Placebo Controlled, Phase 2a Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients with Relapsing Forms of Multiple Sclerosis (RMS): 6 Months Analysis of B cell Subsets

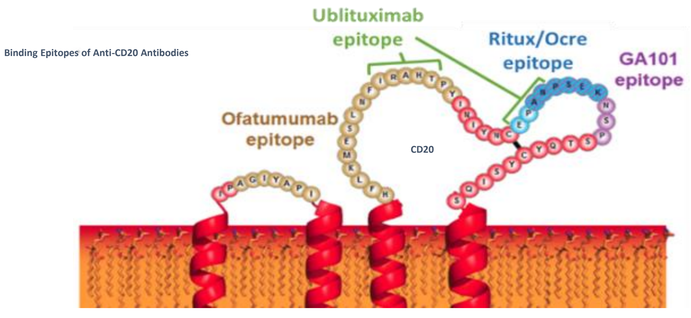
Amy Lovett-Racke[1] , Yue Liu[1], Matthew Gormley[1], Michael Racke[2], Richard Shubin[3], Sibyl Wray[4], Wendy Su[5], James L. Eubanks[5], Edward Fox[6]

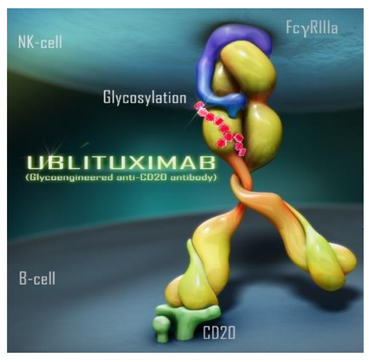
[1]Microbial Infection and Immunity, The Ohio State University, [2]The Ohio State University Medical Center, Wexner Medical Center, [3]Arcadia Neurology Center, [4]Hope Neurology, [5]TG Therapeutics, Inc., [6]Central Texas Neurology Consultants

INTRODUCTION

Introduction & Purpose

- Ublituximab (UTX; TG-1101) is a novel chimeric monoclonal antibody (mAb) that targets a unique epitope on the CD20 antigen. It is also glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab.
- In *in vitro* studies, ublituximab demonstrated 100 times greater natural killer (NK)-cell-mediated ADCC than rituximab in patient-donor CLL cells (Le Garff-Tavernier *et al*, 2011).





- To date, over 600 patients with various B cell malignancies have been treated with ublituximab and two multicenter Phase III trials are complete or in progress (GENUINE and UNITY, respectively). Completed oncology studies have demonstrated robust activity, with excellent safety and tolerability.
- The objective for the ublituximab RMS program is to determine whether the enhanced ADCC potency of ublituximab can translate into additional clinical benefits for MS patients, in the form of lower doses and faster infusion times than current anti-CD20 infused therapies.

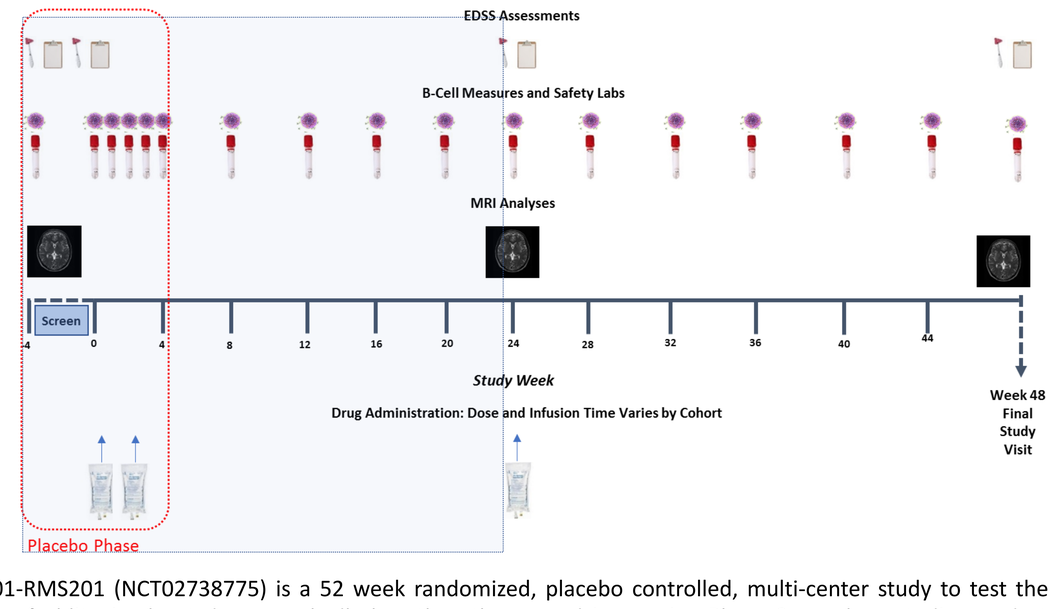
Methods & Study Design

Study Cohorts: Doses and Infusion Times

	Randomization	Treatment Period		
Cohort	Subjects and treatment	Day 1/ infusion time	Day 15/ infusion time	Week 24/ infusion time
1	Placebo (n=2)	Placebo / 4h	Placebo / 3h	-
	UTX (n=6)	150 mg / 4h	450 mg / 3h	450 mg / 1.5h
2	Placebo (n=2)	Placebo / 4h	Placebo / 1.5h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1.5h	450 mg / 1h
3	Placebo (n=2)	Placebo / 4h	Placebo / 1h	-
	UTX (n=6)	150 mg / 4h	450 mg / 1h	600 mg / 1h

- Patients were enrolled sequentially in treatment cohorts 1, 2 and 3 and randomized 3:1 to ublituximab or placebo.
- Ublituximab or placebo was administered via intravenous infusion at the doses and rates shown.
- At study day 28, placebo patients were unblinded and, after re-screening, received the active drug and assessments, as shown here.
- Peripheral blood samples were collected for B-Cell measures and safety labs at the intervals shown here (B-Cell analyses are reported here up to week 25).
- An Independent Data Safety Monitoring Board (DSMB) reviewed laboratory and clinical safety data from the first two subjects of each cohort (one ublituximab and one placebo).

Methods & Study Design (cont'd)



- TG1101-RMS201 (NCT02738775) is a 52 week randomized, placebo controlled, multi-center study to test the safety and efficacy of ublituximab, at doses markedly less than those used in ongoing Phase 3 oncology studies, and at a range of infusion times, with a goal of rapid infusions.
- To qualify for the study, subjects needed to have a diagnosis of relapsing MS, by 2010 McDonald Criteria, and have either one confirmed MS relapse in the past year, 2 relapses in the past two years, or at least one active Gd enhancing T1 lesion at the screening MRI. Other inclusion/exclusion criteria were detailed in the study protocol.
- Primary endpoint is the Responders Rate, defined as percent of subjects with ≥95% reduction in peripheral CD19+ B-cells within 2 weeks after the second infusion (day 15).
- Additional clinical and radiological measures of efficacy are being evaluated. Herein, we report the preliminary safety and efficacy at 24 weeks of the 48 week study, in the first three patient cohorts.

Baseline Demographics

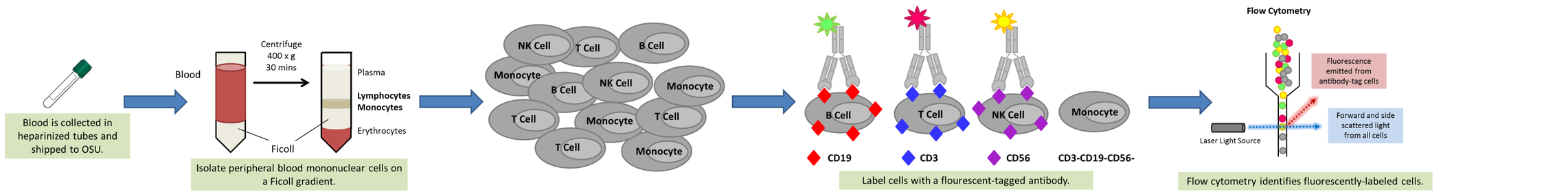
Cohort	Subjects and Treatment	Age (Years)[1]	Gender (% Female)	Disease Duration (Years)[1,2]
1	Placebo (n=2)	39±14	50%	15.5±20.4
	UTX (n=6)	43±12	67%	7.1±7.3
2	Placebo (n=2)	44±1	0%	0.9±1.2
	UTX (n=6)	33±10	100%	5.3±6.4
3	Placebo (n=2)	38±7	50%	11.5±7.5
	UTX (n=6)	40±11	67%	13.4±10.0
Total	N=24	40±11	67%	8.8±9.0

[1] Mean ± Standard Deviation

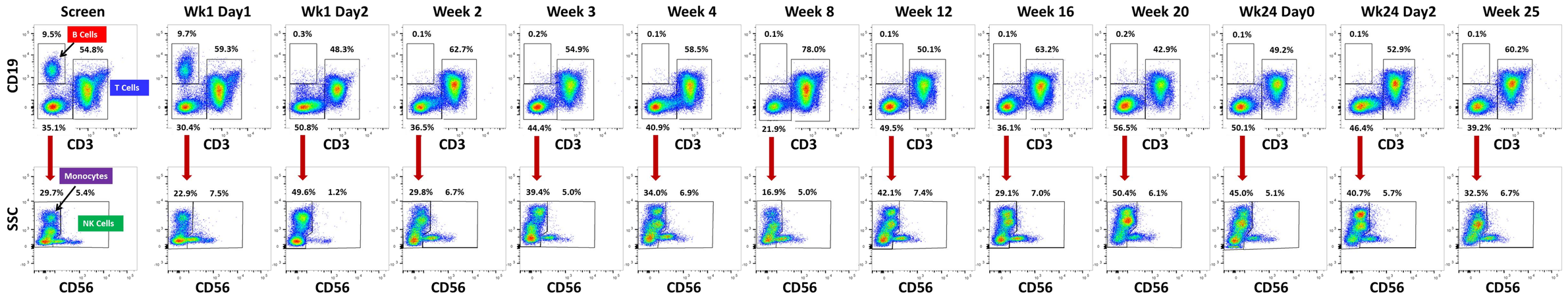
[2] Distribution of times from diagnosis: 11 subjects (45.8%) were less than 5 years, 7 (29.2%) were 5-10 years, and 6 (25%) were greater than 10 years.

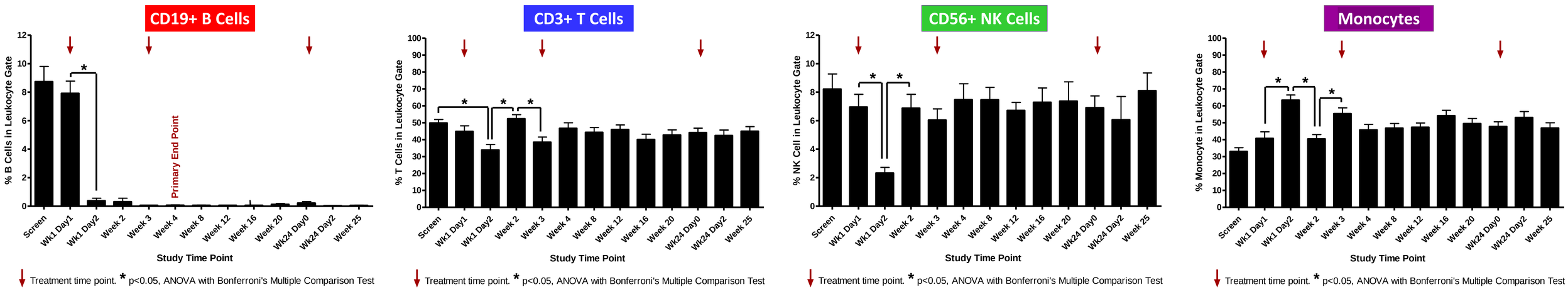
RESULTS

Strategy to Identify Immune Cell Populations

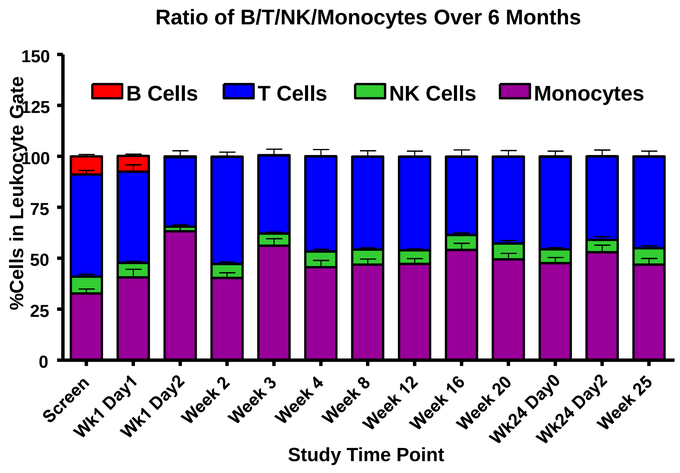


Flow Cytometric Analysis of Immune Cell Populations over 6 Months





B cells are depleted ~99% at 4 weeks, meeting the primary end point. T cells, NK cells and monocytes normalize by 4 weeks and remain stable over 6 month analysis.



Immune homeostasis is restored and maintained in the T cell, NK cell and monocyte populations.

CONCLUSIONS

- **B cells are efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab, with 99% depletion by all patients by week 4 and maintained the significant reduction at Week 24 (6 months; N=24).**
- **NK cells are significantly reduced within 24 hrs of receiving the first dose of ublituximab, indicative of exhaustion due to their role in ADCC of the B cells.**
- **Modest decrease in the percentage of T cells at 24 hours of receiving the first dose of ublituximab, but this appears to be due to an increase in monocytes, likely due to the bone marrow increasing monocyte output due to loss of B cells.**
- **The fluctuation in NK cells, T cells and monocytes that occurred in response to B cell depletion is corrected within 4 weeks post initial ublituximab treatment.**
- **Due to the sustained B cell depletion, there is no significant affect of ublituximab treatment at Week 24 on the NK cells, T cells or monocytes, illustrating the immune homeostasis in the non-B cell.**
- **At Week 24, 96% of subjects were confirmed relapse free and 79% of subjects showed improved or stable EDSS. Detailed clinical results are provided in Poster #793 (26 October 2017).**
- **Ublituximab is well tolerated and demonstrates rapid and robust B cell depletion with shorter infusion times.**
- **These data support the recently announced international Phase 3 program evaluating TG-1101 (ublituximab) for the treatment of relapsing forms of Multiple Sclerosis (RMS). The Phase 3 trials, entitled ULTIMATE I and ULTIMATE II, are being conducted under Special Protocol Assessment (SPA) agreement with the U.S. Food and Drug Administration (FDA) and will be led by Lawrence Steinman, MD, of Stanford University.**

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