PROTOCOL

TITLE:	A PHASE IB/II STUDY OF IBRUTINIB IN COMBINATION WITH GA101 - OBINUTUZUMAB IN PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) PATIENTS > 65 YEARS OF AGE OR WITH COMORBIDITIES THAT PRECLUDE THE USE OF CHEMOTHERAPHY BASED TREATMENT.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC	activated B cell
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
anti-HBc	antibody to hepatitis B core antigen
aPTT	activated partial thromboplastin time
BM	bone marrow
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
BSA	body surface area
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration observed
CNS	central nervous system
CR	complete response or complete remission
Cru	unconfirmed complete response
CSR	Clinical Study Report
D	day
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
F	phenylalanine
FACS	fluorescent-activated cell sorter
FcγR	leukocyte receptors for the Fc portion of IgG
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fleurodeoxyglucose
FFPE	formalin-fixed paraffin-embedded

Abbreviation	Definition
FISH	fluorescence in situ hybridization
GCB	germinal center B cell
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GEP	gene expression profiling
G	GA101
G-FC	GA101 in combination with fludarabine and cyclophosphamide
HAHA	human anti-human antibodies
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HTLV	human T-cell leukemia virus
ICH	International Conference on Harmonization
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
IMC	Internal Monitoring Committee
IRR	infusion-related reaction
IV	intravenous
IL	interleukin
IPI	International Prognostic Index
IVRS	interactive voice response system
LD	low dose
LVEF	left ventricular ejection fraction
LVS. D	left ventricular systolic dysfunction
MCL	mantle-cell lymphoma
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NONMEM	Non-Linear Mixed Effect Model
ORR	overall response rate
OS	overall survival

Abbreviation	Definition
PD	progressive disease
PICC	peripherally inserted central catheter
PK	pharmacokinetic
PET	positron emission tomography
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response or partial remission
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone
SAE	serious adverse event
SD	stable disease
SDI	shorter duration of infusion
SLL	small lymphocytic lymphoma
SOC	Scientific Oversight Committee
TLS	tumor lysis syndrome
ULN	upper limit of normal
U.S.	United States
V	valine
WHO	World Health Organization

SYNOPSIS

Study Title	A phase IB/II study of Ibrutinib in combination with GA101 – Obinutuzumab in previously untreated chronic lymphocytic leukemia (CLL) patients ≥ 65 years of age or with comorbidities that preclude the use of chemotherapy based treatment.
Study Phase	IB/II
Study Duration	24 months
Investigational Products	Ibrutinib will be supplied as hard gelatin 140-mg capsules for oral (PO) administration. **Pharmacyclic**s will provide Ibrutinib during the course of the 6 cycles and after cycle 6, during the following 3 years. GA101 – Obinutuzumab will be supplied as vial of 1,000mg/40Ml for IV infusion. GA101 – Obinutuzumab will be requested to be covered by the insurance as a Standard of Care treatment for previously untreated subjects.
Objectives	**Primary Objective** • The primary objective of the phase IB is to evaluate the safety, tolerability and dose limiting toxicity (DLT) of Ibrutinib in combination with GA101 - Obinutuzumab in previously untreated CLL subjects. • The primary objective of the phase II is to determine the overall response rate (partial response + complete response rate) of Ibrutinib in combination with GA101 - Obinutuzumab in previously untreated subjects with CLL. **Secondary Objective** • To determine progression-free survival (PFS), treatment-free survival (TFS) and overall survival (OS) in previously untreated CLL subjects that will

	receive treatment with Ibrutinib in combination with GA101 – Obinutuzumab. • To determine the percentage of CLL subjects treated with Ibrutinib plus GA101 – Obinutuzumab that achieve negative minimal residual disease (MRD^{neg}) in the bone marrow or peripheral blood using multiparameter flow cytometry (4 colors). • To evaluate correlative studies in samples collected from previously untreated CLL subjects treated with Ibrutinib / GA101 – Obinutuzumab combination regimen including but not limited to the following: assessment of the chemokine and cytokine profile using plasma samples from the subjects and correlation of the results with the presence of Infusion-Related Reactions (IRRs).
Hypothesis	We hypothesize that Ibrutinib in combination with GA101 – Obinutuzumab is well tolerated and will induce higher response rates than the response rate observed in the CLL11 Study (Goede et al., 2014).
Study Design	This is an open label phase IB/II clinical trial designed to determine the safety and clinical activity of Ibrutinib in combination with GA101 – Obinutuzumab. Safety, tolerability and dose-limiting toxicities (DLTs) will be evaluated during the initial cycle of treatment (Cycle 1; Day 1-28) as part of the phase IB of this study (safety run-in). In the phase II the response rate will be determined in all subjects that have received treatment. The study will enroll 32 subjects previously untreated who have active disease requiring treatment (as defined by IWCLL 2008 criteria for initiation of therapy) (Hallek et al., 2008). The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase assessments will be performed within 28 days prior to treatment. The Treatment Phase will extend from first dose until completion of all planned cycles of treatment (#6) or study drug discontinuation.

	All subjects will receive Ibrutinib 420 mg (3 x 140-mg capsules) orally once daily for up to 6 cycles. The treatment with Ibrutinib will continue after cycle 6 for the following 3 years until disease progression, unacceptable toxicity or other reason for treatment discontinuation. All subjects will receive GA101 – Obinutuzumab by IV infusion for up to 6 cycles (28-day cycles) as follow: • On Cycle 1, Day 1, 100 mg GA101-Obinutuzumab will be administered. • On Cycle 1, Day 2, 900 mg of GA101-Obinutuzumab will be administered. • On Cycle 1, Days 8 and 15, 1,000 mg of GA101-Obinutuzumab will be administered. • On Cycles 2 – 6, Day 1, 1,000 mg of GA101-Obinutuzumab will be administered. Subjects will undergo response assessment two months after completion of the study treatment. The initial follow-up evaluations will be made (after the response assessment) every 3 months during 9 months and later every 6 months until initiation of new treatment for CLL, consent withdrawal or death. During the long-term follow-up phase, subjects will be followed for survival (PFS, TFS and OS). The long-term follow-up phase will continue until disease progression, death, loss to follow up, consent withdrawal, or study end, whichever occurs first. An evaluation of the End of Study will be performed due to initiation of new treatment for CLL or withdrawal of consent.
Population	Males and females with previously untreated chronic lymphocytic leukemia (CLL): • ≥ 65 years of age, or • < 65 years that refuse to be treated with

	chemotherapy or subjects that are not candidates for treatment with chemotherapy agents.
Center	UCSD Moores Cancer Center
Key Inclusion Criteria: Refer to Section 4.1 for the complete and detailed list of inclusion criteria.	Subjects must meet the following criteria for study entry: 1. Diagnosis of CLL 2. Indication for treatment as defined by the IWCLL Guidelines. 3. No previous treatment for CLL. 4. Males and females 65 years of age and older. Subjects < 65 years of age that meet any of the following criteria: A. Documented refusal to be treated with chemotherapy agents. B. Subjects that are not candidates for treatment with chemotherapy based on poor performance status (ECOG ≥ 2), Cumulative Illness Rating Scale (CIRS score) ≥ 6 or creatinine clearance <70 mL/min. 5. Laboratory parameters as specified below: • Hematologic: Hemoglobin $\geq$ 8 g/dL (may be post-transfusion); platelet count $\geq$ 40 x10^3/mm^3 (may be post-transfusion). Absolute neutrophil count $\geq$ 1.0 $\times$ 10^9 cells/L (Growth factor use is allowed). • Hepatic: Total Bilirubin < 3 x ULN, and ALT and AST < 3 x ULN • Renal: Creatinine clearance > 30 mL/min (Calculated according to institutional standards or using Cockcroft–Gault formula. Subjects with requirement of hemodialysis will be excluded).

	6. Anticipated survival of at least 6 months. 7. Effective contraception is required while receiving Ibrutinib in combination with GA101 - Obinutuzumab. For women of childbearing potential and men, effective contraception is required while receiving GA101 – Obinutuzumab and for 365 days (12 months) after the last dose of the study drug. 8. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments. 9. Subjects must give written informed consent to participate in this trial.
Key Exclusion Criteria: Refer to Section 4.2 for the complete and detailed list of exclusion criteria.	Subjects who meet any of the following criteria will be excluded from study entry: 1. Pregnant or nursing women. 2. Treatment with chemotherapy, monoclonal antibodies, or biological agents (e.g. lenalidomide) other than the investigational agents during the time of participation in this trial. 3. Grade 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. 4. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, COPD) 5. Participation in any investigational drug study within 28 days prior to initiation of treatment within this protocol. (Subject must have recovered from all acute effects of previously administered investigational agents). 6. History of second malignancy, other than non-

	melanoma skin cancer or in situ carcinoma of the cervix or the breast, unless the tumor was successfully treated at least 2 years before trial entry and with no evidence of relapse or active cancer. 7. Active symptomatic fungal, bacterial and/or viral infection including evidence of infection with human immunodeficiency virus (HIV). 8. Evidence of active acute or chronic Hepatitis B (HBV). 9. Evidence of active Hepatitis C (HCV): subjects with positive hepatitis C serology and positive HCV RNA test. 10. Any illness or condition that in the opinion of the Investigator may affect safety of treatment or evaluation of any the study's endpoints. 11. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy 12. Known hypersensitivity to any of the study drugs. 13. Major surgery (within 4 weeks prior to the start of Cycle 1), except for procedures that are performed for diagnostic purposes. 14. Men or women of childbearing potential who refuse to use an adequate measure of contraception (oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly) unless they have past medical history of surgical sterilization. 15. Vaccination with a live vaccine within 28 days of the initiation of treatment. 16. Concomitant use of warfarin or other Vitamin K antagonists.

	17. Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of Ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor. 18. Subjects with chronic liver disease with hepatic impairment (Child-Pugh class B or C)
Dosage and administration	Ibrutinib 420 mg (3 x 140 mg capsules) will be administered orally once daily beginning on Day 1 of the Treatment Phase. The first dose of Ibrutinib 420 mg will be administered in the clinic on Day 1, no more than 72 hours after enrollment, after which Ibrutinib will be self-administered by the subjects on an outpatient basis. GA101 - Obinutuzumab must be administered in a clinical setting (inpatient or outpatient) by IV infusion for up to 6 cycles (28-day cycles): on cycle 1, GA101 – Obinutuzumab will be administered 100 mg on day 1, 900 mg on day 2 and 1,000 mg on days 8 and 15. On Cycles 2 – 6, Day 1, 1,000 mg of GA101 - Obinutuzumab will be administered (See Table 1 – Section 6.2.6).
Statistical Methods Refer to Section 10 for the complete and detailed Statistical rationale.	For this open-label study, all demographic, disease and relevant clinical characteristics will be summarized using descriptive statistics. Continuous variables will be reported using appropriate measures of dispersion and central tendency (means, medians, ranges and standard deviations) while categorical variables (e.g., gender) will be summarized as number and percentage [proportions and 95% confidence intervals (CI)] of the total Registry cohort. Each phase of this study will be analyzed separately. All tables, figures and listings will therefore be separated by study phase. **Determination of the Sample size for the Phase IB** The phase IB will be performed as a safety run-in with the first 6 subjects enrolled in the study. The sample size of 6 subjects is considered to be sufficient to support preliminary safety, tolerability and DLTs assessments

	(Goede et al., 2013). On this group of subjects, we will evaluate safety, tolerability and dose-limiting toxicities (DLTs) during the first cycle of treatment (4 weeks; Day 1 - 28), Subjects will be enrolled at least one week apart to avoid overlapping time of observation during the first week of treatment when infusion reactions are expected to be higher. • If 0 to 1 DLTs (See DLT definition – Section 10.2.4) are observed in the first 3 subjects, we will proceed to enroll 3 additional subjects. • If 0 to 1 DLTs are observed in the first 6 subjects, we will proceed to the phase II of the study. • If $\geq$ 2 DLTs are observed, we will hold enrollment and revise the study design with the sponsor. **Determination of the Sample size for the Phase II** Our sample size calculation will use an ORR endpoint comparison based on the ORR achieved with the Ibrutinib and GA101 - Obinutuzumab combination. We hypothesize that Ibrutinib in combination with GA101 – Obinutuzumab would induce an ORR of 94%, which is 16% higher than the ORR observed in the study published by Goede et al. (Goede et al., 2014). Based on this, we will use a Simon's two-stage optimal design in this study (Simon, 1989). The null hypothesis that the true overall response rate is 78% will be tested against a one-sided alternative. In the first stage, 10 subjects will be accrued. If there are 8 or fewer responses in these 10 subjects, the study will be stopped. Otherwise, 22 additional subjects will be accrued for a total of 32. The null hypothesis will be rejected if 29 or more responses are observed in 32 subjects. This design yields a type I error rate of 5% and power of 80% when the true response rate is 94%.

Safety and Efficacy Evaluations/Outcomes	**Safety Outcomes** **<u>Phase IB Outcome Measures</u>:** The safety and tolerability of Ibrutinib in combination with GA101 - Obinutuzumab will be assessed using the following primary safety outcome measures: - Type, Incidence, nature, and severity of AEs. - The relationship of AEs to Ibrutinib and/or GA101 – Obinutuzumab - Serious adverse events - Incidence of adverse events leading to Ibrutinib/GA101 - Obinutuzumab discontinuation or dose delays. - Incidence of adverse events of special interest - Clinical laboratory abnormalities - Deaths and cause of death - Dose limiting toxicity (DLT): DLTs will include possibly related or related events that are Grade $\geq$ 3 that do not resolve to Grade $\leq$ 1 within 14 days of initiation despite appropriate medical management. Some exceptions will apply (See section 10.2.4). **Efficacy Outcomes** **<u>Phase IB Outcome Measures:</u>** Safety of the treatment study will be determined by: adverse events (AE), laboratory tests and dose limiting toxicity (DLT) vital signs, and performance status (See section 3.2). **<u>Phase II Outcome Measures:</u>** Response assessment will be performed by physical examination, CT scan evaluation and bone marrow biopsy/aspirate at 2 months after completion of the study treatment using the International Workshop in CLL Guidelines (IWCLL) (Hallek et al., 2008). • **Primary outcome measures:** - *Overall response rate (ORR):* defined as the proportion of subjects who achieve complete response (CR), complete response with incomplete

	marrow recovery (CRi), nodular partial response (nPR), or partial response (PR) per IWCLL 2008 criteria over the course of the study. - *Progression Free Survival (PFS):* Time measured from initiation of therapy until clinical or laboratory evidence of CLL progression. - *Treatment Free Survival (TFS):* Time measured from initiation of therapy until next treatment for CLL. - *Overall Survival (OS):* Time measured from initiation of therapy until death from any cause. • **Secondary outcome measures:** - Rate of MRD^{neg} CRs in the bone marrow or peripheral blood using multiparameter flow cytometry (4 colors). - Clinical, laboratory and radiological evidence of response to administration of Ibrutinib plus GA101 – Obinutuzumab based in the International Workshop in CLL Guidelines (IWCLL) (Hallek et al., 2008).

1. INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder that accounts for approximately 30% of adult leukemias and 25% of non-Hodgkin's lymphomas (NHLs). In 2010, there were approximately 14,900 new cases in the United States (U.S.: American Cancer Society 2010). The median age at diagnosis is 72 years (Hallek, 2010). CLL is a disease of B-cell origin, with a characteristic immunophenotype (CD5 positive, CD23 positive, weak surface expression of CD19, CD20, CD79b, and IgM or IgD) and blood smear morphology (mature lymphocytes, Gumprecht shadows also known as smudge cells).

1.1.1 Natural History and Current Management of Chronic Lymphocytic Leukemia

1.1.1.1 Natural History

CLL often is an indolent disease that does not need treatment for many years. Many CLL subjects initially present with lymphocytosis in the absence of other symptoms. However, when the disease advances, there is the appearance of lymphadenopathy, hepatomegaly or splenomegaly, and bone marrow failure. B-symptoms (i.e., fever, night sweats, and weight loss), general fatigue, and recurrent infections are common in subjects with late-stage CLL but can occasionally be found earlier in the course of the disease.

The individual survival time of CLL subjects is highly variable, with a range of less than 2 years to 20 years or more. There are two clinical staging systems (Rai and Binet) currently in use for CLL that allow a rough division of subjects into three prognostic groups: good, intermediate, and poor prognosis. In the Rai staging system, the low-risk (Rai Stage 0) group accounts for 31% of all subjects with CLL, and these subjects have a median survival of more than 10 years (Dighiero and Binet, 2000). Intermediate-risk (Rai Stages I and II) subjects (61% of all CLL subjects) have a median survival of 7 to 9 years. High-risk (Rai Stages III and IV) subjects (8% of all CLL subjects) have a median survival of 5 years (Hallek et al., 2008a). In the Binet staging system, CLL is divided into three stages of A, B, and C (Binet, 1999)

1.1.1.2 Current Management

B-cell lymphoproliferative disorders describe a heterogeneous group of malignancies, and include slow-growing indolent and incurable diseases (such as follicular lymphoma or chronic lymphocytic leukemia [CLL]) with a median survival of 8-10 years. Despite the availability of various agents for the treatment of NHL and CLL, there is an ongoing need for development of safe and effective therapies to prolong remission in subjects.

Because there is no survival benefit associated with early intervention (Hallek and Pflug, 2011), asymptomatic subjects with early-stage CLL (Rai I, II , Binet Stages A and B) are usually not treated but are followed with a “watch and wait” approach. Treatment is usually initiated when subjects become symptomatic or progress to late stage; 50% of CLL subjects ultimately require therapy. In the recent past, first-line treatment of CLL has evolved from single-agent therapy with alkylating drugs (e.g., chlorambucil -Clb) to combination therapy incorporating purine analogues (i.e., fludarabine, pentostatin, and cladribine) and monoclonal antibodies (i.e., rituximab and alemtuzumab) (Johnson et al., 1996) ; (Rai et al., 2000); (Eichhorst et al., 2006); (Flinn et al., 2007); (Hillmen et al., 2007); (Hallek et al., 2010).

Currently, fludarabine, cyclophosphamide, and rituximab (FCR) are considered a standard chemoimmunotherapy combination for previously untreated subjects with CLL requiring treatment (Hallek et al., 2010). However, the favorable outcome of FCR treatment has been reported only for subjects not suffering from other medical impairments.

Major comorbidities are present in 46% of unselected subjects with newly diagnosed CLL and advanced age (Thurmes et al., 2008). Immunochemotherapy with FCR is often withheld from medically unfit subjects because co-morbid conditions and age-related changes of the organ function may facilitate the occurrence and increase the severity of sustained cytopenia, T-cell depletion, and opportunistic infections.

In December of 2013 GA101 - Obinutuzumab in combination with chlorambucil was approved for previously untreated CLL subjects based on data from study BO21004 (CLL11; NCT01010061) (Phase III) – discussed below. This treatment constitutes an alternative for previously untreated subjects, specially the elderly and those with comorbidities that will prevent them from receiving treatment with FCR chemoimmunotherapy. However, it is important to note that the current FDA approval for GA101 - Obinutuzumab does not have restrictions in terms of age or the presence of comorbidities. Therefore, based on the current FDA approvals, the current standard treatment for untreated CLL subjects could include FCR or GA101 - Obinutuzumab / Chlorambucil. A selection between those regimens is entirely based on clinician assessment or the subject status, comorbidities and potential toxicities of each regimen.

In February of 2014, Ibrutinib was approved for the treatment of subjects with CLL who have received at least one prior therapy. The approval in CLL was based on the results of a multi-center, single-arm trial of 48 subjects with previously treated CLL. All subjects had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 6.7 years and the median number of prior treatments was 4 (range, 1 to 12 treatments). Ibrutinib was administered orally at 420 mg once daily until disease progression or unacceptable toxicity.

The efficacy results demonstrated a 58.3% overall response rate (95% CI: 43.2, 72.4) as assessed by an independent review committee. The response duration ranged from 5.6 to 24.2 months; the median was not reached. The safety profile of ibrutinib for subjects with previously treated CLL was consistent with observations in the mantle cell lymphoma clinical trial.

Additional treatment options for relapse / refractory subjects or those who are older than 65 or with significant comorbidities include the following: chemoimmunotherapy with chlorambucil or bendamustine with or without rituximab. Monoclonal antibody based therapy with Ofatumumab, rituximab or alemtuzumab. Corticosteroids including high dose methylprednisolone in combination with rituximab (Castro et al., 2009) - (National Comprehensive Cancer Care Network, CLL/SLL Guidelines, 2013) and the newly approved Bruton's tyrosine kinase (BTK) inhibitor (Ibrutinib)(Byrd et al., 2013). Typically, with any of those regimens the progression free survival is expected to be less than 3-4 years and ultimately subjects relapse requiring additional treatment. Moreover, Ibrutinib requires continuous administration increase cumulative cost of treatment, does not induce complete responses, induces side effects and toxicities in 40-50% of the subjects, there are cases reported of subjects developing resistance due to BTK mutations and the long term side effect from chronic administration at this time are unknown.

Ultimately, the choice of treatment and its intensity at any particular point in the management of subjects with CLL is largely dependent upon subject age, comorbidities, ability to tolerate treatment, presence of poor-risk molecular features, cumulative toxicities, and in salvage therapy, the duration of the response to prior therapy.

1.2 IBRUTINIB BACKGROUND

1.2.1 Structure and Mechanism of Action of Ibrutinib

Ibrutinib (IMBRUVICA ™) has been approved – by the U.S. Food and Drug Administration (FDA) for the treatment of subjects with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) who have received at least one prior therapy.

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) (Rushworth et al., 2013). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation (Honigberg et al., 2010). In vitro, Ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the BCR, which is activated by binding

to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop GA et al., 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (AL. et al., 2002, Shaffer et al., 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite and Witte, 2000).

Treatment of activated CLL cells with Ibrutinib resulted in inhibition of BTK tyrosine phosphorylation and also effectively abrogated downstream survival pathways activated by this kinase including ERK1/2, PI3K, and NF-κB. Additionally, Ibrutinib inhibited proliferation of CLL cells in vitro, effectively blocking survival signals provided externally to CLL cells from the microenvironment including soluble factors (CD40L, BAFF, IL-6, IL-4, and TNF-α), fibronectin engagement and stromal cell contact (Herman et al., 2011) (de Rooij et al., 2012).

Ibrutinib has been reported to reduce CLL cell chemotaxis towards the chemokines CXCL12 and CXCL13, and inhibit cellular adhesion following stimulation at the B cell receptor. Together, these data are consistent with a mechanistic model whereby Ibrutinib blocks BCR signaling, which drives cells into apoptosis and/or disrupts cell migration and adherence to protective tumor microenvironments (Ponader et al., 2012) (de Rooij et al., 2012)

In early clinical studies, the activity of Ibrutinib has been described to include a rapid reduction in lymphadenopathy accompanied by a transient lymphocytosis, suggesting that the drug might have direct effects on cell homing or migration to factors in tissue microenvironments (Byrd et al., 2012). Data from Study PCYC-04753 demonstrates that although Ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with Ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post-dose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts

and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

1.2.2 Summary of Pharmacokinetic and Pharmacodynamic Data for Ibrutinib

Following oral administration of Ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to Ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of Ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg Ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib is metabolized by hepatic cytochrome P450 (CYP) 3A enzymes and to a minor extent by CYP2D6. Metabolism is the major route of elimination. Ibrutinib is metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to Ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of Ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-Ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-Ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in subjects with severe renal impairment or subjects on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

1.2.3 Clinical Experience with Ibrutinib

1.2.3.1 Tolerability and Efficacy of Ibrutinib in Chronic Lymphocytic Leukemia

The Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 (P) in treatment-naive (TN) Chronic lymphocytic leukemia (CLL) patients (pts): Interim results of a phase Ib/II Study.

A multi-cohort Phase IB/II trial evaluated 2 doses of single-agent P in both TN and relapsed/ refractory (R/R) CLL/SLL pts. Mature follow-up of the TN pts was reported. Pts >65 yrs old with active CLL requiring Tx by IWCLL guidelines were treated with oral P at doses of 420 mg or 840 mg administered daily for 28-day cycles until disease progression (PD). Response was evaluated according to 2008 IWCLL criteria.

31 pts were enrolled- 26 pts (420mg) and 5 pts (840 mg). The 840 mg cohort was terminated after comparable activity and safety between doses was shown in R/R pts. Median age 71 yrs (range 65-84) with 74% of pts >70 yrs. 19/31 (61%) had baseline cytopenias (Hgb < 11g/dl or plts <100,000). Unmutated IgVH was present in 43% of pts. The majority of AEs have been Gr<=2 in severity, most commonly diarrhea, nausea, and fatigue. Gr >3 non-heme AEs potentially related to P in 19% of pts. 10% of pts experienced Gr >3 infections or cytopenias. With a median follow-up of 10.7 mos on 420 mg cohort 73% (19/26) achieved a response by IWCLL criteria with 65% partial responses (PR) and 8% complete remissions with no morphologic evidence of CLL on marrow. An additional 12% (3/26) of pts achieved nodal responses (NR) with lymphocytosis. Median follow-up in the 840 mg cohort is 4.6 mo, at 2 cycle assessment 2/5 achieved a PR and 1 pt with a NR. ORR was independent of high risk factors. 84% of pts remain on study, reasons for discontinuation = AE (3), investigator decision (1) and PD (1). There have been no deaths. Estimated 12 mo median PFS for the 420 mg cohort is 93%.

PCI-32765 is highly active and well tolerated in elderly TN CLL pts. The high ORR, including marrow clearance and very low PD rate with the single agent suggests that P warrants further study as a first-line treatment approach in elderly pts (Byrd et al., 2012).

A Phase 1B/II Fixed-dose Study of Bruton's Tyrosine Kinase (Btk) Inhibitor, PCI-32765, in Chronic Lymphocytic Leukemia (NCT01105247).

This was a phase 1b–2 multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib (PCI-32765) in subjects with relapsed or refractory CLL or small lymphocytic lymphoma. A total of 85 subjects, the majority of whom were considered to have high-risk disease, received ibrutinib orally once daily; 51 received 420 mg, and 34 received 840 mg.

Toxic effects were predominantly grade 1 or 2 and included transient diarrhea, fatigue, and upper respiratory tract infection; thus, subjects could receive extended treatment with minimal hematologic toxic effects. The overall response rate was the same in the group that received 420 mg and the group that received 840 mg (71%), and an additional 20% and 15% of subjects in the respective groups had a partial response with lymphocytosis. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies, and the 17p13.1 deletion. At 26 months, the estimated progression-free survival rate was 75% and the rate of overall survival was 83%.

Ibrutinib was associated with a high frequency of durable remissions in subjects with relapsed or refractory CLL and small lymphocytic lymphoma, including subjects with high-risk genetic lesions (Byrd et al., 2013).

Ibrutinib in combination with Rituximab (IR) is well tolerated and induced a high rate of durable remissions in patients with high-risk chronic lymphocytic Leukemia (CLL): New, update results of a phase II trial in 40 patients.

Single agent ibrutinib induces an overall response rate (ORR) of 71% in relapsed CLL, based on the Phase 1/2 experience. To accelerate and improve responses to ibrutinib in high-risk CLL, ibrutinib was combined with rituximab; this was a Phase 2 single-center clinical trial with a median follow-up of 14 months.

Subjects were treated with ibrutinib 420 mg PO daily continuously throughout the study Rituximab (375 mg/m2) was administered weekly for the first four weeks (cycle 1), then monthly until cycle 6 at which point subjects continued on ibrutinib monotherapy. Study inclusion required high-risk disease (del17p or *TP53* mutation [treated or untreated]), PFS < 36 months after frontline chemo-immunotherapy, or relapsed CLL with del11q.

Characteristics of the 40 subjects enrolled included median age of 65 (range 35–82) with a median of 2 prior therapies. There were14 female and 26 male subjects. 20 subjects had del17p or TP53 mutation (4 without prior therapy), and 13 subjects had del11q. 32 subjects had unmutated *IGHV*, only one subject mutated *IGHV,* the remaining subjects had inconclusive *IGHV* results. The median β2 microglobulin was 4.2 mg/L (2.2 – 12.3), At a median follow up of 14 months, 32 of 40 subjects continue on therapy (16 out of 20 with del17p or *TP53* mutation) without disease progression.

39 subjects were evaluable for response assessment per 2008 IWCLL guidelines; 34 (87%) achieved partial remission (PR), and three (8%) complete remission (CR), accounting for an ORR of 95%. One CR was negative for MRD by flow cytometry, The ORR in the 20 subjects with del17p or *TP53* mutation was 90% (16 PR, 2 CR). Among the 8 subjects that came off study, 3 subject died from unrelated infectious complications (2 cases of sepsis, 1 case of pneumonia), and 1 died from unrelated respiratory and cardiovascular failure. Two subjects came off study because of possibly ibrutinib-related toxicity (one subdural hematoma, one grade 3 mucositis), one subject had progressive disease, and one proceeded to stem cell transplantation. Treatment generally was well tolerated, with infectious complications (6 cases of pneumonia and 3 cases of upper respiratory infections) being the most common complication. There were two Grade 3, possibly related AEs: mucositis (n=1), and peripheral neuropathy (n=1). Milder toxicities included Grade 1-2 bruising (n=7), Grade 1 subdural hematoma (n=1), fatigue (n=2), bone pain, myalgias, and arthralgia (n=5), or

diarrhea (n=1). Questionnaires revealed significantly improved overall health and quality of life (QOL) after 6 months, based on the EORTC-QOL-v.3 questionnaire, which coincided with a significant weight gain at 3 and 6 months.

Ibrutinib in combination with rituximab is a safe, well tolerated regimen for high-risk CLL subjects, which induces high rates of durable responses. Responses were associated with significant improvements in QOL. Compared to ibrutinib monotherapy, the redistribution lymphocytosis resolves more rapidly and completely, and consequently the ORR is higher. Whether the addition of rituximab to ibrutinib therapy translates into longer progression-free and overall survival will be addressed in an upcoming larger, randomized trial of ibrutinib versus IR in relapsed/refractory CLL (Burger et al., 2013).

A Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus Chlorambucil in Patients 65 Years or Older with Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (RESONATE™-2) (PCYC-1115-CA; NCT01722487)

This is a randomized, multicenter, open-label, Phase 3 study designed to compare the safety and efficacy of PCI-32765 versus chlorambucil in treatment-naive subjects 65 years or older who have CLL or SLL. Eligible subjects were randomized in a 1:1 ratio to Treatment Arm A or B:

- Treatment Arm A: Oral chlorambucil 0.5 mg/kg on Days 1 and 15 of each 28-day cycle; the dose can be increased, if well tolerated, in increments of 0.1 mg/kg on Day 1 of each cycle to a maximum of 0.8 mg/kg; subjects receive a minimum of 3 and a maximum of 12 cycles, in the absence of progressive disease or unacceptable toxicity
- Treatment Arm B: Oral PCI-32765 420 mg/day Randomization will be stratified on Eastern Cooperative Oncology Group (ECOG) performance status (0,1 versus 2); presence of advanced Rai stage (yes/no), advanced being defined as Stages 3-4; and geographic region: US versus non-US.

The primary endpoint of this study is PFS as assessed by IRC review according to IWCLL 2008 criteria with modification for treatment-related lymphocytosis. All enrolled subjects have completed at least 12 months of treatment and/or follow-up and either (a) 81 progression or death events have been observed or (b) 15 months have elapsed after the last subject is randomized, whichever occurs first.

Secondary endpoints (efficacy and safety) will be collected for 12 months of treatment and/or follow-up and either (a) 81 progression or death events have been

observed or (b) 15 months have elapsed after the last subject is randomized whichever occurs first.

This study is ongoing, but not recruiting participants.

A Multicenter Phase 2 Study of PCI-32765 (Ibrutinib) in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion (PCYC-1117-CA; NCT01744691) (Phase II).

This is a multicenter, international, open-label, single arm, Phase 2 study designed to evaluate the efficacy and safety of PCI-32765 in subjects with relapsed/refractory CLL or SLL with del 17p. All subjects will receive PCI-32765 until disease progression or unacceptable toxicity occurs.

The primary outcome measures: Overall Response Rate (Time Frame: 6 -12 months after last subject enrolled). Secondary outcome measures: duration of Response (Time Frame: 18 months after last subject enrolled), and safety parameters: number and type of adverse events (Time Frame: 18 months after last subject enrolled.

Other Outcome Measures: progression-free survival (Time Frame: 18 months after last subject enrolled), and overall survival (Time Frame: 18 months after last subject enrolled).

This study is ongoing, but not recruiting participants.

1.2.4 Overview of Safety of Ibrutinib

Safety data are available for 1741 subjects treated in 13 company-sponsored monotherapy and 4 combination therapy studies, as discussed below (Investigator's brochure Version 10, dated February 28, 2017).

1.2.4.1 Monotherapy Studies

Pooled safety data from a total of 1318 subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current IB update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N = 1318):

Most frequently reported TEAEs ≥ 15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3% [b]	Most frequently reported Serious TEAEs ≥ 2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Edema peripheral		

[a] Source is Table 6 of IB (v10), [b] Source is Table 8 of IB (v10), [c] Source is Table 9 of IB (v10).

1.2.4.2 Combination Therapy Studies

Pooled safety data from a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in subjects with B-cell malignancies, are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N = 423):

Most frequently reported TEAEs ≥ 20% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3% [b]	Most frequently reported Serious TEAEs ≥ 2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

[a] Source is Table 10 of IB (v10), [b] Source is Table 12 of IB (v10), [c] Source is Table 13 of IB (v10).

1.2.4.3 Treatment Discontinuations

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects each).

1.2.4.4 Hemorrhagic Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, subdural intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.5 for guidance on ibrutinib management with surgeries or procedures. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed.

1.2.4.5 Cardiac

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

1.2.4.6 Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

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1.2.4.7 Other Malignancies

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer

1.2.4.8 Infection

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.2.4.9 Myelosuppression

Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of subjects. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.

1.2.4.9 Embryo-Fetal Toxicity

Based on findings in animals, Ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in subjects receiving the ibrutinib dose of 560 mg per day. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking Ibrutinib. If this drug is used during pregnancy or if the subject becomes pregnant while taking this drug, the subject should be apprised of the potential hazard to a fetus.

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), cardiac arrest (3 subjects) and Richter's Syndrome (3 subjects).

1.2.4.10 Treatment-related Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (increase in the number of circulating lymphocytes eg, >400,000/μL) is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. This pharmacodynamic effect was less prominent or not observed in other indications.

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. For subject and ibrutinib management guidance..

A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and medical monitor should be contacted.

1.2.4.11 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines.

1.2.4.12 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of TLS are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

1.2.4.13 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines.

1.2.4.14 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.3 GA101 - OBINUTUZUMAB BACKGROUND

1.3.1 Structure and Mechanism of Action of GA101 - Obinutuzumab

Obinutuzumab (GA101, RO5072759), is a glycolengineered, humanized, type II anti-CD20 monoclonal antibody (mAb). GA101 - Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Beers et al., 2010): high antibody-dependent cellular cytotoxicity (ADCC); high affinity binding to the CD20 antigen; low complement-dependent cytotoxicity (CDC) activity; and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction. Given the direct cell death inducing properties of GA101-Obinutuzumab and the significantly enhanced ADCC in preclinical assays, it is possible that GA101-

Obinutuzumab may have greater efficacy than the widely used anti-CD20-mAb rituximab (Rituxan®).

1.3.2 Clinical Experience with GA101 - Obinutuzumab

1.3.2.1 Tolerability and Efficacy of GA101 - Obinutuzumab in Chronic Lymphocytic Leukemia

Phase I Study of RO5072759 (GA101) in Relapse/Refractory Chronic Lymphocytic Leukemia. (Study BO20999; GAUGUIN; NCT00517530)

BO20999 was an open-label, multicenter, Phase I/II study to explore GA101 - Obinutuzumab safety and activity in subjects with CD20+ malignant disease. Thirteen CLL subjectswere enrolled and received GA101 - Obinutuzumab at doses with a range of 400–2,000 mg (given as a flat dose) across four cohorts. There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Infusion-related reactions (IRRs) occurred in all CLL subjects and were characterized predominantly by National Cancer Institute Common Terminology Criteria (NCI-CTC) Grade 1–2 toxicities: chills, nausea, vomiting, fever, pyrexia, hypertension, hypotension, dyspnea, and dizziness. Two subjects experienced four NCI-CTC Grade 3 toxicities: sweats, flushing, asthenia, and hepatic cytolysis (Morschhauser et al., 2009).

Although the safety profile appears otherwise similar between NHL and CLL in the BO20999 study, there was an increase in NCI-CTC v3.0 Grade 3–4 neutropenia noted in CLL subjects, which were observed in 9 subjects across the four dose levels administered. Five subjects experienced NCI-CTC Grade 4 neutropenia and 4 subjects experienced NCI-CTC Grade 3 neutropenia as the maximum severity. Of the 9 subjects, 7 had one NCI-CTC Grade 3–4 event and 2 subjects experienced more than one event. Granulocyte colony-stimulating factor (G-CSF) support was administered to 6 of the 9 subjects, and these subjects responded quickly to G-CSF support. For the 3 subjects who did not receive G-CSF, neutrophil counts normalized spontaneously. Furthermore, it is important to note that these neutropenia events did not appear to be accompanied by a higher incidence of infections. No deaths were reported in Phase I of this study for CLL.

As assessed by the International Workshop on CLL (IWCLL) criteria, the end-of-treatment response rate with GA101 - Obinutuzumab monotherapy was 62% (8 of 13 subjects with partial response – PR) (Morschhauser et al., 2009).

Study BO21003 (GAUSS; NCT00576758) (Phase I)

BO21003 is an open-label, dose-escalating, multicenter Phase I/randomized Phase II study in subjects with relapsed/refractory CD20+ malignant disease. In Study BO21003, 5 CLL subjects have been administered GA101 - obinutuzumab. The fifth

subjects withdrew at Cycle 1, Day 1 because of a Grade 4 IRR, which occurred minutes after the start of infusion in the setting of high tumor burden. Efficacy assessments are available for only the 4 subjects who completed treatment (received 4 cycles of infusion). The end-of-treatment response in subjects with CLL receiving GA101-Obinutuzumab monotherapy in this study included 3 stable disease and 1 progressive disease subjects (Sehn et al., 2012).

Study GAO4768g / GAGE / NCT01414205 (Phase II)

GAO4768g is an open-label, randomized, multicenter, Phase II study evaluating the efficacy and safety of GA101-Obinutuzumab administered at 1,000 mg versus 2,000 mg in subjects with previously untreated CLL. Study GAO4768g is ongoing so data provided here are preliminary. As of July 2012, 51 previously untreated CLL subjects were exposed to GA101-Obinutuzumab in this study. Of these, 38 subjects (75%) have been exposed to treatment for more than 4 weeks, but less than 6 months and one subject (2%) has been exposed for $\geq$6 months.

A total of 41 subjects (80%) have experienced AEs, and SAEs have been reported in 5 subjects (10%). The SAEs include febrile neutropenia, neutropenia, thrombocytopenia, pyrexia, urosepsis, IRR, depressed level of consciousness, hypoxia and hypotension. Twenty-two subjects (43%) have experienced a Grade 3–4 AE, of which 15 subjects (29%) had a Grade 3–4 blood and lymphatic system disorder. AEs of special interest included 37/51 subjects (73%) with AEs of any grade associated with study drug infusion, 13/51 subjects (26%) with infections, 14/51 subjects (28%) with neutropenia, 7/51 subjects (14%) with thrombocytopenia, and 1/51 subjects (2%) with TLS.

Four subjects (8%) have discontinued from the study treatment due to AEs: sneezing and chills; IRR, vomiting, hypotension, depressed level of consciousness, and hypoxia; neutropenia; and thrombocytopenia. No deaths have been reported in this study.

No efficacy data are available yet for study GAO4768g.

Study GAO4779g (GALTON; NCT01300247) (Phase II)

GAO4779g is an open-label, non-randomized, multicenter Phase II study GA101-Obinutuzumab in combination with FC (G-FC) or bendamustine (G-B) in previously untreated subjects with CLL. Study GAO4779g is ongoing so data provided here are preliminary. In this study, a safety run-in analysis was conducted in each treatment arm for the first three subjects per arm treated through Day 28 of Cycle 1 before additional subjects were exposed to treatment.

As of July 2012, 41 previously untreated CLL subjects had been exposed to GA101-Obinutuzumab + FC or GA101-Obinutuzumab + bendamustine with a median follow-up time of 11.9 months. The most common adverse events (AEs) (any grade) occurring in ≥ 9 subjects in the G-FC arm were GA101 infusion–related reactions (IRRs) (91%), nausea (76%), fatigue (57%), constipation (48%), and neutropenia (43%); in the G-B arm, they were GA101 IRRs (90%), nausea (65%), neutropenia (55%), diarrhea (50%), and pyrexia (45%). In both cohorts, Gr 3/4 GA101 IRRs only occurred with the 1st dose. Fourteen subjects experienced serious AEs (6 subjects in G-FC, 8 subjects in G-B), with events including febrile neutropenia (n=5 events); infections (n=4); IRRs (n=3); nausea, vomiting, pyrexia (n=2 each); and diarrhea, fatigue, tachycardia, tumor lysis syndrome, syncope, mental status changes, neutropenia, face swelling, and hypertension (n=1 each). Nine subjects (7 in G-FC, 2 in G-B) had AEs leading to treatment discontinuation, including Gr 3/4 neutropenia (3 in G-FC [1 of 3 subjects also had Gr 4 cellulitis], 2 in G-B), Gr 3 thrombocytopenia (2 in G-FC), Gr 4 pancytopenia (1 in G-FC), and Gr 4 AST/Gr 3 ALT elevation (1 in G-FC).

The overall response rate was 62% (2 CR, 3 CRi, 8 PR) in the G-FC arm, and 90% (4 CR, 5 CRi, 9 PR) in the G-B arm, including 6 subjects (4 in G-FC, 2 in G-B) not evaluable due to inadequate response evaluation. Four subjects in the G-FC arm (0 in G-B) had stable disease during and after therapy. No subject progressed during the study (Brown et al., 2013).

Study BO21004 (CLL11; NCT01010061) (Phase III)

This is an open-label, multicenter, three-arm randomized, Phase III study to compare the efficacy and safety of GA101-Obinutuzumab + chlorambucil (GClb), rituximab + GClb (RClb), or Clb alone in previously untreated CLL subjects with comorbidities. The data from this study were pivotal for the FDA approval of GA101-Obinutuzumab in previously untreated subjects with CLL.

BO21004 enrolled 781 subjects and an additional 6 subjects during a safety run-in period before randomization. An analysis based on data collected by the data cutoff date for these 6 subjects accrued from December 2009 until February 2010 for the BO21004 safety run-in phase showed that all 6 subjects completed 6 cycles of treatment but two subjects had significant dosing delays. IRRs occurred in 5 subjects, all were Grade 1 or 2, with no severe IRRs. All 6 subjects experienced neutropenia, 5/6 subjects reported Grade 3 – 4 afebrile neutropenia with no febrile neutropenia. All 6 reported thrombocytopenia with one case of Grade 3 – 4 thrombocytopenia. No subject died during the safety run-in period. Given that none of the pre-defined stopping criteria were met during this safety run-in period, Study BO21004 opened to randomization in April 2010 (Goede et al., 2013). Study BO21004 includes two separate stages evaluating

efficacy and the primary endpoint is progression-free survival (PFS). Stage 1 evaluated GA101-Obinutuzumab + chlorambucil compared to chlorambucil alone.

Stage 1 of Study BO21004 met its primary endpoint (Goede et al., 2013). Compared to chlorambucil, both GA101 - Obinutuzumab + chlorambucil and rituximab + chlorambucil demonstrated statistically significant PFS benefit compared to chlorambucil alone. Median PFS of chlorambucil vs. GA101 - Obinutuzumab + chlorambucil were 11.1 vs. 26.7 months respectively (HR: 0.18, 95% CI: 0.13 – 0.24, p < 0.001). The difference in PFS was smaller between chlorambucil and rituximab + chlorambucil; median PFS were 11.1 vs. 16.3 months, respectively (HR: 0.44, 95% CI: 0.34 – 0.57, p < 0.001) (Goede et al., 2014).

Treatment with GA101 – Obinutuzumab + chlorambucil, as compared with chlorambucil alone, prolonged overall survival (HR for death, 0.41; 95% CI, 0.23 to 0.74; P = 0.002). Treatment with GA101 – Obinutuzumab + chlorambucil, as compared with rituximab + chlorambucil, resulted in prolongation of progression-free survival (HR: 0.39, 95% CI: 0.31 to 0.49; P<0.001) and higher rates of complete response (20.7% vs. 7.0%) and molecular response. Infusion-related reactions and neutropenia were more common with Obinutuzumab–chlorambucil than with rituximab–chlorambucil, but the risk of infection was not increased (Goede et al., 2014).

1.3.3 Overview of Safety of GA101 - Obinutuzumab

GA101 - Obinutuzumab has been administered to approximately 1310 subjects with CD20-positive malignancies. Both in subjects with NHL and with CLL, IRR were the most common AE in clinical trials conducted to date. They were predominantly associated with the first infusion, generally occurring early during the infusion, shortly after, or in some cases up to 24 hours after the completion of the infusion with GA101 - obinutuzumab. The incidence and intensity of IRRs decreased with subsequent infusions of GA101 - Obinutuzumab.

In a few subjects, concurrent signs of tumor lysis syndrome (TLS) were observed. Other frequently observed AEs include infections, neutropenia and thrombocytopenia. These events appeared to be more common in subjects with CLL compared to NHL.

In trials investigating the combination of GA101-Obinutuzumab and CHOP, FC, chlorambucil or bendamustine, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. So far, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of AEs have been determined.

A pooled analysis of safety data for GA101-Obinutuzumab collected during the monotherapy studies BO20999 and BO21003 was conducted in subjects with NHL (aggressive [aNHL] and indolent []iNHL]) or CLL who participated in those two studies (both Phase I and Phase II) and received monotherapy treatment with GA101-Obinutuzumab and included a total 205 subjects with NHL (49 aNHL and 156 iNHL subjects) and 38 subjects with CLL.

In the group of 38 subjects with CLL, the majority of subjects (25 [66%]) were treated for $\geq$ 4 weeks to $<$ 6 months. Eleven subjects (29%) were exposed for 6 to $<$12 months, and two subjects (5%) were exposed for 12 months or longer. Eight of 38 subjects (21%) with CLL were withdrawn during the treatment phase; 4 subjects (11%) were withdrawn due to AEs, which indicates that AEs were mostly manageable. Almost all subjects (37/38 [97%]) experienced an IRR. The number of subjects with Grade 3–4 IRRs was 11/38 (29%). As is typical for subjects with CLL, blood and lymphatic system disorders were among the most frequently reported AEs, in particular neutropenia (13/38 subjects [34%]), febrile neutropenia (5/38 subjects [13%]), and thrombocytopenia (7/38 subjects [18%]).

Infections and infestations were common AEs, occurring in 21/38 subjects (55%). Infections reported in more than one subject were nasopharyngitis (6 subjects), bronchitis and sinusitis (4 subjects each), influenza and lung infection (3 subjects each), and herpes zoster and oral herpes (2 subjects each).

Thirteen subjects (34%) died, 8 of these due to disease progression. One subject died from an unspecified cause after withdrawal from the study for lack of response. This subjects had received subsequent experimental therapies and had stable CLL at the time she died. For 4 additional subjects, the cause of death was reported as colon cancer, lung adenocarcinoma, metastasis, and septic shock, and all were considered not to be related to treatment.

In the two studies investigating GA101-Obinutuzumab as monotherapy, BO20999 and BO21003, subjects with CLL appeared to be at a higher risk of experiencing an AE of special interest than subjects with NHL. The largest difference in the incidences was seen for neutropenia (occurring in 47% of subjects with CLL [18/38] vs. 8% of subjects with aNHL [4/49] and 8% of subjects with iNHL [13/156]) and treatment-related AEs associated with the infusion (100% [38/38] vs. 80% (39/49) and 83% [129/156]).

To date, a very small number of subjects have experienced TLS (six in total); four subjects in the aNHL population (population including MCL) and one subjects each in the CLL and iNHL populations.

Infections have been reported in 20/49 aNHL subjects (41%), 74/156 iNHL subjects (47%), and 21/38 CLL subjects (55%). One iNHL subjects was withdrawn from the study because of an infection. In addition, one CLL subject and one iNHL subject died from an infection (septic shock in both cases) during survival follow-up 671 days and 494 days after last dose of treatment, respectively.

Three CLL and 3 iNHL subjects were withdrawn from treatment due to an AE of special interest, all for IRRs. An additional subject in the iNHL group discontinued treatment because of an infection. This indicates that these events were generally manageable.

In Study BO21004 (CLL11), 6 previously untreated CLL subjects received GA101-Obinutuzumab in combination with chlorambucil (GA101 – Obinutuzumab 1,000 mg on Days 1, 8, and 15 of Cycle 1, then 1,000 mg on Day 1 for Cycles 2 – 6; chlorambucil 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 – 6). All 6 subjects completed six cycles on treatment, 2 with significant dosing delays. Five of 6 subjects experienced an IRR with no severe IRRs. All 6 subjects experienced neutropenia with no febrile neutropenia, and all 6 subjects reported thrombocytopenia with one case of severe thrombocytopenia.

Most IRRs were associated with the first GA101-Obinutuzumab infusion. Their frequency and intensity decreased with subsequent infusions.

The safety plan for subjects receiving GA101-Obinutuzumab is based on the toxicities observed in nonclinical studies and the clinical experience with this molecule in completed and ongoing studies.

The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined below.

1.3.4 Risks Associated with GA101 - Obinutuzumab Therapy

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate other than those noted in the following sections.

1.3.4.1 Infusion Reactions and Hypersensitivity Reactions (including Anaphylaxis)

In Phase I/II clinical trials of GA101 - Obinutuzumab, the most common AEs were mild or moderate IRRs. To date, the commonly experienced IRRs are characterized, among other symptoms, by fever, chills, nausea, vomiting, hypotension, and fatigue.

Respiratory infusion-related symptoms such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema have also been reported. These IRRs were mostly mild or moderate (NCI-CTC, v3.0, Grade 1–2), occurring predominantly during the first hour or shortly after the first infusion, and resolved with the slowing down or the interruption of the infusion and with supportive care where appropriate. In some subjects, some IRRs occurred up to 24 hours after receiving the first infusion. The incidence and severity of IRRs decreased with subsequent infusions. Cases of tumor flare have also been reported with GA101 - Obinutuzumab. Extensive tumor burden, predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in CLL subjects), may be a predisposing factor for the development of IRRs.

The mechanism of IRRs is unclear, but it is potentially linked to the process of B-cell depletion by ADCC and the rapidity of apoptosis. IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

For the management of IRRs, see Section 6.1.12, For dose delay and modification instructions, see Section 6.1.4.

1.3.4.2 Tumor Lysis Syndrome

Cases of TLS have been reported with GA101-Obinutuzumab administration. To date, no subject has required hemodialysis for renal failure. subjects with a high tumor burden, including subjects with a lymphocyte count of $\geq 25 \times 10^9$/L (particularly, subjects with B-cell CLL and MCL), are at increased risk for TLS and severe IRRs.

1.3.4.3 Thrombocytopenia and Neutropenia

Cases of Grade 3 or 4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with GA101-Obinutuzumab administration. Grade 3 or 4 neutropenia has been observed predominantly in subjects with CLL. Subjects who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of myeloid growth factors has been found to result in a rapid normalization of neutrophils, similar to what has been observed in subjects treated with rituximab.

1.3.4.4 Hepatitis B Reactivation

Due to the potential for hepatitis B reactivation to occur with anti-CD20 therapy, all subjects should be screened for hepatitis B virus (HBV) prior to initiation treatment with GA101 - Obinutuzumab. Subjects with positive serology may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management. subjects with active HBV disease should not be treated with GA101 - Obinutuzumab.

1.3.4.5 Worsening of Pre-Existing Cardiac Conditions

GA101 - Obinutuzumab treatment can result in arrhythmias such as atrial fibrillation and tachyarrhythmia, angina pectoris, acute coronary syndrome, myocardial infarction, and heart failure in subjects with underlying cardiac disease. These events may occur as a part of an infusion reaction and can be fatal. subjects with a history of cardiac disease should be monitored closely and should be hydrated with caution in order to prevent a potential fluid overload.

1.3.4.6 Infection

On the basis of its anticipated mode of action resulting in profound B-cell depletion, GA101 - Obinutuzumab may be associated with an increased risk of infections. Infections have been reported in subjects receiving GA101 - Obinutuzumab. Therefore, GA101-Obinutuzumab should not be administered to subjects with active severe infections.

Serious infections, including fatal, bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C) have been reported with the B cell-depleting antibody rituximab, mainly in subjects who had received the drug in combination with chemotherapy or as part of a hematopoietic stem-cell transplant.

One case of progressive multifocal leukoencephalopathy (PML), which was fatal, has been observed during treatment with GA101 – Obinutuzumab. Physicians should be aware of symptoms suggestive of PML and consider the diagnosis of PML in any subject presenting with new-onset neurologic manifestations. Evaluation of PML includes but is not limited to consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Discontinue GA101-Obinutuzumab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in subjects who develop PML.

There may be additional potential health risks, including hitherto unknown risks, derived from exposure to GA101 – Obinutuzumab.

1.3.5 Summary of Pharmacokinetic and Pharmacodynamic Data for GA101 - Obinutuzumab

A two-compartment model comprising a time-varying clearance pathway and a linear clearance pathway provides an adequate description of the pharmacokinetics of GA101-Obinutuzumab following intravenous (IV) administration in Studies BO20999 and BO21003. Following the infusion of GA101 – Obinutuzumab, the elimination appears to be characterized by a clearance pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day

at steady state) and a linear clearance pathway. Tumor burden may potentially contribute significantly to the clearance of GA101 - Obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the clearance reaches an asymptote, which is believed to be primarily a function of the proteolytic metabolic clearance. Consequently, some subjects with a high tumor burden may appear to clear the drug from the plasma faster than do subjects with a low tumor burden because GA101-Obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time, since repeated treatments with GA101-Obinutuzumab will reduce the quantity of CD20-positive tumor cells. Consequently, the number of GA101-Obinutuzumab administrations during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time varying clearance pathway on GA101-Obinutuzumab exposure.

Treatment with GA101-Obinutuzumab resulted in extensive B-cell depletion, with all subjects showing a reduction in cell count to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but changes have been observed in the levels of interleukin (IL)-6 and IL-8 before and after infusion.

1.4 STUDY RATIONALE

Standard treatment for subjects with chronic lymphocytic leukemia (CLL) is rapidly evolving and gradually has incorporated the use of monoclonal antibodies and targeted therapy with small molecules. Based on the data from the CLL-11 study (Goede et al., 2014), GA101 - Obinutuzumab was approved in 2013 for front line treatment of CLL subjects. In addition, Ibrutinib has been recently approved in February 2014 by the FDA, as a single agent for treatment of subjects with relapse refractory CLL. There is no data available testing the combination of Ibrutinib with GA101 – Obinutuzumab, but their separate mechanism of action and non-overlapping adverse events makes them ideal for administration together with an expected synergistic effect.

The CLL-11 study demonstrated that GA101 – Obinutuzumab in combination with Chlorambucil induce higher overall and complete responses, and conferred a statistically significant benefit in terms of progression free and overall survival compared to subjects receiving single agent chlorambucil. These data provided the support for the FDA approval on November 1, 2013. This and other studies using chlorambucil combination strategies (Hillmen et al., 2013) have shown that the benefit of adding chlorambucil to these combination regimens is questionable and it is likely that, instead of providing additive or synergistic interaction, it may increase the rate of adverse events including cytopenias and infections. Similarly, single agent Ibrutinib has shown to be

effective in previously untreated subjects including those that are older than 65 or considered unfit to receive chemotherapy based combinations (O'Brien et al., 2014). The response rate (Overall response of 71% and complete response of 13%) could be higher in subjects receiving Ibrutinib but the mobilization of lymphocytes, which is typically asymptomatic, decreases the response rate due to lack of complete fulfillment of IWCLL criteria. Ibrutinib-induced lymphocytosis could be ameliorated by using a monoclonal antibody therapy as shown by Burger et al. In this study, when Ibrutinib was administrated in combination with Rituximab, lymphocytosis resolved more rapidly and completely, and consequently the overall response rate was higher (90-95%) (Burger et al., 2013).

There is no data available assessing the combination of Ibrutinib with GA101 – Obinutuzumab in the elderly population (≥ 65 years old) or in those subjects < 65 years of age where the chemotherapy based agents is contraindicated. We hypothesize that Ibrutinib in combination with GA101 – Obinutuzumab will be well tolerated and will induce higher response rates than the response rate observed in the CLL11 Study (Goede et al., 2014).

2. OBJECTIVES

2.1 PRIMARY

- Primary Objective Phase IB:
    - To evaluate the safety, tolerability and dose limiting toxicity (DLT) of Ibrutinib in combination with GA101 - Obinutuzumab in previously untreated CLL subjects.
- Primary objective Phase II:
    - To determine the overall response rate (partial response + complete response rate) of Ibrutinib in combination with GA101 - Obinutuzumab in previously untreated subjects with CLL.

2.2 SECONDARY

- To determine progression-free survival (PFS), treatment-free survival (TFS) and overall survival (OS) in previously untreated CLL subjects that will receive treatment with Ibrutinib in combination with GA101 – Obinutuzumab.
- To determine the percentage of previously untreated CLL subjects treated with Ibrutinib plus GA101 – Obinutuzumab that achieve negative minimal residual disease (MRD^{neg}) in the bone marrow or peripheral blood using multiparameter flow cytometry (4 colors).

- To evaluate correlative studies in samples collected from previously untreated CLL subjects treated with Ibrutinib / GA101 – Obinutuzumab combination regimen including but not limited to the following: assessment of the chemokine and cytokine profile using plasma samples from the subjects and correlation of the results with the presence of Infusion-Related Reactions (IRRs).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open label phase IB/II clinical trial to determine the safety, tolerability and clinical activity of Ibrutinib in combination with GA101 - Obinutuzumab. **Pharmacyclic**s will provide Ibrutinib during the course of the 6 cycles and after cycle 6, during the following 3 years. GA101 – Obinutuzumab will be requested to be covered by the insurance as a Standard of Care treatment for previously untreated subjects. Phase Ib

We will evaluate safety, tolerability and dose-limiting toxicities (DLTs) during the first cycle of treatment (4 weeks; Day 1 – 28). The phase IB will be performed as a safety run-in in the first 6 subjects enrolled. The sample size of 6 subjects is considered to be sufficient to support preliminary safety, tolerability and DLTs assessments (Goede et al., 2013). For additional statistical considerations see section 10.2.6.

Subjects will be enrolled at least one week apart to ovoid overlapping time of observation during the first week of treatment when infusion reactions are expected to be higher.

If no more than one of six subjects experiences DLTs, we will proceed to the Phase II described below.

3.1.1 Phase II

In the phase II we will determine response rate in all subjects that have received treatment. This study will enroll 32 subjects and the sample size has been calculated using a Simon two-stage design (Simon, 1989). In the first stage, 10 subjects will be enrolled. If 8 or fewer responses are observed at the end of this stage, then the study will be terminated for futility. If at least 9 responses are observed, an additional 22 subjects will be enrolled in a second stage, for a total of 32 subjects. If at least 29 responses are observed among the 32, then efficacy of the treatment will be concluded. For additional statistical considerations see section 10.3.4.

Response assessments will be evaluated based on the International Workshop in CLL Guidelines (IWCLL) (Hallek et al., 2008).

The estimated accrual time from first to last subject enrolled in the study will be 24 months (including the safety run-in of the phase Ib)

3.2 OUTCOME MEASURES

3.2.1 Phase IB Outcome Measures:

The safety and tolerability of Ibrutinib in combination with GA101 - Obinutuzumab will be assessed using the following primary safety outcome measures:

- Type, Incidence, nature, and severity of AEs.
- The relationship of AEs to Ibrutinib and/or GA101 – Obinutuzumab
- Serious adverse events
- Incidence of adverse events leading to Ibrutinib/GA101 - Obinutuzumab discontinuation or dose delays.
- Incidence of adverse events of special interest
- Clinical laboratory abnormalities
- Deaths and cause of death
- Dose limiting toxicity (DLT): DLTs will include possibly related or related events that are Grade $\geq$ 3 that do not resolve to Grade $\leq$ 1 within 14 days of initiation despite appropriate medical management. Some exceptions will apply (See section 10.2.4).

3.2.2 Phase II Outcome Measures:

Response assessment will be performed by physical examination, CT scan evaluation and bone marrow biopsy/aspirate at completion of therapy using the International Workshop in CLL Guidelines (IWCLL) (Hallek et al., 2008).

- **Primary:**

  - *Overall response rate (ORR):* defined as the proportion of subjects who achieve complete response (CR), complete response with incomplete marrow recovery (CRi), nodular partial response (nPR), or partial response (PR) per IWCLL 2008 criteria over the course of the study.

  - *Progression Free Survival (PFS):* Time measured from initiation of therapy until clinical or laboratory evidence of CLL progression.

  - *Treatment Free Survival (TFS):* Time measured from initiation of therapy until next treatment for CLL.

  - *Overall Survival (OS):* Time measured from initiation of therapy until death from any cause.

- **Secondary:**

- Rate of MRD^{neg} CRs in the bone marrow or peripheral blood using multiparameter flow cytometry (4 colors).

- Clinical, laboratory and radiological evidence of response to administration of Ibrutinib plus GA101 – Obinutuzumab based in the International Workshop in CLL Guidelines (IWCLL) (Hallek et al., 2008).

4. STUDY POPULATION

- Previously untreated CLL subjects ≥ 65 years of age or subjects < 65 years that refuse to be treated with chemotherapy or that are not candidates for treatment with chemotherapy agents.

4.1 INCLUSION CRITERIA

Subjects must meet the following criteria for study entry:

1. Diagnosis of CLL:

• Monoclonal B-cells co-expressing ≥ one B-cell marker (CD19, CD20, or CD23) and CD5 in peripheral blood or lymph node.

2. Indication for treatment as defined by the IWCLL Guidelines:

• Massive (i.e. > 6 cm below the left costal margin) or progressive/ symptomatic splenomegaly OR

• Massive lymph nodes or nodal clusters (i.e. > 10 cm in longest diameter), or progressive / symptomatic lymphadenopathy OR

• Presence of disease-related constitutional symptoms:

− Weight loss ⩾ 10% over the preceding 6 months

− Significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities).

− Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection.

− Night sweats for more than 1 month without evidence of infection.

• Progressive lymphocytes with an increase of ⩾ 50% over a 2-month period or an anticipated doubling time of less than 6 months. OR

• Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and / or thrombocytopenia.

• Autoimmune anemia and / or thrombocytopenia poorly responsive to corticosteroids or other standard therapy.

3. No previous treatment for CLL.

4. Males and females 65 years of age and older. Subjects < 65 years of age that meet any of the following criteria:

• Subjects that refuse to be treated with chemotherapy based agents (This should be documented in the consent form).

• Subjects that are not candidates for treatment with chemotherapy agents based on any of the following:

  • ECOG Performance status ≥ 2

  • Cumulative Illness Rating Scale (CIRS score) ≥ 6 (Appendix 6)

  • Creatinine clearance <70 mL/min using the Cockcroft-Gault Equation.

5. Laboratory parameters as specified below:

  • Hematologic: Hemoglobin $\geq$ 8 g/dL (may be post-transfusion); platelet count $\geq$ 40 x10^3/mm^3 (may be post-transfusion). Absolute neutrophil count $\geq$ 1.0 $\times$ 10^9 cells/L (Growth factor use is allowed).

  • Hepatic: Total Bilirubin < 3 x ULN, and ALT and AST < 3 x ULN

  • Renal: Creatinine clearance > 30 mL/min (Calculated according to institutional standards or using Cockcroft–Gault formula. Subjects with requirement of hemodialysis will be excluded).

6. Anticipated survival of at least 6 months.

7. Effective contraception is required while receiving Ibrutinib in combination with GA101 - Obinutuzumab. For women of childbearing potential and men, effective

contraception is required while receiving GA101 – Obinutuzumab and for 365 days (12 months) after the last dose of the study drug.

8. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments.

9. Subjects must give written informed consent to participate in this trial.

4.2 EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from study entry:

1. Pregnant or nursing women.

2. Treatment with chemotherapy, monoclonal antibodies or biological agents (e.g. lenalidomide) other than the investigational agents during the time of participation in this trial.

3. Grade 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.

4. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, COPD).

5. Participation in any investigational drug study within 28 days prior to initiation of treatment within this protocol. (Subject must have recovered from all acute effects of previously administered investigational agents).

6. History of second malignancy, other than non-melanoma skin cancer or in situ carcinoma of the cervix or the breast, unless the tumor was successfully treated at least 2 years before trial entry and with no evidence of relapse or active cancer.

7. Active symptomatic fungal, bacterial and/or viral infection including evidence of infection with human immunodeficiency virus (HIV).

8. Evidence of active acute or chronic Hepatitis B (HBV): Subjects with acute or chronic active HBV will be defined based on CDC guidelines (Appendix 1). This will include subjects with positive serology for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc) associated with HBV-DNA positive test by real time quantitative qPCR assessment. Subjects, who are anti-HBc positive and HBsAg negative or HBV-DNA test negative, may be enrolled in the study and should undergo

regular monitoring of HBV viral load using HBV-DNA qPCR. Those subjects may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management including antiviral therapy.

9. Evidence of active Hepatitis C (HCV): subjects with positive hepatitis C serology and positive HCV RNA test.

10. Any illness or condition that in the opinion of the Investigator may affect safety of treatment or evaluation of any the study's endpoints.

11. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy.

12. Known hypersensitivity to any of the study drugs.

13. Major surgery (within 4 weeks prior to the start of Cycle 1), except for procedures that are performed for diagnostic purposes.

14. Men or women of childbearing potential who refuse to use an adequate measure of contraception (oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly) unless they have past medical history of surgical sterilization.

15. Vaccination with a live vaccine within 28 days of the initiation of treatment.

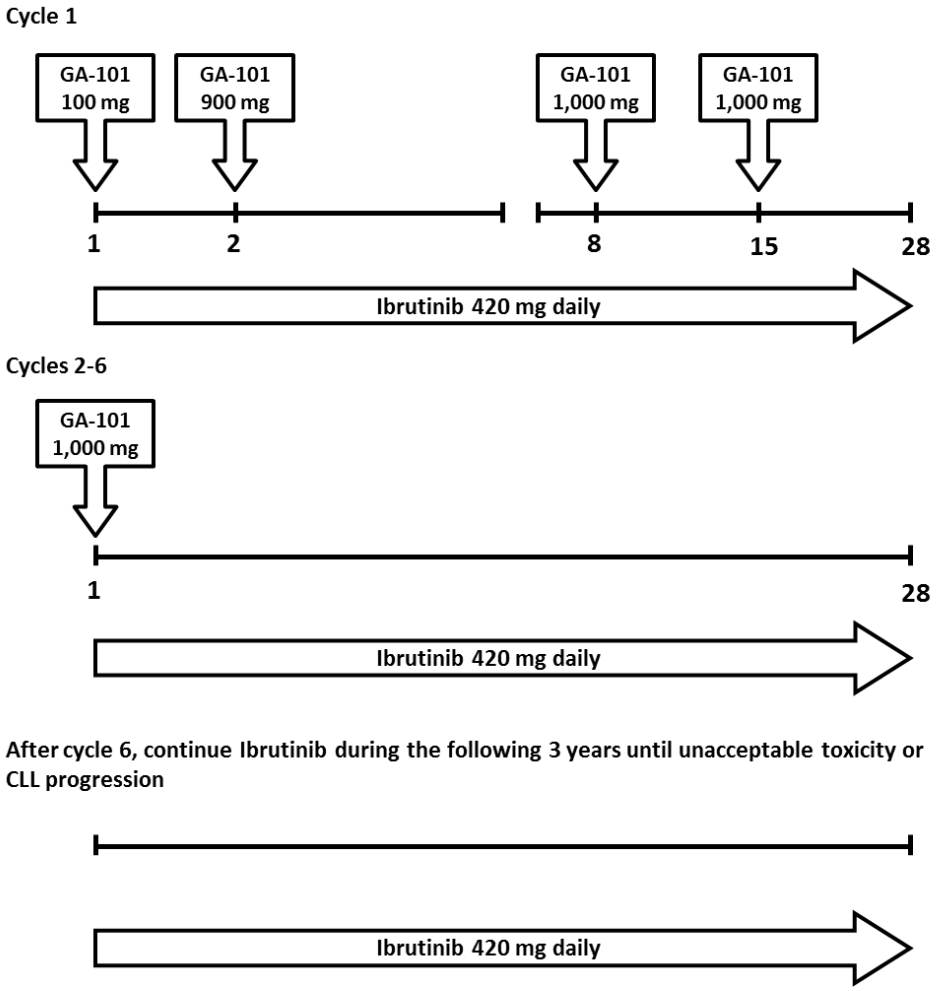
16. Concomitant use of warfarin or other Vitamin K antagonists.

17. Requirement to receive treatment with a strong cytochrome P450 (CYP) 3A inhibitor. Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of Ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor.

18. Subjects with chronic liver disease with hepatic impairment (Child-Pugh class B or C).

5. TREATMENT PLAN

Figure 1. Treatment Schema



This is a phase IB/II study that will investigate the combination of Ibrutinib with GA101 – Obinutuzumab in previously untreated CLL subjects ≥ 65 years of age or subjects < 65 years that either refuse to be treated with chemotherapy or that are not candidates for treatment with chemotherapy agents.

Treatment will be given up to 6 cycles, each cycle will have duration of 28 days (Figure 1 - Appendix 2).

- Ibrutinib will be given at 420 mg po daily during the complete study period (6 cycles) and will continue during the following 3 years until unacceptable toxicity

or CLL progression in those subjects who respond to treatment. The first dose will be delivered in the clinic on Day 1, one to three hours before the GA101 – Obinutuzumab infusion, after which the subsequent dosing will be on an outpatient basis.

- GA101- Obinutuzumab will be given at 1,000 mg / dose. The first dose given on cycle 1 will be split in 2 doses - Day 1 dose of 100mg and Day 2 dose of 900 mg. Subsequent doses of GA101 - Obinutuzumab (1,000 mg) will be administered on Cycle 1 - Days 8, 15; and on Day 1 of Cycles 2-6 (study days 29, 57, 85, 113, 141).

This research study protocol allows the subject to receive up to 8 infusions of GA101- Obinutuzumab. Even if the treatment is shown to be of benefit, additional infusions of GA101- Obinutuzumab beyond that allowed in the protocol cannot be given to the subject while they are participating in this study.

6. STUDY MEDICATIONS

6.1 IBRUTINIB

6.1.1 Formulation

Ibrutinib will be supplied as hard gelatin 140-mg capsules for oral (PO) administration. **Pharmacyclics** will provide Ibrutinib during the complete study period (6 cycles) and after cycle 6, during the following 3 years.

6.1.2 Dosage and Administration

Ibrutinib 420 mg (3 x 140-mg capsules) is administered orally once daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Each dose of Ibrutinib should be taken approximately at the same time each day. The use of CYP3A4/5 inhibitors/inducers, CYP2D6 inhibitors, and grapefruit and Seville oranges (due to CYP3A4/5 inhibition) should be avoided for the duration of the study (appendix 5).

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If the dose is more than 6 hours late, the dose should not be taken and the subjects should take the next dose at the scheduled time the next day. Missed doses should be recorded by the subjects in the drug diary.

The first dose will be delivered in the clinic on Day 1, one to three hours before the GA101 – Obinutuzumab infusion, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused Ibrutinib dispensed during previous visits must be returned to the site and drug

accountability records updated at each visit. Returned capsules must not be re-dispensed to anyone.

After cycle 6, Ibrutinib will be administrated during the following 3 years until unacceptable toxicity or CLL progression and will be dispensed in bottles every 3 or 6 months at each follow-up visit.

6.2 GA101 - OBINUTUZUMAB

6.2.1 Formulation

GA101 - Obinutuzumab is provided as a single-use vial. Each vial contains a sterile liquid formulation in a 50-mL pharmaceutical-grade glass vial containing a nominal dose of 1,000 mg of GA101 - Obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance formulated in histidine/histidine-HCl, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

GA101 – Obinutuzumab will be requested to be covered by the insurance as a Standard of Care treatment for previously untreated subjects.

6.2.2 Storage

The recommended storage conditions for the GA101-Obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for GA101-Obinutuzumab dilutions in 0.9% sodium chloride (NaCl) at concentrations of 0.2 – 20 mg/mL have been demonstrated for 24 hours at 2°C – 8°C and an additional 24 hours at ambient temperature and ambient room lighting. The prepared diluted product should generally be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. GA101 - Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in line filter because of potential adsorption.

6.2.3 Preparation

Split dosing: Splitting the first dose of GA101-Obinutuzumab in Cycle 1 is mandatory. The first dose (1,000 mg) must be administered over Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2).

GA101 - Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl.

One vial may be used to prepare both the 100-mg dose (equals 4 mL) and 900-mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in a controlled and validated aseptic conditions. Subsequently store the 900-mg bag for a maximum of 24 hours at 2°C – 8°C and administer the next day.

To prepare a 100-mg dose: The final drug concentration of a 100-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl withdraw 4 mL of GA101-Obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of GA101-Obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 900-mg dose: The final drug concentration of a 900-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl withdraw 36 mL of GA101-Obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of GA101-Obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 1,000-mg dose: The final drug concentration of a 1,000-mg dose should be 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl withdraw 40 mL of GA101-Obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of GA101-Obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution. Do not shake.

Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Use of a port or peripherally inserted central catheter line is acceptable.

Do not use GA101 - Obinutuzumab beyond the expiration date stamped on the carton.

6.2.4 Dosage and Administration

GA101 - Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles):

- On Cycle 1, Day 1, 100 mg GA101-Obinutuzumab will be administered
- On Cycle 1, Day 2, 900 mg of GA101-Obinutuzumab will be administered

- On Cycle 1, Days 8 and 15, 1,000 mg of GA101-Obinutuzumab will be administered.
- On Cycles 2 – 6, Day 1, 1,000 mg of GA101-Obinutuzumab will be administered (See Table 1).

GA101 - Obinutuzumab **must** be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and Subjects should be under close supervision by the investigator at all times. GA101-Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps (such as Braun Infusomat Space) should be used to control the infusion rate of GA101-Obinutuzumab. Do not administer as an IV push or bolus. After the end of the infusions, the IV line should remain in place for 1 hour ± 30 minutes from the end of infusion; if no AEs occur after 1 hour ± 30 minutes, the IV line may be removed.

6.2.5 Premedication Requirements

Infusion-Related Reactions

Since some subjects may develop hypersensitivity or other IRRs to GA101 - Obinutuzumab, pre-medication is recommended to reduce the risk of infusion reactions as outlined below (Figure 2):

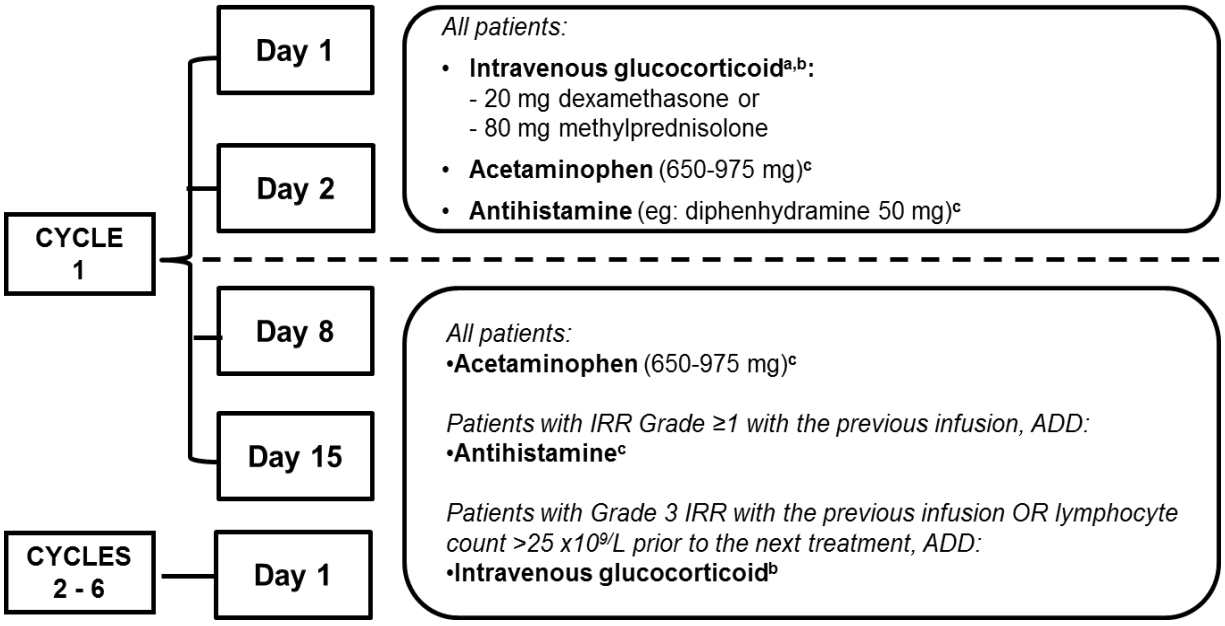
- Cycle 1, Days 1 and 2, all subjects require pre-medication with:
  - IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to GA101-Obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
  - An oral acetaminophen (975 mg) and an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each GA101-Obinutuzumab infusion.
- Cycle 1, Days 8 and 15 and Cycles 2-6, Day 1:
  - All subjects require pre-medication with oral acetaminophen (975 mg) administered at least 30 minutes before starting each GA101-Obinutuzumab infusion.
  - Subjects who experience an IRR (Grade 1 or more) with the previous infusion will require pre-medication with an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each subsequent GA101-Obinutuzumab infusion.
  - Subjects who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9$/L prior to the next treatment will require pre medication with IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to GA101-

Obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

Hypotension may be expected to occur during GA101-Obinutuzumab infusions. Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each GA101-Obinutuzumab infusion and for the first hour after administration. Subjects at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their hypertensive medication.

For TLS prophylaxis, see Section 6.2.12

Figure 2. Recommended Premedication to Reduce Infusion-related Reactions.



[a] Hydrocortisone is not recommended, as it has not been effective in reducing rates of infusion reactions.

[b] Glucocorticoid administration to be completed at least 1 hour prior to GA101 – Obinutuzumab infusion.

[c] Acetaminophen and antihistamine at least 30 minutes prior to GA101 - Obinutuzumab infusion.

6.2.6 Split Dosing

On Cycle 1, Day 1, 100 mg GA101-Obinutuzumab will be administered. On Cycle 1, Day 2, 900 mg of GA101-Obinutuzumab will be administered. On Cycle 1,

Days 8 and 15, and Day 1 of Cycles 2-6, 1,000 mg of GA101-Obinutuzumab will be administered (see Table 1).

Table 1 GA101 - Obinutuzumab Dosing Schedule

<table>
<tr><th colspan="2">Cycle and Day of Administration</th><th>Dose of Obinutuzumab</th><th>Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)</th></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>100 mg</td><td>Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.</td></tr>
<tr><td>Day 2</td><td>900 mg</td><td>Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.</td></tr>
<tr><td>Day 8</td><td>1,000 mg</td><td rowspan="3">Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.</td></tr>
<tr><td>Day 15</td><td>1,000 mg</td></tr>
<tr><td>Cycles 2–6</td><td>Day 1</td><td>1,000 mg</td></tr>
</table>

If a subject experience any grade infusion reaction during infusion, adjust the infusion as outlined below:

- Grade 4 (life threatening): Stop infusion and discontinue therapy.
- Grade 3 (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if subject does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.
- Grade 1 – 2 (mild to moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if subject does not experience any

infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

6.2.7 Dosage Modification/Toxicity Management

A number of measures will be taken to ensure the safety of subjects participating in this study. These measures will be addressed through exclusion criteria (see Section 4.2) and routine monitoring as follows.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for AEs (all grades), SAEs, and AEs requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

6.2.8 Assessment of Hematologic Toxicities

The evaluation of potential treatment-induced toxicity in subjects with advanced CLL may be quite difficult and requires careful consideration of both the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable, especially under circumstances of progressive bone marrow failure from the CLL itself.

Dose modifications for hematologic toxicity in subjects with CLL must be made with consideration of the increased frequency of hematologic compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many subjects would be considered to have Grade 2 – 4 hematologic toxicity at presentation.

As a consequence, dose modification decisions for subjects with cytopenia (below the lower limit of the normal range) at baseline will be based on the International Workshop in CLL (IWCLL) guidelines (Hallek et al., 2008). For subjects with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE, v4.0, will be used.

6.2.9 Administration of Granulocyte Colony-Stimulating Factor

G-CSF may be administered as primary prophylaxis in each cycle of therapy, as per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

6.2.10 Hepatitis B Virus Reactivation

Active acute or chronic Hepatitis B (HBV): Subjects with acute or chronic active HBV will be defined based on CDC guidelines (Appendix 1). This will include subjects with positive serology for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) associated with HBV-DNA positive test by real time quantitative qPCR assessment. Subjects who are anti-HBc positive and HBV-DNA test negative, may be enrolled in the study and should undergo regular monitoring of HBV viral load using HBV-DNA qPCR. Those subjects may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.

For the subset of subjects who are Hepatitis B viral DNA negative and anti-HBc positive and have undetectable Hepatitis B viral DNA levels at screening, Hepatitis B viral DNA levels must be followed approximately every 4 weeks. Guidelines for the management of hepatitis B reactivation are outlined in Table 2.

Table 2 Management of Hepatitis B Reactivation

Hepatitis B Viral DNA Level by Real-Time PCR	**Guideline**
> 100 IU/mL	• Hold GA101 - Obinutuzumab • Begin anti-viral medication and treat for at least 1 year after the last dose of GA101 - Obinutuzumab. • Immediately refer the subject to a gastroenterologist or hepatologist for management. • Resume GA101-Obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels.
> 100 IU/mL while on anti-viral medication	Discontinue GA101 - Obinutuzumab.
29–100 IU/mL	Retest within 2 weeks. If still hepatitis B viral DNA positive: • Hold GA101 - Obinutuzumab

	• Begin anti-viral medication and treat for at least 1 year after the last dose of GA101 - Obinutuzumab. • Immediately refer the subject to a gastroenterologist or hepatologist for management • Resume GA101-Obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels

6.2.11 Management of Infusion-Related Reactions and Anaphylaxis

Please refer to Section 6.4.4 for information relating to concomitant medications. Medications (including subcutaneous epinephrine, corticosteroids, and intravenous diphenhydramine) and resuscitation equipment should be available for immediate use.

Life-Threatening Infusion-Related Reactions and Anaphylaxis.

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, GA101-Obinutuzumab should be discontinued and no additional GA101-Obinutuzumab should be administered (see Table 3). Subjects who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment. Subjects will continue in follow-up until resolution of reactions or clinical stability.

Table 3 Management of Infusion-Related Symptoms

Infusion-Related Symptoms [a]	Guidance
Grades 1–2	• Interrupt or slow the rate of the infusion • Give supportive treatment [b] • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion[c]
Grade 3	• Discontinue infusion until resolution of symptoms

	• Give supportive treatment [b] • Upon symptom resolution, may resume infusion rate escalation, at investigator discretion [c] • Note: If the same adverse event recurs with the same severity, treatment must be permanently discontinued.
Grade 4[d]	• Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug

[a] Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, for the grading of symptoms http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (Appendix 7)

[b] Subjects should be treated with acetaminophen and an antihistamine such as diphenhydramine if they have not been received these within the previous 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. For hypotension, subjects may require vasopressors.

[c] Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hr.

[d] Including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction.

6.2.12 Prophylaxis Tumor Lysis Syndrome

All subjects will receive prophylaxis for tumor Lysis syndrome (TLS) in the first cycle of treatment and will return to the clinic on day 4 for laboratory assessment in order to evaluate the risk for TLS. Diagnosis of TLS and laboratory assessment will be made based on the Cairo-Bishop Laboratory definition (Coiffier B et al., 2008) (Appendix 4).

Prophylaxis for TLS includes:

- Appropriate hydration consisting of a fluid intake of 2- 3 L/day starting 1 to 2 days prior to the first dose of GA101 – Obinutuzumab.

- Administration of allopurinol (300 mg/day orally) or a suitable alternative treatment starting prior to the first infusion of GA101 - Obinutuzumab (Cycle 1 Day 1).

Those subjects with laboratory evidence of TLS will be graded according to the NCI-CTCAE grading system (Version 4.0) (Appendix 4) and will return to the clinic on the day 4 of the subsequent cycles to continue follow-up of laboratory parameters.

For subjects with evidence of TLS ≥ Grade 3, GA101 - Obinutuzumab and Ibrutinib should be discontinued and the subject treated as clinically indicated. A dose delay of up to 8 weeks is permitted for GA101- Obinutuzumab / Ibrutinib to allow recovery of TLS. Following the complete resolution of TLS complications, Ibrutinib and GA101 - Obinutuzumab may be re administered at the full dose during the next infusion in conjunction with prophylactic therapy. If the treatment is delayed more than 8 weeks because there is no improvement of TLS, treatment will be stopped and the subject will continue in follow-up until the beginning of new treatment or death.

6.3 DOSE MODIFICATIONS AND DELAYS FOR IBRUTINIB AND GA101 – OBINUTUZUMAB

6.3.1 Dose Hold, Reduction, or Discontinuation of Ibrutinib

Treatment with Ibrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity. Subjects who require anticoagulant treatment (eg, heparin and/or warfarin) should have study drug hold until stable on anticoagulant therapy.

Ibrutinib may be held for a maximum of 28 consecutive days of toxicity. Ibrutinib should be discontinued in the event of a toxicity > Grade 1 lasting > 28 days.

A hematologic AE grading scheme for hematologic toxicity is included in Appendix 3.

The actions in Table 4 should be taken for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines) (Smith et al., 2006) and use must be recorded in CRF.
- Grade 3 or 4 platelets (< 50,000/μL); or, in subjects with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of bleeding.

- Grade 4 Platelets (< 25,000/μL); or, in subjects with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/μL, whichever is higher.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy, or any other Grade 4 toxicity and any unmanageable Grade 3 toxicity.

Table 4 Dose modifications or discontinuation actions for Ibrutinib

Occurrence ≥ G3 AE	Action
1st	Hold Ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold Ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily)
3rd	Hold Ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg daily)
4th	Discontinue Ibrutinib

6.3.2 Dose Modifications for Ibrutinib for Hepatic Impaired Subject

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation.

Subjects while on study who develop significant clinical and/or laboratory signs and/or symptoms of liver dysfunction (e.g., transaminitis, jaundice, etc.) in the opinion of the investigator, should be assessed with the Child-Pugh Score (Table 5) to determine a dose reduction of Ibrutinib as described in Table 6:

Table 5 Child-Pugh Score

The score employs five clinical measures of liver disease. Each measure is scored 1–3, with 3 indicating most severe derangement.

Clinical and Laboratory Criteria	1 Point	2 Points	3 Points
Hepatic encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)

Total bilirubin (mg/dL)	<2	2 - 3	>3
Seum albumin (gr/dL)	>3.5	2.8 - 3.5	<2.8
International normalized ratio (INR)	<1.7	1.7 - 2.3	>2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

Class A = 5 – 6 points (mild liver disease)

Class B = 7 – 9 points (moderate liver disease)

Class C = 10 – 15 points (severe liver disease)

Table 6 Dose Modifications for Ibrutinib for Hepatic Impaired Subjects

Child-Pugh Class	Points	Dose Reduction for Ibrutinib
A	5 – 6	280 mg (two capsules)
B	7 – 9	140 mg (one capsule)
C	10 – 15	Hold Ibrutinib until resolved to moderate impairment (Child-Pugh class B) or better

Monitor subjects for signs of toxicity and follow dose modification guidance as needed.

6.3.3 Ibrutinib Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in subjects. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed to up to single dose of 1,680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1,680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment. Refer to Section 11.4.3.8 for further information regarding special reporting situations as a result of overdose

Dose Modifications and delays for GA101 – Obinutuzumab

Splitting the first dose of GA101 – Obinutuzumab in Cycle 1 is mandatory. The first dose (1,000 mg) must be administered over Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2). Infusions should be interrupted or slowed if subjects experience infusion reactions (see Section 6.2.11). If a planned dose of GA101 - Obinutuzumab is missed, it should be administered as soon as possible and the next cycle should begin 28 days later. Do not wait until the next planned dose.

No reduction in the dose of GA101 - Obinutuzumab is allowed. A dose delay of up to 8 weeks is permitted for GA101 - Obinutuzumab to allow recovery of hematologic toxicities to ≤ Grade 2 or non-hematologic toxicities to Grade 1 or baseline level. If the treatment is delayed for more than 8 weeks because there is no improvement of cytopenia to ≤ Grade 2, treatment under this protocol will be discontinued and the subject will continue in follow-up until the beginning of new treatment or death.

If a subject experiences grade 3 or 4 cytopenia, the guidelines for GA101 – Obinutuzumab and Ibrutinib dose-delay are outlined in Table 7:

Table 7 Dose Modification for Cytopenias

Grade	GA101 - Obinutuzumab	Ibrutinib
Grade 3 or 4 cytopenia[a, c]	Delay dose for a maximum of 8 weeks. If improvement to ≤ Grade 2[b], administer full dose. If delay more than 8 weeks because there is no improvement of cytopenia < Grade 3, subject will be withdrawn from the study treatment but will continue in follow-up until the beginning of new treatment or death.	Hold Ibrutinib until recovery to Grade ≤ 1[b]; restart Ibrutinib at 420 mg daily. For subjects with recurrent episodes of grade 3 - 4 AEs a dose modification action is described in table 4 (see section 6.3.1). Ibrutinib may be held for a maximum of 28 consecutive days of toxicity. Ibrutinib should be discontinued in the event of a toxicity lasting > 28 days and the subject will be withdrawn from the study treatment but will continue in follow-up until the beginning of new treatment, death or assessment of TFS and OS.

Grade 1 or 2 cytopenia[a, c]	No dose reduction or delay	No dose reduction.

[a] In subjects with cytopenia at baseline, dose modifications will be based on the IWCLL Guidelines for hematological toxicity in CLL studies (Hallek et al., 2008). For subjects with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI-CTCAE v4.0 grading system will be used.

[b] Or baseline.

[c] Subjects with cytopenia at baseline should have hemoglobin $\geq$ 8 g/dL, platelets count $\geq$ 40 x10^3/mm^3 and absolute neutrophil count (ANC) $\geq$ 1.0 $\times$ 10^9 cells/L in order to proceed with the study treatment. Transfusion and Growth factors will be permitted and must be documented in the medical chart.

6.4 CONCOMITANT, EXCLUDED THERAPIES AND DRUG-DRUG INTERACTIONS

6.4.1 Permitted Concomitant Medications

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject between the 14 days preceding the study entry evaluation and the early study treatment termination visit/study treatment completion visit. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith et al., 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

6.4.2 Medications to be used with Caution

6.4.2.1 CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and therefore strong CYP3A inhibitors should be avoided.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, and posaconazole) must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use or withhold ibrutinib treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) is indicated, reduce ibrutinib dose to 140 mg for the duration of the inhibitor use.
- No dose adjustment is required in combination with mild inhibitors.
- Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A (see Section 6.1.2).

Avoid concomitant use of systemic strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in appendix 5. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.4.2.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity.

6.4.2.3 QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

6.4.2.4 Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with Ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use Ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.5).

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib/ placebo held, the sponsor's medical monitor should be contacted, and ibrutinib/placebo should not be restarted until the subject is clinically stable and the re-initiation of ibrutinib/placebo is approved by the sponsor's medical monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.4.3 Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, radiotherapy or live viral vaccines are prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of an underlying disease are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

Erythropoietic growth factors (eg, erythropoietin) and neutrophil growth factors (eg, filgrastim and peg-filgrastim) are also prohibited during (eg, initial treatment, DLT assessment period).

6.4.4 Concomitant Therapy during the study treatment

Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Effective contraception is required while receiving Ibrutinib in combination with GA101 - Obinutuzumab. For women of childbearing potential and men, effective contraception is required while receiving GA101 – Obinutuzumab and for 365 days (12 months) after the last dose of the study drug.

All subjects will receive allopurinol 300mg by mouth daily for 3 days prior to and during the first cycle of treatment. Allopurinol will be continued for the first cycle until the investigator determines there is no longer a concern for hyperuricemia. Subjects allergic to allopurinol will not receive allopurinol.

All subjects will receive premedication with glucocorticoid, acetaminophen and diphenhydramine prior to each dose of GA101 – Obinutuzumab as described in section 6.2.5.

Anti-viral prophylaxis will be given to subjects with CLL during treatment and for up to 2 months after completion of treatment.

Prophylactic antibiotics to prevent the recurrence of an infection diagnosed during treatment may be instituted for any subject if clinically indicated.

6.5 GUIDELINES FOR IBRUTINIB MANAGEMENT WITH SURGERIES OR PROCEDURE

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

6.5.1 Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

6.5.2 Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.5.3 Emergency Procedures

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. CRITERIA FOR SUBJECT DISCONTINUATION

Subjects will remain on study for three years after completion of the last cycle of treatment or until they have progressive disease requiring further treatment or death.

Subjects who meet the following criteria should be discontinued from the study:

- HBV Reactivation that is not responding to appropriate management and antiviral therapy as described in section 6.2.10, or subjects with evidence of HBV associated hepatitis with LFT abnormalities. *Subjects who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.*

- Severe or life-threatening anaphylaxis or hypersensitivity reaction

- Progressive Disease: Subjects with PD will discontinue the study treatment but will continue in follow-up until the beginning of new treatment or death.

- Severe life threatening reactions to GA101 – Obinutuzumab or Ibrutinib administration.

- Medical Prudence/Non-Compliance: The Principal Investigator may remove a subject from study any time deemed medically prudent to do so to assure the subject's health and welfare. A subject will also be removed from study to preserve the integrity of the investigation. The latter includes incidents in which the subject frequently misses study appointments needed to accurately assess response/adverse reactions, or is non-compliant with study directions provided by the investigator or study personnel. "Inevaluable" subjects will be replaced to meet target accrual.

8. CRITERIA FOR STUDY DISCONTINUATION

The study will be discontinued due to the following reasons:

- Lack of meeting statistical end point after Stage I accrual. See section 10.3.

- Excessive toxicity of the regimen with > 1 subject death that is considered related to the study medications.

9. CLINICAL AND LABORATORY EVALUATIONS

9.1 EVALUATIONS PRETREATMENT

9.1.1 Study Entry

Subjects who are interested in participating in this research will have the protocol explained to them by the principal investigator / co-principal investigators or one of the study coordinators. Potential subjects will be given the opportunity to review the informed consent form and have their questions/concerns addressed. After this, if the

subject chooses to enter the study, a screening date will be arranged by one of the study coordinators.

9.1.2 Screening

Screening for this study will occur after the subject has signed the approved informed consent form and received a copy of the “Experimental Subject’s Bill of Rights." Screening labs, diagnostic tests, and physical examination will be performed four weeks prior to beginning treatment. Subjects who do not meet the criteria for study after screening will be excluded and will be considered non-evaluable and therefore replaced to meet the proposed accrual.

9.1.2.1 Screening History and Physical Examination

- Complete medical and surgical history; AND
- Record current medications and past medical history including history of previous treatments for CLL; AND
- Record transfusion (PRBC and platelets) and supportive care (IVIG) history; AND
- Record history of infections (frequency, severity, treatment); AND
- Physical exam including vital signs (T, P, R, BP); AND
- Measure and record lymph node, spleen, and liver size; AND
- Determine performance status (ECOG) and tumor assessment

9.1.2.2 Screening Laboratory Tests

(To be performed within 28 days prior to treatment start date)

- HBsAg, HbsAb, HBcAb (IgG, IgM), HAAb and Hepatitis CAb. (If HBcAb is positive an HBV-DNA viral load qPCR test will be performed)
- HIV serology
- CBC, differential, platelet count, PT, PTT, INR; AND
- comprehensive metabolic panel including: Total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, albumin, creatinine, BUN, total protein, fasting blood glucose, calcium, sodium, potassium, chloride, HCO3, phosphorus, LDH and uric acid; AND

- Beta-2 microglobulin AND
- Quantitative immunoglobulin levels (IgG, IgA, IgM) AND
- Immunophenotyping of blood mononuclear cells: CD3, CD4, CD5, CD8, CD19, CD20.
- Absolute T cell count including CD3+, CD4+, and CD8+ populations; AND
- Serum Pregnancy Test (HcG levels) for FCBP (females of child bearing potential)

9.1.2.3 Screening Diagnostic Tests

- CT scan or MRI of the chest, abdomen and pelvis will be performed in order to assess disease status and confirm Rai stage. Images will be performed within 28 days of treatment initiation.
- Electrocardiogram (EKG) (within 3 months of treatment start) will be performed as clinically indicated, and the investigator will perform an overall interpretation.
- Unilateral (minimum) bone marrow aspirate and biopsy for flow cytometry and histologic staining (within 90 days of treatment start) to assess leukemia cell infiltration and leukemia cell immunophenotype
- FISH and interphase cytogenetics will be performed on all subjects prior to therapy to assess for subjects with common and high-risk CLL genetic abnormalities within 3 months of treatment start
- Assessment of leukemia cell expression of ZAP-70, CD38 and mutational status of IgVH (performed at anytime prior to therapy)

9.1.2.4 Pretreatment Cumulative Illness Rating Scale (CIRS)

The Cumulative Illness Rating Scale (CIRS) (http://eforms.moffitt.org/cirsgScore.aspx) will be assessed prior to therapy or may be scored retroactively based on clinic notes and laboratory assessments (Appendix 6) in order to meet the Inclusion criteria for participation in the study (See section 4.1).

9.1.2.5 Research Studies

Correlatives Studies will be performed at Dr. Kipps laboratory at different time points during the course of cycle #1 in all subjects.

About 40 ml of blood will be collected into BD Vacutainer® Cell Preparation Tubes (CPT) on days 1, 2 and 8 of cycle #1 to perform pharmacodynamics studies including but not limited to the following:

- Assessment of the chemokine and cytokine profile using plasma samples from the subjects and correlation of the results with the presence of Infusion-Related Reactions (IRRs).

9.2 EVALUATIONS DURING STUDY TREATMENT & FOLLOW UP

• Physical examination including vital signs, performance status, lymph node, spleen, and liver measurements, adverse event assessment, concurrent medications, and transfusion requirements will be recorded prior to each new cycle.

• CBC with differential, platelets, complete metabolic panel with uric acid, LDH, albumin, creatinine, BUN, total protein, calcium, sodium, potassium, chloride, phosphorus and HCO3 will be performed during the following dates of treatment and follow up.

- Cycle 1 – Day 1,2,4
- Cycle 1 – Day 8, 15, 22
- Cycle 2 to 5- Day 1, 8, 15, 22
- Cycle 6 - Day 1, 8, 15, 22, 28
- Two months after completion of therapy – Response assessment evaluation.
- After response assessment every 3 months for 9 months.
- Every 6 months until initiation of new treatment for CLL, consent withdrawal or death.

• All subjects will return to the clinic on day 4 of cycle #1 for laboratory assessment in order to evaluate the risk for TLS. Those subjects with laboratory evidence of TLS will return to the clinic on the day 4 of the subsequent cycles to continue follow-up of laboratory parameters.

• Absolute T cell count including CD3+, CD4+, and CD8+ populations will be performed on the following dates:

- At screening or on day 1 of Cycle 1.

- Two months after completion of therapy – Response assessment evaluation.

- End of study

• Pregnancy monitoring for women of child bearing potential before each dose of GA101 – Obinutuzumab (not required more than once monthly).

9.3 EVALUATION OF RESPONSE TO TREATMENT

The response assessment will be performed at 2 months after completion of study treatment in order to satisfy IWCLL criteria. This evaluation will include the following:

• Physical examination including vital signs, lymph node, spleen and liver measurements, performance status, adverse event assessment, concurrent medications, and recording of transfusion of blood products; AND

• Liver chemistries: (ALT, AST, total bilirubin and alkaline phosphatase)

• CBC with differential, platelet count, complete chemistry panel with uric acid, LDH, albumin, creatinine, BUN, total protein, fasting blood glucose, calcium, sodium, potassium, chloride, phosphorus and HCO3.

• Beta-2 microglobulin, and quantitative immunoglobulin levels (IgG, IgA, IgM); AND

• Absolute T cell count including CD3+, CD4+, and CD8+ populations (frequency should be consistent with standard of care evaluations).

• Chest, abdominal and pelvic CT scan or MRI to assess response.

• Unilateral bone marrow aspirate and biopsy will be performed using multiparameter (4 colors) flow cytometry and histologic staining.

• FISH and interphase cytogenetics.

• Serum Pregnancy Test (hCG levels) for FCBP (females of child bearing potential).

9.4 EVALUATIONS EVERY 3 MONTHS FOR NINE MONTHS AFTER RESPONSE ASSESSMENT

After the response assessment (at 2 months after completion of study treatment), the initial follow-up evaluations will be made every 3 months during 9 months. These evaluations will include the following:

- Physical examination including vital signs, lymph node, spleen and liver measurements, performance status, adverse event assessment, current medications, and recording of transfusion of blood products.

- Liver chemistries: (ALT, AST, total bilirubin and Alkaline phosphatase)

- CBC with differential, platelet count, complete metabolic panel with uric acid, LDH, albumin, creatinine, BUN, total protein, fasting blood glucose, calcium, sodium, potassium, chloride, phosphorus and HCO3.

- Beta-2 microglobulin, and quantitative immunoglobulin levels (IgG, IgA, IgM). Continue monitoring of quantitative immunoglobulins (IgG, IgA, and IgM) for up to 2 years after completion of therapy or until they return to baseline.

- Pregnancy monitoring for women of child bearing potential should continue with every follow-up evaluation until 12 months following the last dose of GA101 – Obinutuzumab.

- Chest, abdominal and pelvic CT scan or MRI in those subjects with clinical or laboratory alterations that suggest disease progression based on IWCLL criteria.

- For subjects that maintain a CR, a MRD assessment in peripheral blood using multiparameter (4 colors) flow cytometry will be performed at 6 and 12 months in order to assess MRD.

9.5 EVALUATION EVERY 6 MONTHS UNTIL PROGRESSION OR WITHDRAWAL FROM THE STUDY

Long-term follow-up will continue every 6 months until initiation of new treatment, consent withdrawal from the study or death, whichever occurs first. These evaluations will include the following

- Physical examination including vital signs, lymph node, spleen and liver measurements, performance status, adverse event assessment, current medications, and recording of transfusion of blood products.

- Liver chemistries: (ALT, AST, total bilirubin and Alkaline phosphatase)

- CBC with differential, platelet count, complete metabolic panel with uric acid, LDH, albumin, creatinine, BUN, total protein, fasting blood glucose, calcium, sodium, potassium, chloride, phosphorus and HCO3.

Beta-2 microglobulin, quantitative immunoglobulin levels (IgG, IgA, IgM). Continue monitoring of quantitative immunoglobulins (IgG, IgA, and IgM) for up to 2 years after completion of therapy or until they return to baseline.

- Pregnancy monitoring for women of child bearing potential should continue with every follow-up evaluation until 12 months following the last dose of GA101 – Obinutuzumab.

- Chest, abdominal and pelvic CT scan or MRI in those subjects with clinical or laboratory alterations that suggest disease progression based on IWCLL criteria.

- For subjects that maintain a CR (based on clinical and hematological assessments), additional CT scans of the chest, abdomen and pelvis will be performed after 3 years of completion of study treatment in order to assess response based on clinic and radiologic parameters, and discuss the possibility of Ibrutinib discontinuation.

- For subjects that maintain a CR (based on clinical and hematological assessments), an additional bone marrow biopsy and aspirate will be performed after 3 years of completion of study treatment in order to assess MRD and discuss the possibility of Ibrutinib discontinuation.

9.6 EVALUATIONS AT THE END OF STUDY

An evaluation within 30 days of the end of study will be performed. End of study is defined as initiation of new treatment for CLL or withdrawal of consent. This evaluation will include the following:

- Physical examination including vital signs, lymph node, spleen and liver measurements, performance status, adverse event assessment, concurrent medications, and recording of transfusion of blood products; AND:

- Liver chemistries: (ALT, AST, total bilirubin and alkaline phosphatase)

- CBC with differential, platelet count, and complete metabolic panel with uric acid, LDH, albumin, creatinine, BUN, total protein, fasting blood glucose, calcium, sodium, potassium, chloride, phosphorus and HCO3.

- Beta-2 microglobulin, and quantitative immunoglobulin levels (IgG, IgA, IgM).

- Absolute T cell count including CD3+, CD4+, and CD8+ populations.

- Chest, abdominal and pelvic CT scan or MRI in order to confirm CR base don IWCLL criteria in subjects that meet clinical and laboratory parameter for CR.

- Unilateral bone marrow aspirate and biopsy will be performed to confirm CR (MRD assessment) using multiparameter (4 colors) flow cytometry and histologic staining.

- FISH and interphase cytogenetics.

- Serum Pregnancy Test (hCG levels) for FCBP (females of child bearing potential).

10. STATISTICAL CONSIDERATIONS AND RATIONALE

10.1 STATISTICAL MODEL

For this open-label study, descriptive statistics will be calculated for demographic and baseline characteristics, clinical response variables, immunologic variables and safety data. Each phase of this study will be analyzed separately. All tables, figures and listings will therefore be separated by study phase.

10.1.1 Demographic and Background Characteristics

The study population will be described in terms of general and background characteristics using usual statistics as mean, median, standard deviation and range for continuous variables and frequencies for categorical variables. Study conduct will also be evaluated by an accurate description of protocol deviations, treatment administration and study completion status.

10.1.2 Laboratory Variables

The normal ranges of the local laboratory, including those for liver enzymes, will be used as the normal ranges for the respective subject. All laboratory data will be converted in the International System of Units (SI units) for the analysis, with the exception of the liver enzyme values. For the liver enzymes ALT and AST, the unit U/L will be used. The NCI-CTCAE v4.0 grading system will be used for assessing laboratory abnormalities.

10.1.3 Concomitant Medications

The use of concomitant medications will be recorded at each visit and described using descriptive statistics.

10.1.4 Estimated Time to Complete Enrollment

The estimated time of accrual of the total number of subjects is 24 months.

10.1.5 Data Analysis

The complete analysis of all study data will be contained in the clinical study report at the end of the study.

10.2 STATISTICAL CONSIDERATIONS FOR THE PHASE IB

The primary objective of the Phase Ib of this clinical study is to evaluate the safety, tolerability and DLT of Ibrutinib in combination with GA101 - Obinutuzumab.

10.2.1 Subject Evaluability for the Phase Ib

The first 6 subjects who receive at least one dose of Ibrutinib and/or GA101 – Obinutuzumab will be considered evaluable for safety, tolerability and DLTs.

10.2.2 Safety Analysis

All subjects who have at least one dose of Ibrutinib and/or one infusion of GA101 – Obinutuzumab, and a safety follow-up, whether withdrawn prematurely or not, will be included in the safety analysis.

10.2.3 Clinical Adverse Events

All adverse events, including unrelated adverse events, will be listed and graded according to the NCI-CTCAE grading system (Version 4.0) (Appendix 7). The proportion of subjects with treatment-related adverse events, overall, and by body system, will be tabulated. In addition, subjects with treatment-related adverse events, SAEs, and adverse events leading to withdrawal will be listed overall and, if appropriate, distributions by body system will be provided.

10.2.4 Definition of Dose Limiting Toxicity (DLT)

Dose limiting toxicity (DLT) is defined as any of the adverse events (AEs) noted below that are considered by the investigator to be possibly related or related to Ibrutinib / GA101 - Obinutuzumab treatment. For the purpose of defining DLTs, AE will be tabulated and assessed based on the signs and symptoms present during the first cycle of treatment (Day 1 - 28). Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix 7) except for hematological toxicities that will be graded according to the IWCLL guidelines (Hallek et

al., 2008) (Appendix 3) For subjects with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI-CTCAE v4.0 grading system will be used. ***Dose limiting toxicity will include possibly related or related events that are Grade ≥ 3 that do not resolve to Grade ≤ 1within 14 days of initiation despite appropriate medical management. The following exceptions will apply:***

- Non Hematologic:

  - ≥ Grade 3 nausea, vomiting, or diarrhea only if uncontrolled by maximal antiemetic/antidiarrheal therapy.

- Hematologic:

Hematologic toxicity will be graded according to the IWCLL guidelines (Hallek et al., 2008) - (Appendix 3), with dose-limiting hematologic toxicity defined as follows:

- ≥ Grade 4 granulocytopenia lasting ≥ 14 days. Note that per IWCLL guidelines, subjects are evaluable for toxicity related to granulocytopenia only if the pre-treatment ANC is >1.0 $x10^9$/L.

- ≥ Grade 4 thrombocytopenia lasting ≥ 14 days or thrombocytopenia associated with bleeding. Note that per IWCLL guidelines, subjects are evaluable for toxicity related to thrombocytopenia only if the pre-treatment platelet count is >20,000/μL.

- Grade ≥ 3 infusion-related reactions to GA101 – Obinutuzumab will be considered DLTs under the following circumstances:

  - If subjects experience Grade 3 infusion-related reactions at re-challenge despite appropriate medical management that leads to permanently discontinue GA101 – Obinutuzumab.

  - Any Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction.

10.2.5 Dose Escalation / De-escalation Based on AE - DLT

Dose modifications or discontinuation actions for Ibrutinib are described in table 4 (see section 6.3.1). No dose escalation or de-escalation will occur for GA101 – Obinutuzumab. If a subject experiences grade 3 or 4 cytopenia, the guidelines for Ibrutinib and GA101 – Obinutuzumab dose-delay are outlined in table 7 (Section 6.3.4).

10.2.6 Statistical Operating Characteristics of the Phase IB

The phase IB will be performed as a safety run-in with the first 6 subjects enrolled in the study. The sample size of 6 subjects is considered to be sufficient to support preliminary safety, tolerability and DLTs assessments (Goede et al., 2013). On this group of subjects, we will evaluate safety, tolerability and dose-limiting toxicities (DLTs) during the first cycle of treatment (4 weeks; Day 1 - 28),

Subjects will be enrolled at least one week apart to avoid overlapping time of observation during the first week of treatment when infusion reactions are expected to be higher.

- If 0 to 1 DLTs (See DLT definition – Section 10.2.4) are observed in the first 3 subjects, we will proceed to enroll 3 additional subjects.
- If 0 to 1 DLTs are observed in the first 6 subjects, we will proceed to the phase II of the study.
- If $\geq$ 2 DLTs are observed, we will hold enrollment and revise the study design with the sponsor.

The table below gives the characteristics of this procedure. For a range of underlying dose limiting toxicity rates, the probability that the study will be stopped during the Phase IB (i.e. the probability that there are two or more DLT's within the first six subjects) and the expected number of DLT's are computed.

Table 8 Operating Characteristics of the Phase IB Procedure

Toxicity Rate	Probability of Halting	Expected # Toxicities
5%	3.3%	0.3
10%	11.4%	0.59
15%	22.4%	0.87
20%	34.5%	1.14
25%	46.6%	1.38
30%	58%	1.61
35%	68.1%	1.8
40%	76.7%	1.98
45%	83.6%	2.13
50%	89.1%	2.25

Thus, when the DLT rate is as high as 30%, the probability of stopping the trials will be at least 58%. Conversely, if the DLT rate is no more than 10%, then the chance of stopping the trials during this phase is at most 11.4%.

10.3 STATISTICAL CONSIDERATIONS FOR THE PHASE II

The primary objective of the phase II stage of this clinical trial is to evaluate the overall response rate (partial responses + complete responses) in CLL subjects treated with Ibrutinib in combination with GA101 – Obinutuzumab.

All subjects who receive at least one dose of Ibrutinib and/or GA101 – Obinutuzumab will be considered evaluable for safety, tolerability and DLT.

10.3.1 Clinical and Laboratory Variables

Clinical and laboratory test will be tabulated after subjects have completed treatment under protocol.

10.3.2 Efficacy Population

The Efficacy Population includes all subjects who receive at least one dose of study drug and have baseline and at least one post-baseline efficacy assessment.

10.3.3 Efficacy Analysis

Response assessment will be performed by physical examination, CT scan evaluation and bone marrow biopsy/aspirate at completion of therapy using the International Workshop in CLL Guidelines (IWCLL) (Hallek et al., 2008) (See section 3.2.2). The ORR will be estimated with an exact 95% confidence interval (CI) for the combination regimen of Ibrutinib/GA101 – Obinutuzumab.

Median PFS, TFS and OS, and their 95% CI will be estimated using the Kaplan-Meier method.

10.3.4 Statistical Operating Characteristics of the Phase II

The sample size calculation has been made using a comparative overall response with GA101 – Obinutuzumab in combination with chlorambucil, which is a standard of care regimen for previously untreated CLL subjects. This combination regimen can induce an overall response rate (ORR) of 78% in CLL subjects (Goede et al., 2014). For the purpose of our sample calculation we will use a true ORR of 78% that will be tested against an alternative of 94%, which corresponds to the expected ORR that can be achieved when GA101 – Obinutuzumab is administered in combination with Ibrutinib.

There is no data available using the combination of Ibrutinib and GA101 - Obinutuzumab, therefore we will use as a point of reference for the expected ORR, the recently published data of Ibrutinib in combination with Rituximab in relapse/refractory CLL subjects. In this publication the ORR was in the 90 – 95% range (Burger et al., 2013).

Our sample size calculation will use an ORR endpoint comparison based on the ORR achieved with the Ibrutinib and GA101 - Obinutuzumab combination. We hypothesize that Ibrutinib in combination with GA101 – Obinutuzumab would induce an ORR of 94%, which is 16% higher than the ORR observed in the study published by Goede et al. (Goede et al., 2014)

Based on this, we will use a Simon's two-stage optimal design in this study (Simon, 1989). The null hypothesis that the true overall response rate is 78% will be tested against a one-sided alternative. In the first stage, 10 subjects will be accrued. If there are 8 or fewer responses in these 10 subjects, the study will be stopped. Otherwise, 22 additional subjects will be accrued for a total of 32. The null hypothesis will be rejected if 29 or more responses are observed in 32 subjects. This design yields a type I error rate of 5% and power of 80% when the true response rate is 94%.

10.4 REPLACEMENT OF SUBJECTS

For the safety run-in, subjects will be replaced if they withdraw from the study prior to day 28 of the first cycle for any reason other than withdrawal due to toxicity, progressive disease (PD) or death.

In the phase II, up to 3 subjects will be allowed to be replaced if they have not completed treatment response assessment and, if they withdraw from the study for any reason other than toxicity, progressive disease (PD) or death.

10.5 TRIAL STOPPING AND HOLDING RULES BASED ON DLT AND LACK OF EFFICACY

The trial will be stopped or put on hold and the data will be reviewed with the sponsor for any of the following reasons:

- If there is ≥ 1 deaths that are considered to be related or possibly related to the study medications or procedures related to this clinical trial.
- If the efficacy endpoint is not reached at the end of treatment of the Stage I subjects based on Simon II Stage design (Section 10.3.4).
- If $\geq$ 2 DLTs are observed in the first 6 subjects treated under the phase IB study, we will hold enrollment and revise the study design with the sponsor (Section 10.2.6).
- If the study is put on hold, the decisions regarding continuation of treatment for any subjects who have already received therapy will be made on a case-by-case basis after discussion with the subject and the principal investigator. All subjects will be re-consented.

- All subjects who were on treatment at the time study-stopping criteria were met will continue to be followed by the principal investigator for safety until the end of the study.

10.6 PLANNED EFFICACY EVALUATIONS

- **Phase IB:** We will evaluate AE and determine DLTs as described in Section 10.2.

- **Phase II:** All treated subjects will undergo evaluation for response to treatment 2 months after completion of study treatment. Evaluation tests will include CT / MRI of the chest, abdomen and pelvis, CMP, CBC, LDH, bone marrow biopsy including immunohistochemistry for pathology analysis, FISH and chromosome analysis as well as multiparameter (4 colors) flow cytometry for MRD analysis.

10.7 PRIMARY EFFICACY VARIABLES

- **Phase Ib:** AE that constitute DLT.

- **Phase II:** Response assessment based on IWCLL (Hallek et al., 2008).

10.8 SECONDARY EFFICACY VARIABLES

- PFS, TFS and OS. Clinical parameters that will be measured from initiation of treatment until occurrence of the event.

- MRD measured by multiparameter (4 colors) flow cytometry.

11. REPORTING OF ADVERSE EVENTS

11.1 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to GA101 – Obinutuzumab and Ibrutinib, all events of death, and any study specific issue of concern.

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

11.2 ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

Disease progression is not an adverse event; rather it may be the cause of an adverse event. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression must be reported as all other adverse events. The term "Disease progression" should never be used as an adverse event term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL/SLL that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be

considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

11.2.1 Serious Adverse Events

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and

its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

11.2.2 Severity Criteria

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. Refer to appendix 3 for the grading of hematologic AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subjects experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death.

11.2.3 Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Unlikely: The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Related: The AE is clearly related to use of the investigational product.

11.2.4 Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3 DOCUMENTING AND REPORTING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS BY INVESTIGATORS.

The investigator is responsible for ensuring that all AEs and SAEs, that are observed or reported during the study, are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate IRB(s), and Pharmacyclics. in accordance with CFR 312.32 (IND Safety Reports).

11.3.1 Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes,

There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the subject’s clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment; and/or the AE abates or

resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.

No,

Evidence exists that the AE has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected AEs are those not listed in the Package Insert (P.I.) or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the P.I. or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

11.3.2 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

11.3.3 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per the SAE reporting timelines.

- **Major Hemorrhage**

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*.
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE.

Events meeting the definition of major hemorrhage will be captured as an event of special interest.

- **Intracranial Hemorrhage**

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage, and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

- **Pregnancy**

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The

Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported to Pharmacyclics per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

- **Other Malignancies**

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

11.3.4 Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) (Appendix 8) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to
  study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

11.3.5 Reporting to Regulatory Agencies:

It is the responsibility of the Investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.4 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

11.4.1 Procedures

11.4.1.1 All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All adverse events (with the exception of disease progression) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug. Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided. All Grade 3 or Grade 4 adverse events considered related to study drug must be followed until recovery to baseline or Grade ≤1. Progressive disease should NOT be reported as an adverse event, but instead symptoms/clinical signs of disease progression may be reported. Otherwise, all events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

11.4.2 Eliciting Adverse Events

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

- "How have you felt since your last clinical visit?"

- "Have you had any new or changed health problems since you were last here?"

11.4.3 Specific Instructions for Recording Adverse Events

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

11.4.3.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

11.4.3.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 12.2.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

11.4.3.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

11.4.3.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or

surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

11.4.3.5 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior Ibrutinib and/or GA101 - Obinutuzumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

11.4.3.6 Safety Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Pharmacyclics and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Pharmacyclics will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

11.4.3.7 Adverse Events of Special Interest (AESIs)

AEs of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the Product

The following AEs are considered of special interest and must be reported to the Sponsor expeditiously (see Section 12.3.2.9 for reporting instructions) irrespective of regulatory seriousness criteria:

- TLS (all grades)

- Serious infections

- Serious neutropenia
- Serious infusion related reactions
- Hepatitis B reactivation

11.4.3.8 Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject exposure to the study drug, eg, name confusion).

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

11.4.3.9 Prohibitions and Restrictions

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, Ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure.

For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

11.4.4 Adverse Event Reporting to Pharmacyclics

The investigator must report all SAEs to Pharmacyclics within the timelines specified below. In addition, any protocol specified adverse event reporting requirements should be adhered to, including any Adverse Events of Special Interest ("AESI").

All SAE notifications must be sent to Pharmacyclics via email or fax to the following Pharmacyclics Drug Safety Contact Information:

Email: AEintakeCT@pcyc.com

US Fax: 1-408-215-3500

Reporting timeframe:

The Investigator must report all serious unexpected and suspected adverse reaction to Pharmacyclics in parallel to the applicable regulatory agency submissions. The notifications to Pharmacyclics will include a cover letter detailing the status of the submission to applicable regulatory agency along with submission date.

The Investigator must report all other SAEs and AESIs not meeting the 7 day/15 day regulatory reporting requirements stated above, to Pharmacyclics as soon as possible but no later than 15 calendar days from the Investigator's first awareness date.

Reporting form: The investigator must report such SAEs using the standard FDA Medwatch (Form 3500A) (Appendix 8), Suspect Adverse Reaction Report (CIOMS Form 1) or IRB Reporting Form.

11.4.4.1 Additional reporting requirements to Pharmacyclics include the following:

Any reports of pregnancy following the start of administration with Ibrutinib and within the follow-up period (for female subjects within one year after the last dose of

Ibrutinib or the partner of a male subject within three months of completing therapy) will be transmitted to Pharmacyclics within 24 hours of the Awareness Date.

All non-serious AEs originating from the study will be forwarded to Pharmacyclics:

- Quarterly after Ibrutinib registration

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate subject demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

11.4.4.2 Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e., D.O.B. initial, subject number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Pharmacyclics may contact the reporter for additional information, clarification, or current status of the subject for whom and AE was reported. For

questions regarding SAE reporting, you may contact the Pharmacyclics Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Pharmacyclics Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

11.4.5 Data Safety and Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will review the safety data once the study is opened. Summary reports will be submitted to the DSMB as indicated below:

- After completion of Phase IB and prior to initiation of the Phase II.
- After the enrollment of the first 10 subjects in the Phase II, i.e., at the point at which the decision is made to proceed, or not, to the enrollment of the second 10 subjects.

The summary reports will be written in a standard DSMB report format and will be prepared by the study statistician.

11.5 STUDY CLOSE-OUT

Any study report should be submitted to Pharmacyclics. This includes all IND annual reports (If applicable) and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Pharmacyclics.

12. RETENTION OF RECORDS

The ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, subject records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

13. PROTOCOL AMENDMENTS

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form protocol must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

14. PUBLICATION OF STUDY RESULTS

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

15. STUDY DISCONTINUATION

Per the IST Contract, the Investigator reserves the right to terminate the study at any time. Should this be necessary, both the Investigator will arrange discontinuation procedures in partnership with Pharmacyclics. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (e.g., is listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to subject well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

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Appendix 1 CDC Guideline for Interpretation of Hepatitis B Serology Test Results

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

CDC

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Appendix 2 Study Flowchart

Schedule of Events																	
Treatment Course	**Screening**	**Treatment Period**															
		Cycle 1								**Cycle 2 - 6**							
Visit Number	1	2	3	4	5	6	7	8	9								
Day of the cycle		Day 1	Day 2	Day 3	Day 4[v]	Day 8	Day 15	Day 22	Day 28	Day 1	Day 2	Day 3	Day 4[v]	Day 8	Day 15	Day 22	Day 28[w]
Visit window	≤28 days prior to visit 2	±3d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±3d	±1d	±1d	±1d	±1d	±1d	±1d	±1d
Informed Consent	X																
Enrollment Criteria	X																
Infectious disease screening[a]	X																
Medical and CLL history	X																
MD PE/VS/Ht and Wt	X	X								X							
Nurse Encounter (Infusion Center)			X			X	X										
Lymph node and organ examination	X	X								X							
RAI stage[b]	X	X								X							
Constitutional Symptoms	X	X	X		X	X	X	X		X	X		X	X	X	X	X
ECOG Performance Status	X	X								X							
CBC/Differential/platelets	X	X	X		X	X	X	X		X			X	X	X	X	X
Absolute T cell count[c]	X[d]																
PT/PTT/INR	X																
Comprehensive Chemistry Panel[e]	X	X	X		X	X	X	X		X			X	X	X	X	X
Electorcardiogram[f]	X																
CT, MRI or PET Scan[g]	X																
Adverse Events Screen		X	X		X	X	X	X		X	X		X	X	X	X	X
Concomitant Medication	X	X								X							
Obinutuzumab administration (Infusion Center)		X	X			X	X			X							
Ibrutinib Dispensing[j]		X								X							
Bone marrow aspirate and biopsy	X[k]																
MRD assessment in prheripheral blood (Flow cytometry)																	
Quantitative inmunoglobulins[p]	X																
β2-microglobulin	X																
Cytogenetics/FISH[q]	X																
Full inmunophenotyping[r]	X																
Pregnancy test[s]	X									X							
CLL Prognostic Factors/Correlatives/Data Analysis (Castro's Lab)																	
Sample Collection/Processing		X	X			X											
ZAP-70 Flow Cytometry[u]	X																
VH Immunoglobulin gene mutation[r]	X																
Data Analysis and Statistics																	

Schedule of Events				
Treatment Course	**Study Response Assessment**	**Long Term Follow Up (LTFU)**		**End of Study**
	At 2 months after completion of study treatment	**Every 3 months for 9 months (after response assessment) follow by every 6 months until initiation of new treatment for CLL, consent withdrawal or death.**	**At 3 years after completion of study treatment**	**The evaluation of the end of study will be performed (within 30 days) due to initiation of new treatment for CLL or consent withdrawal.**
Visit Number				
Day of the cycle				
Visit window				
Informed Consent				
Enrollment Criteria				
Infectious disease screening[a]				
Medical and CLL history				
MD PE/VS/Ht and Wt	X	X		X
Nurse Encounter (Infusion Center)				
Lymph node and organ examination	X	X		X
RAI stage[b]	X	X		X
Constitutional Symptoms	X	X		X
ECOG Performance Status	X	X		X
CBC/Differential/platelets	X	X		X
Absolute T cell count[c]	X			X
PT/PTT/INR				
Comprehensive Chemistry Panel[e]	X	X		X
Electorcardiogram[f]				
CT, MRI or PET Scan[g]	X	X[h]	X[i]	X
Adverse Events Screen	X	X		X
Concomitant Medication	X	X		X
Obinutuzumab administration (Infusion Center)				
Ibrutinib Dispensing[j]		X		
Bone marrow aspirate and biopsy	X[l]		X[m]	X[n]
MRD assessment in prheripheral blood (Flow cytometry)		X[o]		
Quantitative inmunoglobulins[p]	X	X		X
β2-microglobulin	X	X		X
Cytogenetics/FISH[q]	X			X
Full inmunophenotyping[r]				
Pregnancy test[s]	X	X[t]		X
CLL Prognostic Factors/Correlatives/Data Analysis (Castro's Lab)				
Sample Collection/Processing				
ZAP-70 Flow Cytometry[u]				
VH Immunoglobulin gene mutation[r]				
Data Analysis and Statistics	X	X		X

a. HIV-1/2, HAAb, HBsAg, HBsAb, HBcAb (IgG, IgM), HCVAb. (If HBcAb is positive, a HBV-DNA viral load qPCR test will be performed).
b. RAI staging system includes detailed assessment of liver, spleen, lymph nodes and hematologic laboratories (Hb, Hto and platelets).
c. Including CD3+, CD4+, and CD8+ populations
d. Or on day 1 of cycle 1
e. Comprehensive Chemistry panel (CMP) that include: ALT, AST, LDH, alkaline phosphatase, total bilirubin, BUN, albumin, creatinine, uric acid, total protein, glucose, calcium, sodium, potassium, chloride, HCO3, phosphorus.
f. As clinically indicated.
g. Of the chest, abdomen and pelvis.
h. CT, MRI or PET scan in those subjects with clinical or laboratory alterations that suggest disease progression based on IWCLL criteria.
i. For subjects that maintain a CR, we will perform additional CT scans of the chest, abdomen and pelvis after 3 years of completion of study treatment in order to assess response based on clinic and radiologic parameters, and discuss the possibility of Ibrutinib discontinuation.
j. Pills will be dispensed to subjects at each monthly visit during the 6 cycles and later, every 3 months during the follow up period. Subjects take 420 mg po daily.
k. Within 90 days of treatment initiation.
l. A unilateral bone marrow biopsy and aspirate will be performed using multiparameter (4 colors) flow cytometry and histologic staining at 2 months after completion of study treatment (response assessment) in order to satisfy the IWCLL criteria.
m. For subjects that maintain a CR, we will perform an additional bone marrow biopsy and aspirate after 3 years of completion of study treatment in order to assess MRD and discuss the possibility of Ibrutinib discontinuation.
n. A unilateral bone marrow biopsy and aspirate will be performed to confirm CR (MRD assessment) using multiparameter (4 colors) flow cytometry and histologic staining at the end of study in subjects that meet clinical and laboratory parameters for CR in order to satisfy the IWCLL criteria.
o. For subjects that maintain a CR, we will perform a MRD assessment in peripheral blood using multiparameter (4 colors) flow cytometry at 6 and 12 months in order to assess MRD.
p. IgG, IgA, IgM.
q. FISH Panel to include 11p, 13q, 17p analysis.
r. Full immunophenotyping of blood mononuclear cells: CD3, 4, 5, 8, 19, 20.
s. Serum βhCG monthly in women child bearing age.
t. During 12 months after the last dose of GA101 – Obinutuzumab.
u. Performed at any time prior to therapy.

v. All subjects will return to the clinic on day 4 of cycle #1 for laboratory assessment in order to evaluate the risk for TLS. The laboratory assessment will be made based on the Cairo-Bishop Laboratory definition (Coiffier B et al., 2008) (Appendix 4). Those subjects with laboratory evidence of TLS will return to the clinic on the day 4 of the subsequent cycles to continue follow-up of laboratory parameters.
w. Visit at last day of the study treatment (Day 28, Cycle #6).

Appendix 3 IWCLL Guideline for Grading Scale for Hematological Toxicity in CLL Studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/μL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20 000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L [20 000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches $< 1 \times 10^9$/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $< 1 \times 10^9$/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

Appendix 4 Cairo-Bishop Clinical Grading and Laboratory Definition of Tumor Lysis Syndrome

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change From Baseline
Uric acid	≥ 476 μmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25%decrease

NOTE. Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy.

Appendix 5 Inhibitors or Inducers of CYP3A4/5

http://medicine.iupui.edu/clinpharm/ddis/main-table/

Appendix 6 Cumulative Illness Rating Scale-Geriatric (CIRS Score)

http://eforms.moffitt.org/cirsgScore.aspx

Appendix 7 Current NCI Common Terminology Criteria for Adverse Events (CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 8 FDA MedWatch 3500 Form

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149236.htm

Appendix 9 Safety Reporting Fax Cover Sheet

PHARMACYCLICS SUPPORTED RESEARCH

AE/SAE FAX No:

Alternate Fax No:

Page 1 of ___

Pharmacyclics Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/_____/_____ dd / mmm / yyyy
Follow-up Report Date	_____/_____/_____ dd / mmm / yyyy
Subject Initials (Please enter a dash if the subject has no middle name)	____ - ____ -____

SAE or Safety Reporting questions, contact Pharmacyclics Safety:

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.