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A Phase I clinical trial to determine the safety and tolerability of UC-961 (Cirmtuzumab), an anti-ROR1 monoclonal antibody, for the treatment of patients with relapsed or refractory Chronic Lymphocytic Leukemia who are ineligible for chemotherapy

PRINCIPAL INVESTIGATORS

Catriona Jamieson, MD/PhD
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0987
Phone: 858-534-7128
Fax: 858-822-6288
Email: cjamieson@ucsd.edu

Michael Choi, MD (Co-PI)
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0820
Phone: (858) 534-1765
Fax: (858) 534-5620
Email: mychoi@ucsd.edu

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Investigational Product: UC-961 (Cirmtuzumab)

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IND Holder: Thomas Kipps, MD/PhD

NCT Number: 02222688

LIST OF INVESTIGATORS

PRINCIPAL INVESTIGATORS

Catriona Jamieson, MD/PhD
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0987
Phone: 858-534-7128
Fax: 858-822-6288
Email: cjamieson@ucsd.edu

Michael Choi, MD (Co-PI)
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0820
Phone: (858) 534-1765
Fax: (858) 534-5620
Email: mychoi@ucsd.edu

STUDY STATISTICIANS

Karen Messer, PhD
Biostatistics
3855 Health Sciences Drive, #0901
La Jolla, CA 92093-0901
Phone: 858-822-4334
Email: kmesser@ucsd.edu

Hongying Li, PhD
Biostatistics
3855 Health Sciences Drive, #0901
La Jolla, CA 92093-0901
Phone: 858-822-4818
Email: hol031@ucsd.edu

CO-INVESTIGATOR(S)

Januario Castro, MD
Hematology/Oncology
3855 Health Sciences Drive, #0960
La Jolla, CA 92093-0960
Phone: 858-822-6386
Fax: 858-822-6844
Email: jecastro@ucsd.edu

Dennis Carson, MD
Medicine
9500 Gilman Drive #0695
La Jolla, CA 92093-0695
Phone: 858-534-5408
Fax: 858-246-1586
Email: dcarson@ucsd.edu

Thomas Kipps, MD/PhD
Hematology/Oncology
3855 Health Sciences Drive, #0820
La Jolla, CA 92093-0820
Phone: 858-534-5400
Fax: 858-534-5620
Email: tkipps@ucsd.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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PROTOCOL SYNOPSIS

INVESTIGATIONAL AGENT	UC-961
TITLE	A Phase I clinical trial to determine the safety and tolerability, of UC-961 (Cirmtuzumab), an anti-ROR1 monoclonal antibody, for the treatment of patients with relapsed or refractory Chronic Lymphocytic Leukemia who are ineligible for chemotherapy
PROTOCOL NUMBER	HRPP #140141
PHASE OF DEVELOPMENT	Phase I
STUDY OBJECTIVES	*Primary Objective:* 1. To determine the maximum tolerated dose (MTD) or biologically active dose of UC-961 when given bi-weekly for 4 doses to patients with relapsed or refractory chronic lymphocytic leukemia (CLL). *Secondary Objectives:* 1. To determine the safety and tolerability of UC-961 by ongoing evaluation of adverse events (AEs). 2. To assess clinical activity based on international working group guidelines (iwCLL 2008). *3.* To assess clinical activity by evaluating progression free survival. *Exploratory Objectives:* 1. To assess the mechanism of action of UC-961 through immunophenotypic, genomic, proteomic and pharmacodynamic studies.
STUDY ENDPOINTS	**Primary Endpoint** Rate of dose limiting toxicities (DLTs) and the maximum tolerated dose or biologically active dose. **Secondary Endpoints** 1. Treatment-emergent adverse events (description, timing, grade [CTCAE v4.03], severity, seriousness, and relatedness) 2. Clinical response rate, determined by International Working Group in CLL (iwCLL) criteria. 3. Progression free survival, as determined by iwCLL criteria **Exploratory Endpoints** 1. ROR1 receptor density on circulating bulk tumor cells and leukemia stem cells (immunophenotypic assay) 2. Plasma pharmacokinetics of UC-961 3. Level of circulating antibodies against UC-961 4. Multiplexed assays of focused CLL signaling pathways via qPCR array and targeted sequencing. 5. ROR1 related Protein assays via western blot and quantitative proteomics.
STUDY DESIGN	This is a first in human phase I study of UC-961, a humanized anti-ROR1 monoclonal antibody, for patients with relapsed or refractory CLL. As this is a Phase 1 study for safety, no formal sample size or power calculations will

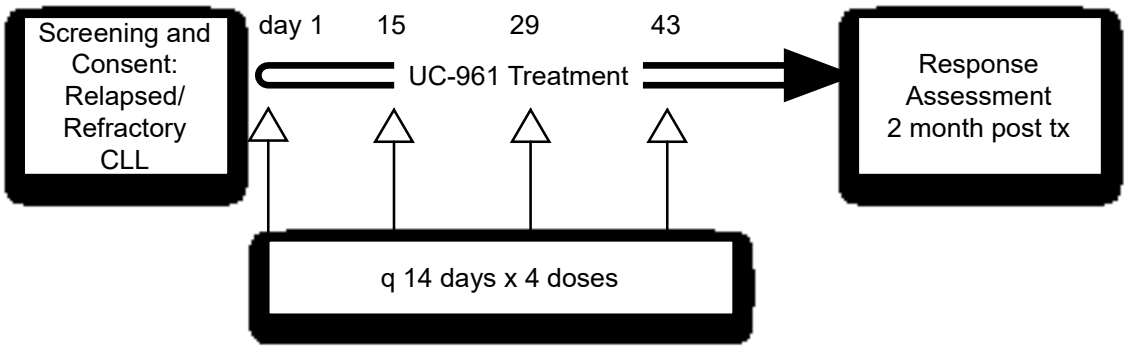
	be made and the 3+3 phase I dose escalation trial design will be used. The starting dose is 15 µg/kg. There is intra-patient dose escalation in the first 4 cohorts, followed by the standard 3+3 design for the next 5 cohorts until an MTD or biologically active dose is reached. If there is a grade ≥ 2 adverse event in the cohorts with intra-patient dose escalation, the trial will switch to the standard 3+3 design without intra-patient dose escalation for all cohorts. An expansion cohort of 6 patients at that dose will also be examined, so that a total of 12 patients will be evaluable at the MTD or biologically active dose.
NUMBER OF PATIENTS	The trial may be completed after 33 patients have been enrolled, based on 8 cohorts with a total of 12 patients at the MTD/biologically active dose. If the dose escalation switches to standard 3+3 design, then up to 78 patients will be enrolled, based on 3-6 patients per cohort for 12 cohorts (if all dose levels require cohorts without intra-dose escalation), and a total of 12 patients at the MTD/biologically active dose.
INCLUSION CRITERIA	1. Ability to understand and the willingness to sign a written informed consent. 2. Clinical and phenotypic verification of B cell CLL and measurable disease. Immunophenotyping of the leukemic cells (blood or marrow) must demonstrate a monoclonal (or light chain positive) B cell population with immunophenotype consistent with CLL (e.g., co-expressing CD19 and CD5). 3. Relapsed or refractory disease, defined by failure to achieve a partial response within 6 months of initiation of therapy, or a 50% increase of baseline disease measurements after achieving a clinical response. 4. Not amenable to approved therapies. 5. Prior Therapy: Must have progressed after purine-analog or alkylator based therapy, or be considered inappropriate for chemo-immunotherapy due to one of the following: • Del 17p, which is associated with poor response to chemo-immunotherapy, or • Age greater than 70, or • Age greater than 65 with one of the following: o Grade ≥ 3 neutropenia, anemia, or thrombocytopenia attributable to cumulative myelotoxicity from prior administration of cytotoxic agents (as documented by bone marrow biopsy obtained since last prior therapy), or o Clinically apparent autoimmune cytopenia which may be exacerbated by fludarabine therapy, or o Estimated creatinine clearance (eC_{Cr}) <70 mL/min (as determined by the Cockcroft-Gault method), or o ECOG performance status greater than 0. 6. Has recovered from the toxic effects of prior therapy to their clinical baseline. 7. Subjects must be aged 18 years or older. 8. Both men and women of all races and ethnic groups are eligible for this trial. 9. Women of childbearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree not to become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of

	the study and until 10 weeks after the final dose of UC-961 (expected to be greater than 5 half-lives from pre-clinical data). 10. Subjects must have at least one of the following indications for treatment: • Symptomatic or progressive splenomegaly; • Symptomatic lymph nodes, nodal clusters, or progressive lymphadenopathy; • Progressive anemia (hemoglobin ≤ 11 g/dL); • Progressive thrombocytopenia (platelets ≤ 100 x 109/L); • Weight loss > 10% body weight over the preceding 6 month period; • Fatigue attributable to CLL; • Fever or night sweats for > 2 weeks without evidence of infection; • Progressive lymphocytosis with an increase of > 50% over a 2-month period or an anticipated doubling time of less than 12 months. 11. Subjects must have an ECOG performance status of 0-2. 12. Adequate hematologic function: • Platelet count ≥ 50,000/μL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate); AND • Hemoglobin ≥ 8.0 g/dL (may be supported by erythropoietin); AND • Absolute neutrophil count > 1000 /uL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate). 13. Adequate renal function: • Serum creatinine <1.5 times upper limit of normal; OR • Calculated Creatinine clearance (CrCl) ≥ 40 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)]. 14. Adequate hepatic function: • Total bilirubin ≤ 2.5 times upper limit of normal; AND • ALT ≤ 2.5 times upper limit of normal. 15. Adequate coagulation tests: • Prothrombin time international normalized ratio (INR) ≤ 2; AND • Partial thromboplastin time ≤ 1.66 times upper limit of normal.
EXCLUSON CRITERIA	1. Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. IgG may cross the placental barrier and cause fetal B- and T-lymphocyte depletion. Therefore, women of child-bearing age must obtain a pregnancy test, and pregnant or breast feeding females are excluded. 2. Patients who are currently receiving another investigational agent are excluded. 3. Patients who have had chemotherapy (e.g., purine analogues, alkylating agents), immunotherapy, radiation therapy, or participation in any investigational drug treatment within 4 weeks of initiation of UC-961 or at any time during the study.

	4. Patients who have had prior (within 8 weeks of initiation of UC-961) or concurrent antibody therapy directed against CLL (i.e., Rituxan® and Campath®) 5. Current infection requiring parenteral antibiotics. 6. Active infection with HIV, HBV, or HCV. 7. Concurrent malignancy or prior malignancy within the previous 3 years (other than completely resected carcinoma in situ, prostate cancer, or localized non-melanoma skin cancer). 8. Known central nervous system (CNS) involvement by malignancy. 9. Untreated autoimmunity such as autoimmune hemolytic anemia, or immune thrombocytopenia. 10. Known uncompensated hypothyroidism (defined as TSH greater than 2x upper limit of normal not treated with replacement hormone). 11. Presence of more than 55% pro-lymphocytes in peripheral blood. Patients with Richter's transformation are not excluded. 12. Insufficient recovery from surgical-related trauma or wound healing. 13. Impaired cardiac function including any of the following: • Myocardial infarction within 6 months of starting study drug; • A past medical history of clinically significant ECG abnormalities, including QTc 481 ms or greater. • Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen) 14. Patients who in the opinion of the investigator may be unable to comply with the safety monitoring requirements of the study.
DURATION OF INVESTIGATIONAL AGENT ADMINISTRATION AND STUDY PARTICIPATION	Duration of UC-961 administration is 8 weeks, consisting of 4 doses of UC-961, given once every 14 days. Patients may remain on the clinical trial protocol until one of the following: • Clinical or radiographic progressive disease (See Section 12). • Adverse Events requiring removal from study (See Section 13). • Refusal of further protocol therapy by patient/parent/guardian • Non-compliance that in the opinion of the investigator does not allow for ongoing participation. • Physician determines it is in the patient's best interest to discontinue participation in the clinical trial. • Completion of all clinical trial procedures. Participation in the study and long-term follow-up will continue until one of the following: • Death. • Loss to follow-up. • Withdrawal of consent for any further data submission. • Progression requiring initiation of subsequent therapy.
STUDY DRUG ADMINISTRATION	UC-961 is administered by intravenous infusion on Day 1 of each 14 day cycle. The initial dose level is 15 µg/kg, based on preclinical studies.
CRITERIA TO EVALUATE SAFETY	Safety will be determined by Principal Investigator, and will be assessed according to the NCI Common Terminology Criteria for Adverse Events

	version 4.03 (NCI CTCAE v4.03) for non-hematologic toxicity and modified iwCLL criteria for hematologic toxicity.
CRITERIA TO EVALUATE EFFICACY	Clinical response rate is the percentage of patients meeting criteria for partial response, nodular partial response, or complete response based on iwCLL criteria. Progression free survival is according to iwCLL definition.

SCHEMA



1.0 BACKGROUND

1.1 Introduction/Rationale for Development

Chronic Lymphocytic Leukemia (CLL) is the most prevalent hematologic cancer in the western hemisphere (Gribben and O'Brien, 2011). At this time, it is considered incurable. Treatment regimens that combine chemotherapy and immunotherapy (eg: Fludarabine + Cyclophosphamide + Rituximab) have produced high response rates and have been associated with an improved overall survival (Hallek et al., 2010). However, patients inevitably relapse and many patients cannot tolerate chemoimmunotherapy regimens in the relapsed/refractory setting due to age, comorbidities, or compromised bone marrow function (Brown, 2011). Obinutuzumab (GA-101) in combination with chlorambucil was approved by the FDA in November 2013 based on efficacy as front-line therapy for patients older than 65. However, responses were not durable with this treatment either (*Goede et al.*, 2014).

Ibrutininb, an oral agent that inhibits the B-cell receptor associated tyrosine kinase, Bruton's tyrosine kinase (BTK), has been approved by the FDA for the treatment of patients with relapsed CLL (Byrd et al., 2013). According to the package insert, the overall response rate is 58.3%, consisting of partial responses with no complete responses and duration of response ranging from 5.6 to 24.2 months. Ibrutinib intolerance related to diarrhea in 62% of patients and thrombocytopenia in over 20% of patients with bleeding events in 63% of patients and subdural hematomas in 4% of patients, infections, fatigue, renal insufficiency and other side effects have limited the number of patients amenable to chronic therapy. In addition, disease progression associated with resistance to ibrutinib has been noted to develop over time. Emergence of mutations in leukemia initiating cells renders patients resistant to ibrutinib therapy (*Woyach et al.*, 2014). Thus, to maximize the therapeutic potential of tyrosine kinase and other inhibitors, to prevent therapeutic resistance, and to obviate relapse, development of combination therapies has become the mainstay of recent CLL eradication strategies. Thus, development and testing of novel therapeutic strategies, such as UC-961, which selectively target tumor initiating cells in CLL, are warranted.

ROR1 (receptor tyrosine kinase-like orphan receptor 1) is a transmembrane protein that is expressed on the surface of CLL cells, from nearly all patients with CLL (94% based on flow cytometry analysis of the CLL research consortium) (Fukuda et al., 2008). It shares homology with other receptor tyrosine kinases, and is believed to participate in Wnt signaling, based on homology to the Wnt receptor, Frizzled. However, its precise function is unknown, and although the protein has a putative kinase domain, it may be a pseudo-kinase serving as a cofactor for other signaling proteins, leading to phosphorylation of Akt.

Importantly, ROR1 is not expressed on the surface of normal adult tissues, with the possible exception of a rare subset of precursor B cells, called hematogones, which are typically observed in the marrow of pediatric patients or patients recovering from myeloablative therapy, but are found in minute levels (<1% of mononuclear cells) in the marrow of healthy adults (Broome et al., 2011). ROR1 plays a key role in fetal development, but based on exhaustive profiling studies in human hematopoietic stem cells, it is no longer detectable by the second trimester fetal liver stage, and is not on marrow stem cells or normal adult tissues (Fukuda et al., 2008, Hudecek et al., 2010, Masiakowski and Carroll, 1992, Matsuda et al., 2001, Zhang et al., 2012). As such, it represents an ideal target for immunotherapy, due to a potential lack of cross-reactivity with normal adult tissues, reduced immunosuppression based on lack of targeting or normal myeloid or lymphoid cells.

UC-961 (Cirmtuzumab) is a fully-humanized monoclonal antibody designed to bind the extracellular immunoglobulin-like domain of ROR1 with high-affinity. Initial preclinical studies (described below) show that it is an ideal potential therapy due to the following features:

- High affinity for cell-surface ROR1
- Activity against cancer cells that express ROR1, which include cancer-stem cells, with a mechanism of cell death that appears to be due to inhibition of Wnt5a/ROR1 mediated Akt signaling and non-canonical Wnt signaling, both important pathways for the survival of CLL cells (*Fukuda et al.*, 2008, *Cui et al.*, 2013, *Widhopf et al.*, 2014).
- Lack of cross reactivity with normal adult tissues
- Reduced immunosuppressive potential based on lack of targeting most normal lymphoid or myeloid cells
- Low immunogenic potential due to substantial humanization of the mAb framework

Based on this biological rationale and the preclinical activity, an open label, phase I clinical trial is proposed herein to evaluate the safety and efficacy of UC-961 for the treatment of patients with relapsed or refractory CLL.

1.2 UC-961 Development and preclinical activity in CLL models

UC-961 is the result of testing and optimization of anti-human ROR1 monoclonal antibodies initially generated by classical hybridoma and phase display technologies. Initially, mice were inoculated with DNA, protein, adenoviral constructs of ROR1, cytokines, and immune stimulatory agents to generate anti-human ROR1 antibodies. These initial murine anti-ROR1 monoclonal antibodies (designated 4A5 and D10) have been tested using *in vivo* and *in vitro* test systems. When tested in an immune deficient murine model, D10 consistently demonstrated potent activity against human CLL patient samples. At this time, the D10 mAb has been tested against human primary CLL cells in hundreds of mice and has consistently eliminated the human cells in a dose dependent manner. Mouse models have included immune-deficient mice with CLL cell xenografts, as well as immune competent transgenic models that spontaneously generate leukemic cells expressing the human ROR1 protein. In these models, the D10 mAb, but not control IgG or 4A5, was able to inhibit the development and expansion of the ROR1 positive leukemic B cells in the blood and spleen of recipient animals. A dose of 10 mg/kg was used.

To improve binding affinity, chimeric truncated ROR1 screening proteins were then used to pan for high affinity anti-human ROR1 mAbs generated through the use of a proprietary enhanced phage library (Alere, Inc., San Diego, CA). High affinity antibodies that bind to the same epitope as D10 and more importantly exhibit the same anti-leukemic activity of this prototypical mAb were

identified. After cell line and animal testing and kinetic binding analysis, we chose a single antibody designated UC-99961 (UC-m961) for advancement in pre-clinical development.

UC-m961 was humanized by BioAtla, Inc. (San Diego, CA). They employed a proprietary recombinant framework grafting technology to generate humanized antibodies that retain the biologic activities of the parent mAb. Over 20 different light and heavy chain humanized variant ROR1 targeting mAbs were screened.

After conducting head-to-head analyses of several candidate humanized anti-ROR1 mAb, a final humanized mAb construct, designated UC-h961, was selected. This humanized mAb is essentially humanized except for a few amino acids adjacent to the CDR borders and framework 4, which for the most part are tucked under CDR3 in an immune protected site. UC-h961 will hereafter be referred to as UC-961 or Cirmtuzumab.

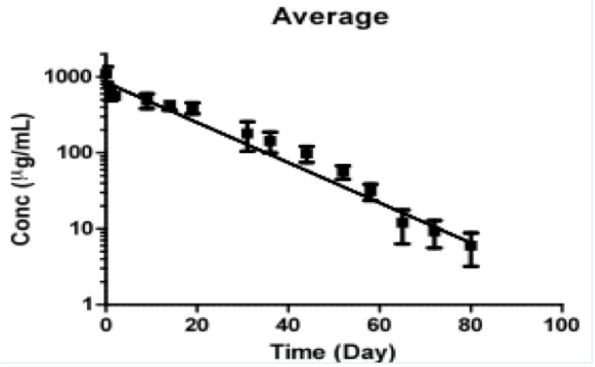
1.2.1 Pre-Clinical Pharmacology and Toxicology

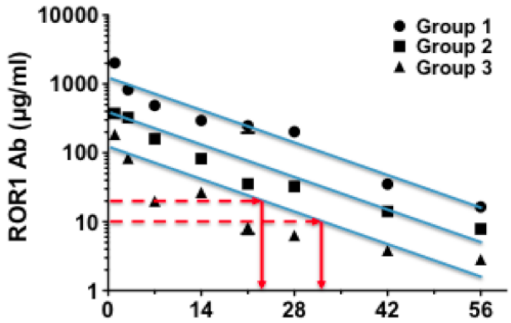
To support the UC-961 phase I clinical trial, a comprehensive single-species pharmacology/toxicology study was conducted in rats. In this study, groups of animals (15 of each sex) received UC-961 at doses of 40, 120 and 400 mg/kg given weekly for 5 doses over 28 days. Three days following the final product administration, 20 animals (10 of each sex) in each dosing cohort were sacrificed and the remaining animals in the recovery phase sacrificed on day 56. During the study, parameters measured included twice-daily clinical signs, food consumption, weekly body weights, ophthalmic examinations (pretreatment, after last dose and last week of drug-free period) urinalysis (prior to sacrifice) and clinical pathology indices including serum chemistries, hematology and coagulation studies (prior to sacrifice). Safety pharmacology measurements including functional observation batteries were conducted weekly. Finally, full necropsy and a complete microscopic analysis was performed on all animals in all groups and a select panel of organs including the liver, spleen, heart, kidneys, brain and ovaries were weighed.

In all dosing cohorts, the UC-961 drug product was well tolerated by the treated rats. No adverse events were noted during the conduct of the study. At terminal sacrifice gross pathologic exams were normal and no untoward effects of product administration were noted.

1.2.2 Pre-Clinical Pharmacokinetics and Metabolism

Comprehensive pharmacokinetic studies were conducted in both immune deficient mice and in Wistar rats. Immune deficient mice (Rag2-/-γc-/-) were injected i.v. (1 mg/mouse), blood was drawn at different time points (left panel) and levels in plasma were measured by ELISA. One-compartment PK description of average data reveals that t1/2 = 11.4 days V= 1.18 mL (47 mL/kg) and CL = 0.072 mL/day (0.12 mL/hr/kg). For studies in rats, cohorts of animals received 400, 120 and 40 mg/kg of UC-961 mAb and were screened at 14, 28, 42 and 56 days after treatment. The





results (right panel) indicate that the UC-961 was removed from the rats with an apparent half-life of 7 days irrespective of the initial dose of administered mAb.

1.3 Rationale for Dose Selection

The starting dose of 15 μg/kg is based upon international guidance for starting dose selection for agents in cancer patients (ICH S9 2010 Guidance for Industry) as well as the guidance on biologics including monoclonal antibody therapies with minimal species cross-reactivity (Agoram, 2009). Since UC-961 is specific for human ROR1 and the target epitope is only found in primates, there are no standard animal models that can be used for initial dose determination.

Calculation of the initial UC-961 dose took into consideration the estimated average amount of UC-961 required to saturate the ROR1 surface molecules on circulating CLL cells. This calculated dose is based on the amount of mAb required to saturate the ROR1 surface molecules on the CLL cells in the blood multiplied by the number of leukemic cells in the blood.

The amount of antibody required to saturate the ROR1 surface molecules on CLL cells was determined using 2-fold dilutions of the UC-961 antibody, which were used to bind CLL cells that subsequently were counter-stained with saturating amounts of fluorescein-conjugated anti-human antibody to detect cell-bound UC-961 by flow cytometry. We determined the amount of UC-961 required to saturate binding of CLL cells. When the primary antibody is not saturating, the relative fluorescent signal is proportional to amount of antibody bound to the cells, which in turn is proportional to the number of ROR1 surface molecules. We determined the amount of UC-961 required to achieve 30% maximal binding to CLL cells. We have analyzed primary CLL cells in this manner from more than 15 patients, and have extrapolated these results to over 800 clinical samples based on mean fluorescent intensity (MFI) of CLL cells stained at saturation. For a representative patient sample, approximately 3.3 ng of UC-961 was required to saturate the 30% of ROR1 surface molecules on 500,000 CLL cells, as assessed by flow cytometry.

Along with the number of ROR1 surface molecules, the circulating CLL cell concentration may vary widely depending on the clinical parameters of the disease. CLL patients may have wide-ranging numbers of circulating CLL cells, from the thousands to over several hundred thousand.

To be inclusive and have a weight-based dosing regimen, we calculated the initial dose for a patient with a low body weight and a high circulating CLL count and high number of ROR1-surface molecules. Therefore, for a patient with an absolute lymphocyte count of 20,000/mm3, body weight of 50 kg, and circulating blood volume of 5L, the calculation for a first dose to saturate 30% of circulating ROR1 in such a patient is as follows:

3.3 ng / 500,000 cells * 20,000 cells/mm^3 * 1000mm^3/ml * 5000 ml / 50kg = 13.2 µg/kg

Therefore, we set the starting dose at 15 µg/kg (rounded up to account for variability of the ROR1 MFI between other CLL samples).

Similarly, we calculated the dose that would occupy 60% of ROR1 on CLL cells in a typical patient. Based on preclinical data, 8.6 ng occupied 60% of ROR1 in 500,000 CLL cells. Based on calculation, the following dose saturates 60% of ROR1 in a patient with an absolute lymphocyte count of 20,000/mm3, body weight of 50 kg, and circulating blood volume of 5L:

8.6 ng / 500,000 cells * 20,000 cells/mm^3 * 1000mm^3/ml * 5000 ml / 50kg = 34.4 µg/kg

A two-fold increase in the rounded starting dose of 15 µg/kg would be 30 µg/kg, which is at or below the amount required to achieve 60% saturation of ROR1 on CLL cells in the blood.

Finally, although there is no species cross-reactivity, the starting dose is well below the NOEL for rodent studies for any non-specific activity. In the 28-day rat study, the highest dose group was 400 mg/kg for both males and females. No adverse events were noted, and no organ toxicity was noted on pathologic exams after terminal sacrifice. Therefore the STD_{10} was not reached. The rat NOEL was therefore determined to be 400 mg/kg, which in theory would predict a human equivalent dose of 40 mg/kg. However, as the critical amino acids required for binding of the anti-ROR1 mAb are only found in primates, the starting dose is also based on an estimate of the amount of antibody needed to saturate the ROR1 receptors on circulating CLL cells.

1.4 Overview of Proposed Study

UC-961 will be examined for safety and tolerability in patients with documented and verified relapsed or refractory CLL requiring treatment for their disease in a first in man, phase I physician-sponsored clinical study. The eligible patient population is appropriate for a phase 1 trial because of a lack of any standard treatment options that are capable of inducing complete or durable treatment-free responses. The primary endpoint of the phase I trial will be to define the maximum tolerated dose (MTD) or biologically active dose of UC-961 administered as a single agent given on a bi-weekly (every two week) schedule for a total of four doses. Secondary endpoints to be measured include the assessment of clinical activity according to iwCLL working group criteria and progression free survival. Additionally, pharmacokinetic parameters will be assessed and blood samples will be collected for correlative analysis. We anticipate that 33 (but up to 56) patients will be enrolled..

2.0 STUDY OBJECTIVES

Primary Objective:

1. To determine the maximum tolerated dose (MTD) or biologically active dose of UC-961 when given bi-weekly for 4 doses to patients with relapsed or refractory chronic lymphocytic leukemia (CLL).

Secondary Objectives:

1. To determine the safety and tolerability of UC-961 by ongoing evaluation of adverse events (AEs).
2. To assess clinical activity based on international working group guidelines (iwCLL 2008).
3. To assess clinical activity by evaluating progression free survival.

Exploratory Objective:

1. To assess the mechanism of action of UC-961 through immunophenotypic, genomic, proteomic, and pharmacodynamic studies.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Ability to understand and the willingness to sign a written informed consent.

2. Clinical and phenotypic verification of B cell CLL and measurable disease. Immunophenotyping of the leukemic cells (blood or marrow) must demonstrate a monoclonal (or light chain positive) with immunophenotype consistent with B cell population (e.g., co-expressing CD19 and CD5).

3. Relapsed or refractory disease, defined by failure to achieve a partial response within 6 months of initiation of first line therapy, or a 50% worsening of baseline disease measurements (i.e., lymph node size, splenomegaly, lymphocytosis, anemia, thrombocytopenia, hepatomegaly) after achieving a clinical response.

4. Not amenable to approved therapies.

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5. Prior Therapy: Must have progressed after purine-analog or alkylator based therapy, or be considered inappropriate for chemo-immunotherapy due to one of the following:
   - Del 17p, which is associated with poor response to chemo-immunotherapy, or
   - Age greater than 70, or
   - Age greater than 65 with one of the following:
     - Grade $\geq$ 3 neutropenia, anemia, or thrombocytopenia attributable to cumulative myelotoxicity from prior administration of cytotoxic agents (as documented by bone marrow biopsy obtained since last prior therapy), or
     - Clinically apparent autoimmune cytopenia, which may be exacerbated by fludarabine therapy, or
     - Estimated creatinine clearance (eC_{Cr}) <70 mL/min (as determined by the Cockcroft-Gault method), or
     - ECOG performance status greater than 0.

6. Has recovered from the toxic effects of prior therapy to their clinical baseline.

7. Subjects must be aged 18 years or older.

8. Both men and women of all races and ethnic groups are eligible for this trial.

9. Women of childbearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree not to become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of the study and until 10 weeks after the final dose of UC-961 (expected to be greater than 5 half-lives from pre-clinical data).

10. Subjects must have at least one of the following indications for treatment:
    - Symptomatic or progressive splenomegaly;
    - Symptomatic lymph nodes, nodal clusters, or progressive lymphadenopathy;
    - Progressive anemia (hemoglobin ≤ 11 g/dL);

- Progressive thrombocytopenia (platelets ≤ 100 x 109/L);
- Weight loss > 10% body weight over the preceding 6 month period;
- Fatigue attributable to CLL;
- Fever or night sweats for > 2 weeks without evidence of infection;
- Progressive lymphocytosis with an increase of > 50% over a 2-month period or an anticipated doubling time of less than 12 months.

11. Subjects must have an ECOG performance status of 0-2.

12. Adequate hematologic function:
    - Platelet count ≥ 50,000/μL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate); AND
    - Hemoglobin ≥ 8.0 g/dL (may be supported by erythropoietin); AND
    - Absolute neutrophil count > 1000 /uL unless due to heavily infiltrated bone marrow (> 80% CLL cell infiltrate).

13. Adequate renal function:
    - Serum creatinine <1.5 times upper limit of normal; OR
    - Calculated Creatinine clearance (CrCl) ≥ 40 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)].

14. Adequate hepatic function:
    - Total bilirubin ≤ 2.5 times upper limit of normal; AND
    - ALT ≤ 2.5 times upper limit of normal.

15. Adequate coagulation tests:
    - Prothrombin time international normalized ratio (INR) ≤ 2; AND
    - Partial thromboplastin time ≤ 1.66 times upper limit of normal.

3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. IgG may cross the placental barrier and cause fetal B- and T-lymphocyte depletion. Therefore, women of child-bearing age must obtain a pregnancy test and pregnant or breast feeding females are excluded.

2. Patients who are currently receiving another investigational agent are excluded.

3. Patients who have had chemotherapy (e.g., purine analogues, alkylating agents), immunotherapy, radiation therapy, or participation in any investigational drug treatment within 4 weeks of initiation of UC-961, or at any time during the study.

4. Patients who have had prior (within 8 weeks of initiation of UC-961) or concurrent antibody therapy directed against CLL (i.e., Rituxan® and Campath®**)**

5. Current infection requiring parenteral antibiotics.

6. Active infection with HIV, HBV, or HCV.

7. Concurrent active malignancy or prior malignancy that was active within the previous 3 years (other than completely resected carcinoma in situ, prostate cancer, or localized non-melanoma skin cancer).

8. Known central nervous system (CNS) involvement by malignancy.

9. Untreated autoimmunity such as autoimmune hemolytic anemia, or immune thrombocytopenia.

10. Known uncompensated hypothyroidism (defined as greater than 2x upper limit of normal not treated with replacement hormone).

11. Presence of more than 55% pro-lymphocytes in peripheral blood. Patients with Richters transformation are not excluded.

12. Insufficient recovery from surgical-related trauma or wound healing.

13. Impaired cardiac function including any of the following:
    - Myocardial infarction within 6 months of starting study drug;
    - A past medical history of clinically significant ECG abnormalities, including QTc 481 ms or greater.
    - Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

14. Patients who in the opinion of the investigator may be unable to comply with the safety monitoring requirements of the study.

4.0 INVESTIGATIONAL TREATMENT PLAN

4.1 Dose Assignment

This is a first in human, open-label single institution, Phase I dose escalation study of in patients with relapsed or refractory CLL. Treatment cycle (14 days) will consist of UC-961 administered intravenously on a bi-weekly (every two weeks) schedule for a total of 4 doses. Twelve dose levels are planned (in 8 cohorts) with dose escalation described in Table 1. Seven dose cohorts (of 3 to 6 patients in size) plus an expansion cohort of 6 patients are planned. In the first 4 dose cohorts, there is intra-patient dose escalation to monitor for acute toxicities, such as tumor lysis syndrome. If any grade ≥ 2 adverse event occurs in the cohort with intra-patient dose escalation, then the dose-escalation scheme will switch to standard 3+3 dose-escalation design without intra-patient dose escalation. All adverse events should be considered relevant unless the event can clearly be determined to be unrelated to the drug, e.g., clearly related to disease progression.

Table 1. Dose escalation scheme

	Dose Cohort	Dose of UC-961
Starting Dose Intra-patient dose escalation	1	Cycle 1 = 15 µg/kg Cycle 2 = 15 µg/kg Cycle 3 = 30 µg/kg Cycle 4 = 30 µg/kg
Intra-patient dose escalation	2	Cycle 1 = 60 µg/kg Cycle 2 = 120 µg/kg Cycle 3 = 240 µg/kg Cycle 4 = 240 µg/kg
Intra-patient dose escalation	3	Cycle 1 = 500 µg/kg Cycle 2 = 1000 µg/kg Cycle 3 = 1000 µg/kg Cycle 4 = 1000 µg/kg
Intra-patient dose escalation	4	Cycle 1 = 2 mg/kg Cycle 2 = 2 mg/kg Cycle 3 = 4 mg/kg Cycle 4 = 4 mg/kg
	5	8 mg/kg
	6	16 mg/kg (or maximum 2000mg)
	7	20 mg/kg (or maximum 2000mg)

Dose escalation will be performed in serial patient cohorts. Up to six patients can be studied at each dose level. There will be a minimum interval of 48 hours or more between the initiation of therapy for new patients within each cohort. Safety and clinical data will be tabulated and the decision to open the next cohort level will be the responsibility of the principal investigator. Dose escalation will be based on the dose-limiting toxicities encountered during the dose-limiting toxicity (DLT) evaluation period (see 4.2 for DLT definitions).

- If none of the 3 patients in the dosing cohort experience a DLT, then dose escalation may proceed.
- If 1 of the 3 patients experiences a DLT, then the cohort will be expanded to 6 patients. If none of these additional patients experience a DLT, then dose escalation will continue.
- If 2 patients in the dose level experience a DLT, no further escalation will occur. The MTD will be defined as 1 dose level lower than the dose level at which at least 2 of 6 patients experienced a DLT.
- Successive dose reductions of 50% from the dose proposed in the initial cohort (2 mg/kg) will be used until a tolerated dose is identified, if DLTs are seen in 2 or more patients in the initial cohort.
- The Maximum Tolerated Dose (MTD) is defined as the highest dose studied at which no more than 1 in 6 patients experience a DLT in the DLT observation period.

DLT observation period is 56 days from the start of the first infusion for cohorts with intra-patient dose escalation; and 28 days after the start of the first infusion of UC-961 for subsequent cohorts. The subsequent cohort will not be enrolled until this DLT observation period has been completed for all patients in the prior dose cohort.

Replacement patients may be enrolled in a cohort for patients who withdraw for a reason that is definitely unrelated to toxicity of UC-961 (e.g. disease progression). Replacement patients will ensure enough patients are enrolled in each cohort to determine the MTD.

The Biologically Active Dose will be determined at a dose below or equal to the MTD upon review of study data by the investigators. The final determination will also take into account any cumulative or delayed toxicity (e.g., an adverse event that occurs later than the DLT observation period).

Expansion cohort: Six additional patients will be enrolled at the maximum tolerated dose or biologically active dose.

4.2 Dose Limiting Toxicity

Dose-Limiting Toxicity (DLT) is defined as any of the following adverse events that are considered by the investigator to be possibly, probably, or definitely related to the study agent UC-961 within the DLT observation period (56 days from the first infusion for cohorts with intrapatient dose escalation, and 28 days of the start investigational treatment for cohorts without intrapatient dose escalation):

a. Grade 3 or greater non-hematologic toxicity with the exception of Grade 3 infusion reaction.
b. Grade 4 neutropenia lasting more than 5 days despite appropriate medical management.
c. Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding or any requirement for platelets transfusion.
d. Grade 3 or greater febrile neutropenia (temperature ≥ 38.5ºC).
e. Grade 4 anemia unexplained by underlying disease.
f. Any AE requiring a dose delay of greater than 14 days.
g. Patients with baseline cytopenias or starting blood counts in the grade 2 range are evaluable for hematologic DLT.

All AEs occurring in the first two cycles should be considered relevant to determining DLTs and to reporting unless the event can clearly be determined to be unrelated to the study drug.

4.3 Recommended Pre-Medications and Concomitant Medications

1. Antibiotics: per investigator discretion.

2. Tumor lysis syndrome prophylaxis: Patients will receive allopurinol or another uric acid lowering agent. Blood samples will be drawn upon completion of the infusion and 24 hours (+/- 4 hours) later to perform a comprehensive metabolic panel and to test serum levels of uric acid, phosphorous, and calcium. Management of tumor lysis syndrome is described in section 4.6.3.

3. Infusion reaction prophylaxis:

   - Acetaminophen 325-1000 mg PO prior to UC-961 administration, or per investigator discretion.
   - Benadryl 50 mg IV or PO, or other antihistamine per investigator discretion, prior to UC-961 administration.
   - Optional: Hydrocortisone 100 mg IV bolus (or infusion over 30 +/-10 minutes) or other equivalent corticosteroid, prior to UC-961 infusion.

4.4 UC-961 infusion plan

FOR COHORT 1 (i.e., DOSES ≤ 30 µg/kg)
Initial Infusion (Cycle 1, Day 1, FOR COHORT 1)

- Test dose: Infuse 100 µg/hour for 10 minutes, then stop infusion (or sooner if not tolerated prior to 10 minutes). 10 minutes (+/-5 minutes) following completion of test dose, monitor for any signs or symptoms of infusion reaction, including: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards.
- In the absence of any of vital sign instability or signs/symptoms of infusion reaction, or after normalization of them, begin infusion:
- Initiate infusion at 100 µg/hr x 30 min (+/- 5 minutes)
- Check vital signs every 30 minutes (+/- 5 minutes).
- If vital signs are stable (SBP is within 20 mm Hg of baseline, HR > 60 or < 120 beats per minute or within 10% of baseline, and temperature <101.3 F) and without sign/symptoms of infusional toxicity, the rate of infusion is doubled every 30 minutes (+/- 5 minutes) to a maximum of 800 µg/hr for remainder of infusion.
- If a patient is unable to tolerate faster rate, continue infusion at the best tolerated rate until infusion is completed. Monitor for acute infusion-related reactions during and for 30 minutes (+/- 5 minutes) after infusion completed.
- Hold infusion and immediately notify MD if any of the following occur: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards. Infusion of UC-961 is resumed at half the previous rate once vital signs and symptoms have returned to baseline.

Subsequent Infusions (Day 1 of Cycles 2-4, FOR COHORT 1)

- Test dose is not required.
- Initiate infusion at rate of 200 µg/hr (or at highest previously tolerated rate if it is lower than 200 µg/hr). Maximum infusion rate is 1600 µg/hr. Remainder of infusion, vital sign monitoring, and management of infusion reaction as above.

FOR COHORT 2 (or doses 60 µg/kg to 240 µg/kg):
Initial Infusion (Cycle 1, Day 1, FOR COHORT 2)

- Test dose: Infuse 400 µg/hour for 10 minutes, then stop infusion (or sooner if not tolerated prior to 10 minutes). 10 minutes (+/-5 minutes) following completion of test dose, monitor for any signs or symptoms of infusion reaction, including: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards.
- In the absence of any of vital sign instability or signs/symptoms of infusion reaction, or after normalization of them, begin infusion:
- Initiate infusion at 400 µg/hr x 30 min (+/- 5 minutes)
- Check vital signs every 30 minutes (+/- 5 minutes).
- If vital signs are stable (SBP is within 20 mm Hg of baseline, HR > 60 or < 120 beats per minute or within 10% of baseline, and temperature <101.3 F) and without sign/symptoms of infusional toxicity, the rate of infusion is doubled every 30 minutes (+/- 5 minutes) to a maximum of 3200 µg/hr for remainder of infusion.
- If a patient is unable to tolerate faster rate, continue infusion at the best tolerated rate until infusion is completed. Monitor for acute infusion-related reactions during and for 30 minutes (+/- 5 minutes) after infusion completed.
- Hold infusion and immediately notify MD if any of the following occur: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards. Infusion of UC-961 is resumed at half the previous rate once vital signs and symptoms have returned to baseline.

Subsequent Infusions (Day 1 of Cycles 2-4, FOR COHORT 2)

- Test dose is not required.
- Initiate infusion at rate of 1600 µg/hr (or at highest previously tolerated rate if it is lower than 1600 µg/hr). Maximum infusion rate is 6400 µg/hr. Remainder of infusion, vital sign monitoring, and management of infusion reaction as above.

FOR COHORT 3 (doses 500 µg/kg to 1000 µg/kg)
Initial Infusion (Cycle 1, Day 1, cohorts 3)

- **Test Dose:** Infuse 2 mg/hour for 10 minutes, then stop infusion (or sooner if not tolerated prior to 10 minutes). 10 minutes (+/-5 minutes) following completion of test dose, monitor for any signs or symptoms of infusion reaction, including: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards.
- In the absence of any of vital sign instability or signs/symptoms of infusion reaction, or after normalization of them, begin infusion:
- Initiate infusion at 2 mg/hr x 30 min (+/- 5 minutes)
- Check vital signs every 30 minutes (+/- 5 minutes).
- If vital signs are stable (SBP is within 20 mm Hg of baseline, HR > 60 or < 120 beats per minute or within 10% of baseline, and temperature <101.3 F) and without

sign/symptoms of infusional toxicity, the rate of infusion is doubled every 30 minutes (+/- 5 minutes) to a maximum of 24 mg/hr for remainder of infusion.
- If a patient is unable to tolerate faster rate, continue infusion at the best tolerated rate until infusion is completed. Monitor for acute infusion-related reactions during and for 30 minutes (+/- 5 minutes) after infusion completed.
- Hold infusion and immediately notify MD if any of the following occur: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards. Infusion of UC-961 is resumed at half the previous rate once vital signs and symptoms have returned to baseline.

Subsequent Infusions (Day 1 of Cycles 2-4, cohorts 3)
- Test dose is not required.
- Initiate infusion at rate of 8 mg/hr (or at highest previously tolerated rate if it is lower than 8 mg/hr). Maximum infusion rate is 48 mg/hr. Remainder of infusion, vital sign monitoring, and management of infusion reaction as above.

FOR COHORT 4-8 (doses 2mg/kg and higher)
Initial Infusion (Cycle 1, Day 1, cohorts 4-8)
- **Test Dose:** Infuse 25 mg/hour for 10 minutes, then stop infusion (or sooner if not tolerated prior to 10 minutes). 10 minutes (+/-5 minutes) following completion of test dose, monitor for any signs or symptoms of infusion reaction, including: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards.
- In the absence of any of vital sign instability or signs/symptoms of infusion reaction, or after normalization of them, begin infusion:
- Initiate infusion at 25 mg/hr x 30 min (+/- 5 minutes)
- Check vital signs every 30 minutes (+/- 5 minutes).
- If vital signs are stable (SBP is within 20 mm Hg of baseline, HR > 60 or < 120 beats per minute or within 10% of baseline, and temperature <101.3 F) and without sign/symptoms of infusional toxicity, the rate of infusion is doubled every 30 minutes (+/- 5 minutes) to a maximum of 800 mg/hr for remainder of infusion.
- If a patient is unable to tolerate faster rate, continue infusion at the best tolerated rate until infusion is completed. Monitor for acute infusion-related reactions during and for 30 minutes (+/- 5 minutes) after infusion completed.
- Hold infusion and immediately notify MD if any of the following occur: hypotension (greater than 30 mm Hg drop in systolic blood pressure from baseline); fever (temperature greater than 101.3 degrees Fahrenheit); rigors. Management / supportive measures for these events is per institutional standards. Infusion of UC-961 is resumed at half the previous rate once vital signs and symptoms have returned to baseline.
-

Subsequent Infusions (Day 1 of Cycles 2-4, cohorts 4-8)
- Test dose is not required.
- Initiate infusion at rate of 50 mg/hr (or at highest previously tolerated rate if it is lower than 50 mg/hr). Maximum infusion rate is 800 mg/hr. Remainder of infusion, vital sign monitoring, and management of infusion reaction as above.

4.5 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 14 days if the patient has at least stable disease by clinical examination (or interim response assessment) and has again met hematologic, renal, and hepatic laboratory parameters as defined in the eligibility section, and is without ongoing Grade 3 non-hematologic or Grade 4 hematologic toxicities attributable to UC-961.

4.6 Dose Modifications and Dosing Delays

Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03 for non-hematologic toxicity or modified iwCLL criteria (section 7.1.2) for hematologic toxicity. Patients experiencing a DLT as defined in section 4.2 will be discontinued from study treatment. Otherwise, dose adjustments should be made according to the system showing the greatest degree of toxicity, as per 4.6.1, unless the adverse event is definitely unrelated to the study drug.

4.6.1 Dose Modification Guidelines

Toxicity – NCI CTCAE Grade (Hematologic- modified iwCLL)	**Occurrence**	**Dose Modification**
Autoimmune anemia or autoimmune thrombocytopenia		
Grade ≥ 2	any	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at same dose level.
Tumor Lysis Syndrome		
Grade ≥ 3	1st	Withhold study treatment until clinical and laboratory signs resolved to baseline. Resume study treatment at same dose level.
	Repeat	Discontinue therapy
Confusion / Delirium		
Grade ≥ 2	1st	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy
Pneumonitis		
Grade ≥ 2	1st	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy
Acute kidney injury		
Grade ≥ 2 (serum creatinine > 2 x baseline)	1st	Withhold study treatment until resolved to Grade ≤ 1. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy
Cardiac - QTc		
ECGs with a QTc 481-500 msec (Grade 2)	1st	Suspend study treatment and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. Perform a repeat ECG within one hour of the first QTc of > 480 msec. If QTc remains >480 msec, repeat ECG as clinically indicated until the QTc returns to <480 msec.

		- Study treatment may be restarted at the current dose level, if the reason for the QTc elevation is identified, corrected and QTc returns to baseline (pre-dose Cycle 1 day 1) within 7 days. - If QTc is repeated and is greater than baseline, reduce study treatment to the lower dose level. - An ECG should be repeated approximately 7 days after dose re-start for all patients who had therapy suspended due to QTcF > 480 msec. - If QTc remains >480 msec for greater than 7 days, discontinue treatment.
	Repeat	Discontinue study treatment.
ECGs with a QTc ≥ 501 msec (Grade 3)	1st	Discontinue study treatment.
ECGs with QTc ≥ 501 or > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms (Grade 4)	1st	Discontinue study treatment.
Other Non-hematologic		
Grade ≥ 3	1st	Withhold study treatment until resolved to Grade ≤ 2. Resume study treatment at the next lower dose level.
	Repeat	Discontinue therapy.
Hematologic*		
ANC <1000/mm^3; Hemoglobin < 8 gm/dL; Platelet count ≥ 50% decrease from baseline (and/or platelet count ≤ 50,000/mm^3)	1st	Withhold study treatment until resolved to ANC ≥1000/mm^3, hemoglobin is ≥ 8 gm/dL, and platelet count ≥50,000/mm^3. Resume study treatment at same dose.
	2nd	Withhold study treatment until resolved to ANC ≥1000/mm^3, hemoglobin is ≥ 8 gm/dL, and platelet count ≥50,000/mm^3. Resume study treatment at the next lower dose level.
	3rd	Permanently discontinue study treatment.
*Dose adjustments or dose holds for hematologic toxicity will apply even if the baseline values are lower than these thresholds due to heavily infiltrated marrow. In those cases, growth factors and/or blood product transfusion may be administered prior to continuing with UC-961.		

Notes:

1. If any of the above are noted, the patient will be re-assessed within 7 days by the treating physician or investigator. Isolated laboratory abnormalities may be re-evaluated by laboratory draw only, or based on physician or investigator discretion.
2. UC-961 infusions can be delayed for a maximum of 28 days; if not restarted in that time-

span, study treatment will be permanently discontinued.
3. If dose is decreased for Grade 3 or 4 toxicity, dose re-escalation is not planned.
4. For invasive procedures, not including biopsies or venous catheter placement: withhold study treatment for 1 week prior to procedure, and at least 1 week following surgery until satisfactory wound healing has been achieved.

4.6.2 Modifications for Infusion Reactions

Patients will be monitored for the presence of infusion-related reactions. Treatment for infusion-related reactions will be managed according to the following guidelines:

Infusion Reaction	Occurrence	Management Guidelines
Grade ≤ 2	any	Institute supportive measures. When resolved, resume study treatment at same dose level. Infusion rate adjustment per 4.4.
Grade 3	1st	Institute supportive measures. When resolved, resume study treatment at the same dose level. Infusion rate adjustment per 4.4. Pre-medications listed in protocol are mandatory for re-challenge.
	2nd	Institute supportive measures. Permanently discontinue study treatment.
Grade 4	any	Institute institutional procedures for adult medication reaction/anaphylactic response. Permanently discontinue study treatment.

4.6.3 Management of tumor lysis syndrome

Event	Management Guidelines
Hyperkalemia	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium is within normal limits [WNL])	- Recheck K+, Phos, uric acid, calcium & creatinine in 1 hour STAT. - If further ≥ 0.2 mmol/L increase in K+, but still < ULN, manage as per K+ ≥ ULN. Otherwise recheck in 1 hour. - If change in K+is < 0.2 mmol/L 1 hour later, and K+ < ULN, and no other evidence of tumor lysis, resume per protocol monitoring.
Potassium > ULN	- Perform STAT EKG - Administer Kayexalate 60 g - administer furosemide 20 mg IV x 1 - Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is EKG evidence of arrhythmia - Recheck K+, Phos, uric acid, calcium, and creatinine in 1 hour STAT

Event	Management Guidelines
	- If L+ < ULN 1 hour later, repeat K+, Phos, uric acid, calcium, and creatinine 1, 2, and 4 hours, if no other evidence of tumor lysis syndrome - At discretion of investigator, admission to hospital, and nephrology consultation for consideration of initiating dialysis. - Admission required for any increase ≥ 1 mmol/L
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g. muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	- Perform STAT EKG - Administer Kayexalate 60 g - Administer furosemide 20 mg IV x 1 - Administer insulin 0.1 U/kg IV + D25 2 ml/kg IV - Administer sodium bicarbonate 1 to 2 mEq IV push. - If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. - Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is EKG evidence of arrhythmia - Recheck K+, Phos, uric acid, calcium, and creatinine in 1 hour STAT - If L+ < ULN 1 hour later, repeat K+, Phos, uric acid, calcium, and creatinine 1, 2, and 4 hours, if no other evidence of tumor lysis syndrome - Admission to hospital, and nephrology consultation for consideration of initiating dialysis, unless all repeat labs are WNL.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL	- Consider rasburicase (dose per institutional guidelines) - Recheck K+, Phos, uric acid, calcium, and creatinine in 1 hour STAT
Uric acid ≥ 10 mg/dL OR uric acid ≥ 8.0 mg/dL with 25% increase and Creatinine increase ≥ 0.3 mg/dL from pre-dose level	- Administer rasburicase (dose per institutional guidelines) - Recheck K+, Phos, uric acid, calcium, and creatinine in 1 hour STAT - If uric acid < 8.0 mg/dL 1 hour later, repeat K+, Phos, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. - Admission to hospital, and nephrology consultation for consideration of initiating dialysis, unless all repeat labs are WNL. -
Calcium ≤ 7.0 mg/dL AND patient symptomatic (e.g. muscle cramps, hypotension, tetany, arrhythmias)	- Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. - Recheck K+, Phos, uric acid, calcium, and creatinine in 1 hour STAT - If Ca normalized 1 hour later, repeat K+, Phos, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. - Calculate corrected calcium and check ionized calcium if albumin low.

Event	Management Guidelines
Phosphorous ≥ 5.0 with ≥ 0.5 mg/dL increase	- Administer phosphorous binder - Recheck K+, Phos, uric acid, calcium, and creatinine in 1 hour STAT - Admission to hospital and nephrology consultation (dialysis required for phosphorous ≥ 10 mg/dL - If Phos < 5.0 mg/dL 1 hour later, repeat K+, Phos, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine ≥ 25% from baseline	- Administer IV fluids at 100 to 200 ml/hr for 4 hours - Recheck K+, Phos, uric acid, calcium, and creatinine in 1-2 hours STAT - Admission to hospital and nephrology consultation if creatinine increase by ≥ 10% on repeat check. - If not admitted, ensure oral hydration of at least 3 L/ day.

4.7 Permitted concomitant therapy

Supportive Care
Appropriate antibiotics, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary.

Blood Products and Growth Factors
Blood products or myeloid growth factors can be administered for grade 4 toxicities (DLT), per investigator discretion for patient safety. The Principal Investigator (C. Jamieson, MD PhD of M. Choi, MD) should be called before growth factors are initiated. Erythropoietin or thrombopoietin mimetics are not to be used, unless continuation of a therapy that started ≥ 1 day prior to Cycle 1, Day 1.

4.8 Prohibited concomitant therapy

Concurrent Anticancer Therapy
Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. Corticosteroids administration, even if for treatment of conditions other than CLL, at doses greater than prednisone 20 mg daily (or equivalent dose of other steroids) are prohibited for greater than 14 days. If these treatments are administered the patient will be removed from study.

Investigational Agents
No other investigational agents may be given while the patient is on study.

4.9 Duration of Therapy

The investigational agent UC-961 will be administered every two weeks for four doses or until:

a) Clinical or radiographic progressive disease.
b) Unacceptable toxicities.
c) Refusal of further protocol therapy by patient.

d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of therapy.
f) Physician determines it is in the patient's best interest to discontinue study agent.

Clinical Study Stopping Rules: Enrollment will be held pending review and approval by the UC San Diego Moores Cancer Center Data Safety Monitoring Board (DSMB) in the event of either of the following:

- Death, or
- 2 or more non-hematologic Grade 4 events at least possibly attributable to the study drug not resolving with standard therapy within 7 days. Grade 4 hematologic events will not stop the study, but do meet protocol-defined criteria for Dose Limiting Toxicity.

4.10 Duration of Follow Up

Patients removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed after removal from study treatment every 28 days (+/-7 days) for 8 visits, then every 56 days (+/- 7 days) until death, lost to follow-up, withdrawal of consent, or initiation of subsequent therapy for disease progression (*see Section 5 for assessments*).

4.11 Criteria for Removal from Study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

a) Death.
b) Loss to follow-up.
c) Withdrawal of consent for any further data submission.
d) Disease progression requiring initiation of subsequent therapy.
e) Administration of any concurrent cancer therapy (including chemotherapy, radiation therapy, immunotherapy, or biologic therapy).
f) Administration of corticosteroids at doses greater than prednisone 20 mg daily (or equivalent dose of other steroids) for greater than 14 days.

5.0 STUDY PROCEDURES

A cycle is considered to be 14 days. The total duration of study drug administration is 4 cycles. Each cycle consists of clinical and laboratory evaluation on Day 1 (+/- 1 day), and safety assessments on Days 3 and 8.

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to Cycle 1 Day 1 of the study

unless otherwise stated. The screening procedures include:

5.1.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.1.2 Current medications will be recorded in the subject's medical record but not captured in case report forms.

5.1.3 12 lead ECG. ECG is required on screening. Subsequent ECG will be performed during the study as clinically indicated.

5.1.4 Laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH, amylase, lipase.

5.1.5 Coagulation parameters: PT/PTT.

5.1.6 Serum β2-microglobulin, T-cell subsets, and quantitative immunoglobulins (IgG, IgA, IgM).

5.1.7 Infectious disease screening unless known within 56 days, including: HBsAG, anti-HBs, total anti-HBc, IgM anti-HBc), Hep C virus antibody + RNA if antibody positive, anti-CMV IgG and IgM, anti-VZV IgG, anti-HIV, and EBV anti-IgG and IgM. Positive tests will have follow-up/ confirmatory testing as clinically indicated to assess for active infection.

5.1.8 If female of child-bearing potential: serum pregnancy test within 14 days of Cycle 1 Day 1.

5.1.9 Subjects will have bone marrow aspirate and biopsy with samples sent for differential, morphology, and flow cytometry for MRD within 90 days prior to Cycle 1 Day 1, so long as there has been no intervening CLL therapy.

5.1.10 Subjects will have prognostic factors characterized on blood or bone marrow, including presence of cytogenetic abnormalities (chromosome analysis and FISH for 13q-, +12, 11q-, and 17p-), Immunoglobulin gene heavy chain variable region (IGVH) gene mutation status, and expression of ZAP-70 and CD38. If already known, ZAP-70 and IGVH prognostic factors do not need to be reevaluated since they are not expected to change.

5.1.11 Disease staging to include CT scan or MRI as clinically indicated (typically including chest, abdomen, pelvis to measure non-palpable lymph nodes) within the last 60 days prior to Cycle 1 Day 1 if there has been no intervening CLL treatment. Any appropriate radiological examinations should be performed as clinically indicated.

5.1.12 Research Tests: peripheral blood and serum collection for one or more of the following (i) Leukemia cell immunophenotype, (ii) T and B cell immune response, (iii) plasma cytokine levels. (see Correlative Studies Section 5.9).

5.2 To be completed on Day 1 of all Cycles

5.2.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.2.2 Current medications will be recorded in the subject's medical record but not captured in case report forms.

5.2.3 Adverse events assessment and grading per patient reporting.

5.2.4 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.2.5 Blood collection for correlative studies.

5.2.6 Pre-medications: Recommendations are in section 4.3.

5.2.7 ECG prior to UC-961 infusion.

5.2.8 Infusion of UC-961 according to section 4.4.

5.2.9 Post-infusion monitoring: patients will be observed for at least 1 hour following the infusion of UC-961, with continued measurement of blood pressure, pulse, temperature every 30 minutes (+/- 10 minutes).

5.2.10 ECG within 1 hour following the infusion of UC-961.

5.2.11 Peripheral blood draw at the end of the infusion (+/- 10 minutes), including comprehensive metabolic panel (CMP), phosphorous, uric acid, LDH.

5.2.12 Pharmacokinetic (PK) samples are drawn at times points indicated in Pharmacokinetic Studies Section 5.8.

5.3 To be completed on Day 2 and Day 8 of each cycle

5.3.1 Focused physical examination including vital signs (blood pressure, heart rate, temperature, weight).

5.3.2 Current medications will be recorded in the subject's medical record but not captured in case report forms.

5.3.3 History, including adverse events assessment and grading.

5.3.4 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.3.5 Collection of correlative laboratory samples.

5.3.6 Pharmacokinetic (PK) samples are drawn at times points indicated in Pharmacokinetic Studies Section 5.8.

5.4 To be completed on Day 3 and Day 10 of Cycle 1 (and any additional cycles when the dose level changes during intra-patient dose escalation)

5.4.1 Pharmacokinetic (PK) samples are drawn at times points indicated in Pharmacokinetic Studies Section 5.8.

5.5 End of treatment safety assessment 28 days after final infusion (+/- 3 day)

5.5.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.5.2 Adverse events grading and reporting

5.5.3 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.5.4 Collection of correlative lab samples.

5.6 Response Assessment 56 days after final infusion (+/- 3 day),

Not all activities are required on the same day.

5.6.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.6.2 Adverse events grading and reporting.

5.6.3 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH. Also: amylase; lipase.

5.6.4 Collection of correlative lab samples.

5.6.5 Serum β2-microglobulin, quantitative T-cell subsets, quantitative immunoglobulins (IgG, IgA, IgM).

5.6.6 Flow cytometry of peripheral blood for T-cell subtypes and CLL MRD.

5.6.7 CT scan or MRI of chest, abdomen, and pelvis.

5.6.8 Bone marrow biopsy if clinically indicated to evaluate complete response / minimal residual disease.

5.7 Long term follow-up

Every 28 days (+/- 7 days) for 8 visits then every 56 days (+/- 7 days), until discontinuation of trial participation:

5.7.1 Complete history and physical examination including vital signs (blood pressure, heart rate, temperature, weight) and organ measurements (i.e., lymph nodes, spleen, liver).

5.7.2 Adverse events grading and reporting.

5.7.3 Standard laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH.

5.7.4 Collection of correlative lab samples.

5.8 Pharmacokinetic (PK) Studies

Serum samples will be banked for analysis. ELISA assay will be utilized for serum antibody levels.

Sampling Schedule:
Cohorts 1-3 are planned to have intra-patient dose escalation and will have serum samples collected for PK analysis at more time points at each new dose level (Tables 5-7). If at any time dose escalation switches to the standard 3+3 dose escalation design without intra-patient dose escalation, the serum sample collection for PK analysis will follow the time points listed in Table 8.

Table 2. PK sampling schedule for Planned Cohort 1 (intra-patient) dose escalation

Cycle	Day	Time point
1	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
	10	216 hours (+/- 4 hours) post completion of Day 1 infusion
2	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
3	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 8 hours) post completion of Day 1 infusion
	10	216 hours (+/- 8 hours) post completion of Day 1 infusion
4	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion

Table 3. PK sampling schedule for Planned Cohort 2 (intra-patient) dose escalation

Cycle	Day	Time point
1	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
	10	216 hours (+/- 4 hours) post completion of Day 1 infusion
2	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
	10	216 hours (+/- 4 hours) post completion of Day 1 infusion
3	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 8 hours) post completion of Day 1 infusion
	10	216 hours (+/- 8 hours) post completion of Day 1 infusion
4	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion

Table 4. PK sampling schedule for Planned Cohort 3 (intra-patient) dose escalation

Cycle	Day	Time point
1	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 46 hours) post completion of Day 1 infusion
	3	48 hours (+/- 64 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 8hours) post completion of Day 1 infusion
	10	216 hours (+/- 84 hours) post completion of Day 1 infusion
2	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 64 hours) post completion of Day 1 infusion
	3	48 hours (+/- 64 hours) post completion of Day 1 infusion
	8	168 hours (+/- 84 hours) post completion of Day 1 infusion
	10	216 hours (+/- 84 hours) post completion of Day 1 infusion
3	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 84 hours) post completion of Day 1 infusion
	8	168 hours (+/- 8 hours) post completion of Day 1 infusion
4	**1**	pre-dose

Table 5. PK sampling schedule for Planned Cohort 4 (intra-patient) dose escalation

Cycle	Day	Time point
1	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
	10	216 hours (+/- 4 hours) post completion of Day 1 infusion
2 **3**	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion

	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
	1	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
3	**3**	• 48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 8 hours) post completion of Day 1 infusion
	10	216 hours (+/- 8 hours) post completion of Day 1 infusion
4	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and 1 hour (+/- 5 minutes) post completion of the infusion

Table 6. PK sampling for Cohorts without intra-patient dose escalation

Cycle	Day	Time point
1	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	3	48 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
	10	216 hours (+/- 4 hours) post completion of Day 1 infusion
2	**1**	• pre-dose, • 5-10 minutes prior to the completion of the infusion, • 30 minutes (+/- 5 minutes) post completion of the infusion, and • 1 hour (+/- 5 minutes) post completion of the infusion
	2	24 hours (+/- 4 hours) post completion of Day 1 infusion
	8	168 hours (+/- 4 hours) post completion of Day 1 infusion
3	**1**	pre-dose
4	**1**	pre-dose

Sample Collection and Handling Instructions

Blood samples (up to 10 ml) will be collected in anti-coagulated tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. The exact time that the sample is drawn along with the exact time that the drug is administered should be recorded.

Sample Processing: Plasma will be isolated in the translational laboratory (Kipps) and stored at minus 20 degrees.

Sample Labeling
Each tube must be labeled with the patient's de-identified study number, and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

Sample Shipping Instructions
Samples may be shipped to third-party vendor for PK analysis. Samples will be shipped as per assay manufacturer recommendations.

5.9 Correlative Studies

Studies will be performed in the Kipps laboratory, to correlate with PK and clinical responses. Samples will be taken at baseline/screening, during treatment and after treatment. However, not all assays will be performed for all time points for all patients, based on sample availability and leukemic cell number. Specimens will be banked in the CLL research consortium tissue repository (see below).

Assays from patient serum may include:
- Measurement of cytokine levels (IL2, IL12, and TNFα),
- Assessment for anti-UC-961 antibody production.
    - Anti-UC-961 antibody production will be assessed on Day 1 of cycles 2, 3, and 4; at the end of treatment; and at the time of response assessment (2 months post final UC-961 dose). If UC-961 interferes with the assay, an additional sample collected during follow-up will be assessed.
    - If the binding anti-drug antibody (ADA) is positive, samples will be banked to assay the neutralizing capacity of the ADA.

Isolation of leukemic cells by Ficoll-hypaque separation and assessment, which may include:
- UC-961 antibody binding, ROR1 expression and receptor occupancy
- ZAP-70, CD38, and Immunoglobulin heavy chain variable region (IgVH) mutation in CLL cells
- Assessment of down-stream signaling by multiplex qPCR
- Measurement of Akt and phospho-Akt levels prior to and after therapy.
- Expression of co-stimulatory molecules (CD80 and CD86), apoptosis related receptors (CD95 and DR5), and expression of genes and proteins related to apoptosis, from pre-treated and post-treated samples.

5.9.1 Sample Collection Guidelines

Sampling Schedule
Blood sample for correlative studies will be collected at the following time points and amounts:
- Screening
- Day 1 of each cycle:
    - pre-infusion
    - 5-10 minutes prior to the end of the infusion,
    - 30 minutes (+/- 5 minutes) post infusion
- Day 2 of each cycle
- Day 8 of each cycle

- End of Treatment visit
- Response assessment
- Long-Term Follow-up visits

Sample Collection and Handling Instructions
Blood samples will be collected in anti-coagulated tubes (up to 20 mL) at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. The exact time that the sample is drawn along with the exact time that the drug is administered should be recorded.

Sample Processing

Samples will be processed in the translational lab of Dr. Thomas Kipps, with separation of plasma, followed by isolation of mononuclear cells or neutrophils by Ficoll or Percoll differential centrifugation, respectively.

Sample Labeling
Each tube must be labeled with the patient's study number and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

5.9.2 Specimen Banking

Patient samples collected for this study will be retained at the UCSD School of Medicine (Kipps Laboratory). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. Samples will be labeled with the subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

Dr. Kipps will be responsible for reviewing and approving requests for research specimens from potential research collaborators outside of UCSD. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimens will be the property of UCSD for publication and any licensing agreement will be strictly adhered to.

The study research coordinator will review the subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. Samples and data extracted from the subject's medical record will be coded with a de-identified study number, and the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered

The specimens and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

6.0 SCHEDULE OF EVENTS

Treatment Cycle	Screening	Cycle 1					Cycle 2			Cycle 3			Cycle 4			End of Treatment	Response Assessment	Long-Term Follow-up
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Visit Day		C1 D1	C1 D2	C1 D3 [8]	C1 D8	C1 D10 [8]	C2 D1	C2 D2	C2 D8	C3 D1	C3 D2	C3 D8	C4 D1	C4 D2	C4 D8	28 days after last dose	56 days after last dose	Q28d x8, then q56d
Visit window	≤ 30 days prior to visit 2	±1d			±1d		±1d		±1d	±1d		±1d	±1d		±1d	±3d	±3d	±7d
Informed Consent	X																	
Eligibility Checklist	X																	
Infectious disease screening[1]	within 56 days of C1D1																	
History and Symptoms	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
VS/Ht and Weight	X	X					X			X			X			X	X	X
Comprehensive PE	X	X					X			X			X			X	X	X
Focused / Abbreviated PE (nurse or MD)			X		X			X	X		X	X		X	X			
ECOG Performance Status	X	X					X			X			X			X	X	X
CBC and differential	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry panel[2]	X	X [9]	X		X		X [9]	X	X	X [9]	X	X	X [9]	X	X	X	X	X
PT/aPTT	X																	
ECG[3]	X	X					X			X			X					
Adverse Events Screen		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X					X			X			X			X	X	X
UC-961 Administration		X					X			X			X					

Treatment Cycle	Screening	Cycle 1					Cycle 2			Cycle 3			Cycle 4			End of Treatment	Response Assessment	Long-Term Follow-up
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Visit Day		C1 D1	C1 D2	C1 D3 [8]	C1 D8	C1 D10 [8]	C2 D1	C2 D2	C2 D8	C3 D1	C3 D2	C3 D8	C4 D1	C4 D2	C4 D8	28 days after last dose	56 days after last dose	Q28d x8, then q56d
Visit window	≤ 30 days prior to visit 2	±1d			±1d		±1d		±1d	±1d		±1d	±1d		±1d	±3d	±3d	±7d
CT scan Chest/ Abdomen/ Pelvis [4]	within 60 days of C1D1																X	
Bone marrow aspirate and biopsy [5]	within 90 days of C1D																X	
Cytogenetics/FISH from bone marrow or peripheral blood [6]	X																X	
Quantitative inmunoglobulins [7]	X																X	
serum β2-microglobulin	X																X	
Serum hCG for female of child bearing potential	within 14 days of C1D1																	
Quantitative T-cell subsets	X																X	
Collection of Pharmacokinetic and /or Pharmacodynamic Samples [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Infectious disease screening: HBsAG, anti-HBs, total anti-HBc, IgM anti-HBc), Hep C virus antibody + RNA if antibody positive, anti-CMV IgG and IgM, anti-VZV IgG, anti-HIV, and EBV anti-IgG and IgM. Positive tests will have follow-up/confirmatory testing as clinically indicated to assess for active infection.

2. Chemistry panel to include: comprehensive metabolic panel (Na+, Cl-, K+, CO2, BUN, Creatinine, Glucose, Ca2+, total protein, albumin, total bilirubin, SGPT, SGOT, alkaline phosphatase), phosphorous, magnesium, uric acid, LDH, amylase, and lipase.
   NOTE: amylase and lipase are not measured in long-term follow-up unless clinically indicated.
3. ECG: To be performed during screening and then prior to and within 1 hour post end of study drug infusion.
4. Or MRI.
5. In the case of a CR, an additional bone marrow will be taken two months after patient first achieves CR
6. Chromosome analysis and FISH Panel to include 11q, 12p, 13q, 17p analysis.
7. Quantitative IgG, IgA, IgM.
8. Blood samples are collected for PK, PD, and/or immunogenicity analysis at the following time points of each cycle (refer to section 5.8 and 5.9).
   Note: PK collection on Days 3 and 10 may be added to additional cycles in cohorts with intra-patient escalation as described in section 5.8.
9. Comprehensive metabolic panel, LDH, uric acid, and phosphorous drawn at the completion (+/- 5 minutes) of UC-961 infusion.

7.0 Measurement of Effect

7.1 Safety/tolerability

7.1.1 Common Terminology Criteria for Adverse Events (CTCAE)

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of non-hematologic adverse events.

7.1.2 International Working group for Chronic Lymphocytic Leukemia (IWCLL) criteria for hematologic toxicity

As is the case with virtually all of the hematological malignancies, an evaluation of the hematological toxicity in patients with CLL must consider the high frequency of marrow involvement and consequent medullar compromise at the initiation of therapy. A substantial proportion of patients may have hematological parameters within the range of Grade 2 hematological toxicity before therapy is given; therefore, a modified schema will be used to monitor hematological toxicity in patients with CLL. The modified hematological toxicity schema is displayed:

Modified Grading Scale for Hematological Toxicity in CLL Studies

Grade[1]	Decrease in platelets (nadir) from pretreatment value (%)[2]	ANC/µl (nadir)[3]	Hemoglobin[4]
0 (not AE)	10%, or above lower limit of normal	≥ 2000	Baseline or higher, or above lower limit of normal
1	11-24%	≥ 1500 and < 2000	> 10.0 g/dL and below baseline
2	25-49%	≥ 1000 and < 1500	< 10.0 – 8.0 g/dL and less than baseline
3	50-74%	≥ 500 and < 1000	< 8.0 – 6.5 g/dL and less than baseline
4	≥75% or ≤ 25,000/mm3 [2]	< 500	< 6.5 g/dL and less than baseline

*This schema concurs with the CTEP CTCAE 4.03, except for the platelet values are taken from the iwCLL-WG guidelines working group criteria and hemoglobin toxicity modified from CTCAE only to account for low baseline values in CLL patients. No hematologic toxicity will be registered unless hemoglobin falls below baseline level.

[1] 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 a Grade 5.

[2] Treatment will be held for platelet count ≤ 50,000/mm3, even if it does not meet grade 4 criteria based on percent decrease. See section 4.6.1 for dose hold/adjustment guidelines.

[3] If baseline ANC is <1,000/µL, neutrophil toxicity cannot be evaluated. In that case, if the neutrophil count is less than 1000/µL, it is still recommended to hold therapy until ANC is greater than 1000/µL. See section 4.6.1 for dose hold/adjustment guidelines.

[4] If baseline Hemoglobin is < 8.0, hemoglobin toxicity cannot be evaluated. In that case, if the

hemoglobin is less than 8.0, it is still recommended to hold therapy until Hgb is greater than 8.0. See section 4.6.1 for dose hold/adjustment guidelines.

7.2 Response Criteria for Patients with Chronic Lymphocytic Leukemia

Criteria for response will utilize the IWCLL Guidelines for response, which includes clinical, hematological, and bone marrow features as outlined below (Hallek et al., 2008).

Minimal Residual Disease negative: less than 0.01% CLL cell involvement by 4-color flow cytometry of bone marrow aspirate (less than 1 in 10,000 events) and meeting all other criteria for complete response.

Complete response: Requires all of the following for a period of at least two months from completion of therapy:

- Absence of significant lymphadenopathy (e.g. >1.5cm in diameter) on physical exam;
- No hepatomegaly or splenomegaly on physical exam;
- Absence of constitutional symptoms;
- Blood counts corresponding to the following values: Lymphocytes < 4,000/uL, polymorphonuclear leukocytes >1500/µL, platelets >100,000/µL, hemoglobin >11.0 g/dL (untransfused)
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules must be absent. If the marrow is hypocellular, a repeat determination should be performed in one month.
- The marrow should be analyzed by flow cytometry and/or immunohistochemistry to demonstrate that the marrow is free of clonal B- CLL cells.
- A CT scan or MRI documenting absence of significant lymphadenopathy should be performed if previously abnormal.
- Patients who fulfill the criteria for CR with the exception of a persistent cytopenia that is believed to be treatment related will be considered CR with incomplete bone marrow recovery (CRi). Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid nodules will be considered a nodular PR.

Partial response: Requires at least 2 of the following criteria from group A, and at least one of the criteria from group B, and for a period of at least 2 months:

Group A:

- ≥50% decrease in peripheral absolute lymphocyte count from pretreatment value, or less than 4,000/uL.
- ≥50% reduction in lymphadenopathy by examination or scan, or less than 1.5cm in size.
- ≥50% reduction in splenomegaly (cm below costal margin) by examination or scan
- ≥50% reduction hepatomegaly (total liver span) by examination or scan
- ≥50% reduction in marrow infiltrate or B-lymphoid nodules

Group B:

- Polymorphonuclear leukocytes ≥1,500/µL or 50% improvement from pre-treatment value;
- Platelets >100,000/µL or 50% improvement from pre-treatment value;
- Hemoglobin >11.0 g/dl (un-transfused) or 50% improvement from pre-treatment value.

Progressive Disease: Characterized by any one of the following events:

- ≥50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥2 cm); appearance of new palpable lymph nodes.

- ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥56% prolymphocytes).
- *During therapy,* patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin >2 gm/dL, decrease >50% in platelet or granulocyte count will not be rated as progressive disease because these may occur as both a consequence of therapy. A bone marrow biopsy in such settings is strongly encouraged. Furthermore, during therapy, patients with progressive lymphocytosis but not any other findings of hemoglobin, platelet count, lymph node size, or spleen size meeting criteria for progressive disease will not be rated as progressive disease as agents that target the akt pathway have been demonstrated to induce a redistributive lymphocytosis as part of the mechanism of action (Byrd et al., 2013).
- *After treatment,* The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100 000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease: Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

7.2.1 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death.

8.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

8.2 Severity

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html. All hematologic adverse events will be graded according to the modified iwCLL criteria.

If no grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

8.3 Seriousness

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent

one of the outcomes listed in the definition of “Serious Adverse Event“.

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the toxicities listed in the agent information section of this protocol.

8.6 Reporting Requirements for Adverse Events

8.6.1 Expedited Reporting

- The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The **UCSD Human Research Protections Program (HRPP)** must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.
- The **FDA** should be notified within 7 calendar days of any unexpected fatal or

life-threatening adverse event with possible relationship to study drug, and 15 calendar days of any adverse event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.6.2 Routine Reporting Requirements

- The UCSD HRPP will be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- The FDA will be notified of all non-serious adverse events annually at the time of the annual report.

9.0 AGENT INFORMATION

9.1 UC-961 (Cirmtuzumab)

Please refer to Investigator's Brochure for more comprehensive information.

Structure: Monoclonal antibody

Supplied by: UC-961 will be produced at Pacific GMP (San Diego, CA) in compliance with cGMP standards.

Formulation
The agent is supplied as a liquid formulation at a concentration of 40 mg/ml protein, with 7.2 to 7.8 mL/vial. Each ml of the formulation contains 40 mg UC-961, 14.7 mg sodium citrate, 10 mg trehalose, 216 µg Polysorbate 80, 15 µg sodium EDTA and adjusted to pH 5.2 ± 0.2.

UC-961 will be filled into 10ml clear borosilicate Type 1 glass vials with 20 mm grey butyl siliconized rubber stopper and 20 mm aluminum royal blue flip off seals.

Storage
UC-961 is to be kept refrigerated (2-8°C) until use, in single use vials.

Solution Preparation
To prepare the agent for administration, it will be dissolved in normal saline to the following final concentrations:

- 100 µg/mL for cohorts 1 and 2 (or doses 15 µg/kg to 240 µg/kg);
- 500 µg/mL for cohorts 3 and 4 (or dose 500 µg/kg to 2 mg/kg)
- 1 mg/mL for cohort 5 (or dose 4 mg/kg)
- 2 mg/mL for cohort 6 (or dose 8 mg/kg)
- 4 mg/mL for cohorts 7 and 8 (or doses 16mg/kg and 20 mg/kg)

Administration
The drug will be administered by intravenous infusion with infusion rate according to section 4.4.

Toxicities
No toxicities have been established, as this is a first-in-human study. There is no off-target binding identified in initial preclinical assays. Infusion reaction, fluid retention, tumor lysis syndrome, and immunogenicity are possible class effects of monoclonal antibody therapy. Depletion of precursor B cells and B cell lymphopenia are possible as well. Other ROR1 antibodies, distinct from UC-

961, have demonstrated binding to pancreatic islet cells and adipose tissue (Hudecek et al., 2010). Glucose levels and body weight will therefore be monitored.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a phase I study of UC-961, a humanized anti-ROR1 monoclonal antibody, for patients with relapsed or refractory CLL.

The primary endpoints are the rate of dose limiting toxicities (DLTs) and the maximum tolerated dose or biologically active dose of UC961.

Secondary endpoints include treatment-emergent adverse events, the complete/overall response rate (2008 iwCLL criteria, which is based on reduction in leukemia count, reduction in lymphadenopathy and splenomegaly, and improvement in BM function), and the progression-free survival in patients treated with repeated doses of UC-961.

Exploratory endpoints include circulating UC-961 levels in peripheral blood, antibody production against UC-961, leukemia cell immunophenotype, leukemia cell akt/ phospho-akt levels, and plasma cytokine levels.

10.2 Statistical Design

As this is a hypothesis testing study for safety, no formal sample size or power calculations will be made. The dose levels will start from 15 μg/kg and increase as per table in section 4.1.
In order to start at low doses of UC-961 to evaluate for acute toxicities like tumor lysis syndrome, but not expose large numbers of patients to potentially sub-therapeutic doses that do not saturate circulating ROR1 (and therefore may not affect nodal or bone marrow compartments), patients in the first 4 cohorts will have intra-patient dose escalation. If there is a grade ≥ 2 adverse event, in cohorts with intra-patients dose escalation, then the dose escalation scheme will switch to the standard 3 + 3 design without intra-patient dose escalation, starting at the dose at which the grade ≥ 2 toxicity occurred. Otherwise, cohorts 5 to 7 will utilize a standard 3+3 dose escalation design. This design is based on phase 1 design guidance by the NCI (*Le Tourneau et al.*, 2009). All adverse events should be considered relevant unless the event can clearly be determined to be unrelated to the drug, e.g., clearly related to disease progression.

Dose Escalation Rules
For the first 4 cohorts with intra-patient dose escalation, three subjects will be enrolled. Each subject will be treated according to the dose levels in Table 1. If there is no grade 2 or above adverse reaction in the first 56 days starting from the first infusion of UC961, we will escalate to the next cohort. If there is one or more grade 2 or above adverse event, the study will switch to a standard 3+3 design. All adverse events should be considered relevant unless the event can clearly be determined to be unrelated to the drug, e.g., clearly related to disease progression.

After a standard 3+3 design begins, a minimum of three subjects will be treated at each dose level. All three subjects in a cohort will be evaluated for DLT in the defined DLT evaluation period (within 28 days of starting study treatment) before enrollment of subjects at the next dose level may begin. For all dose levels, if no DLTs are observed during the evaluation period among the three treated patients, escalation to the next dose level may begin. If a DLT is observed in one of

the first three subjects in the cohort, the cohort will be expanded to six subjects. If zero or one of six subjects in the cohort experiences a DLT within the evaluation period, escalation to the next dose level will occur. If a DLT is seen in two or more subjects in a cohort, escalation will be stopped and the Maximum Tolerated Dose (MTD) will be considered to have been exceeded. The next lower dose will be considered as MTD if six patients have already been treated at that dose. Otherwise if only three patients were treated at the next lower dose, then an additional three patients should be enrolled at the next lower dose level for a total of six patients. If zero or one has DLTs among the 6 patients, then this dose is declared as MTD. Otherwise, there is further de-escalation according to the same scheme. As a result, the MTD is the highest dose where at most one-sixth of the patients developed DLT.

In addition, an expansion cohort of 6 patients will be added at the recommended dose (MTD or biologically active dose) once that dose has been determined.

10.2.1 Probability of Dose Escalation

For the first 3 cohorts, we will escalate according to table 1 as long as there is no grade 2 or above adverse reaction occurred. After we switch to a standard 3+3 design, there will be two possible outcomes that would permit escalation to occur: (1) no DLT observed in the first three subjects; or (2) one DLT observed in the first three subjects, followed by no DLT observed in three additional subjects at the same dose level. The following probabilities of dose escalation (Table 6) are calculated as the sum of the binomial probabilities of the two possible outcomes. For example, when the underlying DLT rate is no more than 20%, the probability of dose escalation will be over 71%.

Table 6. Probability of dose escalation

Underlying DLT Rate	Probability of Dose Escalation
10%	91%
20%	71%
30%	49%
40%	31%

10.2.2 Determination of the MTD

Definition of MTD: The maximum tolerated dose (MTD) is defined as the highest dose studied at which no more than one in six patients experience a DLT. However, the final determination will also take into account any cumulative or delayed toxicity (e.g. an adverse event that occurs in later cycles). Accrual is suspended when a cohort of three subjects has been enrolled until toxicity data for that cohort for the DLT evaluation period have been reported, or when the study endpoints have been met.

At the MTD or biologically active dose, an expansion cohort of an additional 6 patients will be enrolled, again evaluated after each 3 for DLTs.

10.3 Evaluable Cohort and Subject Replacement

The trial may be completed after 33 patients have been enrolled, based on 8 cohorts with a total of 12 patients at the MTD/biologically active dose. If the dose escalation switches to standard 3+3 design, then up to 78 patients will be enrolled, based on 3-6 patients per cohort for 12 cohorts (if all dose levels require cohorts without intra-patient escalation), and a total of 12 patients at the

MTD/biologically active dose. A subject will be considered evaluable for assessment of DLT if the subject receives at least 2 doses of UC-961 and completes the safety follow-up through the DLT evaluation period, or the subject experiences a DLT at any time during the DLT evaluation period. Any non-evaluable subject will be replaced in the same dose cohort to complete the number of evaluable subjects for the MTD analysis.

The Safety population will include all subjects who receive any treatment of UC-961. The Safety population will be used to evaluate baseline characteristics as well as all descriptive endpoints for safety.

10.4 Statistical Analysis

The adverse events from the treatment beginning to two months after treatment completion will be recorded. Incidence of adverse events will be summarized by event type, grade and body system. Particularly, the rates of infusion reactions, major infection and grade 3 or above non-infection adverse events will be reported.

Secondary endpoints.
The following will be reported overall and by dose cohort: as available, median progression-free survival will be estimated using the Kaplan-Meier method. Clinical activity will be assessed based on iwCLL criteria, assessed from baseline visit to the response assessment visit.

Exploratory endpoints to be analyzed include the following mechanism of action studies, by dose cohort:

1. ROR1 receptor density on circulating bulk tumor cells and stem cells (flow assays)
2. Plasma pharmacokinetics of UC-961 levels
3. Level of circulating antibodies against UC-961
4. Multiplexed assay of focused CLL signaling pathways via qPCR array and targeted sequencing.
5. ROR1 related protein assays via western blot and quantitative proteomics.

PK/PD studies using non-compartmental models will be reported based on assays 1-3. Assays 4 and 5 will be assessed at baseline and the response assessment visit. Within patient changes will be assessed for statistical significance at the 5% level, using t-tests on appropriately transformed data or non-parametric tests as necessary. Comparisons across dose cohorts will use generalized linear models or anova.

Standard laboratory examinations including hematology, comprehensive metabolic panel, etc (see section 5.0) will be performed before, during and after the treatment. We will test if the average level of these measurements after the treatment is higher or lower than the pre-treatment level by a paired t-test at 5% significance level. For each marker, a Wilcoxon rank sum test will be used to assess the association of a baseline level or changes from baseline to the last measurement against tumor response status at the time of the response assessment visit.

The overall response rate, complete response rate, MRD negative rate will also be reported, overall and by dose cohort.

All statistical analyses will be at the 5% significance level using 2-sided tests.

10.5 Exposure-response modeling

Following the FDA Guidance for Industry on Exposure-Response Relationships, exposure-response modeling of effectiveness and toxicity will be conducted as part of the secondary endpoint evaluation. The goal of these analyses will be to identify a dose-response relationship, if any, between exposure to UC-961 and clinical response (effectiveness) or adverse events (toxicity). Dose of UC-961 will be defined using both administered dose and PK/PD derived measures, as described in detail below.

10.5.1 Exposure-response modeling of effectiveness.

The primary response variable will be the overall response rate, defined as CR, PR or PR with persistent lymphocytosis at final assessment (section 7.2).
Secondary response variables will include:

- the average percent reduction in the pretreatment lymphocyte count,
- the average sum of the products of lymph nodes,
- the percent of patients experiencing sustained improvement in cytopenias, defined as improvement by more than 50% of baseline value, or hemoglobin level higher than 11 g per deciliter, an absolute neutrophil count higher than 1500 cells per cubic millimeter, or a platelet count higher than 100,000 cells per cubic millimeter, as measured at both end of treatment and final response assessment.

Two analyses will be conducted using two different primary exposure variables. The first analysis will be by actual total doses received. A second analysis will use the primary PK exposure variable of $AUC_{0\text{-}t}$,defined as the area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t), calculated by the linear trapezoidal rule from a two-compartment PK model. This last quantifiable concentration will be cycle 4 day 1, prior to start of infusion. The $AUC_{0\text{-}t}$ will be computed by the third-party vendor for PK. Other potential secondary exposure variables considered will be ROR1 receptor occupancy measured during treatment.

The primary covariates will be age > 70 years, RAI stage, presence of Del 17p or Del 11q, number of prior therapies, mutational status, ZAP-70 status, baseline presence of nodes > 5 cm, baseline myelotoxicity (Grade $\geq$ 3 neutropenia, anemia, or thrombocytopenia), and baseline ECOG performance status >0.

The modeling approach will be logistic regression of response (or alternatively a GLM for the appropriately transformed outcome of percent reduction), using the primary exposure variable and including covariates. Covariates will be screened one at a time for association with response using chi-squared tests; variables significant at the 20% level will be retained in the final model. A dose-response relation between UC-961 exposure and response will be tested for using a one sided test at the 5% significance level. A positive statistical association will provide preliminary causal evidence of efficacy. Lack of association may be due to small sample sizes at the biologically effective dose, in this Phase I study.

10.5.2 Exposure-response modeling of toxicity.

The primary response variable will be the overall rate of grade 3 or higher adverse events (Section 8) of any attribution.

Secondary response variables will include:

- The overall rate of grade 1 or higher adverse events.

- Individual analysis of any category of adverse event which occurs at higher than 50% rate (others will be too few for individual analysis at the small anticipated sample size)

As in the efficacy models, two analyses will be conducted using two different primary exposure variables. The first analysis will be by actual total doses received. The second analysis will use the primary PK exposure variable of $AUC_{0\text{-}t}$, defined as in the efficacy analysis.
The primary covariates will be age > 70 years, RAI stage, presence of Del 17p or Del 11q, number of prior therapies, mutational status, ZAP-70 status, baseline presence of nodes > 5 cm, baseline myelotoxicity (Grade $\geq$ 3 neutropenia, anemia, or thrombocytopenia), and baseline ECOG performance status >0.

The modeling approach will be logistic regression, using the primary exposure variable and including covariates. Covariates will be screened one at a time for association with response using chi-squared tests; variables significant at the 20% level will be retained in the final model. A dose-response relation between UC-961 exposure and response will be tested for using a one sided test at the 5% significance level.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

11.4 Data and Safety Monitoring

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by the clinical trials office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported after every 6 patients or sooner if required for clinical study stopping rules (Section 4.9), and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

11.5 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

13.1 Appendix A. Performance Status

PERFORMANCE STATUS CRITERIA ECOG Performance Status	
Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead