Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions

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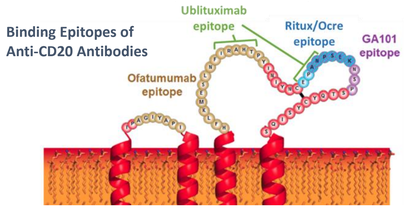
INTRODUCTION

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 1000 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.

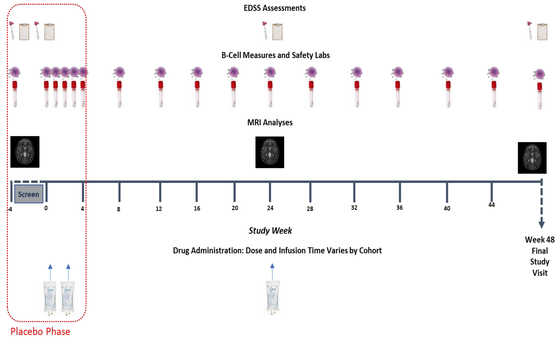
OBJECTIVES

- 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 all six patient cohorts.

MRI ACQUISITIONS

- Acquisition of the MR images were performed at 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 analyses were performed at Ichan School of Medicine at Mt Sinai in NY, NY.

METHOD & STUDY DESIGN



Cohort	Randomization: Subjects and treatment	Treatment Period: 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
6	Placebo (n=2)	Placebo / 1h	Placebo/ 1h	-
	UTX (n=6)	150 mg / 1h	600 mg / 1h	600 mg/ 1h

- Patients were enrolled sequentially in treatment Cohorts 1 through 6 and randomized 3:1 to ublituximab or placebo.
- Ublituximab or placebo was administered via intravenous infusion at the above doses and rates.
- At study day 28, placebo patients were unblinded and, after re-screening, received the active drug and assessments, as shown above.
- Peripheral blood samples were collected for B-Cell measures and safety labs at the intervals shown above (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).

RESULTS / BASELINE DATA

PATIENT CHARACTERISTICS

Cohort	Baseline Demographics: 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
6	Placebo (n=2)	28±1	50%	5.7±2.5
	UTX (n=6)	40±8	33%	8.5±8.4
Total	N=48	40±10	65%	8.0±8.1

[1] Mean ± Standard Deviation
[2] Distribution of time from diagnosis: 22 subjects (46%) were less than 5 years, 10 (21%) were 5-10 years, and 16 (33%) were greater than 10 years

PATIENT DISPOSITION

- 48 subjects were randomized to treatment in Cohort 1 through Cohort 6.
- 46/48 subjects completed 6 months of ublituximab treatment; 12 (2 per cohort) received placebo infusions, before crossing over to the ublituximab arm
  - One subject in Cohort 2 withdrew from study after having received 2 ublituximab infusions due to pregnancy, but continued to be followed with safety lab monitoring and immunological analyses.
  - One subject in Cohort 6 missed the Week 24 infusion but continues on study

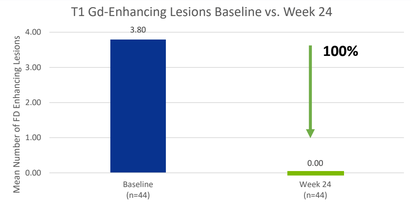
BASELINE T1 GD-ENHANCING LESIONS

Baseline T1 Gd –Enhancing Lesions: Number of Gd enhancing lesions	Number of Subjects N=48 (%)
0	30 (63%)
1	1 (2%)
2	1 (2%)
3	4 (8%)
≥4	12 (25%)

- 17 subjects (35%) presented with ≥2 Gd-enhancing lesions at baseline
- Mean number of T1-Gd lesions at baseline was 3.48 ± 7.66 (N=48)
- Mean T2 lesion volume at baseline was 14.87 ± 20.45 cm^3

RESULTS

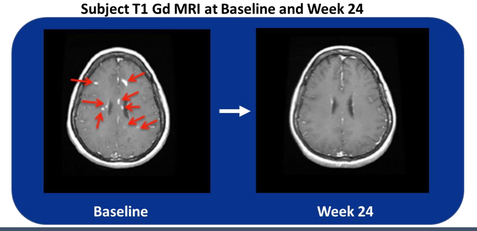
T1 GD-ENHANCING LESIONS



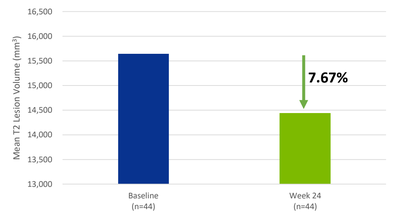
** 2 of the total 48 patients missed the week 24 MRI, and an additional 2 patients had a week 24 MRI however the data has not yet been analyzed*

- No T1 Gd-enhancing lesions detected in any subjects at Week 24 (p=0.003)
- Mean number of T1 Gd lesions at baseline was 3.80

Subject T1 Gd MRI at Baseline and Week 24

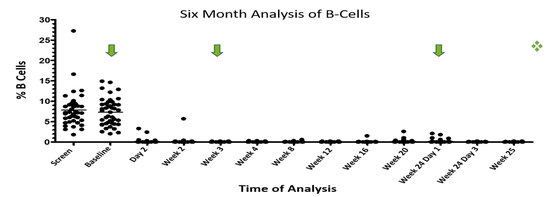


T2 LESION VOLUME



- There was a decrease of 7.67% (p=0.004) in T2 lesion volume at Week 24 compared to baseline
- The mean number of New/Enlarging T2 lesions from baseline to Week 24 was 0.2 ± 0.45

B-CELL DEPLETION



- At week 4, median 99% B cell depletion was observed and maintained at week 24 (n=44)

SAFETY & TOLERABILITY

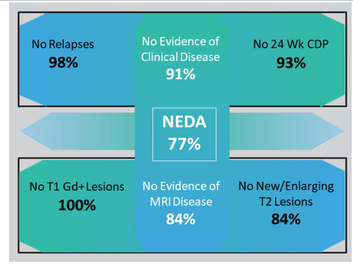
Event, n (%)	(N=48)	
Any adverse event[1]	40 (83%)	
Most frequently reported adverse events[2]	All Grades	Grade 3/4
Infusion-related reaction	20 (42%)	- (-)
Headache	10 (21%)	- (-)
Fatigue	9 (19%)	3 (6%)
Dizziness	7 (15%)	- (-)
Numbness	6 (13%)	- (-)
Nausea/Vomiting	5 (10%)	- (-)
Common Cold	5 (10%)	- (-)

[1] Reflects total number of patients that experienced one or more adverse event.
[2] These events were reported by at least 10% of patients and are 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 (AEs) were deemed possibly related to ublituximab.
- A total of 41 infusion related reactions (IRRs) were reported in 20 subjects. All were Grade 1 or Grade 2.
- 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.

ANNUALIZED RELAPSE RATE & NEDA

Annualized Relapse Rate (ARR): 0.05 (n=48) observed at Week 24

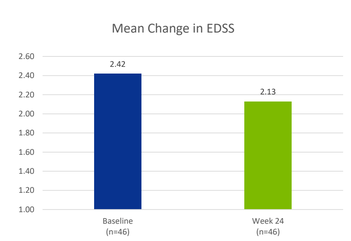


CDP = Confirmed Disability Progression based on Week 24 EDSS Assessment vs baseline

- At Week 24, 43* of 48 subjects had received all assessments to be evaluated for NEDA:
  - 98% of subjects were relapse free
  - 93% of subjects did not experience 24 week confirmed disability progression
  - 100% of subjects did not have any Gd-enhancing lesions
  - 84% of subjects did not have any new/enlarging T2 lesions
  - 76% of subjects achieved clinical and MRI outcomes consistent with NEDA

** 3 of the total 48 patients did not have week 24 MRI, 1 patient did not have week 24 MRI or week 24 EDSS evaluation and 1 additional patient did not have a week 24 EDSS evaluation therefore only 43 patients had received all assessments to be evaluated for NEDA*

DISABILITY/EDSS



- 83% of subjects showed improved or stable EDSS
- Mean EDSS at baseline was 2.42 ± 1.39; Median=2.5
- At Week 24, the mean EDSS was 2.13. The mean change from baseline was an improvement of 0.29 ± 0.93 points.

** 2 of the total 48 patients did not complete the week 24 EDSS evaluation*

CONCLUSIONS

- An Annualized Relapse Rate (ARR) of 0.05 was observed at Week 24.
- No T1 Gd-enhancing lesions were detected in any subjects at Week 24 (p=0.003).
- 7.67% Reduction in T2 lesion volume at Week 24 from baseline (p=0.004), suggestive of a decrease in burden of disease.
- 98% of subjects were relapse free at Week 24.
- 83% of subjects showing improved or stable EDSS and Mean EDSS improvement from baseline of 0.29.
- B-cells are efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab, with >99% depletion in all patients by Week 4 and maintained the significant reduction at Week 24.
- Ublituximab was well tolerated, most frequent AEs were infusion related reactions (IRRs); all Grade 1 or 2.
- 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 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 led by Lawrence Steinman, MD, of Stanford University.

Presented at the American Academy of Neurology Annual Conference, Los Angeles, CA, April 24, 2018