

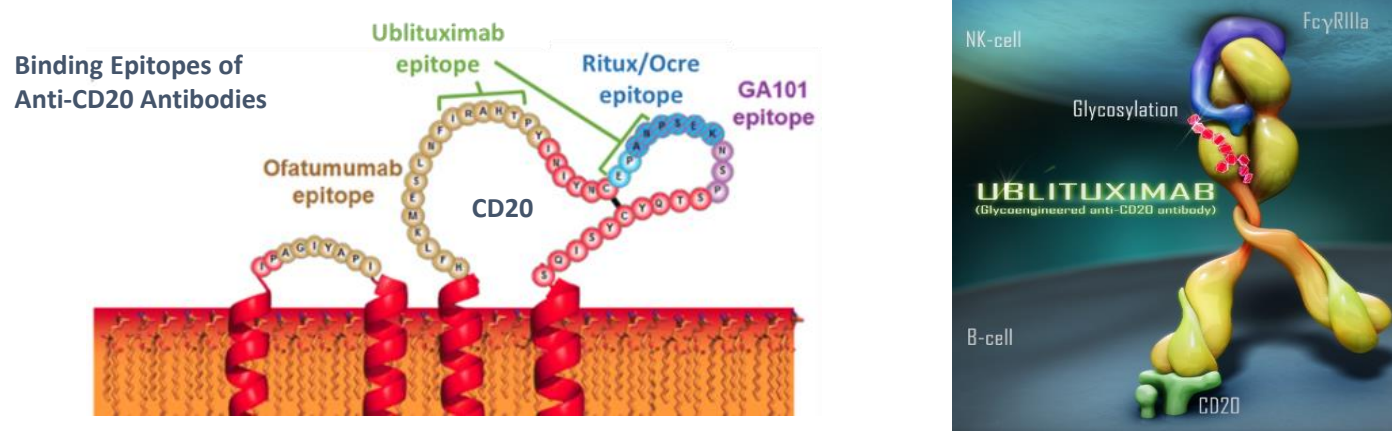
# Patient Characteristics, Safety, and Preliminary Results of a Placebo Controlled, Phase 2a Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients with Relapsing Forms of Multiple Sclerosis

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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.

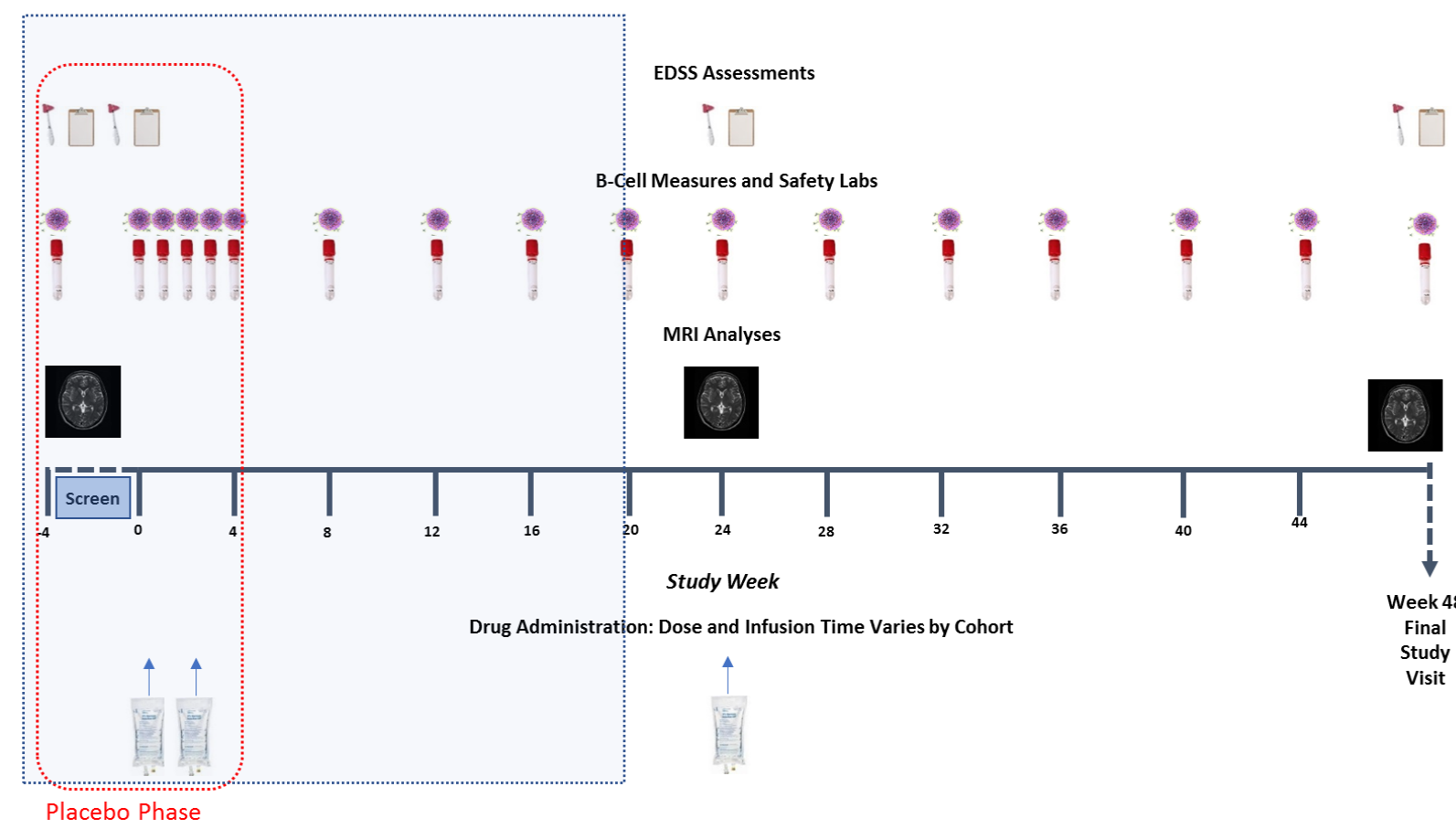
### Methods & Study Design

#### Study Cohorts: Doses and Infusion Times

Cohort	Randomization	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

- 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.

## RESULTS

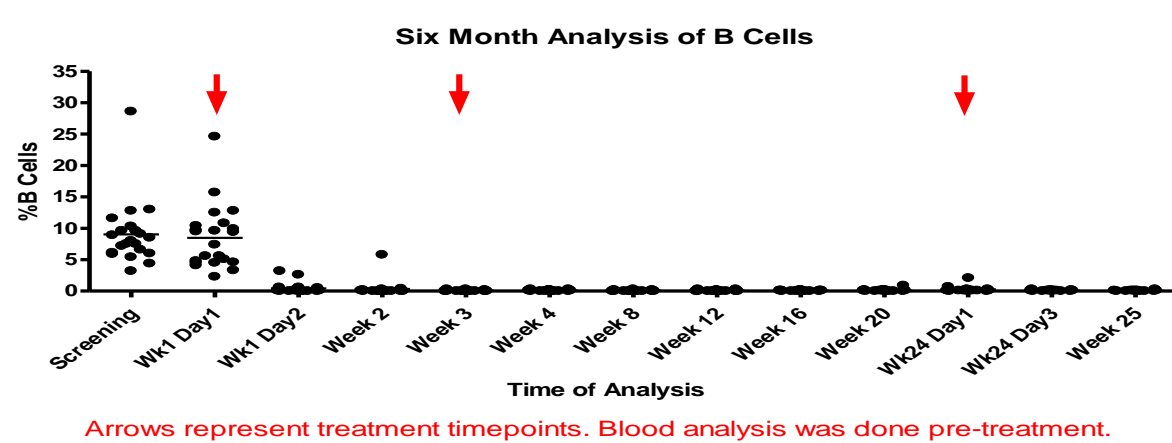
### Patient Characteristics

Baseline Demographics				
Cohort	Subjects and Treatment	Age (Years) <sup>1</sup>	Gender (% Female)	Disease Duration (Years) <sup>1,2</sup>
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
<b>Total</b>	<b>N=24</b>	<b>40±11</b>	<b>67%</b>	<b>8.8±9.0</b>

<sup>1</sup> Mean ± Standard Deviation  
<sup>2</sup> 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.

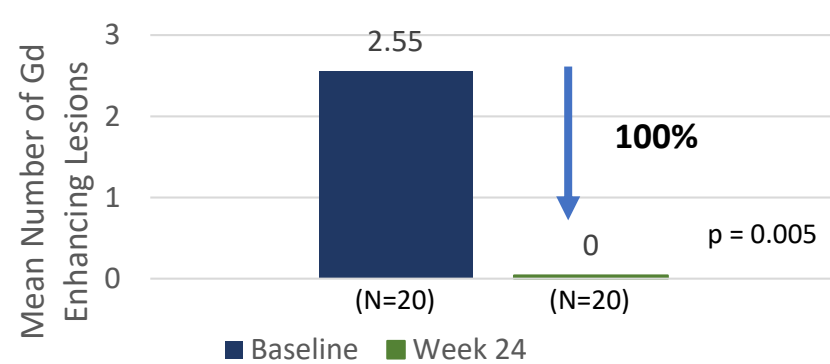
- 24 subjects were randomized to treatment in Cohorts 1-3.
- 23/24 subjects completed 6 months of ublituximab treatment; 6 (2 per cohort) received placebo infusions.
- One subject withdrew from study due to pregnancy after having received 2 ublituximab infusions, but continued to be followed with safety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

### B-Cell Depletion



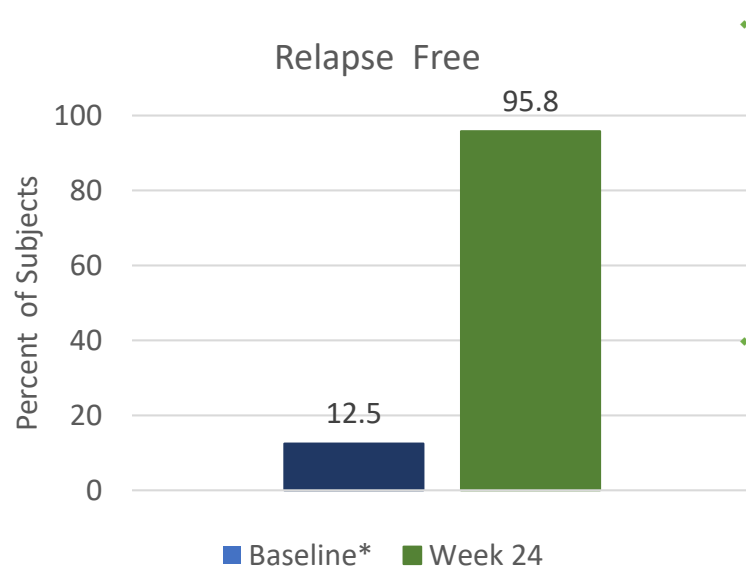
### MRI

#### T1 Gd Enhancing Lesions Baseline vs. 24 Weeks



- No T1 Gd-enhancing lesions detected in any subjects at 24 weeks (p=0.005) (n=20)

### Relapses



- 23/24 (95.8%) of subjects were confirmed relapse free at 24 weeks.

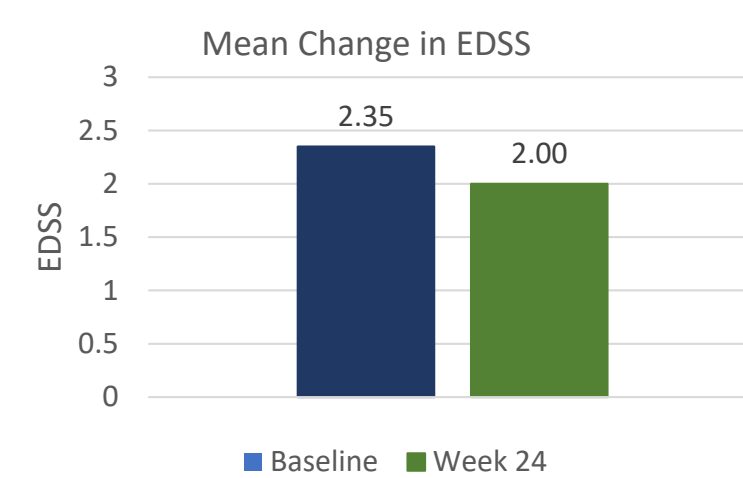
- One confirmed relapse was reported. The subject was initially randomized to the placebo arm. The relapse occurred 12 days after the subject's first infusion of 150mg of ublituximab. The subject remains on study and has received the second and third infusions of ublituximab. To date, the subject has remained relapse free.

- \*21/24 (87.5%) subjects had experienced 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 1.42.

- The mean time between last reported relapse and enrollment was 5.77 months.

### Disability/EDSS



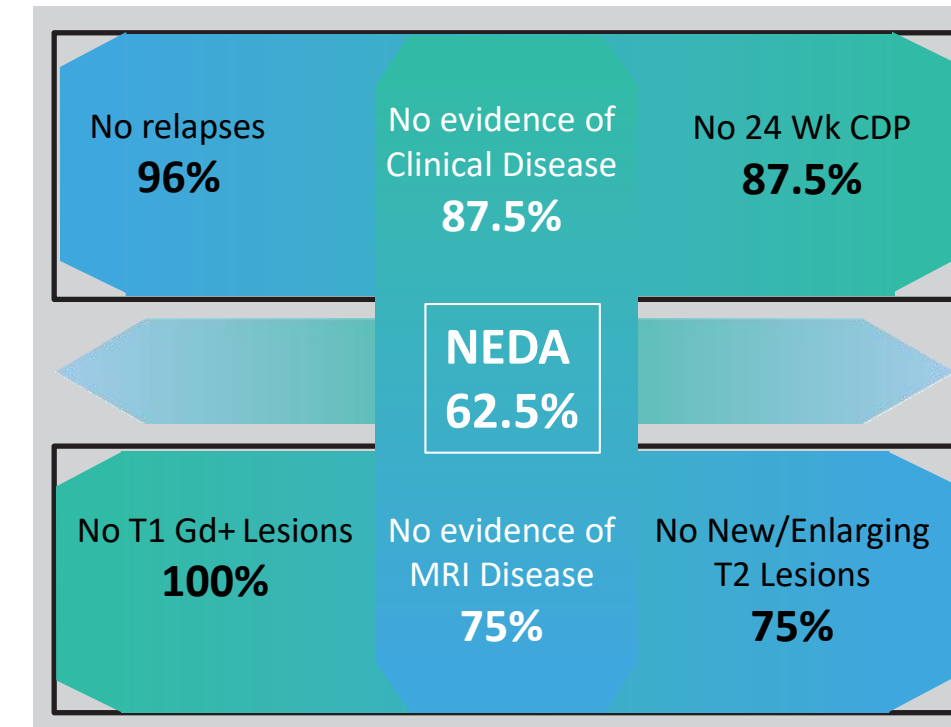
- Mean EDSS at baseline was 2.35 ±0.60; (Standard Deviation; Median = 2.0)

- At 24 weeks, the mean EDSS was 2.0. The mean change from baseline was an improvement of 0.35 ±0.89 points (p=0.15)

- 87.5% of subjects did not experience 24 week confirmed disability progression

- 79% of subjects showed improved or stable EDSS

### NEDA (No Evidence of Disease Activity) at Week 24



#### At 24 Weeks:

- 96% of subjects were relapse free
- 87.5% of subjects did not experience 24 week confirmed disability progression
- 100% of subjects did not have any Gd-enhancing lesions
- 75% of subjects did not have any new/enlarging T2 lesions
- 62.5% of subjects achieved NEDA

CDP = Confirmed Disability Progression based on 24 Week EDSS Assessment

### Safety & Tolerability

Event, n (%)	(N=24)	
Any adverse event <sup>1</sup>	18 (75%)	
Most frequently reported adverse events <sup>2</sup>	All Grades	Grade 3/4
Infusion-related reaction	7 (29%)	- (-)
Nausea/Vomiting	5 (21%)	- (-)
Numbness	5 (21%)	- (-)
Urinary tract infection	5 (21%)	- (-)
Fatigue	4 (17%)	2 (8%)
Headache	4 (17%)	- (-)
Upper respiratory infection	4 (17%)	1 (4%)
Yeast infection	3 (12%)	1 (4%)
<b>Infusion-related reactions</b>		
Patients with at least one infusion-related reaction	7 (29%)	
Total number of reactions	15	
Grade	(N=24)	
1	2 (8%)	
2	5 (21%)	
3	- (-)	
4	- (-)	
5	- (-)	

- 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 Grade 1 or 2.

- No infusion related AEs were deemed related to ublituximab in Cohort 3, which had the fastest infusion times, and highest combined dose.

- There were a total of 11 Adverse Events ≥ Grade 3, only one of which was deemed possibly related to ublituximab, an MS relapse occurring 12 days after the subject's first infusion of 150mg of ublituximab. This subject was initially randomized to the placebo arm.

- 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.

<sup>1</sup> Reflects total number of patients that experienced one or more adverse event.

<sup>2</sup> These events were reported by at least 10% of patients and are listed by decreasing incidence.

## 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).
- No T1 Gd-enhancing lesions detected in any subjects at 24 weeks (p=0.005).
- 96% of subjects (23/24) were relapse free at 24 weeks; Mean EDSS improvement from baseline of 0.35 with 79% of subjects showing improved or stable EDSS.
- Ublituximab 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 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.