Efficacy and Safety of Ublituximab vs Teriflunomide in Patients with Relapsing Multiple Sclerosis: Results from Two Phase 3 Studies ULTIMATE I & II

Lawrence Steinman, MD;1 Edward Fox, MD, PhD;2 Hans-Peter Hartung, MD;3 Enrique Alvarez, MD, PhD;4 Pelqing Oian, MD;5 Sibyl Wray, MD;6 Derrick Robertson, MD;7 DeRen Huang, MD, PhD;8 Krzysztof Selma, MD, PhD;9 Daniel Wynn, MD;10 Michael S. Weiss;11 Jenna A. Bosco;12 Sean A. Power;13 Kody Mok, PhD;14 Bruce Cree, MD, PhD, MAS;15

1Stanford University, Stanford, CA, USA 2Central Texas Neurology Consultants, Round Rock, TX, USA 3Heinrich Heine University, Duesseldorf, Germany 4University of Colorado, Aurora, CO, USA 5Swedish Medical Center, Seattle, WA, USA 6Hope Neurology, Bronxville, NY, USA 7UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA 8Improvis Medical, Inc, Scottsdale, AZ, USA 9Department of Neurology, Medical Academy of Lodz, Lodz, Poland 10Innoviris, Brussels, Belgium 11Department of Neurology, Mount Sinai Health System, New York, NY, USA 12Department of Neurology, Mount Sinai Health System, New York, NY, USA

BACKGROUND

• Ublituximab (UTX; TG-1101) is a novel chimeric monoclonal antibody (mAb) that targets a unique epitope on the CD20 antigen (Figure 1). It is glycoengineered to enhance affinity for all FcγRIIIa receptors, thereby conferring greater antibody-dependent cellular cytotoxicity (ADCC).

• In vitro studies, ublituximab demonstrated 300 times greater natural killer (NK)-cell-mediated ADCC than rituximab in patient-derived CLL cells.

• To date, over 2100 patients with various B-cell mediated diseases have been treated with ublituximab. Completed oncology studies have demonstrated robust activity, with excellent safety and tolerability.

• The ublituximab phase 2 RMS study showed >99% B-cell depletion by week 4 and benefits on MRI and clinical parameters1.

STUDY DESIGN

STUDY OBJECTIVES

To evaluate the efficacy and safety of ublituximab compared with teriflunomide in patients with relapsing multiple sclerosis

STUDY ENDPOINTS

By individual study

• Primary endpoint: Diagnosis of MS per 2010 Revised McDonald criteria

• Secondary endpoints: Time to CDI for at least 12 weeks, Time to CDP for at least 24 weeks

• Safety endpoint: Incidence of reactions, adverse events

• Inclusion criteria:
  - Age ≥18 to 55 years (inclusive) at screening and ≤60 years (inclusive) at start of treatment
  - Diagnosis of MS per 2010 Revised McDonald criteria
  - At least one relapse in the year prior to randomization or ≥2 relapses within 2 years prior to screening or a positive Gd+ MRI scan during the year prior to randomization

• Exclusion criteria:
  - History of malignancy (previous malignancies are allowed if in remission for ≥5 years)
  - Treatment with myelin basic protein (MBP), polocyclic guanyl nucleotide activating protein (Gi, Gq, Go) antagonists, or other immunomodulatory or immunosuppressive treatments within 90 days prior to screening or 15 days prior to randomization

RESULTS

Table 1: Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th>Race, %</th>
<th>Relapsing Remitting</th>
<th>Secondary Progressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>265 (97.1)</td>
<td>264 (97.4)</td>
</tr>
<tr>
<td>African American</td>
<td>6 (22.2)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Total</td>
<td>271 (97.1)</td>
<td>270 (97.0)</td>
</tr>
</tbody>
</table>

Mean ± standard deviation or n (%)

- Total MS N = 544
- Ublituximab N = 274
- Teriflunomide N = 273

DISCUSSION

- Ublituximab was well-balanced between ULTIMATE I and ULTIMATE II studies, and between treatment arms

RESULTS - DISPOSITION

- Ublituximab was associated with lower relapse rates compared to teriflunomide

RESULTS - SAFETY

- Ublituximab was associated with lower incidence of adverse events compared to teriflunomide

RESULTS - Efficacy

- Ublituximab was associated with lower disability progression compared to teriflunomide

Presented at the 2021 American Academy of Neurology (AAN) Virtual Annual Meeting, April 17 – 22, 2021
Serious AEs were reported in 6.2% of teriflunomide-treated patients and 9.5% of ublituximab-treated patients. Ublituximab significantly reduced protocol-defined ARR by 60% in ULTIMATE I and by 88% in ULTIMATE II (Table 2).

The proportion of patients reporting AEs was 88.7% for teriflunomide and 88.6% for ublituximab. In prespecified pooled analysis of ULTIMATE I and ULTIMATE II, 12-week CDP and IRRs were most frequent on the 1st dose: 43% in the ublituximab group and 9.7% in the teriflunomide group.

Three total malignancies were reported:
- 2 ublituximab (endometrial, uterine) versus teriflunomide 1 (tongue)
- 1 death was deemed possibly related to treatment (pneumonia)

No cases of progressive multifocal leukoencephalopathy (PML)

### MRI

#### MNI: Gd+11 Lesions

- **Confirming Disability Progression (CDP)**
  - **Teriflunomide**
    - N = 274
    - Time since Randomization (weeks)
  - **Ublituximab**
    - N = 272
    - Time since Randomization (weeks)

- **Confirming Disability Improvement (CDI)**
  - **Teriflunomide**
    - N = 274
    - Time since Randomization (weeks)
  - **Ublituximab**
    - N = 272
    - Time since Randomization (weeks)

#### MNI: New or Enlarging Lesions

- **No Evidence of Disease Activity**
  - **Teriflunomide**
    - N = 274
  - **Ublituximab**
    - N = 272

### Serious Adverse Events

- **SAEs**
  - **Ublituximab**
    - N = 545
  - **Teriflunomide**
    - N = 548

- **Most common SAEs** by SOC
  - **Teriflunomide**
    - N = 548
  - **Ublituximab**
    - N = 545

### Infusion Related Reactions

- **Ublituximab**
  - No infusion-related events
  - **Teriflunomide**
    - 5 cases (0.9%)

### Conclusions

- **In the Phase III UTMATE I & II studies, ublituximab, compared with teriflunomide, significantly reduced ARR and MRI parameters**
- A very low rate of disability progression was observed with ublituximab, with >94% of patients showing no 12-week CDP, and >96% of patients showing no 24-week CDP, although neither was statistically different from teriflunomide.
- In a pre-specified pooled tertiary analysis, ublituximab increased the proportion of patients with 12-week CDI and 24-week CDI.
- A significantly higher percentage of patients treated with ublituximab compared with teriflunomide achieved NEDA.
- A favorable safety and tolerability profile with no unexpected safety signals.
- These data are being prepared for a Biological License Application.