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 (RMS): 6 Months Analysis of B cell Subsets

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Introduction & Purpose

**Ublituximab (UTX)** 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 Fy(a,b) receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and rituximab-zetakizumab.

**In vivo studies, ublituximab demonstrated 100% greater natural killer (NK) cell-mediated ADCC than rituximab in patient-donor CL cells.**

To date, over 600 patients with various B cell malignancies have been treated with ublituximab and two multicenter Phase II 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**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Subjects and treatment</th>
<th>Randomization</th>
<th>Day 1/Infusion time</th>
<th>Day 15/Infusion time</th>
<th>Week 24/Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=2)</td>
<td>Placebo / 4h</td>
<td>UTX (n=6)</td>
<td>200 mg / 3h</td>
<td>450 mg / 3h</td>
<td>1,450 mg / 3h</td>
</tr>
<tr>
<td>Placebo (n=2)</td>
<td>Placebo / 3h</td>
<td>UTX (n=6)</td>
<td>300 mg / 3h</td>
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</tbody>
</table>

**Patients were enrolled sequentially in treatment cohorts 1, 2 and 3 and randomized 1:1 to ublituximab or placebo.**

**Ublituximab or placebo was administered via an 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 measured here.**

**Peripheral blood samples were collected for B-cell measures and safety lab tests at the intervals shown below (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

**Flow Cytometric Analysis of Immune Cell Populations over 6 Months**

- **B cells are depleted ~95% at 4 weeks, meeting the primary end point.**
- **T cells, NK cells and monocytes normalize by 4 weeks and remain stable over 6 month analysis.**

Conclusions

- B cells are efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab, with 98% of patients by week 4 and maintained the significant reduction at Week 24 (46 months; N=36).
- NK cells are significantly reduced within 24 hrs of receiving the first dose of ublituximab, indicative of exhaustion due to their role in ADCC of the B cells.
- Monocyte depletion in the percentage of T cells at 24 hours of receiving the first dose of ublituximab, but this appears to be due to an increase in monocytes, likely due to bone marrow increasing monocyte output due to loss of B cells.
- The fluctuation in NK cells, T cells and monocytes that occurred in response to B cell depletion is corrected within 4 weeks post initial ublituximab treatment.
- Due to the sustained B cell depletion, there is no significant effect of ublituximab treatment at Week 24 on the NK cells, T cells or monocytes, illustrating the immune homeostasis in the non-B cell.
- At Week 24, 50% of patients were confirmed relapse free and 79% of subjects showed improved or stable EDSS. Detailed clinical results are provided in Poster P4706 (25 October 2020).
- Ublituximab is well tolerated and demonstrates rapid and robust B cell depletion with shorter infusion times.
- These data support the recently announced International Phase 3 program evaluating TG-110 (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.