Final Results of a Placebo Controlled, Phase 2 Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients with Relapsing Forms of Multiple Sclerosis (RMS)

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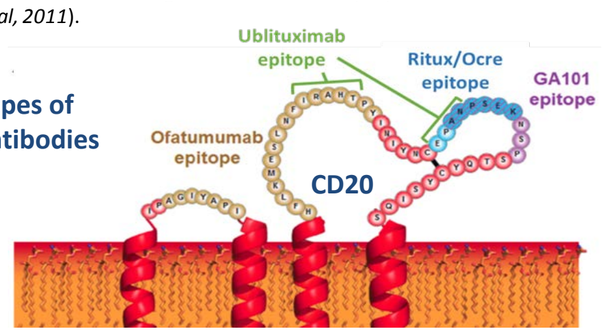
INTRODUCTION AND METHODS

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 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 Phase 2 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.

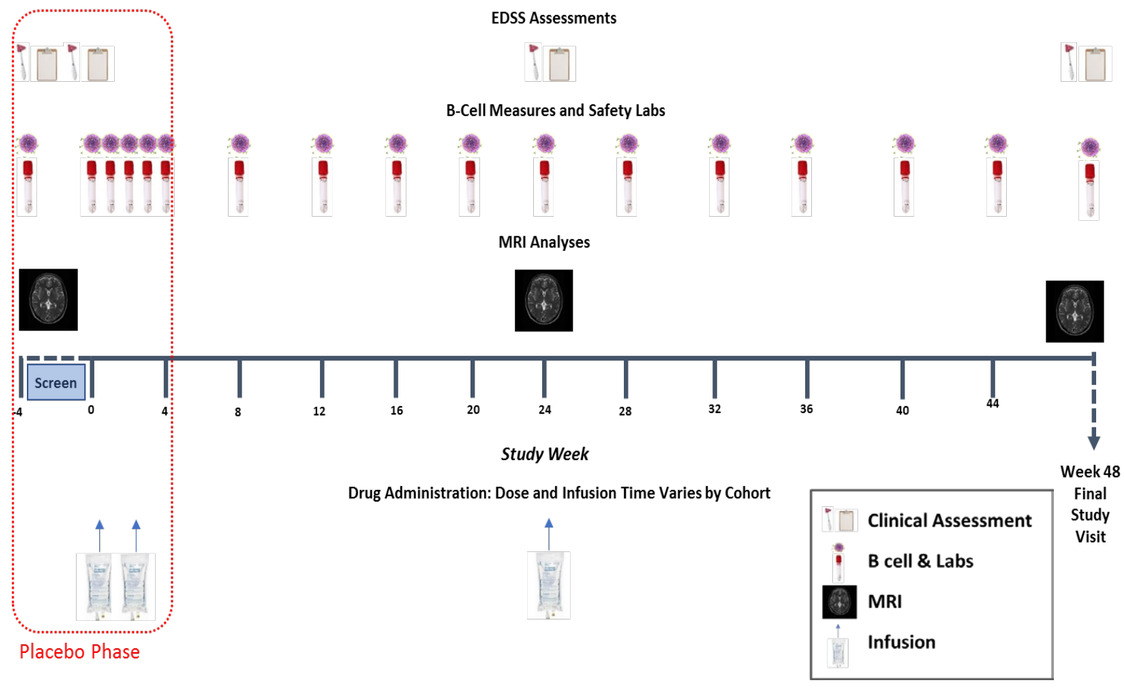
METHOD & STUDY DESIGN

	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
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 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.
- 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).

METHOD & STUDY DESIGN

Primary Efficacy Endpoint: Responders Rate
Responders Rate = Subjects with ≥95% B-cell depletion at Week 4



- 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 Day 15 infusion.
- Additional clinical and radiological measures of efficacy were evaluated. Here, we report the final results of the Phase 2 study.

RESULTS

PATIENT DISPOSITION & BASELINE CHARACTERISTICS

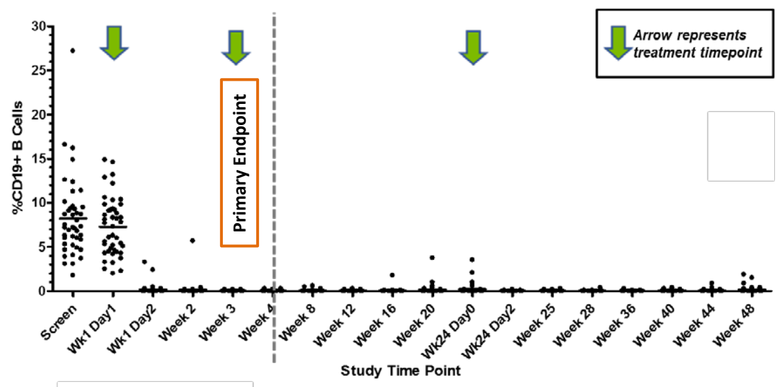
Baseline Demographics				
Cohort	Subjects and treatment	Age (Years)[1]	Gender (% Female)	Disease Duration (Years)[1,2]
1	Placebo (n=2)	39±14	50%	15.5±20.4
	UTX (n=6)	43±12	67%	7.1±7.3
2	Placebo (n=2)	44±1	0%	0.9±1.2
	UTX (n=6)	33±10	100%	5.3±7.0
3	Placebo (n=2)	38±7	50%	11.5±7.5
	UTX (n=6)	40±11	67%	13.4±10.0
4	Placebo (n=2)	31±1	67%	0.2±0.1
	UTX (n=6)	39±12	50%	4.4±5.4
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%	7.7±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

At Study Entry:

- 86% of subjects experiences ≥1 relapse in the year prior to screening
- Mean number of relapses = 1.45
- Median number of relapses = 2

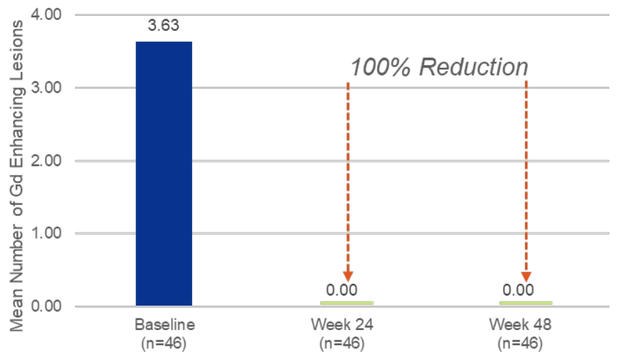
PRIMARY ENDPOINT: B-CELL DEPLETION



- **100% Responders Rate**
  - (48/48) subjects met the primary endpoint of >95% B-cell depletion from baseline to Week 4, p<0.001
- At Week 4, median 99% B-cell depletion was observed and maintained at Week 24 and Week 48

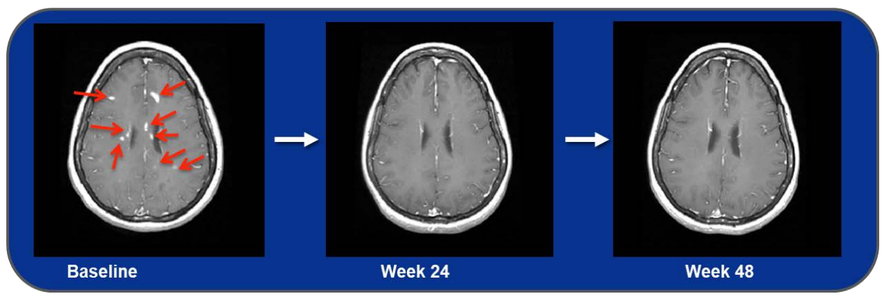
MRI ANALYSES

T1 Gd Enhancing Lesions at Baseline, Week 24 & Week 48



- **No T1 Gd enhancing lesions were detected in any subjects at Week 24 or at Week 48 (100% reduction; p=0.003)**

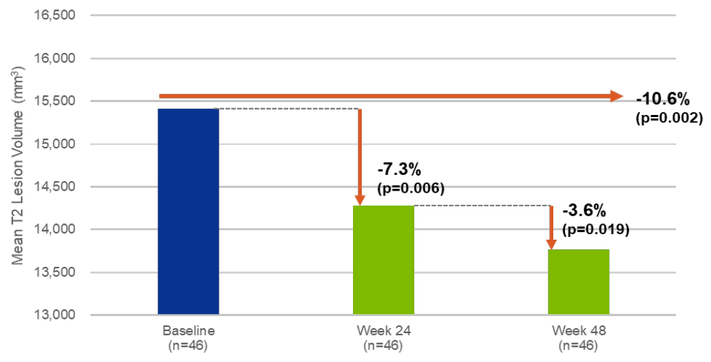
Subject T1 Gd MRI at Baseline, Week 24 & Week 48



At Baseline (n=46):

- **39% had ≥1 T1 Gd lesions and 26% had ≥4 T1 Gd lesions**

T2 Lesion Volume at Baseline, Week 24 & Week 48



- **The mean number of new/enlarging (NEL) T2 lesions from baseline to Week 24 was 0.20 ± 0.43; from Week 24 to Week 48, it was 0.04 ± 0.29 NEL/subject**

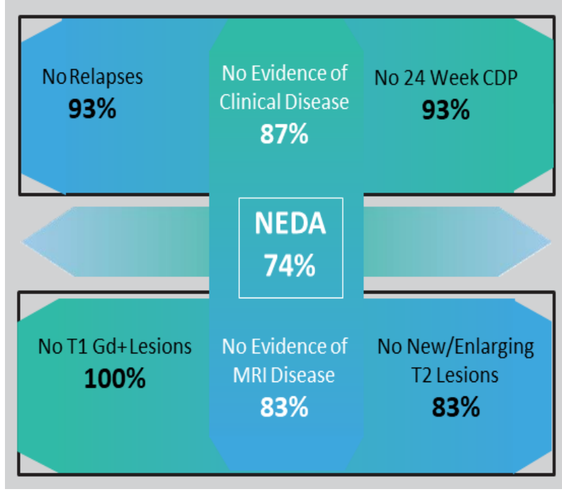
RELAPSE RATE, DISABILITY & NEDA

Annualized Relapse Rate (ARR):

- **ARR = 0.07**
  - Calculated based on 48 subjects with a mean follow up of approximately 47 weeks (range = 20 – 48 weeks)
- 93% of subjects were relapse free at Week 48

Disability (EDSS):

- **Mean EDSS at baseline = 2.44 ± 1.36, (n=48)**
- At Week 48:
  - 7% of subjects showed 24 Week Confirmed Disability Progression (CDP)*
  - 17% of subjects showed 24 Week Confirmed Disability Improvement (CDI)*



*24 Week Confirmed Disability Progression (CDP) is defined as an increase of ≥ 1.0 point from the baseline EDSS score (that is not attributable to another etiology e.g. fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5, that is confirmed in a subsequent EDSS assessment 24 weeks later. CDI follows the same criteria, but with a decrease ≥ 1.0 EDSS points from baseline.

**NEDA is defined as subjects without relapses, MRI activities (no T1 Gd+ lesions and no new/enlarging T2 lesions), and no 24-week confirmed disability progression; 2 of the total 48 patients did not have Week 24 MRI or EDSS assessments therefore only 46 patients had received all assessments to be evaluated for NEDA.

SAFETY & TOLERABILITY

Adverse Event Summary

	Regardless of Causality n (%)	Related to Ublituximab n (%)
Patients with an Adverse Event (AE)	48 (100%)	12 (25%)
Patients with a Serious Adverse Event (SAE)	8 (17%)	1 (2%)
AEs leading to Withdrawal	1 (2%)	0 (0%)

All AEs Related to Ublituximab

Event, n (%)	(N=48)	
Most frequently reported adverse events	All Grades	Grade 3/4
Infusion Related Reaction	23 (48%)	- (-)
Headache	4 (8%)	- (-)
Dry Throat	1 (2%)	- (-)
Ear Infection	1 (2%)	- (-)
Ecchymosis	1 (2%)	- (-)
Fatigue	1 (2%)	1 (2%)
Influenza	1 (2%)	- (-)
Neutropenia	1 (2%)	- (-)
Oral Herpes	1 (2%)	- (-)
Pain	1 (2%)	- (-)
Rash	1 (2%)	- (-)
Staphylococcal Infection	1 (2%)	- (-)
Throat Irritation	1 (2%)	- (-)

All IRRs Related to Ublituximab

	Ublituximab Infusions			Total Patients with ≥1 IRRs
	Day 1 (n=48)	Day 15 (n=48)	Week 24 (n=46)	
Total IRRs by Day	21 (44%)	5 (10%)	7 (15%)	23 (48%)

Day 1 Infusion Time	n	Day 1 IRRs
4 hours	24	7 (33%)
≤3 hours	24	14 (58%)

ULTIMATE Phase 3 Dose

- **Ublituximab was well tolerated and no drug related discontinuations occurred**
- Most common Adverse Events (AEs) were Infusion Related Reactions (IRRs), all Grade 1 or 2
- IRRs were most frequent with the first infusion (Day1) and Day 1 dose infused in ≤3 hours resulted in higher rates of IRRs
- IRRs were infrequent on Day 15 and Week 24 and did not appear to increase with higher doses and faster infusions
- 77% of total infusions did not result in an IRR

CONCLUSIONS

- **Annualized Relapse Rate (ARR) of 0.07 was observed at Week 48, with 93% of subjects being relapse free. 74% of subjects fulfilled the criteria for NEDA.**
- **Median B cell depletion was >99% at the primary analysis point of Week 4 (n=48), and maintained at Week 24 and Week 48.**
- **No T1 Gd-enhancing lesions detected in any subjects at Week 24 or 48 (100% reduction; p=0.003). Subjects saw 10.6% reduction in total T2 lesion volume from baseline to Week 48 (p=0.002).**
- **Ublituximab was well tolerated and the most frequent AEs (all Grade 1 or 2) were Infusion Related Reactions (IRRs). No subjects discontinued due to an AE related to ublituximab.**
- **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 in MS.**

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