6 Month Results of a Phase 2a Multicenter Study of Ublituximab, a Novel Glycoengineered Anti-CD20 Monoclonal Antibody, in Relapsing Multiple Sclerosis

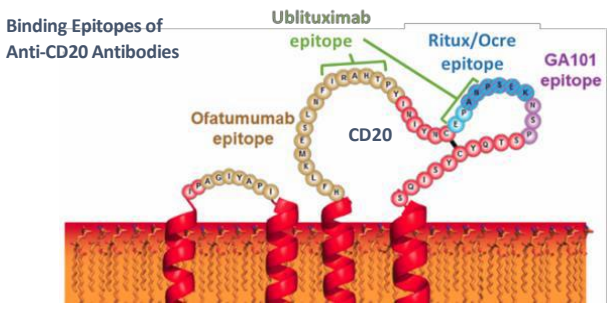
Edward Fox[1], Amy Lovett-Racke[2], Yue Liu[2], Matthew Gormley[2], Michael Racke[3], Richard Shubin[4], Sibyl Wray[5], Matilde Inglese[6], Maria Petracca[6], James L. Eubanks[7], Wendy Su[7]

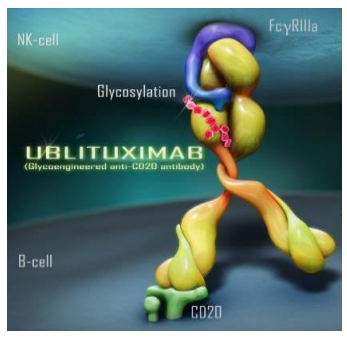
[1]Central Texas Neurology Consultants , [2]Microbial Infection and Immunity, The Ohio State University, [3]The Ohio State University Medical Center, Wexner Medical Center, [4]Arcadia Neurology Center, [5]Hope Neurology, [6]Mount Sinai Medical Center , [7]TG Therapeutics, Inc.

INTRODUCTION AND METHODS

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).





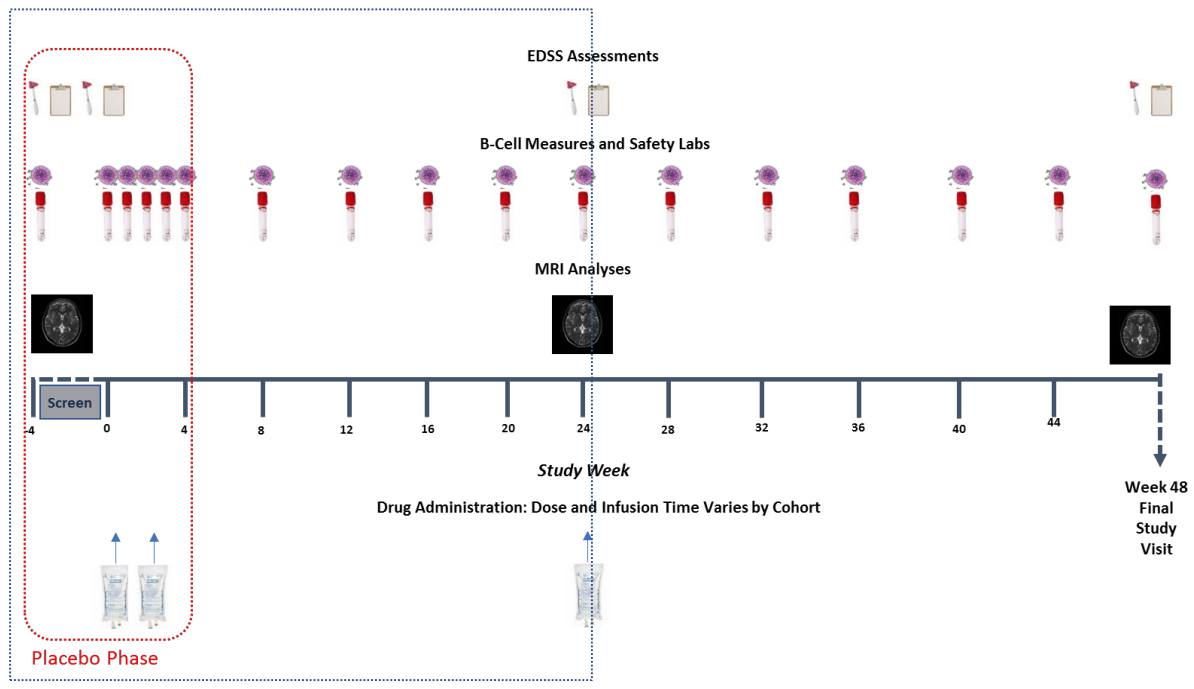
- To date, over 800 patients with various B cell malignancies have been treated with ublituximab and two multicenter Phase III trials are complete or in progress (GENUINE and UNITY, respectively). Completed oncology studies have demonstrated robust activity, with excellent safety and tolerability. In addition to the oncology studies, two Phase III trials in MS are ongoing.
- 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

	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
4	Placebo (n=2)	Placebo / 3h	Placebo / 1h	-
	UTX (n=6)	150 mg / 3h	600 mg / 1h	600 mg/ 1h
5	Placebo (n=2)	Placebo / 2h	Placebo / 1h	-
	UTX (n=6)	150 mg / 2h	600 mg / 1h	600 mg/ 1h

- Patients were enrolled sequentially in treatment Cohorts 1 through 5 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 five patient cohorts.

RESULTS

Patient Characteristics

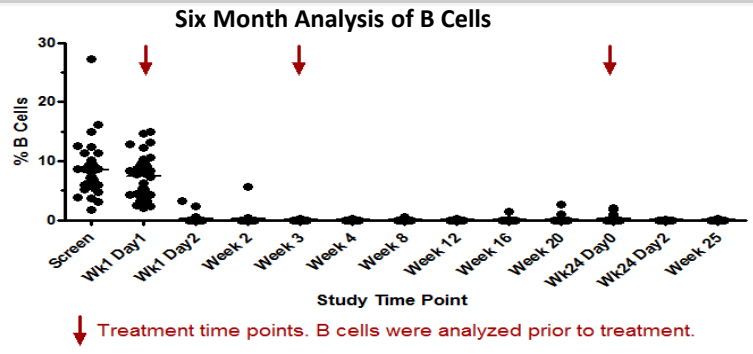
Baseline Demographics

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
4	Placebo (n=2)	31±1	67%	6.8±7.7
	UTX (n=6)	39±12	50%	0.20±0.10
5	Placebo (n=2)	36±12	100%	15.4±9.6
	UTX (n=6)	46±1	100%	6.3±5.6
Total	**N=40**	**40±10**	**70%**	**8.0±8.4**

[1] Mean ± Standard Deviation
[2] Distribution of times from diagnosis: 20 subjects (50%) were less than 5 years, 7 (17.5%) were 5-10 years, and 13 (32.5%) were greater than 10 years.

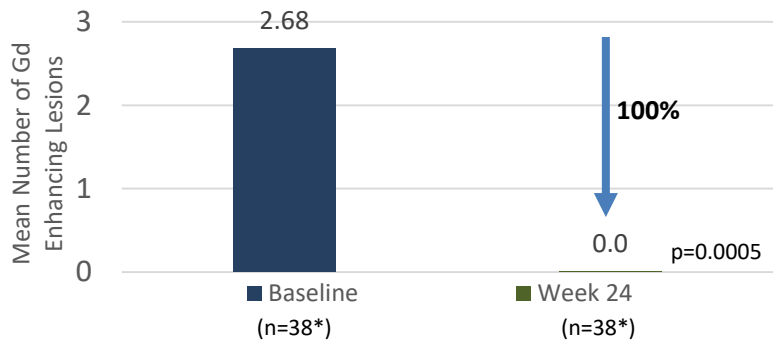
- 40 subjects were randomized to treatment in Cohort 1- Cohort 5.
- 39/40 subjects completed 6 months of ublituximab treatment; 10 (2 per cohort) received placebo infusions, before crossing over to the ublituximab arm
  - One subject in Cohort 2 withdrew from study due to pregnancy after having received 2 ublituximab infusions, but continued to be followed with safety lab monitoring and immunological analyses.

B Cell Depletion



- At week 4, median 99% B cell depletion was observed and maintained at week 24 (N=40)

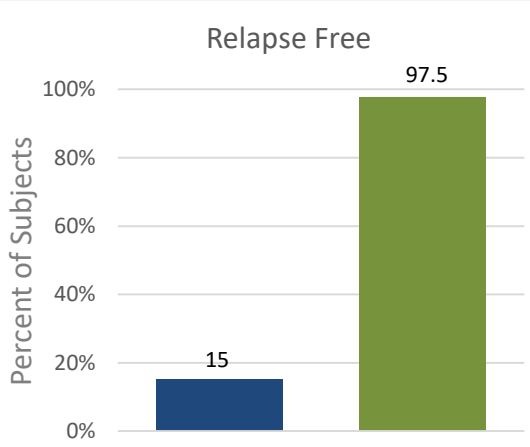
MRI



- ***No T1 Gd-enhancing lesions detected in any subjects at Week 24 (p=0.0005; n=38)***

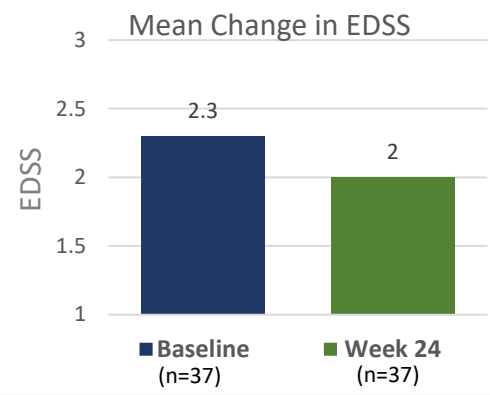
** 2 subjects missed the week 24 MRI scan, but are still in active treatment.*

Relapses



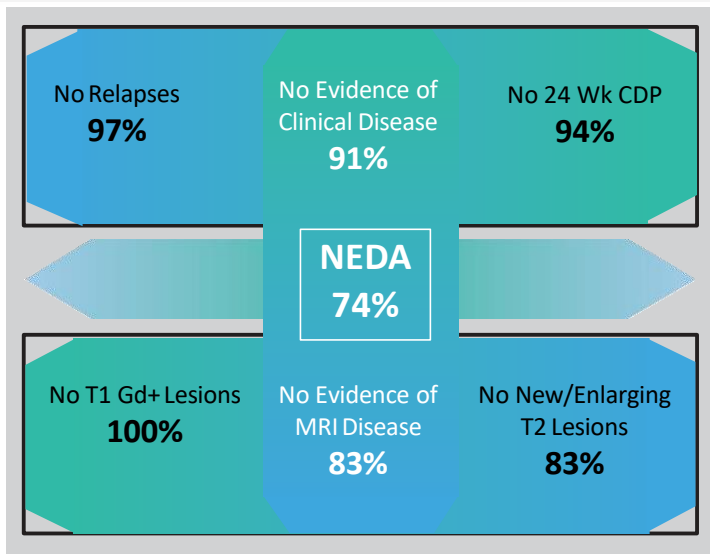
- **39/40 (97.5%) of subjects were confirmed relapse free after 24 weeks of ublituximab treatment.**
  - One confirmed relapse was reported, in Cohort 1. The subject was initially randomized to the placebo arm. The relapse occurred 12 days after the subject's first infusion of 150mg of ublituximab. The subject remains on study and has received the second and third infusions of ublituximab. To date, the subject has remained relapse free.
- *34/40 (85%) subjects had experienced at least one relapse in the past year or two relapses in the past two years.
  - Among patients who had relapses in the year prior to screening, the mean number of relapses per subject was 1.38.

Disability/EDSS



- Mean EDSS at baseline was 2.30 ±1.42; (Standard Deviation; Median = 2.0).
- At 24 weeks, the mean EDSS was 2.0. The mean change from baseline was an improvement of 0.30 ±1.0 points.
- 78% of subjects showed improved or stable EDSS.

NEDA (No Evidence of Disease Activity) at Week 24



At Week 24, 35/40 subjects had received all assessments to be evaluated for NEDA:

- 97% of subjects were relapse free
- 94% of subjects did not experience 24 week confirmed disability progression
- 100% of subjects did not have any Gd-enhancing lesions
- 83% of subjects did not have any new/enlarging T2 lesions
- 74% of subjects achieved clinical and MRI outcomes consistent with NEDA

CDP = Confirmed Disability Progression based on Week 24 EDSS Assessment vs baseline

Safety & Tolerability

Event, n (%)	(N=40)	
Any Adverse Event[1]	37 (93%)	
Most Frequently Reported Adverse Events- All Causality[2]	All Grades	Grade 3/4
Infusion-related reaction	16 (40%)	- (-)
Headache	8 (20%)	- (-)
Fatigue	7 (18%)	3 (8%)
Dizziness	5 (13%)	- (-)
Nausea/Vomiting	5 (13%)	- (-)
Upper Respiratory Infection	4 (10%)	1 (3%)
Numbness	4 (10%)	- (-)
Infusion Related Reactions (IRRs)		
Total number of IRRs	36	
Patients with at least one IRR	16 (40%)	
	Grade 1/2	
Cohort 1	2 (5%)	
Cohort 2	4 (10%)	
Cohort 3 (Phase 3 Dose)	1 (3%)	
Cohort 4	3 (8%)	
Cohort 5	6 (15%)	

[1] Reflects total number of patients that experienced one or more adverse event
[2] Events reported by at least 10% of patients regardless of causality, listed by decreasing incidence.

- **Ublituximab was well tolerated and no drug related discontinuations from study have occurred to date.**
- No Grade 3/4 Adverse Events were deemed possibly related to ublituximab.
- A total of 36 infusion related reactions (IRRs) were reported in 16 subjects. All were Grade 1 or Grade 2.
- IRRs were most frequent in the first infusion and were most prevalent in Cohorts 4 and 5 which include faster infusion times and higher doses than our selected Phase 3 dose.
  - 21 of 36 IRRs occurred in Cohorts 4 and 5
- There were no events of death reported on study.
- The Data Safety Monitoring Board (DSMB) has reviewed safety labs and adverse events for all subjects to date, and has not found any lab abnormalities or safety signals that would warrant a change in protocol.

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=40).
- No T1 Gd-enhancing lesions detected in any subjects at 24 weeks (p=0.0005).
- 97.5% of subjects (39/40) were relapse free at 24 weeks; Mean EDSS improvement from baseline of 0.3 with 78% of subjects showing improved or stable EDSS.
- Ublituxmab was well tolerated, most frequent AEs were infusion related reactions (IRRs); all Grade 2 or less.
- A rapid infusion time, as low as one hour, of 450mg was well tolerated, produced high levels of B cell depletion and is now being studied in the Phase 3 ULTIMATE trials.
- These data presentations support the international Phase 3 ULTIMATE program evaluating ublituximab (TG-1101) for the treatment of relapsing forms of Multiple Sclerosis (RMS). The Phase 3 ULTIMATE trials are currently enrolling and 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.

Presented at the 3rd Annual ACTRIMS Meeting, February 1-3, 2018, San Diego, California