represent 40% of all non-Hodgkin's lymphoma subtypes, with follicular lymphoma occurring with the greatest frequency (Harris 1999). Indolent lymphomas present with a broad spectrum of disease characteristics. Patients often experience a chronic relapsing and remitting disease course and are exposed to several successive treatment regimens, resulting eventually in death due to disease progression. In general, treatment is reserved for patients who develop significant symptoms or who are sufficiently high risk to merit early therapy (Gribben 2007). The most common frontline therapies include a combination of alkylators (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or bendamustine) in combination with the anti-CD20 monoclonal antibody rituximab. In addition, single agent rituximab is also often administered as frontline therapy, particularly in patients with lower disease burden or who may not tolerate combination chemo-immunotherapy (Sousou 2010). Rituximab was originally approved for use in patients with relapsed and refractory follicular lymphoma and low grade lymphoma.

For patients with indolent NHL who initially respond (complete or partial response with a time to progression of at least 6 months) and then experience relapse after single-agent rituximab, retreatment with either rituximab alone or in combination with chemotherapy is frequently given (Kahl 2014; Gribben 2007; NCCN Guidelines Version 3 2016). Patients who become refractory to rituximab alone or in combination with chemotherapy have limited options for effective treatment.

One approach to enhancing the efficacy of rituximab is the addition of other biologic agents that could potentiate its activity. There is strong nonclinical evidence demonstrating that Hu5F9-G4, an anti-CD47 antibody, can synergize with rituximab to eliminate both the indolent and aggressive lymphoma subtypes (Chao 2010a). This trial will explore clinical proof of concept of the combination of Hu5F9-G4 with rituximab to treat indolent and aggressive NHL.

1.1.2. Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of NHL that accounts for approximately 30% of all NHL (Non-Hodgkin's Lymphoma Classification Project 1997). Combination chemotherapy with the addition of rituximab is standard of care for patients with newly diagnosed DLBCL. However, approximately 40% of patients with DLBCL relapse following initial immunochemotherapy (Vaidya 2014). For patients who are eligible, salvage chemotherapy regimens followed by autologous stem cell transplantation is standard of care. However, many patients are not eligible for transplantation due to age and other medical co-morbidities. While multiple salvage regimens comprising combination chemotherapy are available for relapsed/refractory disease, no standard salvage regimen exists currently. The development of more effective therapies for relapsed/refractory DLBCL represents a high unmet medical need. In addition to indolent lymphoma, this study will investigate the use of an anti-CD47 antibody, Hu5F9-G4, in combination with rituximab for patients with DLBCL.

1.2. Study Drug: Hu5F9-G4

1.2.1. Nonclinical Background

The Stanford researchers in the laboratories of Weissman and Majeti have identified CD47 as a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system. CD47 appears to be an indispensable means by which cancer cells, including cancer stem cells, overcome intrinsic expression of their prophagocytic, "eat me," signals (Jaiswal 2009; Majeti 2009). The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death (PCD) and programmed cell removal (PrCR; Chao 2012). Many of the steps in cancer progression subvert the multiple mechanisms of PCD, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint (Chao 2012). The Weissman laboratory originally identified increased CD47 expression on leukemic stem cells (LSC) in human acute myeloid leukemia (AML; Majeti 2009) and have since found that CD47 expression is increased on the surface of cancer cells from a large number of diverse human tumor types.

In mouse xenografts, CD47-blocking mAbs inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors (Majeti 2009; Chao 2010a; Chao 2011a; Chao 2011b; Edris 2012; Kim 2012; Willingham 2012). Binding of CD47 on cancer cells to its ligand signal-regulatory protein alpha (SIRPα) expressed on phagocytes leads to inhibition of tumor phagocytosis. Thus, blockade of the CD47-SIRPα signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of pro-phagocytic signals expressed mainly on tumor cells and not on normal cell counterparts (Chao 2010b).
In addition, the anti-CD47 antibody induces an anti-cancer T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis (Tseng 2013; Liu 2015a). Furthermore, CD47-blocking mAbs have shown synergistic efficacious activity with cancer-specific targeting antibodies, including anti-CD20 antibody rituximab in NHL (Chao 2010a).

The nonclinical studies referred to in the publications referenced in this section have been conducted with a commercially available CD47-blocking monoclonal antibody (clone B6H12, mouse IgG1), and additional nonclinical studies have been conducted with the humanized CD47-blocking monoclonal antibody Hu5F9-G4.

Hu5F9-G4 is an anti-human CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells (Liu 2015b). The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector functions, although the presence of the IgG4 Fc domain is required for its full activity. For this reason, Hu5F9-G4 was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47 expressing cells (Liu 2015b). Nonclinical studies using xenograft cancer models provide compelling evidence that Hu5F9-G4 triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, Hu5F9-G4 is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

Most normal cells lack expression of pro-phagocytic signals and are unaffected by Hu5F9-G4 binding to and blocking CD47. Red blood cells (RBCs) are a notable exception because CD47 expression protects RBCs from elimination by splenic red pulp macrophages, as well as sinusoidal macrophages, in liver and bone marrow. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. Administration of Hu5F9-G4 accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger cells. Moreover, the potential for severe anemia in these nonclinical studies is ameliorated by administration of a low priming dose of the antibody that results in mild-to-moderate anemia and stimulates reticulocytosis.

The Hu5F9-G4 anti-CD47 program represents a novel strategy for the treatment of cancer and is the first therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute lymphoblastic leukemia [ALL], NHL, myeloma, and others).

1.2.2. Clinical Background

1.2.2.1. Summary of Hu5F9-G4 Clinical Safety

The safety of Hu5F9-G4 is currently being evaluated in two ongoing Phase 1 trials. The initial first-in-human Phase 1 trial (SCI-CD47-001) started dosing patients on 26 August 2014, and it is designed to determine the optimal dose and schedule of Hu5F9-G4 and to characterize its preliminary safety, pharmacokinetics (PK), and pharmacodynamics. This single institution study is enrolling patients with solid tumors and lymphomas; however, only solid tumor patients have been enrolled to date. A second Phase 1 trial (SCI-CD47-002) in relapsed/refractory AML patients began dosing patients on 30 November 2015, and it is designed to define the maximum tolerated dose (MTD) and to evaluate the safety, PK, and pharmacodynamics of Hu5F9-G4 in this patient population.

In the 17 patients (16 with solid tumors and 1 with AML) treated thus far, Hu5F9-G4 has been well tolerated. The most common treatment-associated effects are related to the targeting of CD47 on erythrocytes, with anemia and RBC agglutination being most prominent. Other common treatment-related adverse events (AEs) include mild headache, fatigue, nausea, photopsia, urine discoloration, low back pain, and abdominal pain. Common drug-related abnormal laboratory findings include transient reticulocytosis, spherocytosis, hyperbilirubinemia, D-dimer elevation, and decreased haptoglobin. The majority of these findings occur following the first infusion, with very few study drug-related toxicities reported beyond the first cycle. In patients with solid tumors, the recommended priming dose of 1 mg/kg of Hu5F9-G4 was defined by the dose-limiting toxicities (DLTs) of acute abdominal pain and headache associated with hemagglutination. However, using a priming and maintenance dose schedule in these patients has allowed for the further escalation of the maintenance dose to 10-20 mg/kg.

As expected, the most common, clinically relevant toxicity is an acute anemia manifested as a 1- to 2-g/dL fall in hemoglobin observed during the first 1 to 2 weeks of treatment. In solid tumor patients, this is followed by a compensatory reticulocytosis and a gradual return to baseline by Week 3 or 4 despite continued dosing. These clinical observations are completely consistent with the known MOA of Hu5F9-G4 and the physiologic role of CD47 in regulating the turnover of aging erythrocytes. Other associated laboratory abnormalities including reticulocytosis, spherocytosis, transient hyperbilirubinemia (predominantly unconjugated), and decreased haptoglobin are all indicative of extravascular hemolysis consistent with phagocytic removal of RBCs due to blockade of CD47. No solid tumor patient has required a blood transfusion; however, the single patient enrolled to date in the AML Phase 1 study (SCI-CD47-002) was transfusion-dependent prior to study entry and has received frequent RBC transfusions without complications throughout the first 5 weeks on study. Cross-matching of blood products while on Hu5F9-G4 has been successful, without need for specialized cross-matching procedures.

A second treatment-related effect on erythrocytes is hemagglutination, which is presumed to result from the direct interaction of Hu5F9-G4 with CD47 on red blood cells. In Part A of the solid tumor Phase 1 study (SCI-CD47-001), hemagglutination was observed on peripheral blood smears in 8 out of 11 patients, typically within 24 hours of study drug administration. Although D-dimer elevation was also common, there was no evidence of disseminated intravascular coagulation, nor were there any signs of thrombocytopenia, coagulopathy, microangiopathy, thromboembolic disease, or other clinical sequelae associated with the hemagglutination findings. No hemagglutination has been noted in any solid tumor patient beyond Cycle 1. An asymptomatic solitary cotton wool spot was noted on retinal photographic examination in 1 solid tumor patient, but this was not associated with any hemagglutination and subsequently resolved. Because RBC agglutination may be related to the early, rapid rise in Hu5F9-G4 concentration in the blood of treatment-naïve patients, the duration of infusion of the initial 1-mg/kg priming dose has been extended from 1 to 3 hours in all patients starting in the maintenance dose phase of the solid tumor Phase 1 study. Although current numbers are small, only mild hemagglutination has been observed in 1 of 5 patients treated using the 3-hour priming dose infusion. In contrast, hemagglutination was

observed in 6 of 6 previous patients treated with a 1-hour priming infusion (1 mg/kg). The duration of the maintenance dose infusions remains the same at 2 hours.

1.2.2.2. Summary of Hu5F9-G4 Clinical Pharmacology

No formal clinical pharmacology trials have been completed with Hu5F9-G4; however, preliminary PK data are available from the first 15 patients on the ongoing solid tumor Phase 1 study (SCI-CD47-001). Patients have been treated with Hu5F9-G4 doses ranging from 0.1 to 3 mg/kg with increasing concentrations associated with increasing dose. Nonlinear pharmacokinetics consistent with target-mediated clearance has been observed over this dose range with the apparent observed half-life ranging from 7 to 27 hours. Two of fifteen patients tested positive for anti-drug antibodies against Hu5F9-G4, but the impact on drug PK could not be ascertained due to the limited amount of available PK data. Dose escalation with pharmacokinetic monitoring is continuing in the two ongoing Hu5F9-G4 Phase 1 trials.

1.2.2.3. Summary of Hu5F9-G4 Clinical Efficacy

In both clinical studies, dose escalation is continuing and efficacy data from patients with systemic Hu5F9-G4 exposures in the range associated with nonclinical activity is still pending. No objective responses have been observed in 10 of the 13 patients with solid tumors who were evaluable for tumor response at the time of data cutoff in the ongoing dose escalation solid tumor Phase 1 study (SCI-CD47-001). Two patients with adenoid cystic carcinomas had stable disease for 33 and 72 weeks. In Study SCI-CD47-002, the single patient with AML treated thus far has had stable disease based on a Day 25 bone marrow evaluation and remains on study with stable disease after 5 weeks of treatment. No objective responses have been observed to date in patients with solid tumor or AML but dose escalation in these ongoing Phase 1 studies is continuing.

1.2.2.4. Summary of Hu5F9-G4 Clinical Safety

In summary, the expected adverse effects of anemia and hemagglutination have been observed in solid tumor and AML patients treated with Hu5F9-G4, but the overall safety profile to date is manageable and consistent with nonclinical toxicology studies. All non-hematological Hu5F9-G4-associated toxicities have been transient and easy to manage.

Supportive care with frequent RBC transfusions has been safely and successfully administered to an AML patient who was concurrently treated with Hu5F9-G4. Furthermore, implementation of a priming and maintenance dose strategy, coupled with the extension of the priming infusion duration to 3 hours, appears to substantially modulate the hematological toxicities of this novel agent, thereby allowing dose escalation to continue in the ongoing Phase 1 studies. Nonclinical studies with Hu5F9-G4 in combination with rituximab have been conducted in lymphoma xenograft mouse models. No evidence of systemic toxicity such as body weight loss was observed in these combinations studies; although Hu5F9-G4 does not cross-react with murine CD47 (Chao 2010a).

1.3. Rituximab

Rituxan®/MabThera® (rituximab), manufactured by Roche/Genentech, is a chimeric murine/human IgG1 kappa monoclonal antibody that targets CD20. Its MOAs are thought to be antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis after binding to the CD20 antigen on the cell surface. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow. Rituximab is the first commercially available monoclonal antibody for the treatment of lymphoma, and is currently approved for several NHL indications including low-grade indolent lymphoma, chronic lymphocytic leukemia, and DLBCL. Rituximab is widely used in frontline and salvage regimens in B-cell NHL, either alone or in combination with chemotherapy. The estimated median terminal elimination half-life is 22 days (range 6.1 to 52 days), based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every 3 weeks (Appendix A).

1.4. Correlative Studies Background

Blockade of the CD47-SIRPα signaling axis on tumor cells by a monoclonal blocking anti-CD47 antibody leads to tumor elimination by activation of both the innate and adaptive immune system. Anti-CD47 antibody-mediated tumor elimination by the innate immune system occurs through phagocytic elimination of tumor cells by macrophage and other phagocytes. It is well known that macrophages are a common immune cell infiltrate in many tumor types, with degree of intratumoral macrophage infiltrate correlating with clinical

prognosis. Correlation of macrophage infiltration to clinical disease course is often dependent on the presence of either classically activated (M1) type macrophages that suppress tumor progression or alternatively, activated (M2) type macrophages that promote tumor progression (Pollard 2004). Given the frequent infiltration of M2 macrophages in many tumor types and its role in promoting tumorigenesis, there is widespread interest in developing therapies that shift tumor macrophage polarization from the pro-tumorigenic M2 to the anti-tumorigenic M1 macrophages. In nonclinical studies, anti-CD47 antibody-mediated tumor cell phagocytosis has been demonstrated to occur through both M1 and M2 macrophages (Zhang 2016). In addition, in vivo treatment of human xenograft tumors with an anti-CD47 antibody demonstrated increased M1 intratumoral macrophages post-treatment (Zhang 2016), suggesting that an anti-CD47 antibody can also shift the phenotype of macrophages from the M2 towards the M1 phenotype in vivo. Since the recruitment of macrophage effectors is a key mechanism for anti-tumor activity by anti-CD47 antibody, the characterization of macrophage tumor infiltration pre- and post-treatment in patients treated with anti-CD47 antibody may provide insights into patient and cancer subtypes and macrophage biomarkers that will enrich for anti-tumor efficacy.

In addition to modulating the innate immune system, anti-CD47 antibody therapy also activates the adaptive immune system towards an anti-tumor response. Phagocytosis of tumor cells by phagocytes (macrophages and/or dendritic cells) leads to cross-presentation of tumor antigens to T cells, enabling a T-cell anti-tumor response (Tseng 2013; Liu 2015a). In one nonclinical study, anti-CD47 antibody mediated a specific CD8 T-cell anti-tumor response without proliferation of regulatory T cells (which are generally thought to be tumor-promoting; Tseng 2013). Currently, there is intense interest in investigating the relationship between T-cell subsets that infiltrate the tumor and clinical response with the use of immune-oncology therapeutics. Indeed, increased T-cell infiltration in the tumor has been associated with clinical response in oncology patients treated with T-cell checkpoint inhibitors (Herbst 2014; Tumeh 2014). Given the role of anti-CD47 antibody in mediating an anti-tumor T-cell response, the clinical investigation of the contribution of T-cell effectors to anti-CD47 antibody-mediated efficacy is important to select for patients and tumor subtypes that respond to therapy.

1.5. Study Rationale and Risk-Benefit

The development of therapeutic monoclonal antibodies (mAbs) has substantially impacted treatment of NHL with the clinical use of the anti-CD20 antibody, rituximab. However, apart from anti-CD20 antibodies, the development of other targeted mAbs for NHL has been limited.

A monoclonal antibody targeting CD47 enables selective phagocytosis and elimination of tumor cells, but not normal cells, and is a potentially beneficial therapy for NHL. In murine patient xenograft studies, it has been shown that CD47-blocking antibodies inhibit human lymphoma growth and dissemination by enabling the phagocytosis and elimination of lymphoma cells (Chao 2010a; Chao 2011b). Furthermore, CD47-blocking antibodies have been shown to exhibit potent synergy with tumor-specific mAbs, such as the anti-CD20 antibody rituximab in non-Hodgkin's lymphoma. In nonclinical models of NHL (including both indolent lymphoma and DLBCL), anti-CD47 antibody synergized with rituximab to yield dramatic levels of tumor phagocytosis in vitro compared to either monotherapy. In mice transplanted with aggressive NHL, combination therapy with anti-CD47 antibody and rituximab led to approximately 80% long-term remissions compared to only a partial tumor response with either agent alone (Chao 2010a; Liu 2015b). This mechanism of synergy was due to the engaging of 2 mechanisms of phagocytosis: anti-CD47 antibody-mediated phagocytosis through inhibition of CD47-SIRPα signaling and rituximab-mediated phagocytosis through delivery of a pro-phagocytic signal through the Fc receptor leading to antibody-dependent cellular phagocytosis (Chao 2010a). These nonclinical experiments provide the rationale for the use of anti-CD47 antibody in combination with rituximab for the treatment of patients with B-cell NHL.

B-cell NHL patients with both indolent lymphomas and DLBCL who have relapsed or are refractory to treatment regimens containing rituximab have limited options for effective treatment. Specific indolent lymphomas, particularly follicular lymphoma, are deemed incurable, as described by frequent patterns of relapse during several lines of therapy. While overall survival for follicular lymphoma can be more than 10 years, approximately 15% to 20% of patients with newly diagnosed follicular lymphoma have rapidly evolving, progressive disease (PD) that results in death within 2 to 3 years (Swenson 2005). Patients

suffering from indolent lymphoma with high-risk disease features who have early disease recurrence after treatment with rituximab, are refractory to rituximab containing therapies, or are ineligible for more aggressive therapies, represent an unmet medical need. Of patients with DLBCL, 30%-40% relapse after first-line therapy and 10% experience refractory disease (Vaidya 2014; Morrison 2015). For patients with chemosensitive disease, the standard treatment for relapsed/refractory DLBCL is salvage chemotherapy followed by autologous hematopoietic cell transplantation (Philip 1995). Patients with DLBCL who are refractory to frontline therapy, relapse, or are refractory to second line salvage regimens or autologous hematopoietic cell transplantation have an extremely poor prognosis (Gisselbrecht 2010; Crump 2014; Van Den Neste 2016). In these settings, there is no standard treatment. Thus, relapsed/refractory DLBCL represents a significant unmet need.

Treatment with the proposed combination therapy of Hu5F9-G4 and rituximab is not anticipated to pose a significantly increased risk to patients enrolled on this trial compared to the risk of treatment with either agent alone. To date, no significant overlapping toxicities between Hu5F9-G4 and rituximab have been observed in preclinical models. The current Phase 1 clinical trial experience with Hu5F9-G4 (Section 1.2.2) has revealed primarily RBC-mediated toxicities, while rituximab toxicities are generally associated with B-cell depletion, infusion reactions, and/or tumor lysis syndrome.

Given the strong nonclinical evidence of activity for combination therapy with an anti-CD47 antibody and rituximab in both indolent lymphomas and DLBCL, the individual safety profiles of both Hu5F9-G4 and rituximab to date showing tolerability, and the significant unmet medical need for these patient populations, the clinical combination therapy proposed for investigation in this trial has an acceptable risk-benefit profile for the patients proposed for enrollment.

1.6. Dose Rationale

1.6.1. Hu5F9-G4

Hu5F9-G4 selectively eliminates tumor cells while sparing normal cells through blockade of the CD47-SIRPα phagocytic signaling axis. Most normal cells are spared due to the expression of pro-phagocytic signals that are expressed on tumor cells but not normal cells

(Chao 2010b). RBCs are a notable exception because CD47 expression protects RBCs from elimination by macrophages in the reticuloendothelial system. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. Administration of Hu5F9-G4 accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical and clinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger cells.

These nonclinical studies show that the potential for severe anemia is ameliorated by administration of a low priming dose of the antibody that results in mild to moderate anemia and stimulates reticulocytosis. Similar to the Phase 1 studies of Hu5F9-G4, this study will employ a dose strategy utilizing an initial low priming dose followed by a weekly higher maintenance dose. In the Phase 1 trial of Hu5F9-G4 conducted in relapsed/refractory solid tumors (NCT02216409), this dosing strategy was found to result in a mild anemia associated with the priming dose only, and no significant anemia has been observed during maintenance dosing.

In addition to using a priming and maintenance dose strategy, this trial will also investigate the clinical safety and efficacy of a priming, loading, and maintenance dose strategy of Hu5F9-G4 in combination with rituximab. Because CD47 is widely expressed on normal tissues, effective tumor penetration by Hu5F9-G4 requires a dose regimen that ensures adequate saturation of the internal CD47 receptor sink and achieves effective circulating drug levels. In the Phase 1 trial of Hu5F9-G4 in solid tumors, maintenance dose concentrations between 10 and 30 mg/kg weekly were associated with circulating Hu5F9-G4 drug levels that correlated with nonclinical anti-cancer efficacy. This trial will investigate a 1-mg/kg priming dose followed by weekly maintenance doses of 10, 20, or 30 mg/kg. In addition, a regimen of a 1-mg/kg priming dose, followed by 20- or 30-mg/kg twice-weekly loading dose for 1 week, with a maintenance dose of 10, 20, or 30 mg/kg weekly thereafter will be explored. If PK data evaluation suggests that additional twice-weekly loading doses are

warranted beyond Week 2 to Weeks 3, 4, or beyond, the CTSC may evaluate extending the loading dose period for new patient cohorts.

At the discretion of the CTSC, maintenance and loading doses higher than 30 mg/kg may be explored at up to a 50% increment in new dose cohorts using a 3+3 design to further refine the MTD or RP2DS.

1.6.2. Rituximab

Rituximab will be administered at the clinically approved dose concentration of 375 mg/m^2 intravenously. Rituximab will be given in a loading/maintenance dose regimen that includes weekly doses of 375 mg/m^2 on Days 8, 15, and 22 during the first cycle, followed by one dose of 375 mg/m^2 per cycle for up to 6 total cycles. This dose regimen has been selected on the basis of the pharmacokinetic profile of rituximab, as well as evidence that a loading/maintenance regimen enhances efficacy in pretreated NHL patients (Ghielmini 2004).

1.6.3. Starting Dose Rationale

In the Phase 1b part of the trial, the first dose escalation cohort will employ a Hu5F9-G4 dose of 1-mg/kg priming, followed by 10-mg/kg maintenance doses. This starting dose was selected based on safety and pharmacokinetic data obtained in the "First in Human Phase 1 Dose Escalation Trial of Hu5F9-G4 in Patients with Advanced Solid Tumor Malignancies" (NCT02216409). The 1-mg/kg priming followed by 10-mg/kg maintenance dose was demonstrated to be safe and tolerable (with no observed DLTs), and achieved Hu5F9-G4 drug exposure levels associated with nonclinical efficacy. Further dose escalation of Hu5F9-G4 will be employed as indicated in the protocol. Rituximab will be administered at the standard clinical dose concentration of 375 mg/m^2 for all dose escalation cohorts.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives for this study are:

- To investigate the safety and tolerability, and to define the recommended Phase 2 dose for Hu5F9-G4 in combination with rituximab.
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in patients with indolent lymphoma and DLBCL as measured by the overall response rate (ORR).

2.1.2. Secondary Objectives

The secondary objectives for this study are:

- In Phase 1b and 2, to evaluate the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with rituximab
- In Phase 1b and 2, to evaluate the immunogenicity of Hu5F9-G4 in combination with rituximab
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in indolent lymphoma and DLBCL as measured by the duration of response, best overall response, progression-free survival, and overall survival
- To evaluate response rates according to the LYRIC criteria for lymphomas

2.1.3. Exploratory Objective

The exploratory objective for this study is:

- To assess biomarkers of immune cell efficacy and tumor penetration of Hu5F9-G4 in combination with rituximab
- To assess efficacy in molecular subtypes of NHL

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints for this study are:

- Dose-limiting toxicities (Phase 1b only) and adverse events according to NCI CTCAE, Version 4.03 (Appendix B)
- Phase 2: Objective response as defined by the Investigator according to the Lugano Classification for lymphomas (Appendix C)

2.2.2. Secondary Endpoints

The secondary endpoints for this study are:

- Phase 1b and 2: Concentration versus time measurements for Hu5F9-G4 in combination with rituximab and PK parameters including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), terminal half-life ($t_{1/2}$), area under the curve (AUC), clearance (CL), and volume of distribution during the terminal phase (V_z).
- Phase 1b and 2: Anti-drug antibodies to Hu5F9-G4 and rituximab.
- Phase 2: Duration of response (DOR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS).
- Objective response as defined by the Investigator according to the LYRIC criteria for lymphomas.

2.2.3. Exploratory Endpoints

The exploratory endpoints for this study are:

- CD47 receptor occupancy on peripheral RBCs and white blood cells (WBCs), and lymphoma cells, where applicable.
- Pharmacodynamic markers of Hu5F9-G4 biological activity potentially including, but not limited to, circulating cytokine profiles, T-cell receptor sequencing on circulating T cells, mass cytometry (CyTOF)/flow cytometry of circulating leukocytes, and T-cell activation studies.

- In patients undergoing tumor biopsies, Hu5F9-G4 saturation of tumor cells and changes in the tumor microenviroment, including, but not limited to, macrophage and T-cell tumor infiltration.
- In patients undergoing tumor biopsies, correlation of anti-cancer response to molecular subtypes of NHL including, but not limited to, cell-of-origin in DLBCL and BCL2, BCL6, and MYC mutation/expression status.

3. STUDY DESIGN

3.1. Overall Study Design

This trial is an open label, multicenter, Phase 1b/2 trial investigating the combination of Hu5F9-G4 and rituximab in relapsed/refractory B-cell non-Hodgkin's lymphoma. The study will be conducted in 2 parts:

1. Dose escalation Phase 1b open to patients with B-cell non-Hodgkin's lymphoma
2. Phase 2 study with 2 treatment arms (indolent lymphoma and DLBCL), conducted according to a Simon two-stage minimax design

The Phase 1b dose escalation part of the study will be conducted using a standard 3+3 dose escalation design to determine the MTD, if one exists, and to identify recommended Phase 2 doses and schedules (RP2DS) for Hu5F9-G4 in combination with rituximab. Three dose level cohorts are anticipated in the Phase 1b dose escalation part of the study. Additional dose levels may be added, at the discretion of the CTSC, based on emerging PK and safety data. The Phase 2 part of the study will explore the combination of Hu5F9-G4 and rituximab at the RP2DS determined from the Phase 1b in 2 separate cohorts: patients with indolent lymphoma (to include follicular lymphoma and marginal zone lymphoma) and DLBCL. The CTSC may explore alternate RP2DS after the initiation of Phase 2 part of the study, based on emerging clinical, PK and PD data. More than one RP2DS may be defined in this trial, but only one will be formally evaluated in the Phase 2 part of this trial.

3.2. Phase 1b Study Design

3.2.1. Phase 1b Dose Levels

All patients will receive Hu5F9-G4 and rituximab. All patients will receive an Hu5F9-G4 priming dose of 1 mg/kg on Day 1. This will be followed by weekly maintenance doses of 10, 20, 30 mg/kg. In addition, a regimen comprising a 1-mg/kg priming dose, followed by a 20- or 30-mg/kg twice-weekly loading dose for 1 week, and a maintenance dose of 10 or 20 mg/kg weekly thereafter, will be explored based on ongoing PK evaluation and clinical data review by the Clinical Trial Steering Committee (CTSC). The dose of Hu5F9-G4 will be determined by cohort assignment. At the discretion of the CTSC, maintenance and loading

doses higher than 30 mg/kg may be explored at up to a 50% increment in new dose cohorts using a 3+3 design to further refine the MTD or RP2DS.

Rituximab will be administered intravenously at the clinically approved dose concentration of 375 mg/m^2. Rituximab will be given in a loading/maintenance regimen that includes weekly doses of 375 mg/m^2 on Days 8, 15, and 22 during Cycle 1, followed by 1 dose of 375 mg/m^2 on Day 1 of Cycles 2-6. During Cycle 1, Weeks 2-4, and for Cycles 2-6, Hu5F9-G4 and rituximab will be administered on the same day. On days on which both rituximab and Hu5F9-G4 are given, rituximab will be given first. Hu5F9-G4 will be given at least 1 hour after the rituximab infusion is completed.

For the Phase 1b part of the study, the maintenance dose for the first cohort will be 10 mg/kg. Dose escalation of Hu5F9-G4 will proceed through the designated dose levels, as shown in Table 1. Decisions related to dose escalation will be based on the first 4 weeks of treatment in the current cohort, referred to as the "Dose-Limiting Toxicity (DLT) Assessment Period," in conjunction with ongoing assessments for patients on prior cohorts who continued therapy beyond 4 weeks. Decisions regarding additional cohorts to further refine the MTD or RP2DS will be made by the CTSC. Dose Level 3 exploration will based on ongoing PK evaluation and clinical data review, and as decided by the CTSC. If Dose Level 3 is explored, the selection of either 20-mg/kg or 30-mg/kg dosing for both the loading and maintenance doses will be determined by the CTSC based on ongoing PK evaluation and clinical data review. The CTSC may create additional dose cohorts including, but not limited to, dose levels higher than 30 mg/kg at increments of up to 50%, adding intermediate dose steps (e.g., a maintenance dose cohort of 15 mg/kg weekly), or exploring a dose schedule of every 2 or 3 weeks, if supported by emerging PK and clinical data. Up to 10 patients may be added to the any dose cohort previously demonstrated to be safe for the purpose of confirming the tolerability of Hu5F9-G4 and to provide additional PK data to assist in the selection of an RP2D. The decision to add patients will be made by the CTSC.

Table 1. Dose Levels and Schedule

Dose Level	Drug/Dose (IV)	Dose Schedule (Day per 28-day Cycle)	
		Cycle 1	Cycle 2+
Ph 1b: Level 1	Hu5F9-G4 1 mg/kg	Day 1	—
(Prime/maintenance)	Hu5F9-G4 10 mg/kg	Day 8, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8,15 ,22	C2-C6, Day 1
Ph 1b: Level 2	Hu5F9-G4 1 mg/kg	Day 1	—
(Prime/maintenance)	Hu5F9-G4 20 mg/kg	Day 8, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	C2-C6, Day 1
Ph 1b: Level 3	Hu5F9-G4 1 mg/kg	Day 1	—
(Prime/load/maintenance)	Hu5F9-G4 20 or 30 mg/kg[a]	Day 8, 11, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	C2-C6, Day 1
Ph 2	Hu5F9-G4 1 mg/kg	Day 1	—
	Hu5F9-G4 RP2DS from Ph1b	Day 8, (11)[b], 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	C2-C6, Day 1

Abbreviations: CTSC = Clinical Trial Steering Committee; IV = intravenous; Ph = Phase; RP2DS = recommended Phase 2 dose and schedule.
a. 20- or 30-mg/kg loading and maintenance dose will be determined by the CTSC.
b. Additional dosing day included if Dose Level 3 is selected as the RP2DS.

3.2.2. Phase 1b Dose Escalation

Dose escalation in Phase 1b will follow a 3+3 dose escalation design. Three to six patients may be enrolled in each dose cohort. If none of the first 3 patients experiences a DLT, dose escalation will proceed to the next higher dose cohort. If 1 of the first 3 patients experiences a DLT, the cohort will be expanded to 6 patients. If 2 or more of these 6 patients experience DLTs, the MTD dose level will have been exceeded, dose escalation will halt, and additional patients will be treated at a lower dose level. The MTD for the Phase 1b is the maximum dose level at which at least 6 patients are treated with Hu5F9-G4 and rituximab and less than 33% of these patients experience a DLT. The RP2DS will be determined by the CTSC (Section 11.6) based on review of all available safety, efficacy, and PK data. Dose escalation and cohort expansion decisions are reviewed and approved by the CTSC. The CTSC may decide that a fourth patient can be recruited to the same cohort prior to the first 3 patients

completing the DLT assessment period. The rationale for such an addition is to have an extra patient in the cohort should 1 of the 3 earlier patients be unevaluable, or, if a patient within the cohort experiences a DLT, requiring cohort expansion to 6 patients. The first patient in each dose cohort must complete at least 1 week of treatment before additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The third patient in a cohort requires observation for 28 days prior to proceeding to the next dose cohort. The CTSC may add up to 10 patients to any dose level previously determined to be safe to collect additional safety and PK information.

3.2.3. Dose-Limiting Toxicity Evaluation

Dose escalation decisions will be made by the CTSC based on the first 4 weeks of treatment for each patient, referred to as the "Dose-limiting Toxicity (DLT) Assessment Period." The first patient in each dose cohort must complete at least 1 week of treatment before additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The third patient in a cohort must complete the DLT Assessment Period prior to escalating to the next dose level.

3.2.4. Definition of DLT-evaluable Patients

Patients assigned to a particular dose cohort in Phase 1b are considered evaluable for assessment of DLT if EITHER of the following criteria are met during the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of either Hu5F9-G4 or rituximab.
- The patient completed at least 3 infusions of Hu5F9-G4 and 2 infusions of rituximab.

For the Phase 1b part of the study, patients who withdraw before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

3.3. Definition of Dose-limiting Toxicity

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (Appendix B). A DLT is defined as any Grade 3 or greater AE that is assessed as related to study drug (Hu5F9-G4 and/or rituximab) that occurs during the 4-week DLT observation period. DLTs apply only to patients in the Phase 1b part of the study.

The following are exceptions to the DLT definition and are NOT considered a DLT:

- Grade 3 anemia, however, Grade 3 hemolytic anemia that is medically significant, requires hospitalization or prolongation of existing hospitalization, is disabling, or limits self-care activities of daily life (ADLs) is considered a DLT.
- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 1 week and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ Grade 2 with supportive care within 72 hours.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study
- Grade 3 Hu5F9-G4 infusion reactions in the absence of pretreatment
- Grade 3 tumor lysis syndrome or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 within 7 days
- Grade 3 or 4 lymphopenia
- Grade 3 infusion reactions attributed to rituximab; an infusion reaction can only be attributed to rituximab alone if the infusion reaction occurs after the start of rituximab infusion but prior to Hu5F9-G4 infusion on days where rituximab and Hu5F9-G4 are both dosed

3.4. Phase 2 Study Design

For the Phase 2 part of the study, the loading and/or maintenance dose for each arm will be determined by the Phase 1b MTD or RP2DS (see Table 1). Once the Phase 1b dose escalation phase of the trial is completed and an RP2DS determined, the CTSC will open the Phase 2 part of the study. For the Phase 2 part of the study, patients may be enrolled simultaneously without an observation time between patients. Patients in the Phase 2 part will be enrolled in either an indolent lymphoma arm or a DLBCL arm. Treatment for patients in both of these arms will be conducted according to a Simon two-stage minimax design. After the appropriate number of initial-stage patients in each arm have been enrolled and followed for at least 8 weeks, an efficacy analysis will be performed as described in the Statistical Analysis Plan (SAP). The CTSC will convene to review and approve proceeding with full accrual of either or both arms, or terminate the study according to the pre-specified Simon two-stage minimax design stopping rules described in Section 11.11. Full accrual in either arm may be opened earlier by the CTSC at any point at which sufficient anti-cancer activity is observed.

3.5. Number of Sites

Approximately 16 sites located in the US and United Kingdom will be included in this trial. Additional sites may be included based on enrollment and study timelines.

3.6. Estimated Study Duration and End of Study

It is anticipated that this study will take approximately 22 months to complete.

Subject participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined. Treatment with Hu5F9-G4 may be continued until an unacceptable drug related toxicity occurs or until disease progression. Post treatment, subjects will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Interim study database lock may be implemented at the discretion of the CTSC once all Phase 2 patients enrolled have achieved at least 1 tumor efficacy assessment.

The end of the study for all patients occurs at the primary completion date, which is defined as the date on which the last patient completes follow-up for safety, disease progression or survival, or when the CTSC decides to end the study.

4. SUBJECT SELECTION AND ENROLLMENT

4.1. Study Entry Criteria

4.1.1. Inclusion Criteria

1. Adults ≥ 18 years old
2. Phase 1b only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy
3. DLBCL Phase 2 Cohort: Histologically confirmed de novo or transformed DLBCL expressing CD20 by IHC or flow cytometry, refractory to frontline therapy, or relapsed or refractory to second line salvage regimens or autologous hematopoietic cell transplantation
4. Indolent lymphoma Phase 2 Cohort: Histologically confirmed marginal zone or follicular lymphoma (Grade 1-3a) expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least 2 prior lines of therapy
5. Eastern Cooperative Oncology Group (ECOG) Score 0-2 (Appendix D)
6. Disease that is measurable or assessable for response according to Lugano Classification for lymphomas (Appendix C)
7. Laboratory measurements, blood counts:

    - Hemoglobin ≥ 9.5 g/dL
    - Absolute neutrophil count (ANC) ≥ 1.0×10^9/mL
    - Platelets ≥ 50×10^9/mL

8. Laboratory measurements, hepatic function:

    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN)
    - Bilirubin < 1.5 × ULN or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent

9. Laboratory measurements, renal function:

   - Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) > 40 mL/min/1.73 m^2

10. Negative urine or serum pregnancy test within 30 days before enrollment and within 72 hours before the first administration of Hu5F9-G4 for women of childbearing potential.
11. Females of childbearing potential must be willing to use 1 highly effective method of contraception during and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9-G4, whichever occurs later (Section 9.3.1.8)
12. Males must be willing to use 1 effective method of contraception during the study and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9-G4, whichever occurs later, if the partner is a female of childbearing potential
13. Subject has provided informed consent
14. Must be willing and able to comply with the clinic visits and procedures outlined in the study protocol
15. Phase 2 only: Willing to consent to 1 mandatory pre-treatment and 1 on-treatment tumor biopsy, unless determined to not be feasible by the Investigator (reasons include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues)

4.1.2. Exclusion Criteria

1. Patients with active brain metastases (patients with stable treated central nervous system [CNS] lesions who are off corticosteroid therapy for at least 3 weeks are not considered active)
2. Prior anti-cancer therapy including chemotherapy, hormonal therapy, and investigational agents within 2 weeks or within at least 4 half-lives prior to Hu5F9-G4 dosing (up to a maximum of 4 weeks), whichever is longer. In all situations, the maximum required washout period will not exceed 4 weeks prior to the day of first treatment with Hu5F9-G4.

   NOTE: Low dose steroids (oral prednisone or equivalent ≤ 20 mg per day), localized

non-CNS radiotherapy, previous hormonal therapy with LHRH agonists for prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion.

3. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV)
4. RBC transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening and prior to enrollment to meet the hemoglobin inclusion criteria.
5. History of hemolytic anemia or Evans syndrome in the last 3 months
6. Positive Direct Antiglobulin Test (DAT)
7. Prior treatment with CD47 or SIRPα-targeting agents
8. Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancy for which patients are not on active anti-cancer therapy, as defined in Exclusion Criterion 2
9. Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients of rituximab listed in Appendix A
10. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, severely immunocompromised state, and congestive heart failure NYHA Class II-IV.
11. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent
12. Pregnancy or active breastfeeding

4.2. Patient Screening and Enrollment Procedures

All patients who enter the screening period for the study, which starts when the patient signs the informed consent form, receive a unique subject identification number before any study procedures are performed. This number is used to identify the patient throughout the clinical

trial and must be used on all study documentation related to that patient, including if a patient is rescreened.

Patient screening laboratory assessments may be repeated beyond the initial screening assessments within the 30-day screening period. Patients who screen fail may undergo repeated screening if the patient's medical condition has changed.

All patients who provide informed consent must be registered in the electronic data capture (EDC) system, including any screen failures.

A patient is defined as enrolled in the study once all eligibility criteria have been satisfied and the Sponsor has approved the cohort or study arm assignment. After signing the informed consent, eligible patients are expected to receive the first dose of Hu5F9-G4 (Study Day 1) within 30 days.

4.3. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the Institutional Review Board/Research Ethics Committee (IRB/REC)-approved informed consent form (ICF) prior to participation in any study specific procedure. Data from assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period. The participant must receive a copy of the signed and dated consent documents. A signed copy (in paper or electronic format) of the consent documents must be retained in the medical record or research file.

4.4. Registration Process

Patient will be assigned the subject identification number at the time of consent. The site will register the patient via interactive web response technology (IWRS) with the Sponsor or representative within 2 days of consent.

Prior to being assigned a dose cohort or treatment arm, subjects must have signed the informed consent and satisfied all of the eligibility criteria. Once a subject has been assigned

to a dose cohort, they will be considered enrolled. The Investigator and clinical team will determine the eligibility of the patient. The Sponsor will review the inclusion/exclusion worksheet prior to dose cohort assignment.

5. STUDY DRUG INFORMATION

Detailed instructions for Hu5F9-G4 and rituximab preparation and handling are provided in the Pharmacy Manual.

5.1. Hu5F9-G4

5.1.1. Physical Description of Study Drug

The active pharmaceutical ingredient (API) is Hu5F9-G4, a humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce Fab arm exchange. It comprises a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid heavy gamma chains and two identical 219 amino acid kappa light chains. Hu5F9-G4 targets the human CD47 antigen. Hu5F9-G4 drug product is a sterile, clear, colorless, preservative-free liquid intended for intravenous (IV) infusion.

Hu5F9-G4 API is manufactured under current Good Manufacturing Practices.

Hu5F9-G4 is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies.

Additional details about Hu5F9-G4 are provided in the Pharmacy Manual.

5.2. Rituximab

5.2.1. Physical Description of Study Drug

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen (Appendix A). Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration.

Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL),

sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5. Diluted solutions should be stored refrigerated (2°C−8°C).

Rituximab vials (100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials) are stable at 2°C−8°C (36°F−46°F). Rituximab vials should be protected from direct sunlight.

Diluted rituximab solution should be stored at 2−8°C because there is no preservative. The diluted solution is stable for 24 hours at 2°C−8°C.

6. TREATMENT PLAN

6.1. Study Drug Administration

The dose of each study drug will be calculated based on actual weight at enrollment (using weight obtained either at Screening or on Day 1) and remains constant throughout the study, unless there is a > 10% change in weight from baseline. Modifications to the study drug doses administered should be made for a > 10% change in body weight and according to local and regional prescribing standards. Dose modifications for changes in body weight < 10% may be made according to local institutional guidelines.

In addition, a 90-minute rituximab infusion may be given as an alternative to standard rituximab infusion times for the Cycle 2 rituximab dose and beyond, if in accordance with local clinical guidelines.

All patients will receive an Hu5F9-G4 priming dose of 1 mg/kg on Day 1. The duration of the infusion of the priming dose will be 3 hours (± 30 minutes). For the priming dose, patients should be premedicated with acetaminophen 650 mg and oral or intravenous diphenhydramine 25-50 mg, or comparable regimen. The priming dose will be followed by either a weekly maintenance dose or twice a week loading doses for 1 week, then a weekly maintenance dose. For the first maintenance Hu5F9-G4 dose administration or first Hu5F9-G4 loading dose administration in the loading dose cohort, patients should be premedicated with acetaminophen 650 mg and oral or intravenous diphenhydramine 25-50 mg, or comparable regimen. Premedication is not required for subsequent maintenance or loading dose administrations unless prior Grade 3 infusion reactions occur. (See Section 6.2.2.2, Management of Infusion Reactions). The weekly maintenance dose schedule may be changed to every 2 or 3 weeks by the CTSC, based on PK and clinical data review. The duration of the infusion of the maintenance dose or loading dose will be 2 hours (± 10 minutes). The first maintenance dose (or loading dose) will be administered starting on Day 8, after the completion of the first dose of rituximab. When both study drugs are given on the same visit day, Hu5F9-G4 will be administered at least 1 hour after the completion of rituximab administration.

For the loading dose cohort (Cohort 3), the loading doses will be administered on Days 8 and 11 (± 1 day), with the maintenance dose administered on Day 15 and repeated weekly thereafter.

All patients should be monitored for 1 hour post-infusion for Cycle 1. Post-infusion monitoring should begin after the last study drug is given. Post-infusion monitoring is not required for doses after Cycle 1, Day 22. Patients who experience any treatment-related AEs during the observation period should be further monitored, as clinically appropriate.

Patients will receive a rituximab dose of 375 mg/m^2 given intravenously starting on Day 8, followed by Days 15 and 22. Starting at Cycle 2, rituximab will be given on Day 1 of each cycle up to Cycle 6.

6.2. Dose Delays, Dose Modifications, and Safety Management Guidelines

6.2.1. Dose Reductions and Delay Guidelines

6.2.1.1. Hu5F9-G4

Dose modification or dose delay of Hu5F9-G4 may not occur for patients in the initial 28-day DLT assessment period in the Phase 1b part of the study or for the first cycle for patients in the Phase 2 part of the study. After the initial 28-day treatment period for evaluation of DLTs, Hu5F9-G4 may be withheld if treatment-emergent Hu5F9-G4-related AEs occur, which include all AEs that constitute a DLT, as defined in Section 3.3. Hu5F9-G4 may be re-introduced at a 50% dose reduction if the severity has recovered to Grade 0-1 within 4 weeks and in the absence of disease progression. With 2 exceptions, patients who experience a DLT will have their treatment held for up to 4 weeks to allow sufficient time for recovery, but may restart dosing at a lower dose level if they still meet study eligibility criteria. Patients who experience a DLT of either hemolytic anemia or Grade ≥ 4 non-hematological toxicity will not restart Hu5F9-G4 and will be withdrawn from study drug treatment. Data from patients who restart dosing after the recovery period will not contribute to the MTD evaluation at the lower dose level. Treatment delays of more than 4 weeks (such as for an unrelated medical condition with expected recovery) must be approved by the CTSC.

Interruption of Hu5F9-G4 Treatment

Treatment interruption for up to 2 weeks will be allowed after the start of Cycle 3 at the discretion of the Investigator and with Sponsor approval. An interruption is defined as a non-protocol-specified interruption from treatment, assessments, and procedures. Patients with an interruption of longer than 2 weeks (2 weeks is maximum allowed for an elective drug holiday) or a treatment delay of longer than 2 weeks or more must be "re-primed" by receiving the priming dose of 1 mg/kg IV over 3 hours (± 30 minutes) again prior to resuming the assigned maintenance treatment dose. For patients on a priming/maintenance/loading dose cohort who have an interruption, the maintenance dose will be resumed after re-priming.

Maintenance Dose Schedule Modification

Patients who have completed at least 8 weeks on weekly maintenance therapy may stay at the same infusion dose but may have their Hu5F9-G4 schedule of administration extended to every 2 or 3 weeks, if supported by PK data and approved by the CTSC.

Intra-patient Dose Escalation

When an RP2DS has been determined, patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their maintenance dose escalated to the dose level that has been previously determined to be safe in this study, at the discretion of the Investigator and the CTSC.

6.2.1.2. Rituximab

Administration, Hypersensitivity, and Infusion Reactions

Available at the bedside prior to rituximab administration should be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions. Premedication with an antihistamine and acetaminophen/paracetamol is required prior to rituximab dosing, in accordance with local best practices. Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hour. If hypersensitivity or infusion-related events do not occur, infusion rate may be escalated in 50-mg/hour

increments every 30 minutes, to a maximum of 400 mg/hour. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms resolve. Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hour, and increased at 30-minute intervals by 100-mg/hour increments to a maximum of 400 mg/hour. If, in accordance with local clinical guidelines, a 90-minute rituximab infusion is given and the patient experiences an infusion reaction, refer to local prescribing information for infusion adjustments (Appendix A).

During the rituximab infusion, the patient should be monitored until the infusion is discontinued according to standard practice guidelines for rituximab. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after 1 hour of observation, the intravenous line may be discontinued. Additional details about rituximab infusion are provided in Appendix A.

Presence of Circulating Lymphoma Cells

In patients with evidence of circulating lymphoma cells in the peripheral blood, it is recommended that the initial infusion rate be reduced to 25 mg/hour as these patients may have increased propensity to infusion reactions and tumor lysis syndrome.

Cardiovascular

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions, including arrhythmias and angina, and who have had recurrences of these events during rituximab therapy, should be monitored throughout the infusion and immediate post-infusion period.

Tumor Lysis Syndrome

Rituximab rapidly decreases the number of benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first

rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy was administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

6.2.2. Specific Safety Management Guidelines

6.2.2.1. Rituximab

Safety management guidelines for rituximab are described in Section 6.2.1.2.

6.2.2.2. Hu5F9-G4

Hemagglutination and Microangiopathy

In the Phase 1 trial experience with Hu5F9-G4 in solid tumors and AML, agglutination of RBCs has been observed on peripheral smear. Hu5F9-G4-related microangiopathy is a possible sequela of hemagglutination, however it has not been observed in the current Phase 1 clinical trials to date. In addition, AEs may be associated with findings of hemagglutination. Monitoring of hemagglutination/microangiopathy includes physical exam assessments, CBCs, peripheral smears, serum chemistries, and D-dimer testing as outlined in the schedule of assessments (SOA). Peripheral smears will be read by local sites with reporting of RBC agglutination, spherocytosis, and evidence of RBC destruction (e.g., schistocytosis, fragments) when present. The presence or absence of hemagglutination and/or microangiopathy on peripheral smear will be incorporated into the AE severity grading for hemagglutination and microangiopathy, as described below. The degree of peripheral smear findings will be quantified according to the appropriate scale (Appendix E) for sites that have the capability to do so, but it is not required. Peripheral smear slides will be retained by the Sponsor and stored for future analyses. AEs relating to hemagglutination and microangiopathy will be graded for toxicity according to the scale below.

AE severity grading for hemagglutination and microangiopathy

Grade 1: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are asymptomatic or mild, not requiring intervention

Grade 2: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that require medical intervention

Grade 3: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care ADLs

Grade 4: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that are life threatening or require urgent intervention

Grade 5: Evidence of hemagglutination and/or microangiopathy on peripheral blood smear AND associated clinical sequelae that result in death

Anemia, Blood Cross-Matching, and Packed Red Blood Cell Transfusion Procedures

Hu5F9-G4 binds to red cells and leads to erythrophagocytosis. This, coupled with anemia from other causes in patients with cancers, means that care has to be taken with red blood cell cross matching and packed red blood cell transfusions. There is a possibility that treatment with Hu5F9-G4 may obscure assessment of red blood cell phenotyping, although this has not been observed in patients to date.

During the screening period prior to initiation of Hu5F9-G4 therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and Direct Antiglobulin Test (DAT) will be performed for each patient as described in Section 7.3.4. This, together with using the prior phenotype, will facilitate allocation of properly cross-matched blood should a blood transfusion be warranted.

For patients after exposure to Hu5F9-G4:

1. ABO, Rh, and DAT may be pan-reactive due to Hu5F9-G4 binding to red cells. Therefore, if a non-urgent transfusion is ordered by the Investigator, perform the following procedures:

i. Front Type: EGA Treat cells (×2 Maximum) and Warm Wash ×4 (Minimum) with 0.9% Saline.
ii. Back Type: Perform reverse anti-human globulin for both A and B.
iii. If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.

2. Antibody screen
   If a pan-agglutinin/warm autoantibody is present in low ionic strength solution (LISS), repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

Blood Components for Transfusion

For all elective red cell transfusions, leukocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all the specified blood groups proves impractical (e.g., for MNS), local sites will decide on the best matched donor units to be used. Cytomegalovirus (CMV) matching (i.e., CMV seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

If the cross match is incompatible, the RBC units that are Coombs crossmatch-incompatible will be selected (e.g., phenotype-matched or least incompatible) for issue at the discretion of the local site's Transfusion Service Medical Director or equivalent person, where available. Such instances will be documented in the Transfusion Service medical exception log, along with consent signatures obtained from ordering physicians according to best practices in blood bank policies and procedures.

For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rhesus negative units if phenotyped units are not available.

Blood plasma therapy will be blood-type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

Management of Infusion Reactions

Infusion-related reactions are defined by the NCI CTCAE (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances." (See Appendix B.) For the purposes of this study, the time frame for infusion reaction assessment is the 24-hour period beginning from the start of the infusion. Recommendations for the management of infusion-related reactions are provided below.

- For Grade 1 signs and symptoms, described as mild transient reaction; infusion interruption not indicated; intervention not indicated:
    - Remain at bedside and monitor patient until recovery from symptoms.
- For Grade 2 symptoms, described as infusion interruption indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); and prophylactic medications indicated for ≤ 24 hours:
    - Stop the Hu5F9-G4 infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500-750 mg oral acetaminophen.
    - Remain at bedside and monitor patient until resolution of symptoms.
    - Corticosteroid therapy may also be given at the discretion of the Investigator.
    - If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
    - If no further complications occur after 60 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
    - If symptoms recur, stop infusion and disconnect patient from the infusion apparatus.
    - No further Hu5F9-G4 will be administered at that visit.
    - The amount of Hu5F9-G4 infused must be recorded on the case report form (CRF).
    - Patients who experience a Grade 2 infusion reaction during the post-infusion observation period that does not resolve during that time should be observed until

the AE resolves or stabilizes, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the AE.

- For Grade 3 or Grade 4 signs and symptoms, where:
  Grade 3 is described as prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates).
  Grade 4 is described as life-threatening consequences; urgent intervention indicated.

  - Immediately discontinue infusion of Hu5F9-G4.
  - Begin an IV infusion of normal saline, and treat the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
  - The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
  - Patients who have Grade 4 infusion reactions occurring with the first dose will be permanently discontinued from study treatment.
  - Patients who experience Grade 3 infusion reactions must be given premedication prior to subsequent doses. In this setting, premedication with acetaminophen (650 mg PO), diphenhydramine (25-50 mg PO or IV) and dexamethasone (4-20 mg IV), or comparable regimen, is recommended.
  - Patients who receive premedication and still have a Grade 3 or 4 infusion reaction will be permanently discontinued from study treatment.
  - Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
  - All patients with Grade 3 or greater infusion related reactions will be observed until the AEs resolve or stabilize, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

Tumor Lysis Syndrome

In the case of evidence for tumor lysis syndrome associated with Hu5F9-G4, patients will be admitted to the hospital as clinically indicated. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes. Study treatment should be held until the patient's condition resolves or stabilizes.

6.3. Prohibited Medication

Hu5F9-G4

Anti-cancer therapies (including chemotherapy, hormonal therapy, and investigational agents) are prohibited within 2 weeks or within at least 4 half-lives (up to a maximum of 4 weeks), whichever is longer, before Hu5F9-G4 administration and during the study. However, low dose steroids (oral prednisone or equivalent ≤ 20 mg per day), localized non-CNS radiotherapy, previous hormonal therapy with LHRH agonists for prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion of patients from the study and are permitted during the study.

Rituximab

Because the safety of immunization with live viral vaccines following Rituximab therapy has not been studied, vaccination with live virus vaccines is not recommended while the patient is being treated with Rituximab or while peripherally B cell depleted (Appendix A).

6.4. Duration of Therapy

Rituximab will be given for a total of 6 cycles. Hu5F9-G4 will also be given for a total of 6 cycles. In addition, patients who have not demonstrated disease progression may continue to receive Hu5F9-G4 therapy beyond 6 cycles.

All patients will have a repeat anti-drug antibody testing for Hu5F9-G4 during the Safety Follow-up Visit (30 days ± 7 days after the last dose of study drug) to assess for positive immunogenicity.

6.5. Patient Completion of the Study

Patients are expected to remain on study until completion of Cycle 6. Patients who have not demonstrated disease progression may continue to receive Hu5F9-G4 therapy beyond 6 cycles. Patients are considered to have completed active study participation when they finish the Safety Follow-up Visit 30 days (± 7 days) after their last dose of study drug.

Following the Safety Follow-up Visit, patients with ongoing drug-related AEs and serious adverse events (SAEs) will be followed for safety. If any study drug-related AEs or SAEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least every 4 weeks until resolution to baseline or stabilization of these events, unless the patient starts another anti-cancer treatment. Follow-up will stop when a patient begins another anti-cancer treatment.

All patients, including those who discontinue study treatment early, will be followed for response until disease progression and for survival for 5 years from the date of enrollment. For any patient who dies during this period, the cause of death must be reported to the Sponsor. All patients must also be followed through completion of all study treatment.

Patients are considered to have completed study participation when they are no longer followed for disease progression or survival.

7. STUDY EVALUATIONS

7.1. Schedules of Assessment for Phase 1b and Phase 2

The SOA for the Phase 1b part of the study is presented in Table 2. The SOA for the Phase 2 part of the study is provided in Table 3. Unless otherwise noted, procedures are to be completed prior to any study drug infusion. Table 4 details post-treatment assessments for both phases of the study. The SOAs for PK assessments are presented in Table 5 for Phase 1b and in Table 6 for Phase 2, correlative studies for both phases are presented in Table 7, and CD47 receptor occupancy assessments are presented in Table 8 for Phase 1b and in Table 9 for Phase 2.

Table 2. Schedule of Assessments, Phase 1b

Examination		Study 5F9003, Phase 1b: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**±2**											
Assessments																										
Informed consent	X																									
Demographics	X																									
Medical and cancer history	X																									
Inclusion/exclusion criteria	X																									
Enrollment cohort assignment [a]	X																									
Pregnancy test [b]	X	X[c]													X								Q8W			
CBC with differential, platelets, reticulocytes [b]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral blood smear [d]	X	X[b]	X	X			X	X	X						X											
Serum chemistry [b]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous [b]	X	X	X	X			X																			
Haptoglobin, D-dimer, thrombin time, and plasma fibrinogen [b]	X	X	X	X			X	X							X				X				X			
PT/INR, aPTT [b]	X			X					X						X				X				X			
Type and screen (ABO/Rh), DAT	X																									

Examination		Study 5F9003, Phase 1b: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**±2**											
Assessments																										
Lymphocyte subset analysis		X							X						X				X				X			
Urinalysis [b]	X						X																			
Correlative studies [e]		X					X		X						X[q]											
Pharmacokinetics [f]		X		X	X	X	X	X	X	X	X	X	X	X	X				X				X[o]			
Antidrug antibodies		X		X					X						X				X				X			
CD47 receptor occupancy [g]		X	X	X		X	X	X	X			X			X								X[o]			
ECOG performance status	X	X		X			X	X	X						X				X				X			
Vital signs [h]	X	X	X	X		X[n]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [i]	X	X[b]		X			X		X				X		X		X		X				X			
DLT assessment [j]									X																	
Visual acuity	X	X[b]		X			X	X	X						X				X				X			
ECG [k]	X	X		X					X																	
Tumor/lymph node biopsy, optional (within the screening period and ± 1 week for later samples)	X											X														
Diagnostic imaging [l]	X														X								Q8W[p]			
Bone marrow biopsy [m]	X														X											

Examination		Study 5F9003, Phase 1b: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**±2**											
Assessments																										
Response assessment															X								Q8W[p]			
Adverse events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Study Drug Administration																										
Rituximab				X			X	X	X						X				X				C5+C6			
Hu5F9-G4		X		X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 (Loading Dose Cohort only)		X		X[n]		X[n]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Examination		Study 5F9003, Phase 1b: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																							
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**		**±1**				**±2**											
Assessments																										

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle; CBC = complete blood count; DLT = dose-limiting toxicity; ECG = electrocardiogram; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; RO = receptor occupancy; SC = Screening; W = week(s).

a. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
b. Pre-infusion assessments tests may be collected up to 72 hours before study drug administration during the initial dose, however with subsequent doses pre-infusion assessments maybe collected up to 24 hours before study drug administration.
c. May use screening pregnancy test performed within 72 hours of first dose.
d. Peripheral blood smear slides will be retained and sent to the Sponsor for storage. Details are provided in Section 7.3.7.
e. Time point details for correlative studies are provided in Table 7.
f. Time point details for PK studies are provided in Table 5.
g. Time point details for RO studies are provided in Table 8.
h. Prior to infusion and within 30 minutes after the end of each infusion. Details are provided in Section 7.3.2.
i. Full PE at screening, symptom-directed PE thereafter.
j. DLT will be assessed through the first 4 weeks of the study.
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to rituximab infusion and within 30 minutes of the end of Hu5F9-G4 infusion. (Section 7.3.3)
l. (± 1 week) See Section 7.3.5 Diagnostic Imaging for details.
m. Bone marrow biopsy will be performed for response assessment in patients with known bone marrow disease involvement and to confirm CR at any response assessment, where clinically appropriate, and at disease progression.
n. Loading Dose Cohort only: Loading doses of Hu5F9-G4 administered on Days 8 and 11 may be shifted ± 1 day, provided that loading doses are not administered on consecutive days.
o. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).
p. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. After Cycle 3, window is ± 14 days.
q. To be performed with Diagnostic Imaging (± 7 days from Cycle 3, Day 1).

Table 3. Schedule of Assessments, Phase 2

Examination		Study 5F9003, Phase 2: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Informed consent	X																							
Demographics	X																							
Medical and cancer history	X																							
Inclusion/exclusion criteria	X																							
Enrollment cohort assignment [a]	X																							
Pregnancy test [b]	X	X[c]											X								Q8W			
CBC with differential, platelets, reticulocytes [b]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral blood smear [d]	X	X[b]	X	X			X	X	X				X											
Serum chemistry [b]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous [b]	X	X	X	X			X																	
Haptoglobin, D-dimer, thrombin time and plasma fibrinogen [b]	X	X	X	X			X	X					X				X				X			
PT/INR, aPTT [b]	X			X					X				X				X				X			
Type and screen (ABO/Rh), DAT	X																							
Lymphocyte subset analysis		X							X								X				X			

Examination		Study 5F9003, Phase 2: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Urinalysis [b]	X						X																	
Correlative studies [e]		X							X				X [q]											
Pharmacokinetics [f]		X		X			X		X	X	X		X				X				X [o]			
Antidrug antibodies		X		X					X				X				X				X			
CD47 receptor occupancy [g]		X		X					X	X			X				X				X [o]			
ECOG performance status	X	X		X			X	X	X				X				X				X			
Vital signs [h]	X	X	X	X		X [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [i]	X	X [c]		X			X	X	X		X		X		X		X				X			
Visual acuity	X	X [c]		X			X	X	X				X				X				X			
ECG [k]	X																							
Tumor/lymph node biopsy, mandatory (within the screening period and ± 1 week for later samples)	X									X														
Diagnostic imaging [l]	X												X								Q8W [p]			
Bone marrow biopsy [m]	X												X											
Response assessment													X								Q8W [p]			
Adverse events	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	——►
Concomitant medications	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	——►

Examination		**Study 5F9003, Phase 2: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab**																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Study Drug Administration																								
Rituximab				X			X	X	X				X				X				C5+C6			
Hu5F9-G4		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 (Loading Dose Cohort only)		X		X^n		X^n	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Examination		Study 5F9003, Phase 2: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DLT = dose-limiting toxicity; ECG = electrocardiogram; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; RO = receptor occupancy; SC = screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
b. Pre-infusion assessments tests may be collected up to 72 hours before study drug administration during the initial dose, however with subsequent doses pre-infusion assessments may be collected up to 24 hours before study drug administration.
c. May use screening pregnancy test performed within 72 hours of first dose.
d. Peripheral blood smear slides will be retained and sent to the Sponsor for storage. Details are provided in Section 7.3.7.
e. Time point details for correlative studies are provided in Table 7.
f. Time point details for PK time points are provided in Table 6.
g. Time point details for RO are provided in Table 9.
h. Prior to infusion and within 30 minutes after the end of each infusion. Details are provided in Section 7.3.2.
i. Full PE at screening, symptom-directed PE thereafter.
j. Not applicable to Phase 2.
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to rituximab infusion and within 30 minutes of the end of Hu5F9-G4 infusion. (Section 7.3.3)
l. (± 1 week) Details are provided in Section 7.3.5 Diagnostic Imaging.
m. Bone marrow biopsy will be performed for response assessment in those patients with known bone marrow disease involvement and also performed to confirm CR at any response assessment, where clinically appropriate, and at disease progression.
n. Loading Dose Cohort only: Loading doses of Hu5F9-G4 administered on Days 8 and 11 may be shifted ± 1 day, provided that loading doses are not administered on consecutive days.
o Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).
p. Response assessments may be adjusted by ± 4 weeks to coordinate with treatment cycle timing.
q. To be performed with Diagnostic Imaging (± 7 days from Cycle 3, Day 1).

Table 4. Post-treatment Assessments, Phase 1b and Phase 2

Examination	Study 5F9003, Post-treatment Assessments: Phase 1b/2 NHL Trial with Hu5F9-G4 + Rituximab			
Cycle (28-day Cycles)	**End of Treatment**	**Safety Follow-up**	**Long-term Follow-up**	**Survival Follow-up**
	Within 7 Days of EOT Decision	30 Days After Last Dose	Until disease progression or new anti-cancer therapy	Up to 60 months from LSE
Visit Window		**± 7 Days**	**± 14 Days**	**± 1 Month**
Assessments				
Serum or urine pregnancy test		X		
CBC w diff, platelets, retics		X		
Peripheral Blood Smear		X		
Serum chemistry		X		
Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen		X		
PT/INR, aPTT		X		
Lymphocyte subset analysis		X		
Pharmacokinetics	X[a]	X		
Antidrug Antibodies	X	X		
CD47 Receptor Occupancy	X			
ECOG performance status		X		
Vital signs		X		
Physical examination (symptom directed)		X		
Correlative studies	X		X[b]	
Tumor/lymph node biopsy, optional			X[b]	
Diagnostic Imaging		X[c]	Q8W	
Bone marrow biopsy (for response assessment if disease involvement)			X[b]	
Response assessment	X[d]	X[c]	Q8W	
Adverse events	X	X[b]		
Concomitant medications	X	X		
Survival follow-up and new anti-cancer therapy				Q3M

Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; EOT = end of treatment; LSE = last subject enrolled; M = month(s); NHL = non-Hodgkin's lymphoma; PT/INR = prothrombin time/international normalized ratio; W = week(s).

a. Required only in Phase 1b.
b. Details provided in Section 7.6.
c. Required only if not completed within the last 4 weeks.
d. Details provided in Section 7.9.

Table 5. Pharmacokinetic Assessments, Phase 1b

Phase 1b	Cycle 1						Cycle 2						C3-C6	C7+	EOT
Day	**1**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**1**	**—**
Pre-rituximab infusion (within 12 hr)		X			X	X	X						X[a]		X
Pre-Hu5F9-G4 infusion (within 12 hr)	X	X[b]			X[b]	X[b]	X[b]			X[b]	X[b]	X[b]	X[a,b,]	X[a]	X
1 hr (± 15 min) after Hu5F9-G4 infusion	X	X			X	X	X			X			X[a]	X[a]	
24 hr (± 8 hr) after most recent Hu5F9-G4 infusion (Cycle 1 Day 8 or Cycle 2 Day 1)			X					X							
72 hr (± 12 hr) after most recent Hu5F9-G4 infusion (Cycle 1 Day 8 or Cycle 2 Day 1)				X[c]					X						
1 hr (± 15 min) after rituximab infusion		X					X						X		

Abbreviations: C = cycle; EOT = end of treatment; hr = hour(s); min = minute(s).

a. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).
b. Sample to be collected before rituximab infusion when applicable.
c. Sample to be collected before Hu5F9-G4 dose when applicable to Loading Dose Cohort.

Table 6. Pharmacokinetic Assessments, Phase 2

Phase 2	Cycle 1			Cycle 2			C3-C6	C7+
Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**
Before rituximab infusion (within 12 hr)		X	X	X		X	X[b]	
1 hr (±15 min) after rituximab infusion		X	X	X			X[b]	
Before Hu5F9-G4 infusion (within 12 hr)	X	X[a]	X[a]	X[a]	X	X	X[a,b]	X[b]
1 hr (±15 min) after Hu5F9-G4 infusion	X	X	X	X	X	X	X[b]	X[b]

Abbreviations: C = cycle; EOT = end of treatment; hr = hour(s); min = minute(s).
a. Sample to be collected before rituximab infusion when applicable.
b. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).

Table 7. Correlative Studies Sample Time Points, Phases 1b and 2

Time Points	Cycle 1		Cycle 2	Cycle 3	EOT	LTFU
Day	**1**	**15**	**1**	**1**		
Phase 1b						
Pre-study drug infusion[a,b]	X	X	X	X[c]	X	
1 hour (± 15 min) after Hu5F9-G4 infusion	X					
Phase 2						
Pre-study drug infusion[a,b]	X		X	X[c]	X	
1 hour (±15 min) after Hu5F9-G4 infusion	X					
Phase 1b and Phase 2						X[d]

Abbreviations: EOT = end of treatment; LTFU = long-term follow-up; min = minute(s).
a. Sample to be collected before rituximab infusion when applicable.
b. Pre-infusion laboratory tests may be collected up to 72 hours before study drug treatment.
c. To be performed with Diagnostic Imaging (± 7 days from Cycle 3, Day 1).
d. Obtained at the time of disease progression or relapse.

Table 8. CD47 Receptor Occupancy Sample Time Points, Phase 1b

Time Points	Cycle 1						Cycle 2		Cycle 3+	EOT
Day	**1**	**2**	**8**	**11**	**15**	**22**	**1**	**8**	**1**	**—**
Pre-study drug infusion [a]	X		X	X[c]	X	X	X	X	X[b]	X
1 hr (± 15 min) after Hu5F9-G4 infusion	X		X	X[c]	X	X			X[b]	
24 hr (± 8 hr) after Hu5F9-G4 infusion on Day 1		X								
72 hour (±-12 hr) after Hu5F9-G4 infusion on Day 8				X[c]						

Abbreviations: D = day; EOT = end of treatment; hr = hour(s); min = minute(s).
a. Sample to be collected before rituximab infusion when applicable.
b. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).
c. 72 hour samples to be collected for non-loading dose cohort only. Predose and 1-hr samples to be collected for patients in the loading dose cohort only.

Table 9. CD47 Receptor Occupancy Sample Time Points, Phase 2

Time Points	Cycle 1		Cycle 2		Cycle 3+	EOT
Day	**1**	**8**	**1**	**8**	**1**	**—**
Pre-study drug infusion[a]	X	X	X	X	X[b]	X
1 hr (± 15 min) after Hu5F9-G4 infusion	X	X	X	X		

Abbreviations: EOT = end of treatment; hr = hour(s); min = minute(s).
a. Sample to be collected before rituximab infusion when applicable.
b. Starting with Cycle 5, samples to be collected every other cycle (e.g., Cycle 5, 7, and so on).

7.2. Screening Assessments

7.2.1. Screening Assessments

The following procedures are to be completed during the screening period:

- Confirmation that the Informed Consent Form has been signed and consent process has been documented.
- Confirmation that all inclusion/exclusion criteria have been met.
- Demographic data including sex, date of birth, age, race, and ethnicity.
- Vital signs: blood pressure, heart rate, respiration, temperature, height and weight.
- Physical examination (complete) and ECOG (Appendix D).
- Visual acuity assessment using a Snellen chart or comparable eye chart.
- Single electrocardiogram (ECG).
- Relevant medical and cancer history will be completed through consent (all findings recorded on the medical history eCRF).
- Documentation of concomitant and prior medications.
- Adverse Events related to Screening procedures and any serious adverse event reporting.
- Reporting of adverse events caused by a protocol-mandated intervention (e.g., AEs related to invasive procedures such as biopsies)
- Urine or serum pregnancy test (in women of childbearing potential).
- Local laboratory values, including hematology, serum chemistry, and urinalysis (Table 10).
- Local laboratory Type and Screen (ABO/Rh) and DAT. (Details are provided in Section 6.2.2.2 and Section 7.3.4).
- Local laboratory Peripheral Blood Smears. (Details are provided in Section 7.3.7).
- Tumor/lymph node biopsy: optional for Phase 1b, mandatory for Phase 2.
- Bone marrow biopsy for patients with disease involvement prior to treatment: mandatory for Phase 1b and Phase 2.
- Diagnostic imaging (Historic imaging may be used for screening if performed within 30 days of the first dose of Hu5F9-G4. Details are provided in Section 7.3.5).

Screening assessments will be completed within a 30-day screening period prior to the enrollment. Patients may qualify for enrollment at any time during the 30-day screening period. Assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period.

7.3. Description of Study Procedures

Study procedure timing is provided in Section 7.1, Schedule of Assessments Tables.

7.3.1. Physical Examination/Visual Acuity

Complete physical exam should be performed at Screening. Thereafter, symptom-directed physical exams are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and central nervous system (CNS). For patients who experience a change in visual acuity of 3 lines or more on a Snellen chart or comparable eye chart, an ophthalmologist should be consulted for additional evaluation.

7.3.2. Vital Signs

Vital signs should include heart rate, respiratory rate, blood pressure, temperature, and weight. Height should be recorded during Screening only. Weight should be recorded during Screening and on Day 1 of each cycle. Vital signs are to be recorded prior to infusion and within 30 minutes of the end of infusion. On visits that include infusions of both study drugs, vital signs are to be recorded prior to infusion and within 30 minutes of the end of infusion of each study drug.

7.3.3. Electrocardiographs

One ECG will be performed at screening. Triplicate ECGs will be performed before the rituximab dose (within 2 hours of infusion) and at peak concentration within 30 minutes of the end of Hu5F9-G4 infusion for Phase 1b only.

7.3.4. Type and Screen (ABO/Rh), DAT

Due to the risk of developing anemia, blood phenotyping, type and screen (ABO/Rh), and direct antiglobulin test (DAT) should be performed at screening before exposure to Hu5F9-G4. Full phenotyping should be performed if the patient has not been transfused in

last 3 months and should include ABO, Rh, D, C, E, Kell, Kidd, Duffy, MNS, and antibody screen. Treatment with Hu5F9-G4 may make phenotyping difficult due to expected coating of the RBC membrane. In addition, patients who experience a drop in hemoglobin to below 9 g/dL at any time, or patients in whom clinical findings indicate a possible need for transfusions, it is recommended but not required that a Type and Screen and DAT be performed.

7.3.5. Diagnostic Imaging

Appropriate cancer staging assessments should be performed (e.g., fluorodeoxyglucose [FDG] positron emission tomography/ computed tomography [PET/CT] for patients with lymphoma). Imaging assessments should be conducted according to Lugano Classification for lymphomas and lymphoma response to immunomodulatory therapy criteria (LYRIC), when appropriate (Appendix C). The same imaging modality used at screening should be used throughout the study whenever possible. It is understood that some circumstances may require a different imaging modality. An alternate imaging modality is acceptable and may be performed at the investigator's discretion.

7.3.6. Pregnancy Test

Pregnancy tests are required only for women of childbearing potential (excluding patients who are post-menopausal with absence of menses for at least 1 year and/or surgically sterilized). A urine or serum pregnancy test is required at screening and within 72 hours before administration of Hu5F9-G4 on Day 1. The Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before administration of Hu5F9-G4. Pregnancy tests will be performed every 8 weeks.

7.3.7. Peripheral Blood Smear Assessment

Peripheral smears will be collected prior to selected study drug infusions and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. These samples should be collected from the arm contralateral to the arm being used for drug infusion, if possible. Peripheral smears will be evaluated according to the guidelines provided in Appendix E. For patients undergoing blood transfusion, samples for peripheral smears will be collected 1 hour (± 30 minutes) after completion of the transfusion.

Peripheral smear slides will be collected, shipped to the Sponsor, and stored for future analyses.

7.3.8. Adverse Events

At each visit all AEs observed by the Investigator or reported by the patient that occur after the first dose of study drug through 30 days after the last dose of study drug, are to be reported using the applicable electronic case report form (eCRF; Section 9). AEs that occur prior to assignment of study treatment that are assessed as related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies) must also be reported.

Following 30 days after the last dose of investigational product, investigators should report any SAEs that are felt to be related to Hu5F9-G4.

7.3.9. Concomitant Medications

All concomitant medications taken by a patient while on study are to be documented. Changes in baseline concomitant medication information is to be collected after consent through the end of 30-day Safety Follow-up Period. Concomitant medication associated with procedure-related AEs will be captured from the time of informed consent on. Information to be collected includes therapy name, indication, dose, unit, frequency, route, start date, and stop date, and are to be reported using the applicable eCRF.

7.4. End-of-treatment Visit

End of Treatment visit to be completed within 7 days of the decision to end treatment with Hu5F9-G4.

- Pharmacokinetic sample collection (for Phase 1b only). Separate PK samples will be collected for Hu5F9-G4 and rituximab.
- Antidrug Antibodies
- CD47 Receptor Occupancy
- Correlative Studies
- Response Assessment (See Section 10.1.1)
- Adverse Events
- Concomitant Medications

7.5. Safety Follow-up Visit

Safety Follow-up visit to be completed within 30 days (±7 days) after the last dose of Hu5F9-G4 or prior to beginning a new anti-cancer therapy, whichever is earlier.

- Local Laboratory
    - CBC (w diff, platelets, retics)
    - Serum chemistry
    - Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen
    - PT/INR, aPTT
- Local laboratory Peripheral Blood Smear
- Serum or urine pregnancy test (in women of childbearing potential)
- Pharmacokinetic sample collection. Separate PK samples will be collected for Hu5F9-G4 and rituximab.
- Antidrug Antibodies
- ECOG performance status (Appendix D)
- Vital signs
    - blood pressure
    - heart rate
    - respiration
    - temperature
    - weight
- Physical examination (symptom-directed)
- Diagnostic Imaging. (± 7 days), if not performed within the last 4 weeks. (Section 7.3.5)
- Response Assessment (± 7 days), if not performed within the last 4 weeks. (Section 10.1.1)
- Adverse Events
- Concomitant Medications

7.6. Long-term Follow-up

Patient will be followed until disease progression or until they begin a new anti-cancer therapy.

- Diagnostic imaging (± 14 days), every 8 weeks (Section 7.9).
- Bone marrow biopsy (for response assessment if disease involvement (± 14 days) for confirmation of complete response (CR) (Section 7.9)
- Response Assessment (± 14 days), every 8 weeks (Section 10.1.1)

For patients who achieve a partial response (PR) or CR while on study, a repeat disease assessment will be obtained at the time of disease progression or relapse whenever possible. These assessments include:

- Blood sample for correlative studies, optional tumor/lymph node core, or excisional biopsy
- An additional (optional) bone marrow aspirate and biopsy for correlative studies, for patients who receive a bone marrow aspirate and biopsy for response assessment

Following the Safety Follow-up Visit, patients with ongoing drug-related AEs and SAEs will be followed for safety. If any study drug-related AEs or SAEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least every 4 weeks until resolution to baseline or stabilization of these events, unless the patient starts another anti-cancer treatment. Follow-up will stop when a patient begins another anti-cancer treatment.

7.7. Survival Follow-up

All patients who permanently discontinue all study treatment for disease progression (according to the Lugano Classification or LYRIC criteria for lymphomas; Appendix C), clinical progression, unacceptable toxicity, partial withdrawal of consent, or administrative decision will be contacted during a clinic visit or by telephone to assess survival, disease progression (if not documented previously), and the commencement of new cancer therapy

following the last administration of study drug. Patients will be contacted every 3 months (± 1 month) from the date of the Safety Follow-up Visit, until 60 months from the date that the last patient is enrolled into the study or full withdrawal of consent. For any patient who dies during this period, the cause of death must be reported to the Sponsor.

7.8. Safety Assessments

Analytes to be assessed by the local laboratory or specialty laboratories are presented in Table 10.

Table 10. Laboratory Analyte Listing for Safety and Other Assessments

Chemistry	Hematology	Urinalysis	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus [b] Glucose BUN or Urea Creatinine Uric acid [b] Total bilirubin Direct bilirubin Indirect bilirubin Alkaline phosphatase LDH AST (SGOT) ALT (SGPT) Alkaline Phosphatase	RBC Hemoglobin Hematocrit Platelets WBC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes Reticulocytes Haptoglobin D-Dimer PT, aPTT, and INR Thrombin Plasma fibrinogen Peripheral Blood Smear	Red blood cell Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity	Pregnancy Correlative studies [a] Pharmacokinetics [a] CD47 Receptor Occupancy [a] Anti-drug Antibodies [a] Type and Screen (ABO/Rh), DAT Lymphocyte subset analysis

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SOA = Schedule of Assessments; WBC = white blood cells

a. These assays may be performed at a specialty laboratory.
b. Refer to Section 7.1 SOA tables for collection time points.

7.9. Efficacy Assessments

Patients will be assessed for response using the Lugano Classification and LYRIC criteria for lymphomas (Appendix C). The first response assessment will occur at Cycle 3 Day 1 (± 7 days). Subsequent response assessments will occur every 8 weeks and may be adjusted by ± 4 weeks to coordinate with treatment cycle timing. Response assessment will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 7 days or at a prior response assessment that documented PD.

For patients with disease involvement in the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at first response assessment on Cycle 3 Day 1. In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a CR, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the investigator's discretion.

7.9.1. Immunogenicity

Peripheral blood for immunogenicity assessments for anti-drug antibodies against Hu5F9-G4 will be collected on Days 1 and 8 before infusion and then approximately every 4 weeks from Day 1, and 30 days after the last dose. When collected on the day of study drug dosing, the blood sample must be collected pre-dose. A precise, sensitive, and reproducible qualitative electrochemiluminescent (ECL) assay will be used to measure antibodies to Hu5F9-G4 in serum samples. This assay has been validated in cynomolgus monkey serum and has been used for the IND-enabling non-human-primate toxicology study for Hu5F9-G4 (PR013/20044845) and in Phase 1 clinical trials with Hu5F9-G4 (Studies SCI-CD47-001 and SCI-CD47-002). For patients who have tested positive for antidrug antibodies (ADA), the impact of ADA on PK, safety, and biologic activity will be assessed. Neutralizing antibodies to Hu5F9-G4 will also be assessed for patients who test positive for ADA. Antidrug antibodies to rituximab may be assessed if the CTSC or Sponsor determines such testing is needed.

7.10. Pharmacodynamic and Biomarker Assessments

CD47 Receptor Occupancy

Testing for CD47 receptor occupancy on select target cells enables pharmacodynamic testing of Hu5F9-G4 to inform both safety and efficacy parameters. First, the degree of saturation of CD47 receptors on red blood cells serves as a pharmacodynamic assessment for degree of anemia. Second, CD47 receptor occupancy on WBCs and circulating or bone marrow-resident lymphoma cells provides information on the level of CD47 saturation of the internal CD47 tissue sink and drug exposures on tumor cells, respectively. Samples for CD47 receptor occupancy studies in the peripheral blood will be collected according to the schedule presented in Table 8 and Table 9. In settings in which there is disease involvement of the bone marrow, a bone marrow aspirate sample will be obtained on Cycle 3 Day 1 (± 7 days) for response assessment. For patients who have consented, a separate bone marrow aspirate sample will be collected at the same time to assess CD47 receptor occupancy in the bone marrow, additional correlative study assessments, and biobanking. CD47 receptor occupancy studies, as described in Section 7.1 SOA tables, will performed in both the Phase 1b and Phase 2 parts of the study. However, at the discretion of the CTSC, CD47 receptor occupancy studies may not be performed in Phase 2 if sufficient data are collected in the Phase 1b part of the study.

Correlative Blood Samples

Correlative studies will be performed on peripheral blood samples to determine the biologic activity of Hu5F9-G4 in combination with rituximab on circulating immune cells and molecular subtypes of NHL. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating T cells, and other studies. Where applicable, blood samples will be collected according to the schedule presented in Table 7. If at any point in the study the CTSC determines that sufficient correlative data have been generated, it may halt the collection and analysis of these samples.

Measurement of Plasma Cytokines

Cytokine release by immune cells is one surrogate measure of immune cell activation (including T cells and macrophages). Since Hu5F9-G4 activates both macrophages and

T cells, it is hypothesized that a specific cytokine profile relating to immune cell activation will correlate with clinical response to therapy. The platform allows for a high-throughput analysis of a multitude of cytokines and chemokines with high sensitivity (Swartzman 1999). This predefined multiplex panel of human cytokines will be measured from a small thawed vial of plasma, detecting and quantifying the soluble proteins and peptides which help control cellular function. The observed systemic biochemical changes in the blood may provide a further correlate with tumor progression and therapeutic response and help provide a much broader understanding of disease. A specific focus on cytokines involved in macrophage, dendritic cell, and T-cell activation/repression will be explored given the nonclinical mechanism for Hu5F9-G4 to engage these immune cells.

Characterization of Circulating T Cells

In nonclinical studies, macrophage-mediated phagocytosis of tumor cells by an anti-CD47 antibody leads to cross-presentation of antigens and subsequent T-cell activation (Tseng 2013). It is therefore predicted that Hu5F9-G4 administration may lead to T-cell activation in patients. Peripheral blood samples will be collected and T-cell activation/repression markers/studies may be performed on CyTOF, in vitro T-cell activation assays, and T-cell receptor sequencing. Additional peripheral blood mononuclear cells (PBMCs), serum, and plasma at the specified time points will also be cryopreserved and biobanked for future analyses.

Tumor and Bone Marrow Biopsies

Tumor and bone marrow biopsies will be collected to investigate study drug modulation of the tumor environment, penetration into the tumor, and correlation of anti-cancer response to molecular subtypes of NHL. Analysis of immune cell composition within these tumor samples will be performed by IHC, immunofluorescence, or other similar assay to include macrophage, lymphocyte, and other immune cell subsets. Markers of immune cell activation may also be investigated by flow cytometric analysis or other similar method, in addition to frequency of immune cell infiltrates within the tumors. The degree of immune cell infiltrates pre- and post-treatment will be correlated with response rates as described in the SAP. It is

hypothesized that higher levels of macrophage and/or T-cell infiltration in the tumor either pre-treatment or post-treatment will correlate with a clinical response to therapy.

From the tumor biopsies obtained according to Section 7.1, detection of the presence of study drug (Hu5F9-G4 and/or rituximab) saturation in tumors will be determined. Saturation of tumor cells with Hu5F9-G4 and/or rituximab will be determined by measuring levels of Hu5F9-G4, human IgG4, and/or anti-rituximab antibodies. Analysis of Hu5F9-G4 penetration into tumor tissue will be analyzed in paired treatment biopsies obtained from study patients. The proportion of patients with Hu5F9-G4 presence in tumor tissues as measured by IHC (1+ or greater) will be calculated for each expansion cohort independently, and the 95% confidence intervals (CI) for each will be determined. The degree of study drug tumor saturation pre- and post-treatment will be correlated with response rates as described in the SAP.

From the same tumor biopsies, DNA/RNA sequencing may be performed to assess for genomic mutations, gene expression changes, cell-of-origin status, and presence of neoantigens pre and post initiation of therapy. Paired peripheral blood samples may also be used for sequencing to aid in determining germline status. Remaining tumor samples at the specified time points may be cryopreserved and biobanked for future analyses.

Tumor and bone marrow biopsies will be obtained in both Phase 1b and Phase 2 parts of the study. In the Phase 1b part, tumor and bone marrow biopsies are optional. For the Phase 2 part, tumor and bone marrow biopsies are mandatory, unless the Investigator determines that it is not feasible. Reasons for biopsy not being feasible could include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues. A tumor (lymph node) biopsy will be obtained during the screening period and on Cycle 2 Day 8 (± 7 days). Core biopsies will be collected at these time points. Where possible, excisional biopsies are preferred over core biopsies. In cases in which there is known disease involvement of the bone marrow, a bone marrow aspirate and biopsy will be conducted prior to treatment and on Cycle 3 Day 1 (± 7 days) for response assessment. A separate aspirate sample is also to be collected at the same time to assess CD47 receptor occupancy in the bone marrow, additional correlative study assessments, and biobanking. Additional histology slides of the bone

marrow core biopsy are to be collected for exploratory studies. It is not necessary to collect a separate core biopsy from the one collected for clinical diagnosis.

In addition, for patients who achieve a PR or CR while on study, a repeat tumor biopsy and bone marrow aspirate/biopsy (where applicable) will be collected at the time of disease progression or relapse whenever possible. This will be a core or excisional biopsy that is optional, based on patient consent. A separate (optional) bone marrow aspirate and biopsy will be collected from patients for whom there is evidence of bone marrow disease at time of progression/relapse or evidence of bone marrow disease pre-treatment.

8. STUDY DISCONTINUATION

8.1. Withdrawal of Subjects from Study Drug Treatment

Patients (or a legally acceptable representative) may decline to continue receiving study drug at any time during the study. The patient's health and welfare is the primary consideration in any determination to discontinue study drug treatment. Patients who withdraw from study drug during the treatment period should be encouraged to return for an End of Treatment visit for evaluation of safety within 7 days of the decision to end Hu5F9-G4 treatment. The studies to be performed at end of treatment are listed in the Schedules of Assessments, Section 7.1. It is strongly encouraged that patients to return for their Safety Follow-up Visit 30 days (± 7 days) after their last dose of study drug. The Safety Follow-up Visit assessments are described in Table 4. All patients who withdraw from study drug treatment will be followed for disease response and survival.

Reasons for patient withdrawal from study drug treatment may include, but are not limited to, the following:

- Patient's request, with or without a stated reason
- Evidence of tumor progression
- Clinically significant deterioration of the patient's condition including clinically significant study drug-related adverse events
- Adverse Event
- Noncompliance
- Pregnancy

8.2. Withdrawal of Subjects from Study

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. Patients (or a legally acceptable representative) may decline to continue receiving study drug and/or other protocol-required therapies or procedures at any time during the study. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data may be included after withdrawal of consent. The Investigator is to discuss with the patient the

appropriate procedures for withdrawal from the study. The Investigator or Sponsor has the right to discontinue any patient from study participation.

Reasons for patient discontinuation may include, but are not limited to, the following:

- Patient's request, with or without a stated reason
- Protocol-specified reason
- Clinically significant deterioration of the patient's condition
- Noncompliance
- Sponsor's discretion
- Lost to follow-up

8.3. Study Termination

Forty Seven Inc. reserves the right to terminate the study at any time. Both Forty Seven Inc. and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The Investigator is to notify the IRB/independent ethics committee (IEC) in writing of the study's completion or early termination and send a copy of the notification to Forty Seven Inc.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters and Definitions

Safety assessments will consist of recording all AEs and SAEs; protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Forty Seven Inc. or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive, and/or local regulatory requirements.

Forty Seven Inc. or its designee is responsible for reporting, in writing, all unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event.
Forty Seven Inc. or its designee will report other relevant SAEs associated with the use of the study medication to the regulatory agencies and competent authorities within 15 calendar days of notification.

9.1.1. Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with a patient's cancer that were not present prior to the AE reporting period (see Section 9.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)

- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies)
- Preexisting medical conditions, judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

9.1.2. Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death at the time of the event; it does not refer to an event which might hypothetically have caused death if it were more severe)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the Investigator (i.e., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the eCRF, SAEs are reported on the SAE report form, and reported to the Sponsor in accordance with protocol instructions. SAEs must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware.

9.2.1. Adverse Event Reporting Period

After signing of informed consent, but prior to initiation of study medications, all SAEs in addition to AEs caused by a protocol-mandated intervention will be collected (e.g., AEs related to invasive procedures such as biopsies).

After initiation of the study treatment, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or the study discontinuation/early termination visit, whichever is later. After this period, Investigators are to report only SAEs that they assess to be related to Hu5F9-G4 treatment.

See Section 9.5 for post-treatment AE reporting.

9.2.2. Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

> "How have you felt since your last clinic visit?"
> "Have you had any new or changed health problems since you were last here?"

9.2.3. Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF and SAEs will be recorded on the SAE report form.

For each AE and SAE, the Investigator will make an assessment of seriousness (see Section 9.1.2 for seriousness criteria), severity (Table 11), and cause. A causality assessment

will be made for Hu5F9-G4 and rituximab. Table 12 provides guidance for assessing the causal relationship to the investigational product.

The AE grading (severity) scale NCI CTCAE v4.03 (Appendix B) will be used for AE reporting as shown in Table 11. Regardless of severity, some events may also meet regulatory serious criteria (see Section 9.1.2).

Table 11. Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to adverse event	

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03

a. Use the alternative descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE listing.

To ensure consistency of causality assessments for either study drug, Investigators should apply the following general guidelines:

Table 12. Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Abbreviations: AE = adverse event; SAE = serious adverse event.
Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, Forty Seven Inc. or its designee, will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

9.3. Procedures for Recording Adverse Events

9.3.1. Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs and SAEs. Avoid colloquialisms and abbreviations.

A separate Adverse Event eCRF should be used for each medical concept that needs to be recorded. Drug-related AEs and SAEs should be recorded as either attributed to Hu5F9-G4, rituximab, or both drugs.

9.3.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on a separate eCRF. If a diagnosis is subsequently established, it should be reported to Forty Seven Inc. according to the CRF Completion Guidelines.

9.3.1.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE on the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

9.3.1.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

9.3.1.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be

recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

9.3.1.5. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 9.2.1), regardless of attribution, will be recorded on an eCRF and SAE report form, and expeditiously reported to the Sponsor. This includes death attributed to progression of disease.

If the death is attributed to progression of disease, record "disease progression" as the SAE term on the SAE Report Form.

When recording a death on an eCRF or SAE Report Form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept.

9.3.1.6. Worsening of Disease

Worsening of and/or progression of disease should not routinely be recorded as an AE or SAE if not resulting in death. These data will be captured as efficacy assessment data. However, worsening and/or progression of lymphoma should be recorded as an SAE if fatal (Section 9.3.1.5) or if the Investigator assesses the disease progression to be related to study treatment.

9.3.1.7. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

9.3.1.8. Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

Pregnancy

Any pregnancy occurring in a patient or a patient's partner during treatment with either study drug or within 6 months of last study drug administration must be reported to the Sponsor's safety CRO (Section 9.4.2) within 24 hours of the site staff becoming aware of it, using a Pregnancy Notification Form (provided in the Investigator Trial File). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner.
The safety CRO will follow-up all pregnancies for the pregnancy outcome through the Investigator, using a Pregnancy Outcome Form. Data will be collected regarding the pregnancy, fetal status, and neonate status, and in the event that the neonate has abnormalities at birth, additional data will be collected for the infant regarding those abnormalities. Spontaneous abortion should always be classified as serious (as the Sponsor considers this medically significant), recorded on a Serious Adverse Event Form (SAE Form), and expeditiously reported to the Sponsor as described in Section 9.4.2.
Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be recorded and reported as an SAE.

Female patients of childbearing potential who have a negative serum or urine pregnancy test before enrollment must agree to use 1 of the following highly effective forms of contraception (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly):

- Bilateral tubal occlusion
- Vasectomized partner

- Intra-uterine device (IUD)
- Intra-uterine hormone-releasing system (IUS)
- Oral combined hormonal contraception (estrogen and progestogen containing) associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Abstinence

  Defined as: refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, post-ovulation methods), nor is the withdrawal method (coitus interruptus). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Contraception must be effective at the first administration of Hu5F9-G4, throughout the trial, and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9-G4, whichever occurs later.

Male patients with partners of child-bearing potential must agree to take measures not to father children by using 1 of the following forms of effective contraception:

- Methods Considered Highly Effective
  (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly)

  - Vasectomy
  - Partner with bilateral tubal occlusion
  - Abstinence

    Defined as: refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, post-ovulation methods), nor is the withdrawal method (coitus interruptus). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

- Method Not Considered Highly Effective
  (defined as methods that result in a failure rate of more than 1% per year)

  - Condom plus spermicide

Contraception must be effective at the first administration of Hu5F9-G4, throughout the trial, and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9-G4, whichever occurs later.

It should be explained to the patient that if his partner is pregnant or breastfeeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn fetus or the baby being exposed to investigational product.

Overdose

An overdose is a dose higher than that indicated in the protocol, with or without an AE.

Abuse or Misuse

Abuse or misuse of a study drug is use for nonclinical reasons, with or without experiencing an AE.

9.4. Expedited Reporting Requirements for Serious Adverse Events

9.4.1. Reporting Requirements for Fatal/Life-threatening SAEs Related to Investigational Products

Any life-threatening (i.e., imminent risk of death) or fatal AE that occurs while on study should be submitted to the Medical Monitor with written case details on an SAE Form within 24 hours, as described in Section 9.4.2.

Medical Monitor Contact Information for Sites:

Medical Monitor: Mark Chao M.D., Ph.D.
Telephone No.: 1-650-776-7388
Alternate Telephone No.: 1-650-352-4141
email: safety@fortysevenInc.com

Alternate Medical Monitor Contact Information for Sites:

Medical Monitor: Chris Takimoto M.D., Ph.D.
Telephone No.: 1-210-394-9716
Alternate Telephone No.: 1-650-352-4132

9.4.2. Reporting Requirements for All SAEs

Investigators will submit reports of all SAEs, regardless of attribution, within 24 hours according to the instructions provided in the Study Reference Manual.

The Sponsor or designee will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and central IRBs/IECs in compliance with reporting requirements according to local regulations and good clinical practice (GCP).

The investigator is to notify the appropriate local IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from the Sponsor or designee in accordance with local procedures and statutes.

9.5. Type and Duration of Follow-up of Patients after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, are determined to be irreversible by the Investigator, the patient initiates alternate therapy for their cancer, the patient is lost to follow-up, or it has been determined that the study treatment is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF, the SAE report form, and in the patient's medical record to facilitate source data verification (SDV).

The Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

9.6. Post-Study Adverse Events

For patients who discontinue the study treatment and have completed the 30-day safety follow-up visit, Investigators are to report any death, other SAE, or event occurring beyond 30 days following the last administration of Hu5F9-G4 that the Investigator assesses as related to Hu5F9-G4.

Investigators are to report these events as described in Section 9.4.2.

10. MEASUREMENT OF EFFECT

10.1. Anti-cancer Effect – Hematologic Tumors

Patients will be assessed for response using the Lugano Classification and LYRIC criteria for lymphomas (Appendix C). Preliminary efficacy will be assessed by the evaluation of response of target lesions, evaluation of BOR of target lesions from the start of the treatment until disease progression/recurrence, and the duration of response of target lesions. The first response assessment will occur at Cycle 3, Day 1 (± 1 week). Subsequent response assessments will occur every 8 weeks (± 1 week). Response assessment will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 7 days or at a prior response assessment that documented PD. Definitions of response parameters are provided below. For patients with disease involvement in the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at the first response assessment at the beginning of Cycle 3 In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a CR, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

10.1.1. Overall Response Rate

Response rate is determined by Lugano Classification and LYRIC criteria for lymphomas (Appendix C). ORR is defined as PR+CR. Response rates for this endpoint will be defined as those patients who have received Hu5F9-G4 and rituximab at the RP2DS for whom a baseline (before study drug exposure) and the first 8-week (± 1 week) tumor assessment are available.

10.1.2. Best Overall Response

BOR is measured as the best response recorded from start of study treatment until the first date that recurrent or PD is objectively documented.

10.1.3. Duration of Response

DOR is measured from when first response is met (i.e., CR or PR) until the first date that recurrent or progressive disease is objectively documented.

10.1.4. Progression-Free Survival

The length of PFS is defined in whole days as the time from entry into the study until disease progression or death from any cause. Patients who are not observed to progress or die during the course of the trial will be censored at their last known progression-free follow-up date.

10.1.5. Overall Survival (OS)

The length of OS is defined in whole days as the time from entry into the study until death from any cause. Patients who are not observed to die during the course of the trial will be censored at their last known follow-up date.

10.2. Evaluation of Response

Hematologic tumor response and progression will be evaluated in this study using Lugano Classification, reproduced from Cheson 2014 (Appendix C), according to Table 13 below. Immune response will be evaluated using the LYRIC criteria, as described above and in Appendix C; Cheson 2016).

Table 13. Lugano Classification of Response in Non-Hodgkin's Lymphoma

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 13. Lugano Classification of Response in NHL (Continued)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.

For patients staged with PET/CT, focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For patients staged with CT, up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (e.g., hepatic nodules) may be included in the 6 representative, measured lesions.

A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target disease (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites). In patients in whom a discordant histology or malignant transformation is suspected, a PET/CT may identify the optimal site to biopsy for confirmation.

The following modifications to the Lugano Classification will be made for this study protocol:

Bone marrow assessment: For patients with disease involvement of the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at first response assessment at the beginning of Cycle 3. In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a CR, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

Refinement of the Lugano Classification, LYRIC criteria: Based on emerging data in immunomodulatory agents, of which Hu5F9-G4 is one, it appears that these agents may be associated with clinical and imaging findings during treatment suggestive of progressive disease, despite evidence of clinical benefit. Thus, according to the LYRIC criteria, an indeterminant response (IR) criteria will be utilized for response assessment. A patient will be considered to have IR in 1 or more of the 3 following circumstances:

1. Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration [IR(1)]
2. Appearance of new lesions or growth of one or more existing lesion(s) ≥ 50% at any time during treatment; occurring in the context of lack of overall progression (< 50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment [IR(2)]
3. Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number [IR(3)]

For patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the patient should be considered to have true PD if the SPD of target lesion has increased further, with the considerations below:

- In the case of IR(1), the comparison should be between the first IR(1) and the current SPD, with an increase of ≥ 10% constituting PD. In addition, there should be an increase

of ≥ 5 mm (in either dimension) of ≥ 1 lesion for lesions ≤ 2 cm and 10 mm for lesions > 2 cm, to be consistent with the Lugano classification. The 10% threshold is empiric but designed to account for variability in measurement, particularly when taken along with the minimum increase. If the target SPD increase is < 10%, the response would still be categorized as IR(1), and the patient could continue treatment until a subsequent scan shows either true PD [≥ 10% increase from first IR(1) time point and an increase of > 5 mm in either dimension of ≥ 1 lesion] or response (≥ 50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4 to 8 weeks of the original IR(1) time point to ensure absence of significant further increase.

- In the case of IR(2), the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased ≥ 50% from their nadir value (which may precede the IR time point), the patient should be considered to have PD.
- In the case of IR(3), because inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted above.

10.2.1. Assessment of Evaluable Rather Than Measurable Disease

Patients with evaluable but not measurable response will be assessed with the study used to establish evaluable disease at least every 8 weeks.

10.2.2. Assessment of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for PD the smallest measurements recorded since the treatment started.

10.2.3. Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively

documented (taking as reference for PD the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease (SD) is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment began.

10.2.4. Time-to-Progression

The time-to-progression is the time from enrollment until PD is documented according to the Lugano Classification and LYRIC criteria (Appendix C).

11. STATISTICAL CONSIDERATIONS

11.1. Hypotheses

It is hypothesized that the combination of Hu5F9-G4 and rituximab will be safely tolerated and provide improved anti-cancer efficacy over rituximab therapy alone in patients with NHL. These hypotheses are supported by both nonclinical and current clinical data demonstrating a toxicity profile of Hu5F9-G4 that does not appear to overlap with that of rituximab and nonclinical data demonstrating synergistic activity of Hu5F9-G4 with rituximab.

11.2. Study Endpoints

The primary, secondary, and exploratory study endpoints are provided in Section 2.2.

11.3. Number of Patients

The total number of patients included in this trial will be between 57 and 66 patients. For the Phase 1b part, 9 to 18 patients will be enrolled depending on dose escalation and expansion. For the Phase 2 part, a total of 48 patients (24 patients for the indolent lymphoma arm, 24 patients for the DLBCL arm) will be enrolled assuming progression to Stage 2 for both arms.

11.4. Analysis Sets

11.4.1. Phase 1b

DLT Analysis Set

The DLT Analysis Set includes all enrolled subjects who receive at least 1 dose of Hu5F9-G4 or rituximab and have had the opportunity to be followed for the 28-day cycle or have experienced a DLT within 28 days after initiating study drug treatment.

11.4.2. Phase 1b and Phase 2

Efficacy Analysis Set

The Efficacy Analysis Set (EAS) includes all enrolled subjects who receive at least 1 dose of study drug and for whom a baseline and at least 1 post-study drug treatment tumor assessment are available.

The analysis of ORR, BOR, and DOR will be performed on the Efficacy Analysis Set.

Full Analysis Set

The Full Analysis Set includes all enrolled subjects who receive at least one dose of study drug.

The analysis of Safety, PFS, and OS will be performed on the Full Analysis Set.

Per Protocol Analysis Set

The Per Protocol Analysis Set includes all enrolled subjects who do not have any important protocol deviations that might affect the efficacy outcomes.

A sensitivity analysis of ORR may be performed on the Per Protocol Analysis Set.

PK Analysis Set

The PK Analysis Set includes all subjects in the Full Analysis Set from whom PK blood samples are collected during the study and who have measurable concentrations of Hu5F9-G4.

11.5. Sample Size Determination

The overall sample size for this study is estimated to be between 57 and 66 patients. This sample size includes both the Phase 1b and Phase 2 parts of the study. In the Phase 1b part of the study, a standard 3+3 dose escalation design is employed to explore the MTD of the investigational combination. There are 3 dose cohort levels, with an estimated total of 9 to 18 patients in the Phase 1b depending on possible cohort expansion in a 3+3 design. In Phase 1b, patients who are not evaluable for DLT will be replaced. The Phase 2 part of the study includes two arms, enrolling indolent lymphoma or DLBCL, in which sample size

is determined according to a Simon two-stage minimax design. The Phase 2 part of the study will comprise a total of 48 patients (24 with indolent lymphoma, 24 with DLBCL) if both stages of each arm are fully accrued. For Phase 2, the sample size was determined using a one-sided alpha level of 0.10 and a power of 0.80 based on a null hypothesis of 20% response rate compared to an alternative/desired response rate of 40% for indolent lymphoma and a null hypothesis of 20% response rate compared to an alternative/desired response rate of 40% for DLBCL. The null hypothesis response rates of 20% for both indolent lymphoma and DLBCL are based on historical data for single-agent rituximab in the protocol-specified patient populations with modification (Davis 2000; Sehn 2015; Wang 2013).

11.6. Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC. The CTSC will have representation from each participating site in the study. The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol specific amendments, expansion of cohorts, using higher or lower dose levels, defining any new dose cohorts, identification of the recommended dose for Phase 2 trials, and interim efficacy analysis decisions according to the Simon two-stage minimax design. The CTSC will meet at a minimum at the completion of each dosing cohort during dose escalation phase of the trial, at any protocol-specified formal interim analyses, and when emergent critical safety data are reported. The composition, structure, and function of the CTSC are defined in the CTSC Charter.

CTSC decisions in this study are included in the following sections of this document: Section 1.6.1, Hu5F9-G4; Section 3.1; Overall Study Design; Section 3.2.1, Phase 1b Dose Level; Section 3.2.2, Phase 1b Dose Escalation; Section 3.2.3, Dose-Limiting Toxicity Evaluation; Section 3.4, Phase 2 Study Design; Section 3.6, Estimated Study Duration and End of Study; Section 6.1, Study Drug Administration; Section 6.2.1, Hu5F9-G4; Section 7.9.1, Immunogenicity; Section 7.10, Pharmacodynamic and Biomarker Assessments; Section 11.9.2, Additional Secondary Endpoints; and Section 11.11, Interim Analysis.

11.7. Data Monitoring Committee

Data Monitoring Committee functions for this trial will be performed by the CTSC, as defined and described in Section 11.6.

11.8. Analysis of the Conduct of the Study

The CTSC, in conjunction with the Sponsor, will be the main body responsible for the analysis of the conduct of the study, as outlined in the CTSC charter.

11.9. Statistical Methods

All analyses will be descriptive and hypothesis-generating in nature. Descriptive statistics will be provided for all safety and efficacy endpoints.

All analyses will be conducted separately for patients in the Phase 1b and Phase 2 parts of the study. However, safety analyses may be conducted for patients in both Phase 1b and Phase 2. In addition, efficacy analyses will be conducted separately for the 2 cohorts in Phase 2.

For continuous variables, the mean, standard deviation, median, and ranges will be provided. For categorical variables, the frequency and percentage in each category will be provided, along with confidence intervals for primary and secondary efficacy endpoints. For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided. Details regarding the statistical analysis to be conducted, including the handling of missing data and patient withdrawal, will be provided in the SAP.

11.9.1. Efficacy Analyses

11.9.1.1. Primary Efficacy Endpoint: Overall Response Rate

The analysis of ORR will be conducted on the Efficacy Analysis Set. The point estimate of the ORR and the corresponding exact binomial two-sided 95% confidence interval will be generated. A sensitivity analysis of ORR will be conducted on the Per Protocol Analysis Set if more than 10% of patients in the Efficacy Analysis Set are excluded from the Per Protocol Analysis Set.

11.9.1.2. Secondary Efficacy Endpoints

Duration of Response

The analysis of DOR will be conducted on the responders only.

The KM estimate and corresponding two-sided 95% interval for the median and quartiles will be provided. The KM plot may also be provided.

Best Overall Response

The analysis of BOR will be conducted on the Efficacy Analysis Set using the same methods as the analysis of ORR.

Progression-Free Survival and Overall Survival

The analysis of PFS and OS will be conducted on the Full Analysis Set.

The KM estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided.

11.9.2. Additional Secondary Endpoints

Pharmacokinetic Analyses

PK analysis will be conducted for Hu5F9-G4 and rituximab on the PK Analysis Set. Based on the distinct MOAs of Hu5F9-G4 and rituximab, overlapping drug PK interactions are not expected. Thus, samples for PK analysis for rituximab will be banked and will be conducted based on CTSC recommendation.

The pharmacokinetic analysis set (PAS) consists of all patients who have at least 1 blood sample that provides evaluable PK data. The PAS will be used for summaries of PK concentration data, and PK parameters. Individual patients may be removed from the estimation of particular PK parameters based on the number of available blood samples for them. These patients will be identified at the time of analysis.

The PK parameters to be assessed are presented in Table 14.

Table 14. Noncompartmental Pharmacokinetic Parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (t_{last}) (mass × time × volume - 1)
AUC_{inf}	The AUC from time zero to infinity (mass × time × volume - 1)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount × time × volume - 1)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume - 1)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume × time - 1)
V_z	The apparent volume of distribution during terminal phase (associated with λz) (volume)

PAS will be used in all PK data analysis and PK summary statistics, except for the dose-exposure analysis for Phase 1.

Pharmacokinetic variables:

The following pharmacokinetic parameters will be determined by profile using non-compartmental method(s) for Hu5F9-G4:

- AUC_{inf}
- $AUC_{0\text{-}168h}$
- C_{max}
- T_{max}
- $T_{1/2}$
- CL
- V_z

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Descriptive statistics of all PK parameters will include arithmetic and geometric mean, median, SD, CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be provided for this parameter.

Summary statistics will be presented for Hu5F9-G4 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration-versus-time profiles and mean concentration-versus-time profiles will be generated.

Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as zero in summary statistics, and reported as is in data listings. Any missing PK parameter data will not be imputed.

Dose Proportionality

The analysis of dose proportionality will be conducted for the AUC and C_{max} of Hu5F9-G4 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in a summary table.

Immunogenicity Analyses

The rate and magnitude of anti-Hu5F9-G4 antibody positivity will be evaluated for individual patients, for all patients in the Phase 1b and 2 parts of the trial, and for the pooled patient population. Exploratory evaluations may be conducted to determine the relationship between immunogenicity assay positivity and one or more safety, PK, or efficacy parameters (for example, drug clearance, AEs, tumor response). Immunogenicity analysis will also be performed for rituximab. However, it is not expected that Hu5F9-G4 will impact the immunogenicity of rituximab and vice versa.

Immunogenicity: Exposure and/or Adverse Event Relationship

The concentration-versus-adverse event/immunogenicity relationship will be explored graphically, tabulated, and, if appropriate, evaluated by a mixed effects model in order to

characterize a relationship between the changes from screening immunogenicity presence and serum concentration of Hu5F9-G4.

In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy, and biomarker parameters) may be evaluated. This will be done in 2 steps. First, a descriptive analysis will be performed graphically between immunogenicity change from screening values and major safety, efficacy, and biomarker parameters (either as categories or continuous variables). Second, for any potential correlation identified, further investigation will be performed using a mechanism-based modeling approach, as appropriate.

11.9.3. Safety Analyses

The statistical analysis of safety data will be conducted for patients in the FAS and will include patients with non-missing data for the particular safety endpoint being analyzed. Safety variables may include, but are not limited to: DLTs, treatment-emergent adverse events (TEAEs; AEs worsening or occurring during or after a patient's first exposure to study drug), vital signs, physical examinations, laboratory tests, receptor occupancy, and anti-drug antibody assessments.

Data will be presented by Phase 1b dose cohort and Phase 2 arm. Some safety data may be summarized over all Phase 1b dose cohorts and across both Phase 1b and Phase 2 parts. Data may be graphed, summarized, or listed, depending on the amount of data to be reported. Where relevant, safety data will also be presented by the study day/study day interval corresponding to dose administrations within each dose cohort.

11.9.3.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later and the NCI CTCAE v 4.03 (Appendix B) will be used to grade severity of adverse events and laboratory toxicities. Patient incidence of TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized using Investigator assessment of the relationship to study drug (related or not related). SAEs, including deaths, will be summarized and/or listed for each dose cohort and for all dose cohorts combined. These events will also be summarized by Phase 2 arm (indolent

lymphoma and DLBCL) and across all Phase 2 patients. TEAEs resulting in withdrawal from study drug or further study participation will be tabulated and/or listed. DLTs will also be listed.

Adverse events that occurred during screening but before exposure to study drug will be reported in the AE line listings and appropriately identified as non-TEAEs.

Adverse events and SAEs occurring during screening will be reported separately for patients who were screened but not entered into the study with line listings and/or summary tables, along with relevant demographic data collected.

11.9.3.2. Analysis of Other Safety Endpoints

For select laboratory parameters, changes of laboratory values over time, grade shifts in laboratory value from baseline to worst on-study value and Grade 3 or higher laboratory toxicities will be summarized. The number and incidence of subjects developing receptor occupancy and anti-drug antibodies at any time will be summarized. Vital signs and physical exam will be summarized at select time points. Details will be provided in the SAP.

11.10. Handling of Missing Data

Details regarding the handling of missing data will be described in the SAP.

11.11. Interim Analysis

A Simon two-stage minimax design (Simon 1989) will be used in the Phase 2 part of the study. In accordance with this design, after 14 patients in the indolent lymphoma arm and/or 14 patients in the DLBCL arm are evaluable for response assessment, the CTSC will convene and provide recommendations to the Sponsor to proceed with full accrual of either or both arms, or terminate the study according to the pre-specified Simon two-stage minimax design stopping rules. For the indolent lymphoma arm, the study will proceed to accrue the second stage if there are ≥ 3 objective responses in 14 patients. In this case 10 additional patients will be enrolled. These rules are based on the combination of Hu5F9-G4 and rituximab achieving a desired 40% ORR compared to the null hypothesis response rate of 20%, which represents single-agent rituximab activity in the protocol-specified indolent lymphoma population. For the DLBCL arm, the study will proceed to accrue the second stage if there

are ≥ 3 objective responses in 14 patients. These results are based on the combination of Hu5F9-G4 and rituximab achieving a desired 40% objective response rate compared to the null hypothesis response rate of 20% which represents single-agent rituximab activity in the protocol-specified DLBCL population.

If, at the interim analysis, > 33% of patients in a Phase 2 arm experience any Grade 3 or greater AE that is assessed as related to study drug (Hu5F9-G4 and/or rituximab) and results in permanent discontinuation, withdrawal, or death, then that Phase 2 arm will be stopped. If either > 4 of 14 patients in either the indolent lymphoma arm or > 5 of 15 patients in the DLBCL arm experience a serious adverse event at least possibly related to the study drug, the corresponding study arm will be stopped for unacceptable toxicity. The trial may also be stopped at any time if the CTSC deems that there is an unacceptable safety risk to patients with the study treatment. The trial may otherwise proceed to accrue the second stage if the response criteria described above are met.

12. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1. Compliance Statement

This study will be conducted in accordance with the protocol and with US Food and Drug Administration (FDA) and the ICH GCP guidelines, the Declaration of Helsinki, and any applicable local health authority and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

To the extent applicable, all references to the FDA, Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations (CFR), ICH, GCP, and the like shall be interpreted as also referring to any corresponding requirements of local regulatory agencies, regulations, and laws. If there is any discrepancy between FDA, ICH, and local requirements, the most stringent standard shall apply.

12.2. Investigator Responsibilities

As required by FDA regulation (21 CFR Part 56) and ICH guidelines for GCP, the Investigator at each study site must obtain IRB/IEC review and approval of the study protocol, ICFs, patient recruitment materials, and any other pertinent documents before any study-related activities involving patients are performed.

As required in 21 CFR Part 50 and ICH guidelines for GCP, the Investigator or designee must comply with the informed consent process, and ensure that each patient enrolled in this clinical study understands the information presented in the IRB/IEC approved ICF and agrees voluntarily to participate in the clinical study.

The Investigator or designee must submit to the IRB/IEC any written safety report or update (e.g., amended Investigator's Brochure or safety amendments and updates) provided by the Sponsor or representative, according to the IEC specific reporting requirements.

The Investigator must inform the IRB/IEC of the progress of the clinical study and report any non-administrative changes made to the protocol; in any case, the Investigator must provide an update to the IRB/IEC at least once a year or in accordance with IRB/IEC continuing approval requirements.

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Forty Seven Inc. Delegation of Authority Form.

The clinical study report must be signed by the Investigator or, in the case of multi-center studies, the Coordinating Investigator. The Coordinating Investigator, identified by Forty Seven Inc., will be any or all of the following:

- A recognized expert in the therapeutic area.
- An Investigator who provided significant contributions to either the design or interpretation of the study.
- An Investigator contributing a high number of eligible patients.

12.3. Institutional Review Board or Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Forty Seven Inc. before recruitment of patients into the study and shipment of Hu5F9-G4.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document.
The Investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Forty Seven Inc., in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval/renewal as applicable throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Forty Seven Inc.

12.4. Informed Consent and Human Subject Protection

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be

communicated formally in writing from the Forty Seven Inc. Study Monitor to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The Investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the Investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the patient's medical record. The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient, or a legally acceptable representative, and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.5. Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Forty Seven Inc., including the following.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment
- For Serious Adverse Events reported to Forty Seven Inc., patients are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Forty Seven Inc. (e.g., signed informed consent forms) are to be kept in confidence by the Investigator, except as described below.

In compliance with the Code of Federal Regulations(CFR)/International Conference on Harmonisation (ICH) GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

12.6. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The trial may continue with the urgent safety measures in place. **The Investigator must inform Forty Seven Inc. IMMEDIATELY if the study site initiates an urgent safety measure**.

The notification must include:

- Date of the urgent safety measure;
- Who made the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable Forty Seven Inc. to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and closeout.

12.7. Serious Breaches and Fraud

Within the UK, the Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the Medicines and Healthcare products Regulatory Agency (UK) (MHRA) within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial; or
- the scientific value of the trial”

Investigators must notify Forty Seven Inc. immediately if any serious breach of GCP is suspected.

If there is any proof of fraud this must also be reported to Forty Seven Inc. All instances of confirmed clinical trial fraud occurring at sites in the UK will be treated according to the procedure for dealing with a serious breach and must be reported to the MHRA within 7 days of the Sponsor becoming aware.

12.8. Study Monitoring

The Forty Seven Inc. representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Forty Seven Inc. representative(s) are responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Forty Seven Inc. representative(s) are to have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the Forty Seven Inc. representative(s) to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

12.9. Audits and Inspections

As stipulated by 21 CFR §312.58 and ICH guidelines for GCP, a representative of the Sponsor, the FDA, or other regulatory agencies may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including CRFs and supporting source documents. In addition, the Investigator or other qualified study site personnel are to be available to answer questions, hold interviews, and provide facility tours if requested.

12.10. Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies), as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the SOA (as described in Section 7.1), the Investigator may search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. Data collection will involve the use of the electronic data capture (EDC) system, to which only authorized personnel will have access.
The Investigator agrees to maintain accurate electronic Case Report Form (eCRFs) (or paper

Case Report Forms [CRFs]) and source documentation as part of the case histories. Forty Seven Inc. will supply the eCRF, which will be completed in English.

The Investigator or designee must enter all results collected during the clinical study into eCRFs (or CRFs). Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study specific documents.

All entries made on the eCRF (or CRF), must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure patient confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data must be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the Sponsor or designee for destruction.

12.11. Maintenance of Source Documents and Record Retention

As stipulated by 21 CFR §312.57 and ICH E6 GCP Consolidated Guidance Section 8, the Investigator or designee will maintain source documentation for this clinical study that documents the treatment and study course of patients as described in the study manual.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office

charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Forty Seven Inc. and/or applicable regulatory authorities.

The Investigator must retain all essential documents for this clinical study 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 Hu5F9-G4. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. A Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. Before destroying any records, the Investigator must notify the Sponsor and reach agreement on record destruction, or the Sponsor may request an additional retention period.

12.12. Long-term Retention of Samples for Additional Future Research

Blood, tumor, or bone marrow specimens will be cryopreserved for additional analyses. These samples will be retained for long-term storage by the Sponsor and described in the informed consent.

Any blood, tissue, or biomarker sample collected according to the SOA (Section 7.1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study patients. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. It may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the

samples for the study. Results are stored in a secure database to ensure data integrity and control.

If permitted by local law and if informed consent is provided by the patient, Forty Seven Inc. may do additional testing on remaining samples (i.e., residual and back-up) to investigate and better understand NHL and the dose response and/or prediction of response to Hu5F9-G4; to characterize antibody response; and to characterize aspects of the molecule (e.g., MOA/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples may be retained for up to 20 years.

Since the evaluations are not expected to benefit the patient directly or to alter the patient's treatment course, the results of these exploratory studies are not placed in the patient's medical record and are not to be made available to the patient, members of the patient's family, the patient's personal physician, or other third parties, except as specified in the Informed Consent Form.

The patient retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the patient, the Investigator is to provide the Sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures have been completed.

Information collected from samples prior to the request for destruction will be retained by the Sponsor. The Sponsor is the exclusive owner of any data, discoveries, and derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the Investigator, at the end of the storage period or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

12.13. Financing and Insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

12.14. Publication Policy

The Forty Seven Inc. publication policy is detailed in the Publication Charter.

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Zhang M, Hutter G, Kahn S, et al. Anti-CD47 treatment stimulates phagocytosis of glioblastoma by M1 and M2 polarized macrophages and promotes M1 polarized macrophages in vivo. PLoS One. 2016;11(4):e0153550.

14. APPENDICES

Appendix A: RITUXAN®/MabThera (rituximab) Prescribing Information

RITUXAN®(rituximab) prescribing information

Available online:
http://www.gene.com/download/pdf/rituxan_prescribing.pdf

Accessed 27 April 2017

MabThera®(rituximab) prescribing information

Available online:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf

Accessed 27 April 2017

Appendix B: National Cancer Institute Common Terminology Criteria for Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), Version 4.03

Publication date: 28 May 2009 (v4.03: 14 June 2010)
https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Accessed 27 April 2017

Appendix C: The Lugano Classification and LYRIC Criteria for Lymphomas

Publication:

Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016 Sep 20;128(21):2489-2496.

Available online:

http://www.bloodjournal.org/content/bloodjournal/128/21/2489.full.pdf

Accessed 25 April 2017

Appendix D: ECOG Performance Status

Eastern Cooperative Oncology Group Scale of Performance Status

Publication:

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Karnofsky Performance Status

Publication:

Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

Available online:

http://ecog-acrin.org/resources/ecog-performance-status

Accessed 7 June 2016

Appendix E: Peripheral Smear Assessment

Peripheral smears will be assessed by the designated hematopathology service using the following guidelines:

RBC Agglutination	
0–9%	Not reported
10-19%	1+
20–50%	2+
51–75%	3+
> 75%	4+
Spherocytes	
0–1 cells/100 RBCs	Not reported
2–5 cells/100 RBCs	1+
>5–10 cells/100 RBCs	2+
>10–30 cells/100 RBCs	3+
> 30 cells/100 RBCs	4+
RBC Fragments/Schistocytes	
0 cells/100 RBCs	Not reported
1–2 cells/100 RBCs	1+
>2–5 cells/100 RBCs	2+
>5–10 cells/100 RBCs	3+
> 10 cells/100 RBCs	4+

All other observed findings: report according to local laboratory hematopathology standard procedures.

These guidelines are based on the Stanford Health Care Peripheral Blood Slide Review Manual, Version 3.0, 2015, modified by Forty Seven Inc. for clarification of the following items in the original manual:

- RBC agglutination, 1+ = 10%, 3+ = 60-75%
- Spherocytes, 2+ = 5-10 cells/100 RBCs, 3+ = 10-30 cells/100 RBCs
- RBC Fragments/Schistocytes, 2+ = 2-5 cells, 3+ = 5-10 cells

If sites are not able to quantify the degree of peripheral smear findings noted above, then the presence or absence of RBC agglutination, spherocytes, and/or RBC fragments/schistocytes must be reported at a minimum.

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma
Protocol Number:	5F9003
Investigational Products:	Hu5F9-G4 and rituximab
Indication:	Non-Hodgkin's Lymphoma
Development Phase:	1b/2
US IND Number:	118300
EudraCT Number:	2015-000720-29
Sponsor:	Forty Seven Inc. 1661 Page Mill Road, Suite C Palo Alto, CA 94304, USA Telephone: 1-650-352-4150 Fax: 1-650-618-2308
Medical Monitor:	Mark Chao, MD, PhD Medical Director, Forty Seven Inc. Telephone: 1-650-352-4141 email: mchao@fortyseveninc.com
Study Monitor:	David Rhodes Associate Director Clinical Operations, Forty Seven Inc. Telephone: 1-650-352-4142 email: drhodes@fortyseveninc.com
Investigator(s):	Ranjana Advani, MD Study Lead Principal Investigator Professor of Lymphoma, Stanford University 875 Blake Wilbur Drive Clinic C Stanford, CA 94305, USA Telephone: 1-650-498-6000 Professor John G. Gribben, MD DSc FMedSci United Kingdom Lead Principal Investigator Chair of Medical Oncology, Barts Cancer Institute Queen Mary University of London John Vane Science Centre, Third Floor Charterhouse Square, London EC1M 68Q Telephone: 020 7882 3804
Original Protocol Date:	14 July 2016

Confidentiality Statement:

The concepts and information contained herein are confidential and proprietary and shall not be disclosed in whole or part without the express written consent of Forty Seven Inc.

Compliance Statement:

This study will be conducted in accordance with Protocol 5F9003, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL APPROVAL PAGE

I have read the document described above, and my signature below indicates my approval:

Chris H. Takimoto, M.D, Ph.D.
Chief Medical Officer
Forty Seven Inc.

7/14/2016
Date

PROTOCOL ACCEPTANCE PAGE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, the Code of Federal Regulations (CFR) Title 21, my local and regional clinical trial regulatory requirements, and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of Institution/Site: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Concept and Rationale:

Non-Hodgkin's lymphoma (NHL) is among the most common cancers in the USA and Europe, with more than 70,000 and 93,000 new cases diagnosed every year, respectively (Ferlay 2015). Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of NHL with high relapse rate and poor long-term survival. In addition, few treatment options are available to patients with indolent lymphoma who have relapsed or are refractory to rituximab. Novel and effective therapies are needed to address these high unmet medical needs. Hu5F9-G4 is a monoclonal antibody that targets CD47, an anti-phagocytic cell surface protein. Nonclinical studies have demonstrated that blockade of CD47 signaling through this antibody eliminates human tumor cells including NHL, through facilitating phagocytosis by macrophages. Additional nonclinical studies demonstrate that anti-CD47 antibodies can synergize with Fc receptor-activating anti-cancer antibodies including rituximab. Combination therapy with Hu5F9-G4 and rituximab, an anti-CD20 monoclonal antibody, demonstrated a synergistic antitumor response compared to either agent alone in nonclinical models of NHL.

It is hypothesized that the combination of Hu5F9-G4 and rituximab will be safely tolerated in NHL. This Phase 1b/2 trial will establish the safety and tolerability and optimal dosing strategy of Hu5F9-G4 in combination with rituximab in patients with relapsed/refractory B-cell NHL. Hu5F9-G4 and rituximab will both be administered intravenously. Initially, this trial will utilize a reduced starting dose of Hu5F9-G4 in combination with full doses of rituximab. Subsequent dose cohorts will escalate the dose of Hu5F9-G4. In addition, preliminary antitumor activity will be investigated with this antibody combination.

Patient Eligibility:

Inclusion Criteria:

- Adults ≥ 18 years
- Phase 1b only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, relapsed or refractory to at least one prior regimen of NHL chemotherapy or antibody therapy with curative intent
- DLBCL Phase 2 cohort: Histologically confirmed de novo or transformed DLBCL expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least one prior regimen of NHL chemotherapy that included rituximab
- Indolent lymphoma Phase 2 cohort: Histologically confirmed relapsed or refractory marginal zone or follicular lymphoma (Grade 1-3b) expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least one prior systemic therapy that included rituximab
- Eastern Cooperative Oncology Group (ECOG) score 0-2
- Disease that is measurable or assessable for response per Lugano classification for lymphomas
- Laboratory measurements, blood counts:
  - Hemoglobin > 9.5 g/dL
  - Absolute neutrophil count (ANC) > 1.0×10^9/mL
  - Platelets > 50×10^9/mL
- Laboratory measurements, hepatic function:
  - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5x upper limit of normal (ULN)
  - Bilirubin < 1.5x or 3.0x ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent
- Laboratory measurements, renal function:
  - Serum creatinine < 1.5x ULN or calculated glomerular filtration rate (GFR) < 40 mL/min/1.73 m^2
- Negative urine or serum pregnancy test within 30 days before administration of Hu5F9-G4 for women of childbearing potential
- Females of childbearing potential must be willing to use 2 effective methods of contraception during and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9, whichever occurs later

- Males must be willing to use 1 highly effective method of contraception during and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9, whichever occurs later, if the partner is a female of childbearing potential
- Subject has provided informed consent
- Must be willing and able to comply with clinic visits and procedures outlined in the study protocol
- Phase 2 only: Willing to consent to 1 mandatory pre-treatment and 1 on-treatment tumor biopsy, unless not feasible as determined by the Investigator (reasons include but are not limited to lack of accessible tumor tissue to biopsy and patient safety issues)

Exclusion Criteria:

- Patients with active brain metastases (patients with stable treated central nervous system [CNS] lesions who are off corticosteroid therapy for at least 3 weeks are not considered active)
- Prior allogeneic hematopoietic cell transplantation (autologous transplant permitted)
- Prior anticancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 4 half-lives prior to Hu5F9-G4 dosing (up to a maximum of 4 weeks), whichever is longer. Low dose steroids (oral prednisone or its equivalent ≤ 20 mg per day) and localized non-CNS radiotherapy are not criteria for exclusion
- Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV)
- Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening and prior to enrollment to meet the hemoglobin inclusion criteria.
- History of hemolytic anemia or Evans syndrome in the last 3 months
- Positive Direct Antiglobulin Test (DAT)
- Prior treatment with CD47 or signal regulatory protein alpha (SIRPα) targeting agents
- Second malignancy, except treated basal cell or localized squamous skin carcinomas, or other malignancy for which treatment was completed at least 3 years ago and for which there is no evidence of recurrence
- Significant medical diseases or conditions, as assessed by the Investigators and Sponsor that would substantially increase the risk/benefit ratio of participating in the study. This includes but is not limited to acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, severely immunocompromised state, and congestive heart failure New York Heart Association (NYHA) Class II-IV.
- History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent.
- Pregnancy or active breastfeeding

Study Objectives:

Primary Objectives:

- To investigate the safety and tolerability, and to define the recommended Phase 2 dose for Hu5F9-G4 in combination with rituximab.
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in patients with indolent lymphoma and DLBCL as measured by the overall response rate (ORR)

Secondary Objectives:

- In Phase 1b and 2, to evaluate the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with rituximab
- In Phase 1b and 2, to evaluate the immunogenicity of Hu5F9-G4 in combination with rituximab
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in indolent lymphoma and DLBCL as measured by the duration of response, best overall response, progression free survival, and overall survival

Exploratory Objective:

- To assess biomarkers of immune cell efficacy and tumor penetration of Hu5F9-G4 in combination with rituximab
- To assess efficacy in molecular subtypes of NHL

Study Endpoints:

Primary Endpoints:

- Dose-limiting toxicities (DLTs) (Phase 1b only) and adverse events (AEs) according to NCI CTCAE, Version 4.03
- Phase 2: Objective response as defined by the Investigator according to the Lugano classification for lymphomas

Secondary Endpoints:

- Phase 1b and 2: Hu5F9-G4 concentration versus time measurements and PK parameters of Hu5F9-G4 in combination with rituximab including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), terminal half life ($t_{1/2}$), area under the curve (AUC), clearance (CL), and volume of distribution during the terminal phase (V_z).
- Phase 1b and 2: Anti-drug antibodies to Hu5F9-G4.
- Phase 2: Duration of response (DOR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS).

Exploratory Endpoints:

- Receptor occupancy on peripheral RBCs and white blood cells (WBCs), and lymphoma cells, where applicable.
- Pharmacodynamics markers of Hu5F9G4 biological activity potentially including, but not limited to, circulating cytokine profiles, T-cell receptor sequencing on circulating T cells, mass cytometry (CyTOF)/flow cytometry of circulating leukocytes, and T-cell activation studies.
- In patients undergoing tumor biopsies, Hu5F9-G4 saturation of tumor cells and changes in the tumor microenvironment including, but not limited to, and T-cell tumor infiltration.
- In patients undergoing tumor biopsies, correlation of anti-tumor response to molecular subtypes of NHL including, but not limited to, cell-of-origin in DLBCL and BCL2, BCL6, and MYC mutation/expression status.

Intervention and Mode of Delivery:

Hu5F9-G4 is a humanized monoclonal antibody against CD47 and rituximab is a chimeric monoclonal antibody against CD20. Both drugs are administered intravenously. Hu5F9-G4 will be administered on Days 1,9, 15, and 22 on the first 28-day cycle while rituximab will be administered on Days 8, 15, and 22 for the first cycle followed by once every 4 weeks thereafter. In Cycle 2 and later, Hu5F9-G4 will be administered on Days 1, 8, 15, and 22.

Duration of Intervention and Evaluation:

Phase 1b/2: For the Phase 1b part of the study, patients will be treated with Hu5F9-G4 and rituximab in a standard 3+3 dose escalation design. DLT safety evaluation used for determination of the maximum tolerated dose (MTD) will occur within the first four weeks. A response assessment will occur every 2 cycles (8 weeks) until disease progression. Rituximab will be administered for a total of 6 cycles, while Hu5F9-G4 treatment can extend beyond 6 cycles for those who do not have disease progression.

Number of Patients:

Phase 1b: 9 to 18 patients total

Per dose level:

Level 1: 3-6

Level 2: 3-6

Level 3: 3-6

Phase 2: 54 patients (28 patients for indolent lymphoma; 26 patients for DLBCL)

Study Total: 63-72 patients (assuming progression to Stage 2 of Phase 2)

Statistical Methods:

The Efficacy Analysis Set (EAS) will be used for the analysis of the primary efficacy endpoint in Phase 2. The DLT Analysis Set will be used in Phase 1b to determine the MTD. The Full Analysis Set (FAS) will be used for OS, PFS, and safety analysis in Phase 2. Per Protocol (PP) and PK analysis sets will be used for additional analyses. Data from Phase 1b and Phase 2 will be summarized separately. In Phase 2, data for indolent lymphoma and DLBCL will be summarized separately.

Sample Size Calculations

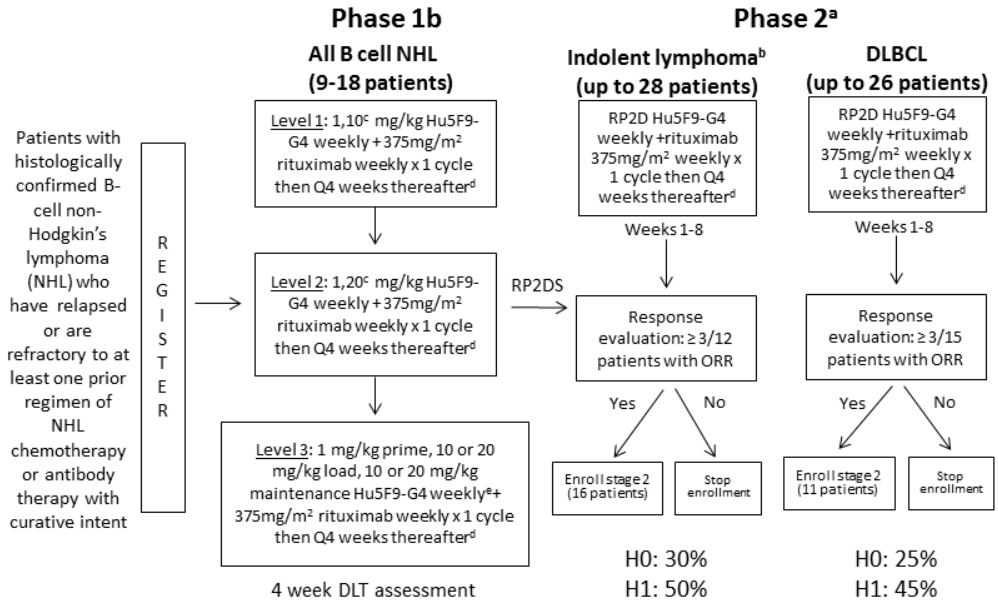
Phase 1b: The sample size will be determined based on the number of dose levels evaluated and the emerging study drug-related toxicities. This phase will consist of up to 18 patients.

Phase 2: Simon's Two-Stage Design

- Indolent lymphoma: The null hypothesis that the true response rate is 30% will be tested against a one-sided alternative. The null hypothesis of 30% is based on single agent rituximab activity in patients previously treated with rituximab. The assumption is that Hu5F9-G4 in combination with rituximab will result in an overall response rate (ORR) of at least 50%. In the first stage, 12 patients will be accrued. If there are 3 or fewer responses after at least 8 weeks of study participation in these 12 patients, enrollment into this arm will be stopped. Otherwise, 16 additional patients will be accrued for a total of 28. The null hypothesis will be rejected if 12 or more responses are observed in 28 patients. This design yields a type I error rate of 0.10 and power of 0.80 when the true response rate is 50%
- DLBCL: The null hypothesis that the true response rate is 25% will be tested against a one-sided alternative. The null hypothesis of 25% is based on single agent rituximab activity in patients receiving two prior lines of rituximab containing therapies. The assumption is that Hu5F9-G4 in combination with rituximab will result in an ORR of at least 45%. In the first stage, 15 patients will be accrued. If there are 3 or fewer responses after at least 8 weeks of study participation in these 15 patients, enrollment into this arm will be stopped. Otherwise, 11 additional patients will be accrued for a total of 26. The null hypothesis will be rejected if 10 or more responses are observed in 26 patients. This design yields a type I error rate of 0.10 and power of 0.80 when the true response rate is 45%.

STUDY DESIGN SCHEMA

Study 5F9003: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B Cell Non-Hodgkin's Lymphoma



Abbreviations: CTSC = Clinical Trial Steering Committee; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; H0 = null hypothesis; H1 = alternative hypothesis; ORR = overall response rate; Q4 weeks = every 4 weeks; RP2DS = recommended Phase 2 dose and schedule

a. Simon's two-stage minimax design with an alpha of 0.1 and a power of 0.80

b. Indolent lymphoma will include follicular and marginal zone lymphoma

c. 1,10 mg/kg represents a first priming dose of 1 mg/kg followed by a maintenance dose of 10 mg/kg of Hu5F9-G4 weekly thereafter, similarly for 1,20 mg/kg

d. Treatment cycles are 4 weeks. Rituximab is given weekly at weeks 2-4 in cycle 1 only. Up to 6 cycles of rituximab will be given

e. Level 3 Hu5F9-G4 dosing regimen will consistent of 1 mg/kg priming dose on day 1, then a loading dose of either 10 or 20 mg/kg twice weekly x 1 week, followed by weekly maintenance doses of 10 or 20 mg/kg. Dose concentration to be determined by the CTSC

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITIONS

ADA	antidrug antibodies
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BOR	best overall response
BUN	blood urea nitrogen
CBCs	complete blood counts
CFR	Code of Federal Regulations
CHOP	alkylator combination of cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form (paper)
CT	computed tomography
CTSC	Clinical Trial Steering Committee
CyTOF	mass cytometry
DAT	direct antiglobulin test
DLBCL	diffuse large b-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response

EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H0	null hypothesis
H1	alternative hypothesis
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IXRS	interactive web/voice response technology
kg	kilogram
KM	Kaplan-Meier
L	liters
LDH	lactate dehydrogenase
LDi	longest diameter
LISS	low ionic strength solution
LSC	leukemic stem cells
LSE	last subject enrolled
M1	macrophages that suppress tumor progression

M2	macrophages that promote tumor progression
mAb	monoclonal antibody
MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOA	mechanism of action
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMCs	peripheral blood mononuclear cells
PCD	programmed cell death
PD	progressive disease
PE	physical examination
PeG	polyethylene glycol
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	Per Protocol
PR	partial response
PRBC	packed red blood cell (transfusions)
PrCR	programmed cell removal
PT	prothrombin time
RBCs	red blood cells
REC	research ethics committee
RP2DS	recommended Phase 2 dose and schedule
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease or standard deviation
SDV	source data verification

SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIRPα	signal regulatory protein alpha
SOA	schedule of assessments
S-P	Ser-Pro
SPD	sum of the product of the diameters
T_{max}	time to maximum concentration
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
V_z	volume of distribution during the terminal phase
WBCs	white blood cells

1. BACKGROUND

1.1. Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is among the most common cancers in the United States and Europe with more than 70,000 and 93,000 new cases diagnosed every year, respectively (Ferlay 2015). NHL is a heterogeneous group of malignancies with varying clinical characteristics that are optimally managed through a range of different treatment modalities. The spectrum of NHL includes more indolent variants such as follicular and marginal zone lymphomas, to more aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL). While systemic chemotherapy is a mainstay of treatment for most NHL variants, antitumor directed monoclonal antibodies (mAb) have an important role in the treatment of this disease (Oflazoglu 2010). Antibodies such as rituximab, which targets the B-cell antigen CD20, are now part of the standard treatment regimens for many B-cell non-Hodgkin's lymphomas (Keating 2010). However, once NHL becomes refractory to standard chemotherapy and antibody-based therapies, the overall prognosis is poor, with limited long-term survival. Thus, novel and effective therapies are needed to address this high unmet medical need.

1.1.1. Indolent Lymphoma

Indolent lymphomas represent 40% of all non-Hodgkin's lymphoma subtypes, with follicular lymphoma occurring with the greatest frequency (Harris 1999). Indolent lymphomas present with a broad spectrum of disease characteristics. Patients often experience a chronic relapsing and remitting disease course and are exposed to several successive treatment regimens, resulting eventually in death due to disease progression. In general, treatment is reserved for patients who develop significant symptoms or who are sufficiently high risk to merit early therapy (Gribben 2007). The most common frontline therapies include a combination of alkylators (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or bendamustine) in combination with the anti-CD20 monoclonal antibody rituximab. In addition, single agent rituximab is also often administered as frontline therapy, particularly in patients with lower disease burden or who may not tolerate combination chemo-immunotherapy (Sousou 2010). Rituximab was originally approved for use in patients with relapsed and refractory follicular lymphoma and low grade lymphoma.

For patients with indolent NHL who initially respond (complete or partial remission with a time to progression of at least 6 months) and then experience relapse after single-agent rituximab, retreatment with either rituximab alone or in combination with chemotherapy is frequently given (Kahl 2014; Gribben 2007; NCCN Guidelines Version 3.2016). Patients who become refractory to rituximab alone or in combination with chemotherapy have limited options for effective treatment.

One approach to enhancing the efficacy of rituximab is the addition of other biologic agents that could potentiate its activity. There is strong nonclinical evidence demonstrating that Hu5F9-G4, an anti-CD47 antibody, can synergize with rituximab to eliminate both the indolent and aggressive lymphoma subtypes (Chao 2010a). This trial will explore clinical proof of concept of the combination of Hu5F9-G4 with rituximab to treat indolent and aggressive NHL.

1.1.2. Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive subtype of NHL that accounts for approximately 30% of all NHL (Non-Hodgkin's Lymphoma Classification Project 1997). Combination chemotherapy with the addition of rituximab is standard of care for patients with newly diagnosed DLBCL. However, approximately 40% of patients with DLBCL relapse following initial immunochemotherapy (Vaidya 2014). For those patient who are eligible, salvage chemotherapy regimens followed by autologous stem cell transplantation is standard of care. However, many patients are not eligible for transplantation due to age and other medical co-morbidities. While multiple salvage regimens comprising combination chemotherapy are available for relapsed/refractory disease, no standard salvage regimen exists currently. The development of more effective therapies for relapsed/refractory DLBCL represents a high unmet medical need. In addition to indolent lymphoma, this study will investigate the use of an anti-CD47 antibody, Hu5F9-G4, in combination with rituximab for patients with DLBCL.

1.2. Study Drug: Hu5F9-G4

1.2.1. Nonclinical Background

The Stanford researchers in the laboratories of Weissman and Majeti have identified CD47 as a key molecule mediating cancer cell evasion of phagocytosis by the innate immune system. CD47 appears to be an indispensable means by which cancer cells, including cancer stem cells, overcome intrinsic expression of their prophagocytic, "eat me," signals (Jaiswal 2009; Majeti 2009). The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death (PCD) and programmed cell removal (PrCR) (Chao 2012). Many of the steps in cancer progression subvert the multiple mechanisms of PCD, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint (Chao 2012). The Weissman laboratory originally identified increased CD47 expression on leukemic stem cells (LSC) in human acute myeloid leukemia (AML, Majeti 2009) and have since found that CD47 expression is increased on the surface of cancer cells from a large number of diverse human tumor types.

In mouse xenografts, CD47-blocking mAbs inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors (Majeti 2009; Chao 2010a; Chao 2011a; Chao 2011b; Edris 2012; Kim 2012; Willingham 2012). Binding of CD47 on cancer cells to its ligand signal-regulatory protein alpha (SIRPα) expressed on phagocytes leads to inhibition of tumor phagocytosis. Thus, blockade of the CD47-SIRPα signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of pro-phagocytic signals expressed mainly on tumor cells and not on normal cell counterparts (Chao 2010b).
In addition, the anti-CD47 antibody induces an anti-tumor T-cell response through cross-presentation of tumor antigens by macrophage and antigen-presenting cells after tumor cell phagocytosis (Tseng 2013; Liu 2015a). Furthermore, CD47-blocking mAbs have shown synergistic efficacious activity with cancer-specific targeting antibodies, including anti-CD20 antibody rituximab in NHL (Chao 2010a).

The nonclinical studies referred to in the publications referenced in this section have been conducted with a commercially available CD47-blocking monoclonal antibody (clone B6H12, mouse IgG1), and additional nonclinical studies have been conducted with the humanized CD47-blocking monoclonal antibody Hu5F9-G4.

Hu5F9-G4 is an anti-human CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells (Liu 2015b). The activity of Hu5F9-G4 is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of Fc-dependent effector functions, although the presence of the IgG4 Fc domain is required for its full activity. For this reason, Hu5F9-G4 was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47 expressing cells (Liu 2015b). Nonclinical studies using xenograft cancer models provide compelling evidence that Hu5F9-G4 triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, Hu5F9-G4 is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

Most normal cells lack expression of pro-phagocytic signals and are unaffected by Hu5F9-G4 binding to and blocking CD47. Red blood cells (RBCs) are a notable exception because CD47 expression protects RBCs from elimination by splenic red pulp macrophages, as well as sinusoidal macrophages, in liver and bone marrow. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. Administration of Hu5F9-G4 accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger cells. Moreover, the potential for severe anemia in these nonclinical studies is ameliorated by administration of a low priming dose of the antibody that results in mild-to-moderate anemia and stimulates reticulocytosis.

The Hu5F9-G4 anti-CD47 program represents a novel strategy for the treatment of cancer and is the first therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (AML, acute lymphoblastic leukemia [ALL], NHL, myeloma, and others).

1.2.2. Clinical Background

1.2.2.1. Summary of Hu5F9-G4 Clinical Safety

The safety of Hu5F9-G4 is currently being evaluated in two ongoing Phase 1 trials. The initial first-in-human Phase 1 trial (SCI-CD47-001) started dosing patients on 26 August 2014, and it is designed to determine the optimal dose and schedule of Hu5F9-G4 and to characterize its preliminary safety, pharmacokinetics (PK), and pharmacodynamics. This single institution study is enrolling patients with solid tumors and lymphomas; however, only solid tumor patients have been enrolled to date. A second Phase 1 trial (SCI-CD47-002) in relapsed/refractory AML patients began dosing patients on 30 November 2015, and it is designed to define the maximum tolerated dose (MTD) and to evaluate the safety, PK, and pharmacodynamics of Hu5F9-G4 in this patient population.

In the 17 patients (16 with solid tumors and 1 with AML) treated thus far, Hu5F9-G4 has been well tolerated. The most common treatment-associated effects are related to the targeting of CD47 on erythrocytes, with anemia and RBC agglutination being most prominent. Other common treatment-related adverse events (AEs) include mild headache, fatigue, nausea, photopsia, urine discoloration, low back pain, and abdominal pain. Common drug-related abnormal laboratory findings include transient reticulocytosis, spherocytosis, hyperbilirubinemia, D-dimer elevation, and decreased haptoglobin. The majority of these findings occur following the first infusion, with very few study drug-related toxicities reported beyond the first cycle. In patients with solid tumors, the recommended priming dose of 1 mg/kg of Hu5F9-G4 was defined by the dose-limiting toxicities (DLTs) of acute abdominal pain and headache associated with hemagglutination. However, using a priming and maintenance dose schedule in these patients has allowed for the further escalation of the maintenance dose to 10 mg/kg, with further dose escalation planned.

As expected, the most common, clinically relevant toxicity is an acute anemia manifested as a 1- to 2-g/dL fall in hemoglobin observed during the first 1 to 2 weeks of treatment. In solid tumor patients, this is followed by a compensatory reticulocytosis and a gradual return to baseline by Week 3 or 4 despite continued dosing. These clinical observations are completely consistent with the known MOA of Hu5F9-G4 and the physiologic role of CD47 in regulating the turnover of aging erythrocytes. Other associated laboratory abnormalities including reticulocytosis, spherocytosis, transient hyperbilirubinemia (predominantly unconjugated), and decreased haptoglobin are all indicative of extravascular hemolysis consistent with phagocytic removal of RBCs due to blockade of CD47. No solid tumor patient has required a blood transfusion; however, the single patient enrolled to date in the AML Phase 1 study (SCI-CD47-002) was transfusion-dependent prior to study entry and has received frequent RBC transfusions without complications throughout the first 5 weeks on study. Cross-matching of blood products while on Hu5F9-G4 has been successful, without need for specialized cross-matching procedures.

A second treatment-related effect on erythrocytes is hemagglutination, which is presumed to result from the direct interaction of Hu5F9-G4 with CD47 on red blood cells. In Part A of the solid tumor Phase 1 study (SCI-CD47-002), hemagglutination was observed on peripheral blood smears in 8 out of 11 patients, typically within 24 hours of study drug administration. Although D-dimer elevation was also common, there was no evidence of disseminated intravascular coagulation, nor were there any signs of thrombocytopenia, coagulopathy, microangiopathy, thromboembolic disease, or other clinical sequelae associated with the hemagglutination findings. No hemagglutination has been noted in any solid tumor patient beyond Cycle 1. An asymptomatic solitary cotton wool spot was noted on retinal photographic examination in 1 solid tumor patient, but this was not associated with any hemagglutination and subsequently resolved. Because RBC agglutination may be related to the early, rapid rise in Hu5F9-G4 concentration in the blood of treatment-naïve patients, the duration of infusion of the initial 1-mg/kg priming dose has been extended from 1 to 3 hours in all patients starting in the maintenance dose phase of the solid tumor Phase 1 study. Although current numbers are small, only mild hemagglutination has been observed in 1 of 5 patients treated using the 3-hour priming dose infusion. In contrast, hemagglutination was

observed in 6 of 6 previous patients treated with a 1-hour priming infusion (1 mg/kg). The duration of the maintenance dose infusions remains the same at 2 hours.

1.2.2.2. Summary of Hu5F9-G4 Clinical Pharmacology

No formal clinical pharmacology trials have been completed with Hu5F9-G4; however, preliminary PK data are available from the first 15 patients on the ongoing solid tumor Phase 1 study (SCI-CD47-001). Patients have been treated with Hu5F9-G4 doses ranging from 0.1 to 3 mg/kg with increasing concentrations associated with increasing dose. Nonlinear pharmacokinetics consistent with target-mediated clearance has been observed over this dose range with the apparent observed half-life ranging from 7 to 27 hours. Two of fifteen patients tested positive for anti-drug antibodies against Hu5F9-G4, but the impact on drug PK could not be ascertained due to the limited amount of available PK data. Dose escalation with pharmacokinetic monitoring is continuing in the two ongoing Hu5F9-G4 Phase 1 trials.

1.2.2.3. Summary of Hu5F9-G4 Clinical Efficacy

In both clinical studies, dose escalation is continuing and efficacy data from patients with systemic Hu5F9-G4 exposures in the range associated with nonclinical activity is still pending. No objective responses have been observed in 10 of the 13 patients with solid tumors who were evaluable for tumor response at the time of data cutoff in the ongoing dose escalation solid tumor Phase 1 study (SCI-CD47-001). Two patients with adenoid cystic carcinomas had stable disease for 33, and 72 weeks. In Study SCI-CD47-002, the single patient with AML treated thus far has had stable disease based on a Day 25 bone marrow evaluation and remains on study with stable disease after 5 weeks of treatment. No objective responses have been observed to date in patients with solid tumor or AML but dose escalation in these ongoing Phase 1 studies is continuing.

1.2.2.4. Summary of Hu5F9-G4 Clinical Safety

In summary, the expected adverse effects of anemia and hemagglutination have been observed in solid tumor and AML patients treated with Hu5F9-G4, but the overall safety profile to date is manageable and consistent with nonclinical toxicology studies. All non-hematological Hu5F9-G4-associated toxicities have been transient and easy to manage.

Supportive care with frequent RBC transfusions has been safely and successfully administered to an AML patient who was concurrently treated with Hu5F9-G4. Furthermore, implementation of a priming and maintenance dose strategy, coupled with the extension of the priming infusion duration to 3 hours, appears to substantially modulate the hematological toxicities of this novel agent, thereby allowing dose escalation to continue in the ongoing Phase 1 studies. Nonclinical studies with Hu5F9-G4 in combination with rituximab have been conducted in lymphoma xenograft mouse models. No evidence of systemic toxicity such as body weight loss was observed in these combinations studies; although Hu5F9-G4 does not cross-react with murine CD47 (Chao 2010a).

1.3. Rituximab

Rituxan®/MabThera® (rituximab), manufactured by Roche/Genentech, is a chimeric murine/human IgG1 kappa monoclonal antibody that targets CD20. Its MOAs are thought to be antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis after binding to the CD20 antigen on the cell surface. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow. Rituximab is the first commercially available monoclonal antibody for the treatment of lymphoma, and is currently approved for several NHL indications including low-grade indolent lymphoma, chronic lymphocytic leukemia, and DLBCL. Rituximab is widely used in frontline and salvage regimens in B-cell NHL, either alone or in combination with chemotherapy. The estimated median terminal elimination half-life is 22 days (range 6.1 to 52 days), based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every 3 weeks (Appendix A).

1.4. Correlative Studies Background

Blockade of the CD47-SIRPα signaling axis on tumor cells by a monoclonal blocking anti-CD47 antibody leads to tumor elimination by activation of both the innate and adaptive immune system. Anti-CD47 antibody-mediated tumor elimination by the innate immune system occurs through phagocytic elimination of tumor cells by macrophage and other phagocytes. It is well known that macrophages are a common immune cell infiltrate in many tumor types, with degree of intratumoral macrophage infiltrate correlating with clinical

prognosis. Correlation of macrophage infiltration to clinical disease course is often dependent on the presence of either classically activated (M1) type macrophages that suppress tumor progression or alternatively, activated (M2) type macrophages that promote tumor progression (Pollard 2004). Given the frequent infiltration of M2 macrophages in many tumor types and its role in promoting tumorigenesis, there is widespread interest in developing therapies that shift tumor macrophage polarization from the pro-tumorigenic M2 to the anti-tumorigenic M1 macrophages. In nonclinical studies, anti-CD47 antibody-mediated tumor cell phagocytosis has been demonstrated to occur through both M1 and M2 macrophages (Zhang 2016). In addition, in vivo treatment of human xenograft tumors with an anti-CD47 antibody demonstrated increased M1 intratumoral macrophages post-treatment (Zhang 2016), suggesting that an anti-CD47 antibody can also shift the phenotype of macrophages from the M2 towards the M1 phenotype in vivo. Since the recruitment of macrophage effectors is a key mechanism for anti-tumor activity by anti-CD47 antibody, the characterization of macrophage tumor infiltration pre- and post-treatment in patients treated with anti-CD47 antibody may provide insights into patient and cancer subtypes and macrophage biomarkers that will enrich for anti-tumor efficacy.

In addition to modulating the innate immune system, anti-CD47 antibody therapy also activates the adaptive immune system towards an anti-tumor response. Phagocytosis of tumor cells by phagocytes (macrophages and/or dendritic cells) leads to cross-presentation of tumor antigens to T cells, enabling a T-cell anti-tumor response (Tseng 2013; Liu 2015a). In one nonclinical study, anti-CD47 antibody mediated a specific CD8 T-cell anti-tumor response without proliferation of regulatory T cells (which are generally thought to be tumor-promoting; Tseng 2013). Currently, there is intense interest in investigating the relationship between T-cell subsets that infiltrate the tumor and clinical response with the use of immune-oncology therapeutics. Indeed, increased T-cell infiltration in the tumor has been associated with clinical response in oncology patients treated with T-cell checkpoint inhibitors (Herbst 2014; Tumeh 2014). Given the role of anti-CD47 antibody in mediating an anti-tumor T-cell response, the clinical investigation of the contribution of T-cell effectors to anti-CD47 antibody-mediated efficacy is important to select for patients and tumor subtypes that respond to therapy.

1.5. Study Rationale and Risk-Benefit

The development of therapeutic monoclonal antibodies (mAbs) has substantially impacted treatment of NHL with the clinical use of the anti-CD20 antibody, rituximab. However, apart from anti-CD20 antibodies, the development of other targeted mAbs for NHL has been limited.

A monoclonal antibody targeting CD47 enables selective phagocytosis and elimination of tumor cells, but not normal cells, and is a potentially beneficial therapy for NHL. In murine patient xenograft studies, it has been shown that CD47-blocking antibodies inhibit human lymphoma growth and dissemination by enabling the phagocytosis and elimination of lymphoma cells (Chao 2010a; Chao 2011b). Furthermore, CD47-blocking antibodies have been shown to exhibit potent synergy with tumor-specific mAbs, such as the anti-CD20 antibody rituximab in non-Hodgkin's lymphoma. In nonclinical models of NHL (including both indolent lymphoma and DLBCL), anti-CD47 antibody synergized with rituximab to yield dramatic levels of tumor phagocytosis in vitro compared to either monotherapy. In mice transplanted with aggressive NHL, combination therapy with anti-CD47 antibody and rituximab led to approximately 80% long-term remissions compared to only a partial tumor response with either agent alone (Chao 2010a; Liu 2015b). This mechanism of synergy was due to the engaging of 2 mechanisms of phagocytosis: anti-CD47 antibody-mediated phagocytosis through inhibition of CD47-SIRPα signaling and rituximab-mediated phagocytosis through delivery of a pro-phagocytic signal through the Fc receptor leading to antibody-dependent cellular phagocytosis (Chao 2010a). These nonclinical experiments provide the rationale for the use of anti-CD47 antibody in combination with rituximab for the treatment of patients with B-cell NHL.

B-cell NHL patients with both indolent lymphomas and DLBCL who have relapsed or are refractory to treatment regimens containing rituximab have limited options for effective treatment. Specific indolent lymphomas, particularly follicular lymphoma, are deemed incurable, as described by frequent patterns of relapse during several lines of therapy. While overall survival for follicular lymphoma can be more than 10 years, approximately 15% to 20% of patients with newly diagnosed follicular lymphoma have rapidly evolving, progressive disease that results in death within 2 to 3 years (Swenson 2005). Patients

suffering from indolent lymphoma with high-risk disease features who have early disease recurrence after treatment with rituximab, are refractory to rituximab containing therapies, or are ineligible for more aggressive therapies, represent an unmet medical need. Of patients with DLBCL, 30%-40% relapse after first-line therapy and 10% experience refractory disease (Vaidya 2014; Morrison 2015). For patients with chemosensitive disease, the standard treatment for relapsed/refractory DLBCL is salvage chemotherapy followed by autologous hematopoietic cell transplantation (Philip 1995). Patients with DLBCL who are refractory to frontline therapy, relapse, or are refractory to second line salvage regimens or autologous hematopoietic cell transplantation have an extremely poor prognosis (Gisselbrecht 2010; Crump 2014; Van Den Neste 2016). In these settings, there is no standard treatment. Thus, relapsed/refractory DLBCL represents a significant unmet need.

Treatment with the proposed combination therapy of Hu5F9-G4 and rituximab is not anticipated to pose a significantly increased risk to patients enrolled on this trial compared to the risk of treatment with either agent alone. To date, no significant overlapping toxicities between Hu5F9-G4 and rituximab have been observed. The current Phase 1 clinical trial experience with Hu5F9-G4 (Section 1.2.2) has revealed primarily RBC mediated toxicities, while rituximab toxicities are generally associated with B-cell depletion, infusion reactions, and/or tumor lysis syndrome.

Given the strong nonclinical evidence of activity for combination therapy with an anti-CD47 antibody and rituximab in both indolent lymphomas and DLBCL, the individual safety profiles of both Hu5F9-G4 and rituximab to date showing tolerability, and the significant unmet medical need for these patient populations, the clinical combination therapy proposed for investigation in this trial has an acceptable risk/benefit profile for the patients proposed for enrollment.

1.6. Dose Rationale

1.6.1. Hu5F9-G4

Hu5F9-G4 selectively eliminates tumor cells while sparing normal cells through blockade of the CD47-SIRPα phagocytic signaling axis. Most normal cells are spared due to the expression of pro-phagocytic signals that are expressed on tumor cells but not normal cells

(Chao 2010b). RBCs are a notable exception because CD47 expression protects RBCs from elimination by macrophages in the reticuloendothelial system. As RBCs age, they gradually lose CD47 expression and reorganize membrane phospholipids in a manner that enhances pro-phagocytic signaling, ultimately leading to their elimination by phagocytosis. Administration of Hu5F9-G4 accelerates this process by substituting gradual loss of CD47 with immediate blockade of CD47 on aging RBCs, changing the balance between anti-phagocytic and pro-phagocytic signals in the RBC pool. In nonclinical and clinical studies, the premature loss of aging RBCs is compensated by an ensuing reticulocytosis, and the initial anemia resolves as aged RBCs are replaced with younger cells.

These nonclinical studies show that the potential for severe anemia is ameliorated by administration of a low priming dose of the antibody that results in mild to moderate anemia and stimulates reticulocytosis. Similar to the Phase 1 studies of Hu5F9-G4, this study will employ a dose strategy utilizing an initial low priming dose followed by a weekly higher maintenance dose. In the Phase 1 trial of Hu5F9-G4 conducted in relapsed/refractory solid tumors (NCT02216409), this dosing strategy was found to result in a mild anemia associated with the priming dose only, and no significant anemia has been observed during maintenance dosing.

In addition to using a priming and maintenance dose strategy, this trial will also investigate the clinical safety and efficacy of a priming, loading, and maintenance dose strategy of Hu5F9-G4 in combination with rituximab. Because CD47 is widely expressed on normal tissues, effective tumor penetration by Hu5F9-G4 requires a dose regimen that ensures adequate saturation of the internal CD47 receptor sink and achieves effective circulating drug levels. In the Phase 1 trial of Hu5F9-G4 in solid tumors, maintenance dose concentrations between 10 and 20 mg/kg weekly were associated with circulating Hu5F9-G4 drug levels that correlated with nonclinical antitumor efficacy. This trial will investigate a 1-mg/kg priming dose followed by weekly maintenance doses of either 10 or 20 mg/kg. In addition, a regimen of a 1-mg/kg priming dose, followed by 20-mg/kg twice-weekly loading dose for 1 week, with a maintenance dose of 20 mg/kg weekly thereafter will be explored.

1.6.2. Rituximab

Rituximab will be administered at the clinically approved dose concentration of 375 mg/m^2 intravenously. Rituximab will be given in a loading/maintenance dose regimen that includes weekly doses of 375mg/m^2 on Days 8, 15, and 22 during the first cycle, followed by one dose of 375 mg/m^2 per cycle for up to 6 total cycles. This dose regimen has been selected on the basis of the pharmacokinetic profile of rituximab, as well as evidence that a loading/maintenance regimen enhances efficacy in pretreated NHL patients (Ghielmini 2004).

1.6.3. Starting Dose Rationale

In the Phase 1b part of the trial, the first dose escalation cohort will employ a Hu5F9-G4 dose of 1-mg/kg priming, followed by 10-mg/kg maintenance doses. This starting dose was selected based on safety and pharmacokinetic data obtained in the "First in Human Phase 1 Dose Escalation Trial of Hu5F9-G4 in Patients with Advanced Solid Tumor Malignancies" (NCT02216409). The 1-mg/kg priming followed by 10-mg/kg maintenance dose was demonstrated to be safe and tolerable (with no observed DLTs), and achieved Hu5F9-G4 drug exposure levels associated with nonclinical efficacy. Further dose escalation of Hu5F9-G4 will be employed as indicated in the protocol. Rituximab will be administered at the standard clinical dose concentration of 375 mg/m^2 for all dose escalation cohorts.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives for this study are:

- To investigate the safety and tolerability, and to define the recommended Phase 2 dose for Hu5F9-G4 in combination with rituximab.
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in patients with indolent lymphoma and DLBCL as measured by the overall response rate (ORR).

2.1.2. Secondary Objectives

The secondary objectives for this study are:

- In Phase 1b and 2, to evaluate the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with rituximab
- In Phase 1b and 2, to evaluate the immunogenicity of Hu5F9-G4 in combination with rituximab
- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in indolent lymphoma and DLBCL as measured by the duration of response, best overall response, progression-free survival, and overall survival

2.1.3. Exploratory Objective

The exploratory objective for this study is:

- To assess biomarkers of immune cell efficacy and tumor penetration of Hu5F9-G4 in combination with rituximab
- To assess efficacy in molecular subtypes of NHL

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints for this study are:

- Dose-limiting toxicities (Phase 1b only) and adverse events according to NCI CTCAE, Version 4.03 (Appendix B)
- Phase 2: Objective response as defined by the Investigator according to the Lugano classification for lymphomas (Appendix C)

2.2.2. Secondary Endpoints

The secondary endpoints for this study are:

- Phase 1b and 2: Hu5F9-G4 concentration versus time measurements and PK parameters of Hu5F9-G4 in combination with rituximab including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), terminal half life ($t_{1/2}$), area under the curve (AUC), clearance (CL), and volume of distribution during the terminal phase (V_z).
- Phase 1b and 2: Anti-drug antibodies to Hu5F9-G4
- Phase 2: Duration of response (DOR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS)

2.2.3. Exploratory Endpoints

The exploratory endpoints for this study are:

- Receptor occupancy on peripheral RBCs and white blood cells (WBCs), and lymphoma cells, where applicable.
- Pharmacodynamic markers of Hu5F9-G4 biological activity potentially including, but not limited to, circulating cytokine profiles, T-cell receptor sequencing on circulating T cells, mass cytometry (CyTOF)/flow cytometry of circulating leukocytes, and T-cell activation studies.
- In patients undergoing tumor biopsies, Hu5F9-G4 saturation of tumor cells and changes in the tumor microenviroment, including, but not limited to, macrophage and T-cell tumor infiltration.

- In patients undergoing tumor biopsies, correlation of anti-tumor response to molecular subtypes of NHL including, but not limited to, cell-of-origin in DLBCL and BCL2, BCL6, and MYC mutation/expression status.

3. STUDY DESIGN

3.1. Overall Study Design

This trial is an open label, multicenter, Phase 1b/2 trial investigating the combination of Hu5F9-G4 and rituximab in relapsed/refractory B-cell non-Hodgkin's lymphoma. The study will be conducted in 2 parts:

1. Dose escalation Phase 1b open to patients with B-cell non-Hodgkin's lymphoma
2. Phase 2 study with 2 treatment arms (indolent lymphoma and DLBCL), conducted in a Simon's two-stage Minimax design

The Phase 1b dose escalation part of the study will be conducted using a standard 3+3 dose escalation design to determine the MTD, if one exists, and to identify a recommended Phase 2 dose and schedule (RP2DS) for Hu5F9-G4 in combination with rituximab. Up to 3 dose level cohorts are anticipated. The Phase 2 part of the study will then explore the combination of Hu5F9-G4 and rituximab at the RP2DS determined from the Phase 1b in 2 separate cohorts: patients with indolent lymphoma (to include follicular lymphoma and marginal zone lymphoma) and DLBCL.

3.2. Phase 1b Study Design

3.2.1. Phase 1b Dose Levels

All patients will receive Hu5F9-G4 and rituximab. All patients will receive an Hu5F9-G4 priming dose of 1 mg/kg on Day 1. This will be followed by weekly maintenance doses of either 10 mg/kg or 20 mg/kg. In addition, a regimen comprising a 1-mg/kg priming dose, followed by a 10-mg/kg or 20-mg/kg twice-weekly loading dose for 1 week, and a maintenance dose of 10 mg/kg or 20 mg/kg weekly thereafter, will be explored based on ongoing PK evaluation and clinical data review by the Clinical Trial Steering Committee (CTSC). The dose of Hu5F9-G4 will be determined by cohort assignment.

Rituximab will be administered intravenously at the clinically approved dose concentration of 375 mg/m^2. Rituximab will be given in a loading/maintenance regimen that includes weekly doses of 375 mg/m^2 during Days 8, 15, and 22 during the first cycle, followed by

1 dose of 375 mg/m^2 per cycle for up to 6 total cycles. During Week 2, rituximab will be administered on Day 8, one day prior to the next Hu5F9-G4 dose, to distinguish AEs that may be related to either rituximab or Hu5F9-G4. On days on which both rituximab and Hu5F9-G4 are given, rituximab will be given first. After the rituximab infusion is completed, Hu5F9-G4 will be given.

For the Phase 1b part of the study, the maintenance dose for the first cohort will be 10 mg/kg. Dose escalation of Hu5F9-G4 will proceed through the designated dose levels, as shown in Table 1. Decisions related to dose escalation will be based on the first 4 weeks of treatment in the current cohort, referred to as the "Dose-Limiting Toxicity (DLT) Assessment Period," in conjunction with ongoing assessments for patients on prior cohorts who continued therapy beyond 4 weeks. Decisions regarding additional cohorts to further refine the MTD or RP2DS will be made by the CTSC. For Dose Level 3, the selection of either 10-mg/kg or 20-mg/kg dosing for both the loading and maintenance doses will be determined by the CTSC based on ongoing PK evaluation and clinical data review. The CTSC may create additional dose cohorts including, but not limited to, adding intermediate dose steps (e.g., a maintenance dose cohort of 15 mg/kg weekly) or exploring a dose schedule of every 2 or 3 weeks, if supported by emerging PK and clinical data.

Table 1. Dose Levels and Schedule

Dose Level	Drug/Dose (IV)	Dose Schedule (Day per 28-day Cycle)	
		Cycle 1	Cycle 2+
Ph 1b: Level 1	Hu5F9-G4 1 mg/kg	Day 1	—
(Prime/maintenance)	Hu5F9-G4 10 mg/kg	Day 9, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8,15 ,22	C2-C6, Day 1
Ph 1b: Level 2	Hu5F9-G4 1 mg/kg	Day 1	—
(Prime/maintenance)	Hu5F9-G4 20 mg/kg	Day 9, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	C2-C6, Day 1
Ph 1b: Level 3	Hu5F9-G4 1 mg/kg	Day 1	—
(Prime/load/maintenance)	Hu5F9-G4 10 or 20 mg/kg[a]	Day 9, 11, 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	C2-C6, Day 1
Ph 2	Hu5F9-G4 1 mg/kg	Day 1	—
	Hu5F9-G4 RP2DS from Ph1b	Day 9, (11)[b], 15, 22	Day 1, 8, 15, 22
	Rituximab 375 mg/m^2	Day 8, 15, 22	C2-C6, Day 1

Abbreviations: CTSC = Clinical Trial Steering Committee; IV = intravenous; Ph = Phase; RP2DS = recommended Phase 2 dose and schedule.
a. 10- or 20-mg/kg loading and maintenance dose will be determined by the CTSC.
b. Additional dosing day included if Dose Level 3 is selected as the RP2DS.

3.2.2. Phase 1b Dose Escalation

Dose escalation in Phase 1b will follow a 3+3 dose escalation design. Three to six patients may be enrolled in each dose cohort. If none of the first 3 patients experiences a DLT, dose escalation will proceed to the next higher dose cohort. If 1 of the first 3 patients experiences a DLT, the cohort will be expanded to 6 patients. If more than 2 patients experience DLTs, the MTD dose level will have been exceeded, dose escalation will halt, and additional patients will be treated at a lower dose level. The MTD for the Phase 1b is the maximum dose level at which at least 6 patients are treated with Hu5F9-G4 and rituximab and less than 33% of these patients experience a DLT. The RP2DS will be determined by the CTSC (Section 11.6) based on review of all available safety, efficacy, and pharmacokinetic data. Dose escalation and cohort expansion decisions are reviewed and approved by the CTSC. The first patient in each dose cohort must complete at least 1 week of treatment before

additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The third patient in a cohort requires observation for 28 days prior to proceeding to the next dose cohort. The CTSC may add up to 6 patients to any dose level previously determined to be safe to collect additional safety and PK information.

3.2.3. Dose-Limiting Toxicity Evaluation

Dose escalation decisions will be made by the CTSC based on the first 4 weeks of treatment for each patient, referred to as the "Dose-limiting Toxicity (DLT) Assessment Period." The first patient in each dose cohort must complete at least 1 week of treatment before additional patients may be enrolled in the cohort. Subsequent patients may be enrolled simultaneously. The third patient in a cohort must complete the DLT Assessment Period prior to escalating to the next dose level.

3.2.4. Definition of DLT-evaluable

Patients assigned to a particular dose cohort in Phase 1b are considered evaluable for assessment of DLT if EITHER of the following criteria are met during the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first infusion of both Hu5F9-G4 and rituximab.
- The patient completed at least 3 infusions of Hu5F9-G4 and 2 infusions of rituximab.

For the Phase 1b part of the study, patients who withdraw before completing the 4-week DLT assessment period for reasons other than a DLT, or who do not fulfill either of the criteria above, will not be evaluable for assessment of DLT for dose review decisions and will be replaced in the cohort.

3.3. Definition of Dose-limiting Toxicity

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03 (Appendix B). A DLT is defined as any Grade 3 or greater AE that is assessed as related to study drug (Hu5F9-G4 and/or rituximab) that occurs during the 4-week DLT observation period. DLTs apply only to patients in the Phase 1b part of the study.

The following are exceptions to the DLT definition and will NOT be considered a DLT:

- Grade 3 anemia
- Grade 3 indirect/unconjugated hyperbilirubinemia without significant clinical consequences as determined by the Investigator
- Grade 3 nausea or vomiting in patients who have not received optimal treatments with anti-emetics, and that resolves to ≤ Grade 2 within 7 days
- Grade 3 diarrhea in patients who have not received optimal treatments with anti-diarrheals, and that resolves to ≤ Grade 2 within 7 days
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study
- Grade 3 Hu5F9-G4 infusion reactions in the absence of pretreatment
- Grade 3 tumor lysis syndrome or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 within 7 days
- Any grade infusion reaction attributed to rituximab
- Isolated Grade 3 laboratory abnormalities that are not deemed clinically significant by the CTSC

3.4. Phase 2 Study Design

For the Phase 2 part of the study, the loading and/or maintenance dose for each arm will be determined by the Phase 1b MTD or RP2DS (see Table 1). Once the Phase 1b dose escalation phase of the trial is completed and an RP2DS determined, the CTSC will open the Phase 2 part of the study. For the Phase 2 part of the study, patients may be enrolled simultaneously without an observation time between patients. Patients in the Phase 2 part will be enrolled in either an indolent lymphoma arm or a DLBCL arm. Treatment for patients in both of these arms will be conducted according to a Simon's two-stage Minimax design. After the appropriate number of initial-stage patients in each arm have been enrolled and followed for at least 8 weeks, an efficacy analysis will be performed as described in the Statistical Analysis Plan (SAP). The CTSC will convene to review and approve proceeding with full accrual of either or both arms, or terminate the study according to the pre-specified Simon's two-stage stopping rules described in Section 11.11. Full accrual in either arm may be opened earlier by the CTSC at any point at which sufficient antitumor activity is observed.

3.5. Number of Sites

Approximately 12 sites located in the US and United Kingdom will be included in this trial. Additional sites may be included based on enrollment and study timelines.

3.6. Estimated Study Duration and Study Closure

It is anticipated that this study will take 14 months to complete.

Subject participation will include screening, treatment, and follow-up. Screening will last up to 30 days before first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined. Treatment with Hu5F9-G4 may be continued until an unacceptable drug related toxicity occurs or until disease progression. Post treatment, subjects will be observed for disease progression and survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Interim study database lock may be implemented at the discretion of the CTSC once all Phase 2 patients enrolled have achieved at least 1 tumor efficacy assessment. The end of the study for all patients occurs at the primary completion date, which is defined as the date on which the last patient completes follow-up for safety, disease progression or survival, or when the CTSC decides to end the study.

4. SUBJECT SELECTION AND ENROLLMENT

4.1. Study Entry Criteria

4.1.1. Inclusion Criteria

1. Adults ≥ 18 years old
2. Phase 1b only: B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, relapsed or refractory to at least 1 prior regimen of NHL chemotherapy or antibody therapy with curative intent
3. DLBCL Phase 2 Cohort: Histologically confirmed de novo or transformed DLBCL expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least 1 prior regimen of NHL chemotherapy that included rituximab
4. Indolent lymphoma Phase 2 Cohort: Histologically confirmed relapsed or refractory marginal zone or follicular lymphoma (Grade 1-3b) expressing CD20 by IHC or flow cytometry, relapsed or refractory to at least 1 prior systemic therapy that included rituximab
5. Eastern Cooperative Oncology Group (ECOG) Score 0-2 (Appendix D)
6. Disease that is measurable or assessable for response according to Lugano classification for lymphomas (Appendix C)
7. Laboratory measurements, blood counts:

    - Hemoglobin > 9.5g/dL
    - Absolute neutrophil count (ANC) > $1.0x10^9$/mL
    - Platelets > $50x10^9$/ mL

8. Laboratory measurements, hepatic function:

    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5x upper limit of normal (ULN)
    - Bilirubin < 1.5x ULN or 3.0x ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent

9. Laboratory measurements, renal function:

- Serum creatinine < 1.5x ULN or calculated glomerular filtration rate (GFR) < 40 mL/min/1.73 m^2

10. Negative urine or serum pregnancy test within 30 days before administration of Hu5F9-G4 for women of childbearing potential
11. Females of childbearing potential must be willing to use 2 effective methods of contraception during and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9, whichever occurs later
12. Males must be willing to use 1 highly effective method of contraception during and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9, whichever occurs later, if the partner is a female of childbearing potential
13. Subject has provided informed consent
14. Must be willing and able to comply with the clinic visits and procedures outlined in the study protocol
15. Phase 2 only: Willing to consent to 1 mandatory pre-treatment and 1 on-treatment tumor biopsy, unless determined to not be feasible by the Investigator (reasons include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues)

4.1.2. Exclusion Criteria

1. Patients with active brain metastases (patients with stable treated central nervous system [CNS] lesions who are off corticosteroid therapy for at least 3 weeks are not considered active)
2. Prior allogeneic hematopoietic cell transplantation (autologous transplant permitted)
3. Prior anticancer therapy including chemotherapy, hormonal therapy, or investigational agents within 2 weeks or within at least 4 half-lives prior to Hu5F9-G4 dosing (up to a maximum of 4 weeks), whichever is longer. Low dose steroids (oral prednisone or its equivalent ≤ 20 mg per day) and localized non-CNS radiotherapy are not criteria for exclusion
4. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV)

5. RBC transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening. RBC transfusions are permitted during screening and prior to enrollment to meet the hemoglobin inclusion criteria.
6. History of hemolytic anemia or Evans syndrome in the last 3 months
7. Positive Direct Antiglobulin Test (DAT)
8. Prior treatment with CD47 or SIRPα-targeting agents
9. Second malignancy, except treated basal cell or localized squamous skin carcinomas, or other malignancy for which treatment was completed at least 3 years ago and for which there is no evidence of recurrence
10. Significant medical diseases or conditions, as assessed by the Investigators and Sponsor, that would substantially increase the risk/benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, severely immunocompromised state, and congestive heart failure NYHA Class II-IV
11. History of psychiatric illness or substance abuse likely to interfere with ability to comply with protocol requirements or give informed consent
12. Pregnancy or active breastfeeding

4.2. Patient Screening and Enrollment Procedures

All patients who enter the screening period for the study, which starts when the patient signs the informed consent form, receive a unique subject identification number before any study procedures are performed. This number is used to identify the patient throughout the clinical trial and must be used on all study documentation related to that patient, including if a patient is rescreened.

Patient screening laboratory assessments may be repeated beyond the initial screening assessments within the 30-day screening period. Patients who screen fail may undergo repeated screening if the patient's medical condition has changed.

All patients who provide informed consent must be registered in the electronic data capture (EDC) system, including any screen failures.

A patient is defined as enrolled in the study once all eligibility criteria have been satisfied and the Sponsor has approved the cohort or study arm assignment. After signing the informed consent, eligible patients are expected to receive the first dose of Hu5F9-G4 (Study Day 1) within 30 days.

4.3. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the Institutional Review Board/Research Ethics Committee (IRB/REC)-approved informed consent form (ICF) prior to participation in any study specific procedure. Data from assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period. The participant must receive a copy of the signed and dated consent documents. A signed copy (in paper or electronic format) of the consent documents must be retained in the medical record or research file.

4.4. Registration Process

Patient will be assigned the subject identification number at the time of consent. The site will register the patient via interactive web/voice response technology (IXRS) with the Sponsor or representative within 2 days of consent.

Prior to being assigned a dose cohort or treatment arm, subjects must have signed the informed consent and satisfied all of the eligibility criteria. Once a subject has been assigned to a dose cohort, they will be considered enrolled. The Investigator and clinical team will determine the eligibility of the patient. The Sponsor will review the inclusion/exclusion worksheet prior to dose cohort assignment.

5. STUDY DRUG INFORMATION

Detailed instructions for Hu5F9-G4 and rituximab preparation and handling are provided in the Pharmacy Manual.

5.1. Hu5F9-G4

5.1.1. Physical Description of Study Drug

The active pharmaceutical ingredient (API) is Hu5F9-G4, a humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce Fab arm exchange. It comprises a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid heavy gamma chains and two identical 219 amino acid kappa light chains. Hu5F9-G4 targets the human CD47 antigen. Hu5F9-G4 drug product is provided in a liquid dosage form intended for intravenous (IV) infusion.

Hu5F9-G4 API is manufactured under current Good Manufacturing Practices.

Hu5F9-G4 is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies.

Additional details about Hu5F9-G4 are provided in the Pharmacy Manual.

5.2. Rituximab

5.2.1. Physical Description of Study Drug

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen (Appendix A). Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration.

Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL),

sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5. Rituximab solutions do not contain a preservative. Diluted solutions should be stored refrigerated (2°C−8°C).

Rituximab vials (100 mg/10 mL single-use vials and 500 mg/50 mL single-use vials) are stable at 2°C−8°C (36°F−46°F). Rituximab vials should be protected from direct sunlight.

6. TREATMENT PLAN

6.1. Study Drug Administration

The dose of each study drug will be calculated based on actual weight at enrollment (using weight obtained at either Screening or Day 1) and remains constant throughout the study, unless there is a > 10% change in weight from baseline. Modifications to the administered study drug doses should occur for a > 10% change in body weight and for dose modifications as described in Section 6.2.

All patients will receive an Hu5F9-G4 priming dose of 1 mg/kg on Day 1. The duration of the infusion of the priming dose will be 3 hours (± 30 minutes). The priming dose will be followed by either a weekly maintenance dose or twice a week loading doses for 1 week, then a weekly maintenance dose. The weekly maintenance dose schedule may be changed to every 2 or 3 weeks by the CTSC, based on PK and clinical data review. The duration of the infusion of the maintenance dose or loading dose will be 2 hours (± 10 minutes). The first maintenance dose (or loading dose) will be administered starting on Day 9, one day after the completion of the first dose of rituximab. This sequencing is being used to distinguish adverse event relationship to either rituximab or Hu5F9-G4. All subsequent maintenance doses of Hu5F9-G4 will be administered at the start of each study week (± 1 day). When both study drugs are given on the same visit day, Hu5F9-G4 will be administered at least 1 hour after the completion of rituximab administration.

For the loading dose cohort (Cohort 3), the loading doses will be administered on Days 9 and 11 (± 1 day), with the maintenance dose administered on Day 15 and repeated weekly thereafter.

All patients should be monitored for 2 hours post-infusion for Cycle 1. Post-infusion monitoring should begin after the last study drug is given. Post-infusion monitoring is not required for doses after Cycle 1, Day 22. Patients who experience any treatment-related AEs during the observation period should be further monitored as clinically appropriate.

Patients will receive a rituximab dose of 375 mg/m^2 given intravenously starting on Day 8, followed by weekly dosing on Days 15 and 22. Starting at Cycle 2, rituximab will be given on Day 1 of each cycle up to Cycle 6.

6.2. Dose Delays, Dose Modifications, and Safety Management Guidelines

6.2.1. Dose Reductions and Delay Guidelines

6.2.1.1. Hu5F9-G4

Dose modification or dose delay of Hu5F9-G4 may not occur for patients in the initial 28-day DLT assessment period in the Phase 1b part of the study or for the first cycle of patients in the Phase 2 part of the study. After the initial 28-day treatment period for evaluation of DLTs, Hu5F9-G4 may be withheld if treatment-emergent Hu5F9-G4-related AEs (as described in Section 6.4) occur. Hu5F9-G4 may be re-introduced at a 50% dose reduction if the severity has recovered to Grade 0-1 within 4 weeks and in the absence of disease progression. Patients who experience a DLT will have their treatment held for up to 4 weeks to allow sufficient time for recovery, but may restart dosing at a lower dose level if they still meet study eligibility criteria. Data from these patients will not contribute to the MTD evaluation at the lower dose level. Treatment delays of more than 4 weeks (such as for an unrelated medical condition with expected recovery) must be approved by the CTSC.

Interruption of Hu5F9-G4 Treatment

Treatment interruption for up to 2 weeks will be allowed after the start of Cycle 3 at the discretion of the Investigator and with Sponsor approval. An interruption is defined as a non-protocol-specified interruption from treatment, assessments, and procedures. Patients with an interruption of longer than 2 weeks (2 weeks is maximum allowed for an elective drug holiday) or a treatment delay of longer than 2 weeks or more must be “re-primed” by receiving the priming dose of 1 mg/kg IV over 3 hours (± 30 minutes) again prior to resuming the assigned maintenance treatment dose. For patients on a priming/maintenance/loading dose cohort who have an interruption, the maintenance dose will be resumed after re-priming.

Maintenance Dose Schedule Modification

Patients who have completed at least 8 weeks on weekly maintenance therapy may stay at the same infusion dose but may have their Hu5F9-G4 schedule of administration extended to every 2 or 3 weeks, if supported by PK data and approved by the CTSC.

Intra-patient Dose Escalation

When the RP2DS has been determined, and at the discretion of the Investigator, patients enrolled in the Phase 1b part of the study who have been on study for at least 8 weeks may have their maintenance dose escalated to the dose level that has been previously determined to be safe in this study, at the discretion of the CTSC.

6.2.1.2. Rituximab

Administration, Hypersensitivity, and Infusion Reactions

Available at the bedside prior to rituximab administration should be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions. Premedication with an antihistamine and acetaminophen is required prior to rituximab dosing, in accordance with local best practices. Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hour. If hypersensitivity or infusion-related events do not occur, infusion rate may be escalated in 50-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms resolve. Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hour, and increased at 30-minute intervals by 100-mg/hour increments to a maximum of 400 mg/hour. Rituximab infusion rate adjustments are detailed in Table 2.

Table 2. Rituximab Infusion Rate Adjustments

Infusion Rate	Fever	Rigors	Mucosal Congestion/Edema	Hypotension
Decrease ½	> 38.0°C	Mild	Mild	Mild
Interrupt	> 39.0°C	Moderate	Moderate	Mild to Moderate

NOTE: Rate adjustments should be made if any one of the above symptoms is present. Rate adjustments may proceed after symptoms resolve.

During the rituximab infusion, the patient should be monitored until the infusion is discontinued according to standard practice guidelines for rituximab. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after 1 hour of observation, the intravenous line may be discontinued. Additional details about rituximab infusion are provided in Appendix A.

Presence of Circulating Lymphoma Cells

In patients with evidence of circulating lymphoma cells in the peripheral blood, it is recommended that the initial infusion rate be reduced to 25 mg/hour as these patients may have increased propensity to infusion reactions and tumor lysis syndrome.

Cardiovascular

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions, including arrhythmias and angina, and who have had recurrences of these events during rituximab therapy, should be monitored throughout the infusion and immediate post-infusion period.

Tumor Lysis Syndrome

Rituximab rapidly decreases the number of benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory

monitoring performed. Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome. Following treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy was administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

6.2.2. Specific Safety Management Guidelines

6.2.2.1. Rituximab

Safety management guidelines for rituximab are described in Section 6.2.1.2.

6.2.2.2. Hu5F9-G4

Hemagglutination/Microangiopathy

In the Phase 1 trial experience with Hu5F9-G4 in solid tumors and AML, agglutination of RBCs has been observed on peripheral smear. Microangiopathy is a possible sequelae of hemagglutination, however this has not been observed in the current Phase 1 clinical trials to date. In addition, AEs may be associated with findings of hemagglutination. Monitoring of hemagglutination/microangiopathy includes physical exam assessments, CBCs, peripheral smears, serum chemistries, and D-dimer testing as outlined in the schedule of assessments. Peripheral smears will be read by local sites with reporting of RBC agglutination, spherocytosis, and evidence of RBC destruction (e.g., schistocytosis, fragments) when present and degree of findings quantified according to the appropriate scale (Appendix E). The degree of hemagglutination, spherocytes, and schistocytosis on peripheral smear will be captured by as not reported or 1+ to 4+ by the scoring system provided in Appendix E. Peripheral smear slides from Cycle 1will be retained by the Sponsor and stored for future analyses.

Anemia, Blood Cross-Matching, and Packed Red Blood Cell (PRBC) Transfusion Procedures

Hu5F9-G4 binds to red cells and leads to erythrophagocytosis. This, coupled with anemia from other causes in patients with cancers, means that care has to be taken with red blood cell cross matching and PRBC transfusions. There is a possibility that treatment with Hu5F9-G4 may obscure assessment of red blood cell phenotyping, although this has not been observed in patients to date.

During the screening period prior to initiation of Hu5F9-G4 therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and Direct Antiglobulin Test (DAT) will be performed for each patient as described in Section 7.3.4. This, together with using the prior phenotype, will facilitate allocation of properly cross-matched blood should a blood transfusion be warranted.

For patients after exposure to Hu5F9-G4:

1. ABO, Rh, and DAT may be pan-reactive due to Hu5F9-G4 binding to red cells. Therefore, if a non-urgent transfusion is ordered by the Investigator, perform the following procedures:

    i. Front Type: EGA Treat cells (x2 Maximum) and Warm Wash x 4 (Minimum) with 0.9% Saline.
    ii. Back Type: Perform reverse anti-human globulin for both A and B.
    iii. If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.

2. Antibody screen
   If a pan-agglutinin/warm autoantibody is present in low ionic strength solution (LISS), repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

Blood Components for Transfusion

For all elective red cell transfusions, leukocyte-reduced irradiated units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all the specified blood groups proves impractical (e.g., for MNS, local sites will decide on the best matched donor units to be used). Cytomegalovirus (CMV) matching (i.e., CMV seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

If the cross match is incompatible, the RBC units that are Coomb's crossmatch-incompatible will be selected (e.g., phenotype-matched or least incompatible) for issue at the discretion of the local site's Transfusion Service Medical Director or equivalent person, where available.

Such instances will be documented in the Transfusion Service medical exception log, along with consent signatures obtained from ordering physicians according to best practices in blood bank policies and procedures.

For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rhesus negative units if phenotyped units are not available.

Blood plasma therapy will be blood-type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

Management of Infusion Reactions

Infusion-related reactions are defined by the NCI CTCAE (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances." (See Appendix B.) For the purposes of this study, the time frame for infusion reaction assessment is the 24-hour period beginning from the start of the infusion. Recommendations for the management of infusion-related reactions are provided below.

- For Grade 1 signs and symptoms, described as mild transient reaction; infusion interruption not indicated; intervention not indicated:
    - Remain at bedside and monitor patient until recovery from symptoms.
- For Grade 2 symptoms, described as infusion interruption indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); and prophylactic medications indicated for ≤ 24 hours:
    - Stop the Hu5F9-G4 infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500-750 mg oral acetaminophen.
    - Remain at bedside and monitor patient until resolution of symptoms.
    - Corticosteroid therapy may also be given at the discretion of the Investigator.

- If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.
- If no further complications occur after 60 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.
- If symptoms recur, stop infusion and disconnect patient from the infusion apparatus.
- No further Hu5F9-G4 will be administered at that visit.
- The amount of Hu5F9-G4 infused must be recorded on the case report form (CRF).
- Patients who experience a Grade 2 infusion reaction during the post-infusion observation period that does not resolve during that time should be observed or until the AE resolves or stabilizes, with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the AE.

- For Grade 3 or Grade 4 signs and symptoms, where:
  Grade 3 is described as prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates).
  Grade 4 is described as life-threatening consequences; urgent intervention indicated.

  - Immediately discontinue infusion of Hu5F9-G4.
  - Begin an IV infusion of normal saline, and treat the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
  - The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.
  - Patients who have Grade 4 infusions occurring with the first dose will be permanently discontinued from study treatment.

- Patients who have Grade 3 infusion reactions with the first dose can be offered the opportunity to stay on study and must be given pre-medication prior to the second and subsequent doses.
- Patients with Grade 3 infusion reactions that occur for the first time with any subsequent dose may be offered the opportunity to stay on study and must be given pre-medication prior to the second and subsequent doses.
- Patients who receive premedication and still have a Grade 3 or 4 infusion reaction will be permanently discontinued from study treatment.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
- All patients with Grade 3 or greater infusion related reactions will be observed until the AEs resolve or stabilize, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

Tumor Lysis Syndrome

In the case of evidence for tumor lysis syndrome associated with Hu5F9-G4, patients will be admitted to the hospital as clinically indicated. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes. Study treatment should be held until the patient's condition resolves or stabilizes.

6.3. Duration of Therapy

Rituximab will be given for a total of 6 cycles. Hu5F9-G4 will also be given for a total of 6 cycles. In addition, patients who have not demonstrated disease progression may continue to receive Hu5F9-G4 therapy beyond 6 cycles.

All patients will have a repeat anti-drug antibody testing for Hu5F9-G4 during the Safety Follow-up Visit (30 days ± 7 days after the last dose of study drug) to assess for positive immunogenicity.

6.4. Patient Completion of the Study

Patients are expected to remain on study until completion of Cycle 6. Patients who have not demonstrated disease progression may continue to receive Hu5F9-G4 therapy beyond 6 cycles. Patients are considered to have completed active study participation when they finish the Safety Follow-up Visit 30 days (± 7 days) after their last dose of study drug.

Following the Safety Follow-up Visit, patients with ongoing drug-related AEs and serious adverse events (SAEs) will be followed for safety. If any study drug-related AEs or SAEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least every 4 weeks until resolution to baseline or stabilization of these events, unless the patient starts another anti-tumor treatment. Follow-up will stop when a patient begins another anti-tumor treatment.

All patients, including those who discontinue study treatment early, will be followed for response until disease progression and for survival for 5 years from the date of enrollment. For any patient who dies during this period, the cause of death must be reported to the Sponsor. All patients must also be followed through completion of all study treatment.

Patients are considered to have completed study participation when they are no longer followed for disease progression or survival.

7. STUDY EVALUATIONS

7.1. Schedules of Assessment for Phase 1b and Phase 2

The Schedule of Assessments (SOA) for the Phase 1b part of the study is presented in Table 3. The SOA for the Phase 2 part of the study is provided in Table 4. Unless otherwise noted, procedures are to be completed prior to any study drug infusion. Table 5 details post-treatment assessments for both phases of the study. The SOAs for pharmacokinetic assessments are presented in Table 6 for Phase 1b and in Table 7 for Phase 2, correlative studies for both phases are presented in Table 8, and CD47 receptor occupancy assessments for both phases are presented in Table 9.

Table 3. Schedule of Assessments Phase 1b

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11[n]**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**± 2**											
Assessments																										
Informed Consent	X																									
Demographics	X																									
Medical and Cancer History	X																									
Inclusion/Exclusion Criteria	X																									
Enrollment Cohort assignment [a]	X																									
Pregnancy test	X	X[b,c]													X								Q8W			
CBC w diff, platelets, retics	X	X[c]	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral Blood Smear[d]	X	X[c]	X	X			X	X	X						X								X			
Serum chemistry	X	X[c]	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous	X	X[c]	X	X			X																			
Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen	X	X[c]	X	X			X	X							X				X				X			
PT/INR, aPTT	X			X				X							X				X				X			
Type and Screen (ABO/Rh), DAT	X																									
Urinalysis	X						X																			
Correlative studies [e]		X					X		X						X											

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11[n]**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**± 2**											
Assessments																										
Pharmacokinetics [f]		X		X	X		X	X	X	X	X	X	X	X	X				X				X			
Antidrug Antibodies		X							X						X				X				X			
CD47 Receptor Occupancy [g]		X			X	X[n]	X		X																	
ECOG performance status	X	X		X			X	X	X						X				X				X			
Vital signs [h]	X	X	X	X	X	X[n]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [i]	X	X[c]		X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Assessment [j]									X																	
Visual acuity	X																									
ECG [k]	X	X			X				X																	
Tumor/lymph node biopsy, optional (within 10 days prior to first dose and (± 1 week for later samples)	X											X														
Diagnostic Imaging [l]	X														X								Q8W			
Bone marrow biopsy (for response assessment if disease involvement) [m]	X														X											
Response assessment															X								Q8W			
Adverse events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Study Drug Administration																										

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11[n]**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**		**±1**				**± 2**											
Assessments																										
Rituximab administration				X			X	X	X						X				X				C5+C6			
Hu5F9-G4 administration		X			X		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 administration (Loading Dose Cohort only) [n]		X			X	X[n]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DLT = dose-limiting toxicity; ECG = electrocardiogram; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; RO = receptor occupancy; SC = Screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
b. May use screening pregnancy test performed within 72 hours of first dose.
c. Pre-infusion assessments tests may be collected up to 72 hours before study drug treatment.
d. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage. See Section 7.3.7 for details.
e. Refer to Table 8 for Correlative studies time point details.
f. Refer to Table 6 for PK time point details.
g. Refer to Table 9 for RO time point details.
h. Prior to infusion and within 30 minutes after the end of each infusion. See Section 7.3.2 for details.
i. Full PE at screening, symptom-directed PE thereafter.
j. DLT will be assessed through the first 4 weeks of the study.
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to infusion and within 30 minutes of the end of infusion on treatment.
l. (± 1 week) See Section 7.3.5 Diagnostic Imaging for details.
m. Bone marrow biopsy will also be performed to confirm CR at any response assessment where appropriate and at disease progression.
n. Loading Dose Cohort only: For loading doses of Hu5F9-G4 administered on Days 9 and 11 may be shifted by ± 1 day, with the exception that the loading doses should not be administered on consecutive days.

Table 4. Schedule of Assessments Phase 2

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11[n]**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Informed Consent	X																							
Demographics	X																							
Medical and Cancer History	X																							
Inclusion/Exclusion Criteria	X																							
Enrollment Cohort assignment [a]	X																							
Pregnancy Test	X	X [b,c]											X								Q8W			
CBC w diff, platelets, retics	X	X [c]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral Blood Smear [d]	X	X [c]	X	X			X	X	X				X											
Serum chemistry	X	X [c]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous	X	X [c]	X	X			X																	
Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen	X	X [c]	X	X			X	X					X				X				X			
PT/INR, aPTT	X			X				X					X				X				X			
Type and Screen (ABO/Rh), DAT	X																							
Urinalysis	X						X																	
Correlative studies [e]		X							X				X											

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11[n]**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Pharmacokinetics [f]		X		X	X		X	X	X	X	X	X	X				X				X			
Antidrug Antibodies		X							X				X				X				X			
CD47 Receptor Occupancy[g]		X			X	X[n]	X		X															
ECOG performance status	X	X		X			X	X	X				X				X				X			
Vital signs [h]	X	X	X	X	X	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [i]	X	X [c]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual acuity	X																							
ECG [k]	X																							
Tumor/lymph node biopsy, mandatory (within 10 days prior to first dose and (± 1 week for later samples)	X									X														
Diagnostic Imaging [l]	X												X								Q8W			
Bone marrow biopsy (for response assessment if disease involvement) [m]	X												X											
Response assessment													X								Q8W			
Adverse events		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Study Drug Administration																								
Rituximab administration				X			X	X	X				X				X				C5+C6			

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SC**	**1**	**2**	**8**	**9**	**11[n]**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Hu5F9-G4 administration		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 administration (Loading Dose Cohort only) [n]		X			X	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DLT = dose-limiting toxicity; ECG = electrocardiogram; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; RO = receptor occupancy; SC = screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
b. May use screening pregnancy test performed within 72 hours of first dose.
c. Pre-infusion laboratory tests may be collected up to 72 hours before study drug treatment.
d. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage. See Section 7.3.7 for details.
e. Refer to Table 8 for Correlative studies time point details.
f. Refer to Table 7 for PK time point details.
g. Refer to Table 9 for RO time point details.
h. Prior to infusion and within 30 minutes after the end of each infusion. See Section 7.3.2 for details.
i. Full PE at screening, symptom-directed PE thereafter.
j. This footnote is not applicable to Phase 2.
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to infusion and within 30 minutes of the end of infusion on treatment.
l. (± 1 week) See Section 7.3.5 Diagnostic Imaging for details.
m. Bone marrow biopsy will also be performed to confirm CR at any response assessment where appropriate and at disease progression.
n. Loading Dose Cohort only: For loading doses of Hu5F9-G4 administered on Days 9 and 11 may be shifted by ± 1 day, with the exception that the loading doses should not be administered on consecutive days.

Table 5. Post-treatment Assessments, Phase 1b and Phase 2

Examination	**Study 5F9003, Post-treatment Assessments: P1b/2 NHL trial with Hu5F9-G4 + rituximab**			
Cycle (28-day Cycles)	**End of Treatment**	**Safety Follow-up**	**Long-term Follow-up**	**Survival Follow-up**
Cycle Day	Within 7 Days of EOT Decision	30 Days After Last Dose	Until disease progression or new anticancer therapy	60 months from LSE
Visit Window (Days)		**± 7 Days**		
Assessments				
Serum or urine pregnancy test		X		
CBC w diff, platelets, retics		X		
Peripheral Blood Smear		X		
Serum chemistry		X		
Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen		X		
PT/INR, aPTT		X		
Pharmacokinetics	X[c]			
Antidrug Antibodies	X	X		
CD47 Receptor Occupancy	X[d]			
ECOG performance status		X		
Vital signs		X		
Physical examination		X		
Correlative studies	X		X[a]	
Tumor/lymph node biopsy, optional			X[a]	
Diagnostic Imaging		X[b]	Q8W	
Bone marrow biopsy (for response assessment if disease involvement)			X[a]	
Response assessment	X	X[b]	Q8W	
Adverse events	X	X		
Concomitant medications	X	X		
Survival follow-up and new anticancer therapy				Q3M

Abbreviations: aPTT = activated partial thromboplastin time; CBC = complete blood count; EOT = end of treatment; LSE = last subject enrolled; M = months; NHL = non-Hodgkin's lymphoma; PT/INR = prothrombin time/international normalized ratio; W = weeks.

a. Obtained at the time of disease progression or relapse.
b. Required only if not completed within the last 4 weeks.
c. Required only in Phase 1b.
d. Required only if EOT visit is prior to Cycle 2.

Table 6. Pharmacokinetic Assessments, Phase 1b

Phase 1b	Cycle 1					Cycle 2						C3-C6	C7+	EOT
Day	1	8	9	15	22	1	2	4	8	15	22	1	1	—
Pre-rituximab infusion (within 12 hrs)		X		X	X	X						X		X
Pre-Hu5F9-G4 infusion (within 12 hrs)	X		X	X[a]	X[a]	X[a]			X[a]	X[a]	X[a]	X[a]	X	X
15min (±5 min) post Hu5F9-G4 infusion	X		X	X	X	X			X	X	X	X	X	
1 hr (±15 min) post Hu5F9-G4 infusion						X								
4 hr (±15 min) after Hu5F9-G4 infusion						X								
24 Hr (±4 hrs) after D1							X							
72 Hr (±4 hrs) after D1								X						
15min (±5 min) after Rituximab infusion		X				X						X		

C = cycle number; D = day; EOT = end of treatment; hrs = hours; min = minutes.
a. Sample to be drawn before rituximab infusion at same time as "pre-rituximab infusion" PK time point.

Table 7. Pharmacokinetic Assessments, Phase 2

Phase 2b	Cycle 1					Cycle 2				Cycle 3-6	Cycle 7+	EOT
Day	1	8	9	15	22	1	8	15	22	1	1	—
Before rituximab infusion (within 12 hrs)		X			X	X				X		
Before Hu5F9-G4 infusion (within 12 hrs)	X		X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	
15min (±5 min) after Hu5F9-G4 infusion	X		X	X	X	X	X	X	X	X	X	
15min (±5 min) after Rituximab infusion		X				X				X		

D = day; EOT = end of treatment; hrs = hours; min = minutes.
a. Sample to be drawn before rituximab infusion at same time as "pre-rituximab infusion" PK time point.

Table 8. Correlative Studies Sample Time Points, Phases 1b and 2

Time Points	Cycle 1		Cycle 2	Cycle 3	EOT
Day	1	15	1	1	—
Phase 1					
Pre-study drug infusion	X	X	X	X[a]	X
2 hours (± 15minutes) after Hu5F9-G4 infusion	X				
Phase 2					
Pre-study drug infusion	X		X	X[a]	X
2 hours (±15minutes) after Hu5F9-G4 infusion	X				

EOT = end of treatment.
a. Should be performed with Diagnostic Imaging (± 7 days from Cycle 3, Day 1).

Table 9. CD47 Receptor Occupancy Sample Time Points, Phases 1b and 2

Time Points	Cycle 1				Cycle 2	EOT
Day	1	9	11	15	1	—
Pre-study drug infusion	X	X	X[a]	X	X	X
2 hours (± 15minutes) after Hu5F9-G4 infusion	X	X	X[a]			

EOT = end of treatment.
a. For loading dose cohort only.

7.2. Screening Assessments

7.2.1. Screening Assessments

The following procedures are to be completed during the screening period:

- Confirmation that the Informed Consent Form has been signed and consent process has been documented.
- Confirmation that all inclusion/exclusion criteria have been met.
- Demographic data including sex, date of birth, age, race, and ethnicity.
- Vital signs: blood pressure, heart rate, respiration, temperature, height and weight.
- Physical examination (complete) and ECOG (Appendix D).
- Visual acuity assessment using a Snellen chart or comparable eye chart.

- Single electrocardiogram (ECG).
- Relevant medical and cancer history will be completed through consent (all findings recorded on the medical history eCRF).
- Documentation of concomitant and prior medications.
- Serious adverse event reporting.
- Reporting of adverse events caused by a protocol-mandated intervention (e.g., AEs related to invasive procedures such as biopsies)
- Urine or serum pregnancy test (in women of childbearing potential).
- Local laboratory values, including hematology, serum chemistry, and urinalysis (Table 10).
- Local laboratory Type and Screen (ABO/Rh) and DAT. (Details are provided in Section 6.2.2.2).
- Local laboratory Peripheral Blood Smears. (Details are provided in Section 7.3.7).
- CD47 Receptor Occupancy. (Details are provided in Section 7.10).
- Tumor/lymph node biopsy (within 10 days prior to first dose of drug): optional for Phase 1b, mandatory for Phase 2.
- Diagnostic imaging (Historic imaging may be used for screening if performed within 30 days of the first dose of Hu5F9-G4. Details are provided in Section 7.3.5).

Screening assessments will be completed within a 30-day screening period prior to the enrollment. Patients may qualify for enrollment at any time during the 30-day screening period. Assessments performed as part of standard of care prior to ICF signature may be used if they are within the required screening period.

7.3. Description of Study Procedures

Study procedure timing is provided in Section 7.1, Schedule of Assessments Tables.

7.3.1. Physical Examination

Complete physical exam should be performed at Screening. Thereafter, symptom-directed physical exams are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and central nervous system (CNS).

7.3.2. Vital Signs

Vital signs should include heart rate, respiratory rate, blood pressure, temperature, and weight. Height should be recorded during Screening only. Weight should be recorded during Screening and on Day 1 of each cycle. Vital signs are to be recorded prior to infusion and within 30 minutes of the end of infusion. On visits that include infusions of both study drugs, vital signs are to be recorded prior to infusion and within 30 minutes of the end of infusion of each study drug.

7.3.3. Electrocardiographs

One ECG will be performed at screening. Triplicate ECGs will be performed pre-dose (within 2 hours of infusion) and at peak concentration within 30 minutes of the end of infusion for Phase 1b only.

7.3.4. Type and Screen (ABO/Rh), DAT

Due to the risk of developing anemia, blood phenotyping, type and screen (ABO/Rh), and direct antiglobulin test (DAT) should be performed at screening before exposure to Hu5F9-G4. Full phenotyping should be performed if the patient has not been transfused in last 3 months and should include ABO, Rh, D, C, E, Kell, Kidd, Duffy, MNS, and antibody screen. Treatment with Hu5F9-G4 may make phenotyping difficult due to expected coating of the RBC membrane. In addition, patients who experience a drop in hemoglobin to below 9 g/dL at any time, or patients in whom clinical findings indicate a possible need for transfusions, it is recommended but not required that a Type and Screen and DAT be performed.

7.3.5. Diagnostic Imaging

Appropriate cancer staging assessments should be performed (e.g., fluorodeoxyglucose [FDG] positron emission tomography/ computed tomography [PET/CT] for patients with lymphoma). Imaging assessments should be conducted according to Lugano classification for lymphomas (Appendix C). The same imaging modality used at screening should be used throughout the study. Because patients treated with immunotherapies may show

pseudoprogression, patients with progressive disease (PD) may remain on treatment until PD is confirmed > 4 weeks later (Nishino 2013; Hodi 2016) by repeat imaging.

7.3.6. Pregnancy Test

Pregnancy tests are required only for women of childbearing potential (excluding patients who are post-menopausal with absence of menses for at least 1 year and/or surgically sterilized). A urine or serum pregnancy test is required at screening and within 72 hours prior to dosing on Day 1. The Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was done within the 72 hours prior to dosing. Pregnancy tests will be performed every 8 weeks.

7.3.7. Peripheral Blood Smear Assessment

Peripheral smears will be collected prior to study drug infusion and assessed for the presence of hemagglutination in addition to standard cell morphology assessment. These labs should be drawn in arm contralateral to the drug infusion if possible. Peripheral smears will be evaluated per Appendix E. For patients undergoing blood transfusion, peripheral smears will be performed prior to blood transfusion and again 2 hours (± 30 minutes) after completion of the transfusion. Peripheral smear slides from Cycle 1 (first 28 days) will be collected, shipped to the Sponsor, and stored for future analyses.

7.3.8. Adverse Events

At each visit all AEs observed by the Investigator or reported by the patient that occur after the first dose of study drug through 30 days after the last dose of study drug, are reported using the applicable electronic case report form (eCRF; Section 9). Procedure-related AEs will be captured from the time of informed consent on.

Following 30 days after the last dose of investigational product, Investigators should report any SAEs that are felt to be related to Hu5F9-G4.

7.3.9. Concomitant Medications

All concomitant medications taken by a patient while on study are to be documented. Concomitant medication information is to be collected after the first dose of study drug

through the end of 30-day Safety Follow-up Period. Concomitant medication associated with procedure related AEs will be captured from the time of informed consent on. Information to be collected includes therapy name, indication, dose, unit, frequency, route, start date, and stop date, and are to be reported using the applicable electronic case report form (eCRF).

7.4. End-of-treatment Visit

End of Treatment visit to be completed within 7 days of the decision to end treatment with Hu5F9-G4.

- Pharmacokinetic sample collection (for Phase 1b only). Separate PK samples will be collected for Hu5F9-G4 and rituximab.
- Antidrug Antibodies
- CD47 Receptor Occupancy
- Correlative Studies
- Response Assessment (See Section 10.1.1)

7.5. Safety Follow-up Visit

Safety Follow-up visit to be completed within 30 days (±7 days) after the last dose of Hu5F9-G4.

- Local Laboratory
    - CBC (w diff, platelets, retics)
    - Serum chemistry
    - Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen
    - PT/INR, aPTT
- Local laboratory Peripheral Blood Smear
- Serum or urine pregnancy test (in women of childbearing potential)
- Antidrug Antibodies
- ECOG performance status (Appendix D)
- Vital signs

  - blood pressure
  - heart rate
  - respiration
  - temperature
  - weight

- Physical examination (symptom-directed)
- Diagnostic Imaging. (± 7 days), if not performed within the last 4 weeks. (Section 7.3.5)
- Response Assessment (± 7 days), if not performed within the last 4 weeks. (Section 10.1.1)

7.6. Long-term Follow-up

Patient will be followed until disease progression or until they begin a new anticancer therapy.

- Diagnostic imaging (± 7 days), every 8 weeks. (Section 7.9).
- Bone marrow biopsy (for response assessment if disease involvement (± 7 days) for confirmation of complete response (CR) (Section 7.9)
- Response Assessment (± 7 days), every 8 weeks (Section 10.1.1)

For patients who achieve a partial or complete response while on study, a repeat disease assessment will be obtained at the time of disease progression or relapse whenever possible. These assessments include:

- Blood sample for correlative studies, optional tumor/lymph node core, or excisional biopsy
- An additional (optional) bone marrow aspirate and biopsy for correlative studies, for patients who receive a bone marrow aspirate and biopsy for response assessment

Following the Safety Follow-up Visit, patients with ongoing drug-related AEs and SAEs will be followed for safety. If any study drug-related AEs or SAEs are ongoing after the Safety Follow-up Visit, follow-up with the patient will occur at least every 4 weeks until resolution

to baseline or stabilization of these events, unless the patient starts another anti-tumor treatment. Follow-up will stop when a patient begins another anti-tumor treatment.

7.7. Survival Follow-up

All patients who permanently discontinue all study treatment for disease progression (according to the Lugano classification for lymphomas; Appendix C), clinical progression, unacceptable toxicity, partial withdrawal of consent, or administrative decision will be contacted during a clinic visit or by telephone to assess survival, disease progression (if not documented previously), and the commencement of new cancer therapy following the last administration of study drug. Patients will be contacted every 3 months (± 1 month) from the date of the Safety Follow-up Visit, until 60 months from the date that the last patient is enrolled into the study or full withdrawal of consent. For any patient who dies during this period, the cause of death must be reported to the Sponsor.

7.8. Safety Assessments

All analytes will be assessed by the local laboratory or specialty laboratories according to Table 10.

Table 10. Analyte Listing

Chemistry	Hematology	Urinalysis	Other Laboratory Measurements
Sodium	RBC	Red blood cell	Pregnancy
Potassium	Hemoglobin	Glucose	Correlative studies [a]
Chloride	Hematocrit	Protein	Pharmacokinetics [a]
Bicarbonate	Platelets	Urine pH	CD47 Receptor Occupancy [a]
Total protein	WBC Differential	Ketones	Anti-drug Antibodies [a]
Albumin	• Neutrophils	Bilirubin	Type and Screen (ABO/Rh), DAT
Calcium	• Eosinophils	Urine specific gravity	
Magnesium	• Basophils		
Phosphorus[b]	• Lymphocytes		
Glucose	• Monocytes		
BUN or Urea			
Creatinine	Reticulocytes		
Uric acid[b]	Haptoglobin		
Total bilirubin	D-Dimer		
Direct bilirubin	PT, aPTT, and INR		
Alkaline phosphatase	Thrombin		
LDH	Plasma fibrinogen		
AST (SGOT)	Peripheral Blood Smear		
ALT (SGPT)			
Alkaline Phosphatase			

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DAT = direct antiglobulin test; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = erum glutamic pyruvic transaminase; SOA = Schedule of Assessments; WBC = white blood cells

a. These assays may be performed at a specialty laboratory.
b. Refer to Section 7.1 SOA tables for collection time points.

7.9. Efficacy Assessments

Patients will be assessed for response using the Lugano classification for lymphomas (Appendix C). The first response assessment will occur at Cycle 3 Day 1 (± 7 days). Subsequent response assessments will occur every 8 weeks (± 7 days). Because patients treated with immunotherapies may show pseudoprogression, patients with PD may remain on treatment until progressive disease is confirmed > 4 weeks later (Nishino 2013; Hodi 2016). Response assessment will be obtained at treatment termination, unless a prior radiographic

assessment has been performed within the last 7 days or at a prior response assessment that documented progressive disease.

For patients with disease involvement in the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at first response assessment at end of Cycle 2. In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a complete response, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

7.9.1. Immunogenicity

Peripheral blood for immunogenicity assessments for anti-drug antibodies against Hu5F9-G4 will be collected on Day 1 before infusion and then approximately every 4 weeks and 30 days after the last dose. When collected on the day of study drug dosing, the blood sample must be collected pre-dose. A precise, sensitive, and reproducible qualitative electrochemiluminescent (ECL) assay will be used to measure antibodies to Hu5F9-G4 in serum samples. This assay has been validated in cynomolgus monkey serum and has been used for the IND-enabling non-human-primate toxicology study for Hu5F9-G4 (PR013/20044845) and in Phase 1 clinical trials with Hu5F9-G4 (Studies SCI-CD47-001 and SCI-CD47-002). For patients who have tested positive for antidrug antibodies (ADA), the impact of ADA on PK, safety, and biologic activity will be assessed. Neutralizing antibodies to Hu5F9-G4 will also be assessed for patients who test positive for ADA. Antidrug antibodies to rituximab may be assessed if the CTSC or Sponsor determines such testing is needed.

7.10. Pharmacodynamic and Biomarker Assessments

CD47 Receptor Occupancy

Testing for CD47 receptor occupancy on select target cells enables pharamcodynamics testing of Hu5F9-G4 to inform both safety and efficacy parameters. First, the degree of saturation of CD47 receptors on red blood cells serves as a pharmcodynamics assessment for degree of anemia. Second, CD47 receptor occupancy on WBCs and circulating or bone marrow-resident lymphoma cells provides information on the level of CD47 saturation of the

internal CD47 tissue sink and drug exposures on tumor cells, respectively. Samples for CD47 receptor occupancy studies in the peripheral blood will be collected according to the schedule presented in Table 9. In settings in which there is disease involvement of the bone marrow, a bone marrow aspirate sample will be obtained on Cycle 3 Day 1 (± 7 days) for response assessment. For patients who have consented, a separate bone marrow aspirate sample will be collected at the same time to assess CD47 receptor occupancy in the bone marrow, additional correlative study assessments, and biobanking. CD47 receptor occupancy studies, as described in Section 7.1 SOA tables, will performed in both the Phase 1b and Phase 2 parts of the study. However, at the discretion of the CTSC, CD47 receptor occupancy studies may not be performed in Phase 2 if sufficient data is collected in the Phase 1b part of the study.

Correlative Blood Samples

Correlative studies will be performed on peripheral blood samples to determine the biologic activity of Hu5F9-G4 in combination with rituximab on circulating immune cells and molecular subtypes of NHL. These studies may include, but are not limited to, investigations of plasma cytokine levels, characterization of circulating T cells, and other studies. Where applicable, blood samples will be collected according to the schedule presented in Table 8. If at any point in the study the CTSC determines that sufficient correlative data have been generated, it may halt the collection and analysis of these samples.

Measurement of Plasma Cytokines

Cytokine release by immune cells is one surrogate measure of immune cell activation (including T cells and macrophages). Since Hu5F9-G4 activates both macrophages and T cells, it is hypothesized that a specific cytokine profile relating to immune cell activation will correlate with clinical response to therapy. The platform allows for a high-throughput analysis of a multitude of cytokines and chemokines with high sensitivity (Swartzman 1999). This predefined multiplex panel of human cytokines will be measured from a small thawed vial of plasma, detecting and quantifying the soluble proteins and peptides which help control cellular function. The observed systemic biochemical changes in the blood may provide a further correlate with tumor progression and therapeutic response and help provide a much

broader understanding of disease. A specific focus on cytokines involved in macrophage, dendritic cell, and T-cell activation/repression will be explored given the nonclinical mechanism for Hu5F9-G4 to engage these immune cells.

Characterization of Circulating T Cells

In nonclinical studies, macrophage-mediated phagocytosis of tumor cells by an anti-CD47 antibody leads to cross-presentation of antigens and subsequent T-cell activation (Tseng 2013). It is therefore predicted that Hu5F9-G4 administration may lead to T-cell activation in patients. Peripheral blood samples will be collected and T-cell activation/repression markers/studies may be performed on CyTOF, in vitro T-cell activation assays, and T-cell receptor sequencing. Additional peripheral blood mononuclear cells (PBMCs), serum, and plasma at the specified time points will also be cryopreserved and biobanked for future analyses.

Tumor and Bone Marrow Biopsies

Tumor and bone marrow biopsies will be collected to investigate study drug modulation of the tumor environment, penetration into the tumor, and correlation of anti-tumor response to molecular subtypes of NHL. Analysis of immune cell composition within these tumor samples will be performed by IHC, immunofluorescence, or other similar assay to include macrophage, lymphocyte, and other immune cell subsets. Markers of immune cell activation may also be investigated by flow cytometric analysis or other similar method, in addition to frequency of immune cell infiltrates within the tumors. The degree of immune cell infiltrates pre- and post-treatment will be correlated with response rates as described in the SAP. It is hypothesized that higher levels of macrophage and/or T-cell infiltration in the tumor either pre-treatment or post-treatment will correlate with a clinical response to therapy.

From the tumor biopsies obtained according to Section 7.1, detection of the presence of study drug (Hu5F9-G4 and/or rituximab) saturation in tumors will be determined. Saturation of tumor cells with Hu5F9-G4 and/or rituximab will be determined by measuring levels of Hu5F9-G4, human IgG4, and/or anti-rituximab antibodies. Analysis of Hu5F9-G4 penetration into tumor tissue will be analyzed in paired treatment biopsies obtained from study patients. The proportion of patients with Hu5F9-G4 presence in tumor tissues as

measured by IHC (1+ or greater) will be calculated for each expansion cohort independently, and the 95% confidence intervals for each will be determined. The degree of study drug tumor saturation pre- and post-treatment will be correlated with response rates as described in the SAP.

From the same tumor biopsies, DNA/RNA sequencing may be performed to assess for genomic mutations, gene expression changes, cell-of-origin status, and presence of neoantigens pre and post initiation of therapy. Paired peripheral blood samples may also be used for sequencing to aid in determining germline status. Remaining tumor samples at the specified time points may be cryopreserved and biobanked for future analyses.

Tumor and bone marrow biopsies will be obtained in both Phase 1b and Phase 2 parts of the study. In the Phase 1b part, tumor and bone marrow biopsies are optional. For the Phase 2 part, tumor and bone marrow biopsies are mandatory, unless the Investigator determines that it is not feasible. Reasons for biopsy not being feasible could include, but are not limited to, lack of accessible tumor tissue to biopsy and patient safety issues. A tumor (lymph node) biopsy will be obtained prior to treatment (within 10 days prior to first dose of study drug) and on Cycle 2 Day 8 (± 7 days). Core biopsies will be collected at these time points. Where possible, excisional biopsies are preferred over core biopsies. In cases in which there is known disease involvement of the bone marrow, a bone marrow aspirate and biopsy will be conducted prior to treatment (within 10 days prior to first dose of study drug) and on Cycle 3 Day 1 (± 7 days) for response assessment. A separate aspirate sample is also to be collected at the same time to assess CD47 receptor occupancy in the bone marrow, additional correlative study assessments, and biobanking. Additional histology slides of the bone marrow core biopsy are to be collected for exploratory studies. It is not necessary to collect a separate core biopsy from the one collected for clinical diagnosis.

In addition, for patients who achieve a partial or complete response while on study, a repeat tumor biopsy and bone marrow aspirate/biopsy (where applicable) will be collected at the time of disease progression or relapse whenever possible. This will be a core or excisional biopsy that is optional, based on patient consent. A separate (optional) bone marrow aspirate

and biopsy will be collected from patients for whom there is evidence of bone marrow disease at time of progression/relapse or evidence of bone marrow disease pre-treatment.

8. STUDY DISCONTINUATION

8.1. Withdrawal of Subjects from Treatment

Subjects who withdraw from study drug during the treatment period should be encouraged to return for an End of Treatment visit for evaluation of safety within 7 days of the decision to end Hu5F9-G4 treatment. The studies to be performed at end of treatment are listed in the Schedules of Assessments, Section 7.1. It is strongly encouraged that patients to return for their Safety Follow-up Visit 30 days (± 7 days) after their last dose of study drug. The Safety Follow-up Visit assessments are described in Table 5. All patients who withdraw from study drug treatment will be followed for disease response and survival.

8.2. Withdrawal of Subjects from Study

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. Patients (or a legally acceptable representative) may decline to continue receiving study drug and/or other protocol-required therapies or procedures at any time during the study. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data may be included after withdrawal of consent. The Investigator is to discuss with the patient the appropriate procedures for withdrawal from the study. The patient's health and welfare is the primary consideration in any determination to discontinue study drug. The Investigator or Sponsor has the right to discontinue any patient from study participation.

Reasons for patient discontinuation may include, but are not limited to, the following:

- Patient's request, with or without a stated reason
- Evidence of tumor progression
- Protocol specified reason
- Clinically significant deterioration of the patient's condition including clinically significant study drug-related adverse events
- Noncompliance
- Pregnancy
- Sponsor's discretion

8.3. Study Termination

Forty Seven Inc. reserves the right to terminate the study at any time. Both Forty Seven Inc. and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The Investigator is to notify the IRB/independent ethics committee (IEC) in writing of the study's completion or early termination and send a copy of the notification to Forty Seven Inc.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters and Definitions

Safety assessments will consist of recording all AEs and SAEs; protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Forty Seven Inc. or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive, and/or local regulatory requirements.

Forty Seven Inc. or its designee is responsible for reporting, in writing, all unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event.
Forty Seven Inc. or its designee will report other relevant SAEs associated with the use of the study medication to the regulatory agencies and competent authorities within 15 calendar days of notification.

9.1.1. Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with a patient's cancer that were not present prior to the AE reporting period (see Section 9.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)

- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies)
- Preexisting medical conditions, judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

9.1.2. Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the Investigator (i.e., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

9.2.1. Adverse Event Reporting Period

After signing of informed consent, but prior to initiation of study medications, all SAEs in addition to AEs caused by a protocol-mandated intervention will be collected (e.g., AEs related to invasive procedures such as biopsies).

After initiation of the study treatment, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or the study discontinuation/early termination visit, whichever is later. After this period, Investigators are to report only SAEs that they assess to be related to Hu5F9-G4 treatment.

See Section 9.5 for post-treatment AE reporting.

9.2.2. Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

> "How have you felt since your last clinic visit?"
> "Have you had any new or changed health problems since you were last here?"

9.2.3. Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the Investigator will make an assessment of seriousness (see Section 9.1.2 for seriousness criteria), severity (Table 11), and cause. Table 12 provides guidance for assessing the causal relationship to the investigational product.

The AE grading (severity) scale NCI CTCAE v4.03 (Appendix B) will be used for AE reporting as shown in Table 11. Regardless of severity, some events may also meet regulatory serious criteria (see Section 9.1.2).

Table 11. Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03

a. Use the alternative descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE listing.

To ensure consistency of causality assessments for either study drug, Investigators should apply the following general guidelines:

Table 12. Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Abbreviations: AE = adverse event; SAE = serious adverse event.

NOTE: The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, Forty Seven Inc. or its designee, will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

9.3. Procedures for Recording Adverse Events

9.3.1. Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs on the eCRF. Avoid colloquialisms and abbreviations.

A separate Adverse Event eCRF should be used for each medical concept that needs to be recorded. Drug-related AEs and SAEs should be recorded as either attributed to Hu5F9-G4, rituximab, or both drugs.

9.3.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on a separate eCRF. If a diagnosis is subsequently established, it should be reported to Forty Seven Inc. according to the CRF Completion Guidelines.

9.3.1.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE on the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

9.3.1.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

9.3.1.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

9.3.1.5. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 9.2.1), regardless of attribution, will be recorded on an eCRF and expeditiously reported to the Sponsor. This includes death attributed to progression of disease.

If the death is attributed to progression of disease, record "disease progression" as the SAE term on the SAE Report Form.

When recording a death on an eCRF or SAE Report Form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept.

9.3.1.6. Worsening of Disease

Worsening of and/or progression of disease should not routinely be recorded as an AE or SAE if not resulting in death. These data will be captured as efficacy assessment data. However, worsening and/or progression of lymphoma should be recorded an SAE if fatal (Section 9.3.1.5) or if the Investigator assesses the disease progression to be related to study treatment.

9.3.1.7. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

9.3.1.8. Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

Pregnancy

Any pregnancy occurring in a patient or a patient's partner during treatment with either study drug or within 6 months of last study drug administration must be reported to the Sponsor's safety CRO (Section 9.4.2) within 24 hours of the site staff becoming aware of it using a Pregnancy Notification Form (provided in the Investigator Trial File). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner.
The safety CRO will follow-up all pregnancies for the pregnancy outcome through the Investigator, using a Pregnancy Outcome Form. Data will be collected regarding the pregnancy, fetal status, and neonate status, and in the event that the neonate has

abnormalities at birth, additional data will be collected for the infant regarding those abnormalities. Spontaneous abortion should always be classified as serious (as the Sponsor considers this medically significant), recorded on a Serious Adverse Event Form (SAE Form) and expeditiously reported to the Sponsor as described in Section 9.4.2. Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be recorded and reported as an SAE. Those patients who have a negative serum or urine pregnancy test before enrollment must agree to use two highly effective forms of contraception (oral; injected or implanted hormonal contraception and condom; have an intra-uterine device and condom; diaphragm with spermicidal gel and condom), effective at the first administration of Hu5F9-G4, throughout the trial, and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9, whichever occurs later.

Male patients with partners of child-bearing potential must agree to take measures not to father children by using one form of highly effective contraception (condom plus spermicide), effective at the first administration of Hu5F9-G4, throughout the trial, and for 12 months after the last dose of rituximab or 4 months after the last dose of Hu5F9, whichever occurs later. It should be explained to the patient that if his partner is pregnant or breastfeeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn fetus or the baby being exposed to study drug.

Overdose

An overdose is a dose higher than that indicated in the protocol) with or without an AE.

Abuse or Misuse

Abuse or misuse of a study drug is use for nonclinical reasons, with or without experiencing an AE.

9.4. Expedited Reporting Requirements for Serious Adverse Events

9.4.1. Reporting Requirements for Fatal/Life Threatening SAEs Related to Investigational Products

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the Investigator to either of the study drugs will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an SAE Form within 24 hours as described in Section 9.4.2.

Medical Monitor Contact Information for Sites:

Medical Monitor: Mark Chao M.D., Ph.D.
Telephone No.: 1-650-776-7388
Alternate Telephone No.: 1-650-352-4141
email: safety@fortyseveninc.com

Alternate Medical Monitor Contact Information for Sites:

Medical Monitor: Chris Takimoto M.D., Ph.D.
Telephone No.: 1-210-394-9716
Alternate Telephone No.: 1-650-352-4132

9.4.2. Reporting Requirements for All SAEs

Investigators will submit reports of all SAEs, regardless of attribution according to the instructions provided in the Study Reference Manual.

9.5. Type and Duration of Follow-Up of Patients after Adverse Events

The Investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, are determined to be irreversible by the Investigator, the patient initiates alternate therapy for their cancer, the patient is lost to follow-up, or it has been determined that the study treatment is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

The Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

9.6. Post-Study Adverse Events

For patients who discontinue the study treatment and have completed the 30-day safety follow-up visit, Investigators are to report any death, other SAE, or event occurring beyond 30 days following the last administration of Hu5F9-G4 that the Investigator assesses as related to Hu5F9-G4.

Investigators are to report these events as described in Section 9.4.2.

10. MEASUREMENT OF EFFECT

10.1. Antitumor Effect – Hematologic Tumors

Patients will be assessed for response using the Lugano Classification for lymphomas (Appendix C). Preliminary efficacy will be assessed by the evaluation of response of target lesions, evaluation of best overall response of target lesions from the start of the treatment until disease progression/recurrence, and the duration of response of target lesions. The first response assessment will occur at Cycle 3, Day 1 (± 1 week). Subsequent response assessments will occur every 8 weeks (± 1 week). However, because patients treated with immunotherapies may show pseudoprogression, patients with PD may remain on treatment until progressive disease is confirmed > 4 weeks later (Nishino 2013; Hodi 2016). Response assessment will be obtained at treatment termination, unless a prior radiographic assessment has been performed within the last 7 days or at a prior response assessment that documented progressive disease. Definitions of response parameters are provided below. For patients with disease involvement in the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at the first response assessment at the beginning of Cycle 3
In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a complete response, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

Overall Response Rate

Response rate is determined by Lugano classification for lymphomas (Appendix C). ORR is defined as PR+CR. Response rates for this endpoint will be defined as those patients who have received Hu5F9-G4 and rituximab at the RP2DS for whom a baseline (before study drug exposure) and the first 8-week (± 1 week) tumor assessment are available.

Best Overall Response

BOR is measured as the best response recorded from start of study treatment until the first date that recurrent or progressive disease is objectively documented.

Duration of Response

DOR is measured from when first response is met (i.e., CR or PR) until the first date that recurrent or progressive disease is objectively documented.

Progression-Free Survival

The length of PFS is defined in whole days as the time from entry into the study until disease progression or death from any cause. Patients who are not observed to progress or die during the course of the trial will be censored at their last known progression-free follow-up date.

Overall Survival (OS)

The length of OS is defined in whole days as the time from entry into the study until death from any cause. Patients who are not observed to die during the course of the trial will be censored at their last known follow-up date.

10.1.1. Evaluation of Response

Response and progression will be evaluated in this study using Lugano classification, reproduced from Cheson et al., 2014 (Appendix C), according to Table 13 below.

Table 13. Lugano Classification of Response in Non Hodgkin's Lymphoma

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 13 Lugano Classification of Response in NHL (Continued)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson 2014.

For patients staged with PET/CT, focal uptake in nodal and extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. For patients staged with CT, up to 6 of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in 2 diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

A measurable node must have an LDi greater than 1.5 cm. Measurable extranodal disease (e.g., hepatic nodules) may be included in the 6 representative, measured lesions.

A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target disease (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites). In patients in whom a discordant histology or malignant transformation is suspected, a PET/CT may identify the optimal site to biopsy for confirmation.

The following modifications to the Lugano classification will be made for this study protocol:

- **Progressive disease:** Because patients treated with immunotherapies may show pseudoprogression, patients with PD may remain on treatment until PD is confirmed > 4 weeks later (Nishino 2013; Hodi 2016).
- **Bone marrow assessment:** For patients with disease involvement of the bone marrow prior to treatment, a bone marrow aspirate and biopsy will be performed at first response assessment at the beginning of Cycle 3 In addition, a bone marrow assessment will be conducted to confirm CR, which may occur at any response assessment time point. If a patient achieves a complete response, subsequent bone marrow aspirate and biopsies are not required to be performed, but may be performed at the Investigator's discretion.

10.1.2. Assessment of Evaluable Rather Than Measurable Disease

Patients with evaluable but not measurable response will be assessed with the study used to establish evaluable disease at least every 8 weeks.

10.1.3. Assessment of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for PD the smallest measurements recorded since the treatment started.

10.1.4. Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease (SD) is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment began.

10.1.5. Time to Progression

The time to progression is the time from enrollment until PD is documented according to the Lugano classification (Appendix C).

11. STATISTICAL CONSIDERATIONS

11.1. Hypotheses

It is hypothesized that the combination of Hu5F9-G4 and rituximab will be safely tolerated and provide improved antitumor efficacy over rituximab therapy alone in patients with NHL. These hypotheses are supported by both nonclinical and current clinical data demonstrating a toxicity profile of Hu5F9-G4 that does not appear to overlap with that of rituximab and nonclinical data demonstrating synergistic activity of Hu5F9-G4 with rituximab.

11.2. Study Endpoints

The primary, secondary, and exploratory study endpoints are provided in Section 2.2.

11.3. Number of Patients

The total number of patients included in this trial will be between 63 and 72 patients. For the Phase 1b part, 9 to 18 patients will be enrolled depending on dose escalation and expansion. For the Phase 2 part, a total of 54 patients (28 patients for the indolent lymphoma arm, 26 patients for the DLBCL arm) will be enrolled assuming progression to Stage 2 for both arms.

11.4. Analysis Sets

11.4.1. Phase 1b

DLT Analysis Set

The DLT Analysis Set includes all enrolled subjects who receive at least 1 dose of Hu5F9-G4 + rituximab (study drug) and have had the opportunity to be followed for the 28-day cycle or have experienced a DLT within 28 days after initiating study drug treatment.

11.4.2. Phase 1b and Phase 2

Efficacy Analysis Set

The Efficacy Analysis Set (EAS) includes all enrolled subjects who receive at least 1 dose of study drug and for whom a baseline and at least 1 post-study drug treatment tumor assessment are available.

The analysis of ORR, BOR, and DOR will be performed on the Efficacy Analysis Set.

Full Analysis Set

The Full Analysis Set includes all enrolled subjects who receive at least one dose of study drug.

The analysis of Safety, PFS, and OS will be performed on the Full Analysis Set.

Per Protocol Analysis Set

The Per Protocol Analysis Set includes all enrolled subjects who do not have any important protocol deviations that might affect the efficacy outcomes.

A sensitivity analysis of ORR may be performed on the Per Protocol Analysis Set.

PK Analysis Set

The PK Analysis Set includes all subjects in the Full Analysis Set from whom PK blood samples are collected during the study and who have measurable concentrations of Hu5F9-G4.

11.5. Sample Size Determination

The overall sample size for this study is estimated to be between 63 and 72 patients. This sample size includes both the Phase 1b and Phase 2 parts of the study. In the Phase 1b part of the study, a standard 3+3 dose escalation design is employed to explore the MTD of the investigational combination. There are 3 dose cohort levels, with an estimated total of 9 to 18 patients in the Phase 1b depending on possible cohort expansion in a 3+3 design. In Phase 1b, patients who are not evaluable for DLT will be replaced. The Phase 2 part of the study includes two arms, enrolling indolent lymphoma or DLBCL, in which sample size is determined by Simon's two-stage Minimax design. The Phase 2 will comprise of a total of 54 patients (28 for indolent lymphoma, 26 for DLBCL) if both stages of each arm are fully accrued. For Phase 2, sample size was determined using a one-sided alpha level of 0.10 and a power of 0.80 based on a null hypothesis of 30% response rate compared to an alternative/desired response rate of 50% for indolent lymphoma and a null hypothesis of 25% response rate compared to an alternative/desired response rate of 45% for DLBCL. The null

hypothesis response rates of 30% and 25% for indolent lymphoma and DLBCL, respectively, are based on historical data for single-agent rituximab in the protocol-specified patient populations (Davis 2000; Sehn 2015; Wang 2013).

11.6. Clinical Trial Steering Committee

The CTSC will oversee the conduct of the clinical trial. A representative from the Sponsor, usually the Study Medical Monitor or designee, will chair the CTSC. The CTSC will have representation from each participating site in the study. The CTSC will review safety and efficacy data generated during the trial and make decisions about patient recruitment, trial management, initiation of protocol specific amendments, expansion of cohorts, moving to higher or lower dosing levels, defining any new dosing cohorts, identification of the recommended dose for Phase 2 trials, and interim efficacy analysis decisions for the Simon's two-stage design. The CTSC will meet at a minimum at the completion of each dosing cohort during dose escalation phase of the trial, at any protocol-specified formal interim analyses, and when emergent critical safety data are reported. The composition, structure, and function of the CTSC are defined in the CTSC Charter.

11.7. Data Monitoring Committee

Data Monitoring Committee functions for this trial will be performed by the CTSC, as defined and described in Section 11.4.

11.8. Analysis of the Conduct of the Study

The CTSC, in conjunction with the Sponsor, will be the main body responsible for the analysis of the conduct of the study, as outlined in the CTSC charter.

11.9. Statistical Methods

All analyses will be descriptive and hypothesis-generating in nature. Descriptive statistics will be provided for all safety and efficacy endpoints.

All analyses will be conducted separately for patients in the Phase 1b and Phase 2 parts of the study. However, safety analyses may be conducted for patients in both Phase 1b and

Phase 2. In addition, efficacy analyses will be conducted separately for the 2 cohorts in Phase 2.

For continuous variables, the mean, standard deviation, median, and ranges will be provided. For categorical variables, the frequency and percentage in each category will be provided, along with confidence intervals for primary and secondary efficacy endpoints. For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided. Details regarding the statistical analysis to be conducted, including the handling of missing data and patient withdrawal, will be provided in the SAP.

11.9.1. Efficacy Analyses

11.9.1.1. Primary Efficacy Endpoint: Overall Response Rate

The analysis of ORR will be conducted on the Efficacy Analysis Set. The point estimate of the ORR and the corresponding exact binomial two-sided 95% confidence interval will be generated. A sensitivity analysis of ORR will be conducted on the Per Protocol Analysis Set if more than 10% of patients in the Efficacy Analysis Set are excluded from the Per Protocol Analysis Set.

11.9.1.2. Secondary Efficacy Endpoints

Duration of Response

The analysis of DOR will be conducted on the responders only.

The KM estimate and corresponding two-sided 95% interval for the median and quartiles will be provided. The KM plot may also be provided.

Best Overall Response

The analysis of BOR will be conducted on the Efficacy Analysis Set using the same methods as the analysis of ORR.

Progression-Free Survival and Overall Survival

The analysis of PFS and OS will be conducted on the Full Analysis Set.

The KM estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided.

11.9.2. Additional Secondary Endpoints

Pharmacokinetic Analyses

PK analysis will be conducted for Hu5F9-G4 on the PK Analysis Set. Based on the distinct MOAs of Hu5F9-G4 and rituximab, overlapping drug PK interactions are not expected. Thus, samples for PK analysis for rituximab will be banked and will be conducted based on CTSC recommendation.

Sufficient measureable concentration data is required for estimation of PK parameters. The inclusion of patients with protocol violations will be assessed on a patient-by-patient basis for inclusion in the PK population prior to the analysis.

Immunogenicity Analyses

The rate and magnitude of anti-Hu5F9-G4 antibody positivity will be evaluated for individual patients, for all patients in the Phase 1b and 2 parts of the trial, and for the pooled patient population. Exploratory evaluations may be conducted to determine the relationship between immunogenicity assay positivity and one or more safety, PK, or efficacy parameters (for example, drug clearance, AEs, tumor response). Immunogenicity analysis will not be performed for rituximab as it is not expected that Hu5F9-G4 will impact the immunogenicity of rituximab and vice versa.

11.9.3. Safety Analyses

The statistical analysis of safety data will be conducted for patients in the FAS and will include patients with non-missing data for the particular safety endpoint being analyzed. Safety variables may include, but are not limited to: DLTs, treatment-emergent adverse events (TEAEs; AEs worsening or occurring during or after a patient's first exposure to study drug), vital signs, physical examinations, laboratory tests, receptor occupancy, and anti-drug antibody assessments.

Data will be presented by Phase 1b dose cohort and Phase 2 arm. Some safety data may be summarized over all Phase 1b dose cohorts and across both Phase 1b and Phase 2 parts. Data may be graphed, summarized, or listed, depending on the amount of data to be reported. Where relevant, safety data will also be presented by the study day/study day interval corresponding to dose administrations within each dose cohort.

11.9.3.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later and the NCI CTCAE v 4.03 (Appendix B) will be used to grade severity of adverse events and laboratory toxicities. Patient incidence of TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized using Investigator assessment of the relationship to study drug (related or not related). SAEs, including deaths, will be summarized and/or listed for each dose cohort and for all dose cohorts combined. These events will also be summarized by Phase 2 arm (indolent lymphoma and DLBCL) and across all Phase 2 patients. TEAEs resulting in withdrawal from study drug or further study participation will be tabulated and/or listed. DLTs will also be listed.

Adverse events that occurred during screening but before exposure to study drug will be reported in the AE line listings and appropriately identified as non-TEAEs.

Adverse events and SAEs occurring during screening will be reported separately for patients who were screened but not entered into the study with line listings and/or summary tables, along with relevant demographic data collected.

11.9.3.2. Analysis of Other Safety Endpoints

For select laboratory parameters, changes of laboratory values over time, grade shifts in laboratory value from baseline to worst on-study value and Grade 3 or higher laboratory toxicities will be summarized. The number and incidence of subjects developing receptor occupancy and anti-drug antibodies at any time will be summarized. Vital signs and physical exam will be summarized at select time points. Details will be provided in the SAP.

11.10. Handling of Missing Data

Details regarding the handling of missing data will be described in the SAP.

11.11. Interim Analysis

A Simon's two-stage Minimax design (Simon 1989) will be used in the Phase 2 part of the study. In accordance with this design, after 12 patients in the indolent lymphoma arm and/or 15 patients in the DLBCL arm are evaluable for response assessment, the CTSC will convene and provide recommendations to the Sponsor to proceed with full accrual of either or both arms, or terminate the study according to the pre-specified Simon's two-stage stopping rules. For the indolent lymphoma arm, the study will proceed to accrue the second stage if there are ≥ 3 objective responses in 12 patients. In this case 16 additional patients will be enrolled. These rules are based on the combination of Hu5F9-G4 and rituximab achieving a desired 50% ORR compared to the null hypothesis response rate of 30% which represents single-agent rituximab activity in the protocol-specified indolent lymphoma population. For the DLBCL arm, the study will proceed to accrue the second stage if there are ≥ 3 objective responses in 15 patients. These results are based on the combination of Hu5F9-G4 and rituximab achieving a desired 45% objective response rate compared to the null hypothesis response rate of 25% which represents single-agent rituximab activity in the protocol-specified DLBCL population.

12. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1. Compliance Statement

This study will be conducted in accordance with the protocol and with US Food and Drug Administration (FDA) and the ICH good clinical practice (GCP) guidelines, the Declaration of Helsinki, and any applicable local health authority and Institutional Review Board (IRB) / Independent Ethics Committee (IEC) requirements.

To the extent applicable, all references to the FDA, Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations (CFR), ICH, GCP, and the like shall be interpreted as also referring to any corresponding requirements of local regulatory agencies, regulations, and laws. If there is any discrepancy between FDA, ICH, and local requirements, the most stringent standard shall apply.

12.2. Investigator Responsibilities

As required by FDA regulation (21 CFR Part 56) and ICH guidelines for GCP, the Investigator at each study site must obtain IRB/IEC review and approval of the study protocol, ICFs, patient recruitment materials, and any other pertinent documents before any study-related activities involving patients are performed.

As required in 21 CFR Part 50 and ICH guidelines for GCP, the Investigator or designee must comply with the informed consent process, and ensure that each patient enrolled in this clinical study understands the information presented in the IRB/IEC approved ICF and agrees voluntarily to participate in the clinical study.

The Investigator or designee must submit to the IRB/IEC any written safety report or update (e.g., amended Investigator's Brochure or safety amendments and updates) provided by the Sponsor or representative, according to the IEC specific reporting requirements.

The Investigator must inform the IRB/IEC of the progress of the clinical study and report any non-administrative changes made to the protocol; in any case, the Investigator must provide an update to the IRB/IEC at least once a year or in accordance with IRB/IEC continuing approval requirements.

The Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Forty Seven Inc. Delegation of Authority Form.

The clinical study report must be signed by the Investigator or, in the case of multi-center studies, the Coordinating Investigator. The Coordinating Investigator, identified by Forty Seven Inc., will be any or all of the following:

- A recognized expert in the therapeutic area.
- An Investigator who provided significant contributions to either the design or interpretation of the study.
- An Investigator contributing a high number of eligible patients.

12.3. Institutional Review Board or Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Forty Seven Inc. before recruitment of patients into the study and shipment of Hu5F9-G4.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document.
The Investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Forty Seven Inc., in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval/renewal as applicable throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Forty Seven Inc.

12.4. Informed Consent and Human Subject Protection

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be

communicated formally in writing from the Forty Seven Inc. Study Monitor to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The Investigator is also responsible for asking the patient if the patient has a primary care physician and if the patient agrees to have his/her primary care physician informed of the patient's participation in the clinical study. If the patient agrees to such notification, the Investigator is to inform the patient's primary care physician of the patient's participation in the clinical study. If the patient does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the patient's medical record. The acquisition of informed consent and the patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient, or a legally acceptable representative, and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally acceptable representative.

If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

12.5. Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Forty Seven Inc., including the following.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment
- For Serious Adverse Events reported to Forty Seven Inc., patients are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Forty Seven Inc. (e.g., signed informed consent forms) are to be kept in confidence by the Investigator, except as described below.

In compliance with the Code of Federal Regulations(CFR)/International Conference on Harmonisation (ICH) GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

12.6. Urgent Safety Measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorization. The trial may continue with the urgent safety measures in place. **The Investigator must inform Forty Seven Inc. IMMEDIATELY if the study site initiates an urgent safety measure**.

The notification must include:

- Date of the urgent safety measure;
- Who made the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable Forty Seven Inc. to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and closeout.

12.7. Serious Breaches and Fraud

Within the UK, the Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the Medicines and Healthcare products Regulatory Agency (UK) (MHRA) within 7 days of the Sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial; or
- the scientific value of the trial”

Investigators must notify Forty Seven Inc. immediately if any serious breach of GCP is suspected.

If there is any proof of fraud this must also be reported to Forty Seven Inc. All instances of confirmed clinical trial fraud occurring at sites in the UK will be treated according to the procedure for dealing with a serious breach and must be reported to the MHRA within 7 days of the Sponsor becoming aware.

12.8. Study Monitoring

The Forty Seven Inc. representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Forty Seven Inc. representative(s) are responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Forty Seven Inc. representative(s) are to have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the Forty Seven Inc. representative(s) to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

12.9. Audits and Inspections

As stipulated by 21 CFR §312.58 and ICH guidelines for GCP, a representative of the Sponsor, the FDA, or other regulatory agencies may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including CRFs and supporting source documents. In addition, the Investigator or other qualified study site personnel are to be available to answer questions, hold interviews, and provide facility tours if requested.

12.10. Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including patients not receiving protocol-required therapies), as stipulated in the protocol for each patient in the study. For patients who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (as described in Section 7.1), the Investigator may search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. Data collection will involve the use of the electronic data capture (EDC) system, to which only authorized personnel will have access.
The Investigator agrees to maintain accurate electronic Case Report Form (eCRFs) (or paper

Case Report Forms [CRFs]) and source documentation as part of the case histories. Forty Seven Inc. will supply the eCRF, which will be completed in English.

The Investigator or designee must enter all results collected during the clinical study into eCRFs (or CRFs). Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study specific documents.

All entries made on the eCRF (or CRF), must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure patient confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data must be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the Sponsor or designee for destruction.

12.11. Maintenance of Source Documents and Record Retention

As stipulated by 21 CFR §312.57 and ICH E6 GCP Consolidated Guidance Section 8, the Investigator or designee will maintain source documentation for this clinical study that documents the treatment and study course of patients as described in the study manual.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office

charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Forty Seven Inc. and/or applicable regulatory authorities.

The Investigator must retain all essential documents for this clinical study 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 Hu5F9-G4. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. A Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. Before destroying any records, the Investigator must notify the Sponsor and reach agreement on record destruction, or the Sponsor may request an additional retention period.

12.12. Long-term Retention of Samples for Additional Future Research

Blood, tumor, or bone marrow specimens will be cryopreserved for additional analyses. These samples will be retained for long-term storage by the Sponsor and described in the informed consent.

Any blood, tissue, or biomarker sample collected according to the Schedule of Assessments (Section 7.1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study patients. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. It may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the

samples for the study. Results are stored in a secure database to ensure data integrity and control.

If permitted by local law and if informed consent is provided by the patient, Forty Seven Inc. may do additional testing on remaining samples (i.e., residual and back-up) to investigate and better understand NHL and the dose response and/or prediction of response to Hu5F9-G4; to characterize antibody response; and to characterize aspects of the molecule (e.g., mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples may be retained for up to 20 years.

Since the evaluations are not expected to benefit the patient directly or to alter the patient's treatment course, the results of these exploratory studies are not placed in the patient's medical record and are not to be made available to the patient, members of the patient's family, the patient's personal physician, or other third parties, except as specified in the Informed Consent Form.

The patient retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the patient, the Investigator is to provide the Sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures have been completed.

Information collected from samples prior to the request for destruction will be retained by the Sponsor. The Sponsor is the exclusive owner of any data, discoveries, and derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the Investigator, at the end of the storage period or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

12.13. Financing and Insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

12.14. Publication Policy

The Forty Seven Inc. publication policy is detailed in the Publication Charter.

13. REFERENCES

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14. APPENDICES

Appendix A: RITUXAN®/MabThera (rituximab) Prescribing Information

RITUXAN®(rituximab) prescribing information

Available online:

http://www.gene.com/download/pdf/rituxan_prescribing.pdf

Accessed 7 June 2016

MabThera®(rituximab) prescribing information

Available online:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf

Accessed 5 July 2016

Appendix B: National Cancer Institute Common Terminology Criteria for Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), Version 4.03

Publication date: 28 May 2009 (v4.03: 14 June 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Accessed 7 June 2016

Appendix C: The Lugano Classification for Lymphomas

Publication:

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

Available online:

http://jco.ascopubs.org/content/32/27/3059.full.pdf+html

Accessed 5 July 2016

Appendix D: ECOG Performance Status

Eastern Cooperative Oncology Group Scale of Performance Status

Publication:

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Karnofsky Performance Status

Publication:

Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

Available online:

http://ecog-acrin.org/resources/ecog-performance-status

Accessed 7 June 2016

Appendix E: Peripheral Smear Assessment

Peripheral smears will be assessed by the designated hematopathology service using the following guidelines:

RBC Agglutination	
0–9%	Not reported
10-19%	1+
20–50%	2+
51–75%	3+
> 75%	4+

Spherocytes	
0–1 cells/100 RBCs	Not reported
2–5 cells/100 RBCs	1+
>5–10 cells/100 RBCs	2+
>10–30 cells/100 RBCs	3+
> 30 cells/100 RBCs	4+

RBC Fragments/Schistocytes	
0 cells/100 RBCs	Not reported
1–2 cells/100 RBCs	1+
>2–5 cells/100 RBCs	2+
>5–10 cells/100 RBCs	3+
> 10 cells/100 RBCs	4+

All other observed findings: reported according to local laboratory hematopathology standard procedures.

These guidelines are based on the Stanford Health Care Peripheral Blood Slide Review Manual, Version 3.0, 2015, modified by Forty Seven Inc. for clarification of the following items in the original manual: RBC agglutination, 1+ = 10%, 3+ = 60-75%; Spherocytes, 2+ = 5-10 cells/100 RBCs, 3+ = 10-30 cells/100 RBCs; RBC Fragments/Schistocytes, 2+ = 2-5 cells, 3+ = 5-10 cells.

SUMMARY OF CHANGES TO PROTOCOL 5F9003

The referenced protocol has undergone through 5 versions (amendments 2 through 5) at the time of manuscript submission. Amendment 5 is the current manuscript used for the publication. The summary of changes below represent changes for each amendment.

ORIGINAL PROTOCOL 5F9003 (14 JULY 2016)

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 2 (24 August 2016)

The main purpose of amending the 5F9003 protocol is to incorporate recent revisions to the original 5F9003 protocol that were agreed to between the Food and Drug Administration and Forty Seven Inc.

The following substantial change has been made to the protocol:

• Modification to Inclusion Criterion 2 (Section 4.1.1) restricting the Phase 1b population to those patients who are relapsed or refractory to standard approved therapies.

Rationale: Clarification of prior therapy for required for inclusion in the Phase 1b part of the study.

Editorial changes and updates have been made to improve clarity and consistency throughout the document. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable.

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 3 (28 November 2016)

The main reasons for amending the 5F9003 protocol are to modify the study inclusion criteria and statistical analyses to clarify the intended patient population to be enrolled for increased study feasibility; to modify pharmacokinetic, anti-drug antibody, and correlative study timepoints to provide an enhanced understanding of these profiles for Hu5F9-G4 and rituximab; and to ensure consistency with other clinical studies of Hu5F9-G4 sponsored by Forty Seven Inc.

The following is a list of substantial changes that have been made to the protocol:

• Modified study drug administration during Cycle 1, Weeks 2-4, so that Hu5F9-G4 and rituximab are given on the same day. (Section 3.2.1, Phase 1b Dose Levels and Section 6.1, Study Drug Administration) Rationale: To reduce the time patients must spend in the clinic and increase study assessment feasibility.

• Exception to the DLT definition has been added for Grade 3 or 4 lymphopenia when present at baseline. (Section 3.3, Definition of Dose-limiting Toxicity)

Rationale: Expanded exceptions to the DLT definition based on the evolving safety profile of Hu5F9-G4 in ongoing Phase 1 trials and and to account for the rituximab mechanism of action which is known to cause lymphopenia.

• Modified Inclusion Criterion 2 to replace “standard approved therapies” with “at least 2 prior lines of therapy.” (Section 4.1.1, Inclusion Criterion 2) Rationale: Clarifies possible ambiguity in interpretation of “standard approved therapies” for patient inclusion and addresses significant patient enrollment challenges presented by this language.

• Modified Inclusion Criterion 4 to correct the grade range from Grade 1-3b to Grade 1-3a, and replaced “standard approved therapies” with “at least 2 prior lines of therapy.”

(Section 4.1.1, Inclusion Criterion 4) Rationale: To correct the grade to 3b from 3a and to specify that patients must be relapsed or refractory to "at least 2 prior lines of therapy" rather than "standard approved therapies." Clarifies possible ambiguity in interpretation of "standard approved therapies" for patient inclusion, and addresses significant patient enrollment challenges presented by this language.

• Removed Exclusion Criterion 2, which specified that patients who had prior allogeneic hematopoietic cell transplantation would be excluded from the study. (Section 4.1.2, Exclusion Criterion 2) Rationale: To allow the inclusion of patients who had prior allogeneic hematopoietic cell transplantation based on ongoing clinical data for Hu5F9-G4 and a perceived favorable risk-benefit profile.

• Added to the exclusion criterion for prior anti-cancer therapy that the maximum washout period will not exceed 4 weeks prior to the day of first treatment with Hu5F9-G4 and specified that hormonal therapy with LHRH agonists for prostate cancer and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion. (Section 4.1.2, Exclusion Criterion 2 [formerly 3]) Rationale: Set the maximum washout period and expanded inclusion of select anti-cancer therapies for accepted, well-controlled secondary malignancies and will not confound primary study endpoints.

• Added to the exclusion criterion for secondary malignancies exceptions for patients with localized prostate cancer and patients who are not on active anti-cancer therapy. (Section 4.1.2, Exclusion Criterion 8 [formerly 9]) Rationale: To allow the inclusion of patients with specific secondary malignancies whose disease is well controlled on therapy.

• Added Exclusion Criterion 9 to specify that patients with hypersensitivity to the active substance or to murine proteins, or to any of the other excipients of rituximab will not be allowed to participate in the study. (Section 4.1.2, Exclusion Criterion 9) Rationale: To address MHRA and EMA regulatory requirements.

• Specified that for patients with body weights changes of < 10%, dose modifications may be made according to local prescribing standards. (Section 6.1, Study Drug Administration) Rationale: To allow investigator discretion with respect to modifying doses for patients whose body weight change is less than that requiring a dose modification according to Section 6.2.

• Added an alternative 90-minute rituximab infusion duration for the second and later doses. (Section 6.1, Rituximab) Rationale: Allows for shorter duration of rituximab infusion than the standard infusion duration to reduce the time patients must spend in the clinic.

• Removed Table 2 (Infusion Rate Adjustments) and refer reader to local prescribing standards for guidance. (Section 6.2.1.2, Rituximab) Rationale: Because the study is now being done in more than one country, readers are advised to refer to approved guidance appropriate to their region.

• Removed the requirement that the hemagglutination quantification system of 1+ to 4+ described in Appendix E be used and specified that the presence or absence of hemagglutination and microangiopathy assessed according to the severity grading scale provided for these events. (Section 6.2.2.2, Hu5F9-G4, Hemagglutination/Microangiopathy) Rationale: Removed requirement to quanitify agglutination of 1+ to 4+ due to varying abilities of sites to report quanitification. Instead, sites are required to report presence or absence of hemagglutination only, which is needed for AE grading.

•Added the provision that alternate imaging modalities may be used at the discretion of the investigator. (Section 7.3.5, Diagnostic Imaging) Rationale: To allow for circumstances in which the diagnostic imaging modality used at screening may not be feasible for future imaging.

• Modified the timing for sample collection for peripheral blood smears so that they are performed after blood transfusions rather than before. (Section 7.3.7, Peripheral Blood Smear Assessment) Rationale: Changed peripheral smear timing to evaluate effect of transfusion on peripheral smear findings.
• Specified that AEs that occur prior to assignment of study treatment that are assessed as related to a protocol-mandated intervention must also be reported. (Section 7.3.8, Adverse Events) Rationale: Clarified reporting of AEs prior to study treatment.
• Added abstinence as a highly-effective birth control option. (Section 9.3.1.8, Other Reportable Information, Pregnancy) Rationale: To expand the options for birth control that female patients of childbearing potential and their male partners must agree to use.
• Specified that for all SAEs, reporting is to be done within 24 hours. Added specific language about the responsibilities for reporting and notification. (Section 9.4.2, Reporting Requirements for All SAEs) Rationale: To clarify SAE reporting timing and responsibilities.
• Modified the Simon two-stage minimax parameters and sample sizes for Phase 2 cohorts. (Section 11.5, Sample Size Determination) Rationale: Modifications to the patient inclusion criteria for both Phase 2 cohorts is expected to allow enrollment of a more heavily treated patient population than the prior protocol version; accordingly, the sample sizes have been adjusted and modifications made to the null and alternative hypotheses for the Simon two-stage minimax design in Phase 2.
• Additional specifications provided for the PK analysis including PK parameters, PK variables, handling of missing values, dose proportionality, and immunogenicity. (Section 11.9.2, Additional Secondary Endpoints, Pharmacokinetic Analysis) Rationale: Modified endpoints to include evaluation of the PK and anti-drug antibody profile of rituximab and added additional description of PK/ADA statistical analyses.

Editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document. Changes in sections of the protocol body were also made in the protocol synopsis, study design schema, tabular schedules of assessments, and elsewhere in the document, as applicable.

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 4 (10 February 2017)
The main reasons for amending the 5F9003 protocol is to respond to Medicines and Healthcare products Regulatory Agency (MHRA) Notice of Grounds for Non-Acceptance and Right to Amend Request based on review of Amendment 3 of the protocol submitted as part of the Non-Hodgkin's lymphoma Clinical Trial Application.
The following is a list of changes that have been made to the protocol in response to MHRA feedback:
• Issue 1, definition of qualifying event (Section 11.11, Interim Analysis) Protocol language defining a qualifying event has been modified in accordance with
MHRA feedback.
• Issue 2, pregnancy testing (Section 4.1.1, Inclusion Criterion 10; Section 7.3.6 Pregnancy Test) The wording of Inclusion Criterion 10 has been aligned with Table 3 in accordance with MHRA feedback.
• Issue 3, indirect bilirubin (Section 7.8, Safety Assessments, Table 10 Analyte Listing) Indirect bilirubin has been added to Table 10, Analyte Listing, in the chemistry column.

• Issue 4, addition of prohibited medications section (Section 6.3, Prohibited Medications)
A section has been added in accordance with MHRA feedback to specify prohibited medications based on current Hu5F9-G4 data and the MabThera SmPC and Rituxan USPI.
• Nonclinical Point
(Section 9.3.1.8, Other Reportable Events, Pregnancy; Section 4.1.1, Inclusion Criteria 11 and 12) Entry criteria and content describing contraception requirements have been aligned in accordance with MHRA feedback.

SUMMARY OF CHANGES, PROTOCOL 5F9003 AMENDMENT 5 (18 May 2017)
The main reasons for amending the 5F9003 protocol is to harmonize recent feedback from the Food and Drug Administration (FDA) and Medicines and Healthcare Regulatory Agency (MHRA). Amendment 5 brings together regulatory feedback received from the MHRA and, most recently, the FDA on Amendment 3. Amendment 4 was a region-specific document to respond to MHRA feedback. Additional changes by the Sponsor are also included in this document.
The following changes have been made to the protocol in response to FDA feedback:
• Added requirement for premedication prior to the first 2 doses of Hu5F9-G4.
(Section 6.1, Study Drug Administration)
Rationale: Infusion reactions due to rituximab are observed in non-Hodgkin's lymphoma patients and the theoretical risk of potentiating rituximab-related infusion reactions with Hu5F9-G4, a premedication regimen for Hu5F9-G4 will be instituted to mitigate this potential safety risk. Hu5F9-G4 infusion reactions, when they have occurred, have been experienced primarily with the first or second dose. Thus, premedication for Hu5F9-G4 will be required for the first 2 Hu5F9-G4 doses, where the potential infusion reaction risk is highest.
• Modified the Dose Limiting Toxicity Exclusion Criterion of Grade 3 infusion reactions attributed to rituximab to specifically state that such reactions can only be attributed to rituximab if the adverse event occurs during rituximab infusion but prior to Hu5F9-G4 infusion. (Section 3.3, Definition of Dose-limiting Toxicity)
Rationale: Hu5F9-G4 and rituximab are administered on the same day. Once both treatments are administered, the attribution of any infusion reactions to either Hu5F9-G4 or rituximab is difficult.
The Sponsor has made the following additional changes to the protocol:
• Modified the Dose-limiting Toxicity Exclusion Criterion of Grade 3 indirect/unconjugated hyperbilirubinemia, electrolyte abnormalities, and alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 1 week from 72 hours.
(Section 3.3, Definition of Dose-limiting Toxicity)
Rationale: Clarify DLT exclusions for specific lab abnormalities to align with other Hu5F9-G4 protocols. The extension of AE severity reduction from 72 hours to 7 days represents an adequate risk/benefit ratio, as these lab abnormalities, when observed in other Hu5F9-G4 trials, have resolved or were reduced in severity by 7 days.
• Added the ability to enroll a fourth subject in each cohort.
(Section 3.2.2, Phase 1b Dose Escalation)

Rationale: A fourth patient enrolled in the same cohort is to have an extra patient in case 1 of the 3 earlier patients is unevaluable, or a DLT is experienced by a patient in the cohort, requiring cohort expansion to 6 patients. Given the patient population being studied (particularly relapsed/refractory DLBCL), there is a reasonable possibility that patients may not be able to stay on study until completion of the DLT assessment due to clinical disease course.

• Addition of LYRIC criteria as Secondary Endpoint for immune response evaluation.
(Section 2.1, Study Objectives; Section 2.2, Study Endpoints; Section 7.3.5, Section Diagnostic Imaging; Section 7.9, Efficacy Assessment; Section 10.1.1, Overall Response Rate; Section 10.2, Evaluation of Response; Appendix C)

Rationale: The additional safety and now efficacy data of Hu5F9-G4 suggests a favorable risk/benefit profile for utilizing the LYRIC criteria as a secondary endpoint. Hu5F9-G4 is an immunotherapy that activates both the innate and adaptive immune system and thus immune-mediated response assessments may be important for characterizing Hu5F9-G4 efficacy. One of five patients receiving Hu5F9-G4 + rituximab in this study has achieved a complete response. Additionally, mixed responses (tumor reduction of several lesions with tumor size increase in 1 solitary lesion) have been observed in 2 patients with NHL who have been treated (1 with Hu5F9-G4 monotherapy and 1 with Hu5F9-G4 + rituximab). These patients had been classified as having progressive disease according to the Lugano classification (Cheson 2014). Adding LYRIC criteria enables evaluation of any additional clinical benefit for patients who can be treated beyond progression. Because the long-term safety profile has shown Hu5F9-G4 to have been generally well tolerated to date, it is anticipated that the safety risk of treating patients beyond progression will be acceptable. The LYRIC Criteria for lymphomas will be used as a secondary endpoint in the assessment of response using immune-mediated response criteria. The Lugano classification will still be used as a the primary endpoint.

• Increase the dose level for cohort 3 to 20 or 30 mg/kg.
(Section 1.6.1, Hu5F9-G4; Section 3.2.1, Phase 1b Dose Level).

Rationale: To evaluate the safety profile of Hu5F9-G4 at 30 mg/kg dose level. Emerging pharmacokinetic, pharmacodynamics, and clinical data suggests that Hu5F9-G4 doses of 20 mg/kg or higher (e.g., 30 mg/kg) may enhance the possibility of patients receiving more benefit from treatment. An MTD has not been reached on any Hu5F9-G4 trial at a dose of 20 mg/kg. Based on emerging data, the risk-benefit ratio of exploring higher doses appears to be acceptable.

• Define the roles of the Clinical Trial Steering Committee (CTSC) to allow this body to:
o recommend dose increases of up to 50% intervals from 30 mg/kg to be explored in additional cohorts
o expand the number of patients from 6 to 10 per cohort
o approve the exploration of alternate recommended Phase 2 dose and schedule (RP2DS) after the initiation of the Phase 2 part of the study, based on emerging clinical, PK, and PD data
(Section 1.6.1, Hu5F9-G4; Section 3.1; Overall Study Design; Section 3.2.1, Phase 1b Dose Level)

Rationale: To evaluate the safety profile of Hu5F9-G4 at different dose levels in an expanded group of patients, as well as to provide additional PK data to assist in the

selection of a recommended Phase 2 dose (RP2D).
• Add Lymphocyte subset analysis for local labs on Day 1 of each cycle and at the Safety Follow-up Visit. (Section 7, Study Evaluation; Table 2; Table 3; Table 4)
Rationale: To evaluate the role of Hu5F9-G4 and/or rituximab in inducing B-cell depletion in patients with NHL. This analysis will enable enhanced understanding of potential efficacy signals of the treatment combination.
Add CD47 blood sample collection on Day 11 to evaluate receptor occupancy (RO) in patients in the Loading Dose Cohort. (Section 7, Study Evaluation; Table 8)
Rationale: To obtain RO data pre and post dose for a loading dose to gather more accurate RO data to assist with Hu5F9-G4 dose refinement.
• Obtain tumor/lymph node biopsies during the Screening period.
(Section 7.1, Schedules of Assessment for Phase 1b and Phase 2: Table 2 and Table 3; Section 7.10, Pharmacodynamic and Biomarker Assessments)
Rationale: To expand the window of time during which the screening biopsy can be obtained in order to provide additional accommodation for patient scheduling.

Editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document. Changes in sections of the protocol body have also been made in the protocol synopsis, study design schema, tabular schedules of assessments, and elsewhere in the document, as applicable.

Statistical Analysis Plan

Title: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma

The manuscript in NEJM is reporting the phase 1b portion of the study and the statistics are descriptive. The remainder of the statistical analysis plan is providing guidance for the analysis of the phase 2 portion of the study, which has not yet been completed and does not apply to the analysis of the phase 1 part of the trial. It is possible that modifications in this plan will be needed in the course of the study. Modifications will be IRB approved and documented at the time the phase 2 study is reported.

Statistical Analysis Plan

Sponsor	FortySeven Inc.
Protocol Title:	A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Subjects with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma
Protocol Number:	5F9003
Premier Research PCN:	FORS5690
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Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician	Print Name: Alex Kouassi, PhD Director Biostatistics Sign Name: DocuSigned by: Alex Kouassi Signer Name: Alex Kouassi Signing Reason: I am the author of this document Signing Time: 30-Jan-2018 | 15:37:16 EST 8142FAFE64C541A2AFDA4D770243CA2E	30-Jan-2018 | 15:37:26 EST
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Document History

Version	Date	Author	Description
3.0	12-JAN-2018	Alex Kouassi	Final Version
1.0	29-JAN-2018	Alex Kouassi	Changed the versioning as per SOP
1.0	30-JAN-2018	Alex Kouassi	Updated the final version to correct some formatting errors and include a document history page.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
ADR	adverse drug reactions
AE	adverse event
AESI	adverse events special interest
ATC	anatomical therapeutic chemical
BLQ	beneath limit of quantification
BMI	body mass index
BOR	Best overall response
CI	confidence intervals
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
DB	database
DBL	database lock
DBP	diastolic blood pressure
DLT	dose limiting toxicity

Abbreviation	Definition
DM	data management
DOR	Duration of response
EAS	Efficacy Analysis Set
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European medicines agency
FAS	Full Analysis Set
FDA	food and drug administration
FMP	file management plan
GCP	good clinical practice
HR	heart rate
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
IRB	institutional review board
KM	Kaplan-Meier
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency

Abbreviation	Definition
N	number
NA	not applicable
NCS	non-clinically significant
ORR	Overall response rate
OS	Overall survival
PAS	PK Analysis Set
PD	protocol deviation
PE	physical examination
PFS	Progression free survival
PI	principal investigator
PK	pharmacokinetic
PPS	per-protocol Set
RR	respiratory rate or relative rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
SDTM	study data tabulation model

Abbreviation	Definition
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO-DD	world health organization drug dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Forty seven inc. protocol number 5F9003 A Phase 1b/2 Trial of Hu5F9 G4 in Combination with Rituximab in Subjects with Relapsed/Refractory B cell Non Hodgkin's Lymphoma, dated 28 November 2016 Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to FortySeven inc's study 5F9003 .

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objectives are:

- To investigate the safety and tolerability, and to define the recommended Phase 2 dose for Hu5F9-G4 in combination with rituximab.

- In Phase 2, to evaluate the efficacy of Hu5F9-G4 in combination with rituximab in subjects with indolent lymphoma and DLBCL as measured by the objective response rate (ORR)

2.1.2. Secondary Objectives

The secondary objectives are:

- In Phase 1b and 2:

- To evaluate the pharmacokinetic (PK) profile of Hu5F9-G4 in combination with rituximab
- To evaluate the immunogenicity of Hu5F9-G4 in combination with rituximab

- In Phase 2: To evaluate the efficacy of Hu5F9-G4 in combination with rituximab in indolent lymphoma and DLBCL as measured by the duration of response, best overall response, progression-free survival, and overall survival

2.1.3. Exploratory Objectives

The exploratory objectives for this study are:

- To assess biomarkers of immune cell efficacy and tumor penetration of Hu5F9-G4 in combination with rituximab
- To assess efficacy in molecular subtypes of NHL

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints for this study are:

- Dose-limiting toxicities (Phase 1b only) and adverse events according to NCI CTCAE, Version 4.03.
- Phase 2: Objective response as defined by the Investigator according to the Lugano classification for lymphomas

2.2.2. Secondary Endpoints

The secondary endpoints for this study are:

- Concentration versus time measurements for Hu5F9-G4 in combination with rituximab and PK parameters including maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), terminal half life ($t_{1/2}$), area under the curve (AUC), clearance (CL), and volume of distribution during the terminal phase (V_z).
- Phase 1b and 2: Anti-drug antibodies to Hu5F9-G4
- Phase 2: Duration of response (DOR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS)

2.2.3. Exploratory Endpoints

The exploratory endpoints for this study are:

- CD47 receptor occupancy on peripheral RBCs and white blood cells (WBCs), and lymphoma cells, where applicable.

- Pharmacodynamic markers of Hu5F9-G4 biological activity potentially including, but not limited to, circulating cytokine profiles, T-cell receptor sequencing on circulating T cells, mass cytometry (CyTOF)/flow cytometry of circulating leukocytes, and T-cell activation studies.
- In subjects undergoing tumor biopsies, Hu5F9-G4 saturation of tumor cells and changes in the tumor microenviroment, including, but not limited to, macrophage and T-cell tumor infiltration.
- In subjects undergoing tumor biopsies, correlation of anti-tumor response to molecular subtypes of NHL including, but not limited to, cell-of-origin in DLBCL and BCL2, BCL6, and MYC mutation/expression status.

2.2.4. Safety Endpoints

The safety endpoints of this study include the following:

- Treatment-emergent Adverse events (TEAEs)
- Vital signs
- Clinical laboratory test results
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Physical examination findings
- 12-lead ECG results.
- Volume of distribution during the terminal phase (Vz).

3. Overall Study Design and Plan

3.1. Overall Design

This is an open label, multicenter, Phase 1b/2 trial investigating the combination of Hu5F9-G4 and rituximab in relapsed/refractory B-cell non-Hodgkin's lymphoma. The study will be conducted in 2 parts (See schema below):

- Dose escalation Phase 1b open to subjects with B-cell non-Hodgkin's lymphoma
- Phase 2 study with 2 treatment arms (indolent lymphoma and DLBCL), conducted in a Simon's two-stage Minimax design

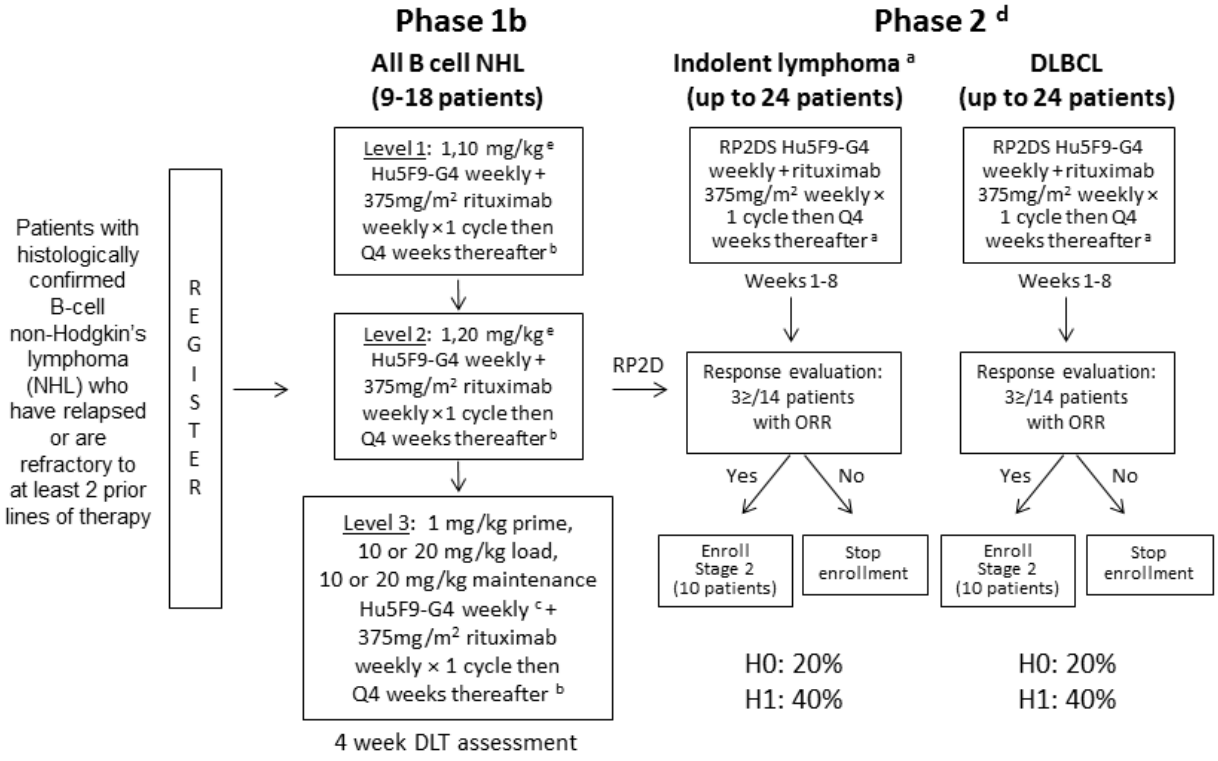
The Phase 1b will be conducted using a standard 3+3 dose escalation design to determine the MTD. Dose escalation decisions will be made by the CTSC based on the first 4 weeks of treatment for each subject. The first subject in each dose cohort must complete at least 1 week of treatment before additional subjects are enrolled in the cohort. Subsequent subjects may be enrolled simultaneously. The third subject in a cohort must complete the DLT Assessment Period (the first 4 weeks of treatment for each subject) prior to escalating to the next dose level. A Subjectsubject assigned to a particular dose cohort is considered evaluable for assessment of DLT if either of the following

criteria are met during the DLT assessment period:

- The subject experienced a DLT at any time after initiation of the first infusion of both Hu5F9-G4 and rituximab.
- The subject completed at least 3 infusions of Hu5F9-G4 and 2 infusions of rituximab.

Subjects who withdraw before meeting the above criteria will be replaced in the cohort.

STUDY DESIGN SCHEMA
Study 5F9003: A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Subjects with Relapsed/Refractory B Cell Non-Hodgkin's Lymphoma



[a] Indolent lymphoma includes follicular and marginal zone lymphoma.
[b] Treatment cycles are 4 weeks. Rituximab is given weekly at Weeks 2-4 in Cycle 1 only. Up to 6 cycles of rituximab will be given.
[c] Level 3 Hu5F9-G4 dosing regimen consists of 1 mg/kg priming dose on Day 1, then a loading dose of either 10 or 20 mg/kg twice weekly × 1 week, followed by weekly maintenance doses of 10 or 20 mg/kg. Dose concentration to be determined by the CTSC.
[d] Simon two-stage minimax design with an alpha of 0.1 and a power of 0.80. H0=null hypothesis; H1=alternative hypothesis.
[e] 1,10 mg/kg represents a first priming dose of 1 mg/kg followed by a maintenance dose of 10 mg/kg of Hu5F9-G4 one week after, similarly for 1,20 mg/kg.

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. A DLT is defined as any Grade 3 or greater AE that is assessed as related to study drug (Hu5F9-G4 and/or rituximab) that occurs during the 4-week DLT observation period.
Any of the followings are exceptions and will NOT be considered a DLT:

- Grade 3 anemia, however, Grade 3 hemolytic anemia that is medically significant, requires hospitalization or prolongation of existing hospitalization, is disabling, or limits self-care activities of daily life (ADLs) is considered a DLT.

- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 72 hours and is not associated with other clinically significant consequences.

- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 72 hours and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase aspartate aminotransferase, or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 72 hours and is not associated with other clinically significant consequences.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 2 weeks on study
- Grade 3 Hu5F9-G4 infusion reactions in the absence of pretreatment
- Grade 3 tumor lysis syndrome or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolve to ≤ Grade 2 within 7 days
- Grade 3 or 4 lymphopenia
- Any grade infusion reaction attributed to rituximab

The Phase 2 part of the study will then explore the combination of Hu5F9-G4 and rituximab at the recommended phase 2 dose and schedule (RP2DS) determined from the Phase 1b in 2 separate arms: subjects with indolent lymphoma (to include follicular lymphoma and marginal zone lymphoma) and DLBCL.

3.2. Sample Size and Power

The overall sample size for this study is estimated to be between 57 and 66 subjects. This sample size includes both the Phase 1b and Phase 2 parts of the study. In the Phase 1b part of the study, a standard 3+3 dose escalation design is employed to explore the MTD of the investigational combination. There are 3 dose cohort levels, with an estimated total of 9 to 18 subjects in the Phase 1b depending on possible cohort expansion in a 3+3 design. In Phase 1b, subjects who are not evaluable for DLT will be replaced.

The Phase 2 part of the study includes two arms, enrolling indolent lymphoma or DLBCL, in which sample size is determined according to a Simon two-stage minimax design. The Phase 2 part of the study will comprise a total of 48 subjects (24 with indolent lymphoma, 24 with DLBCL) if both stages of each arm are fully accrued. For Phase 2, the sample size was determined using a one-sided alpha level of 0.10 and a power of 0.80 based on a null hypothesis of 20% response rate compared to an alternative/desired response rate of 40% for indolent lymphoma and a null hypothesis of 20% response rate compared to an alternative/desired response rate of 40% for DLBCL. The null hypothesis response rates of 20% for both indolent lymphoma and DLBCL are based on historical data for single-agent rituximab in the protocol-specified subject populations with modification.

3.3. Study Population

The subject population for this study is male and female adlults 18 years and older with relapsed/refractory B-cell non-Hodgkin’s lymphoma.

3.4. Treatments Administered

The study treatment is a combination of Hu5F9-G4 and Rituximab. The combination will be administered intravenously to study subjects.

3.5. Method of Assigning Subjects to Treatment Groups

This is an open-label trial with a single treatment arm. Subjects are not randomized to treatment.

3.6. Blinding and Unblinding

Both part of this study will be conducted in an open-label fashion.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in the table below

Table 1. Schedule of Assessments Phase 1b

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																							
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SCR**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**± 2**											
Assessments																										
Informed Consent	X																									
Demographics	X																									
Medical and Cancer History	X																									
Inclusion/Exclusion Criteria	X																									
Enrollment Cohort assignment [a]	X																									
Pregnancy test	X	X[b,c]													X								Q8W			
CBC w diff, platelets, retics	X	X[c]	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral Blood Smear[d]	X	X[c]	X	X			X	X	X						X											
Serum chemistry	X	X[c]	X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous	X	X[c]	X	X			X																			
Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen	X	X[c]	X	X			X	X							X				X				X			
PT/INR, aPTT	X			X				X							X				X				X			

AD-ST-33.04 Effective date: 30-Jun-2017

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SCR**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**± 2**											
Assessments																										
Type and Screen (ABO/Rh), DAT	X																									
Urinalysis	X						X																			
Correlative studies [e]		X					X		X						X											
Pharmacokinetics [f]		X		X	X		X	X	X	X	X	X	X	X	X				X				X			
Antidrug Antibodies		X							X						X				X				X			
CD47 Receptor Occupancy [g]		X			X	X	X		X																	
ECOG performance status	X	X		X			X	X	X						X				X				X			
Vital signs [h]	X	X	X	X	X		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [i]	X	X[c]		X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Assessment [j]									X																	
Visual acuity	X																									
ECG [k]	X	X			X				X																	
Tumor/lymph node biopsy, optional (within 10 days prior to first dose and	X											X														

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																								
Cycle (28-day Cycles)		**1**							**2**						**3**				**4**				**5+**			
Cycle Day	**SCR**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**					**± 2**											
Assessments																										
(± 1 week for later samples)																										
Diagnostic Imaging [l]	X														X								Q8W			
Bone marrow biopsy (for response assessment if disease involvement) [m]	X														X											
Response assessment															X								Q8W			
Adverse events		→													→				→				→			
Concomitant medications		→													→				→				→			
Study Drug Administration																										
Rituximab administration				X			X	X	X						X				X				C5+C6			
Hu5F9-G4 administration		X			X		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 administration (Loading Dose Cohort only) [n]		X			X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DLT = dose-limiting toxicity; ECG = electrocardiogram; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; RO = receptor occupancy; SCR = Screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.

b. May use screening pregnancy test performed within 72 hours of first dose.

Examination		Study 5F9003, Phase 1b: P1b/2 NHL trial with Hu5F9-G4 + rituximab																							
Cycle (28-day Cycles)		1							2						3				4				5+			
Cycle Day	SCR	1	2	8	9	11	15	22	1	2	4	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1					± 2											
Assessments																										

c. Pre-infusion assessments tests may be collected up to 72 hours before study drug treatment.
d. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage.
e. Refer to Table 7 for Correlative studies time point details.
f. Refer to Tables 5 for PK time point details.
g. Refer to Table 8 for RO time point details.
h. Prior to infusion and within 30 minutes after the end of each infusion.
i. Full PE at screening, symptom-directed PE thereafter.
j. DLT will be assessed through the first 4 weeks of the study.
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to infusion and within 30 minutes of the end of infusion on treatment.
l. (± 1 week) See Diagnostic Imaging for details.

Bone marrow biopsy will also be performed to confirm CR at any response assessment where appropriate and at disease progression.
For loading doses of Hu5F9-G4 administered on Day 9 and 11 may be shifted by ± 1 day, with the exception that the loading doses should not be administered on consecutive days.

Table 2. Schedule of Assessments Phase 2

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SCR**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Informed Consent	X																							
Demographics	X																							
Medical and Cancer History	X																							
Inclusion/Exclusion Criteria	X																							
Enrollment Cohort assignment [a]	X																							
Pregnancy Test	X	X [b,c]											X								Q8W			
CBC w diff, platelets, retics	X	X [c]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Peripheral Blood Smear [d]	X	X [c]	X	X			X	X	X				X											
Serum chemistry	X	X [c]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum uric acid, phosphorous	X	X [c]	X	X			X																	
Haptoglobin, D-Dimer, thrombin time and plasma fibrinogen	X	X [c]	X	X			X	X					X				X				X			
PT/INR, aPTT	X			X				X					X				X				X			

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SCR**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Type and Screen (ABO/Rh), DAT	X																							
Urinalysis	X						X																	
Correlative studies [e]		X							X				X											
Pharmacokinetics [f]		X		X	X		X	X	X	X	X	X	X				X				X			
Antidrug Antibodies		X							X				X				X				X			
CD47 Receptor Occupancy [g]		X			X	X	X		X															
ECOG performance status	X	X		X			X	X	X				X				X				X			
Vital signs [h]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [i]	X	X [c]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual acuity	X																							
ECG [k]	X																							
Tumor/lymph node biopsy, mandatory (within 10 days prior to first dose and (± 1 week for later samples)	X									X														
Diagnostic Imaging [l]	X												X								Q8W			

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																						
Cycle (28-day Cycles)		**1**							**2**				**3**				**4**				**5+**			
Cycle Day	**SCR**	**1**	**2**	**8**	**9**	**11**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Visit Window (Days)	**-30**	**None**		**±1**					**±2**	**±1**			**± 2**											
Assessments																								
Bone marrow biopsy (for response assessment if disease involvement) [m]	X												X											
Response assessment													X								Q8W			
Adverse events		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Study Drug Administration																								
Rituximab administration				X			X	X	X				X				X				C5+C6			
Hu5F9-G4 administration		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hu5F9-G4 administration (Loading Dose Cohort only) [n]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle number; CBC = complete blood count; DLT = dose-limiting toxicity; ECG = electrocardiogram; PT/INR = prothrombin time/international normalized ratio; PE = physical exam; PK = pharmacokinetics; RO = receptor occupancy; SCR = screening; W = weeks.

a. First dose of Hu5F9-G4 must be given within 30 days of signing informed consent.
b. May use screening pregnancy test performed within 72 hours of first dose.
c. Pre-infusion laboratory tests may be collected up to 72 hours before study drug treatment.
d. Peripheral blood smear slides from Cycle 1 will be retained and sent to the Sponsor for storage.
e. Refer to Table 7 for Correlative studies time point details.
f. Refer to Tables 6 for PK time point details.

Examination		Study 5F9003, Phase 2: P1b/2 NHL trial with Hu5F9-G4 + rituximab																					
Cycle (28-day Cycles)		1							2				3				4				5+			
Cycle Day	SCR	1	2	8	9	11	15	22	1	8	15	22	1	8	15	22	1	8	15	22	1	8	15	22
Visit Window (Days)	-30	None		±1					±2	±1			± 2											
Assessments																								

g. Refer to Table 8 for RO time point details.
h. Prior to infusion and within 30 minutes after the end of each infusion.
i. Full PE at screening, symptom-directed PE thereafter.
j. (*Footnote "j" not applicable to this table*)
k. Single at screening. For Phase 1b only, triplicate within 2 hours prior to infusion and within 30 minutes of the end of infusion on treatment.
l. (± 1 week) See Diagnostic Imaging for details.
m. Bone marrow biopsy will also be performed to confirm CR at any response assessment where appropriate and at disease progression.
n. For loading doses of Hu5F9-G4 administered on Day 9 and 11 may be shifted by ± 1 day, with the exception that the loading doses should not be administered on consecutive days.

4. Statistical Analysis and Reporting

All final, planned analyses identified in the protocol and in this SAP will be performed after the last subject has completed his/her last visit, all relevant study data have been processed and integrated into the analysis database, and the database has been locked. Any post hoc analysis not identified in this SAP but completed to support planned analyses, will be documented and reported in the clinical study report (CSR). Any results from these unplanned analyses (post hoc) will also be clearly identified in the text of the CSR.

4.1. Introduction

Data processing, statistical analyses and graphical representations will be performed primarily using SAS (release 9.3 or higher). All PK parameter estimations will be performed using Phoenix WinNonlin® software (Version 6.4 or later; Pharsight, Cary, NC). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes. All analyses will be descriptive and hypothesis-generating in nature.

Descriptive statistics will be provided for all safety and efficacy endpoints. Efficacy and safety analyses will be conducted for subjects in both Phase 1b and Phase 2. In addition, analyses for phase 1b will be presented by cohort whereas analyses for phase 2 will be presented by arms (DLBCL, Indolent Lymphoma).

For continuous variables, the number of subjects (n) with non-missing values, the mean, standard deviation, median, and ranges will be provided. The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

For categorical variables, summaries will include the frequency and percentage of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population, unless otherwise specified. Percentages will be presented to 1 decimal place, unless otherwise specified.

For time-to-event variables, the Kaplan-Meier (KM) estimates and corresponding two-sided 95% confidence intervals for the median and quartiles will be provided. The KM plot may also be provided.

4.2. Interim Analysis and Data Monitoring

A Simon two-stage minimax design (Simon 1989) will be used in the Phase 2 part of the study. In accordance with this design, after 14 subjects in the indolent lymphoma arm and/or 14 subjects in the DLBCL arm are evaluable for response assessment, the CTSC will convene and

provide recommendations to the Sponsor to proceed with full accrual of either or both arms, or terminate the study according to the pre-specified Simon two-stage minimax design stopping rules.

For the indolent lymphoma arm, the study will proceed to accrue the second stage if there are ≥ 3 objective responses in 14 subjects. In this case 10 additional subjects will be enrolled. These rules are based on the combination of Hu5F9-G4 and rituximab achieving a desired 40% ORR compared to the null hypothesis response rate of 20%, which represents single-agent rituximab activity in the protocol-specified indolent lymphoma population. For the DLBCL arm, the study will proceed to accrue the second stage if there are ≥ 3 objective responses in 14 subjects. These results are based on the combination of Hu5F9-G4 and rituximab achieving a desired 40% objective response rate compared to the null hypothesis response rate of 20% which represents single-agent rituximab activity in the protocol-specified DLBCL population.

If, at the interim analysis, > 33% of subjects in a Phase 2 arm experience any Grade 3 or greater AE that is assessed as related to study drug (Hu5F9-G4 and/or rituximab) and results in permanent discontinuation, withdrawal, or death, then that Phase 2 arm will be stopped. If either > 4 of 14 subjects in either the indolent lymphoma arm or > 5 of 15 subjects in the DLBCL arm experience a qualifying event, the corresponding study arm will be stopped for unacceptable toxicity. The trial may also be stopped at any time if the CTSC deems that there is an unacceptable safety risk to subjects with the study treatment. The trial may otherwise proceed to accrue the second stage if the response criteria described above are met.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Full Analysis Set (FAS):** The Full Analysis Set includes all enrolled subjects who receive at least one dose of study drug. The FAS population will be used to perform all safety analyses.

- **Efficacy Analysis Set (EAS):** The Efficacy Analysis Set (EAS) includes all enrolled subjects who receive at least 1 dose of study drug and for whom a baseline and at least 1 post-study drug treatment tumor assessment are available. This population will be used to perform analyses on ORR, BOR, DOR, DSD, PFS, and OS.

- **DLT Analysis Set (DLT):** The DLT Analysis Set includes all enrolled subjects who received at least 1 dose of Hu5F9-G4 or rituximab (study drug) and have had the opportunity to be followed for the 28-day cycle or have experienced a DLT within 28 days after initiating study drug treatment (Phase 1b only). This population will be used to summarize the DLTs.

- **Per Protocol Set (PPS):** Includes all subjects from the EAS without any major protocol deviations (Phase 2 only). This population will be used to perform sensitivity analysis on ORR if more than 10% of the subjects in the EAS are excluded.

- **Pharmacokinetic Analysis Set (PAS):** The PK Analysis Set includes all subjects in the Full Analysis Set from whom PK blood samples are collected during the study and who have measurable concentrations of Hu5F9-G4 (Phase 1b and phase 2 combined). The PAS will be used to summarize all PK data.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last non-missing observation recorded prior to the first dose of the study medication will be used as the baseline.

6.1.2. Handling of Dropouts or Missing Data

Phase 1b: Any subject who withdraws from the study before completing the 4-week DLT assessment period for reasons other than a DLT, does not experience a DLT at any time after initiation of the first infusion of both Hu5F9-G4 and rituximab, or does not complete at least 3 infusions of Hu5F9-G4 and 2 infusions of rituximab will be replaced for DLT assessment.

Phase 2:

- For time to event endpoints, dropouts will be censored at the time of last event assessment date with the documentation of no event if the event has not observed at the time of withdrawal. For example, for duration of response, any responder who drops out without documented progressive disease will be censored at the last tumor assessment with the documentation of no disease progression.

6.1.3. Derived Variables

- ORR = The proportion of subjects who experience either CR or PR.

- BOR = Best overall tumor response of a subject is recorded from the start of the treatment until end of study (within 30 days post last treatment dose)

- DOR = Duration of response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or progressive disease is objectively documented (taking as reference for PD the smallest

measurements recorded since the treatment started). The DOR of subjects who did not experience recurrent/progressive disease during the course of the study will be censored at the time of their last disease asseement with no documented progression.

- Time to Progression = Time from treatment initiation until progressive disease is documented according to the Lugano Classification and LYRIC criteria. The time to progression of subjects who did not experience progressive disease during the course of the study will be censored at the time of their last disease assessment with no documented progression.

- PFS = Time from first study dose until disease progression or death from any cause, whichever is first. The PFS of subjects who did not die or experience progressive disease during the course of the study will be censored at their last disease assessment with no documented progression.

- OS = Time from first study dose until death from any cause. The OS of subjects who did not die during the course of the study will be censored at their last known follow-up date.

- Change from baseline = post baseline value– value at baseline.

- Percent change from baseline = 100* change from baseline / value at baseline

- TEAE = Any AE that occurs or worsens in severity after the initiation of treatment and within 30 days after the last dose of the study medication.

- ADR = Any TEAE related to the study medication.

- AE = Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the investigational product.

6.1.4. Data Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All p-values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later thesaurus.

The following conventions apply to study day and duration calculations when incomplete data are present for one or more involved dates. Imputed dates that appear in listings will be marked linking them to the footnote "Imputed date."

Missing Adverse Event End Dates

If the AE is marked "Ongoing/Continuing" on the Adverse Events CRF or if the AE end date is completely missing, then the end date will be noted as "continuing" in AE listings. Otherwise, if only the day portion of the end date is unknown, the day will be assumed to the last of the month (e.g., dd-JAN-2004 will be treated as 31-JAN-2004), or the day of the end of study date if month and year are the same. If both the day and month portions of the end date are unknown, the event will be assumed to have ceased on the last day of the year (e.g., dd-mmm-2004 will be treated as 31-DEC-2004), or the end of study date, whichever is earlier.

Missing Adverse Event Start Dates

If only the day portion of the AE start date is missing, then the missing day portion will be estimated as '01'; except for in the event that the start month and year are the same as the treatment start date and the AE end date is after treatment start date, the start date will be estimated to be equal to the start of the study treatment.

If both the day and month portions of the AE start date are missing and the AE end date is after treatment start date, then the start date will be estimated to be equal to the start of the study treatment, provided the start year is the same as treatment start date, otherwise, the AE start date will be assumed to start on the first day of the given year (e.g., dd-mmm-2006 is estimated as 01-JAN-2006).

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Disposition table will include tabulations of the number of subjects enrolled into each cohort (phase 1b) or each arm DLBCL; Indolent Lymphoma (phase 2). The number of subjects who completed the study, the number of subjects who discontinued from the study, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population (EAS, PPS, FAS and PAS). All enrolled subjects will be used for this summary table.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed. The listing will indicate the cohort (Phase 1b) or the arm (Phase 2) the subject is enrolled into.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, and BMI will be presented for all subjects in the Full Analysis Set.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

The number and percent of subjects reporting cancer history will be summarized, and a listing will be provided.

The number and percent of subjects with prior cancer treatment (radiotherapy, surgery, systemic therapy or transfusion) will be summarized, and a listing will be provided. Similar analysis will be performed for substance use data.

The number and percent of subjects reporting substance use (e.g tobacco) will be summarized, and a listing will be provided.

The number and percent of subjects reporting medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA version 17.1 or later), will be tabulated and a listing will be provided.

The number and percent of subjects who received pre-medication for Hu5F9-G4 or Rituximab will be summarized and a listing will be provided.

7.4. Exposure and Compliance

The maximum number of treatment cycles completed by each subject will be calculated and the number of subjects and proportion for each maximum number of cycles will be provided by cohort (phase 1b) and by arm (Phase 2).

Furthermore, descriptive statistics (number of non-missing values n, mean, standard deviation, minimum, median and maximum) using the maximum number of cycles will be provided by cohort (phase 1b) and by arm (Phase 2).

Total drug exposure (mg/kg), mean dose (mg/kg), and total days of exposure will be summarized descriptively for each cohort (Phase 1b) and arm (Phase 2).

By subject listing for study drug exposure will be provided for all subjects phase 1b and Phase 2 combined.

8. Efficacy Analysis

All the efficacy summaries in this study will include subjects who received Hu5F9-G4 and rituximab and presented by cohort (phase 1b) and by arm (Indolent Lymphoma; DLBCL).

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is Objective Response Rate (ORR). ORR will be estimated and its corresponding exact binomial two-sided 95% confidence interval will be provided by cohort (phase 1b) and by arm (Indolent Lymphoma; DLBCL). The EAS will be used for the primary efficacy analysis. A sensitivity analysis will be performed to assess the robustness of the primary efficacy analysis results using the Per Protocol Analysis Set (PPS) if more than 10% of subjects in the EAS are excluded from the PPS.

8.2. Secondary Efficacy Analysis

The secondary efficacy endpoints include: CR, PR, SD, BOR, DOR, PFS and OS.

- The proportion of CR, PR and Stable Disease will be provided along with the corresponding exact 95% CI.
- BOR - Estimate of BOR and their corresponding exact binomial two-sided 95% CI will be provided.
- DOR – The KM product limit method will be applied to the subset of responders, the median and its 95% CI will be provided.
- PFS and OS – The median PFS and OS will be estimated using the KM product limit method. The median and its 95% CI will be provided.

The EAS will be used to analyze all the efficacy endpoints.

8.3. Exploratory Analysis

Pharmacodynamic markers of Hu5F9-G4 biological activity will be summarized descriptively and a listing will be provided. Similar analyses will be performed for the Hu5F9-G4 saturation of tumor cells, changes in the tumor microenviroment and the correlation of anti-tumor response to molecular subtypes of NHL.

9. Safety and Tolerability Analysis

The statistical analysis of safety data will be conducted for subjects in the FAS and will include subjects with non-missing data for the particular safety endpoint being analyzed. Safety variables may include, but are not limited to: DLTs, treatment-emergent adverse

events (TEAEs), treatment-related adverse events (ADRs), vital signs, physical examinations, laboratory tests, receptor occupancy, and anti-drug antibody assessments.

Data will be presented by Phase 1b dose cohort and Phase 2 arm. Some safety data may be summarized over all Phase 1b dose cohorts and across both Phase 1b and Phase 2 parts. Data may be graphed, summarized, or listed, depending on the amount of data to be reported. Where relevant, safety data will also be presented by the study day/study day interval corresponding to dose administrations within each dose cohort.

9.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later and the NCI CTCAE v 4.03 (Table 3) will be used to grade severity of adverse events and laboratory toxicities. The causal relationship of an AE to the study drug is determined by the investigator as Unrelated, Unlikely Related, Possibly Related, Probably Related, and Definitely Related. These will be mapped to Unrelated (Unrelated and Unlikely Related) and Related (Possibly Related, Probably Related, and Definitely Related). In addition the severity of an AE is measured using NCI CTCAE v 4.03 (Table 3). A summary table will be presented for the following:

- All TEAEs
- TEAEs by maximum severity
- ADRs by maximum severity
- TEAEs leading to discontinuation of study drug
- ADRs leading to discontinuation of study drug
- DLTs (Phase 1b only)
- Serious AEs (SAEs)
- Deaths

Table 3. Adverse Event Grade (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Transient or mild discomfort (48 hours); no interference with the subject's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Mild to moderate interference with the subject's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI CTCAE grading criteria)	Considerable interference with the subject's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable

5	Death related to AE

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03
a. Use the alternative descriptions for Grade 1, 2, 3, and 4 events when the observed or reported AE does not appear in the NCI CTCAE listing.

Subject incidence of TEAEs will be summarized by system organ class and preferred term. TEAEs will also be summarized using Investigator assessment of the relationship to study drug (related or not related) and by maximum severity.

SAEs, including deaths, will be summarized and listed for each dose cohort and for all dose cohorts combined. These events will also be summarized by Phase 2 arm (indolent lymphoma and DLBCL) and across all Phase 2 subjects. TEAEs resulting in withdrawal from study drug or further study participation will be tabulated and/or listed.

A listing of the AEs that occurred during screening but before exposure to study drug (non-TEAEs) will be provided.

Adverse events and SAEs experienced by subjects who were screened but not enrolled into the study will be summarized and listed separately along with relevant demographic data collected.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by cohort (Phase 1b) or arm (Phase 2), SOC, and preferred term will be prepared.

A data listing of TEAEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by cohort (Phase 1b) or arm (Phase 2),

9.1.3. Other Significant Adverse Events

A summary and subject listing of all the DLTs Phase 1b) will be provided.

9.2. Clinical Laboratory Evaluations

Laboratory test results, actual values and changes from baseline, will be summarized descriptively by cohort (Phase 1b) or arm (Phase 2) for each analyte.

The number of subjects with clinical laboratory values below, within, or above the normal range by post baseline visit and in relation to baseline will be tabulated for each clinical laboratory analyte (shift table).

A listing for the laboratory test results will be provided and all values that are outside the normal range will be flagged.

9.3. Vital Signs

Descriptive statistics of the actual values and changes from baseline will be provided by cohort (Phase 1b) or arm (Phase 2).
In addition, the number of subjects with vital signs classified as (normal, Abnormal not clinically significant, Abnormal clinically significant (by Day 2 and in relation to Day 1 will be tabulated for each for each vital sign.

9.4. Visual Acuity

A listing of visual acuity data will be provided.

9.5. Electrocardiograms

The following ECG parameters will be listed for each subject: heart rate, PR interval, RR interval, QRS duration, QT interval, and QTcF interval, along with investigator interpretation. Observed values and change from baseline at each study visit will be summarized by overall subjects within cohort. Subjects with a QTcF value meeting stopping rules (observed QTcF > 500 msec or QT > 600 msec; change from baseline QTcF > 60 msec) will be flagged in the data listings.

9.6. Physical Examinations

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be summarized by cycle for each cohort (Phase 1b) and arm (Phase 2).

9.7. Concomitant Medication

Prior and concomitant medications will be summarized descriptively using counts and percentages. Prior medications will be presented separately from concomitant medications. In addition, a listing of the pre-medications will be provided.

Medications that started prior to Day 1 will be considered prior medications whether or not they were stopped prior to Day1. Any medications continuing or starting post Day 1 will be considered to be concomitant. If a medication starts prior to Day1 and continues

after Day 1 it will be considered both prior and concomitant. Medications will be coded using WHO-DD ATC.

10. Other Planned Analysis

10.1. Pharmacokinetic Analysis

For Phase 1b and Phase 2, the following pharmacokinetic parameters will be estimated: C_{max}, T_{max}, AUC_{inf}, $AUC_{0\text{-}168h}$, CL, $T_{1/2}$, and the volume of distribution during the terminal phase (Vz). PK parameter estimation will be performed using Phoenix WinNonlin® software (Version 6.4 or later; Pharsight, Cary, NC) on individual plasma concentration-time data for the Hu5F9-G4 and rituximab combination.

Plasma concentration data below the limit of quantification (BLQ) occurring before T_{max} will be set to 0, with the exception of a BLQ value occurring between two measurable concentrations, in which case it will be set to missing. BLQ plasma concentrations occurring after T_{max} will be set to missing.

Parameter estimates, C_{max}, T_{max}, AUC_{inf}, $AUC_{0\text{-}168h}$, CL, $T_{1/2}$, and Vz, will be summarized using descriptive statistics, including number of subjects, arithmetic mean, SD, median, maximum, minimum, percent coefficient of variation (%CV), and geometric mean by by study phase. Individual concentration plots and mean data graphs will be produced. All graphs will be presented using both linear and semi logarithmic scales. The above descriptive summary will be performed for the PAS.

All plasma concentrations for the Hu5F9-G4 and rituximab combination will be presented in a by-subject listing.

11. Changes from Planned Analysis

Not applicable

12. References

1. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm

2. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

3. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and

Biologics. May 2007.

4. M. Nishino1, JP. Jagannathan, NH. Ramaiya, AD. Van den Abbeele; Revised RECIST Guideline Version 1.1: AJR 2010; 195:281–289.

13. Tables, Listings, and Figures

All listings, tables, and figures (TLFs) will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (listing or table number).

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number 5F9003. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

13.2. Demographic Data

Table 4: Demographic Data Summary Tables

Table Number	Population	Table Title/Summary
14.1 Displays of Demographics and Disposition Data		
Table 14.1.1*	All Enrolled Subjects	Subject Disposition (Phase 1b and Phase 2)
Table 14.1.2*	FAS	Demographics and Baseline Characteristics (Phase 1b and Phase 2)
Table 14.1.3.1*	FAS	Medical History (Phase 1b and Phase 2)
Table 14.1.3.2*	FAS	Cancer History (Phase 1b and Phase 2)
Table 14.1.4.1*	FAS	Prior Medications (Phase 1b and Phase 2)
Table 14.1.4.2*	FAS	Prior Cancert Treatment Summary (Phase 1b and Phase 2)
Table 14.1.5*	FAS	Substance Use (Phase 1b and Phase 2)
Table 14.1.6	FAS	Overall Hu5F9-G4 Exposure and Compliance (Phase 1b and Phase 2)
Table 14.1.7	FAS	Overall Rituximab Exposure and Compliance (Phase 1b and Phase 2)

*: Renumbered from template

13.3. Efficacy Data

Table 5: Efficacy Data

Table Number	Population	Table Title/Summary
14.2 Displays of Efficacy Summaries		
Table 14.2.1	EAS	Summary of Tumor Response (Phase 1b and Phase 2)
Table 14.2.2	EAS	Summary of Overall Respons Rate (Phase 1b and Phase 2)
Table 14.2.3	EAS	Summary of Duration of response, PFSand OS (Phase 1b and Phase 2)

13.4. Safety Data

Table 6: Safety Data

Table Number	Population	Table Title/Summary
14.3.1 Summary of Treatment Emergent Adverse Events		
Table 14.3.1.1	FAS	Incidence of Overall Treatment-Emergent Adverse Events (Phase 1b and Phase 2)
Table 14.3.1.2	FAS	Incidence of Treatment-Emergent Adverse Events (Phase 1b and Phase 2)
Table 14.3.1.3.1	FAS	Incidence of Adverse Hu5F9-G4 Reactions (Phase 1b and Phase 2)
Table 14.3.1.3.2	FAS	Incidence of Adverse Rituximab Reactions (Phase 1b and Phase 2)
Table 14.3.1.4	FAS	Incidence of Most Common Treatment-Emergent Adverse Events (≥ X % in any cohort or arm) (Phase 1b and Phase 2)

Table 14.3.1.5.1	FAS	Incidence of Treatment-Emergent Adverse Events by Maximum Severity (Phase 1b)
Table 14.3.1.5.2	FAS	Incidence of Treatment-Emergent Adverse Events by Maximum Severity (Phase 1b and Phase 2)
Table 14.3.1.6.1	FAS	Incidence of Treatment-Emergent Adverse Events by Relationship to Study Drug (Phase 1b)
Table 14.3.1.6.2a	FAS	Incidence of Adverse Hu5F9-G4 Reactions by Maximum Severity (Phase 1b and Phase 2)
Table 14.3.1.6.2b	FAS	Incidence of Adverse Hu5F9-G4 Reactions by Maximum Severity (Phase 1b and Phase 2)
Table 14.3.1.6.3a	FAS	Incidence of Adverse Rituximab Reactions by Maximum Severity (Phase 1b)
Table 14.3.1.6.3b	FAS	Incidence of Adverse Rituximab Reactions by Maximum Severity (Phase 1b and Phase 2)
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2.1	FAS	Summary of Deaths (Phase 1b and Phase 2)
Table 14.3.2.2	FAS	Summary of Serious Adverse Events (Phase 1b and Phase 2)
Table 14.3.2.3.1	FAS	Summary of Treatment Emergent Adverse Events Leading to Hu5F9-G4 Discontinuation (Phase 1b and Phase 2)
Table 14.3.2.3.2	FAS	Summary of Treatment Emergent Adverse Events Leading to Rituximab Discontinuation (Phase 1b and Phase 2)
Table 14.3.2.4.1	FAS	Summary of Adverse Drug Reactions Leading to Hu5F9-G4 Discontinuation (Phase 1b and Phase 2)
Table 14.3.2.4.2	FAS	Summary of Adverse Drug Reactions Leading to Rituximab Discontinuation (Phase 1b and Phase 2)
Table 14.3.2.5	DLT Analysis Set	Summary of Dose Limiting Toxicities (Phase 1b only)
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	FAS	Listing of Serious Adverse Events (Phase 1b and Phase 2)
Table 14.3.3.2	FAS	Listing of Treatment Emergent Adverse Events Leading to Discontinuation (Phase 1b and Phase 2)
14.3.4 Abnormal Laboratory Value		
Table 14.3.4.1	FAS	Listing of Clinically Significant Abnormal Laboratory Values (Phase 1b and Phase 2) Listing of Clinically Significant Abnormal Laboratory Values
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1.1	FAS	Summary of Serum Chemistry Laboratory Results (Phase 1b and Phase 2)
Table 14.3.5.1.2	FAS	Shift from Baseline in Serum Chemistry Laboratory Results (Phase 1b
Table 14.3.5.1.3	FAS	Shift from Baseline in Serum Chemistry Laboratory Results (Phase 1b and Phase 2
Table 14.3.5.2.1	FAS	Summary of Hematology Laboratory Results (Phase 1b and Phase 2)
Table 14.3.5.2.2	FAS	Shift from Baseline in Hematology Laboratory Results (Phase 1b)
Table 14.3.5.2.3	FAS	Shift from Baseline in Hematology Laboratory Results (Phase 1b and Phase 2)
Table 14.3.5.3.1	FAS	Summary of Quantitative Urinalysis by cohort and arm (Phase 1b and Phase 2)
Table 14.3.5.3.2	FAS	Shift from Baseline in Urinalysis Laboratory Results (Phase 1b)

Table 14.3.5.3.3	FAS	Shift from Baseline in Urinalysis Laboratory Results (Phase 1b and Phase 2)
Table 14.3.5.3.4	FAS	Summary Qualitative Urinalysis Laboratory Results (Phase 1b and Phase 2)
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1.1	FAS	Summary of Vital Signs (Phase 1b and Phase 2)
Table 14.3.6.1.2	FAS	Shift from Baseline in Vital Signs (Phase 1b)
Table 14.3.6.1.3	FAS	Shift from Baseline in Vital Signs (Phase 1 and Phase 2)
Table 14.3.6.2.1*	FAS	Summary of ECOG Performance Status Score by cohort and arm (Phase 1b and Phase 2)
Table 14.3.6.2.2*	FAS	Shift from Baseline in ECOG Performance Status Scores (Phase 1b)
Table 14.3.6.2.3*	FAS	Shift from Baseline in ECOG Performance Status Scores (Phase 1b and Phase 2)
Table 14.3.6.3.1*	FAS	Summary of Electrocardiogram (ECG) Parameters (Phase 1b and Phase 2)
Table 14.3.6.3.2*	FAS	Summary of Electrocardiogram (ECG) Interpretations (Phase 1b and Phase 2)
Table 14.3.6.4*	FAS	Summary of Concomitant Medications (Phase 1b and Phase 2)

13.5. Pharmacokinetic Data

Table 7: Pharmacokinetic Data

Table Number	Population	Table Title/Summary
14.4 Pharmacokinetic Data Summary Tables		
Table 14.4.1	PAS	Summary of the Plasma Concentrations of Hu5F9-G4 in combination with Rituximab Over Time by Cycle Day (Phase 1b and Phase 2)
Table 14.4.2	PAS	Summary PK Parameters of Hu5F9-G4 in combination with Rituximab Over Time by Cycle Day Phase 2
Figure 14.4.1.2.1	PAS	Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b), Linear Scale
Figure 14.4.1.2.2	PAS	Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b and Phase 2), Linear Scale
Figure 14.4.1.2.3	PAS	Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b), Semi-logarithmic Scale
Figure 14.4.1.2.4	PAS	Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b and Phase 2), Semi-logarithmic Scale
Figure 14.4.1.2.5	PAS	Subject Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab Over Time, Linear Scale
Figure 14.4.1.2.6	PAS	Subject Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab Over Time , Semi-logarithmic Scale

13.6. Planned Listing Descriptions

The following are planned data and subject data listings for protocol number FORS5690.

In general, one listing will be produced per CRF domain.

All listings will be sorted by treatment, site, and subject number.

All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 8: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Enrolled Subjects	Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Enrolled Subjects	Eligibility Criteria Not Met
Listing 16.2.2.2	All Enrolled Subjects	Screen Failures
Listing 16.2.2.3	All Enrolled Subjects	Protocol Deviations
16.2.3 Subjects Excluded from the Efficacy Analyses		
Listing 16.2.3	All Enrolled Subjects	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	FAS	Demographics and Baseline Information
Listing 16.2.4.2	FAS	Medical History
Listing 16.2.4.3	FAS	Cancer History
Listing 16.2.4.4	FAS	Prior Cancer Treatment Summary
Listing 16.2.4.5	FAS	Prior Radiotherapy
Listing 16.2.4.6	FAS	Prior Surgery
Listing 16.2.4.7	FAS	Prior Cancer Systemic Therapy
Listing 16.2.4.8	FAS	Substance Use
Listing 16.2.4.9	FAS	Pre- Medication
Listing 16.2.4.10.1	FAS	Rituximab Administration
Listing 16.2.4.10.2	FAS	Hu5F9-G4 Administration
Listing 16.2.4.11	FAS	Tumor/ Lymph node Biopsy
Listing 16.2.4.12.1	FAS	Bone Marrow Aspirate
Listing 16.2.4.12.2	FAS	Bone Marrow Biopsy
Listing 16.2.4.13	FAS	Correlative Studies Sample
Listing 16.2.4.14	FAS	Receptor Occupancy Sample
16.2.5 Drug Concentration Data		
Data Listing 16.2.5.1*	PAS	Pharmacokinetic Blood Collection and Concentrations

Data Listing 16.2.5.2*	PAS	Calculated Pharmacokinetic Parameters
16.2.6 Individual Efficacy Response Data		
Data Listing 16.2.6.1	FAS	Disease Response
16.2.7 Adverse Event Listings (by Subject)		
Data Listing 16.2.7.1	FAS	Adverse Events
Data Listing 16.2.7.2	FAS	Adverse Events Leading to Study Drug Discontinuation
Data Listing 16.2.7.3	FAS	Severe Adverse Events
Data Listing 16.2.7.4	FAS	Treatment emergent Adverse Events Related to Study Drug
Data Listing 16.2.7.5	FAS	Serious Adverse Events
Data Listing 16.2.7.6	FAS	Deaths
Data Listing 16.2.7.7	DLT Analysis Set	Dose Limiting Toxicities
16.2.8 Laboratory Values by Subject		
Data Listing 16.2.8.1	FAS	Clinical Laboratory Data: Serum Chemistry
Data Listing 16.2.8.2	FAS	Clinical Laboratory Data: Hematology
Data Listing 16.2.8.3	FAS	Clinical Laboratory Data: Urinalysis
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Data Listing 16.2.9.1	FAS	Prior and Concomitant Medications
Data Listing 16.2.9.2	FAS	Vital Signs Measurements
Data Listing 16.2.9.3	FAS	12-Lead Electrocardiogram Measurements
Data Listing 16.2.9.4	FAS	ECOG Performance Status
Data Listing 16.2.9.5	FAS	Physical Examination
Data Listing 16.2.9.6	FAS	Visual Acuity Measurements

*: Renumbered from template

Tables, Figures, and Listing Shells

13.7. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

13.8. Planned Table and Figure Shells

Table 14.1.1
Subject Disposition (Phase 1b and Phase 2)
All Enrolled Subjects

	Phase 1b						Phase 2		Both Phases
			RP2DS						
DISPOSITION	COHORT1 (N=XX)	-- COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	Overall (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Enrolled	XX	XX	XX	XX	XX	XX	XX	XX	XX
Study Populations[1]									
EAS			X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
PPS			X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
DLT	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)				
FAS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
PAS	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Experienced DLT[2]	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)			
Completion Status[3]									
Completed Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Prematurely Discontinued from Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Lack of Efficacy	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Lost to Follow-up	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Protocol Violation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Adverse Event	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Subject Withdrew Consent	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Pi Decision	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Study	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Terminated by Sponsor									
Other	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

[1] Percentages are based on the number of all enrolled subjects.
[2] Percentages are based on the number of subjects in the DLT Set
[3] Percentages are based on the number of subjects in the Full Analysis Set.
RP2DS = Recommended Phase 2 Dose Schedule;
Source: Listing 16.2.1

Table 14.1.2
Demographics and Baseline Characteristics (Phase 1b and Phase 2)
Full Analysis Set

Demographic Parameter	Phase 1b					Phase 2			Both Phases
	RP2DS								
	COHORT1 (N=XX)	COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX)
Age (years)									
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Gender									
Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ECOG Performance Status[1]									
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Ethnicity									
Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Race									
American-Indian or Alaska Native	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Black or African-American	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Native Hawaiian or	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Other Pacific Islander									
White	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Other	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
More than One Race	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Height (cm)									
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Weight (kg)									
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
BMI (kg/m^2)									
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

[1] Baseline ECOG Performance Status
[2] Subjects from Phase 1b with the same cancer type and received the recommended phase 2 dose schedule.
Note: Percentage arebased on the number of subjects in the Full Analysis Set
RP2DS = Recommended Phase 2 Dose Schedule;
Source: Listing 16.2.4.1

Table 14.1.3.1
Medical History (Phase 1b and Phase 2)
Full Analysis Set

Medical History	Phase 1b					Phase 2			Both Phases
			RP2DS						
	COHORT1 (N=XX)	COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX)
Subjects with at least One Recorded Medical History	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1									
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2									
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are n/Number of subjects in the Full Analysis Set*100. AEs were coded using MedDRA version 17.1 or later. Subjects were counted once for each system organ class (SOC) and once for each preferred term (PT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT,
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listing 16.2.4.2

Table 14.1.3.2
Cancer History (Phase 1b and Phase 2)
Full Analysis Set

Medical History	Phase 1b					Phase 2			Both Phases
	RP2DS								
	COHORT1 (N=XX)	...	COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX)
Marginal Zone Lymphoma	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Follicular Lymphoma										
Small Lymphocytic L										
Lymphoplasmacytoid L	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Nodal Marginal Zone L	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Extranodal Marginal ZoneL	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
DLBCL										
Mantle Cell L										
Primary Mediastinal Large B Cell L	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are based on the Number of subjects in the Full Analysis Se. Cancer history is displayed by descending frequency
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listing 16.2.4.3

Table 14.1.4.1
Prior Medications (Phase 1b and Phase 2)
Full Analysis Set

Cancer History	Phase 1b						Phase 2			Both Phases
			RP2DS							
	COHORT1 (N=XX)	-- COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX	
Subjects with at least one Prior Medication	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
ATC Class 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
ATC Class 2										
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	

Note: Percentages are based on number of subjects in the Full Analysis Set. Subjects are summarized by cohort. Medications coded using WHO-DD B2E version March 2017. Prior medications are all medications taken before the date of the first dose of study drug. Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by Preferred Term (PT) within ATC and then alphabetically. Subjects were counted only once for each ATC and PT,
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listing 16.2.9.1

Table 14.1.4.2
Prior Cancer Treatment Summary (Phase 1b and Phase 2)
Full Analysis Set

	Phase 1b						Phase 2			Both Phases
			RP2DS							
Prior Cancer Treatment	COHORT1 (N=XX)	-- -	COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX
Radiotherapy	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Surgery	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Systemic Therapy	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Transfusion	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are n/Number of subjects in the Full Analysis Set*100. Prior Cancer Treatment is displayed by descending frequency
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listings 16.2.4.4

Table 14.1.5
Substance Use (Phase 1b and Phase 2)
Full Analysis Set

Category of Substance	Phase 1b						Phase 2			Both Phases
			RP2DS							
	COHORT1 (N=XX)	-- - COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX	
Tobacco	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Alcohol	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	
Caffeine	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	

Note: Percentages are n/Number of subjects in the Full Analysis Set*100. Prior Cancer Treatment is displayed by descending frequency
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listing 16.2.4.8

Table 14.1.6
Overall Hu5F9-G4 Exposure and Compliance (Phase 1b and Phase 2)
Full Analysis Set

Category Statistic	Phase 1b						Phase 2			Both Phases
			RP2DS							
	COHORT1 (N=XX)	---	COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX
Maximum Number of Cycles Completed	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
0	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2										
.....	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
k										
Total Hu5F9-G4 Exposure (mg)										
n	XX		XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Total Number of Cycles of Exposure										
n	XX		XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

Note: Subjects are summarized by planned cycle.
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listings 16.2.4.10.1 and 16.2.4.10.2

Table 14.1.7
Overall Rituximab Exposure and Compliance (Phase 1b and Phase 2)
Full Analysis Set

Category Statistic	Phase 1b						Phase 2			Both Phases
			RP2DS							
	COHORT1 (N=XX)	---	COHORT k (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OTHER CANCER (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	OVERALL (N=XX
Maximum Number of Cycles Completed	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
0	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2										
.....	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
k										
Total Rituximab Exposure (mg)										
n	XX		XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Total Number of Cycles of Exposure										
n	XX		XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

Note: Subjects are summarized by planned cycle.
RP2DS = Recommended Phase 2 Dose Schedule;
SOURCE: Listings 16.2.4.10.1 and 16.2.4.10.2

Table 14.2.1
Summary of Tumor Response (Phase 1b and Phase 2)
Efficacy Analysis Set

Tumor Response	Phase 1b [1]		Phase 2		OVERALL	
	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)
Primary Endpoint[2]						
ORR	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
[95% CI]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]
Secondary Endpoints[3]						
BOR						
CR	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
[95% CI]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]
PR	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
[95% CI]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]
Stable Disease	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
[95% CI]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]
Progressive Disease	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
[95% CI]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]

Note: Subjects are summarized by planned dose level.
RP2DS = Recommended Phase 2 Dose Schedule; CR= Complete Response; PR= Partial Response
95% CI = Two sided 95% Confidence Interval
[1] Phase 1b Subjects with either Indolent Lymphoma or DLBCL
[2] Based on Efficacy Analysis Set
[3] Based on Full Analysis Set
SOURCE: Listing 16.2.6.1

Table 14.2.2
Summary of Overall Respons Rate (Phase 1b and Phase 2)
Per Protocol Set

	Phase 1b [1]		Phase 2		OVERALL	
Tumor Response	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)
Primary Endpoint						
ORR	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
[95% CI]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]	[XX.X; X.XX]

Note: Subjects are summarized by planned dose level.
RP2DS = Recommended Phase 2 Dose Schedule; CR= Complete Response; PR= Partial Response
95% CI = Two sided 95% Confidence Interval
[1] Phase 1b Subjects with either Indolent Lymphoma or DLBCL
SOURCE: Listing 16.2.6.1

Table 14.2.3
Summary for Duration of Response, PFS and OS (Phase 1b and Phase 2)
Efficacy Analysis Set

Tumor Response	Phase 1b [1]		Phase 2		OVERALL	
	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)
DOR [2]						
n	XX	XX	XX	XX	XX	XX
Median[95% CI]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
PFS						
N (events)	XX	XX	XX	XX	XX	XX
Median [95% CI]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
OS						
N (events)	XX	XX	XX	XX	XX	XX
Median [95% CI]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]	XX.X [XX.X; XX.X]
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

RP2DS = Recommended Phase 2 Dose Schedule; CR= Complete Response; PR= Partial Response
[1] Phase 1b Subjects with either Indolent Lymphoma or DLBCL
[2] Based on Subjects who had either CR or PR
SOURCE: Listing 16.2.6.1

Table 14.3.1.1
Incidence of Overall Treatment-Emergent Adverse Events (Phase 1b and Phase 2)
Full Analysis Set

Subjects with at least one	Phase 1b			Phase 2		Both Phases
	Cohort 1 (N=XX)	------- Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Maximum Severity [1]						
Grade 1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Grade 2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Grade 3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Grade 4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Grade 5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
TEAE by Strongest Relationship [2]						
Unrelated to Any of the Study Drug	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Related to Hu5F9-G4 only	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Related to Rituximab only	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Related to both Hu5F9-G4 and Rituximab	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Discontinuation	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
SAE	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Dose Limiting Toxicity	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE of Special Interest	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
AE leading to Death	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event; SAE = Serious adverse event.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
[1] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
[2] Unrelated TEAEs are those marked as Unrelated or Unlikely Related on the case report form (CRF); Related TEAEs are those marked as Possibly Related, Probably. Related, or Definitely Related on the CRF.
SOURCE: Listing 16.2.7.1

Table 14.3.1.2
Incidence of Treatment Emergent Adverse Events (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	-------	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event;
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
SOURCE: Listing 16.2.7.1

Table 14.3.1.3.1
Incidence of Adverse Hu5F9-G4 Reactions (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	-------	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Adverse Hu5F9-G4 reations are TEAEs related to Hu5F9-G4.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
SOURCE: Listing 16.2.7.1

Table 14.3.1.3.2
Incidence of Adverse Rituximab Reactions (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	-------	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Adverse Rituximab reations are TEAEs related to Rituximab.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
SOURCE: Listing 16.2.7.1

Table 14.3.1.4
Incidence of Most Common Treatment-Emergent Adverse Events (≥ 5 % in any cohort or arm) (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	[1] Indolent Lymphoma (N=XX)	[1]DLBCL (N=XX)	[1]Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1			
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2			
Preferred Term 1	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
[1] Phase 1b Subjects with either Indolent Lymphoma or DLBCL who received the RP2DS are included
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
SOURCE: Listing 16.2.7.1

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Table 14.3.1.5.1
Incidence of Treatment Emergent Adverse Events by Maximum Severity (Phase 1b)
Full Analysis Set

System Organ Class/ Preferred Term	Cohort 1 (N=XX)		...		...	Cohort k (N=XX)		...		Overall (N=XX)		...	
	All Grade	Grade 1	...	Grade 5	All Grade	Grade 1	...	Grade 5	All Grade	Grade 1	...	Grade 5
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 1												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 2												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1. TEAEs with a missing severity were assigned the maximum severity grade; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
TEAEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
Source: Listing 16.2.7.1 and 16.2.7.2

Table 14.3.1.5.2
Incidence of Treatment Emergent Adverse Events by Maximum Severity (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class/ Preferred Term	Indolent Lymphoma[1] (N=XX)				DLBCL[1] (N=XX)				Overall (N=XX)			
	All Grade	Grade 1	... ...	Grade 5	All Grade	Grade 1	... ...	Grade 5	All Grade	Grade 1	... ...	Grade 5
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 1												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 2												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1. TEAEs with a missing severity were assigned the maximum severity grade; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
TEAEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
[1] Phase 1b Subjects with either Indolent Lymphoma or DLBCL who received the RP2DS are included
Source: Listing 16.2.7.1 and 16.2.7.2

Table 14.3.1.6.1
Incidence of Treatment-Emergent Adverse Events by Relationship to Study Drug (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Greatest Relationship [1]	Phase 1b			Phase 2		Both Phases
		Cohort 1 (N=XX)	---- ---	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE								
	Unrelated to Any of the Study Drug	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Hu5F9-G4 only	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Rituximab only	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Hu5F9-G4 and Rituximab	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1								
Preferred Term 1								
	Unrelated to Any of the Study Drug	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Hu5F9-G4 only	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Rituximab only	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Hu5F9-G4 and Rituximab	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2								
	Unrelated to Any of the Study Drug	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Hu5F9-G4 only	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Rituximab only	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Related to Hu5F9-G4 and Rituximab	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1. TEAEs with a missing relationship to drug were assigned the strongest possible relationship to drug; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
[1] Unrelated TEAEs are those marked as Unrelated or Unlikely Related on the case report form (CRF); Related TEAEs are those marked as Possibly Related, Probably Related, or Definitely Related on the CRF.
SOURCE: Listing 16.2.7.1

Table 14.3.1.6.2a
Incidence of Adverse Hu5F9-G4 Reactions by Maximum Severity (Phase 1b)
Full Analysis Set

System Organ Class/ Preferred Term	Cohort 1 (N=XX)		...		...	Cohort k (N=XX)		...		Overall (N=XX)		...	
	All Grade	Grade 1	...	Grade 5		All Grade	Grade 1	...	Grade 5	All Grade	Grade 1	...	Grade 5
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 1													
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....													
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 2													
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....													
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)		X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)

Adverse Hu5F9-G4 reations are TEAEs related to Hu5F9-G4 only or both Hu5F9-G4 and Rituximab.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
TEAEs with a missing severity were assigned the maximum severity grade; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
TEAEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
Source: Listing 16.2.7.1 and 16.2.7.2

Table 14.3.1.6.2b
Incidence of Adverse Hu5F9-G4 Reactions by Maximum Severity (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class/ Preferred Term	Indolent Lymphoma[1] (N=XX)				DLBCL[1] (N=XX)				Overall (N=XX)			
	All Grade	Grade 1	... ...	Grade 5	All Grade	Grade 1	... ...	Grade 5	All Grade	Grade 1	... ...	Grade 5
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 1												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 2												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)

Adverse Hu5F9-G4 reations are TEAEs related to Hu5F9-G4 only or both Hu5F9-G4 and Rituximab.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
TEAEs with a missing severity were assigned the maximum severity grade; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
TEAEs are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
[1] Phase 1b Subjects with either Indolent Lymphoma or DLBCL who received the RP2DS are included
Source: Listing 16.2.7.1 and 16.2.7.2

Table 14.3.1.6.3a
Incidence of Adverse Rituximab Reactions by Maximum Severity (Phase 1b)
Full Analysis Set

System Organ Class/ Preferred Term	Cohort 1 (N=XX)			...	Cohort k (N=XX)			Overall (N=XX)			
	All Grade	Grade 1	...	Grade 5	All Grade	Grade 1	...	Grade 5	All Grade	Grade 1	...	Grade 5
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 1												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 2												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)

Adverse Rituximab reations are TEAEs related to Rituximab only or both Rituximab and Hu5F9-G4.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
TEAEs with a missing severity were assigned the maximum severity grade; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
[1] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
Source: Listing 16.2.7.1 and 16.2.7.2

Table 14.3.1.6.3b
Incidence of Adverse Rituximab Reactions by Maximum Severity (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class/ Preferred Term	Indolent Lymphoma (N=XX)				DLBCL (N=XX)				Overall (N=XX)			
	All Grade	Grade 1	... ...	Grade 5	All Grade	Grade 1	... ...	Grade 5	All Grade	Grade 1	... ...	Grade 5
Subjects with at least One TEAE	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 1												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
System Organ Class 2												
Preferred Term 1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
Preferred Term 3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)
.....												
Preferred Term k	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)

Adverse Rituximab reations are TEAEs related to Rituximab only or both Rituximab and Hu5F9-G4.
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1.
TEAEs with a missing severity were assigned the maximum severity grade; TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
[1] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3
Source: Listing 16.2.7.1 and 16.2.7.2

Table 14.3.2.1
Summary of Deaths (Phase 1b and Phase 2)
Full Analysis Set

Reasons of Death	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	----- --	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Reason 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Reason 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Reason 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.							
.							

Note: Percentages are n/Number of subjects in the Full Analysis Set. Subjects are summarized by cohort or arm at onset of death
SOURCE: Listing 16.2.7.4

Table 14.3.2.2
Summary of Serious Adverse Events (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b			Phase 2		Both Phases
	Cohort 1 (N=XX)	------ -	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One SAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
....							

Abbreviations: SAE = Serious adverse event.
Note: Percentages are based on the Full Analysis Set.
SOURCE: Listing 14.3.3.1

Table 14.3.2.3.1
Summary of Treatment Emergent Adverse Events Leading to Hu5F9-G4 Discontinuation (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b			Phase 2		Both Phases
	Cohort 1 (N=XX)	------ -	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1 TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 14.3.3.2

Table 14.3.2.3.2
Summary of Treatment Emergent Adverse Events Leading to Rituximab Discontinuation (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	------ -	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1 TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 14.3.3.2

Table 14.3.2.4.1
Summary of Adverse Drug Reactions Leading to Hu5F9-G4 Discontinuation (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	------ -	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1 TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 14.3.3.2

Table 14.3.2.4.2
Summary of Adverse Drug Reactions Leading to Rituximab Discontinuation (Phase 1b and Phase 2)
Full Analysis Set

System Organ Class Preferred Term	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	------ -	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least One TEAE	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
System Organ Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event
TEAE = Any AE that occurs or worsens in severity or frequency after the initiation of treatment and within 30 days after the last dose of the study drug.
Note: Percentages are based on the Full Analysis Set. TEAEs were coded using MedDRA version 17.1 TEAEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 14.3.3.2

Table 14.3.2.5
Summary of Dose Limiting Toxicities (Phase 1b only)
DLT Analysis Set

Toxicities[1]	Phase 1b			
	Cohort 1 (N=XX)	-------	Cohort k (N=XX)	Overall (N=XX)
System Organ Class 1				
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)
System Organ Class 2				
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)

Note: Percentages are based on the number of subjects in the DLT Analysis Set
[1] Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.3.
SOURCE: Listing 16.2.7.5

Table 14.3.3.1
Listing of Serious Adverse Events (Phase 1b and Phase 2)
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m^2)	Tumor type	Subject Number	SAE	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (study day)/ End Date (study day)	Duration in weeks*	Severity/ Relationship	Outcome/ Action Taken
Phase 1b/ 1	10 mg/kg / 375 mg/m^2	**XXXX**	**XXXX**	XXXX	XXXX/XXX/XXX	XXX/XXX	xxx	XXX/XXX	XXX/XXX

Abbreviations: SAE = Serious adverse event.
*Use + to flag the duration of a serious AE that is ongoing.

Table 14.3.3.2
Listing of Treatment emergent Adverse Events Leading to Discontinuation (Phase 1b and Phase 2)
Full Analysis Set

(Same shell as Table 14.3.3.1)

Table 14.3.4.1
Listing of Clinically Significant Abnormal Laboratory Values (Phase 1b and Phase 2)
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m^2)	Tumor type	Subject Number	Lab Parameter /Value	Start Date (study day)/ End Date (study day)	Duration in weeks*	Severity	Relationship	Outcome/ Action Taken
Phase 1b/ 1	10 mg/kg / 375 mg/m^2	**XXXX**	**XXXX**	XXXX/XXX/XXX	XXX/XXX	xxx	XXX/XXX	Unrelated	XXX/XXX
Phase 1b/ 3	10 mg/kg / 375 mg/m^2	**XXXX**	**XXXX**	XXXX/XXX/XXX	XXX/XXX	xxx	XXX/XXX	Related to Hu5F9-G4	
Phase 2	10 mg/kg / 375 mg/m^2	**XXXX**	**XXXX**	XXXX/XXX/XXX	XXX/XXX	xxx	XXX/XXX	Related to both	
								Related to Rituximab	

Table 14.3.5.1.1
Summary of Serum Chemistry Laboratory Results (Phase 1b and Phase 2)
Full Analysis Set

Lab Parameter: xxxxxx
Study Cycle: xxxx

Cycle Day/ Stat	Phase 1b						Phase 2						**Both Phases**	
	Cohort 1 (N=XX)		-----	Cohort k (N=XX)		Overall (N=XX)		Indolent Lymphoma (N=XX)		DLBCL (N=XX)		Overall (N=XX)		
	Observed	CFB		Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	
Baseline[1]														
n	XX			XX		XX		XX		XX				
Mean	XX.X			XX.X		XX.X		XX.X		XX.X				
Std Dev	XX.XX			XX.XX		XX.XX		XX.XX		XX.XX				
Median	XX.X			XX.X		XX.X		XX.X		XX.X				
Min, Max	XX, XX			XX, XX		XX, XX		XX, XX		XX, XX				
2														
n	XX	XX		XX	XX	XX	XX	XX	XX	XX	XX			
Mean	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X			
Std Dev	XX.XX	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX			
Median	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X			
Min, Max	XX, XX	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX			
…..														
22														
n	XX	XX		XX	XX	XX	XX	XX	XX	XX	XX			
Mean	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X			
Std Dev	XX.XX	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX			
Median	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X			
Min, Max	XX, XX	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX			

Abbreviations: CFB = change from baseline
[1] Baseline is the last non-missing observation recorded before the first dose on Day 1 of the first cycle.
SOURCE: Listing 16.2.8.1

Table 14.3.5.1.2
Shift from Baseline in Serum Chemistry Laboratory Results (Phase 1b)
Full Analysis Set

Study Cycle: xx; Parameter: xxxx

Cycle Day/ Categories	Cohort 1 (N=XX) Baseilne				--	Cohort k (N=XX) Baseilne			
	Low	Normal	High	Overall		Low	Normal	High	Overall
Day 2									
Low	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
High	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 8									
Low	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
High	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Day 22									
Low	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
High	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Percentages are based on the number of subjects in Full Analysis Set.
SOURCE: Listing 16.2.8.1

Table 14.3.5.1.3
Shift from Baseline in Serum Chemistry Laboratory Results (Phase 1b and Phase 2)
Full Analysis Set

Study Cycle: xx; Parameter: xxx

Cycle Day/ Categories	Indolent Lymphoma (N=XX) Baseilne				DLBCL (N=XX) Baseilne			
	Low	Normal	High	Overall	Low	Normal	High	Overall
Day 2								
Low	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
High	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 8								
Low	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
High	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Day 22								
Low	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
High	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Percentages are based on the number of subjects in the Full Analysis Set
RP2DS=Recommended Phase 2 Dose Schedule
Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included in this table
SOURCE: Listing 16.2.8.1

Table 14.3.5.2.1
Summary of Hematology Laboratory Results (Phase 1b and Phase 2)
Full Analysis Set

(Same shell as Table 14.3.5.1: SOURCE: Listing 16.2.8.2)

Table 14.3.5.2.2
Shift from Baseline in Hematology Laboratory Results (Phase 1b)
Full Analysis Set

(Same shell as Table 14.3.5.1.1: SOURCE: Listing 16.2.8.2)

Table 14.3.5.2.3
Shift from Baseline in Hematology Laboratory Results (Phase 1b and Phase 2)
Full Analysis Set

(Same shell as Table 14.3.5.1.2: SOURCE: Listing 16.2.8.2)

Table 14.3.5.3.1
Shift from Baseline in Urinalysis Laboratory Results (Phase 1b)
Full Analysis Set

Study Cycle: xx; Parameter: xxxxx

Cycle Day/ Categories	Cohort 1 (N=XX) Baseilne			--	Cohort k (N=XX) Baseilne		
	Normal	Abnormal	Overall		Normal	Abnormal	Overall
Day 2	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 8	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)

Day 22							
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)

SOURCE: Listing 16.2.8.3

Table 14.3.5.3.2
Shift from Baseline in Urinalysis Laboratory Results (Phase 1b and Phase 2)
Full Analysis Set

Study Cycle: xx; Parameter: xxxxx

Cycle Day/ Categories	Indolent Lymphoma (N=XX) Baseilne			DLBCL (N=XX) Baseilne		
	Normal	Abnormal	Overall	Normal	Abnormal	Overall
Day 2						
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 8	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Day 22						
Normal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Overall	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Percentages are based on the number of subjects in the Full Analysis Set
Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included in this table
RP2DS=Recommended Phase 2 Dose Schedule
SOURCE: Listing 16.2.8.3

Table 14.3.5.3.4
Summary Qualitative Urinalysis Laboratory Results (Phase 1b and Phase 2)
Full Analysis Set

			Phase 1b			Phase 2		Both Phases
Parameter	Cycle Day	Category	Cohort 1 (N=XX)	------ -	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Parameter 1	1	Category 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		----	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	2	Category 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		----	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

	22	Category 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		----	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Category 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

SOURCE: Listing 16.2.8.3

Table 14.3.6.1
Summary of Vital Signs (Phase 1b and Phase 2)
Full Analysis Set

(Same shell as Table 14.3.5.1; SOURCE: Listing 16.2.9.2)

Table 14.3.6.1.1
Shift from Baseline in Vital Signs (Phase 1b)
Full Analysis Set

(Same shell as Table 14.3.5.3.1; SOURCE: Listing 16.2.9.2)

Table 14.3.6.1.2
Shift from Baseline in Vital Signs (Phase 1b and Phase 2)
Full Analysis Set

(Same shell as Table 14.3.5.3.2; SOURCE: Listing 16.2.9.2)

Table 14.3.6.2.1
Summary of ECOG Performance Status Scores (phase 1b and Phase 2)
Full Analysis Set

Study Cycle: xxxx

	Phase 1b					Phase 2		Both Phases
Cycle Day/ Categories	Cohort 1 (N=XX)	Cohort 2 (N=XX)	----	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Baseline[1]								
0	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 2								
0	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
.....								
Day 22								
0	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

[1] Baseline is the last non-missing observation recorded before the first dose on Day 1 of the first cycle
SOURCE: Listing 16.2.9.4

Table 14.3.6.2.2
Shift from Baseline in ECOG Performance Scores (Phase 1b)
Full Analysis Set

Study Cycle: xx

Cycle Day/ Categories	Cohort 1 (N=XX) Baseilne 0	---	5	Overall	--	Cohort k (N=XX) Baseilne 0	---	5	Overall
Day 2									
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 8									
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Day 22									
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Percentages are based on the number of subjects in the Full Analysis Set
SOURCE: Listing 16.2.9.4

Table 14.3.6.2.3
Shift from Baseline in ECOG Performance Scores (Phase 1b and Phase 2)

Full Analysis Set

Study Cycle: xx

Cycle Day/ Categories	Indolent Lymphoma (N=XX) Baseilne 0	---	5	Overall	DLBCL (N=XX) Baseilne 0	---	5	Overall
Day 2								
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Day 8								
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Day 22								
0	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
1	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
3	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
4	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
5	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Percentages are based on the number of subjects in the Full Analysis Set
Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included in this table
RP2DS=Recommended Phase 2 Dose Schedule
SOURCE: Listing 16.2.9.4

Table 14. 6.3.1
Summary of Electrocardiogram (ECG) Parameters (Phase 1b and Phase 2)
Full Analysis Set

ECG Parameter: Heart Rate Study Cycle: xxxx

	Phase 1b						Phase 2 [1]				Both Phases	
Cycle Day/ Stat	Cohort 1 (N=XX)		-----	Cohort k (N=XX)		Overall (N=XX)		Indolent Lymphoma (N=XX)		DLBCL (N=XX)		Overall (N=XX)	
	Observed	CFB		Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB	Observed	CFB
Baseline[2]													
n	XX			XX		XX		XX		XX			
Mean	XX.X			XX.X		XX.X		XX.X		XX.X			
Std Dev	XX.XX			XX.XX		XX.XX		XX.XX		XX.XX			
Median	XX.X			XX.X		XX.X		XX.X		XX.X			
Min, Max	XX, XX			XX, XX		XX, XX		XX, XX		XX, XX			
2													
n	XX	XX		XX	XX	XX	XX	XX	XX	XX	XX		
Mean	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X		
Std Dev	XX.XX	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX		
Median	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X		
Min, Max	XX, XX	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX		
…..													
22													
n	XX	XX		XX	XX	XX	XX	XX	XX	XX	XX		
Mean	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X		
Std Dev	XX.XX	XX.XX		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX		
Median	XX.X	XX.X		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X		
Min, Max	XX, XX	XX, XX		XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX		

Note: Repeat this table for PR Interval; RR Interval; QRS Interval; QT Interval; QTC Interval
[1]: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included in this table
RP2DS=Recommended Phase 2 Dose Schedule
[2] Baseline is the last non-missing observation recorded before the first dose on Day 1 of the first cycle.
SOURCE: Listing 16.2.9.3

Table 14.3. 6.3.2
Summary of Electrocardiogram (ECG) Interpretations (Phase 1b and Phase 2)
Full Analysis Set

ECG Parameter: Heart Rate Study Cycle: xxxx

	Phase 1b				Phase 2 [1]		Both Phases
Cycle Day/ Categories	Cohort 1 (N=XX)	-----	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Baseline[2]							
Normal	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Evaluable	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Done	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
2							
Normal	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Evaluable	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Done	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
…..							
22							
Normal	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - CS	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Abnormal - NCS	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Evaluable	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Not Done	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Abbreviations: CS = clinically significant; NCS = not clinically significant
Note: Repeat this table for PR Interval; RR Interval; QRS Interval; QT Interval; QTC Interval
[1]: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included in this table
RP2DS=Recommended Phase 2 Dose Schedule
[2] Baseline is the last non-missing observation recorded before the first dose on Day 1 of the first cycle.
SOURCE: Listing 16.2.9.3

Table 14.3.6.4
Summary of Concomitant Medications (Phase 1b and Phase 2)
Full Analysis Set

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Phase 1b				Phase 2		Both Phases
	Cohort 1 (N=XX)	-------	Cohort k (N=XX)	Overall (N=XX)	Indolent Lymphoma (N=XX)	DLBCL (N=XX)	Overall (N=XX)
Subjects with at least one Concomitant Medication	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 1							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
ATC Class 2							
Preferred Term 1	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 2	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Preferred Term 3	X (XX.X%)		X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)

Note: Percentages are based on the number of subjects in the Full Analysis Set
Medications are coded using WHO-DD B2E version March 2017. Any medications starting after first dose of study drug will be considered concomitant.
If a medication started before first dose of study drug and continues after first dose of study drug, it will be considered both prior and concomitant;
Medications are displayed by descending frequency of Anatomic Therapeutic Chemical (ATC) Level 4 classification, by Preferred Term (PT) within ATC and then alphabetically. Subjects were counted only once for each ATC and PT
SOURCE: Listing 16.2.9.1

Table 14.4.1
Summary of the Plasma Concentrations of Hu5F9-G4 in combination with Rituximab
Over Time by Cycle Day (Phase 1b and Phase 2)
PK Analysis Set

Cycle: xxxx; Cycle Day: xxxxx

	Phase 1b			Phase 2 [1]	
Demographic Parameter	COHORT1 (N=XX) ---	COHORT k (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)
Predose					
n	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Geometric Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
%CV	XX.X	XX.X	XX.X	XX.X	XX.X
15 mins post Hu5F9-G4					
n	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Geometric Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
%CV	XX.X	XX.X	XX.X	XX.X	XX.X
-----					
15 mins post Rituximab					
n	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Geometric Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
%CV	XX.X	XX.X	XX.X	XX.X	XX.X

[1] Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included
Abbreviation: CV = Coefficient of variation; RP2DS=Recommended Phase 2 Dose Schedule
SOURCE: Listing 16.2.5.1

Table 14.4.2
Summary of PK Parameters Hu5F9-G4 in combination with Rituximab
Over Time by Cycle Day (Phase 1b and Phase 2)
PK Analysis Set

Cycle: xxxx; Cycle Day: xxxxx

	Phase 1b			Phase 2 [1]	
Demographic Parameter	COHORT1 (N=XX) ---	COHORT k (N=XX)	OVERALL (N=XX)	INDOLENT LYMPHOMA (N=XX)	DLBCL (N=XX)
***AUC_{inf}* (unit)**					
n	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Geometric Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
%CV	XX.X	XX.X	XX.X	XX.X	XX.X
***AUC_{0-168h}* (unit)**					
n	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Geometric Mean	XX.X	XX.X	XX.X	XX.X	XX.X
Std Dev	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
%CV	XX.X	XX.X	XX.X	XX.X	XX.X
-----					

[1] Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included
Abbreviation: CV = Coefficient of variation; RP2DS=Recommended Phase 2 Dose Schedule
Note: Add Cmax(unit), Tmax (unit), CL, $T_{1/2}$ and V_z to the table.
SOURCE: Listing 16.2.5.1

Figure 14.4.1.2.1
Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b)
Linear Scale
PK Analysis Set

Header: Cohort=Cohort x; Cycle=xxx; Day=xxxx
Y-axis: Mean Hu5F9-G4 in combination with Rituximab Concentrations (unit)
X-axis: Time Point (hours postdose)

SOURCE: Table 14.4.1.1

Figure 14.4.1.2.2
Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (phase 1b and Phase 2)
Linear Scale
PK Analysis Set

Header: Cohort=Cohort x; Cycle=xxx; Day=xxxx
Y-axis: Mean Hu5F9-G4 in combination with Rituximab Concentrations (unit)
X-axis: Time Point (hours postdose)
Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included
AbbreviationRP2DS=Recommended Phase 2 Dose Schedule
SOURCE: Table 14.4.1.2

Figure 14.4.1.2.3
Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b)
Semi-logarithmic Scale
PK Analysis Set

Header: Cohort=Cohort x; Cycle=xxx; Day=xxxx
Y-axis: Mean Hu5F9-G4 in combination with Rituximab Concentrations (unit)
X-axis: Time Point (hours postdose)

SOURCE: Table 14.4.1.1

Figure 14.4.1.2.4
Mean Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab over Time (Phase 1b and Phase 2)
Semi-logarithmic Scale
PK Analysis Set

Header: Cohort=Cohort x; Cycle=xxx; Day=xxxx
Y-axis: Mean Hu5F9-G4 in combination with Rituximab Concentrations (unit)
X-axis: Time Point (hours postdose)
Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS are included
AbbreviationRP2DS=Recommended Phase 2 Dose Schedule
SOURCE: Table 14.4.1.1

Figure 14.4.1.2.5
Subject Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab Over Time
Linear Scale
PK Analysis Set

Header: Cohort=Cohort x; Cycle=xxx; Day=xxxx
Y-axis: Mean Hu5F9-G4 in combination with Rituximab Concentrations (unit)
X-axis: Time Point (hours postdose)
Programming Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS most be clearly indicated with an asteric

SOURCE: Table 14.4.1.1

Figure 14.4.1.2.6
Subject Plasma Concentrations by Cycle Day of Hu5F9-G4 in combination with Rituximab Over Time
Semi-logarithmic Scale
PK Analysis Set

Header: Cohort=Cohort x; Cycle=xxx; Day=xxxx
Y-axis: Mean Hu5F9-G4 in combination with Rituximab Concentrations (unit)
X-axis: Time Point (hours postdose)
Programming Note: Subjects from Phase 1b with the same cancer type as subjects in Phase 2 and treated at the RP2DS most be clearly indicated with an asteric
SOURCE: Table 14.4.1.1

13.9. Planned Listing Shells

Global programming note: for all listings, sort by cohort (only Cohort A and Cohort B) and subject number. Further sorting instructions will be provided if needed.

Listing 16.2.1
Subject Disposition
All Enrolled Subjects

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Did Subject Complete Study?	Date of Last Dose (study day)	Date of Completion/ Discontinuation (Study Day)	Reason for Discontinuation
Phase 1b/ 1	10 mg/kg / 375 mg/m^2	XXXX	XXXX	Yes	XXX/XXX	DDMMMYYYY (XX)	XXXXXXXXXXX
						DDMMMYYYY (XX)	

Note: Study day is calculated relative to the date of first dose of study drug
Programming Note: If reason for early termination is other, concatenate the specify text as follows: "Other: XXXXXXXXX". If reason for early termination is lost to follow-up, concatenate with date of last contact as follows: "Lost to follow-up; date of last contact: DDMMMYYYY".. If reason for discontinuation is a PI decision, concatenate PI decision reason as follows: "PI Decision: XXXXXXXXXXX".

Listing 16.2.2.1
Eligibility Criteria Not Met
All Enrolled Subjects

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Date (Study Day) of:		All Inclusion Criteria Met?	Any Exclusion Criteria Met?
				Screening	Informed Consent		
XXXXXX	XXXX	XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 02, 09	No
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	No: 06	No
XXXXXX	XXXX	XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	Yes: 06
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No
XXXXXX	XXXX	XXXXXX	XXXXXX	DDMMMYYYY (-X)	DDMMMYYYY (-X)	Yes	No

Note: Study day is calculated relative to the date of first dose of study drug
Programming note: *If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma. Decode any relevant criteria in the footnotes.*

Listing 16.2.2.2
Screen Failures
All Enrolled Subjects

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Date of Birth	Age	Screen Fail Date (Study Day)	Screen Fail Reason
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYY (XX)	Inclusion #2
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYY (XX)	Inclusion #6
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYY (XX)	Inclusion #4, Exclusion #6
XXXXXX	XXXXXX	XXXXXX	XXXXXX	DDMMMYYYY	XX	DDMMMYYY (XX)	Other: XXXXXXXXXXXX

Programming note: *If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma*

Listing 16.2.2.3
Protocol Deviations
All Enrolled Subjects

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Event Type	Violation Level	Description
XXXXXX	XXXXXX	XXXXXX	XXXXXX	XXXXXXXXXXX	MAJOR	XXXXXXX
				XXXXXXXXXXXXXX	MINOR	XXXXXXXXXXXXXXX
XXXXXX	XXXXXX	XXXXXX	XXXXXX	XXXXXXXXXXXX	MINOR	XXXXXXXXXXXXXXXXXXX
				XXXXXXXXXXXXXXXX	MINOR	XXXXXXXXXXX
XXXXXX	XXXXXX	XXXXXX	XXXX	XXXXXXXXXXXX	MAJOR	XXXXXXXXXXXXXXXXXXXX

Listing 16.2.3
Analysis Populations
All Enrolled Subjects

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	EAS [1]	PPS [2]	FAS [3]	PAS [4]	DLT [5]	Primary Reason(s) for Exclusion
XXXXXX	XXXXXX	XXXXXX	XXXXXX	Yes	Yes	Yes	No	No	PK: Subject did not have at least 1 sample with quantifiable concentration of SPR001.
XXXXXX	XXXXXX	XXXXXX	XXXXXX	Yes	Yes	Yes	Yes	Yes	
XXXXXX	XXXXXX	XXXXXX	XXXXXX	No	No	No	No	No	

Abbreviations: EAS = Efficacy Analysis Set; FAS = Full Analysis Set; PPS = Per Protocol Set; DLT = DLT Analysis Set; PAS = Pharmacokinetic Analysis set;
[1] The EAS is defined as all enrolled subjects who receive at least 1 dose of study drug and for whom a baseline and at least 1 post-study drug treatment tumor assessment are available.
[2] The PP Population is defined as all subjects in the FAS who do not have major protocol violations
[3] The FAS Population is defined as all subjects who received at least one dose of study medication.
[4] The PK Population is defined as all subjects in the FAS who have at least 1 plasma sample with quantifiable concentration of SPR001.
[5] The DLT Population is defined as all all enrolled subjects who received at least 1 dose of Hu5F9-G4 + rituximab (study drug) and have had the opportunity to be followed for the 28-day cycle or have experienced a DLT within 28 days after initiating study drug treatment

Listing 16.2.4.1
Demographics and Baseline Characteristics
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Child-Bearing Potential?	Age (years)	Ethnicity	Race	Weight (kg)	Height (cm)	BMI (kg/m^2)
XXXXXX	XXXXXX	XXXXXX	XXXXXX	No	XX	XXXXXXX	XXXXXXX	XX.X	XX.X	XX.XX
XXXXXX	XXXXXX	XXXXXX	XXXXXX	Yes	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX
XXXXXX	XXXXXX	XXXXXX	XXXXXX	No	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX
XXXXXX	XXXX	XXXXXX	XXXXXX	Yes	XX	XXXXXXX	XXXXX	XX.X	XX.X	XX.XX
XXXXXX	XXXXXX	XXXXXX	XXXXXX	Yes	XX	XXXXXXX	XXXXXX	XX.X	XX.X	XX.XX
XXXXXX	XXX	XXXXXX	XXXXXX	No	XX	XXXXXX	XXXXXX	XX.X	XX.X	XX.XX

Abbreviation: BMI = Body mass index
Note: Height, weight, and BMI are the values at Screening.
Programming Note: *If race is other, concatenate "Other:" with specify text. If subject has multiple races, concatenate them*

Listing 16.2.4.2
Medical History
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	SOC/PT/VT	Start date (Study Day)/ End Date (Study Day)
XXXX	XXXX	XXXX	XXXX	XXXX/XXX/XXX	DDMMMYYY (XX)/ DDMMMYYY (XX)
				XXXX/XXX/XXX	
				XXXX/XXX/XXX	
				XXXX/XXX/XXX	
				XXXX/XXX/XXX	
				XXXX/XXX/XXX	

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.4.3
Cancer History
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Cancer Type	Cell of Origin	Refractory to Rituximab?	Cytogenic Abnormalities?	Progostic Index		Lugano Modified Ann Arbor Staging at		Date of Cancer Diagnosis (Study Day)
								At Screening	At Diagnosis	At Screening	At Diagnosis	
XXX	XXX	Phase 2	DLBCL			YES	YES					DDMMMYYY (XX)
XXX	XXX	Phase 1b	2									DDMMMYYY (XX)
XXX	XXX	Phase 2	DLBCL									
XXX	XXX	Phase 2	Indolent Lymphoma									
XXX	XXX	Phase 1b	3									
XXX	XXX	Phase 1b	2									

Listing 16.2.4.4.
Prior Cancer Treatment Summary
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Prior Cancer Treatment	Start date(Study Day)	End Date(Study Day)
XXX	XXX	XXX	XXX	radiotherapy	DDMMMYYY (XX)	DDMMMYYY (XX)
				Surgery		
				Transfusion		
				Systemic therapy		

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.4.5
Prior Radiotherapy
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Site of radiotherapy	Start date(Study Day)	End Date(Study Day)
XXX	XXX	Phase 2	DLBCL	XXXX	DDMMMYYY (XX)	DDMMMYYY (XX)
XXX	XXX	Phase 1b	2			
XXX	XXX	Phase 2	DLBCL			
XXX	XXX	Phase 2	Indolent Lymphoma			
XXX	XXX		3			
XXX	XXX		2			

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.4.6
Prior Surgery
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Type of Surgery	Reason for Surgery	Start date(Study Day)	End Date(Study Day)
XXX	XXX	XXXX	XXXX	XXXXXXXX	XXXXXXXX	DDMMMYYY (XX)	DDMMMYYY (XX)
XXX	XXX						
XXX	XXX						
XXX	XXX						
XXX	XXX						
XXX	XXX		2				

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.4.7
Prior Cancer Systemic therapy
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Drug Name	Start date (Study Day)	End Date (Study Day)	Reason Drug Stopped	Best Response
XXX	XXX	XXXXX	XXXXX	XXXX	DDMMMYYY (XX)	DDMMMYYY (XX)		
XXX	XXX							
XXX	XXX							
XXX	XXX							
XXX	XXX							
XXX	XXX							

Listing 16.2.4.8
Substance Use
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Category of Substance	Substance Type	Substance Use?	Amount Consumed (unit)	Frequencyof Use
XXX	XXX			XXXX	XXXXXX	XXXXXXX		
XXX	XXX							
XXX	XXX							
XXX	XXX							
XXX	XXX							
XXX	XXX							

Listing 16.2.4.9
Pre medications
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Drug Name	Dose (unit)	Star Date (Study Day)	Indication
XXX	XXX			XXXX	XXXXXX X	MMMYYYY (XX()	
XXX	XXX						
XXX	XXX						
XXX	XXX						
XXX	XXX						
XXX	XXX						

Listing 16.2.4.10.1
Rituximab Administration
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Planned Dose (units)	Total Dose Administered (units)	Total Volume (units)	Was Infusion Interrupted?/ Reason	Was Infusion discontinued Prior to Completion?	Reason for Discontinuation
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								

Listing 16.2.4.10.2
Hu5F9-G4 Administration
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Planned Dose (units)	Total Dose Administered (units)	Total Volume (units)	Was Infusion Interrupted?/ Reason	Was Infusion discontinued Prior to Completion?	Reason for Discontinuation
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								

Listing 16.2.4.11
Tumor/ Lymph node Biopsy
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Biopsy Performed?	Date of Specimen Collection (Study Day)	Location of Biopsy
XXX	XXX			XXXX	DDMMMYYY (XX)	
XXX	XXX					
XXX	XXX					
XXX	XXX					
XXX	XXX					
XXX	XXX					

Listing 16.2.4.12.1
Bone Marrow Aspirate
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Specimen Collected?	Date of Specimen Collection (Study Day)	Aspirate Result	Involved?	Percent Involved
XXX	XXX			XXXX	DDMMMYYYY (XX)			
XXX	XXX							
XXX	XXX							
XXX	XXX							
XXX	XXX							
XXX	XXX							

Listing 16.2.4.12.2
Bone Marrow Biopsy
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Specimen Collected?	Date of Specimen Collection (Study Day)	Biopsy Result	% Cellularity	Involved ?	Percent Involved
XXX	XXX			XXXX	DDMMMYYYY (XX)				
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								
XXX	XXX								

Listing 16.2.4.13
Correlative Studies Sample
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Planned time point	Specimen Collected?	Date of Specimen Collection (Study Day)
XXX	XXX			XXXX		DDMMMYYY (XX)
XXX	XXX					
XXX	XXX					
XXX	XXX					
XXX	XXX					
XXX	XXX					

Listing 16.2.4.14
Receptor Occupancy Sample
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Planned time point	Specimen Collected?	Date of Specimen Collection(Study Day)
XXX	XXX			XXXX		DDMMMYYY (XX)
XXX	XXX					
XXX	XXX					
XXX	XXX					
XXX	XXX					
XXX	XXX					

Listing 16.2.5.1
Pharmacokinetic Blood Collection and Concentrations
PK Analysis Set

Study Cycle: XXXX

Study Phase/ Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Cohort Or Arm	Cycle Day	Time Point	Date/Time of Collection (Study Day)	Specimen not collected	Hu5F9-G4 Concentration (unit)
XXXXXX	XXXXXX		Phase 1b	1	2	Predose	DDMMMYYY/HH:MM (X)		X.XX
						15 mins postdose	DDMMMYYY/HH:MM (X)		X.XX
						1 hour postdose	DDMMMYYY/HH:MM (X)		X.XX
						4 hours postdose	DDMMMYYY/HH:MM (X)		X.XX
						24 hours postdose	DDMMMYYY/HH:MM (X)		X.XX
						72 hours postdose	DDMMMYYY/HH:MM (X)		X.XX
					22	Predose	DDMMMYYY/HH:MM(X)	XXXXXXXXXXXXXXX	
						15 mins postdose	DDMMMYYY/HH:MM (X)		X.XX
						1 hour postdose	DDMMMYYY/HH:MM (X)		X.XX
						...			

Abbreviations: BLQ = Below the limit of quantification.
Note: Cycle day is calculated relative to the date of first dose of study drug.
Any results that are BLQ are displayed as BLQ in the listing.

Listing 16.2.5.2
Calculated Pharmacokinetic Parameters
PK Analysis Set

Study Cycle: XXXXXX

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Cycle Day	AUC_{0-168h} (unit)		CL	$T_{1/2}$	T_{max} (unit)	C_{max} (unit)	Volume of distribution
					AUC_{0-t} (unit)						
XXXXXX	XXXXXX	Phase 1b		2	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
					X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
				22	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX

Note: the number of decimal places depends on the raw data. The above parameters are expected, however the final parameters

Listing 16.2.6.1
Disease Response
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Study Cycle	Date of Assessment(Study Day	Overall Response
XXXX	XXX			1	DDMMMYYY (XX)	Stable Disease
				2	DDMMMYYY (XX)	
XXXX	XXX			1	DDMMMYYY (XX)	Partial Response
				2	DDMMMYYY (XX)	

Listing 16.2.7.1
Adverse Events
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab (mg/m2)	Tumor type	Subject Number	TEAE?	SOC/PT/VT	Start date (Study Day)/ End Date (Study Day)	Severity/ Relationship	Outcome/ Action Taken	Serious?
XXX	XXX			NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XXXX/ XXXX	No
XXX	XXX			YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XXXX/ XXXX	YES
XXX	XXX			NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XXXX/ XXXX	No
XXX	XXX			YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XXXX/ XXXX	No
XXX	XXX			YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XXXX/ XXXX	YES
XXX	XXX			NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XXXX/ XXXX	NO

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.7.2
Adverse Events Leading to Study Drug Discontinuation
Full Analysis Set

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.3
Severe Adverse Events
Full Analysis Set

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.4
Treatment Emergent Adverse Events Related to Study drug
Full Analysis Set

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.5
Serious Adverse Events
Full Analysis Set

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.6
Deaths
Full Analysis Set

(Same shell as Listing 16.2.7.1)

Listing 16.2.7.7
Dose limiting toxicities
DLT Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4 (mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	SOC/PT/VT	Start date (Study Day)/ End Date (Study Day)	Toxicity Grade	Outcome/ Action Taken	Serious? / Criteria met
XXX	XXX			XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	4	XXXX/ XXXX	YES/ XXXXXX
XXX	XXX			XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	3	XXXX/ XXXX	NO
XXX	XXX			XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	4	XXXX/ XXXX	NO
XXX	XXX			XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	4	XXXX/ XXXX	NO
XXX	XXX			XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	5	XXXX/ XXXX	YES/ XXXXXX
XXX	XXX			XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	3	XXXX/ XXXX	

SOC = System Organ Class; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.8.1
Clinical Laboratory Data: Serum Chemistry
Full Analysis Set

Study Cycle: XXXXXXX

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Date of Assessment (Study Day)	Standard Results	Units	Abnormal?/ If Yes, CS	Requisition Number	Comments/Reason not Done
XXX	XXX			DDMMMYYYY (X)	XX	XX	NO	XX	
XXX	XXX			DDMMMYYYY (X)	XX	XX	NO	XX	
XXX	XXX			DDMMMYYYY (X)	XX	XX	YES/ NO	XX	
XXX	XXX			DDMMMYYYY (X)	XX	XX	YES/ YES	XX	
XXX	XXX			DDMMMYYYY (X)	XX	XX	NO	XX	
XXX	XXX			DDMMMYYYY (X)	XX	XX		XX	

CS = Clinically Significant

Listing 16.2.8.2
Clinical Laboratory Data: Hematology
Full Analysis Set

(Same shell as Listing 16.2.8.1)

Listing 16.2.8.4
Clinical Laboratory Data: Urinalysis
Full Analysis Set

(Same shell as Listing 16.2.8.1)

Listing 16.2.9.1
Prior and Concomitant Medications
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab (mg/m2)	Tumor type	Subject Number	Ongoing/Prior	ATC Class (Level 5)/ /PT (ATC Level 4)/VT	Start date (Study Day)/ End Date (Study Day)	Dose (Unit)	Study Cycle	Route	Frequency
XXX	XXX			NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	XXX
XXX	XXX			YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	XXX
XXX	XXX			NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	XXX
XXX	XXX			YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	XXX
XXX	XXX			YES	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	XXX
XXX	XXX			NO	XXXX/XXX/XXX	XXXX(XXX)/ XXXX(XXX)	XXXXX/ XXXXX	XX	XXXX/ XXXX	XXX

ATC = Anatomic Therapeutic Chemical; PT = Preferred Term; VT = Verbatim Term.

Listing 16.2.9.2
Vital Sign Measurements
Full Analysis Set

Study Cycle: XXXX

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Date of Assessment (Study Day)	Body Temp (C)	Pulse Rate (bpm)	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Height (cm)	Weight (kg)	BMI (kg/m^2)
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX
XXXX				DDMMMYYYY (X)	XX.X	XX	XX	XX	XX	XX	XX

Listing 16.2.9.3
12-Lead Electrocardiogram Measurementss
Full Analysis Set

Study Cycle: XXX

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Date of Assessment (Study Day)	Heart Rate (bpm)	Interval (msec)					Investigator Interpretation	Comments
						PR	RR	QRS	QT [1]	QTcF [2]		
XXX				DDMMMYYYY (X)	XX	XX	XX	XX	XX	XX	XXXXXXX	XXXXXXX
					XX	XX	XX	XX	XX	XX	XXXXXXXXXXX	XXXXXXXXXXX
XXX				DDMMMYYYY (X)	XX	XX	XX	XX	XX	XX	XXXXXXX	XXXXXXX
											XXXXXXX	XXXXXXX
XXX				DDMMMYYYY (X)	XX	XX	XX	XX	XX	XX	XXXXXXX	XXXXXXX
XXX				DDMMMYYYY (X)	XX	XX	XX	XX	XX	XX	XXXXXXX	XXXXXXX

[1] QT stopping rule met: # = observed QT > 600 msec
[2] Stopping rules met: * = observed QTcF > 500 msec; change from baseline QTcF > 60 msec.

Listing 16.2.9.4
ECOG Performance Status
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Study Cycle	(Cycle Day)	Date of ECOG Assessment	ECOG Performance Status
XXX				XXX	XXXX	DDMMMYYYY (X)	XXXX
XXX				XXX	XXXX	DDMMMYYYY (X)	XXXX
XXX				XXX	XXXX	DDMMMYYYY (X)	XXXX
XXX				XXX	XXXX	DDMMMYYYY (X)	XXXX

Listing 16.2.9.5
Physical Examinations
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Study Cycle	Exam Date (Study Day)	Body System	Findings
XXXX	XXXXX	1b	1	3	DDMMMYYYY (X)	Cardiovascular	Normal
						Respiratory	Abnormal, CS
						Gastrointestinal	Abnormal, NCS
						Neurological	Normal
						Musculoskeletal	Normal
						HEENT	Normal
						Thyroid	Normal
						Skin	Normal
						Extremities	Normal
						Genitourinary	Normal
						Other: XXXXXX	Abnormal, NCS

Abbreviations: CS = clinically significant; NCS = not clinically significant.
Programming note: if finding is abnormal, concatenate with result from clinically significant as demonstrated in shell. If other body system is reviewed, concatenate result as shown in shell. Retain order of body system as shown here.

Listing 16.2.9.6
Visual Acuity Measurements
Full Analysis Set

Study Phase/Dose Level	Dose Hu5F9-G4(mg/kg) /Rituximab(mg/m2)	Tumor type	Subject Number	Study Cycle	Date of Assessment (Study Day)	Right Eye	Left Eye
XXXX	XXXXX		1	3	DDMMMYYYY (X)	XXXXXX	XXXXXX
XXXX	XXXXX		1	3	DDMMMYYYY (X)	XXXXXX	XXXXXX
XXXX	XXXXX		1	3	DDMMMYYYY (X)	XXXXXX	XXXXXX