The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Active Idiotypic Vaccination versus Control Immunotherapy for Follicular Lymphoma

Levy, et al

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PROTOCOL 2000-03

A Phase 3 Trial to Evaluate the Safety and Efficacy of Specific Immunotherapy, Recombinant Idiotype Conjugated to KLH with GM-CSF, Compared to Non-Specific Immunotherapy, KLH with GM-CSF, in Patients with Follicular Non-Hodgkin's Lymphoma

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Confidential

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GENITOPE CORPORATION PROTOCOL

2000-03 Agreement Page
Principal Investigator

10/23/06, v6.1

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except where mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

Principal Investigator: _____ Date: _____
(Signature)

Name: _____

Institution: _____

Address: _____

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2000-03 Agreement Page
Co-Investigator

10/23/06, v6.1

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Co-Investigator _____ Date: _____

(Signature)

Name: _____

Institution: _____

Address: _____

Abbreviations Used in Protocol

AE	Adverse Events
Ab	Antibodies
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BM	Bone Marrow
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDR	Complementarity Determining Region
CHOP	Cyclophosphamide, Vincristine, Doxorubicin, and Prednisone
CIS	Carcinoma *in situ*
CR	Complete Response
CRF	Case Report Forms
CRO	Contract Research Organization
CRu	Complete Response Unconfirmed
CT	Computed Tomography
CTC	Common Toxicity Criteria
CVP	Cyclophosphamide, Vincristine, and Prednisone
DSMB	Data Safety and Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediamine tetra-acetic acid
ELISA	Enzyme-linked Immunosorbent Assay
FACT-G	Functional Assessment of Cancer Therapy - General
FLC	Follicular large cell
FFP	Freedom From Progression
FSC	Follicular small cleaved cell
FM	Follicular mixed small cleaved cell
G-CSF	Granulocyte-Colony Stimulating Factor
GEE	Generalized Estimating Equations
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GTD	Greatest Transverse Diameter
H&E	Hematoxylin and eosin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
Hpf	High-powered field
HRP	Horseradish Peroxidase
Id	Idiotype
H_0	Null hypothesis
Id-IR	Idiotype Immune Response
Id-KLH	Idiotype conjugated to KLH
IPI	International NHL Prognostic Factors Index
IR	Immune Response

Abbreviations Used in Protocol (cont.)

IRB	Institutional Review Board
ITT	Intent-to-Treat
IWF	International Working Formulation
IVRS	Interactive Voice Randomization System
KLH	Keyhole Limpet Hemocyanin
KLH-KLH	KLH conjugated to KLH
LDH	Lactate Dehydrogenase
LN	Lymph Node
MBR	Major Breakpoint Region
mcr	Minor Cluster Region
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
OD	Optical Density
PBLs	Peripheral Blood Lymphocytes
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PE	Physical Exam
PFS	Progression Free Survival
PIN	Patient Identification Number
PR	Partial Response
QOL	Quality of Life
RD	Relapsed Disease
REAL	Revised European-American Lymphoma
rHu	Recombinant Human
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF-1	Syntex Adjuvant Formulation
SC	Subcutaneous
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPD	Sum of Product Dimensions
TTP	Time Tumor Progression
USP	United States Pharmacopeia
V	Variable region
WBC	White Blood Cells
WHO	World Health Organization

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1.0 BACKGROUND

Immunologic therapies for the treatment of B-cell malignancies have shown promise in initial clinical trials. B-cell malignancies present an attractive target for active immunotherapy due to the expression of a tumor-specific marker by the tumor cells. Mature B-cells exhibit antigen receptors (surface immunoglobulin) that contain unique amino acid sequences in the variable regions of the heavy and light chains. The variable regions combine to form the unique antigen-recognition site of the immunoglobulin molecule, complementarity determining regions (CDRs) that contain determinants that can themselves be recognized as antigens, termed idiotypes (Id). Because B-cell malignancies are clonal in nature, the Id expressed by the tumor provides a specific target for immunotherapy and allows the elimination of neoplastic cells while sparing normal cells (1).

Clinical trials conducted at Stanford University School of Medicine (Stanford) (2, 3) and the National Cancer Institute (NCI) (4, 5) have demonstrated that a specific immune response (Id-IR) can be generated against a self-antigen, the tumor-specific Id. In these trials, the tumor burden was reduced using conventional chemotherapy prior to immunization with the Id protein (produced using a hybridoma technique) coupled to a foreign carrier protein, keyhole limpet hemocyanin (KLH). Immune responses were measured by humoral responses to Id and KLH as well as cellular proliferation assays. A clinical benefit was seen in patients who mounted a specific immune response against their tumor-specific Id. In the Stanford trial, analysis of the first 41 patients (32 in first remission) immunized with Id-KLH plus Syntex Adjuvant Formulation (SAF)-1 adjuvant revealed the following:

- Approximately 50% (20/41) of immunized patients mounted a measurable Id-specific immune response. Fifteen of 21 (71%) patients with minimal or no residual disease (CR) at the time of immunization elicited an Id-IR, while 5 of 20 (25%) PR patients elicited an Id-IR.
- Patients who mounted an Id-IR have a median time of freedom from progression (FFP) at 7.9+ years, while in those who did not mount an Id-IR the median FFP was 1.3 years. These results were statistically significant ($p = 0.0001$). An analysis of case-matched historical controls similarly showed a median FFP of 1.3 years.
- None of the patients who developed an Id-IR have died from lymphoma (one patient died from hepatic disease without evidence of malignancy); an overall disease-related survival of 100% with a maximum follow up of 11 years after immunization (median follow up of 7.3 years from the last chemotherapy given before immunization) (3).
- Toxicity from the immunizations was minimal. Most patients had grade 1 or 2 injection site reactions (erythema, tenderness, and induration). About 75% have myalgias/arthralgias, and 20% of these events were grade 3. No grade 4 or serious adverse events were reported.

The results at Stanford suggest that the immunization with Id-KLH may alter the disease-free survival and overall survival for those patients who mount an Id-IR as compared to those who did not mount an Id-IR. In a study conducted at the NCI (4, 5), indolent B-cell lymphoma patients were also immunized with Id-KLH produced via "rescue fusion" in conjunction with granulocyte-macrophage colony stimulating factor (GM-CSF) as the

adjuvant. In the NCI trial, 20 follicular lymphoma patients in clinical complete remission following chemotherapy were immunized with Id-KLH; 19 of these 20 patients generated an anti-idiotype IR. Eighteen of the 20 immunized patients have remained in continuous first complete remission (median of 36+ months from completion of chemotherapy, range 28+ to 53+ months). Furthermore, the study demonstrated that eight of 11 patients who were positive for the molecular marker bcl-2 after chemotherapy converted to bcl-2 negative following immunization (5, 6).

The hybridoma production technique, "rescue fusion", developed at Stanford is successful in manufacturing an immunotherapy for approximately 80% of biopsied patients. The Id protein production requires up to 12 months of effort for each individual. Several technical improvements in the manufacture of the Id immunotherapy have been made since the immunization of the above patients. A newer molecular biological approach, termed "molecular rescue", is now being used for production of recombinant Id immunotherapy. The "molecular rescue" technique has significantly improved the success rate of immunotherapy production, while decreasing production time. In addition, this approach requires very few cells, obviating the requirement for an excisional biopsy of a fairly large lymph node, and cells can be shipped frozen. The heavy and light chain variable region genes are isolated by polymerase chain reaction (PCR) from the patient's malignant clone. The variable region genes are cloned into expression vectors and the recombinant Id protein is over-expressed in a cultured murine cell line. The recombinant Id protein is purified by affinity chromatography and conjugated to KLH. The molecular rescue approach will be used for the production of recombinant Id immunotherapies in this Phase 3 trial.

A Phase 2 trial sponsored by Genitope (study 9901) was conducted at Stanford and the University of Nebraska Medical Center to examine the ability of recombinant Id-KLH conjugates plus GM-CSF to stimulate an anti-Id immune response in patients who were in remission after having received their first chemotherapy regimen. Tumor specimens from previously untreated patients with low-grade, follicular lymphoma were collected for recombinant idiotype manufacture. Patients then received combination chemotherapy, CVP (cyclophosphamide, vincristine, prednisone) or CVP plus CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone) until they achieved a maximal response (complete response [CR], complete response unconfirmed [CRu] or partial reponse [PR]) using the published criteria by Cheson (7), followed by a "rest period" of approximately 26 weeks to allow the immune system time to recover before beginning immunotherapy. Each patient received a series of five subcutaneous immunizations over a 24-week period, given at 0, 4, 8, 12, and 24 weeks. A 12-week pause between the fourth and fifth injection series was instituted because it was thought this would achieve a booster effect.

Study 9901 was used as the basis for the design and initiation of the Phase 3 study (2000-03), after preliminary data from study 9901 showed that 7 out of 10 patients who had completed at least four immunizations demonstrated Id-specific humoral and/or cellular immune responses. The dosing schedule originally planned in study 2000-03 was consistent with study 9901 and previous published experience (2-5). However, more complete data from study 9901, in combination with data from additional Phase 2 studies conducted by Genitope, suggested that a rest period before the last immunization is not advantageous in boosting the

immunologic response and that antibody titers decline during the 12-week rest period prior to the last immunization. Therefore, the dosing schedule in study 2000-03 was modified (Amendment, Version 3) to implement a series of seven immunizations that are administered every 4 weeks over the planned 24-week immunization schedule and thereby eliminate the 12-week rest period. Increasing the number of immunizations has not been shown to alter the anticipated safety profile of Id-immunotherapy when up to eight immunizations have been administered in various Phase 2 studies. Further information about the Phase 2 studies is provided in the Investigator's Brochure.

1.1 Rationale for Study Design

Both the Stanford and Genitope studies demonstrate that Id-KLH immunizations will elicit specific anti-Id responses in at least 50% of patients with indolent (also known as low-grade) follicular Non-Hodgkin's Lymphoma (NHL) who have responded to their initial course of chemotherapy (3). It appears that these patients experience long periods of remission and have not experienced the continuous relapse pattern that is classic of the indolent lymphoma patient. Immunization with recombinant Id-KLH and GM-CSF appears to be safe and effective in generating specific anti-Id responses in indolent follicular lymphoma. A Phase 3 study is necessary to confirm the efficacy of prolonging remission and preventing relapse in patients with follicular lymphoma who receive patient-specific recombinant Id conjugated to KLH (Id-KLH) with GM-CSF.

This is a double-blind trial that incorporates a control consisting of KLH conjugated to KLH (KLH-KLH) with GM-CSF. All patients must complete eight cycles of CVP chemotherapy and have maintained a clinical disease response status of CR, CRu or PR prior to randomization. There will be a 2:1 randomization of patients with follicular lymphoma to Id-KLH with GM-CSF, versus KLH-KLH with GM-CSF. Patients will receive a series of 7 immunizations over 24 weeks. The primary endpoint is progression free survival (PFS). Patients will have follow-up evaluations at the investigational sites for 24 months after completing their immunizations. Thereafter, patients will be contacted every 6 months until death to collect information about survival status and the course of disease.

Patients known to be Human Immunodeficiency Virus (HIV) antibody positive, Hepatitis B surface antigen positive, Hepatitis C antibody positive or on immunosuppressants are not eligible for this study. Pregnant or nursing women are also not eligible for this study, due to the possibility of congenital abnormalities or harm to the fetus or nursing infant that may be caused by this treatment regimen. Pediatric patients (<18 years of age) are also not eligible, due to the rare occurrence of this disease in this age group and difficulty in ability to measure differences of intervention effects.

2.0 OBJECTIVES

2.1 Primary

- To assess progression free survival (PFS) in patients with previously untreated follicular lymphoma treated with eight cycles of CVP chemotherapy followed by a series of 7 immunizations of patient-specific recombinant Id conjugated to KLH (Id-KLH) with GM-CSF, when compared to a control group treated with eight cycles of CVP chemotherapy followed by a series of 7 immunizations with KLH conjugated to KLH (KLH-KLH) with GM-CSF.

- To assess the safety and toxicity of 7 subcutaneous immunizations of Id-KLH administered with GM-CSF as compared to 7 subcutaneous immunizations of KLH-KLH with GM-CSF.

2.2 Secondary/Exploratory

To assess the effect of Id-KLH with GM-CSF in converting patients with a clinical disease response status of CRu or PR to CR. Additional exploratory analyses will be performed, such as those to correlate the induction of anti-Id immune response with clinical benefit (i.e., PFS and survival) and to correlate clinical disease response status with achieving molecular remission as measured by PCR using patient-specific primers from CDRs within the heavy chain variable region and/or bcl-2 primers. Other examples of key secondary/exploratory analyses include time to use of a subsequent anti-lymphoma therapy, survival, and quality of life (QOL) will also be assessed.

3.0 STUDY DESIGN

3.1 Description of Study

The study is a multi-center, randomized, double-blind Phase 3 trial evaluating the safety and efficacy of a series of 7 immunizations of recombinant Id-KLH with GM-CSF as compared to KLH-KLH with GM-CSF in patients with previously untreated follicular B-cell NHL who have been cytoreduced with CVP chemotherapy. There will be a 2:1, experimental (investigational agent) to control, randomization. The study schema and schedule of events are presented in Appendix I.

All patients must have a tissue specimen obtained for Id manufacture. Patients must meet the screening eligibility criteria identified in Section 3.2 and Section 3.3 prior to having a biopsy submitted. Once patients meet eligibility criteria they are registered to the study by calling into the Interactive Voice Randomization System (IVRS) and are assigned a patient identification number (PIN). After this has been completed, a biopsy may be submitted to Genitope.

Initially, it was estimated that approximately 700 patients would be screened and biopsied to obtain 360 patients randomized for immunization. The rationale for this sample size is further discussed in Section 6.7.2.

In April 2004, registration for the trial was completed with 676 patients screened and biopsied. A total of 287 patients were randomized to receive immunizations.

In order to be eligible for randomization, patients must have completed eight cycles of CVP chemotherapy, have achieved a clinical disease response status of CR, CRu or PR by central review, maintained a clinical disease response status of CR, CRu or PR by central review during a rest period, and have a manufactured Id-KLH immunotherapy. Only patients with a documented response to chemotherapy who continue to meet initial eligibility criteria and have a manufactured Id-KLH immunotherapy will be eligible to be randomized.

The time from biopsy to randomization, which includes the chemotherapy regimen and the rest period, is expected to average 11 months. After randomization, patients will receive a series of 7 immunizations of Id-KLH with GM-CSF, or KLH-KLH with GM-CSF, every 4 weeks over a 24 week period. Patients will have an initial response evaluation 2-4 weeks after completing the series of 7 immunizations. Further follow-up response evaluations will be done at the investigational sites every 3 months for 1 year and then every 6 months for the next year, for a total of 24 months of follow-up after completing immunizations (see Section 4.7.3). Thereafter, patients will be contacted every 6 months to capture information about survival status and course of disease (see Section 4.7.8).

3.2 Patient Selection for Initial Eligibility Screen

3.2.1 All patients must have previously untreated follicular B-cell NHL by Revised European-American Lymphoma (REAL) (8)/World Health Organization (WHO) (9)

classification [the International Working Formulation (IWF) equivalents are listed in parenthesis (10)]:

- Follicular Grade 1, 0-5 centroblasts/high-powered field (Hpf); (IWF B: follicular small cleaved cell/FSC)
- Follicular Grade 2, 6-15 centroblasts/Hpf; (IWF C: follicular mixed small cleaved cell/FM)
- Follicular Grade 3, >15 centroblasts/Hpf; (IWF D: Follicular large cell/FLC)
- Areas of diffuse large B-cell lymphoma should be quantified and classified separately:

  3a. >15 centroblasts but centrocytes still present

  3b. Centroblasts form solid sheets with no residual centrocytes

3.2.2 Pathology Review: Adequate sections from the original diagnostic biopsy specimen or core needle biopsies that are large enough to show the architecture (bone marrow biopsies, needle aspirates and needle biopsies alone are insufficient) are required. Slides from the diagnostic biopsy specimen must be submitted for central pathology review. Every attempt should be made to submit these slides within 2 weeks after the tissue specimen for Id manufacture is sent to Genitope. The following from the diagnostic biopsy should be submitted. If unavailable, these items should be submitted from a subsequent biopsy.

- Hematoxylin and eosin-stained (H&E) slides
- Immunostained slides, stained for CD19 or CD20, and CD3
- Paraffin block or 10 unstained sections
- Pathology Report
- Flow Cytometry Report

3.2.3 Stage III or stage IV disease requiring treatment.

3.2.4 No prior therapy for lymphoma (inclusive of antibody, corticosteroids, or cytotoxic therapies). Previous treatment of ≤ two sites of lymphoma with radiation alone is permissible.

3.2.5 At least one site of disease with bi-dimensional measurements ≥ 1.5 cm x 1.5 cm by radiographic review, in addition to the tumor site removed for biopsy.

3.2.6 Age ≥ 18 years.

3.2.7 Tissue specimen adequate to be used for Id manufacturing. Note: Patients whose tumor is known to be surface immunoglobulin negative are not eligible.

3.2.8 Patients who have been diagnosed and biopsied within the 90 days of registration may have frozen tissue submitted with prior authorization from Genitope. A minimum of 5-10 x 10^7 cells are required.

3.2.9 If a patient has been diagnosed within 90 days of registration, but does not have frozen tissue, a new tissue specimen for Id manufacture should be obtained and submitted to Genitope. This tissue specimen will be verified to contain lymphoma by Genitope and does not require institutional pathology review.

3.2.10 Patients who have not been biopsied within 90 days of registration must have a new tissue sample specimen submitted to Genitope specifically for production of the Id-KLH immunotherapy; a sample of the new tissue specimen and the original diagnostic biopsy must be available for central pathology review.

3.2.11 A sufficient number of lymphoma cells must be obtained. Generally, 5 x 10^7 cells are required to provide an adequate sample for production of recombinant Id-KLH. Tissue specimens may be obtained by:

- Excisional biopsy of safely accessible lymph node (LN).
- Core needle biopsy of LN.
- Fine needle aspirate of LN.
- Extranodal tissue (with prior authorization from Genitope).
- Bone marrow aspiration or core if bone marrow contains greater than 30% lymphoma (with prior authorization from Genitope).
- Phlebotomy if the lymphoma cell count is $\geq$ 5,000 cells/mm^3 by manual differential (with prior authorization from Genitope).

3.2.12 All patients should have a blood specimen submitted to the designated central laboratory for PCR assays (CDR and/or bcl-2) prior to starting CVP.

3.2.13 Patients should be able to be observed for 2 weeks (10 business days) while adequacy of the tissue specimen for Id manufacture is being ascertained.

3.2.14 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institutional and federal guidelines.

Patients will be informed that they are providing a tissue specimen for the purpose of manufacturing a patient-specific immunotherapy. They must complete chemotherapy and their disease must respond to chemotherapy. If their disease is not controlled by chemotherapy they will not be eligible for randomization. Patients will be informed of the risks associated with obtaining a tissue specimen. A separate consent form may be required to receive the immunizations depending on local and institutional regulations or requirements.

3.3 Assessments for Registration

3.3.1 Patients must have a physical exam (PE), including vital signs (temperature, blood pressure, pulse, respiration), and a computed tomography (CT) scan of the chest, abdomen and pelvis within 42 days prior to registration. If disease in the neck is present, a CT scan of the neck should also be performed. Note: if CT scans are more than 90 days old at the time chemotherapy is started, CT scans and the PE must be repeated prior to initiating CVP.

3.3.2 Patients must have a bone marrow biopsy (core at least 2 cm in length) and aspirate (optional) within 90 days prior to registration. The following bone marrow slides and reports will be submitted to central pathology for evaluation within 2 weeks after the tissue specimen is sent to Genitope:

- Hematoxylin and eosin-stained (H&E) slides of the bone marrow (BM) biopsy
- Hematoxylin and eosin-stained (H&E) clot (aspirate) section, if available
- Pathology Report for the bone marrow biopsy
- Flow Cytometry Report for the bone marrow biopsy

3.3.3 Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 recorded within 42 days prior to registration.

3.3.4 Patients must have a serum level of lactate dehydrogenase (LDH) determined within 14 days prior to the date of registration.

3.3.5 Patients must have the following laboratory criteria documented within 14 days prior to registration and meet criteria (unless abnormalities are due to lymphoma):

- White blood cell count (WBC) > 1,500/mm^3
- Platelets > 100,000/mm^3
- Serum bilirubin < 1.5x the institutional upper limit of normal, and
- Serum creatinine < 1.5x the institutional upper limits of normal.

3.3.6 Patients must have no clinical evidence of central nervous system involvement.

3.3.7 Patients with a prior malignancy, who have not been disease free for at least five years, are ineligible. (Adequately treated basal or squamous cell carcinoma of the skin, or cervical carcinoma *in situ* (CIS) who have been treated do not have a five-year time restriction).

3.3.8 Patients known to be HIV antibody positive, Hepatitis B surface antigen positive, or Hepatitis C antibody positive are ineligible; laboratory studies to confirm eligibility must be performed within 14 days prior to the date of registration.

3.3.9 Patients who are pregnant or lactating are ineligible. Women and men of reproductive potential may not participate unless they have agreed to use an effective contraceptive

method throughout the administration of chemotherapy. (See Section 3.7.7 regarding contraception during and after immunization.)

3.3.10 Patients with a history of autoimmune disease or conditions requiring treatment with immunosuppressive agents including corticosteroids who have been treated within 12 months of registration are ineligible. Transient use of oral or injectable corticosteroids (e.g., 1-2 doses prior to CT imaging) or optical solutions are acceptable. Inhaled (both oral and nasal) and topical corticosteroids are not permitted.

3.3.11 International NHL Prognostic Factors Index (IPI) scores must be calculated and documented in the patient chart prior to registration.

3.3.12 Patients who have a concomitant illness or condition that, in the opinion of the investigator, would interfere with any aspect of the planned protocol or add unacceptable risk to the patient are ineligible.

3.4 Cytoreductive Chemotherapy

Patients must complete the following chemotherapy to be eligible for the randomized study.

3.4.1 Patients must start CVP chemotherapy within 6 weeks of receipt by Genitope of the tissue specimen used for Id manufacture.

3.4.2 Patients are to receive CVP chemotherapy every 21 days for 8 cycles. Cyclophosphamide and vincristine are to be given intravenously; prednisone is to be given orally.

3.4.3 Patients are to receive CVP doses as indicated below:

Drug	Dose	Route	Days	Re-Treat (interval)
Cyclophosphamide	1000 mg/m^2	IV (administer in 500 cc D5W over 30–40 minutes)	1	q21 d for 8 cycles
Vincristine	1.4 mg/m^2	IV push	1	q21 d for 8 cycles
Prednisone	100 mg	Oral	1-5	q21 d for 8 cycles

3.4.4 Patients should be treated whenever possible with the maximum dose. It is recommended that G-CSF or GM-CSF not be administered preventatively for neutropenia. However, for patients who experience Grade 3 or 4 neutropenia or develop neutropenic fever between cycles of chemotherapy, G-CSF or GM-CSF may be added to all subsequent cycles of chemotherapy. Both growth factors are commercially available. Genitope will not provide G-CSF or GM-CSF for use while patients are receiving CVP chemotherapy.

3.4.5 Patients should be restaged by CT evaluation of chest, abdomen, and pelvis prior to cycle 5 of CVP to ascertain whether the patient is responding to therapy. If scanned previously, a CT of the neck should be repeated. Patients who are assessed to have stable disease are eligible to continue in the study if they will continue to receive CVP as required by this protocol.

3.5 Assessments after Chemotherapy

3.5.1 Patients must be restaged no earlier than 4 weeks, and no later than 8 weeks, after the first day of the eighth cycle of CVP with physical examination (including vital signs), and CT scans of the chest, abdomen, and pelvis. If scanned previously, a CT of the neck should be repeated. In order to assign an overall clinical disease response status of CR or CRu, a bone marrow biopsy must be performed in those patients who were bone marrow positive (or indeterminate) prior to registration. The bone marrow report must accompany the CT scans for central review. Slides must be available for central pathology review.

Clinical disease response status at week 4-8 post CVP will be determined by central review. Patients achieving a PR, CR, or CRu after eight cycles of CVP, according to the modified Cheson criteria defined in Appendix II, will be considered to be eligible to continue in the study.

3.5.2 Patients who have an inadequate response to chemotherapy, defined as failure to achieve PR or better after 8 cycles of chemotherapy, are ineligible to continue on this protocol.

3.6 Rest Interval

3.6.1 A rest interval between chemotherapy and immunization is required. This rest interval is at least 26 weeks and no longer than 30 weeks from the first day of the eighth cycle of CVP.

3.6.2 Patients must be restaged at week 22 post CVP during the rest interval to confirm clinical disease response status with physical examination (including vital signs), and CT scans of the chest, abdomen, and pelvis. If scanned previously, a CT of the neck should be repeated. Clinical disease response status will be confirmed by central review. In order to assign an overall clinical disease response status of CR or CRu, a bone marrow biopsy must be performed in patients who had a positive (or indeterminate) bone marrow at any time prior to the week 22 post CVP time point. If positive (or indeterminate) at baseline, the BM should be repeated to assign CR or CRu even if negative at week 4-8 post CVP. The bone marrow report must accompany the CT scans for central review. Slides must be available for central pathology review.

Patients should have a blood chemistry panel performed, including creatinine, BUN, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), total bilirubin, and LDH.

A serum pregnancy test in females of childbearing potential must be performed at week 22 post CVP.

3.6.3 Patients who have a continued CR, CRu or PR (confirmed by central review) are eligible for randomization.

3.6.4 Patients whose disease has progressed or transformed to an intermediate- or high-grade lymphoma during the rest interval are not eligible for randomization.

3.7 Subject Eligibility for Randomization

3.7.1 Patients must have maintained a clinical disease response status of CR, CRu or PR at week 22 post CVP as confirmed by central review.

3.7.2 Patient's Id-KLH immunotherapy must have been manufactured.

3.7.3 Patients who have received fewer than 8 cycles of CVP, more than 8 cycles of CVP, regimens other than CVP, or radiation therapy during or following CVP are ineligible.

3.7.4 Patients must not be receiving corticosteroids including topical administration for any concurrent disease within 6 months of the first immunization. Transient use of oral or injectable corticosteroids (e.g., 1-2 doses prior to CT imaging) or optical solutions are acceptable. Inhaled (both oral and nasal) and topical corticosteroids are not permitted.

3.7.5 Patients must have a pretreatment serum bilirubin < 1.5x the institutional upper limit of normal and a serum creatinine < 1.5x the institutional upper limit of normal within 4 weeks prior to randomization.

3.7.6 All patients must be informed of the investigational nature of this study and that they will be randomized to receive either a patient-specific immunotherapy (Id-KLH with GM-CSF) or a control (KLH-KLH with GM-CSF). Patients must give written informed consent in accordance with institutional and federal guidelines.

3.7.7 Women and men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method throughout immunization and for 6 months after their last immunization.

3.8 Randomization

3.8.1 Patients should be randomized during week 26 following the first day of their eighth cycle of chemotherapy. Patients will be randomized in a 2:1 ratio of the investigational agent (Id-KLH) to control (KLH-KLH). The patient, study site personnel, and those responsible for central radiographic/oncologic review and central pathology review will remain blinded to treatment. The Sponsor will remain

blinded with the exception of personnel directly responsible for providing assigned Id-KLH or KLH-KLH conjugates.

3.8.2 A Contract Research Organization (CRO) will be responsible for the randomization schedule. Randomization will be designed to achieve a ratio of 2 patients randomized to Id-KLH for every 1 patient randomized to KLH-KLH, stratifying within investigational site and baseline disease status (CRu/PR versus CR). Treatment assignment will be made using an Interactive Voice Randomization System (IVRS).

3.8.3 Clinical evaluations prior to immunization series #1: All of the following evaluations must be obtained **prior** to immunizing the patient on Day 1 of the first immunization series or within 14 days prior to the patient's first immunization, except for vital signs, which must be taken on Day 1.

- QOL assessment (FACT-G version 4, Appendix VI).
- Vital signs on Day 1 before immunization and at 30 minutes after immunization.
- An interim medical history and physical examination, including performance status, weight, and concomitant medications.
- Complete blood count (CBC) with differential, platelets, chemistry panel (to include SGOT, SGPT, bilirubin, serum creatinine and [blood urea nitrogen] BUN), and LDH.
- Blood for PCR assays (CDR and/or bcl-2) (see Appendix III for directions).
- Blood for flow cytometry of T cells (CD3, CD4, CD8), natural killer (NK) cells (CD56/16) and B cells (CD19).
- Urine for urinalysis.
- Blood for serum immunoglobulins (IgG, IgA, and IgM).
- Blood for immune response assays for serum anti-idiotype and serum anti-KLH antibodies.

4.0 STUDY TREATMENT

4.1 Formulation

a. Investigational Agent: Id-KLH

The investigational agent is a recombinant idiotype immunoglobulin (Id) derived from a patient's B cell lymphoma. The biologic is an IgG3 with either a kappa or lambda light chain and is coupled in a ratio of 1:1 with the foreign carrier protein KLH (0.5 mg of Id with 0.5 mg of KLH). The resulting Id-KLH conjugate is administered with GM-CSF as an immunologic adjuvant.

The Id protein used in the immunization is derived from the patient's own B-cell tumor by molecular biological means. The DNA sequence of the variable (V) region heavy and light chain genes expressed in the patient's tumor is determined by reverse transcriptase PCR (RT PCR). The light chain V region genes are cloned into an expression vector containing the appropriate light chain constant region (κ or λ) and the heavy chain V regions are inserted into an expression vector upstream of the γ3 constant region. The recombinant Id protein is over-expressed in a cultured mouse T cell line (BW5147.G.1.4) and the secreted Id protein is purified by affinity chromatography and conjugated to KLH. This cloning and expression strategy allows the production of all patient Id proteins as IgG3, thus permitting a uniform purification scheme.

KLH is an oligomeric glycoprotein complex with multiepitopic antigen structures. Functionally, KLH is the oxygen-carrying molecule in the hemolymph of the California giant keyhole limpet (*Megathura crenulata*). KLH has been used extensively in humans and animals as a foreign carrier protein to increase the immunogenicity of haptens (11, 12). KLH has also been shown to activate both the cellular and humoral immune responses in the bladder mucosa and has been used in the prophylaxis of recurrent superficial bladder carcinoma.

Keyhole Limpet Hemocyanin Conjugate Autologous Immunoglobulin (Id-KLH) is supplied as a sterile suspension for subcutaneous injection containing 1 mg of autologous recombinant B-cell tumor-derived Id-KLH conjugate with 1 mL of 0.9% sodium chloride, USP. Approximately 1.1 mL of Id-KLH is supplied in a 2.0 mL polypropylene vial at a concentration of 1 mg/mL. No preservative is used; therefore, the vial is designed for single use. CAUTION: The Id-KLH is patient-specific.

b. Control: KLH-KLH

The control agent, Keyhole Limpet Hemocyanin (KLH) conjugated to itself (KLH-KLH) is supplied as a sterile suspension for subcutaneous injection containing 0.5 mg of KLH-KLH with 1 mL of 0.9% sodium chloride, USP. Approximately 1.1 mL of KLH-KLH is supplied in a 2.0 mL polypropylene vial at a concentration of 1 mg/mL. No preservative is used; therefore, the vial is designed for single use.

c. Adjuvant: GM-CSF (Leukine®)

GM-CSF is used as an immunologic adjuvant. GM-CSF is a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoietic progenitor cells (13). GM-CSF activates macrophages, results in an increase in the functional capacity of monocytes, and also serves as the principal mediator of proliferation, maturation, and migration of dendritic cells.

The study will use Leukine® (sargramostim; Berlex Laboratories, Inc.), a commercially available recombinant human granulocyte-macrophage colony-stimulating factor (rHu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system (13). Leukine® is a glycoprotein of 127 amino acids characterized by 3 primary molecular species having molecular masses of 19,500, 16,800 and 15,500 daltons. The amino acid sequence of Leukine® differs from the natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety on the yeast-derived protein may be different from the native protein.

Leukine® liquid is formulated as a sterile, preserved injectable solution and is supplied in vials containing GM-CSF at a concentration of 500 μg/mL. Lyophilized Leukine® is a sterile, white, preservative-free powder (250 μg) that requires reconstitution with 1 mL Sterile Water for Injection, USP, or 1 mL Bacteriostatic Water for Injection, USP. When reconsitituted, vials of lyophilized Leukine® contain GM-CSF at a concentration of 250 μg/mL.

4.2 Dispensing Information: Recommended Preparation

a. Preparation for Administration of Investigational Agent (Id-KLH) and Control (KLH-KLH)

The investigational agent and control are shipped frozen in vials. Each vial should be thawed at room temperature immediately prior to use. Both Id-KLH and KLH-KLH are suspensions, may appear flocculent, and should not be shaken. Aseptically withdraw 0.5 mL into each of two 3 mL syringes for subcutaneous use. Neither the investigational agent nor the control contains an anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared suspensions.

b. Preparation for Administration of Adjuvant GM-CSF

Preparation and administration of GM-CSF (Leukine®) should be in accordance with the manufacturer's labeled instruction (13). Leukine® will be provided for use in this study. Caution: Leukine® liquid and vials of reconstituted lyophilized Leukine® contain different concentrations of GM-CSF. Vials of Leukine® liquid contain GM-CSF at a concentration of 500 μg/mL. When reconsitituted, vials of lyophilized Leukine® contain GM-CSF at a concentration of 250 μg/mL.

4.3 Dosage

a. Investigational Agent: Id-KLH

The dose to be employed, 1 mg Id-KLH conjugate (0.5 mg Id conjugated with 0.5 mg KLH), has previously been evaluated in humans and shown to be sufficient to provoke an immune response (2-5).

b. Control: KLH-KLH

The dose of the control, 0.5 mg KLH-KLH, was assessed to be appropriate.

c. Adjuvant: GM-CSF

The dose to be employed, 250 μg of GM-CSF, has been previously evaluated in humans and has been shown to be safe and thought to be sufficient to provoke a specific immune response.

4.4 Administration of Immunizations

Immunizations must be initiated after randomization (which occurs during week 26) and no later than the end of week 30 following the first day of the eighth cycle of CVP. The dosing schedule consists of a series of 7 immunizations, whereby patients receive the 7 subcutaneous immunizations at 4-week intervals over a period of 24 weeks. Immunizations, consisting of injections of Id-KLH or KLH-KLH with GM-CSF as described below, are administered at weeks 0, 4, 8, 12, 16, 20, and 24.

> Id-KLH and KLH-KLH conjugates should be used for subcutaneous injection without further dilution. Both Id-KLH and KLH-KLH are contained in 1 mL of normal saline. On Day 1, the 1 mL immunization is divided into two equal doses of 0.5 mL each; each 0.5 mL dose is injected bilaterally in the anterior thigh superficially to the quadriceps muscle of each leg. Original sites of injection should be marked. Following injection of Id-KLH or KLH-KLH, GM-CSF (250 μg total dose divided equally between the 2 injection sites) is injected subcutaneously at the original injection sites. On Days 2-4 GM-CSF alone (250 μg total dose divided equally between the 2 injection sites) is injected subcutaneously at the original injection sites.

Patients will receive the same schedule of injections every 4 weeks for all 7 immunizations. All 7 injection series are completed over 24 weeks. No dosage reduction is planned.

Administration of Immunizations				
Drug	Total Dose*	Route	Days	Interval
Investigational Agent (Id-KLH) or Control (KLH-KLH)	Id-KLH 1.0 mg/1ml **or** KLH-KLH 0.5 mg/1 ml	Subcutaneous (SC)	1	Week 0, 4, 8, 12, 16, 20, and 24
GM-CSF	250 μg	Subcutaneous (SC)	1-4	Week 0, 4, 8, 12, 16, 20, and 24

*To be divided equally between two injection sites.

4.5 Storage

a. Stability and storage of Investigational Agent (Id-KLH) and Control (KLH-KLH)

The investigational agent and control are shipped frozen on dry ice in vials and should be stored at ≤-20°C (≤-4°F). The vials should be thawed at room temperature immediately prior to use. If a vial is thawed and not used immediately, and the vial has not been entered, it should be stored at 2-8°C (36-46°F). It is not recommended that thawed vials be used after 24 hours or that thawed vials be refrozen. Do not use beyond the date printed on the vial. Refer to the Investigator's Brochure for more information on stability and storage.

b. Stability and storage of GM-CSF (Leukine®)

Leukine® should be stored at 2-8°C (36-46°F). Do not freeze or shake. Do not use beyond the expiration date printed on the vial (13).

4.6 Dose Modification

The dose will remain constant for each patient throughout the study. In the event of severe or life-threatening anaphylaxis or hypersensitivity reaction, discontinue the patient from the treatment phase. Do not retreat.

4.7 Assessment of Immunization

4.7.1 Evaluation of Injection

- Temperature, pulse, respiration rate, and blood pressure will be obtained before each immunization, and at 30 minutes after immunization on Day 1.
- Patients will be observed for 30 minutes after immunization on Day 1.
- Patients will be asked to complete a 4-day diary, recording their temperature once a day post-injection of GM-CSF as well as information concerning local symptoms of erythema, induration, and pain. Patients are also asked to record information regarding systemic adverse events (AE), concomitant medications, self-administration of GM-CSF, and temperature (see Section 5.0 and Section 8.0 for further information about Adverse Event Reporting).

4.7.2 Clinical Evaluation During Immunization

On Day 1 of immunization series #2, #3, #4, #5, #6, and #7 the following will be obtained **prior** to immunizing the patient. See Section 3.8.3 for assessments done prior to immunizing the patient for immunization series #1.

- PE including performance status, vital signs and weight.
- CBC with differential and platelet count.
- Hepatic (SGOT, SGPT, Bilirubin) and renal profiles (serum creatinine and BUN).
- Urinalysis prior to immunization series #4 and #7 only.

4.7.3 Assessment for Clinical Response

a. Initial Response Evaluation

Patients will be assessed for clinical response (radiographic assessments and PE) following immunizations no sooner than 2 weeks and no later than 4 weeks after the completion of the 7th immunization series. Clinical response assessment will include:

- A QOL assessment.
- PE and interim history, including weight, vital signs, and performance status.
- A CT of the chest, abdomen, and pelvis. If scanned previously, a CT of the neck should be repeated.
- A bone marrow biopsy must be repeated in order to assign an overall clinical disease response status of CR or CRu in patients who were PR at time of randomization and who had a positive (or indeterminate) bone marrow any time prior to randomization. A bone marrow biopsy must be repeated in order to assign an overall clinical disease response status of CR in patients who were CRu at the time of randomization and who had an indeterminate bone marrow any time prior to randomization.
- Laboratory tests should include CBC with differential, platelets, hepatic (SGOT, SGPT, bilirubin) and renal function (serum creatinine, BUN).
- Urinalysis.
- Blood for PCR assays (CDR and/or bcl-2).
- Blood for flow cytometry of T cells (CD3, CD4, CD8), natural killer (NK) cells (CD56/16) and B cells (CD19).
- Blood for serum immunoglobulins (IgG, IgM and IgA)
- Blood for immune response assays for serum anti-idiotype and serum anti-KLH antibodies.

b. Follow-up Evaluation for Response

Patients should be evaluated every 3 months for the first year following the completion of immunization series #7 by the following:

- PE, interim history, and performance status.
- Serum for anti-Id responses and anti-KLH responses.

Patients should have a complete response assessment every 6 months for 2 years after the completion of immunization series #7, including:

- QOL assessment.
- PE, interim history and performance status.
- CT of the chest, abdomen, and pelvis. If scanned previously, a CT of the neck should be repeated.
- A bone marrow biopsy must be repeated in order to assign a clinical disease response status of CR or CRu in patients who were PR at time of randomization and who had a positive (or indeterminate) bone marrow any time prior to randomization. A bone marrow biopsy must be repeated in order to assign a clinical disease response status of CR in patients who were CRu at the time of randomization and who had an indeterminate bone marrow any time prior to randomization.
- Laboratory tests should include CBC with differential, platelets, hepatic (SGOT, SGPT and bilirubin) and renal function (serum creatinine and BUN) to assess for toxicity.
- Blood for PCR assays (CDR and/or bcl-2).

4.7.4 Assessment for Immune Responses

Blood will be collected immediately prior to immunization series #1, #3, #4, #5, #6, and #7 and at the initial response evaluation (2-4 weeks after immunization series #7) for analysis of serum anti-idiotype antibody and serum anti-KLH antibody assays (see Appendix IV). Blood will then be collected for immune response assays at 3 month intervals for 1 year following immunization series # 7. Anti-Id humoral responses are defined in the following two categories: 1) negative and 2) positive (see Appendix IV).

4.7.5 Assessment of Molecular Remission

Blood for PCR assays (CDR and/or bcl-2) will be collected prior to starting CVP, within 14 days prior to the first immunization, at the time of initial response evaluation (2-4 weeks after immunization series #7), and every 6 months for the first two years following immunization #7.

4.7.6 Concomitant Medications

All medications used 7 days prior to the start of immunization, throughout immunization, and through 4 weeks after the last immunization series or until administration of another anti-lymphoma therapy, which ever occurs first, will be

recorded on the Case Report Form. If the 2-4 week evaluation (Initial Response Evaluation) occurs prior to the full 4 weeks after immunization #7, the patient must be contacted in order to collect concomitant medications throughout the collection period. Anti-lymphoma therapy other than that described in this protocol and contemporaneous participation in other therapeutic clinical trials is not permitted from registration to completion of the 24-month follow-up visit or termination, whichever occurs first.

4.7.7 Progression

Any patient who is clinically suspected of progression or relapse should have a complete PE, radiographic assessment and, if indicated, bone marrow biopsy/aspirate. Progression is defined according to the modified Cheson criteria specified in Appendix II. CT scans should be forwarded for central review. If a new lesion identified on PE is the basis for suspecting progression, the lesion should be scanned if possible and the scan sent for central radiographic review.

If progression occurs during the immunization segment of the study, which is defined as Week 0 through 2-4 weeks following Immunization #7 as outlined in Appendix I, Schedule of Events, the investigational site should make every attempt to perform all assessments under Section 4.7.3a and complete appropriate CRFs. If progression occurs during the 2-year "Follow-up Response Evaluation" segment of the study as outlined in Appendix I, Schedule of Events, the investigational site should make every attempt to perform all assessments under Section 4.7.3b and complete appropriate CRFs.

At relapse, a core biopsy or open biopsy of the tumor should be performed prior to subsequent therapy in order to assess for histological change. Tissue specimens should be sent to Genitope for molecular analysis of idiotype expression. Tissue specimens should be sent to Genitope using the same collection and shipping procedures that were used for collection and shipping of the tissue specimen for Id manufacture.

4.7.8 Long Term Follow Up

Screen Failure Patients

Patients who are registered to the study but who do not receive a single dose of CVP chemotherapy will not be contacted for long-term follow-up information. Patients who receive at least one cycle of CVP, but who are not randomized, will be contacted every 6 months for survival status from the first day of chemotherapy until death.

Patients Randomized for Immunization

Patients who are randomized will be contacted every 6 months from the date of randomization until death to collect information about survival status and the course

of disease. Patients will be asked questions about progression(s), date of progression(s), subsequent anti-lymphoma treatment(s) (type), infections requiring parenteral (e.g., intravenous or intramuscular) anti-infective medication, and autoimmune conditions and treatments. For patients who have died, date and cause of death will be collected.

For patients who complete 24 months of follow-up, this long-term follow-up contact will begin after the patient completes visits at the investigational site. For patients who terminate prior to completing 24 months of follow-up, this long-term follow-up contact will begin after the patient terminates.

4.7.9 Early Termination

Patients will have treatment discontinued for any of the following reasons:

- Unacceptable toxicity - excessive toxicity from immunization, including debilitating local or constitutional symptoms or persistent hematologic or metabolic abnormalities.
- Emergence of an illness which by its severity, duration or treatment may interfere with study assessments.
- At a patient's request.

If early termination occurs during the immunization segment of the study, which is defined as Week 0 through 2-4 weeks following Immunization #7 as outlined in Appendix I, Schedule of Events, the investigational site should make every attempt to perform all assessments under Section 4.7.3a and complete appropriate CRFs. If early termination occurs during the 2-year "Follow-up Response Evaluation" segment of the study as outlined in Appendix I, Schedule of Events, the investigational site should make every attempt to perform all assessments under Section 4.7.3b and complete appropriate CRFs.

Genitope Corporation has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

5.0 SAFETY ASSESSMENTS

a. Events Associated with Immunizations

Potential local reactions in patients receiving Id-KLH or KLH-KLH immunizations with GM-CSF include erythema, induration, tenderness, itching and pain. Potential systemic reactions associated with Id-KLH immunization or KLH-KLH immunizations with GM-CSF might include transient fever, chills, headache, body aches, fatigue, nausea and malaise. More severe toxicity might include local muscle inflammation or sterile abscess formation, allergic reaction, such as anaphylaxis, mild anemia, arteritis, or immune complex disease. For more information regarding adverse events that have been reported during the use of Id-KLH or KLH-KLH immunizations refer to the Investigator's Brochure.

b. Safety Plan

The primary safety objective is to compare the safety profile of Id-KLH with GM-CSF to that of KLH-KLH with GM-CSF.

Grading of adverse events will be based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2 (Appendix V). The incidence of adverse events will be summarized by body system and toxicity grade. For each patient and adverse event, the maximum toxicity grade achieved will be considered in the summary. Laboratory changes will be captured using the NCI-CTC criteria.

As outlined in Section 8.0, adverse events will be collected for the period beginning 24 hours prior to the start of the first immunization series and ending 4 weeks after the last immunization series or until administration of another anti-lymphoma therapy, which ever occurs first. On the first day of each immunization series, patients will be monitored closely for 30 minutes after immunization. All AEs that start within the specified reporting period will be followed until resolution (event resolved, event stabilized and not expected by the investigator to worsen, or patient death), until 4 weeks after the last immunization series, or until administration of another anti-lymphoma therapy, whichever occurs first. If the 2-4 week evaluation (Initial Response Evaluation) occurs prior to the full 4 weeks after immunization #7, the patient must be contacted in order to collect AEs throughout the collection period.

A patient diary will be provided to each patient to collect information concerning local injection site reactions. Patients are also asked to record information regarding systemic adverse events, concomitant medications, self-administration of GM-CSF, and temperature.

As outlined in Section 8.1, serious adverse events (SAEs) will be collected for the period beginning 24 hours prior to the start of the first immunization and ending 4 weeks after the last immunization series is administered or until administration of another anti-lymphoma therapy, whichever occurs first. All SAEs will be followed until resolution or until administration of another anti-lymphoma therapy, whichever occurs first. As outlined in Section 8.2, information on the development of infections and autoimmune conditions will also be captured as Protocol-Specific Adverse Events.

6.0 STATISTICAL CONSIDERATIONS

The primary hypothesis to be tested in this study is that treatment with recombinant Id-KLH, administered with GM-CSF, will prolong progression free survival (PFS). The effect of therapy is measured from the date of randomization (as described in Section 3.8) to the first observation of progressive disease or death due to any cause.

The primary goal of this study is to assess PFS in patients with previously untreated follicular lymphoma treated with 8 cycles of CVP chemotherapy followed by a series of 7 immunizations of patient-specific recombinant Id-KLH and GM-CSF, when compared to a control group treated with KLH-KLH and GM-CSF.

The following table presents the analysis populations.

Population. Name	Role	Definition	Use
Intent-to-treat (ITT)	Efficacy analyses	All patients randomized to a therapy	Progression free survival (primary endpoint); survival, time to use of subsequent anti-lymphoma therapy, and quality of life.
Immune Response Evaluable	Secondary/ exploratory	All patients randomized to Id-KLH who receive at least four immunizations	Compare both time to progression and survival for patients who mount an anti-Id immune response vs. those who do not
Clinical Response Group (CRu, PR)	Secondary/ exploratory	All ITT patients classified by baseline disease status (CRu, PR)	Analysis of factors related to clinical response to immunizations
Safety	Safety	All patients randomized who receive at least one dose of study treatment	Safety
Screen Failures	Secondary/ exploratory	All patients registered who are not randomized	Descriptive information. Survival analysis for patients who receive at least one cycle of CVP.

The primary efficacy analysis will be conducted for the intent-to-treat (ITT) population, and all safety analyses will be conducted for the safety population.

The primary efficacy endpoint is progression free survival (PFS). The difference in PFS between the two groups will be considered statistically significant if the overall significance for the trial is 0.01. All tests for statistical significance will be two-sided.

Two interim analyses will be performed according to the schedule indicated in Section 7.0. The first interim analysis is planned after all of the anticipated 287 patients have received at least one immunization and 50% or more information is obtained. The second interim analysis is planned 12 months after the first immunization of the last patient randomized and 75% or more information is obtained.

All secondary endpoints will be considered statistically significant if $p<0.05$. There will be no adjustments for multiple comparisons with the exception of the interim analyses.

6.1 Analyses of Patient Disposition

Patient disposition will be summarized and analyzed for the ITT population (see Section 6.0).

The frequency of eligibility exceptions and protocol deviations will be tabulated and summarized by treatment group.

The incidence of discontinuations (overall and by each specific reason), from study therapy and/or from the study itself, will be tabulated by treatment group.

6.2 Analyses of Treatment Group Comparability

Analyses of treatment group comparability will be performed for the ITT population (see Section 6.0).

Summary statistics by treatment group will be presented for demographic and baseline characteristics. Demographic variables will include age, gender and race. Baseline characteristics include disease status; duration of disease since first diagnosis; histology and degree of large B-cell involvement; disease stage; IPI score at registration; clinical disease response status (i.e., response to chemotherapy) and dose density of chemotherapy administered. The data supporting the baseline diagnosis of follicular B-cell lymphoma will be confirmed by an external central pathologist. The pathologist will be blinded to individual patient treatment assignment. Individuals responsible for the central radiographic review will be blinded to individual patient treatment assignment.

6.3 Efficacy Analyses

6.3.1 Primary Endpoint: Progression Free Survival (PFS)

The primary objective of this study is to assess whether treatment with Id-KLH and GM-CSF will prolong PFS when compared to the control treatment consisting of KLH-KLH and GM-CSF. Progression free survival is defined from randomization to the earliest time point identifying progression or death due to any cause. The primary analysis for PFS will be conducted on the ITT population. The log rank test stratified by baseline clinical disease response status to chemotherapy (CR vs. CRu/PR) and study site will be used for the primary

analysis. Kaplan-Meier curves will be used for statistical descriptions (14). Secondary analyses of PFS will also include Cox regression analyses using the demographic and baseline characteristics identified in Section 6.2 to explore the effects of additional factors on PFS. A secondary sensitivity analysis will be conducted to examine the pattern of patients who terminate from study early for any reason other than disease progression and are last known to be alive without disease progression. A subset analysis of PFS for patients who received the first immunization per-protocol (i.e., the first immunization administered by week 30) will be conducted.

Follow-up evaluations including PE, blood work, bone marrow biopsy and appropriate radiographic assessments will be performed to identify the time point of progression. CT scans and other appropriate radiologic assessments will follow internal disease, and interval CT scans will be performed for suspicion of progression. Tumor measurements at each evaluation will be documented.

Additional secondary and exploratory analyses are listed in Sections 6.3.2 through 6.3.7.

6.3.2 Clinical Response to Immunization

The data will be analyzed with reference to the Clinical Response Group population.

Clinical responses will be assessed radiographically and by serial bone marrow biopsy using the modified Cheson criteria as defined in Appendix II.

The response to immunizations and whether the patients experience any additional reduction in their tumor burden as a consequence of the immunizations will be determined by using the week 22 post CVP assessment prior to randomization compared to the assessment following the final immunization and a subsequent assessment. These responses will be graded by the same criteria as responses to chemotherapy, with baseline values defined as pre-immunization (week 22 post CVP) measurements.

The proportion of patients in the Clinical Response Group population who convert from PR or CRu to CR will be tabulated for each treatment group. These proportions will be compared using Fisher's exact test. In addition, logistic regression analysis will be used to assess the prognostic significance of several factors on probability of conversion. Factors to be considered will include the factors identified in Section 6.2. Additional exploratory analyses will be conducted to evaluate the effect of clinical response on PFS and survival.

6.3.3 Survival

A survival analysis will be conducted for the ITT population.

Time from randomization to death (from any cause) will be compared between the treatment groups using a log-rank test to calculate the p-value, and Kaplan-Meier curves to display the results graphically.

6.3.4 Time to Use of Subsequent Therapy

A time to use of a subsequent therapy analysis will be conducted for the ITT population.

Time to use of a subsequent therapy will be defined as the number of days from randomization until use of the first subsequent anti-lymphoma therapy (other than study treatment) or death due to progressive disease, whichever is earlier. Patients who have progressed but have not received a subsequent therapy for the treatment of lymphoma, who are alive without disease progression, or who died for causes unrelated to disease progression will be considered censored on their last known day of follow-up. Time from randomization to use of a subsequent therapy will be compared between the treatment groups using a log-rank test to calculate the p-value, and Kaplan-Meier curves to display the results graphically.

6.3.5 Immune Response and Effect of Mounting an Anti-Id Immune Response on PFS and Survival

a. Immune Response: Anti-Id and Anti-KLH

The Immune Response Evaluable population is defined as all patients randomized to the Id-KLH treatment group who receive at least four immunizations. Patients will be classified as having mounted an anti-Id immune response (IR positive) or not having mounted an anti-Id immune response (IR negative). The number and percent of patients with positive vs. negative anti-Id immune responses will be tabulated. The number and percent of patients who mount a positive anti-KLH response (anti-KLH positive) vs. those who do not mount anti-KLH response (anti-KLH negative) also will be summarized in a table by treatment group. The criteria for assessing IR are provided in Appendix IV of the protocol.

b. Effect of Mounting an Anti-Id Immune Response on PFS and Survival

Exploratory analyses to evaluate PFS and survival time between patients who have a positive anti-Id IR and those that have a negative anti-Id IR will be compared using log-rank test and a Kaplan-Meier plot. PFS and survival in these groups will be compared to the control group.

c. Time to Positive Immune Response and Duration of Immune Response

Exploratory analyses for time to positive immune response and the duration of immune response will be conducted for patients who mount an anti-Id immune response in the IR evaluable group. Descriptive statistics (N, mean, median, standard deviation, and range) will be calculated for these analyses.

6.3.6 Clinical Benefits of Achieving Molecular Remission

The presence of tumor cells in the peripheral blood is proposed to be examined by PCR using heavy chain variable region CDR-specific primers for each patient and/or bcl-2 primers (to be performed at a central location). PCR assay for bcl-2 rearrangement is described in Appendix III. In the ITT population, patients who have received immunizations with Id-KLH and GM-CSF will be compared by means of exploratory analyses to those patients who received immunizations with KLH-KLH and GM-CSF with respect to the ability of the

immunization to further reduce the minimal residual disease (CR or CRu) that is detectable after chemotherapy. The correlation between molecular disease status and clinical disease status and survival will be examined.

6.3.7 Survival Analysis for the "Screen Failure" Population

A survival analysis from the first day of the first cycle of chemotherapy until death from any cause will be conducted using the Kaplan-Meier method for all registered patients who receive at least one cycle of CVP but are ineligible for randomization.

6.4 Quality of Life Analyses

Quality of life will be assessed using FACT G version 4 (Appendix VI) prior to the start of immunization, 2-4 weeks following the 7th immunization, and every 6 months for 2 years following the 7th immunization (15). Each domain measured in FACT G version 4 will be analyzed separately. At each administration of the QOL instrument, an average score for each domain will be calculated. Changes in average score from baseline to each "6-month" time-point will be summarized by presenting the sample mean, median, and standard deviation for domain by treatment group. The QOL data will be analyzed using a mixed effects model to compare the difference between the treatment groups over time.

6.5 Safety Analyses

All safety analyses will be performed on the Safety population as defined in Section 6.

6.5.1 Serious Adverse Events, Protocol-Specific Adverse Events, and Death

Serious adverse events will be listed by treatment group and patient identification.

Protocol-specific adverse events (infections and autoimmune conditions) will be listed by treatment group and patient identification.

Deaths will be listed by treatment group and patient identification.

6.5.2 Other Adverse Event Analyses (Serious or Non-serious)

Summaries of treatment-emergent adverse events will be presented in three analyses. Each analysis will present calculations for all coded preferred terms by treatment group, with a denominator of all patients in that treatment group based on safety population. The analyses will present:

1) The proportion of patients reporting at least one adverse event will be presented by treatment group, system organ class, and preferred term. Patients who experienced more than one event mapped to the same preferred term will be counted once for that same preferred term.

2) The proportion of patients reporting at least one adverse event will be summarized by treatment group, organ class system, preferred term, and severity. Patients who

experienced more than one event mapped to the same preferred term will be counted once for that same preferred term at the maximal severity.

3) The proportion of patients reporting at least one adverse event reported as possibly/probably related to study treatment, will be summarized by treatment group, organ class system, preferred term, and severity. Patients who experienced more than one possibly/probably related event mapped to the same preferred term will be counted once for that same preferred term at the maximal severity.

6.5.3 Safety Laboratory Assessments

Summary statistics will be presented for baseline laboratories.

Average change from baseline to each point of measurement will be calculated for continuous laboratory measurements for each treatment group. Abnormal values will be reported in a data listing by treatment group and patient identification. Statistical tests will not be performed for safety laboratories.

6.5.4 Vital Signs

Summary statistics will be presented for baseline vital signs.

Average changes from baseline to each pre-immunization point of measurement will be calculated for all vital signs for each therapy group. Statistical tests will not be performed for vital signs.

6.6 Procedures for "Missing" Data

There will be no imputation for missing data in analyses of baseline characteristics, patient disposition, or safety data.

For the primary endpoint (PFS), patients who have been randomized, but who have no further follow-up, will be considered censored (i.e., as non-events) on the date of randomization (Day 1). Patients who are alive without disease progression and have not received subsequent anti-lymphoma therapy will be censored on the date of their last evaluation of disease status. Patients who received subsequent anti-lymphoma therapy either without disease progression occurring or before disease progression occurred will be censored on the date of their first subsequent anti-lymphoma therapy.

For analysis of clinical response to immunizations, patients whose disease status is not reassessed after their first immunization will be considered to have not shown a clinical response.

Procedures for other efficacy variables will be as follows:

- SURVIVAL: Patients who are not known to have died will be considered "censored" on their last known date of follow-up. If no follow-up data are available for the patient, the patient will be considered "censored" on day 1.

- TIME TO USE OF A NEW INTERVENTION: Patients will be considered "censored" on their last known date of follow-up, even if the patient has progressed without receiving any new interventions. If no follow-up data are available for the patient, the patient will be considered "censored" on day 1.
- QUALITY OF LIFE: If a patient is missing one or more (but not all) subscores within a domain, then subscores that are missing will be excluded from the average score for that domain at that timepoint. Patients with missing data for a specific domain (i.e., missing all subscores within that domain) will be excluded from the analyses of that domain at that time point. Patients with missing baseline score for a specific domain will be excluded from all analyses of that domain. Each analysis will clearly denote the number of patients in each treatment group contributing to that analysis.

6.7 Sample Size Determination

6.7.1 Anticipated Number of Patients Screened for Biopsy and Anticipated Accrual

Initially, it was anticipated that 700 patients would need to be screened for biopsy to obtain 360 patients randomized for immunization. About 45% of the patients screened were expected to drop out prior to randomization due to inadequate response to chemotherapy, patient refusal, or other changes in eligibility status, and another 2% were expected to drop out because of inability to produce Id immunotherapies for their tumors. Also, it was anticipated that the accrual rate across all investigational sites would be 15-25 patients registered per month, resulting in approximately nine patients per month who would be randomized for immunization.

Registration for the trial was completed in April 2004 and 676 patients were screened and biopsied. A total of 287 patients were randomized to receive immunizations. Registration for the trial averaged approximately seven patients per month.

6.7.2 Statistical Justification of Sample Size: PFS

The primary endpoint of the study is PFS, which is defined as the number of months from randomization to the earliest time point identifying disease progression (i.e., time to progression [TTP]) or death due to any cause. When the study was designed, assumptions based on TTP alone were used. The original assumptions used for calculating the sample size are as follows:

1) The median TTP was assumed to be 49 months (from the end of chemotherapy) in the experimental group and 28 months (from the end of chemotherapy) in the control group;
2) The accrual rate was assumed to be 24 evaluable patients per month (15 month accrual period), with a total trial duration of 39 months from the time of the first randomization;
3) Patients would be randomized in a 2:1 ratio, experimental:control.

A sample size of 360 patients was calculated in order to detect 21 months difference in TTP between active and control group with 80% power using a two-sided log-rank test at significance level of 0.01.

Assumptions 1) and 2) were changed as follows:

1) The median TTP was assumed from randomization, i.e., to be 43 months (from randomization) in the experimental group and 22 months (from randomization) in the control group;
2) The accrual rate was assumed to be approximately nine evaluable patients per month (39 month accrual period), with a total trial duration of 69 months from the time of the first randomization.

Given these assumptions, a sample size of 360 patients, randomized in a 2:1 ratio (experimental - Id-KLH:control - KLH-KLH) would allow for a power of at least 0.80 to detect a difference of 13 months or greater in TTP between the control group and the experimental group. A two-sided log rank test at significance level 0.01 is assumed. This estimate is assumed to be conservative based on the range of median TTPs found in the literature.

6.7.3 Randomization Technique

Central randomization will be employed using IVRS (interactive voice randomization system) technology. Patient registration and randomization will be accomplished via telephone in an interactive session guided by a validated computer program.

7.0 INTERIM ANALYSES AND DATA SAFETY AND MONITORING BOARD

Two interim analyses will be performed during the course of the study. The first interim analysis is planned after all of the anticipated 287 patients have received at least one immunization and 50% or more information is obtained (i.e., at least 91 progressions are observed). The second interim analysis is planned 12 months after the first immunization of the last patient randomized and 75% or more information is obtained (i.e., at least 136 progressions are observed). The assumptions used to calculate the number of events expected at the end of the study are summarized in the table below.

Direction	Alpha 2-sided
Significance Level	0.01
Power	0.967
Accrual for randomized patients/month	6.83333
Median PFS - control	22 mo
Median PFS - experimental	43 mo
Patient allocation ratio experimental:control	2:1
Accrual duration (6 Nov 01 to 25 May 05)	42 mo
Total study duration	72 mo
Expected number of events under H_0	181

Based on these assumptions, the two-sided significance levels needed to achieve the overall significance level of 0.01 will be 0.0002, 0.0026, and 0.0091 for the first interim analysis (at 50% information), second interim analysis (at 75% information), and final analysis, respectively. These alpha levels are computed using the East 4 interim analysis software, and are based on an alpha spending function derived from the O'Brien-Fleming stopping boundary. East 4 software will be used to adjust significance levels based on the actual number of events at the time of the interim analyses.

The interim analyses will be conducted to evaluate safety and the evidence in favor of the alternate hypothesis. The primary efficacy analysis on which this decision will be based is the log-rank test for PFS stratified by baseline clinical disease response status (CR vs. CRu/PR) and study site. Any decision to substantially alter the design of the trial will be made by the Sponsor of the trial, based on the recommendation of an independent Data Safety Monitoring Board (DSMB). The DSMB will be provided with additional efficacy and safety analyses, so that they may consider benefit and risk in their recommendation to the Sponsor. The DSMB also may request additional analyses.

The DSMB will consist of independent reviewers. The purpose of the DSMB is to advise on: 1) serious safety considerations, 2) early and persuasive efficacy of the Id therapy (taking into account the Type I error level of significance of two-sided 0.01, fixed for the overall trial), or 3) any other considerations within the charge to the Committee as described in the

DSMB Charter. The DSMB may request additional meetings or safety reports as deemed necessary upon discussion with the study Sponsor and CRO.

At each interim analysis, the DSMB will be presented with the analysis of the primary endpoint, as described in Section 6.3.1. They will also be presented with additional efficacy and safety analyses. The DSMB will review clinical disease response status conversion data (CRu and PR to CR) at the same time they meet to evaluate the primary endpoint. The DSMB may inform the Sponsor of any statistical difference between the groups if they have been requested to do so. Patients and investigators will remain blinded to the results and to patient therapy assignments and data will continue to be collected as described in the protocol until the end of the trial.

8.0 ADVERSE EVENT REPORTING

Adverse events (AEs) will be collected for the period beginning 24 hours prior to the start of the first immunization series and ending 4 weeks after the last immunization series is administered or until administration of another anti-lymphoma therapy, whichever occurs first. All AEs that start within the specified reporting period will be followed until resolution (event resolved, event stabilized and not expected by the investigator to worsen, or patient death), until 4 weeks after the last immunization series, or until administration of another anti-lymphoma therapy, whichever occurs first.

All AEs should be graded using the NCI-CTC (see Appendix V). NCI-CTC non-serious and serious adverse events (SAEs) encountered during the treatment and post-treatment periods will be recorded on the appropriate pages of the AE CRFs and/or SAE Notification Form.

For this protocol, an AE is any untoward medical occurrence (i.e., sign, symptom, disease syndrome, intercurrent illness, clinically significant abnormal laboratory finding) that emerges or worsens relative to pretreatment baseline, during the treatment or post-treatment periods, regardless of the suspected cause.

Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms (in accordance with the NCI-CTC) when recording events on the CRF. Do not use colloquialisms and/or abbreviations.
- Where a diagnosis is possible, it is preferable to report this rather than a series of terms relating to the diagnosis (i.e., record "congestive heart failure" rather than dyspnea, rales, and cardiomegaly). Signs and symptoms should be indicated parenthetically following the syndrome rather than as separate events.
- The severity of events reported on the adverse event CRF will be determined by the principal investigator according to the NCI Common Toxicity Criteria (CTC) set forth in Appendix V.
- Medication taken to relieve symptoms of the AE will be recorded, as well as the outcome.
- Using the following criteria, investigators also need to assess whether there is a reasonable possibility that study treatment (Id-KLH or KLH-KLH with GM-CSF) caused or contributed to the AE:
  - Yes (Probably/Possibly related): If there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or there is a biologically plausible mechanism for study treatment causing or contributing to the AE; and the AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.
  - No (Probably not related): The subject was not exposed to the study treatment, or another cause is obvious. The AE is most likely explained by another cause, or the time of occurrence of the AE is not reasonably related to administration of study treatment.

8.1 Serious Adverse Event Reporting Requirements

Serious adverse events (SAEs) will be collected for the period beginning 24 hours prior to the start of the first immunization and ending 4 weeks after the last immunization series is administered or until administration of another anti-lymphoma therapy, whichever occurs first. All SAEs that start within the specified reporting period will be followed until resolution (event resolved, event stabilized and not expected by the investigator to worsen, or patient death) or until administration of another anti-lymphoma therapy, whichever occurs first. Serious AEs require reporting to the Genitope Medical Monitor within 48 hours of the investigator's knowledge of the event regardless of relationship to study drug.

An AE occurring at any dose or time during the collection period should be classified as SERIOUS if:

- Fatal

The AE resulted in death. All deaths are reported, whether or not suspected of being related to study treatment. Death is an outcome of an event. The **event** that resulted in the death should be recorded and reported on the SAE pages of the CRF. In this study, death directly related to underlying lymphoma will not be reported in an expedited fashion.

- Life-threatening

The AE was life threatening, (*i*.e.. the AE placed the patient at immediate risk of death; it does not apply to an AE that hypothetically might have caused death if it were more severe).

- Inpatient hospitalization (initial or prolonged)

The AE required an inpatient hospitalization or prolonged inpatient hospitalization beyond the expected length of stay. Hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by these criteria. The illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

- Disability

The AE was disabling (i.e., it results in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities, or quality of life).

- Congenital anomaly

The AE is a congenital anomaly/birth defect (i.e., and adverse outcome in a child or fetus of a patient exposed to the investigational agent prior to conception or during pregnancy).

- Requires intervention to prevent permanent impairment or damage

An AE that does not meet any of the above serious criteria but may jeopardize the patient or may require medical or surgical intervention to preclude impairment or damage to a subject.

SAEs, whether or not they are thought to be related to the investigational drug, should be reported within 48 hours by faxing an SAE Notification Form to the fax number listed on the Protocol 2000-03 Contact Information Page.

All subjects with serious adverse events must be followed for outcome. A completed Serious Adverse Event Notification Form and other available supporting documentation must be forwarded to Genitope by facsimile within 48 hours of knowledge of the adverse event (fax number provided above). Supporting documentation includes, but is not limited to, evidence of the cause of death, an autopsy report, copies of laboratory reports, etc.

Information that subsequently becomes available must be provided to Genitope Corporation on a follow-up SAE Notification Form as soon as possible.

8.2 Protocol-Specific Adverse Events

Any autoimmune condition, or infection (including opportunistic infections) requiring administration of a parenteral (e.g., intravenous or intramuscular) anti-infective medication that develops from the start of immunization until death is a protocol-specific AE. If a protocol-specific AE develops at any time during immunization or through 24 months following immunization #7, it should be reported to Genitope whether or not the investigational agent is suspected to be the cause and whether or not the event is serious. The event should be reported to the Sponsor within 48 hours according to procedures described in Section 8.1. If a patient terminates prior to completing 24 months of follow-up, information on infections and autoimmune conditions will be collected by contacting the patient as described in Section 4.7.8. Likewise, after a patient completes 24 months of follow-up, information on infections and autoimmune conditions will continue to be collected by contacting the patient as described in Section 4.7.8. Autoimmune conditions include, but are not limited to: serum sickness, vasculitis, arthritis, retinitis, hemolytic anemia, immune thrombocytopenia, immune neutropenia, thyroiditis, pemphigus, or pleuritis. Opportunistic infections include, but are not limited to: fungal infections, toxoplasmosis, pneumocystis carinii, cytomeglovirus or atypical mycobacterium.

Investigational sites should instruct female patients to inform them if they become pregnant during the study and up to 180 days after completion of study treatment. Any pregnancy that occurs during this time, should be reported within 48 hours to the Sponsor to facilitate outcome follow-up. Female patients who become pregnant during the study should be discontinued from study treatment. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancy occurring in the partner of a subject participating in the study should likewise be reported to the investigator and subsequently to the Sponsor. Abortion, whether it be accidental, therapeutic, elective, or spontaneous, should be reported. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the investigational treatment is an SAE and must be reported within 48 hours to the sponsor.

8.3 Reporting to the Institutional Review Board/Ethics Committee

The investigator must report any SAE occurring in their patients to their Institutional Review Board (IRB)/Ethics committee. The Sponsor will notify all investigators of all serious adverse events that are considered unexpected and probably/possibly related to the investigational agent. The investigator must also report these SAEs to their IRB/Ethics Committee responsible for reviewing the study.

9.0 REGULATORY AND ADMINISTRATIVE PROCEDURES AND ADMINISTRATION

9.1 Institutional Review Board/Ethics Committee Review and Approval

The investigator shall assure that an IRB/Ethics Committee, constituted in accordance with the U.S. Code of Federal Regulations, Title 21, Part 56, will provide initial and continuing review of the study.

Prior to shipment of the investigational agent or control and enrollment of study subjects, documented IRB/Ethics Committee approval of the protocol, informed consent form and any advertisement for subject recruitment must be obtained and provided to Genitope. Genitope will require at least seven (7) working days to review such materials.

The IRB/Ethics Committee must also be informed of and approve all protocol amendments prior to implementation and changes in research activity (e.g., the completion, termination or discontinuation of a study).

9.2 Investigational Agent Accountability

Upon receipt, the investigator is responsible for taking an inventory of the investigational agent. A record of this inventory must be kept and usage must be documented on the Investigational Drug Accountability Record provided by Genitope. All unused investigational agent should be destroyed after authorization from the Sponsor unless otherwise instructed according to the institutional guidelines for biologic substances.

The investigational agent is patient specific. The investigator is responsible for ensuring and documenting that the agent is provided to the patient for whom it is designated.

9.3 Informed Consent

A copy of the proposed informed consent documents must be submitted to the Sponsor for review and comment prior to submission to the reviewing IRB/Ethics Committee. The consent forms must be approved by the IRB/Ethics Committee and must contain all elements required by federal, state, local and institutional regulations or requirements. Institutions in the United States must be in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) with regard to obtaining authorizations for use and disclosure of Protected Health Information.

The study will be completely explained to each prospective study subject. Each subject (and/or the legally authorized representative if the patient is mentally incompetent or physically incapacitated) considered for the study must voluntarily provide written informed consent, using the IRB/Ethics Committee-approved consent forms, prior to their enrollment in the study (*i.e.*, before any protocol-dictated procedures that are not part of normal patient care are performed).

9.4 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the Sponsor and to the IRB/Ethics Committee. Any other planned deviations from the protocol will also be reported to the sponsor and IRB.

9.5 Protocol Revisions

Protocol amendments will be prepared and approved by the Sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/Ethics Committee for review and approval prior to implementation. Documentation of IRB/Ethics Committee approval must be forwarded to the Sponsor.

If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/Ethics Committee for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

9.6 Data Collection

The investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. Data collected for each study subject will be recorded on Worksheets and CRFs provided or approved by the Sponsor. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

CRFs must be completed legibly with black ballpoint pen. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction.

For each subject, the completed CRFs must be promptly reviewed, and signed and dated by the investigator. The study monitor representing the Sponsor will review and authorize CRFs for faxing into the database. The investigator must retain a copy of all CRFs.

9.7 Study Monitoring

Study monitors representing the Sponsor will visit study sites routinely throughout the trial. The monitor will review CRFs and compare them with source documents to verify accurate collection of data and that the study is being conducted according to the protocol. Auditors representing the Sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make CRFs and source documents available when requested.

In addition, the study may be evaluated by representatives of the Food and Drug Administration, and the Human Protection Board of Canada, who will also be allowed access

to study documents. The investigator should promptly notify the Sponsor of any audits he/she has scheduled with any regulatory authorities.

9.8 Reports

The investigator must provide the Sponsor with an adequate final report of the trial shortly after the discontinuation of the investigator's participation in the study. The report should contain a listing of patients (identified by assigned PIN) who were initially screened and biopsied, dates of biopsy, listing of patients who were not eligible for randomization with reason and date of termination, listing of patients who underwent randomization and date of randomization, listing of patients who terminated study after registration and dates, listing of patients who died on study with date of death, and listing of patients and dates of patients who experienced SAEs.

9.9 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the Sponsor at the time the study is completed, terminated or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the Sponsor.

10.0 PUBLICATIONS

Information on the study may not be publicly discussed or published without prior written authorization of Genitope Corporation.

11.0 REFERENCES

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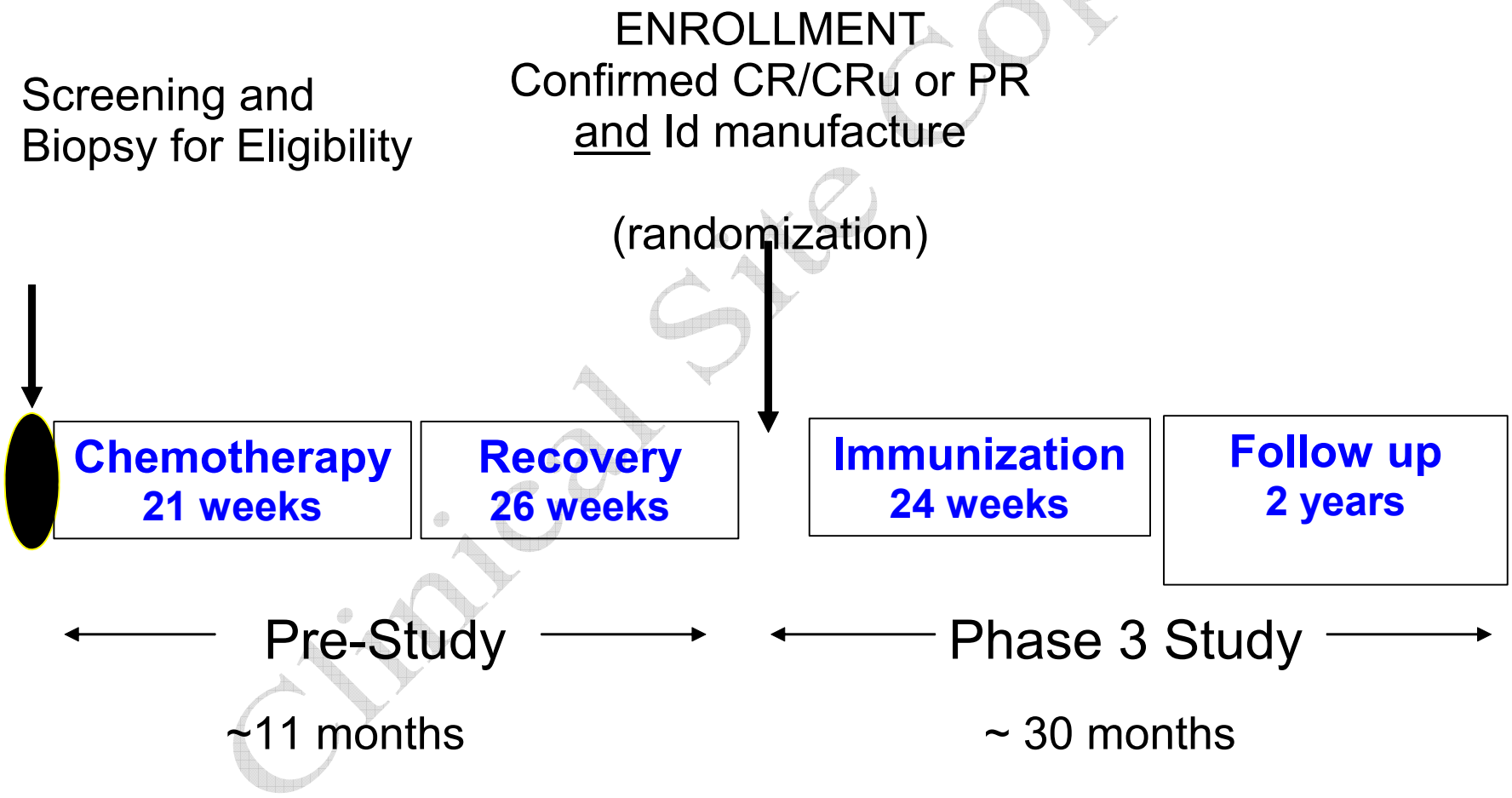
12.0 APPENDICES

12.1 Appendix I: Study Schema and Schedule of Events

APPENDIX I. STUDY SCHEMA
G2000-03



APPENDIX I. Schedule of Events: Pre-immunization Procedures.

PROCEDURE	SCREENING (0-42 days)			0-6 WEEKS	Chemotherapy (24 weeks)	REST PERIOD & RANDOMIZATION (26 weeks)			IMMUNIZATION
	1-42 days before regis-tration	1-14 days before regis-tration	Registration Day		CVP q 21 days x 8 Week 12	Week 4-8 Post CVP	Week 22 Post CVP	**Randomization** Day *During Week 26*	
Physical Exam	√*					√	√		
CT: Chest/Abdomen/Pelvis	√*				√ [2]	√	√		
Bone Marrow Biopsy	√+					√ [3]	√ [3]		
ECOG Performance Status	√								
Serum LDH		√					√		
CBC with Platelets		√							
Chemistry Panel		√					√		
Hep B sAtg		√							
Hep C Ab		√							
HIV Ab		√							
Assign PIN			√						
Randomize Patient								√	
QOL Assessment									
Pregnancy Test		√					√		
Urinalysis									
Blood for PCR			√ [1]						
Blood for Flow Cytometry									
Blood for Serum Ig									

* If CT scans are greater than 90 days old at the time that chemotherapy is started, CT scans and the PE must be repeated prior to initiating CVP.

\+ To occur within 90 days of registration.

[1] Blood for PCR can be sent anytime prior to first chemotherapy

[2] Per Institutional guidelines, but should occur prior to 5th cycle (week 20)

[3] To assign an overall clinical disease response status of CR or CRu, a bone marrow biopsy must be performed in those patients who were previously bone marrow positive (or indeterminate) at any time. Slides must be available for central pathology review.

APPENDIX I. Schedule of Events: Immunization and follow-up procedures.

PROCEDURE	IMMUNIZATIONS (weeks starting from first immunization)							Initial Response Evaluation	Follow-up Response Evaluation	
	Imm. #1 Wk 0	Imm. #2 Wk 4	Imm. #3 Wk 8	Imm. #4 Wk 12	Imm. #5 Wk 16	Imm. #6 Wk 20	Imm. #7 Wk 24	2-4 weeks after Imm. #7	Every 3 months (13 weeks) x 1 yr after Imm. #7	Every 6 months (26 weeks) x 2 yr after Imm. #7
Clinic Visit (immunization)	√	√	√	√	√	√	√			
Pre-injection Vital Signs	√	√	√	√	√	√	√			
Post-injection Vital Signs [a]	√	√	√	√	√	√	√			
Patient Diaries [b]	√	√	√	√	√	√	√			
Physical Exam [c]	√*	√	√	√	√	√	√	√	√	√
Interim History	√*	√#	√#	√#	√#	√#	√#	√	√	√
ECOG Performance Status	√*	√	√	√	√	√	√	√		√
CBC [d]	√*	√	√	√	√	√	√	√		√
Hepatic & Renal Profiles [e]	√*	√	√	√	√	√	√	√		√
Urinalysis	√*			√			√	√		
CT Chest/Abdomen/Pelvis								√		√
Bone Marrow Biopsy [f]								√		√
QOL Assessment	√							√		√
Blood for PCR+	√							√		√
Blood for Flow Cytometry+	√							√		
Blood for Serum Ig+ [g]	√							√		
Blood for Immune Response Assays+	√		√	√	√	√	√	√	√	

***** Can be performed 0-14 days prior to immunization
# Captured via adverse event reporting.
+ Draw prior to immunization.

APPENDIX I: Schedule of Events: Notes for Immunization and follow-up procedures.

a 30 minutes post-injection; vital signs include temperature, blood pressure, pulse, and respiration.

b Temperature and injection site reactions to be recorded daily for 72 hours after each injection.

c To include performance status, and weight

d To include differential and platelet count

e Hepatic profile to include SGOT, SGPT, and bilirubin. Renal profile to include serum creatinine and BUN.

f A bone marrow biopsy must be repeated in order to assign an overall clinical disease response status of CR or CRu in patients who were PR at time of randomization and who had a positive (or indeterminate) bone marrow any time prior to randomization. A bone marrow biopsy must be repeated in order to assign an overall clinical disease response status of CR in patients who were CRu at the time of randomization and who had an indeterminate bone marrow any time prior to randomization.

g Serum immunoglobulins to be analyzed are IgG, IgM, and IgA.

12.2 Appendix II: Clinical Response Criteria

Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria.

1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 8 weeks after the first day of the eighth cycle of CVP has been completed to assess response. If the patient has cervical involvement, a neck CT should be performed.

2. A bone marrow aspirate and biopsy must be performed to confirm a CR or CRu if previously positive (or indeterminate) at any time or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear. Note: Bone marrow involvement on this study is by histologic diagnosis; a BM that is bcl-2 positive by PCR but does not demonstrate involvement by pathology review will be coded as negative.

The following definitions are modified from Cheson *et al.* (1999) J. Clin. Oncol. 17:1244-53.

The sum of bi-dimensional products of six sites of measurable disease on CT scans, imaging all internal nodal groups, to be calculated and recorded at each CT assessment point. All other lesions will be recorded as non-target lesions. Bone lesions will be assessed as non-target lesions.

Response definitions - all responses must be maintained for a minimum of 4 weeks.

Appendix II: Clinical Response Criteria (cont.)

Complete Response (CR) requires the following:

1. Complete disappearance of all detectable clinical, radiographic, or diagnostic evidence of disease (e.g., lactate dehydrogenase [LDH]) definitely assignable to NHL). No disease related symptoms.
2. All lymph nodes and nodal masses must have regressed to normal size
   - If > 1.5 cm before treatment, regressed to ≤ 1.5 cm in their greatest transverse diameter (GTD)
   - If 1.1 to 1.5 cm in GTD before treatment, regressed to ≤ 1 cm in GTD {or 75% in sum of product dimensions (SPD)}
3. Spleen and all previously enlarged organs decreased in size.
4. If bone marrow (BM) was involved by lymphoma before treatment, the BM must clear on repeat aspirate and biopsy of the same site. Note: If a BM is not done at week 22 post CVP, and the BM was negative at week 4-8 post CVP, the result from the week 4-8 post CVP BM will be used to make the response determination.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in GTD that has regressed by >75% in SPD compared with the size of the original mass.
2. Individual nodes previously confluent regressed by >75% in SPD.
3. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

Appendix II: Clinical Response Criteria (cont.)

Partial Response (PR) requires the following:

1. ≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features:
   - They should be clearly measurable in at least two perpendicular dimensions.
   - They should be from as disparate regions of the body as possible, and
   - They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. No new sites of disease.

Stable Disease (SD) is defined as less than a PR but is not progressive disease.

Progressive Disease (**PD**) requires one of the following:

1. In CRu, PR, and SD patients a ≥ 50% increase from nadir in the GTD of any previously identified abnormal node to ≥ 2 cm, or appearance of any new lesion that is > 2 cm in its longest transverse diameter during or at the end of therapy.
2. A bone marrow that was negative becomes positive.

Relapsed Disease (RD) requires one of the following:

1. In CR patients a ≥ 50% increase in GTD of any previously identified abnormal node. In a LN of 1 cm, the increase must be to ≥ 2 cm.
2. Previously involved site has increased by ≥ 50% GTD, provided the site measures ≥ 2 cm.
3. A new node that is ≥ 2 cm in its longest transverse diameter has appeared.
4. Bone marrow becomes positive.

12.3 Appendix III: PCR Assays for the Presence of Lymphoma in PBLs

Blood collected in ethylenediamine tetra-acetic acid (EDTA) anticoagulated tubes (1 purple top, 7 mL) is shipped at ambient temperature via overnight courier to a central laboratory. Specimens must be received by the central laboratory within 48 hours of collection. Specimen Transport Kits (supplied by the central laboratory) will be provided.

Two PCR assays are being developed to look for the presence of lymphoma cells in peripheral blood. One assay utilizes primers that can amplify rearranged bcl-2 genes. The other assay utilizes patient-specific primers that can amplify the rearranged Ig genes expressed in the patient's lymphoma cells.

PCR Assay for the Presence of PBLs Containing *bcl*-2 Gene Rearrangements

Rearrangements between the *bcl*-2 gene and the immunoglobulin locus are commonly observed in B-cell lymphomas [t(14;18)]. The t(14;18) translocation is found in about 80-90% of follicular lymphomas, 30% of large diffuse lymphomas and 50% of undifferentiated lymphomas (20). The presence or absence of peripheral blood lymphocytes (PBLs) containing *bcl*-2 gene rearrangements provides a measure of the tumor burden in a patient. The presence or absence of PBLs containing *bcl*-2 rearrangements is particularly useful in evaluating the anti-tumor effect of Id-KLH immunization in cases where the patient achieved a complete response to chemotherapy and thus shrinkage of tumor detected by CT scan cannot be used to measure the effect of immunization.

The presence or absence of PBLs containing rearranged *bcl*-2 genes is detected by PCR amplification of DNA extracted from PBLs using sets of primers that span the major breakpoint region (MBR) and minor cluster region (mcr). As not all lymphomas contain *bcl*-2 gene rearrangements, evaluable data is obtained only from those patients that demonstrate the presence of PBLs having rearranged *bcl*-2 genes prior to Id-KLH immunization.

PCR Assay for Lymphoma Cells Using Patient-Specific Primers

Ten to 20% of follicular lymphomas do not have rearranged bcl-2 genes that can be detected using primers that span the MBR and mcr. A PCR assay that will utilize primers that bind to sequences within the CDRs of the rearranged Ig genes unique to each patient's lymphoma is being developed. This assay should allow the detection of lymphoma cells in PBLs from all patients.

12.4 Appendix IV: Immune Response Testing

I. Humoral Immune Responses - Blood should be drawn into a red top or serum separator tube. The serum should be separated, labeled with PIN and date/time drawn and shipped ambiently to the designated central laboratory. Serum from each time point listed in the assessment schedule will be assayed in batches by enzyme-linked immunosorbent assay (ELISA) for each patient.

A. Serum Anti-Idiotype Antibody Assays

Sera from treated patients collected prior, during and after treatment will be assessed for humoral response against the administered idiotype. The capacity of individual serum sample to bind to the cognate idiotype will be measured using an idiotype-specific screening ELISA.

Patients will be classified as positive for the humoral response against the administered idiotype if any individual serum sample collected during the treatment is scored positive. Individual serum samples will be scored as positive if the capacity to bind to the cognate idiotype is at least four fold higher than the pre-immune serum sample.

B. Serum Anti-KLH Antibody Assay

Sera from treated patients collected prior, during and after treatment will be assessed for humoral response against KLH. The capacity of individual serum sample to bind to KLH will be measured by ELISA.

Patients will be classified as positive for the humoral response against the KLH if the titer of any individual serum sample collected during the treatment is greater than or equal to 1.0 µg/mL above the baseline plus two standard deviations. Serum samples will also be measured in reference to control rabbit-anti-KLH serum and values of anti-KLH antibody will be reported in µg/mL.

12.5 Appendix V: NCI Common Toxicity Criteria (CTC)

The NCI-CTC version 2.0 published April 30, 1999 will be used on this study.

This document can be accessed on http://ctep.info.nih.gov/CTC3/Download/CTCv20%204-30-992.pdf or on the site call Oncology Tools http://www.fda.gov/cder/cancer.

Copies to the site will be supplied on request.

12.6 Appendix VI: Quality of Life Assessment

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