Ofatumumab in Combination with Glucocorticoids for Primary Therapy of Chronic Graft vs. Host Disease

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I. BACKGROUND AND SCIENTIFIC RATIONALE

Chronic graft vs. host disease (chronic GVHD)

Chronic graft-versus-host disease (chronic GVHD) is a major late complication of allogeneic hematopoietic cell transplantation (HCT), which affects up to 70% of HCT recipients. The syndrome is associated with major transplant-related morbidity, mortality, infectious complications, prolonged duration of immune suppression, and impaired patient-reported quality of life.[1-8] Thus, it represents a major obstacle to recovery and survival following HCT, and its prevention and therapy are of significant importance.

The syndrome is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver. However, most organs can be involved, with parallels to other systemic immune-mediated disorders, such as systemic lupus erythematosis, Sjogren's disease, and systemic sclerosis. Clinical predictors for the development of chronic GVHD reported in published literature most consistently include increasing age of the donor or recipient, donor/recipient HLA disparity and donor relation (greater risk in unrelated vs. matched sibling donors), male recipients of allografts from alloimmunized female donors, prior development of acute GVHD, and the use of peripheral blood mobilized stem cells vs. bone marrow. [9-12]

Chronic GVHD diagnosis and classification

Diagnosis and classification of the syndrome has undergone major revision following the 2005 NIH Consensus Conference on Chronic GVHD. According to the historical classification, acute and chronic GVHD were distinguished by the occurrence of manifestations before or following day 100 post-HCT. The previously accepted severity classification defined limited involvement as restricted to limited cutaneous involvement and/or hepatic dysfunction, while extensive disease denoted more substantial manifestations such as generalized cutaneous involvement, hepatic dysfunction with biopsy confirmation of chronic aggressive hepatitis, bridging necrosis or cirrhosis, or involvement of other target organs, such as the eye, mouth, or lung.[13]

According to the proposed NIH Consensus definitions, chronic GVHD is rather diagnosed according to diagnostic manifestations of the syndrome, rather than the time of onset following HCT. Accordingly, manifestations of acute GVHD occurring before day 100 are defined as acute GVHD, while those occurring after day 100 are considered persistent, recurrent, or late acute GVHD based on the prior occurrence of acute GVHD in the patient. Classic chronic GVHD is defined based on the definitive manifestations of the syndrome in the absence of concurrent acute GVHD manifestations. The concurrent presentation of both operationally defines the overlap subtype of chronic GVHD. In addition, guidelines for severity grading were proposed to replace the previously accepted scheme based on limited vs. extensive involvement. Rather, severity is scored according to objective criteria for each organ involved, which is summarized for an overall severity score of mild, moderate or severe.[14]

Therapy of established chronic GVHD

Accepted standard primary therapy for chronic GVHD includes 1mg/kg or greater of prednisone or equivalent with or without a calcineurin inhibitor.[2,15] The addition of other systemic immune suppressive agents has not provided benefit, as evidenced by trials employing azothioprine, thalidomide, or hydroxychloroquine combined with steroids,[16-18] or the more recent trial evaluating the combination of steroids and mycophenolate mofetil.[19] However, further work remains to improve the success of primary therapy for chronic GVHD, as response is often incomplete.

In the analysis of major published primary chronic GVHD therapy trials,[15-20] the following summarizes current evidence: Complete response rate assessed at 6-9 months following steroid based therapy (either 1mg/kg of prednisone alone or this in combination with additional agents such as azathioprine, thalidomide, hydroxychloroquine or mycophenolate mofetil) includes a range of reported values from 16% to 37%. In the study by *Sullivan, et al*, 9 month complete response rate to prednisone was 33%, prednisone + azathioprine 37%, and prednisone alone among high risk cases 16%.[16] *Arora, et al* reported 6 month complete response rate of 17% in prednisone + thalidomide and cyclosporine, and 28% for prednisone and cyclosporine alone.[17] In a more recent trial comparing activity of prednisone vs. prednisone and mycophenolate mofetil, *Martin, et al* reported a 6 month complete response rate of only 23%.[19] Finally, *Gilman, et al* reported CR rates at 9 months of 38% and 33%, respectively for hydroxychloroquine + prednisone vs. prednisone alone. Thus, available randomized trials suggest an average complete response rate at 6-9 months of 27%. Overall response rate (ORR) (total of complete response (CR) + partial response (PR)) has been reported as the following: *Sullivan, et al* reported ORR of 62% among prednisone treated patients, 64% for prednisone with azathioprine, and only 32% for prednisone treated patients with thrombocytopenia.[16] *Arora, et al* reported ORR of 84% at 6 months for prednisone treated patients and 88% for those treated with prednisone and thalidomide.[17] *Martin, et al* reported an ORR of 62% at 6 months for patients treated with prednisone + mycophenolate mofetil or prednisone + placebo.[19,21] *Gilman, et al* reported ORR at 9 months of 39% and 46% for hydroxychloroquine + prednisone vs. prednisone alone.[18] Thus, published randomized trials support an average ORR at 6-9 months of 60%. Importantly, *Martin, et al* demonstrated that ORR at 6 months of therapy was significantly associated with the ultimate risk for treatment failure, defined as initiation of secondary systemic GVHD treatment, non-relapse death, or development of Bronchiolitis Obliterans. The cumulative incidence of treatment failure was 37% vs. 63% in those with overall response vs. not, $p = 0.01$.[21]

Based on limited response to primary therapy, many will go on to require additional immune suppressive agents for chronic GVHD control. Steroid-refractory chronic GVHD has most commonly been defined as either progressive manifestations despite one month, or rather incomplete response despite two months of 1-2mg/kg of prednisone or equivalent.[2] Multiple immune suppressive agents, including pharmacologic agents, monoclonal antibodies, and strategies such as extracorporeal photopheresis have demonstrated moderate activity in this setting, both ameliorating objective chronic GVHD manifestations, as well as importantly facilitating liberation from systemic steroids. Their activity is incomplete, however, and many with steroid-refractory chronic GVHD will require multiple agents to achieve disease control. The overall burden of chronic GVHD despite routine pharmacologic GVHD prophylaxis, limited response to

primary and salvage therapy, and the attendant morbidity and mortality all speak to the rationale for novel approaches to primary therapy.

Assessment of therapeutic response in chronic GVHD

The established method for response determination in the majority of chronic GVHD therapy trials is that of clinician-determined response. This method relies on the treating clinician's integration of dynamic chronic GVHD manifestations for a summary response categorization of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR indicates complete resolution of all chronic GVHD manifestations; PR signifies reduction in disease activity at response assessment compared to pre-treatment levels, but without complete resolution; SD indicates no response and no progression; and PD indicates progressive chronic GVHD manifestations from baseline to response assessment. This response assessment tool will be utilized for the primary endpoint of 6 month ORR in this trial, and for the purpose of power/sample size estimation with reference to historical published data on 6 month ORR according to this metric.

Following a 2005 NIH Consensus Conference for Chronic GVHD, several additional means of response assessment in chronic GVHD therapeutic trials have been proposed. These include change in overall NIH severity categories, proposed NIH response criteria, 0-4 and 0-10 ordinal scales that rely on clinician assessment, organ-specific tools such as the Vienna skin scale, as well as patient-determined change in chronic GVHD activity, chronic GVHD associated symptom burden, functional limitations, and change in quality of life. A national Chronic GVHD Consortium is currently assessing these competing measures of disease activity and their relationship to longer-reaching outcomes indicating clinical benefit, such as failure-free survival, discontinuation of all immune suppression, overall survival, or patient-reported benefit. However, to date these remain proposed tools that lack validation for the purpose of chronic GVHD clinical trial design and response determination.

Accordingly, clinician-determined response (CR, PR, SD, PD) remains the standard for the primary measure of therapeutic response in clinical trials. However, comprehensive information needed to calculate response according to proposed metrics will be collected (*see appendix* C) during the trial. We will report these data as secondary measures of response, and will study both the level of agreement between these competing response measures and their association with long-term measures of chronic GVHD treatment success.

Clinical Insights into chronic GVHD pathogenesis

While major insights have resulted from investigation into pathobiology of acute GVHD, our understanding of the mechanisms underlying chronic GVHD development and maintenance is limited. Murine and human clinical data suggest a clear role for donor alloreactive T cells in chronic GVHD pathogenesis: Peripheral blood mobilized stem cell products, which contain a greater dose of donor T cells compared to bone marrow harvested stem cells, impose a greater risk for the occurrence and severity of chronic GVHD and an associated prolonged duration of immune suppression.[9] Conversely, *ex-*

vivo T cell depletion strategies, as well as *in vivo* strategies such as anti-thymocyte globulin (ATG) or alemtuzumab,[22-24] are associated with decreased risk of chronic GVHD. Basic and human correlative studies also suggest a relationship between regulatory T cells and chronic GVHD.[25] Allied clinical and basic data, however, suggest other important mechanisms.

Major clinical observations support the role of loss of B-cell tolerance and altered B cell homeostasis following transplantation in chronic GVHD pathogenesis: First, autoantibodies are often detected in patients with chronic GVHD.[26-28] As well, reduced levels of immature B cells in patients with chronic GVHD support altered B cell homeostasis.[29] After sex mismatched HCT, allo-antibodies directed against the Y chromosome associated minor histocompatibility antigens, or H-Y antibodies, have been detected 4-9 months after HCT and correlate with the occurrence of chronic GVHD.[30,31] These humoral immune responses were associated with coordinated T cell response to HY minor histocompatibility antigen epitopes.[32] In the setting of cutaneous sclerosis of chronic GVHD, activating anti-PDGFR antibodies have been detected,[27] and agents with activity against this receptor kinase such as imatinib have demonstrated activity in this condition.[33] Additionally, multiple clinical trials have demonstrated activity of the anti-CD20 monoclonal antibody, Rituximab, in the treatment of chronic GVHD which has failed standard glucocorticoid therapy.[34-36] Finally, HCT patients treated preemptively with Rituximab appeared to have less risk for steroid-requiring chronic GVHD compared to historical controls that did not receive prophylactic Rituximab.

Altered B cell homeostasis and excess BAFF in chronic GVHD development

In a minor histocompatibility-mismatched murine model of chronic GVHD, donor B cells were required for the development of chronic GVHD.[37] Following transplant conditioning, recipient B cells are depleted, and donor B cells demonstrate altered reconstitution. Pre-clinical models demonstrate that B cell–activating factor (BAFF) has a key role in B cell reconstitution and homeostasis. In such models, B cell survival is dependent on B cell receptor and BAFF signaling, and B cell homeostasis is dependent on soluble BAFF concentration. BAFF levels, as well as the balance of autoreactive B cells and competing naïve B cells determine the fate of autoreactive B cells.[38,39] Importantly, investigators have similarly demonstrated aberrant B cell homeostasis and elevated BAFF levels in human HCT recipients who developed chronic GVHD. *Sarantopoulos, et al* performed phenotypic and functional studies of peripheral blood B cells in 82 patients following HCT.[40] These included ‘group 1’ of 57 patients (22 with active chronic GVHD, 23 with inactive chronic GVHD, and 12 with no chronic GVHD), and ‘group 2’ of 25 patients prospectively followed with samples obtained every 3 months from time of HCT (including 8 who did not develop chronic GVHD by 12 months post-HCT and 17 who developed chronic GVHD between 3 and 12 months post-HCT). B cell phenotype was studied following isolation of lymphocytes from whole blood samples using the Ficoll method. Soluble BAFF from plasma samples was determined using enzyme-linked immunosorbent assay (ELISA). In the group 1, comparisons were made in BAFF level, CD19+ B cell numbers, and BAFF to B cell ratio: Those with active chronic GVHD had significantly greater BAFF, lower CD19+ B cell number, and greater BAFF to B cell ratio compared to those with inactive chronic GVHD, no prior chronic

GVHD, and 33 healthy controls. As well, antigen naïve B cells (CD19+IgD+CD38LoCD27-) were significantly lower in those with chronic GVHD compared to patients without chronic GVHD. Conversely, CD27+ B cell subsets (IGD+ memory B, Pre-GC, Post-GC memory B, and plasmablast/plasma cell (PB/PC)) proportions were greater in those with active chronic GVHD compared to other groups. Increasing BAFF levels correlated with increasing numbers of activated pre-GC and PB/PC cells in chronic GVHD.

In the prospective ('group 2') cohort, serial BAFF levels, B cell numbers and phenotype were measured at 3 month intervals from HCT. In patients (n=8) who did not develop chronic GVHD and patients following autologous transplant (n=8), BAFF levels were elevated early after transplant at 1 and 3 months. In these two groups, BAFF levels declined as B cell numbers increased. In the 17 patients who developed chronic GVHD, BAFF levels remained high despite low B cell numbers. While the proportion of CD27+ B cells decreased as BAFF levels returned to normal in those who did not develop chronic GVHD, those with chronic GVHD had elevated CD27+ B cells that persisted over 12 months following HCT. A consolidative model suggests that, in patients who develop chronic GVHD, high BAFF levels and decreased numbers of naïve B cells (high BAFF/B cell ratio) support alloreactive pre- and post-germinal center CD27+ B cells that contribute to chronic GVHD development.

Ofatumumab – summary of pharmacokinetics, toxicology, and human clinical trial data

Ofatumumab (also known as HuMax-CD20) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) which targets a unique epitope on the CD20 molecule.

Nonclinical Pharmacology

Binding of ofatumumab causes clustering of CD20 on the cell surface and cell death through the induction of complement mediated cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). *In vitro* studies showed that ofatumumab is able to kill tumor B cells including those with low CD20 expression, such as primary chronic lymphocytic leukaemia (CLL) cells, and cells with high expression of complement defense molecules. Compared to rituximab, ofatumumab showed potential in nonclinical studies to be more potent at inducing CDC, especially in cells with low CD20 expression. As a fully human antibody, ofatumumab is predicted to be less immunogenic than rituximab, which is a chimeric monoclonal antibody.

Nonclinical Pharmacokinetics and Toxicology

An *in vitro* human tissue cross-reactivity study has confirmed that ofatumumab binding is restricted to B cells within the peripheral blood circulation and human lymphoid tissues, suggesting there is little likelihood of non-pharmacologically mediated effects. In monkey repeat dose toxicity studies, ofatumumab elicited the predicted pharmacological response; specific binding of ofatumumab to CD20+ B cells and the induction of cell death. Intravenous (IV) administration to monkeys for up to 7 months

profoundly decreased circulating B cells and resulted in moderate germinal center and follicular atrophy in the lymph nodes, Peyer's patches and spleen. Following clearance of ofatumumab, repletion of B cell counts and a reversal of the tissue changes noted during the study were observed. Subcutaneous (SC) administration to monkeys in the 2 dose subcutaneous and intravenous bridging study demonstrated similar changes in the depletion and recovery of B cells. The pharmacokinetics of ofatumumab was typical of a monoclonal antibody with low clearance, a small volume of distribution and a relatively long half-life.

There were no other ofatumumab-related systemic effects (including effects on the delayed type hypersensitivity response) or histopathological changes in monkeys following chronic exposure to ofatumumab. However, a minor reduction in the magnitude of the immunoglobulin G (IgG) response to the keyhole limpet haemocyanin (KLH) antigen was noted in monkeys dosed at 20 and 100 mg/kg.

There were 5 unscheduled deaths in the intravenous 7 month repeat dose study. Three out of 42 monkeys succumbed to a probable *C. jejuni* infection; a common yet problematic fecal-oral transmitted pathogen in monkeys. This infection was not considered to be ofatumumab treatment-related and no increase in susceptibility to infection has been reported in the clinical studies. Hemolytic anemia occurred in 2 out of 42 monkeys in the 7 month study. Both of these monkeys had a positive direct Coombs' test indicative of the presence of anti-drug antibodies (ADAs). It is most likely that the hemolytic anemia was due to a strong ADA response to ofatumumab, which induced immune complex formation. Binding of immune complexes to the surface of the red blood cells is thought to have resulted in sequestration of the coated red cells in the spleen causing the hemolytic anemia.

ADAs have been detected in several monkey toxicity studies following both IV and SC administration. However, no toxicities directly associated with the ADAs have been reported and an ADA response in monkeys is not considered indicative of an ADA response in humans. No maternal toxicity, adverse effects on embryofetal development or teratogenicity occurred in the monkey embryofetal development study at doses up to 100 mg/kg. The effect on human pregnancy is unknown.

Effects in Humans

Pharmacokinetics and pharmacodynamics

Pharmacokinetic data are currently available from eight completed studies (Study Hx-CD20-001, Study Hx-CD20-402, Study Hx-CD20-406, Study OMB111148, Study OMB112758, Study Hx-CD20-403, Study OFA110867, and Study EN414/OMS115102), three concluded studies (Study Hx-CD20-405, Study Hx-CD20-407, and Study Hx-CD20-409), and two ongoing studies (Study GEN410/OFA110635 [double-blind and open-label treatment periods completed], and Study GEN411/OFA110634 [completed up to 24 weeks]). Ofatumumab was administered by IV infusion in all studies except Study OFA110867, in which it was given by subcutaneous (SC) injection. After repeated IV administration, clearance and volume of distribution values were low and half-life values were long for ofatumumab, as seen with other monoclonal antibodies. Statistically significant increases in AUC, Cmax, and t½ values and decreases in CL

values were found between the first and last infusions. These findings are likely due to the rapid and sustained depletion of CD20+ B cells after first infusion, leaving a reduced number of B cells available for the antibody to bind at subsequent infusions. Subcutaneous administration of a single dose of ofatumumab ≥30 mg in subjects with RA similarly resulted in rapid and sustained B-cell depletion.

Summary of safety data

Infusion reactions in the IV program are common adverse events (AEs) that are generally mild to moderate in severity, and have been mitigated by premedication and slower IV administration. Severe infusion reactions have been reported, and have occasionally led to temporary interruption or withdrawal of ofatumumab. Adverse events in the SC program to date have also shown severe reactions, but overall, most AEs have been generally mild to moderate, and have been considered as post-injection systemic reactions (PISRs). Infectious events including lower respiratory tract infections and cytopenias that include neutropenia, anemia, and thrombocytopenia have been observed in oncology trials with ofatumumab, but these events are commonly reported with the diseases under study and/or other concomitant therapies. Neutropenia and serious infections have also been reported in RA studies, but these generally occurred at a similar frequency between the ofatumumab and placebo groups.

Safety data from clinical trials utilizing the proposed dose/schedule of ofatumumab

In a phase I/II study of escalating dose ofatumumab (300mg, 700mg or 1,000mg delivered on days 0 and 14) for rheumatoid arthritis (RA) patients who had failed prior disease modifying (DMARD) therapy, the study therapy was generally well tolerated. Part A was a double-blind, placebo-controlled, dose escalation study with randomized treatment allocation within each of 3 sequential dose cohorts. Subjects received 2 infusions on Day 0 and Day 14 of either ofatumumab (300 mg: n=12; 700 mg: n=10; 1000 mg: n=10) or placebo (n=7) and were followed for safety, efficacy, and PK measurements for 24 weeks. Part B was a double-blind, placebo-controlled parallel group study with randomization (1:1:1:1) into 1 of 4 treatment arms. Subjects received 2 infusions on Day 0 and Day 14 of either ofatumumab 300 mg (n=58), 700 mg (n=57), 1000 mg (n=54), or placebo (n=56) and were followed for safety, efficacy, and PK measurements for 24 weeks. In addition, following implementation via a protocol amendment, efficacy data, selected safety data (B cells, immunoglobulins, and SAEs) and samples for HAHA analysis were collected at Weeks 36 and 48. Pre-medication with corticosteroids was not initially required; however, based on severe infusion-related reactions reported during Part A and Part B, the protocol was amended to include pre-medication with corticosteroids, an additional dose of antihistamine, and an increased infusion volume and infusion time.

A total of 214 AEs in 37 subjects were reported in Study 403 Part A. The most frequently reported AEs were nausea, fatigue, urticaria, hypotension, rash, pyrexia, vomiting, diarrhea, chills, dyspnea, headache, hyperhidrosis, and leukocyturia. A total of 164 AEs were reported in the ofatumumab treatment groups; these AEs were generally of mild or moderate intensity, while 7% (12 events) were severe and one was life-

threatening (anaphylactoid-like reaction). Adverse events judged as related to study product were mainly infusion-related and were also those most frequently reported. The most frequent symptoms reported on an infusion day were rash, urticaria, and hypotension. Of the AEs reported in the ofatumumab groups, 79/164 (48%) were reported on an infusion day. Among these, AEs were reported with substantially higher frequency on the first infusion day (74/79, 94%) compared with the second infusion day, with no evidence of a dose effect.

MedDRA Preferred term	Placebo (N=7)		Ofatumumab Dose 300 mg (N=12)		700 mg (N=10)		1000 mg (N=10)		Total (N=39)	
	n	E	n	E	n	E	n	E	n	E
Nausea	4	6	3	3	1	1	1	1	9	11
Fatigue	4	4	1	1	1	1	2	5	8	11
Urticaria	1	1	3	3	1	1	2	2	7	7
Hypotension			5	5	1	1	1	1	7	7
Rash			1	2	3	4	2	2	6	8
Pyrexia	1	1	4	4	1	1			6	6
Vomiting	2	4	2	2	1	1			5	7
Diarrhea	1	7			1	1	2	2	4	10
Chills	1	2	2	2	1	1			4	5
Dyspnea			1	1	1	2	2	2	4	5
Headache	1	2			1	1	2	2	4	5
Hyperhidrosis			1	1	2	2	1	1	4	4
Leukocyturia	1	1	1	1			2	2	4	4
Flushing					1	3	2	3	3	6
Upper respiratory tract infection	1	1	1	1	1	2			3	4
Dyspepsia	1	1	2	2					3	3
Dyphagia					2	2	1	1	3	3
Toothache	1	1	1	1			1	1	3	3
Pruritus			1	1	2	2			3	3
Chest discomfort					2	2	1	1	3	3
Edema peripheral					2	2	1	1	3	3
Urinary tract infection					2	2	1	1	3	3
Bronchospasm			1	1	1	1	1	1	3	3
Cough			1	1	1	1	1	1	3	3
Rhinitis allergic			1	1	1	1	1	1	3	3
Throat irritation			1	1			2	2	3	3
Myalgia	1	1	1	1			1	1	3	3
Dizziness	1	1	1	1			1	1	3	3
Swelling face							2	3	2	3
Nasopharyngitis							2	3	2	3
Hypertension	1	2					1	1	2	3
Herpes simplex			2	2					2	2
Nasal congestion			2	2					2	2
Proteinuria	1	1	1	1					2	2
Anxiety	2	2							2	2
Tooth extraction	1	1					1	1	2	2

N = number of subjects exposed to study drug; n = number of subjects with adverse events (AEs); E = number of AEs

The safety population for Part B comprised all 225 exposed subjects. A total of 81%, 84%, 85%, and 57% of subjects in the 300 mg, 700 mg, 1000 mg, and placebo groups, respectively, reported at least one AE. Among the 675 AEs reported, 66% (356/540) in the active dose groups and 41% (55/135) in the placebo group were considered as related to study drug. The most frequently reported AEs in the total active treatment group were rash, throat irritation, dyspnea, pharyngolaryngeal pain, nausea, pruritus, and urticaria (Table 36). A total of 540 AEs were reported in the ofatumumab treatment

group; these AEs were generally of mild-to-moderate intensity, with 32 severe and 2 life-threatening events (breast cancer and pneumonitis).

MedDRA Preferred term	Placebo (N=56)		Ofatumumab Dose 300 mg (N=58)		700 mg (N=57)		1000 mg (N=54)		Total Active (N=169)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Total number of subjects with AEs	32 (57)	135	47 (81)	179	48 (84)	207	46 (85)	154	141 (83)	540
Rash			6 (10)	6	14 (25)	15	10 (19)	12	30 (18)	33
Throat irritation			9 (16)	10	5 (9)	5	6 (11)	7	20 (12)	22
Dyspnea	1 (2)	2	3 (5)	4	7 (12)	8	8 (15)	8	18 (11)	20
Pharyngolaryngeal pain	2 (4)	2	5 (9)	6	5 (9)	6	5 (9)	5	15 (9)	17
Pruritus			3 (5)	3	6 (11)	13	4 (7)	4	13 (8)	20
Nausea	4 (7)	9	4 (7)	4	6 (11)	6	4 (7)	4	14 (8)	14
Urticaria			3 (5)	3	4 (7)	5	5 (9)	6	12 (7)	14
Headache	4 (7)	6	4 (7)	4	4 (7)	5	2 (4)	3	10 (6)	12
Upper respiratory tract infection	3 (5)	3	3 (5)	3	4 (7)	4	3 (6)	4	10 (6)	11
Fatigue	2 (4)	4	3 (5)	3	4 (7)	6	2 (4)	2	9 (5)	11
Cough	6 (11)	9	5 (9)	5	4 (7)	4			9 (5)	9
Rhinitis	2 (4)	2	1 (2)	1	2 (4)	2	5 (9)	5	8 (5)	8
Hypertension	3 (5)	3	2 (3)	2	5 (9)	6	2 (4)	2	9 (5)	10
Rheumatoid arthritis	5 (9)	5	5 (9)	6	1 (2)	3	1 (2)	1	7 (4)	10
Dysphagia			2 (3)	3	1 (2)	1	4 (7)	4	7 (4)	8
Dry throat			3 (5)	4			3 (6)	3	6 (4)	7
Throat tightness			1 (2)	1	5 (9)	5			6 (4)	6
Infusion-related reaction	1 (2)	1	2 (3)	2	1 (2)	1	3 (6)	3	6 (4)	6
Hypersensitivity					5 (9)	5	1 (2)	1	6 (4)	6
Flushing	1 (2)	2	3 (5)	3	1 (2)	1	2 (4)	2	6 (4)	6

N = number of subjects exposed to study drug; n = number of subjects with adverse events (AEs); % = proportion of subjects reporting AE; E = number of AEs.
For rash, urticaria, hypertension and upper respiratory tract infection, the numbers include NOS (not otherwise specified).

A total of 3 SAEs were reported in Study 403 Part A; 2 in the 300 mg dose group and 1 in the 1000 mg dose group. In the 300 mg dose group, 1 event each of anaphylactoid reaction and urticaria were reported and both were considered related to ofatumumab.

The anaphylactoid-like reaction occurred in a subject premedicated only with paracetamol and antihistamine and prior to optimized rate of administration and was of Grade 4 intensity. Symptoms included urticaria, hypotension, loss of consciousness, and vomiting. The subject recovered after treatment with calcium and corticosteroids. One subject experienced Grade 2 urticaria; ofatumumab infusion was paused, but when restarted the urticaria worsened. Treatment was discontinued and the urticaria resolved after 2.5 hours. One event of cardiac ischemia was reported in the 1000 mg dose group and was considered unrelated to treatment with ofatumumab. No deaths were reported.

Two SAEs were reported during the Part A follow-up period as follows: cellulitis in one subject in the 700mg group and intervertebral disc protrusion in one subject in the 1000mg group. Neither event was considered related to treatment with ofatumumab by the investigator. In part B, a total of 36 SAEs were reported in 26 subjects (24 events up to Week 24 and 12 events between Week 24 and Week 48). A higher incidence of SAEs, primarily infusion-related events, was observed in the 1000 mg group compared with the placebo, 300 mg, or 700 mg groups. No AEs had a fatal outcome. Of the 11 SAEs considered related to ofatumumab, 5 were infusion related, with 4 of the 5 infusion-related SAEs having occurred prior to implementation of the final protocol amendment that optimized the pre-medication regimen to decrease the frequency and

intensity of infusion-related reactions. Of the remaining, there were 3 infections (bronchopneumonia, urinary tract infection, cellulitis) and 1 event each of pneumonitis, exacerbation of RA, and breast adenocarcinoma. The subject with the pneumonitis had been receiving MTX, for 5 years. Other than infusion-related events, a review of the safety data including the serious events from this study did not provide evidence of a causal relationship between the reported events and ofatumumab use.

MedDRA System Organ Class / Preferred term	Placebo (N=58)		300 mg (N=58)		700 mg (N=57)		1000 mg (N=54)		Total Active (N=169)	
	n	E	n	E	n	E	n	E	n	E
Total number of subjects with SAEs	5	7	5	9	6	6	10	14	21	29
Infections and Infestations	**4**	**4**	**1**	**1**			**3**	**4**	**4**	**5**
Bronchopneumonia			1	1					1	1
Cellulitis							1	1	1	1
Clostridium colitis							1	1	1	1
Joint tuberculosis							1	1	1	1
Urinary tract infection							1	1	1	1
Appendicitis	1	1								
Bursitis infective	1	1								
Streptococcal sepsis	1	1								
Tuberculosis	1	1								
Musculoskeletal and Connective Tissue Disorders	**1**	**1**	**3**	**4**	**1**	**1**	**1**	**1**	**5**	**6**
Rheumatoid arthritis	1	1	1	2			1	1	2	3
Localized osteoarthritis			1	1					1	1
Lumbar spinal stenosis			1	1					1	1
Osteoarthritis					1	1			1	1
General Disorders and Administration Site Conditions					**1**	**1**	**3**	**3**	**4**	**4**
Infusion related reaction							3	3	3	3
Non-cardiac chest pain					1	1			1	1
Gastrointestinal Disorders			**2**	**2**					**2**	**2**
Gastritis			1	1					1	1
Rectal prolapsed			1	1					1	1
Cardiac Disorders	**1**	**1**	**1**	**1**			**1**	**2**	**2**	**3**
Atrial fibrillation							1	2	1	2
Pericarditis			1	1					1	1
Angina unstable	1	1								
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	**1**	**1**			**1**	**1**	**1**	**1**	**2**	**2**
Breast cancer					1	1			1	1
Keratocanthoma							1	1	1	1
Neoplasm of appendix	1	1								
Respiratory, Thoracic and Mediastinal Disorders					**1**	**1**	**1**	**1**	**2**	**2**
Bronchospasm					1	1			1	1
Pneumonitis							1	1	1	1
Surgical and Medical Procedures							**1**	**2**	**1**	**2**
Shoulder arthroplasty							1	1	1	1
Spinal decompression							1	1	1	1
Nervous System Disorders			**1**	**1**					**1**	**1**
Carpal tunnel syndrome			1	1					1	1
Renal and Urinary Disorders					**1**	**1**			**1**	**1**
Nephrolithiasis					1	1			1	1
Skin and Subcutaneous Tissue Disorders					**1**	**1**			**1**	**1**
Urticaria, NOS					1	1			1	1

Summary of efficacy data

Efficacy in follicular lymphoma

In Study Hx-CD20-001, 15 of 37 (41%) evaluable subjects with FL obtained objective responses across all ofatumumab dose groups (300 mg, n=8: 63%; 500 mg, n=9: 33%; 700 mg, n=10: 20%; and 1000 mg, n=10: 50%) and included 4 (11%) subjects with complete response (CR), 3 (8%) subjects with CRu, and 8 (22%) subjects with PR. A

total of 19 (51%) subjects had SD and 3 subjects had PD. The median TTP for all subjects was 8.8 months and the median duration of response was 29.9 months. The time to next FL therapy was not reached during the study. In Study Hx-CD20-405, a total of 116 subjects were treated with two dose levels of single-agent ofatumumab. The ORR in the total population was 11%. This group of subjects was highly refractory with 65% refractory to their last chemotherapy. Subjects in the study had previously received a median of 4 prior treatment regimens. The 1000 mg dose group (n=86) demonstrated an ORR of 10% (1 CR, 8 PR). In addition, 50% of subjects in the 1000 mg treatment arm had stable disease (SD). The ORR among subjects in both treatment arms who were refractory to prior rituximab monotherapy (n=27) was 22%. The ORR in subjects who were refractory to rituximab in combination with chemotherapy was 7%, and the ORR among subjects refractory to rituximab maintenance was 9%. Median PFS was 3.2 months in the 500 mg dose group and 6.0 months in the 1000 mg dose group. At the time of this analysis, median OS was 31.7 months in the 1000 mg dose group (not estimable in the 500 mg dose group, as the estimated curve for OS did not cross the horizon line that represents the survival probability of 50%). In Study Hx-CD20-409 (N=58), subjects with previously untreated FL were randomized to two dose levels of ofatumumab in combination with CHOP: 300 mg of ofatumumab (cycle 1) followed by 500 or 1000 mg of ofatumumab (cycles 2-6), in combination with CHOP, every 3 weeks for 6 cycles. Results demonstrated an ORR of 90% in the 500 mg group (n=29) and 100% in the 1000 mg group (n=29). For the secondary endpoint of complete response, the rate was 21% for the 500 mg group and 31% for the 1000 mg group.

Efficacy in chronic lymphocytic leukemia (CLL)

In Study Hx-CD20-402 (N=33), ofatumumab treatment in subjects with relapsed or refractory CLL led to a 48% ORR in the highest dose group, Group C (n=27; 1st dose: 500 mg; 2nd, 3rd, and 4th dose: 2000 mg), and included 12 (44%) subjects with PR and 1(4%) subject with nodular partial response (nPR). One of the subjects showed all features of an nPR at Week 19 except that residual lymphadenopathy was identified by computed tomography (CT). For Group C, the median TTP was 15.6 weeks in the full analysis population and 23 weeks in the subgroup of responders. The median duration of response was 16 weeks and the median time to next CLL therapy was 52.4 weeks. In Study Hx-CD20-406 (N=154 as of the interim data cutoff of 19 May 2008;N=223 in the final CSR analysis), the protocol-defined results of ORR as assessed by an Independent Review Committee (IRC), demonstrated that the ofatumumab regimen is effective in subjects with CLL who are either refractory to both fludarabine and alemtuzumab (i.e., DR) or who are refractory to fludarabine and considered inappropriate for alemtuzumab treatment due to the presence of bulky (>5cm) lymphadenopathy (i.e., BFR). Additionally, ofatumumab was effective in “Other” subjects who failed fludarabine but were enrolled in the study prior to Amendment 3 and did not meet the further classification criteria of either DR or BFR defined in the amendment. The information from this interim data analysis formed the basis of the regulatory approval in the US, EU, Australia, Switzerland, and Croatia as ARZERRA™, for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Improvements in the individual components (i.e., constitutional symptoms, organomegaly, lymphadenopathy) of the response assessment as well as ECOG performance were observed. Of note, the median lymphocyte count and median lymph

node size decreased rapidly and continued to decrease during the treatment period in the majority of subjects [ARZERRA Prescribing Information, 2010]. The primary endpoint analysis of 223 subjects in Study Hx-CD20-406 included subjects in the DR (N= 95), BFR (N= 112), and Other (N=16) groups. The ORR was 49% (47/95) in the DR group, 43% (48/112) in the BFR group, and 63% (10/16) in the Other group. Among the 105 responders, 2 subjects in the BFR group achieved CR, 47 subjects in the DR group achieved PR, 46 subjects in the BFR group achieved PR, and 9 subjects in the Other group achieved PR. An additional 33 subjects in the DR group, 52 subjects in the BFR group, and 4 subjects in the Other group achieved SD. The median duration of response was 5.5 months, 6.4 months, and 7.4 months in the DR, BFR, and Other groups, respectively. The median PFS was 4.6 months, 5.5 months, and 8.9 months in the DR, BFR and Other groups, respectively. The median overall survival (OS) was 13.9 months in the DR group, 17.4 months in the BFR group, and 28.3 months in the Other group. In Study Hx-CD20-407 (N=61), subjects with previously untreated CLL obtained objective responses. The ORR in the 500 mg group was 77% and in the 1000 mg group was 73%. CR were observed in 32% of subjects (10/31) in the 500 mg group and in 50% of subjects (15/30) in the 1000 mg group. Overall, across both dose groups 25 subjects had CR, 19 subjects had PR, 2 subjects had nPR, 5 subjects had SD and 7 subjects had PD. Time-to-event endpoints were measured over 2 years. Median duration of response was 32.0 months for the 500 mg group (not estimable for the 1000 mg group). Median PFS was 33.0 months for the 500 mg group and 23.5 months for the 1000 mg group. Time to next anti-CLL therapy was 31.9 months for the 500 mg group and 26.7 months for the 1000 mg group. In Study OMB111148 (N=6), a total of 6 subjects with CLL were treated with two dose levels of single-agent ofatumumab. The ORR in the 6 subjects was 50%. All 3 subjects in the 1000 mg group had PR. In the 500 mg group, 1 subject had SD and 2 subjects had PD. The median PFS for all subjects was 32.1 weeks and the median duration of response was 30.8 weeks in the 1000 mg group. In Study OMB112758, conducted in Japan and Korea, 10 subjects received 8 weekly intravenous infusions of ofatumumab (1st dose: 300 mg; 2nd – 8th dose: 2000 mg) followed 5 weeks later by 4 monthly infusions of 2000 mg ofatumumab. For the 10 subjects, the overall response rate (PR or better) was 70% as assessed by the independent reviews; all of the seven responders had PR. The remaining 3 subjects had SD.

Efficacy in diffuse large B-cell lymphoma

In Study GEN415/OMB111776, 81 subjects with CD20+ relapsed DLBCL ineligible for autologous stem cell transplantation or DLBCL which had relapsed or progressed after autologous stem cell transplantation were treated with ofatumumab 300 mg for the first IV infusion, followed by seven weekly infusions of ofatumumab 1000 mg. The ORR was 11% (3 CR and 6 PR). In Study OMB110927, 61 subjects with relapsed or refractory CD20+ aggressive B-cell NHL who were transplant eligible were treated with ofatumumab + ICE (n=35) or ofatumumab + DHAP (n=26). Chemotherapy was dosed every 21 days for 3 cycles, while ofatumumab was dosed on Day 1 and Day 8 of Cycle 1, and on Day 1 of Cycles 2 and 3 (initial dose 300 mg, n=21; or 1000 mg, n=40; all subsequent doses 1000 mg). The ORR in the 59 evaluable subjects was 61% with CR in 37%.

Efficacy in rheumatoid arthritis

As of 21 December 2011, efficacy results are available from 3 studies in subjects with RA: Study Hx-CD20-403/OFA112657 Part A and Part B clinical study reports (completed Sept 2008) and follow-up period addenda (completed Dec 2010 and Jan 2011, respectively); Study GEN410/OFA110635 (two interim clinical study reports for the double-blind and open-label periods, completed June 2010 and Dec 2011, respectively); Study GEN411/OFA110634 (one interim clinical study report for the double-blind period, completed August 2011).

In Study Hx-CD20-403 Part A and B, all of the doses tested (300 mg, 700 mg and 1000 mg) resulted in profound B-cell depletion and B-cell levels below normal range or baseline were sustained for approximately 20-34 months. For the primary endpoint analysis (ACR20 response at 24 weeks) in Part B, all doses of ofatumumab were significantly better than placebo, with an ACR20 response being achieved by 40% ($p<0.001$), 49% ($p<0.001$), and 44% ($p<0.001$) of subjects in the 300 mg (n=58), 700 mg
(n=57), and 1000 mg (n=54) ofatumumab groups, respectively, compared with 11% in the placebo group (n=55). For the 700 mg and 1000 mg groups, significantly better improvements in ACR20 and ACR50 response rates were maintained out to 48 weeks compared with placebo. Subgroup analyses for the subjects on background MTX (n=174) showed slightly higher response rates in this subject group.

Study GEN410/OFA110635, a double-blind, randomized, placebo-controlled trial of the efficacy of ofatumumab in RA patients with an inadequate response to MTX, completed its 24-week double-blind period during the previous IB reporting period, and the open-label extension part was prematurely terminated by the Sponsor during the current reporting period as the clinical development of the intravenous route of ofatumumab administration in RA will no longer be pursued; the follow-up period is still ongoing. For the double-blind period, eligible subjects were randomized (1:1) to receive two intravenous infusions of either ofatumumab 700 mg or placebo two weeks apart (one course), in addition to background MTX treatment. In the intention-to-treat study population, comprising 260 patients, results demonstrated that a statistically significantly better ACR20 response at 24 weeks (primary endpoint) of 50% (64/129; $p<0.001$) was achieved for patients receiving ofatumumab compared to 27% (35/131) in the placebo group. Efficacy appeared to be observed by 8 weeks and the response was sustained throughout the double-blind period. Statistically significant improvements in favour of ofatumumab were also observed for all other key secondary efficacy endpoints [(ACR50, ACR70, ACRn, EULAR (European League Against Rheumatism) and Disease Activity Score (DAS28)] [Taylor, 2011]. All subjects who completed the 24-week double-blind period without receiving rescue disease-modifying anti-rheumatic drug (DMARD) treatment were eligible to proceed into the 120-week open-label period to receive repeat treatment courses with ofatumumab, which were given at individualized time intervals only if a clinical response had been achieved following the previous treatment course. As this study was prematurely terminated by the Sponsor ofatumumab treatment was discontinued by protocol amendment 5, dated 28 October 2010, and subjects proceeded to the ongoing Follow-up period at their next scheduled visit. An interim analysis of the open-label period was performed. No statistical analyses were

performed on data from the open-label period; data were summarized per “treatment course” using appropriate descriptive statistics. The open-label population (subjects who received ofatumumab during the open-label period) included 231 subjects. The mean (SD) for the minimum DAS28-ESR score (i.e. average lowest level of disease activity) was 4.01 (1.396) during the first ofatumumab treatment course and ranged from 3.34 (1.326) to 3.82 (1.588) for treatment courses 2 to 6; the seventh treatment course only included 2 subjects. The mean (SD) for the minimum change from baseline in DAS28-ESR score (i.e. average greatest change in disease activity) was -2.32 (1.192) for the first treatment course; a negative change represents an improvement in symptoms of disease. For subsequent treatment courses the mean (SD) for the minimum change from baseline in DAS28-ESR score ranged from -1.45 (0.845) to -1.77 (1.015) except for the seventh treatment course which only included 2 subjects. Based on DAS28-ESR, 90 subjects (37%) achieved disease remission (DAS28 score <2.6) and an additional 83 (34%) subjects had low disease activity (DAS28 ≥2.6 and <3.2) at some time during the double-blind and/or open label periods. When considered by treatment course, the percentage of subjects achieving disease remission ranged from 16 to 42%, and the percentage of subjects with low disease activity ranged from 9 to 28% (except for the seventh treatment course which only included 2 subjects). Based on DAS28-CRP, 125 subjects (51%) achieved disease remission and an additional 88 (36%) subjects had low disease activity at some time during the double-blind and/or open label periods. When considered by treatment course, the percentage of subjects achieving disease remission ranged from 29 to 46%, and the percentage of subjects with low disease activity ranged from 13 to 18% (except for the seventh treatment course which only included 2 subjects). Therefore, during each treatment course there was an improvement in disease activity following ofatumumab treatment, in addition to background MTX. Disease remission or low disease activity was achieved at some time during the double-blind and/or open label periods by 71% of subjects based on DAS28-ESR, and by 88% of subjects based on DAS28-CRP.

Study GEN411/OFA110634, a double-blind, randomized, placebo-controlled trial of the efficacy of ofatumumab in RA subjects with an inadequate response to TNF-α antagonist therapy, was prematurely terminated by the Sponsor during the current reporting period. An interim analysis of the double-blind period has been completed. Because of premature termination only 169 subjects (out of 236) were randomized. This was an insufficient number of subjects to achieve 90% power for the primary endpoint, and therefore no statistical testing was performed for the primary and secondary endpoints. Data were summarized using appropriate descriptive statistics. For the double-blind period, eligible subjects were randomized (1:1) to receive 2 infusions of either ofatumumab 700 mg or placebo 2 weeks apart (one treatment course), in addition to background MTX treatment. Ofatumumab, in addition to background MTX treatment, reduced the clinical signs and symptoms of RA in this population of patients with an inadequate response to TNF-α antagonist therapy, after a single treatment course of 2 infusions separated by 2 weeks. Efficacy was sustained throughout the double-blind period.

Efficacy in multiple sclerosis

Study GEN414/OMS115102 has completed both the 48-week (with 24 week cross-over), double-blind, placebo controlled treatment phase and the individualized follow-up phase. In the Week 0 to 24 period the majority of subjects'CD19+ and CD20+ levels were suppressed to zero; recovery started for the 100 mg and 300 mg active/placebo groups after approximately 12 and 20 weeks, respectively. In the 700 mg active/placebo group, all but one subject had a persistent and complete CD19+ suppression at Week 24 In the Week 24 to 48 period the majority of the subjects' CD19+ and CD20+ levels were suppressed to zero (mm3) within one week in subjects who received active treatment after the treatment cross-over phase. Recovery started for the subjects in the 100 mg placebo/active group after approximately 16 weeks (from these subjects' first infusion). In the 300 mg and 700 mg placebo/active groups, all subjects but one (700 mg) had persistent and complete CD19+ suppression at Week 48. Review of the raw summary statistics highlight the minimal amount of observed new MRI lesion activity following administration of IV ofatumumab in both the Week 0-24 and Week 24-48 treatment periods. Statistical analyses supported the observations from the raw data, showing statistically significant benefits in favour of ofatumumab; caution is needed in the interpretation of the analyses in this small dataset due to the extreme skew in the dataset collected and the assumptions made in the analyses. The observations were consistent in the majority of the exploratory endpoints (cumulative number of new T1 Gd-enhancing lesions, cumulative number of total T1 Gd-enhancing lesions and cumulative number of new and/or enlarging T2 lesions). The assessment of relapses did not show statistically significant differences in ofatumumab treatment from placebo. Although this was primarily a safety and tolerability trial, it also aimed to confirm CD20+ depletion and to obtain preliminary evidence of efficacious effect on MRI and clinical endpoints. The data demonstrated that ofatumumab induced a disease activity response and, as expected, ofatumumab caused profound and selective CD20+ reductions. Overall, the efficacy endpoints indicated that ofatumumab is potentially effective in RRMS patients.

Summary of trial rationale

Chronic GVHD is a major source of morbidity, mortality, and impaired quality of life after HCT. Despite prophylactic immune suppressive agents delivered prior to and following HCT, the majority of patients will develop chronic GVHD. The currently accepted primary therapy of chronic GVHD, namely 1mg/kg or greater of prednisone or equivalent, is ineffective, and available immune suppressive agents have limited activity in those who fail primary therapy. These all speak to the need for more effective primary therapy for chronic GVHD. Based on compelling clinical and basic insights into chronic GVHD biology, anti-CD20 based therapy has great potential to improve the success of chronic GVHD therapy. Thus, we propose a phase I-II study of combined ofatumumab and standard glucocorticoids to study the safety and efficacy of this approach.

II. STUDY OBJECTIVES

Primary Objectives:

1. Phase I: Determine the safety of ofatumumab in combination with steroids in the primary therapy of chronic GVHD
2. Phase II: Determine overall response rate (CR+PR) at 6 months to ofatumumab and glucocorticoid primary therapy of chronic GVHD.

Secondary Objectives:

1. Determine 6 month complete response rate to ofatumumab and steroids in the primary therapy of chronic GVHD.
2. Examine cumulative incidence of non-relapse mortality and primary disease relapse, and estimate overall survival from time of therapy.
3. Report utilization of second-line immune suppressive therapies.
4. Examine incidence of complete discontinuation of immune suppressive therapy .
5. Determine failure-free survival (composite outcome of death, relapse and requirement for secondary immune suppressive agents) and treatment success (composite outcome defined as complete resolution of all reversible chronic GVHD manifestations, discontinuation of all systemic immune suppressive agents, and freedom from death or primary malignancy relapse).
6. Evaluate serial measures of patient-reported outcomes following therapy, including functional ability, symptom burden, and quality of life.
7. Perform allied biologic studies for total B cells, B cell subsets, immune globulin levels, BAFF levels, and examine association between these biologic endpoints and clinical response to primary therapy.

III. STUDY DESIGN AND ENROLLMENT CRITERIA

Summary of Trial design

This is a phase I-II trial to examine the safety and efficacy of prednisone and escalating dose of ofatumumab for the primary therapy of chronic GVHD. Prednisone will uniformly be initiated at 1 mg/kg/day, and the phase I component will test an escalating dose of ofatumumab at cohorts of 300mg, 700mg, and 1000mg given on day 0 and 14 of study. In the phase II component, patients will be followed for total of 24 months (including study therapy day 0 and day 14, and then months 1, 3, 6, 12 after therapy, then at 18 and 24 months following therapy), and the primary efficacy endpoint of overall response to therapy will be determined at 6 months following initiation of therapy. Additional secondary endpoints and biologic correlative studies will be performed at the indicated time points.

Inclusion Criteria:

1. HCT recipients ≥ 18 years of age
2. HCT recipients newly requiring systemic glucocorticoid therapy (at ≥ 1mg/kg/day prednisone or equivalent) for chronic GVHD
    i. See **appendix B** for definitions of chronic GVHD severity for individual organs and determination of global composite score
    ii. In the phase I component of the trial, only those with overall moderate or severe global composite score are eligible
    iii. In the phase II component of the trial, patients of any global composite score are eligible, provided they have need for systemic therapy for chronic GVHD
3. Patients can be enrolled and begin study therapy with ofatumumab within 14 days from initiation of 1 mg/kg/day prednisone for therapy of chronic GVHD.

Exclusion Criteria:

1. Relapse of primary hematologic malignancy that served as indication for HCT.
2. Previous systemic glucocorticoid therapy (at ≥ 1mg/kg/day prednisone or equivalent) for chronic GVHD.
    - Prior systemic glucocorticoid therapy for acute GVHD is permitted
    - Prior or ongoing systemic immune suppressive agents (including, but not limited to common examples such as calcineurin inhibitors, sirolimus, mycophenolate mofetil) provided for either prevention or treatment of acute GVHD are permitted and part of routine standard of care
    - Patients with progressive, uncontrolled manifestations of acute or chronic GVHD despite ≥ 1mg/kg/day prednisone (or equivalent) therapy have steroid-refractory disease, and are therefore not eligible for this study
3. Current active hepatic or biliary disease (with exception of liver disease secondary to chronic GVHD, or patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment)
    - **Patients with abnormal liver function tests (bilirubin, alkaline phosphatase, ALT, AST) due to chronic GVHD are specifically not excluded from the study. This is a common manifestation of chronic GVHD, and thus a major target for the study therapy.**
4. Treatment with experimental non-FDA approved therapy within 5 terminal half lives or 4 weeks prior to enrollment, whichever is longer
5. Other past or current solid tumor malignancy
    - **Subjects who have been free of malignancy for at least 5 years, or have a history of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma are eligible.**

6. Prior treatment with anti-CD20 monoclonal antibody or alemtuzumab within 3 months prior to start of therapy.
7. **Uncontrolled** infectious complications not responsive to appropriate antimicrobial therapy.
8. History of significant cerebrovascular disease (i.e. stroke or TIA) in the past 6 months or ongoing event with active symptoms or sequelae
9. HIV positivity
10. Uncontrolled, current significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to randomization, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.
    - **Patients with history of cardiac disease, such as coronary disease, arrhythmia or congestive heart failure that are on appropriate medical therapy and without evidence of current decompensation are eligible.**
11. Significant concurrent, **uncontrolled** medical condition including, but not limited to, renal, hepatic, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease which in the opinion of the investigator may represent a risk for the patient.
    - **Those patients with medical conditions that are controlled with medical therapy are eligible.**
12. Clinically active Hepatitis B defined as positive HBsAg; or positive HBcAb with detectable HBV DNA viral load. Patients who are HBcAb with undetectable HBV DNA viremia are eligible.
13. Positive serology for hepatitis C (HC) defined as a positive test for HCAb and confirmed by HC RIBA or HCV RNA viral load
14. Screening laboratory value exclusion criteria:
    - platelets

      (no minimum platelet count is required by this trial, as this is a frequent manifestation of poor-risk chronic GVHD, and such patients may benefit from this protocol therapy)
    - neutrophils $<1.0 \times 10^9/L$

      (neutrophil count should be >1000 without growth factor support, unless neutropenia is caused by anti-neutrophil antibodies or other manifestation of chronic GVHD)
    - creatinine >2.0 times upper normal limit
    - total bilirubin >1.5 times upper normal limit (**unless due to chronic GVHD)**
    - ALT >2.0 times upper normal limit (**unless due to chronic GVHD)**

- alkaline phosphatase >2.5 times upper normal limit (**unless due to chronic GVHD)**

15. Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening.
16. Women of child bearing potential must undergo pregnancy testing within 7 days of the first dose of study therapy. Women must also undergo pregnancy test at 6 months after the last dose.
17. Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from study start to one year after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.
18. Male subjects unable or unwilling to use adequate contraception methods from study start to one year after the last dose of protocol therapy.

IV. STUDY THERAPY

i. Prednisone therapy

Starting dose of prednisone will be 1mg/kg body weight per day. If patients are treated with alternative steroid agents (e.g. methylprednisolone), this should be dosed to the corresponding prednisone equivalent of 1 mg/kg actual body weight.

The specific duration of prednisone therapy and tapering schedule for prednisone is not dictated by this protocol. However, the following serves as a guide for management of prednisone and other immune suppressive agents:

1. Start prednisone at 1 mg/kg/day
2. Continue this dose for 2-4 weeks or longer as needed in the setting of ongoing clinical improvement in chronic GVHD manifestations
3. With stable or improving chronic GVHD manifestations, begin taper on an every 1-2 week schedule with a target of reaching 0.5mg/kg/day
4. Continue 0.5mg/kg/day for 4 week plateau
5. Then taper by 10-20% of total dose per month as tolerated
6. In setting of increase chronic GVHD activity upon taper, increase prednisone dose as needed, with upper limit of 1-2mg/kg/day
7. Following complete discontinuation of prednisone, begin taper of other immune suppressive agents as tolerated.

ii. Ofatumumab

Ofatumumab Administration

Ofatumumab will be administered by IV infusion, with cohort-dependent dosing in the phase I dose escalation component of this study. Following definition of the ofatumumab MTD in the phase I component, this dose will be carried forward as the recommended phase II dose.

The following dose cohorts to be tested in the phase I component:

(cohort -1): 100mg days 0 and 14

cohort 1: 300mg days 0 and 14

cohort 2: 700mg days 0 and 14

cohort 3: 1000mg days 0 and 14

cohort/dose level -1 (100mg days 0 and 14) will be pursued only if 2/3 patients in cohort 1 (300mg days 0 and 14) experience DLT.

The following instructions are to be followed for infusion of ofatumumab:

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment:

Pre-medication Requirements prior to Ofatumumab Infusions

Infusion #	**Acetaminophen (po)** or equivalent	**Antihistamine (iv or po)** diphenhydramine or equivalent	**Glucocorticoid (iv)*** methylprednisolone or equivalent
1st	1000 mg	50 mg	50 mg
2nd	1000 mg	50 mg	50 mg

*This is in addition to the daily prednisone (or equivalent) therapy

Vital sign monitoring during Ofatumumab infusion:

Vital signs will be monitored every 30 (+/- 5) minutes as standard procedure during ofatumumab infusion, or more frequently if needed based on the clinician's judgment.

First Infusion of Ofatumumab:

The initial rate of the first infusion of ofatumumab (300mg at 0.3 mg/mL; 700mg at 0.7mg/mL; and 1000mg at 1mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate may be increased as tolerated every 30 minutes, to a maximum of 400 mL/h, according to the following table. If this schedule is followed, the infusion duration will be approximately 4.6 hours.

Infusion rate at 1st ofatumumab infusion

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

*acceptable window surrounding each time frame for escalation of infusion rate is +/- 10 minutes.

Dose Modification

• If an infusion reaction develops, the infusion should be temporarily slowed or interrupted.
• For Grade 4 infusion reactions, do not resume the infusion (subjects who experience a grade 4 toxicity at least possibly due to ofatumumab will not receive further doses of ofatumumab).
• For Grade 1, 2, or 3 infusion reaction, if the infusion reaction resolves or remains less than or equal to Grade 2, resume infusion with the following modifications according to the initial Grade of the infusion reaction:

Grade 1 or 2: Infuse at one-half of the previous infusion rate.

Grade 3: Infuse at a rate of 12 mL/hour.

Thereafter, the infusion rate may be increased as tolerated.

Subsequent Infusions of Ofatumumab:

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of ofatumumab (300mg at 0.3 mg/mL; 700mg at 0.7mg/mL; and 1000mg at 1mg/mL) can start at a rate of 25 mL/hour and may be doubled approximately every 30 minutes up to a maximum of 400 mL/h, according to the following table. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion-associated AEs, the subsequent infusion should start at a rate of 12 mL/hour. However, actual dose delivered (e.g. 300mg, 700mg or 1,000mg dose cohort level) will not be modified on day 14 dose.

Dose Modification for subsequent infusions of Ofatumumab:

• If an infusion reaction develops, the infusion should be temporarily slowed or interrupted.
• For Grade 4 infusion reactions, do not resume the infusion (subjects who experience a grade 4 toxicity at least possibly due to ofatumumab will not receive further doses of ofatumumab)
• For Grade 1, 2, or 3 infusion reaction, if the infusion reaction resolves or remains less than or equal to Grade 2, resume infusion with the following modifications according to the initial Grade of the infusion reaction:

Grade 1 or 2: Infuse at one-half of the previous infusion rate.

Grade 3: Infuse at a rate of 12 mL/hour.

Thereafter, the infusion rate may be increased as tolerated.

Infusion rate at subsequent ofatumumab infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

*acceptable window surrounding each time frame for escalation of infusion rate is +/- 10 minutes.

During infusion the patient should be monitored closely and appropriate measurements should be performed whenever judged necessary.

Technical details of Ofatumumab composition and dosing:

Medication

Novartis will supply ofatumumab to the investigator as content-labeled Ofatumumab vials presented as either 100 mg – acetate formulation, 20 mg/mL, 5 mL fill vials, or 1000 mg – acetate formulation, 20 mg/mL, 50 mL fill vials. The investigational medical product, ofatumumab, is a liquid concentrate for solution for infusion presented in glass vials. Ofatumumab will be infused intravenously according to the study schema. The ofatumumab infusions will be prepared in 1000 mL NaCl sterile, pyrogen free 0.9% NaCl to yield the appropriate concentration per study dose level. Ofatumumab vials must be stored at 2-8°C. Protect from light and do not freeze. No special packaging components, other than the outer white cardboard carton in which the vials are placed, will be used to afford light protection.

Ofatumumab open-labeled product will be for intravenous infusion. The site is responsible for labeling individual vials for investigational use. All items required for administration of study medication (e.g., infusion bags, filters, etc.) are to be provided by the site.

Composition of Ofatumumab Injection 20 mg/mL

The quantitative composition of acetate formulation 20 mg/mL. This is available in two fill volumes, 5 mL / vial (100 mg/vial) and 50 mL/vial (1000 mg/vial).

Ingredient	Quantity/ mL
Ofatumumab	20.0 mg
Sodium Acetate, Trihydrate	6.80 mg
Edetate Disodium, Dihydrate (EDTA)	0.019 mg
Polysorbate 80	0.20 mg
L-Arginine	10.0 mg
Sodium Chloride	2.98 mg
Hydrochloric Acid	to give pH 5.5
Water for Injection	*q.s.* to 1.0 mL

Preparation of Ofatumumab Infusion

Ofatumumab will be prepared as 1000 mL dilution of ofatumumab in sterile, pyrogen-free 0.9% NaCl. The exact time of dilution into the 0.9% NaCl must be written on the label of the infusion bag.

Once diluted into saline, the product is stable for up to 24 hours at ambient temperature. The product must be discarded after 24 hours following preparation. However, the product contains no preservative and should be used as soon as possible after dilution.

Preparation of drug solution for intravenous injection by the site pharmacist or designee will be done in accordance with the protocol, and in these dilution instructions. Ofatumumab intravenous solution will be prepared using standard dilution methods and following general aseptic practice standard to preparation of IV medications. Eyes and hands should be protected when handling ofatumumab.

For intravenous administration, compatibility of the following components for ofatumumab in clinical studies (i.e., not for commercial product) has been established:

Dosing Components for Ofatumumab in Clinical Studies

Dosing component	Material of construction	Suggested Vendor
1L Saline Bags	Polyvinyl Chloride (PVC)	Baxter
	Polyolefin [polyethylene* (PE)/polypropylene (PP)]	Baxter, B. Braun
Administration Set	PVC	Baxter
	PVC lined with Polyethylene	B. Braun
Filter Extension Set	Sterilizing-grade (0.22 μm) hydrophilic filter	Durapore brand by Millipore
	Lines made of PVC, filter membrane material polyether sulfone	Baxter
	Lines made of PVC lined with Polyethylene, filter membrane material polyether sulfone	Alaris/Cardinal Health (Ref # 10010454)
1 Liter 0.9% Sodium Chloride	NDC #00338-0049-04	McKesson, Mck Item # 148-2538

Preparation of the 1000 mL infusion bags should be done on the day of planned infusion.

* polyethylene (IUPAC name: polyethene)

Materials for Preparation and Administration of Infusion

The following materials are needed when preparing and administering the infusion:

1000 mL sterile pyrogen free 0.9% saline (NaCl) infusion bag(s).

The solution can be kept at ambient temperature for a maximum of 48 hours after preparation; however, the product does not contain a preservative and dosing should begin as soon as possible after dose preparation.

Ofatumumab 100 mg and 1000 mg vials (supplied by Novartis)

Needles and syringes (50 mL sterile syringe) not supplied by Novartis

Intravenous (IV) cannula (not required if subject has central venous access) [not supplied by Novartis]

Infusion pump and infusion tubing set (not supplied by Novartis)

In-line low protein binding, polyether sulfone filter 0.2 μm (please make sure a spare filter is available in case the filter needs to be changed) [not supplied by Novartis]. Please note that the commercial filters are sterilizing-grade (0.22 μm) hydrophilic Durapore by Millipore.

Dilution of Ofatumumab

- Ensure the correct container number is used.
- Take a 1000 mL infusion bag (sterile pyrogen free 0.9% saline), remove and dispose of the appropriate amount of saline according to tables below.
- Draw the required amount of ofatumumab according to the table below (100 mg vials)
- Inject ofatumumab into the saline bag
- Invert the infusion bag slowly 3 times, avoiding formation of any foam
- Label the infusion bag with the completed label

Preparation of Ofatumumab Infusion: 100 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
700 mg	1000 mL	35 mL	35 mL (7 vials, 5mL/vial)
1000 mg	1000 mL	50 mL	50 mL (10 vials, 5 mL/vial)

Ofatumumab Infusion Set up

Ofatumumab must be administered by i.v. infusion through an in-line filter and through a well-functioning i.v. catheter (i.v. cannula) into a vein in the arm (or other venous access) by an infusion pump.

Please Note: It is mandatory to use an in-line low protein binding 0.2 micron polyether sulfone filter for all IV dosing of ofatumumab drug product.

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

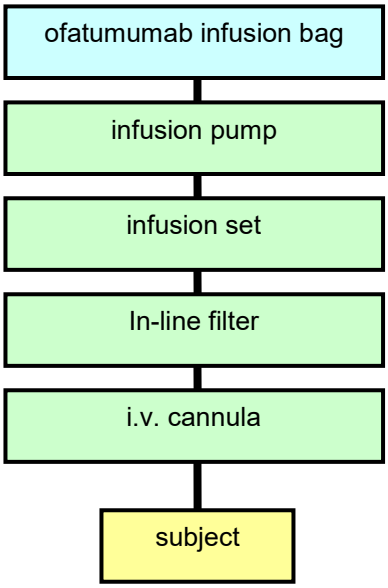
Ofatumumab should not be mixed with any other medication. If ofatumumab is to be dosed through an in-dwelling catheter, then, any previous medication should be removed by flushing with normal saline prior to dosing with ofatumumab.

Please note that the infusion site can be used for blood sampling only if there is no risk of contamination of the infusion needle with the saline, infusion solutions, or any other fluid(s). Only a newly inserted needle can be used for the predose blood samples.

- Check subject ID against the label on the infusion bag and ensure the expiry of the solution. The solution must be administered in its entirety to the subject within 24 hours from time of preparation.
- Attach the 1000mL infusion bag to the infusion set (if not done at the pharmacy).
- Attach the in-line filter to the infusion set (closest to the subject; see schematic below). **Note: The in-line filter must be used during the entire infusion.**
- Prime the infusion set and filter with ofatumumab (if not done at the pharmacy).
- In case of a problem with the filter (i.e. clogging/blockage), please change, re-prime the new filter, and continue the infusion.

- In case of problem with infusion set, follow local procedures.
- Collect the pre-dose blood samples, if required.
- Check the backflow from the i.v. cannula according to routine practice at site
- Set the pump at the initial infusion rate 12mL/hr for the first infusion and 25mL/hr for the subsequent infusions (see below infusion guidelines)

Infusion Set-Up Schematic



iii. Use of topical (non-systemic) therapies for chronic GVHD

The use of topical agents for control of chronic GVHD manifestations is part of usual clinical care for affected patients. Common examples include various eye drops and artificial tears for ocular sicca, steroid or other immune suppressive agent mouth rinses for oral involvement, or topical steroid creams for mild cutaneous involvement. Use of these agents for patients on study will not be controlled or directed by this protocol. Rather, use of these agents will be directed by treating clinicians as part of usual clinical care. Use of these agents will be recorded in data capture on each study visit. Use of these non-systemic therapies will not inform study endpoints that include requirement for additional systemic immune suppressive therapies.

iv. Supportive antimicrobial prophylaxis on study

i. All patients on study must receive antimicrobial prophylaxis per BMT guidelines and standards for the prevention of bacterial, viral, fungal, and pneumocystis infections.

V. STUDY OUTCOMES/ANALYSIS ENDPOINTS

1. Safety

a. Definition of DLT for phase I component:

i. In the phase I study, dose escalation will proceed as previously described. The dose limiting toxicity (DLT) will be defined using CTCAE version 4.0 as the following:

- Events occurring within 46 days of the last dose of drug (4 half-lives) that are:
  a) Grade 4 infusion reactions,
  b) Grade 4 constitutional symptoms at least possibly due to ofatumumab,
  c) Grade 3 organ toxicities (neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, hepatic, cutaneous) at least possibly due to ofatumumab,
  d) Grade 4 neutropenia lasting more than 14 days

ii. Importantly, known infusional toxicities of ofatumumab are managed appropriately with modification of infusion rate or temporary halting of infusion, as well as with supportive care including IV fluids, anti-histamines, and steroids.

iii. Specifically, grade 1-3 infusion-associated adverse events defined by CTC version 4.0 are not considered DLT in this trial. The occurrence of grade 4 infusion-associated adverse event is considered DLT.

iv. According to observed toxicities in the phase I component, the greatest dose tolerated in the dose escalation will be carried forward into the phase II component of the trial as the recommended phase II dose.

v. Events clearly related to chronic GVHD, relapse of the primary hematological disorder, concurrent medication, or infection will not be included as a DLT.

vi. Plan for patients not able to be evaluated for outcome on phase I component:

1. If an enrolled patient dies or comes off study following occurrence of DLT as defined above, this data will inform the

determination of DLT, and there will be no need to replace such patients.

2. Rather, if an enrolled patient does not experience DLT during follow up, but decides to withdraw from the study for other non-DLT related reasons prior to the minimum follow up of 46 days, such a patient would be replaced by a newly accrued patient.

2. Efficacy

a. Overall response rate

i. Overall response rate (ORR) at 6 months following initiation of therapy represents the composite outcome of complete and partial response (CR + PR).

ii. Complete response is defined as resolution of all reversible manifestations in each organ or site of chronic GVHD involvement

iii. Partial response is defined as improvement in at least one organ or site without progression in any other organ or site

b. Complete response rate

i. Complete response (CR) at 6 months following initiation of therapy requires complete resolution of all chronic GVHD manifestations in all affected organs.

c. Cumulative incidence of non-relapse mortality and primary malignancy relapse

i. The cumulative incidence of non-relapse mortality (defined as death in the absence of primary malignancy relapse after transplant) and relapse (defined by usual definitions in clinical practice including, but not limited to morphologic, immunophenotypic, or molecular methods) will be estimated from time of study therapy initiation. These are treated as competing-risk events.

d. Overall survival

i. Overall survival will be determined from date of study therapy initiation, with death from any cause as the event of interest, and censoring at last follow up date for those with incomplete observations.

e. Utilization of second-line systemic immune suppressive therapies

i. The use of second-line systemic immune suppressive agents will be captured at each study visit.

ii. This specifically refers to systemic therapies only, not topical or local therapies, such as topical eye drops, mouth rinses, topical steroid skin cream, or topical vaginal steroid agents.

iii. Adjustment in prednisone dose according to disease manifestations is not considered second-line therapy

iv. Adjustment in the dose of existing immune suppressive agents that require dose modification to maintain therapeutic serum drug levels (e.g. tacrolimus, cyclosporine, sirolimus) is not considered a second-line therapy or change in therapy

v. New initiation of extra-corporeal photopheresis (ECP) for progressive chronic GVHD manifestations following study intervention of prednisone and ofatumumab is considered second-line therapy.

f. Discontinuation of all systemic immune suppressive therapies

i. The incidence of complete discontinuation of all systemic immune suppressive therapies will be determined.

g. Failure-free survival

i. This time-to-event outcome will be estimated with the composite event of death from any cause, relapse and addition of secondary immune suppressive agents for progressive chronic GVHD.

h. Treatment success

i. This endpoint will be estimated with a composite outcome of complete resolution of all reversible chronic GVHD manifestations, discontinuation of all systemic immune suppressive agents, and freedom from death or primary malignancy relapse after transplant.

i. Patient-reported outcomes and functional measures

i. Patients will provide assessment of their functional ability (grip strength, 2 minute walk test), symptom burden (Lee symptom scale), and quality of life using validated instruments recommended by the NIH Consensus Development Project on Chronic GVHD (Lee Chronic GVHD Symptom Scale,[41] HAP functional scale,[42] QOL instruments SF-36[43] and FACT-BMT[44])

ii. These data will be collected at baseline, 3, 6, and 12 months on study

j. Biologic studies

Peripheral blood samples will be obtained from study patients at baseline, and then 3, 6, and 12 months. From these peripheral blood samples, the following major analyses will be performed: (1) quantification of plasma B cell stimulatory factor (BAFF), (2) quantification of immune globulin levels, and (3) enumeration of total B cells, as well as characterization of B cell subsets by surface phenotype through flow cytometric analysis.

From whole blood samples, plasma will be separated, and utilized for determination of soluble BAFF levels by enzyme-linked immunosorbent assay (ELISA). From peripheral blood mononuclear cells (PBMC), B cells will be isolated. Antibodies targeting surface antigens CD19, CD20, CD38, CD27, and IgD will be utilized for staining, and the respective cell subsets will be characterized by flow cytometry according to phenotype: Naïve B cells ($IgD^{+}CD38^{Low}CD27^{-}$), transitional B cells ($IgD^{+}CD38^{High}CD27^{-}$), IgD^{+} memory B cells ($IgD^{+}CD38^{Low}CD27^{+}$), pre-germinal center B cells ($IgD^{+}CD38^{High}CD27^{+}$), post-germinal center memory B cells ($IgD^{Low}CD38^{Low}CD27^{+}$), and plasmablast/plasma cell ($IgD^{Low}CD38^{High}CD27^{+}$).

3. Summary of pre-treatment and on-study testing to be performed

- Pre-treatment assessments / screening

i. Evaluation of eligibility: Inclusion, exclusion criteria

ii. Laboratory studies (CBC with differential, chemistry, liver function tests, review of prior hepatitis B and C, as well as HIV testing – may utilize prior HIV/hepatitis testing done for purpose of transplant eligibility)

iii. Pregnancy - Women of childbearing potential must have current negative pregnancy test, and both men and women must agree to adequate contraception methods.

iv. EKG

v. assessment of Karnofsky Performance Status (KPS)

- On-study assessments (windows described in study calendar)

i. history and physical examination, standard laboratory tests (CBC, chemistry, LFT)

- completed screening, day 0, day 14, months 1, 3, 6, 9, 12, 18, 24

ii. Chronic GVHD activity

- completed screening, day 14, months 1, 3, 6, 9, 12, 18, 24

- includes scoring of chronic GVHD severity per NIH 0-3 severity, clinician-reported severity measures, patient reported severity

- includes recording of immune suppressive medications at each visit

iii. Patient-reported outcomes

- completed screening, day 14, months 1, 3, 6, 9, 12, 18, 24

- includes quality of life, Lee symptom scale, and HAP (human activity profile)

iv. Functional measures

- completed screening, day 14, months 1, 3, 6, 9, 12, 18, 24
- includes grip strength and 2 minute walk test

v. Biologic samples

- baseline, then months 3, 6, 12
- includes the above-described B cell subset studies and BAFF levels

4. Criteria for patient termination from study

a. Patient decision to withdraw from study
b. Death
c. Relapse of primary hematologic malignancy
d. End of study
    a. Phase I (those patients in dose levels that are not the MTD to be carried forward into the phase II component)
        i. patients will complete 46 days of follow up from last dose of ofatumumab to monitor for DLT
        ii. for those not in the MTD cohort, limited data will be collected at 6 and 12 months (clinical response, pharmacodynamics)
    b. Phase II (including patients who are carried forward from the phase I component) – patients will complete 24 total months of follow up on study

e. Clarification on duration of follow up and assessments for phase I patients
    a. As the MTD will not be known in real-time, patients on any of the phase I dose levels may potentially be those carried forward from the MTD cohort as the recommended phase II dose
    b. Accordingly, patients in all dose levels of the phase I trial will need to have all of the above outlined on-study assessments performed until the MTD is defined.
    c. Once the MTD is defined, only those patients in the MTD cohort will continue to have all of the ongoing assessments performed
    d. Conversely, those in the non-MTD cohorts will complete an abbreviated assessment measure set to include only the chronic GVHD activity assessments/response determination and the biologic studies (B cell

subsets, BAFF levels) at 6 and 12 month time points. These limited assessments for the non-MTD dose level patients will be included to examine the relationship between dose and clinical response, and dose/pharmacodynamic activity.

VI. STATISTICAL ANALYSIS:

Study design and sample size estimation:

In the phase I component, dose escalation procedure is modeled after the data reported for ofatumumab in treatment of rheumatoid arthritis. Here, doses of 300, 700, and 1000mg were delivered on days 0 and 14. As this dose/schedule was well tolerated, led to significant and sustained (up to 48 weeks) depletion of peripheral blood CD19+ B cells, and there was an association between escalating dose and clinical response (***appendix A***), this dose/schedule will be adapted to a phase I design in the primary treatment of chronic GVHD.

The study design of the phase I component represents a traditional (3+3) dose escalation design with the following cohorts of ofatumumab in combination with 1mg/kg/day prednisone therapy:

(cohort -1): 100mg days 0 and 14

cohort 1: 300mg days 0 and 14

cohort 2: 700mg days 0 and 14

cohort 3: 1000mg days 0 and 14

**cohort/dose level -1 (100mg days 0 and 14) will be pursued only if 2/3 patients in cohort 1 (300mg days 0 and 14) experience DLT.*

Phase I trial endpoint:

Safety of escalating dose of ofatumumab in combination with prednisone.

Definition of dose-limiting toxicity (DLT):

Dose-limiting toxicity attributable to ofatumumab within 46 days of initiation of ofatumumab therapy is defined in the *above section V.1 safety for definition of DLT*. The occurrence of DLT attributable to ofatumumab in ≤ 17% serves as the boundary for the maximally tolerated dose (MTD) of ofatumumab.

Phase I trial procedures and analysis:

The initial group of 3 patients will be enrolled in the cohort 1. Dose escalation of ofatumumab will proceed according to the following: If no DLT is observed among 3 patients in a cohort, the next group of 3 will be treated at the next highest dose level. If the current level (i.e., the level at which no DLTs are observed) is the highest dose

level, three additional patients will be enrolled (total of six). If one DLT is observed among 3 patients in a cohort, the next group of 3 will be treated at this same dose level. If no more DLT is observed among the 3 additional patients (i.e. one DLT in total is observed among the 6 patients), then the next 3 patients will be treatment at the next highest dose level. If at least 1 more DLT is observed among the 3 additional patients, then the MTD is exceeded. If 6 patients have been treated at the next lower dose level, it will be considered as the MTD. If not, three additional patients will be enrolled. This escalation approach will then be continued until a dose is identified where at most 1 of 6 patients has a DLT. That dose will be considered to be the MTD. If two DLTs are observed among 3 (or fewer) patients in a cohort, the next group of 3 will be treated at the next lowest dose level. If the current level (i.e. the level at which 2 DLTs are observed) is the lowest dose level (300mg days 0 and 14), then a dose level -1 will be pursued, in which a de-escalated dose of 100mg ofatumumab will be given on days 0 and 14.

The total number treated on the phase I component will depend on the occurrence of dose limiting toxicity (DLT), however the maximal number accrued on the phase I study would approximate 12 to 18 total subjects. GSK reviewed phase I data prior to moving forward with the phase II component.

Phase II component:

Following definition of the maximal tolerated dose (MTD) in the phase I component, this MTD will be taken forward in a phase II trial to characterize the efficacy of this approach. The primary endpoint of interest in the phase II component is overall response rate (ORR) to therapy at 6 months. Overall response is defined as the composite of complete response and partial response. In the assessment of response for this primary endpoint, response will be determined according to clinician assessment. The Simon's two-stage optimum design is used to minimize the expected sample size. With a historical baseline ORR proportion of 60% (*justification for this baseline proportion in background section)*, anticipated effect leading to ORR of 80% in this investigational treatment (prednisone + ofatumumab), power of 90%, and alpha of 0.1, a total of 38 subjects are needed for this analysis of efficacy. As 6 total patients from the phase I component will have been treated at the recommended phase II dose, these will be included for efficacy analysis. Early termination will occur if 6 or fewer out of 11 (≤6/11) subjects in first stage have a overall response (CR or PR). If the trial goes on the second stage and a total number of responders (CR or PR) is less than or equal to 26 (≤26/38), the null hypothesis fails to be rejected. To provide total of 38 subjects for this efficacy analysis, 32 additional patients will be enrolled in the phase II component. Thus, the net total number of patients to be enrolled on the combined phase I-II study will be a maximum of 50.

Statistical Analysis plan:

The 'All Treated population' will be used for the analysis of the efficacy and safety endpoints. Specifically, this will consist of all patients who receive at least one dose of study treatment. For Complete Response (CR) rate and Overall Response rate: A

patient with unknown or missing response will be treated as a non-responder (i.e. the patient will be included in the denominator when calculating the percentage).

Overall response (ORR) rate will be determined at 6 months and will be reported with associated 95% confidence interval. Complete response rate will be similarly reported. Association between clinical variables (chronic GVHD severity, organ involvement, patient socio-demographic data, disease and transplantation variables) and response will be examined. Patient reported outcomes will be reported, and association between scores on individual measures (chronic GVHD symptom scale, human activity profile, QOL instruments including SF-36 and FACT-BMT) and clinical response to therapy will be explored. Cumulative incidence of relapse and non-relapse mortality will be estimated, accounting for competing risk events. Overall survival from date of therapy initiation will be estimated by Kaplan-Meier method, and survival curves among relevant subgroups will be compared utilizing the log-rank test. In the analysis of survival time between responders and non-responders, landmark analysis will be utilized to avoid biased survival estimation. Other time-to-event secondary endpoints (e.g. failure-free survival) will similarly be estimated using the Kaplan-Meier method. Biologic endpoints (total B cell numbers, B cell subsets, immune globulin levels, BAFF levels) will be summarized. Comparisons between relevant groups will be made at specific time points utilizing parametric (e.g. t-test) or non-parametric (e.g. Wilcoxon rank-sum) as appropriate per the nature of the data. Additionally, change in these values over time will be examined according to response vs. non-response to primary therapy with mixed-model approach.

Early Stopping Rule for Toxicity

An early stopping rule for toxicity is constructed to continuously monitor the rate of DLT (i.e. grade 4 AE attributable to ofatumumab per the above definitions) for the 38 patients in a Phase II component. The DLT is defined in Section V.1. Safety. The stopping boundaries for monitoring the DLT is constructed as a Pocock-type boundary as described in “Continuous Toxicity Monitoring in Phase II Trials in Oncology” by Ivanova, Qaqish, and Schell (Biometrics, 2005; 61(2):540-45). Table below shows the number of DLTs allowed for a given number of “assessable” patients up to that point. Patients are considered to be “assessable” when they have either experienced a DLT or completed the surveillance period (death without a DLT or 30 days after infusion of Ofatumumab) without having experienced a DLT so that their outcomes are identifiable. Up to 20% of DLT rate is expected or acceptable. The table below contains the stopping boundaries for toxicity, based on which the probability of early stopping is at most 0.05 if the DLT rate is equal to 6.5%. Given the first 6 patients on the phase II component were treated on the phase I component of the trial (and assessed for DLT in the phase I component), the starting number of sequentially enrolled patients for assessment of this toxicity stopping boundary in the phase II component of the trial has been modified (see below table). When the DLT rate is unacceptably high (30%), the stopping rule has greater than 97% probability of early stopping. If a stopping boundary is reached, the accrual will be halted, and the data will be reviewed by the Moffitt Cancer Center Protocol Monitoring Committee.

# Assessable	Stopping boundaries for DLT	# Assessable	Stopping boundaries for DLT
1	NA	20	5
2	NA	21	5
3	NA	22	5
4	NA	23	5
5	NA	24	5
6	NA	25	5
7	NA	26	6
8	3	27	6
9	3	28	6
10	3	29	6
11	3	30	6
12	4	31	6
13	4	32	6
14	4	33	7
15	4	34	7
16	4	35	7
17	4	36	7
18	4	37	7
19	5	38	7

* These stopping boundaries apply to both the MTD cohort patients from the phase I component that move forward to the phase II trial, as well as those patients enrolled initially in the phase II component of the trial

* If these stopping boundaries are met, accrual will be suspended and the data will be reviewed in detail by the Protocol Monitoring Committee (PMC). The study will not be terminated, however. Resumption of accrual will be dictated by the review of the data by the study investigators and the PMC.

VII. DATA AND SAFETY MONITORING:

The principal investigator is obligated to report all serious adverse events (SAE) to the FDA, IRB, and Novartis.

All events reported to the FDA by the investigator will be filed utilizing the Form FDA 3500A (MedWatch Form).

Definition of Adverse Events:

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medial and scientific judgment of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

Definition of Severe Adverse Events (SAE):

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

   An overnight hospital stay due to slow infusion rates will not be considered a Serious Adverse Event.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

- Abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.

- All events meeting liver stopping criteria must be recorded as an SAE.

- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

- B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.

- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.

Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Severity scoring and attribution of adverse events:

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

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Collection of adverse events – study calendar driven collection schedule:

- All grades (1-5) adverse events will be collected within 24 hours of start of infusion of ofatumumab
- Grades 3-5 adverse events occurring by study day 60 must be collected, excepting those that are directly attributable to chronic GVHD or to relapse of the primary hematologic disorder
- From study day 61 onward, only adverse events deemed related to the investigational agent ofatumumab will be collected

<u>Established post-transplantation complications that are anticipated, and thus will not inform study-related reporting of events attributable to ofatumumab from study day 61 onward:</u>

i. **Chronic GVHD disease activity** – adverse consequences of chronic GVHD activity itself will not be considered as adverse events. These are described in *appendix B*.

ii. **Renal or hepatic impairment** related to post-transplant medications or complications – Renal or hepatic impairment temporally associated with known transplant-related insults will not be considered adverse events attributable to ofatumumab. Common examples include worsening in renal function associated with calcineurin inhibitors, volume depletion, or end-organ complications from thrombotic microangiopathy (TMA).

iii. **Electrolyte abnormalities** related to post-transplant medications – Abnormalities in electrolytes including sodium, potassium, magnesium, calcium, and phosphorus are commonly observed following transplant, and are managed with supplementation. All grade electrolyte abnormalities are not considered adverse events attributable to ofatumumab.

iv. **Infectious complications** following transplant – Infectious complications are frequent after transplant. Anticipated frequencies of infectious complications are listed in the table below (3.g.iii).

Bacterial, viral, fungal infections are anticipated, as well as pneumocystis jiroveci (PCP), and reactivation of cytomegalovirus (CMV) and Ebstein Barr virus (EBV). The frequency of infectious complications will be monitored during the study, and will be compared to historical rates. However, these will not be considered adverse events.

The following table serves as a current best estimate of incidence of infectious complications following systemic therapy for chronic GVHD (reproduced from *Martin, et al. Blood. 2009).*[19] Standard anti-microbial prophylaxis was delivered on this trial according to institutional guidelines.

	Prednisone+MMF	Prednisone+placebo	p value
Any infection	74%	87%	0.05
Bacterial infection	24%	21%	0.6
Viral infection	36%	35%	0.86
Fungal infection	24%	31%	0.35
Pneumonia	23%	13%	0.11
Conjunctivitis	5%	14%	0.07
Empiric antibiotic treatment	31%	18%	0.06

(Cytopenias

v. **leukopenia, anemia, thrombocytopenia** – the listed cytopenias are common following transplant, and often the result of transplant medications, or TMA. All grades of hematologic events related to complications of transplant and associated transplant medications are not reportable as adverse events attributable to ofatumumab.

vi. **Hyperglycemia** – This is a common occurrence in the setting of steroid therapy for GVHD, and is controlled with insulin or other medications. Therefore, this will not be reported as an adverse event attributable to ofatumumab.

vii. **Relapse of primary hematologic malignancy** – relapse of malignancy is an established risk after transplant, and therefore will not be considered an adverse event attributable to ofatumumab.

Specific criteria for hepatic function monitoring, pregnancy, hepatitis B screening, and monitoring for PML:

a. **Liver monitoring:** Liver chemistries will be obtained pre-treatment, as specified below for treatment phase and at least 6 months after the last dose of

ofatumumab. Liver chemistries consist of ALT, AST, total bilirubin, and alkaline phosphatase. Patients will have liver function tests performed before study therapy. Study patients will have liver function tests performed at least at each study visit. Patients with elevated liver function tests due to chronic GVHD are eligible. Grade 4 hepatic toxicity attributable to ofatumumab will inform the determination of dose-limiting toxicity in the phase I component of the study. In the phase II component, ongoing monitoring of AEs will capture any grade 4 hepatic toxicity attributable to ofatumumab, and review of these AEs will ensure patient safety.

Liver interruption/stopping criteria:

- Liver chemistry stopping and follow up criteria has been designed to assure subject safety and to evaluate liver event etiology. The sponsor-investigator is to review all events which meet liver chemistry stopping criteria to determine if the event was due to:

- tumor lysis (this is not likely in this study, as relapse of primary malignancy is an exclusion criterion), disease related liver involvement, or specifically hepatic chronic GVHD
- concomitant chemotherapy (or other medications)
- other identified cause and to exclude drug induced liver injury (DILI) due to Ofatumumab

These criteria are relevant for Ofatumumab studies because transient elevations in LFTs may be due to disease related liver involvement (particularly hepatic chronic GVHD in this study) or due to other chemotherapy (or other medication insults) rather than drug induced liver injury from Ofatumumab.

If the event is determined to be due to causes other than Ofatumumab DILI and improvement is observed after withdrawal of Ofatumumab, rechallenge may be attempted if deemed appropriate by the sponsor-investigator and in addition to consent of the subject.

Oncology Ofatumumab Protocols Liver Interruption/Stopping Criteria:

1. ALT >3 times upper limit of normal (ULN) **and** bilirubin >2 times ULN (>35% direct bilirubin; bilirubin fractionation required‡)
2. ALT >8 times ULN
3. ALT >5 times ULN for more than 2 weeks

‡ **NOTE:** *If serum bilirubin fractionation not immediately available, study drug should be discontinued if ALT > 3xULN and bilirubin >2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury*.

NOTE: *These criteria hold true for patients without LFT abnormalities before initiation of therapy for chronic GVHD. Thus, in these cases, new development of LFT abnormalities following administration of the study drug would necessarily prompt this evaluation. However, for patients with established LFT abnormalities due to chronic GVHD before initiation of study therapy, these rules will be based on progression of LFT abnormalities beyond these thresholds based on the pre-therapy starting point.

When any of the liver chemistry stopping criteria is met, do the following:

Immediately stop study treatment

Hold Ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and report to sponsor-investigator to discuss the possibility of re-challenging with Ofatumumab. *Medication is interrupted and it is a clinical and patient decision if Ofatumumab may be re-started.*

Report SAE to Novartis within 24 hours

All events of ALT > 3xULN **and** bilirubin > 2xULN (>35% direct bilirubin) (or ALT>3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT > 3xULN **and** bilirubin > 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

Liver chemistry follow-up assessments are to be followed until liver chemistries resolve, stabilize or return to baseline values.

Liver Chemistry Follow-up Assessments; (these chemistry tests/ assessments below are to be performed at the time of the event and then continued and/or discontinued at the discretion/judgment of the sponsor-investigator; please refer to stopping criteria within this document below)

Viral hepatitis serology including:

- *Hepatitis A IgM antibody;*
- *Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);*
- *Hepatitis C RNA;*
- *Cytomegalovirus IgM antibody;*

- *Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);*
- *Hepatitis E IgM antibody*

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)

Fractionate bilirubin, if total bilirubin >2xULN

Obtain complete blood count with differential to assess eosinophilia

Record the appearance or worsening clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash

Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins

Increased alcohol use

The following assessments are required for subjects with ALT >3xULN and bilirubin >2xULN (.35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Stopping Criteria:

- For subject meeting liver stopping criteria 1:
    - A repeat of liver chemistries within 24 hours, liver event follow-up assessments and close monitoring
    - A specialist or hepatology consultation is recommended
    - Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- For subjects meeting criteria 2 or 3:
    - A repeat of liver chemistries within 24 to 72 hours for repeat liver chemistries and liver event follow-up assessments
    - Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values
- After holding Ofatumumab for two weeks:
    - If the treatment is exhibiting efficacy **and** the subject wants to continue therapy after being informed of the results of liver chemistry testing, then the Ofatumumab may be re-started.
    - Liver chemistries and follow-up assessments should be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to

baseline values, at which point monitoring should be continued per protocol

- Subjects with ALT >3xULN **but** <5xULN **and** bilirubin <2xULN without hepatitis symptoms or rash, and who may be monitored weekly for at least 4 weeks, then the following actions should be taken:

    - Subjects can continue Ofatumumab
    - Weekly repeat of liver chemistries until they resolve, stabilize, or return to baseline values, then monitor liver chemistries as per protocol assessment schedule

If at any time the subject meets any of the liver chemistry stopping criteria, then proceed as described above

If after 4 weeks of monitoring, ALT<3xULN and bilirubin<2xULN monitor twice monthly until liver chemistries normalize or return to within baseline values

b. **Pregnancies:** Pregnancies must be reported to Novartis; however are not to be reported as SAEs unless they meet serious criteria.

2. Special safety monitoring requirements on study:

a. **Hepatitis B Screening**

Follow-up monitoring must be included in the study protocol:
• If HBV DNA is negative, subject may be included
• Monitoring during the follow-up period will be performed during routine study visits for a minimum follow-up period of six months after the last dose, as long as the subject remains on study. Monitoring frequency during follow-up should occur at a minimum of every 3 months. Whenever possible, the monitoring should occur as part of the routine follow-up visit
• Prophylactic antiviral therapy, in addition to the monitoring described above, may be initiated at the discretion of the investigator.

HBsAg positive (regardless of other Hepatitis B serologies):

- exclude

HBsAg negative, HBcAb negative, HBsAb positive

- include

HBsAg negative, HBcAb positive (regardless of HBsAb status)
HBV DNA must be performed

- if HBV DNA is positive the subject is excluded

- If HBV DNA is negative, subject may be included but must undergo at least every 2 month HBV DNA PCR testing from the start of treatment during the treatment course.
- Monitoring during the on treatment periods is required at least every 2 months and during follow-up at a minimum of every 2-3 months up to 6 months after the last dose.
- Prophylactic antiviral therapy, in addition to the monitoring described above, may be initiated at the discretion of the investigator.

If the subjects' HBV DNA becomes positive during the study, the investigator should manage the clinical situation as per the standard of care of that institution, and the Novartis medical monitor should be notified. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab should be discussed with the medical monitor before appropriate treatment decisions are made for that individual subject.

b. **Progressive Multifocal Leukoencephalopathy (PML)**

Progressive multifocal leukoencephalopathy (PML) is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual. JC virus infection resulting in PML and death has been reported in rituximab-treated subjects with hematologic malignancies or with systemic lupus erythematosus (SLE), an indication for which rituximab has not been approved. In the literature, PML has been reported to occur in 0.52% of CLL subjects and in approximately 5% of fludarabine-treated B-CLL subjects. One case of PML was reported in a very ill CLL subject treated with ofatumumab, previously treated with alemtuzumab and fludarabine and with very low CD4 cell count.

1. Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.

2. If a subject develops neurological signs or symptoms consistent with PML treatment should be halted and the subject referred to a neurologist for evaluation. At a minimum, blood JCV PCR and/or MRI will be performed and if either is positive perform Cerebrospinal Fluid (CSF) JCV PCR. If blood JCV PCR and MRI are negative, the investigator will contact the Novartis for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the subject should proceed to the Follow-Up Period. All such subjects will be followed until resolution. Any subject with a diagnosis of PML will be withdrawn from ofatumumab. There are no known tests that can reliably determine who is at increased risk for developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

Neurological Symptoms Questions*

		YES	NO
1.	Does the subject report any new weakness?		
2.	Does the subject report any new difficulty with coordination or walking?		
3.	Does the subject report any new signs of confusion, impaired memory or attention?		
4.	Does the subject appear apathetic compared to previous contacts?		
5.	Does the subject report any new visual disturbances?		
6.	Has the subject had any new trouble speaking, either slurring speech, difficulty getting out words, difficulty understanding words, or difficulty comprehending spoken language:		
7.	Does the subject have any other new neurological symptoms, including but not limited to: New onset seizure New sensory loss New emotional liability		

*If neurologic symptoms are otherwise explained by a competing etiology, the clinician should indicate 'no' on the above checklist, and urgent contact of the medical monitor is not indicated. As stated above, the study investigator should exercise judgment in deciding to report signs and symptoms.

If any of the above are answered "Yes" at any visit, the investigator will contact the medical monitor and the patient will be referred to a neurologist.

Adverse Events annual report:

In the annual report of adverse events, the following will be provided:

1. Complete summary of adverse events
2. Separate listing and analysis of infusion reactions
3. Presentation of adverse event data by ofatumumab dose level

SAE Reporting Procedures:

The study PI will have primary responsibility to rapidly communicate SAE to the monitoring agencies as follows:

NOVARTIS:

Once an investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Novartis within 24 hours of being notified of the event. All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product up to a minimum of 6 months after the last dose of investigational product or until the end of the follow-up period whichever is longer. All SAEs regardless of causality will be collected until the end of the follow-up period. SAEs are no longer required to be reported if a subject begins treatment with another therapy. From the time a subject consents to participate in and completes the study all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or **related to Novartis concomitant medication**, will be reported promptly to Novartis.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to Novartis.

Pregnancy

Any pregnancy that occurs during study participation must be reported to Novartis. To ensure subject safety, each pregnancy must be reported to Novartis within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis. In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

All SAEs will be reported to Novartis within 24 hours of the PI being notified of the SAE. The following represents the contact information for this reporting:

Report SAE Information to Novartis via Fax to:
U.S. Drug Safety & Epidemiology: Fax # 877-778-9739

Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com

Novartis SAE Fax Coversheet must be attached to the SAE Submission

SAE submissions must reference Novartis Study Code: COMB157EUS03T

University of South Florida IRB:

Unanticipated problems that are serious adverse events should be reported to the IRB immediately of the investigator becoming aware of the event.

Any other unanticipated problem involving risks to subjects or others should be reported to the IRB immediately of the investigator becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institutions written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

FDA:

IND Safety Reporting Requirements

This protocol is associated with an Investigational New Drug Application ("IND") sponsored by Dr. Joseph Pidala at Moffitt Cancer Center. IND Safety Reports are required for any adverse experience associated (or possibly associated) with the use of the investigational product(s) that is both serious and unexpected. To meet the IND Safety Reporting requirements set forth in 21 CFR §312.32, FDA Form 3500A (MedWatch form) will be completed and provided to the Moffitt Office of Institutional Regulatory Affairs for Investigational Drugs and Devices. All other adverse events will be reported to the FDA as part of the annual reporting requirement of the IND.

The initial report will be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) will be documented on a follow-up report. A final report to document resolution of the serious adverse event is required if it is not documented in the initial report.

The Moffitt Office of Institutional Regulatory Affairs will complete the necessary documents and provide the report to the FDA as an official submission to the IND. This will occur independently of any other use of the MedWatch form or required reporting of serious adverse events. Submission of the MedWatch form to any other agency, including the FDA, does not fulfill this IND Safety Reporting requirement. Follow-up to

the safety report must also be submitted to the Office of Institutional Regulatory Affairs in a timely manner.

Upon completion of the report, a copy of all initial and follow-up MedWatch forms will be FAXed to the Manager of the Office of Institutional Regulatory Affairs (813-745-8332) and a telephone call or email will be made to confirm receipt.

For unexpected fatal or life threatening experiences associated with the use of the investigational product(s), the Office of Institutional Regulatory Affairs will be contacted within 24 hours. Notification to the FDA will be made as soon as possible, but no later than 7 calendar days after initial receipt of the information.

Data Safety and Monitoring Plan

The Data Safety & Monitoring Plan (DSMP) will ensure that this trial is well designed, responsibly managed, appropriately reported, and that it protects the rights and welfare of patients. The following internal and external review and monitoring processes provide oversight and active monitoring of this trial:

- The Principal Investigators (PI)
- The Scientific Review Committee (SRC)
- The Protocol Monitoring Committee (PMC)
- The Research Compliance Division of the Cancer Center's Compliance Office (RCD**)**
- Institutional Review Board (IRB)

The protocol includes what constitutes an adverse event (versus what is a serious adverse event), the entities to which adverse events should be reported, the timing of this reporting, and the person or persons responsible for reporting.

Initial and Ongoing Monitoring and Review

Principal Investigator (PI)

The PI of the study has primary responsibility for ensuring that the protocol is conducted as approved by the SRC and the IRB. The PI will review weekly with the trial coordinator patient eligibility and accrual. The PI will continuously monitor data both for efficacy and toxicity through weekly meetings conducted together with the clinical trial coordinator, and in monthly review of data in the Moffitt BMT Program research meeting. The PI will also be responsible for monitoring recorded data for accuracy through review of primary clinical records. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to the Scientific Review Committee (SRC), Protocol Monitoring Committee (PMC) and IRB as required, and that all adverse events are appropriately reported.

The Scientific Review Committee (SRC)

The Cancer Center's internal Scientific Review Committee (SRC) provides for a formal internal peer review of all protocols and general scientific oversight of interventional clinical research. The Committee has a defined membership representing all of the major research divisions of the Cancer Center, including biostatisticians. All new protocol submissions must contain the required elements of the protocol, and must includes a DSMP prior to approval by the Committee. The plan has to be appropriate for the phase and risk of the proposed study.

The Protocol Monitoring Committee (PMC)

The Protocol Monitoring Committee (PMC) will monitor this trial for safety, progress, protocol compliance, accrual, adverse event reporting, and data integrity. The membership of the PMC includes physician representation from each program area and a biostatistician. In addition to the existing stopping rules, the PMC is authorized to suspend a trial for non-compliance with a DSMP or as a result of audit findings deemed unacceptable. The PMC will report significant findings to the IRB, and applicable regulatory bodies. Interim meetings are scheduled to address specific issues that require immediate attention to ensure safety of research participants.

Phase I: Safety and monitoring reports are to be submitted to the Protocol Monitoring Committee (PMC) after completing each odd numbered dose level (i.e., 1, 3, 5, etc), or more frequently if requested by the PMC. A final safety and monitoring report must be submitted to the PMC within three months of defining the maximum tolerated dose (MTD).

Phase II: Safety and monitoring reports are to be submitted to the Protocol Monitoring Committee (PMC) once 30% of the total accrual has been met or once the early stopping rule threshold has been met. A final safety and monitoring report must be submitted to the PMC within three months of last subject enrollment.

The Research Compliance Division of the Cancer Center's Compliance Office (RCD)

The Cancer Center's Research Compliance Division (RCD) of the Corporate Compliance Department coordinates internal audits of all investigator-initiated trials conducted at the Cancer Center and its affiliates. The frequency of the audits is driven by the rate of accrual on a specific trial as well as the perceived patient risk for participating in the trial. Internal audits are conducted by the RCD in accordance with applicable regulatory standards.

The purpose of the internal audit program is to:

- Ensure protocol compliance and the validity and integrity of data, thereby promoting patient safety and maintaining scientific validity
- Recommend modification of research practices as necessary and provide education on issues that are critical to good research practices

The following elements of trial documentation may be incorporated into this review:

- Source documentation verification of eligibility and compliance with the protocol
- Compliance with adverse and serious adverse event reporting standards
- Regulatory review of IRB compliance and external reporting requirements
- Drug/device accountability and handling
- Completeness and quality of data

RCD auditors report findings to the PI and PMC, as appropriate, for review and audit determinations along with a statement from the PI. The PI is encouraged to proactively implement corrective actions to remedy any deficiencies noted in the audit. The PMC determines the findings as one of the following: A*cceptable, Acceptable with corrective action, Tabled for Additional Information,* or *Unacceptable.* The PI and IRB are then informed of the audit determinations made by the PMC. The PI and IRB are then informed of the audit determinations made by the PMC. Audit results may then be presented to the Corporate Compliance Steering Committee, chaired by the Center Director, and to the Joint Corporate Compliance Committee of the Board

Trial monitoring by Moffitt Monitoring Core (MMC)

Trial monitoring by the Moffitt Monitoring Core (MMC) will verify that the rights and wellbeing of human subjects enrolled in specific Moffitt sponsored principal investigator (PI) initiated clinical research are protected. PI initiated clinical trials will be monitored on-site regularly to verify the reported trial data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, data safety-monitoring, Good Clinical Practice (GCP), and applicable regulatory requirements. Routine monitoring visits will be conducted, at a minimum, annually.

Institutional Review Board (IRB)

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments will be approved by the IRB in compliance with current regulations of the Food and Drug Administration prior to initiation unless necessary to protect the safety and welfare of subjects; in which case, the IRB will be notified within 24 hours of implementing the change. The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

Protocol amendments or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that will be reviewed and approved by the Moffitt Cancer Center SRC and the Institutional Review Board (IRB).

Data management

Data collection

Investigators must enter the information required by the protocol onto Case Report Forms (CRFs).

Records to be kept

Data will be kept confidential and will be entered into Oncore and the BMT research database. In computer generated reports for external review, patients will only be referred to by a unique identification number.

Both Oncore and the BMT research database is password protected and limited only to designated personnel. In order to assure quality, both physicians and clinical research personnel regularly audit specified data that is manually entered into the system.

Representatives of the IRB, the FDA, and other governmental regulatory authorities will have access to patient information as it pertains to the study. Privacy and confidentiality of the information will be protected to the extent provided by law.

Ethics and Good Clinical Practice

This study will be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Informed consent

The investigator and/or designated members of the research study team will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject will read and consider the statement before signing

and dating it, and will be given a copy of the signed document. No patient will be entered on the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted by the investigator with it for IRB approval.

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h. Appendices

Appendix A – CD19+ profile and treatment response according to escalating dose of ofatumumab (rheumatoid arthritis study)

Figure 9 **Mean CD19+ Profiles by Treatment Group, Safety Population (Study 403 Part B)**

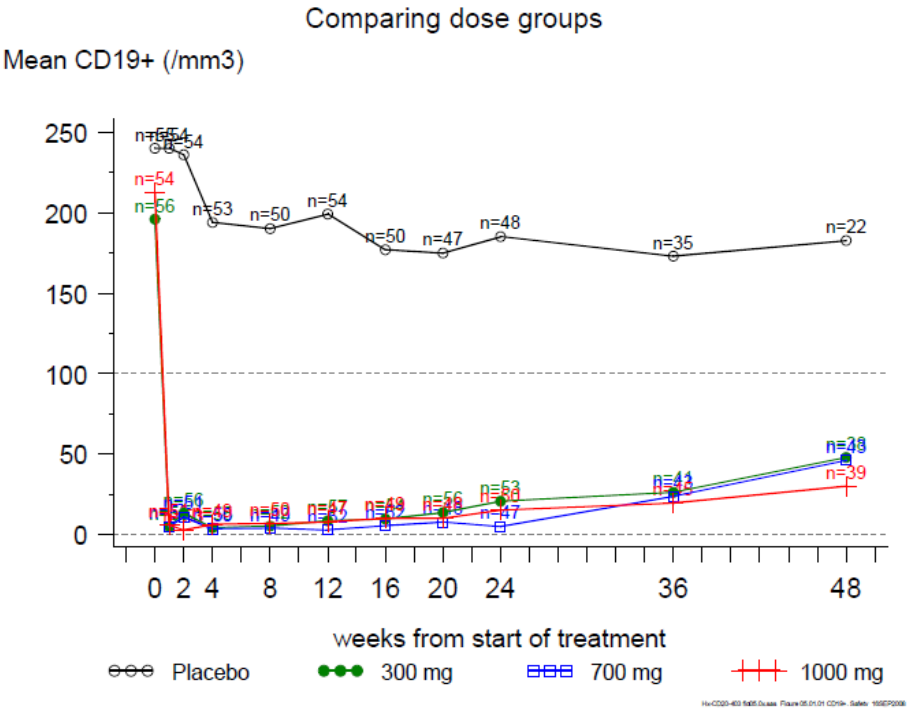
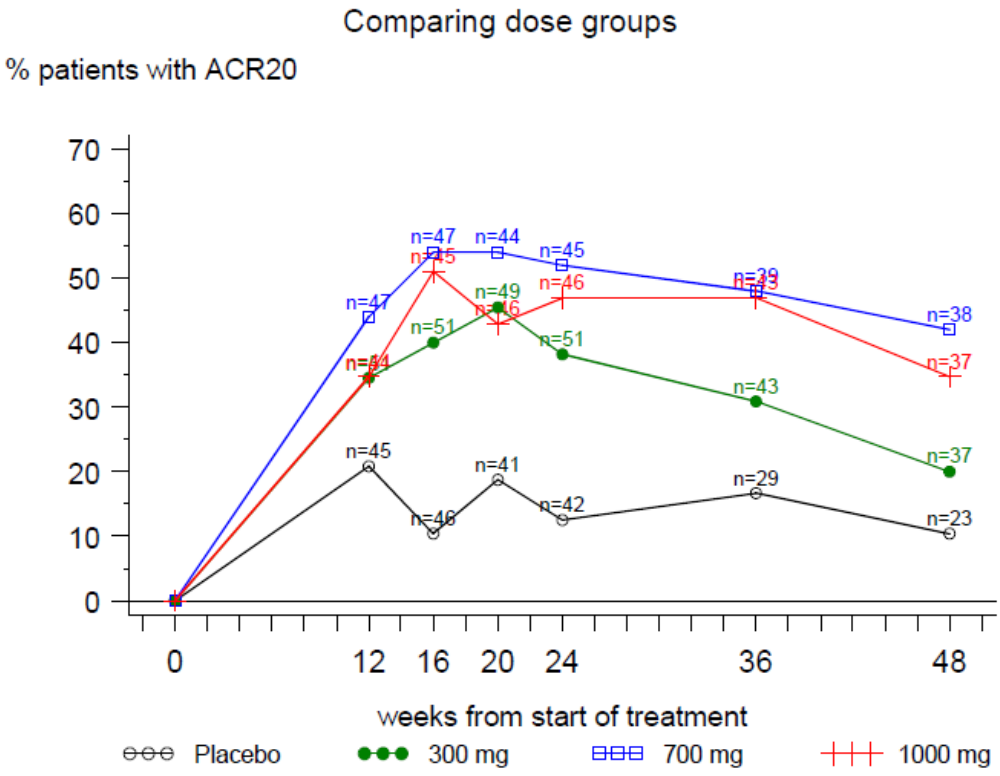


Figure 10 **Percentage of FASmod Subjects with an ACR20 Response from Baseline to Week 48 (Study 403 Part B)**



Appendix B – NIH criteria for diagnosis and severity grading of chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS† FEV1 ☐ DLCO ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

Global assessment score for chronic GVHD

a. Mild chronic GVHD
   i. Involves only 1 or 2 organs or sites (except lung) with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites.

b. Moderate chronic GVHD
   i. Involves at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site)
   ii. Or, 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites).

1. A score of 1 involving the lung is also considered moderate chronic GVHD

c. Severe chronic GVHD
    i. Major disability caused by chronic GVHD (score of 3 in any organ or site)
    ii. Lung score of 2 or greater also considered chronic GVHD

Appendix C – Chronic GVHD activity scoring, and patient-reported outcome measures

cGVHD DATA FORMS
under separate document

i. Study Calendar

Procedure	Screening	Baseline (within 14 days following initiation of steroid therapy for chronic GVHD)	Treatment (+/- 3 days)		Follow Up (+/- 14 days)					Long-term follow up (+/- 28 days)
			Day 0	Day 14	Month 1	3	6	9	12	18 and 24 months
Ofatumumab administration										
			X	X						
Screening Procedures										
Eligibility criteria	X									
Informed consent	X									
Efficacy Assessments										
Chronic GVHD activity - NIH score - clinician severity assessments - clinician response assessments - patient-reported severity **		X		X	X	X	X	X	X	X
Patient-reported outcomes - QOL - HAP - Lee symptom scale		X		X	X	X	X	X	X	X
Functional measures - grip strength - 2 minute walk test		X		X	X	X	X	X	X	X
Record systemic immune suppressive		X		X	X	X	X	X	X	X

agents										
Biologic samples		X				X	X		X	
Survival			X	X	X	X	X	X	X	X
Safety Assessments										
Physical exam	X	X	X	X	X	X	X	X	X	X
Karnofsky Performance Status	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X									
CBC, LFT	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X									
Adverse events			X	X	X	X	X	X	X	X

*Enrollment may occur within 14 days of initiation of prednisone for chronic GVHD. Screening tests may occur between start of prednisone and ofatumumab.
*As the MTD will not be known in real-time, patients on any of the phase I dose levels may potentially be those carried forward from the MTD cohort as the recommended phase II dose. Accordingly, patients in all dose levels of the phase I trial will need to have all of the above outlined on-study assessments performed until the MTD is defined. Once the MTD is defined, only those patients in the MTD cohort will continue to have all of the ongoing assessments performed. Conversely, those in the non-MTD cohorts will complete an abbreviated assessment measure set to include only the chronic GVHD activity assessments/response determination and the biologic studies (B cell subsets, BAFF levels) at 6 and 12 month time points. These limited assessments for the non-MTD dose level patients will be included to examine the relationship between dose and clinical response, and dose/pharmacodynamic activity.
**Schirmer test can be done as needed for supportive information in diagnosis of ocular sicca, however is not required by the trial, and does not need to be done on serial visits