Preliminary Results of Phase 2 Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients with Relapsing Forms of Multiple Sclerosis (RMS) Demonstrate Rapid Gd-enhancing Lesions Decrease

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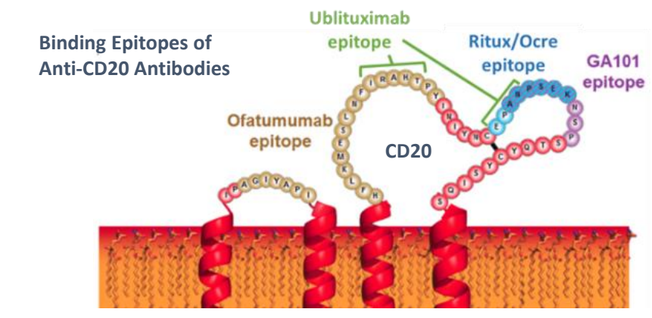
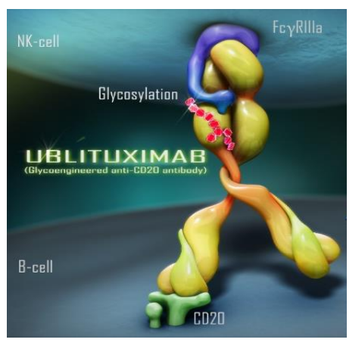
INTRODUCTION

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.

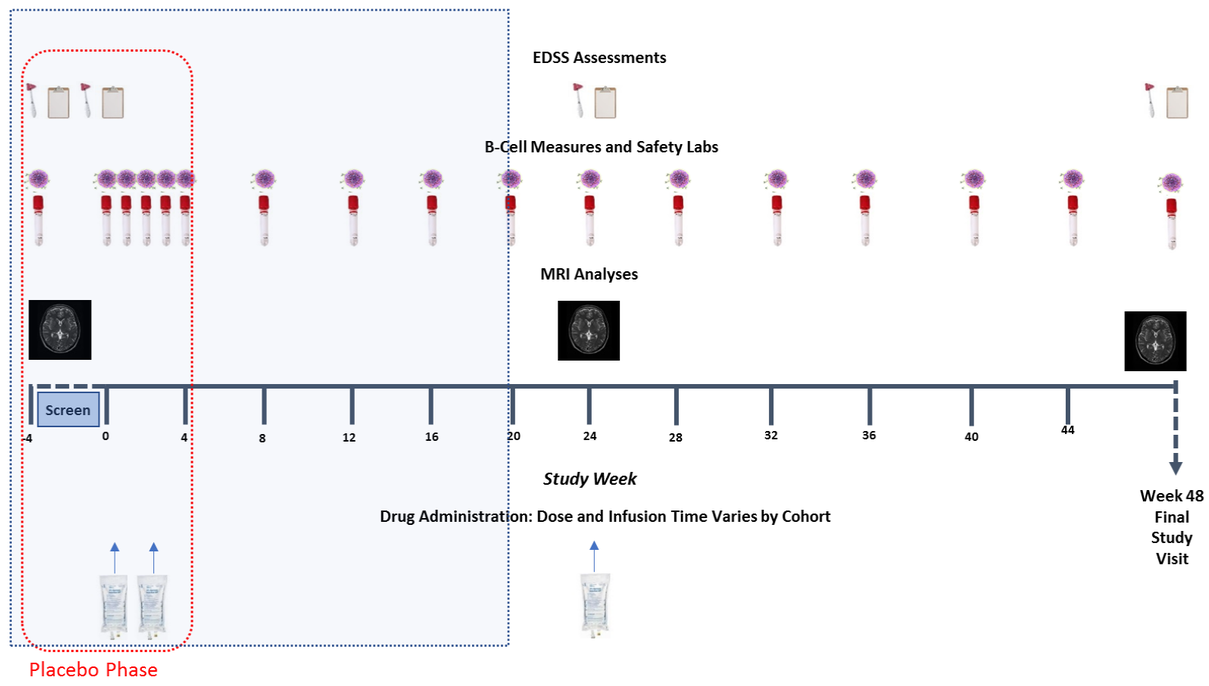
Methods & Study Design

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.

MRI Acquisitions

- Acquisition of the MR images were performed at the individual sites using existing MRI equipment operating at 1.5 and at 3.0 Tesla, using commercially available (multi-channel) head coils.
- MRI acquisitions were obtained at baseline, Week 24 and Week 48
- All MRI analysis were performed at Ichan School of Medicine at Mt Sinai in NY, NY

RESULTS

Patient Characteristics

Patient Demographics at Baseline

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.

Subject Disposition

- 24 subjects were randomized to treatment in Cohorts 1-3
- At the time of data analysis, received confirmed MRI readings at Week 24 for 20 subjects
- 23/24 subjects completed 6 months of ublituximab treatment; 6 (2 per cohort) received placebo infusions.
  - One subject withdrew from study due to pregnancy after having received 2 ublituximab infusions, but continued to be followed with safety lab monitoring and immunological analyses.

Baseline Characteristics

Baseline T1-Gd Lesions

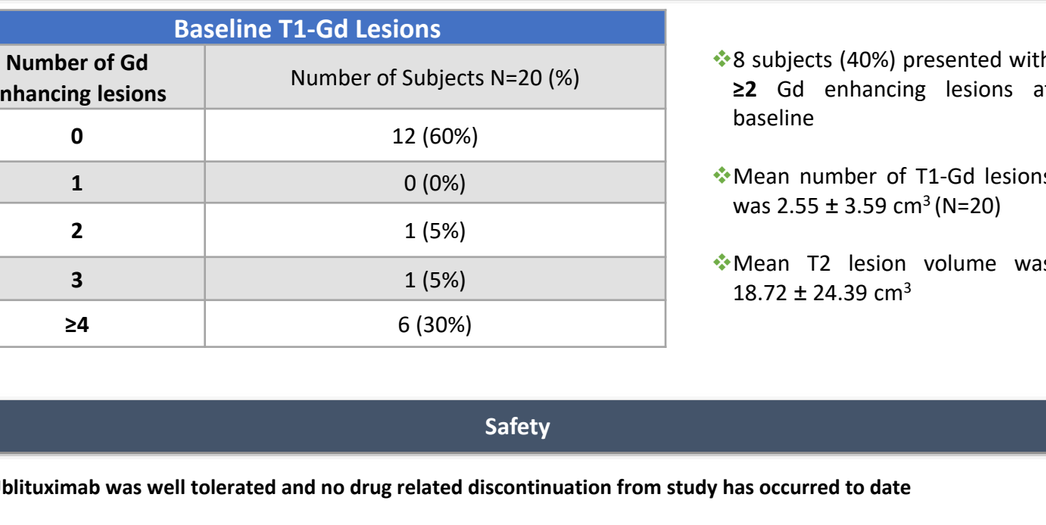
Number of Gd enhancing lesions	Number of Subjects N=20 (%)
0	12 (60%)
1	0 (0%)
2	1 (5%)
3	1 (5%)
≥4	6 (30%)

- 8 subjects (40%) presented with **≥2** Gd enhancing lesions at baseline
- Mean number of T1-Gd lesions was 2.55 ± 3.59 cm^3 (N=20)
- Mean T2 lesion volume was 18.72 ± 24.39 cm^3

Safety

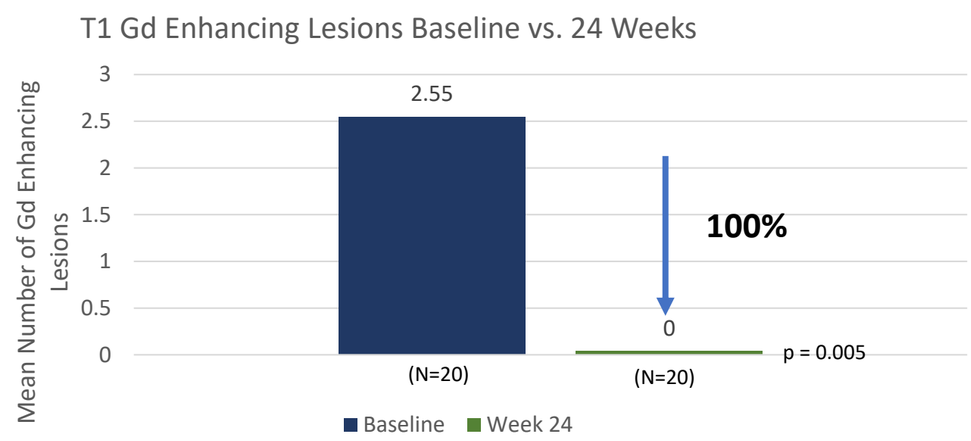
- **Ublituximab was well tolerated and no drug related discontinuation from study has occurred to date**
- **A total of 15 infusion related adverse events (AEs) were reported in 7 subjects. All infusion related AEs were grade 1 or 2.**
- Only 1 of the 15 infusion related AEs (qualified as not related to ublituximab) occurred in Cohort 3, with the fastest infusion times, and highest combined dose
- The majority of AEs were Grade 1 or 2.
- There were no events of death reported on study.
- Detailed safety data are reported in Poster #793 (26 October 2017)

T1 Hypointense Lesion Volume (Pre-Gd)



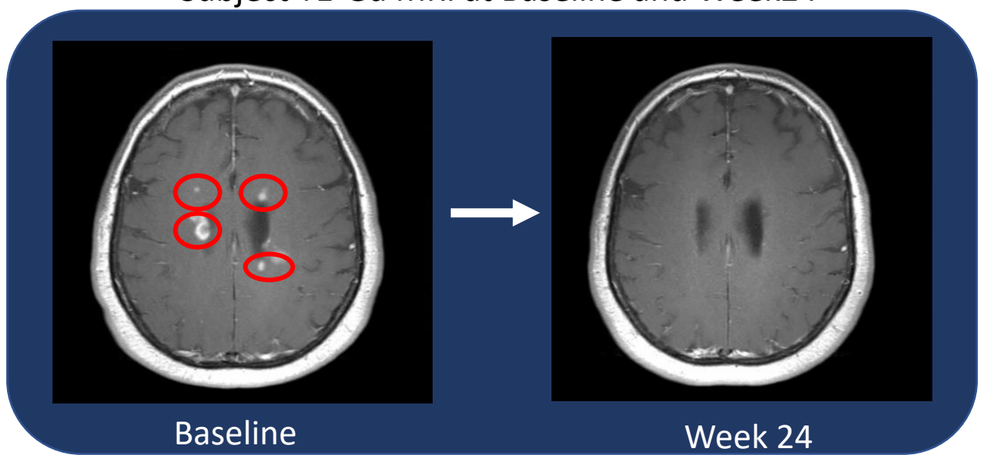
There was a decrease of 6.6% (p=0.03) in T1 Hypointense Lesion Volume at Week 24 compared to baseline (N=20)

T1 Gd-enhancing Lesions

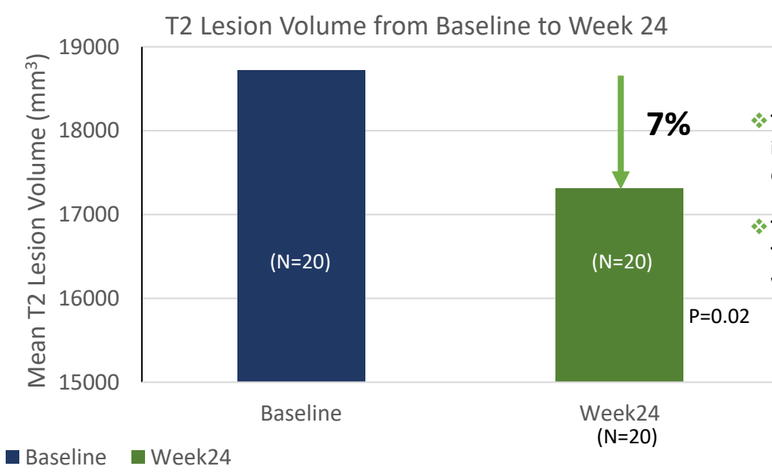


- Subjects (N=20) had a mean of 2.55 ± 3.59 T1 Gd-enhancing lesions at baseline (±Standard Deviation).
- **No T1 Gd enhancing lesions were detected in any subjects at 24 weeks (p=0.005).**

Subject T1-Gd MRI at Baseline and Week24



T2 Lesions Volume



- **There was a decrease of 7.5% (p=0.02) in T2 lesion volume at Week 24 compared to baseline (N=20)**
- **The mean number of New/Enlarging T2 lesions from baseline to Week 24 was 0.3 ± 0.4 (N=20)**

CONCLUSIONS

- No T1 Gd-enhancing lesions detected in any subjects at 24 weeks (p=0.005).
- 7% Reduction in the T2 lesion volume at Week 24 from baseline (p=0.02), suggestive of a decrease in burden of disease.
- 6.5% Reduction in T1 hypointense lesion volume at Week 24 from baseline (p=0.03).
- B cells are efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab, with 99% depletion by all patients at Week 4. Detailed immunological results are provided in Poster #1158 (27 October 2017).
- Mean EDSS improvement from baseline of 0.35 with 79% of subjects showing improved or stable EDSS. Detailed clinical results are provided in Poster #793 (26 October 2017)
- 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, was well tolerated, and produced similar levels of B cell depletion, with no identified change in IRR or overall safety profile
- These data presentations support the recently announced international Phase 3 program evaluating TG-1101 (ublituximab) for the treatment of relapsing form 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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