Long-term Follow-up Results From the Phase 2 Multicenter Study of Ublituximab (UTX), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody (mAb), in Patients With Relapsing Multiple Sclerosis (RMS)

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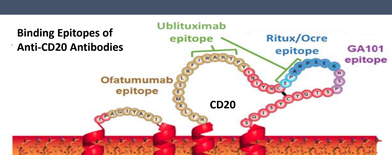
INTRODUCTION AND METHODS

INTRODUCTION

- 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, ofatumumab or ocrelizumab.
- 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).

Binding Epitopes of Anti-CD20 Antibodies



- To date, over 1500 patients with various B-cell mediated diseases have been treated with ublituximab, with completed relapsing multiple sclerosis (RMS) and oncology studies demonstrating robust activity, with favorable safety and tolerability. In addition, two Phase III trials in RMS are fully enrolled, the ULTIMATE I & II trials.

OBJECTIVES

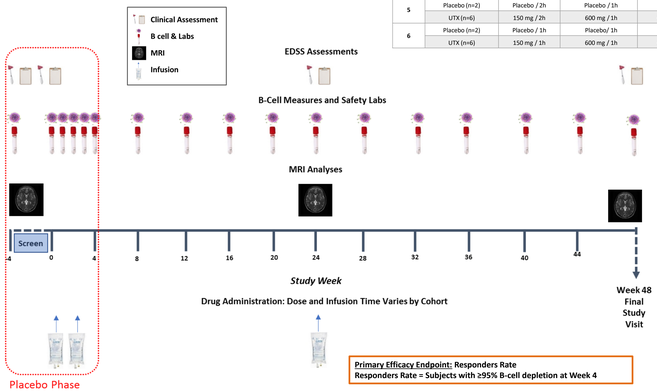
- The objective for the ublituximab RMS Phase 2 study (TG-1101-RMS201) was to determine whether the enhanced ADCC potency of ublituximab translates into additional clinical benefits for MS patients, in the form of lower doses and faster infusion times than current anti-CD20 infused therapies.
- The objective for the Open Label Extension (OLE) of the Phase 2 study is to evaluate the long-term safety and tolerability and long-term disability outcomes of ublituximab treatment in subjects continuing treatment after completion of TG-1101-RMS201 Phase 2 trial.

PHASE 2 METHODS & STUDY DESIGN

- TG1101-RMS201 (NCT02738775) was a 52 week randomized, placebo controlled, multi-center Phase 2 study to test the safety and efficacy of ublituximab 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.

Phase 2 Treatment Schedule

	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



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

OLE METHODS & STUDY DESIGN

- To qualify for the OLE, subjects must have completed three infusions of ublituximab, have completed the scheduled assessments up to the Week 48 visit of TG-1101-RMS201, and be in good health with stable disease.
- All subjects enrolled on the OLE, regardless of their cohort assignment in the Phase 2, will receive 450mg of ublituximab administered in a one hour infusion every 24 weeks with the first infusion given within 60 days of completing the Phase 2.
- Each infusion visit is accompanied by routine physical exam, routine blood chemistry, and an assessment of adverse events to evaluate long-term safety and tolerability.
- EDSS assessments are conducted every 48 weeks to assess long-term disability outcomes.

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

Phase 2:

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

OLE:

- 45 subjects entered the OLE
  - Mean Age: 41 years
  - 64% Female

OLE SAFETY UPDATE

Adverse Event (AE) Summary [1]

	Phase 2 (N=48)		OLE (N=45)	
	Regardless of Causality n (%)	Related to UTX n (%)	Regardless of Causality n (%)	Related to UTX n (%)
Patients with an AE	48 (100%)	12 (25%)	24 (53%)	3 (7%)
Patients with a Grade 3/4 AE	8 (17%)	1 (2%)	4 (9%)	1 (2%)
AEs leading to Withdrawal	1 (2%)	0 (0%)	0 (0%)	0 (0%)

[1] Excludes Infusion Related Reactions (IRRs)

All AEs Deemed at Least Possibly Related to UTX [1]

Event, n (%)	Phase 2 (N=48)		OLE (N=45)	
Most frequently reported Adverse Events (AEs)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Headache	4 (8%)	- (-)	- (-)	- (-)
Dry Throat	1 (2%)	- (-)	- (-)	- (-)
Ear Infection	1 (2%)	- (-)	- (-)	- (-)
Ecchymosis	1 (2%)	- (-)	- (-)	- (-)
Fatigue	- (-)	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%)	- (-)	- (-)	- (-)
Cellulitis	- (-)	- (-)	- (-)	1 (2%)
Chest Pain	- (-)	- (-)	1 (2%)	- (-)
Viral Infection	- (-)	- (-)	1 (2%)	- (-)

[1] Excludes Infusion Related Reactions (IRRs)

- Ublituximab (UTX) was well tolerated with a median duration of follow-up of 124.7 weeks.
- No drug related discontinuations occurred during the Phase 2 or on the OLE.

INFUSION RELATED REACTIONS

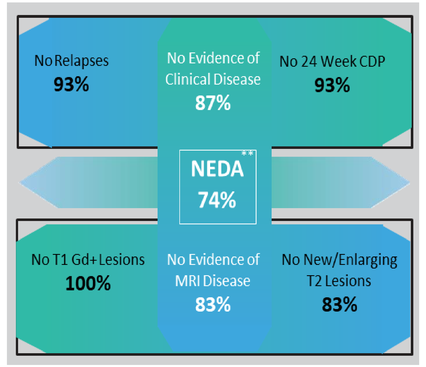
- All patients on the OLE received 450mg administered in a one hour infusion, with 100% of patients receiving at least one infusion, and 96% of patients receiving 2 or more infusions.
- IRRs were infrequent during the OLE, occurring in 5 patients (11%), all Grade 1 or 2; with no patient experiencing an IRR for the first time on the OLE.
- During the Phase 2, IRRs were most frequent on Day 1 with 33% of patients experiencing an IRR on Day 1 when given 150mg of UTX over 4 hours (the Phase 3 Day 1 dose).

RESULTS CONTINUED

FINAL PHASE 2 WEEK 48 EFFICACY RECAP

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

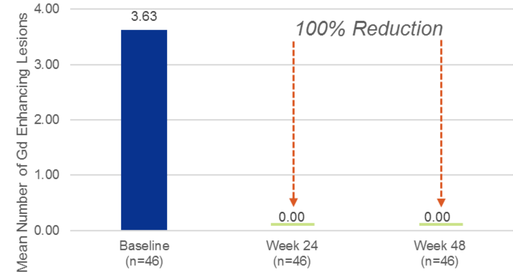
Disability (EDSS):
At Week 48:
- 7% of subjects showed 24 Week Confirmed Disability Progression (CDP)*
- 17% of subjects showed 24 Week Confirmed Disability Improvement (CDI)*



**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.*

T1 Gd Enhancing Lesions Baseline vs. Week 24 & Week 48



CONCLUSIONS

- **Ublituximab continues to be well tolerated, with a median duration of follow-up of 124.7 weeks.**
- **AEs deemed at least possibly related to UTX were infrequent during the OLE with all doses of 450mg administered in a one hour infusion (Phase 3 dose).**
- **Infusion Related Reactions (IRRs) were rare during the OLE, occurring in only 5 patients (11%), all Grade 1 or 2. No subjects discontinued due to an AE related to ublituximab on the Phase 2 or during the OLE.**
- **At the conclusion of the Phase 2 an ARR of 0.07 was observed at Week 48, with 93% of subjects being relapse free and 74% of subjects fulfilling the criteria for NEDA. Additionally, no T1 Gd-enhancing lesions were detected in any subjects at Week 24 or 48 (100% reduction; p=0.003).**
- **Phase 2 efficacy data and long term safety data support the fully enrolled Phase 3 ULTIMATE trials evaluating a rapid one hour infusion of 450mg of ublituximab in patients with Relapsing Forms of Multiple Sclerosis (RMS).**

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