# Ublituximab for Multiple Sclerosis

Zoya Kakar

PharmD Candidate 2019

Philadelphia College of Pharmacy

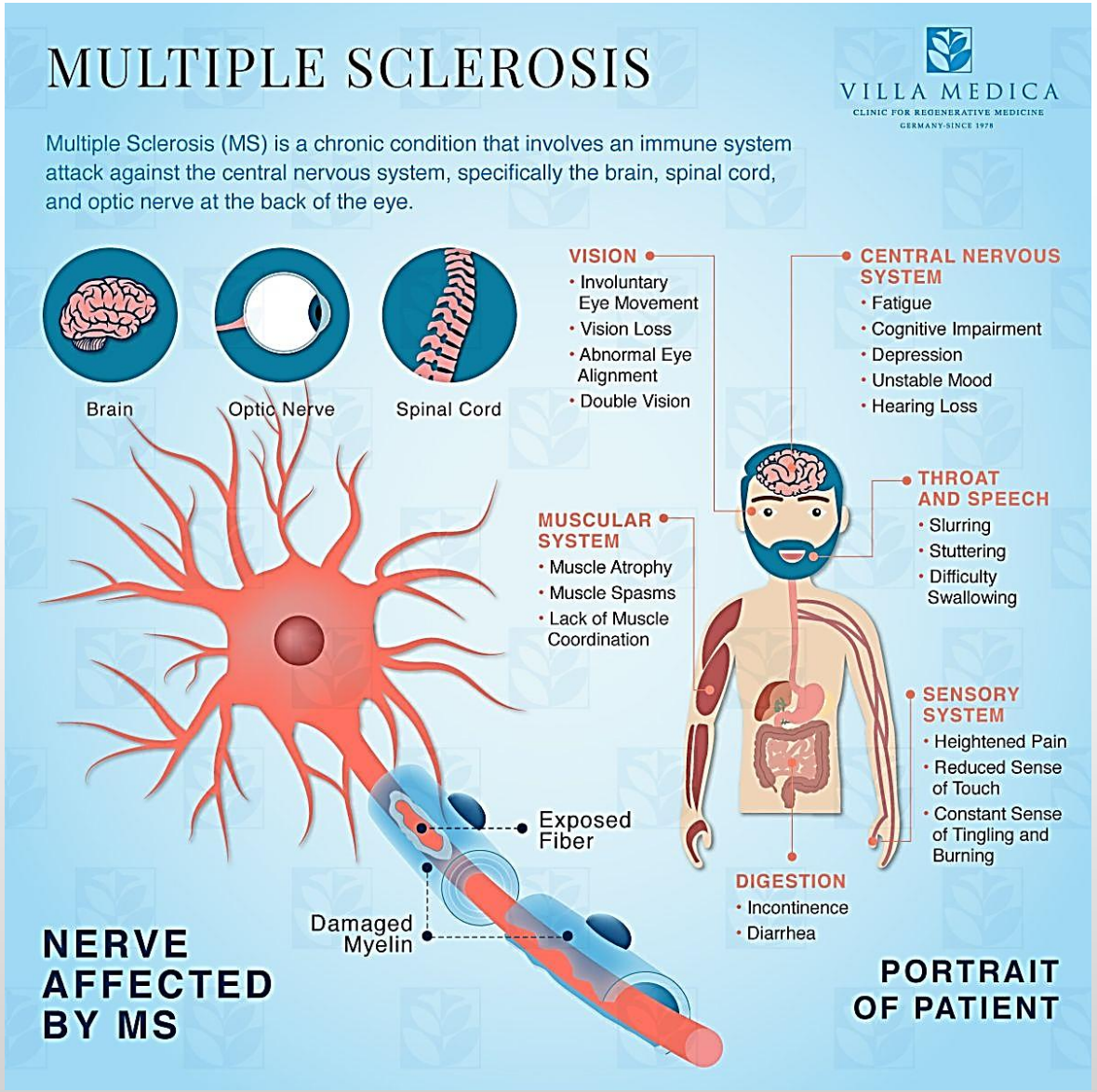
# TABLE OF CONTENTS


- Overview of Multiple Sclerosis
- Treatment of MS
- Ublituximab
- Phase 2 Clinical Trial
- Phase 3 Clinical Trial
- Competitor Products
- Conclusion

# MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a debilitating autoimmune disease in which the immune system attacks the central nervous system

This abnormal attack on the brain, spinal cord, and optic nerve leads to various physical and mental symptoms, such as loss of vision, difficulty coordinating movements, and difficulty speaking



# EPIDEMIOLOGY

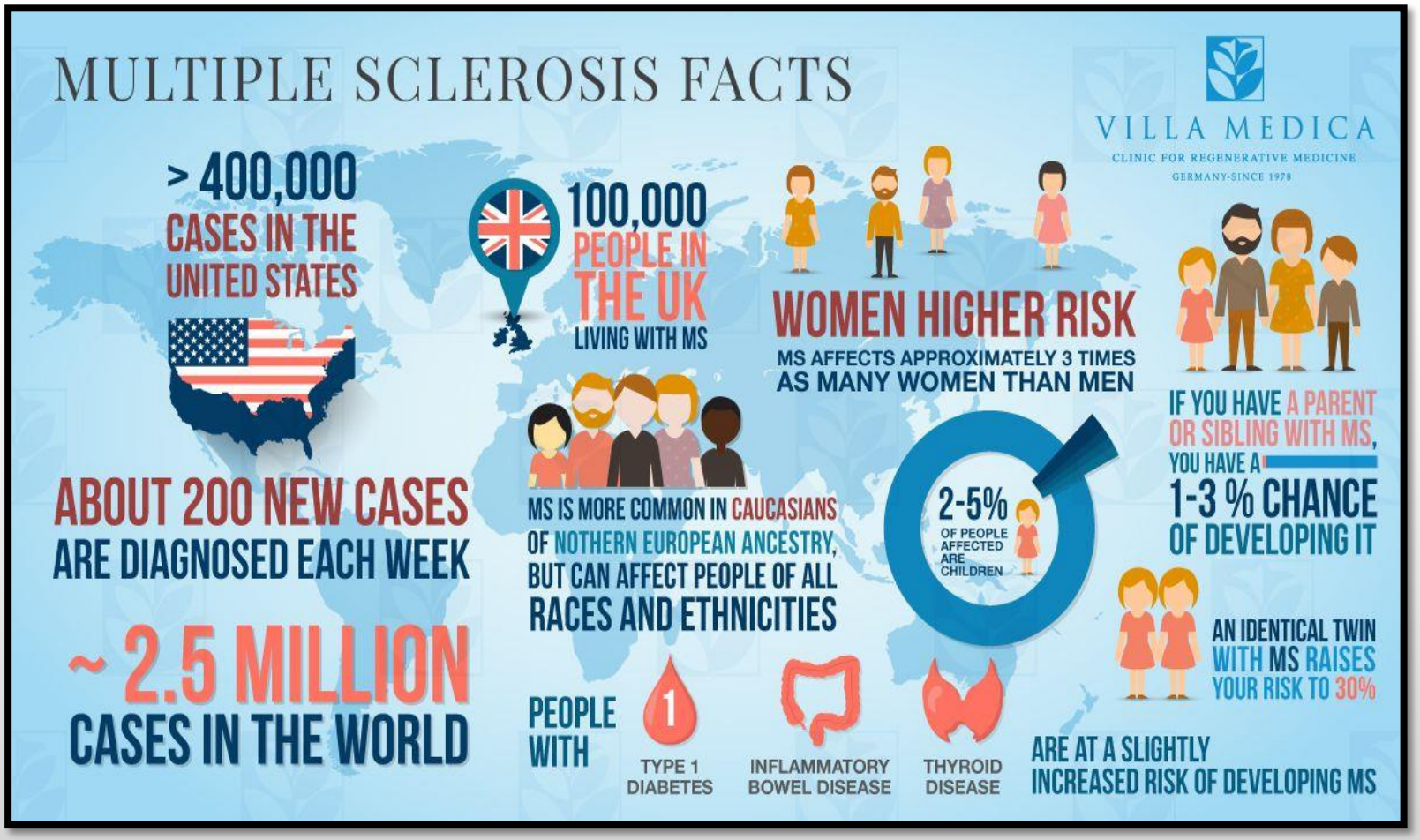
MS is most common in North America and Europe

- Prevalence of MS is 0.1-0.2% of the population (200 out of 100k people)
- Incidence of MS is 5-6 per 100k

Seen 2-3x more in women than men

Clinically, MS commonly appears in patients between the ages of 15-45 y/o, however can be seen earlier or later in life

Patients have a reduced life expectancy by 6-7 years



# PATHOPHYSIOLOGY

## Potential Causes

- Immunologic factors
- Environmental factors (low vitamin D, smoking, obesity)
- Infectious factors (Epstein-Barr virus, measles)
- Genetic factors

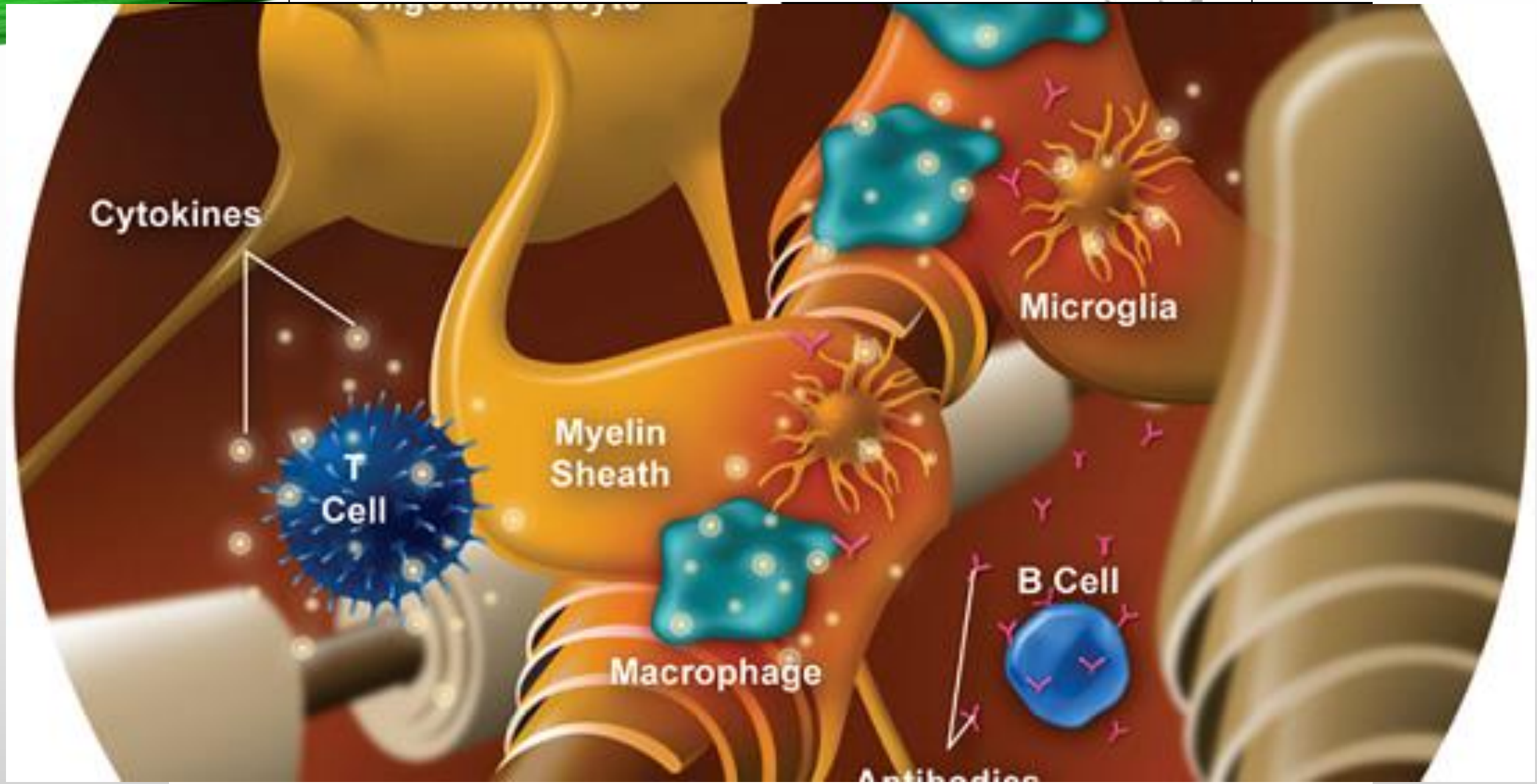
## CNS Inflammation

- Immune mediated attack of T-cells on myelin and nerve fibers
- B-cells also add to inflammatory activity by presenting antigens to T-cells and activating complement cascade

**Damaged nerves have scarring/ lesions called plaque that builds up, resulting in further demyelination**

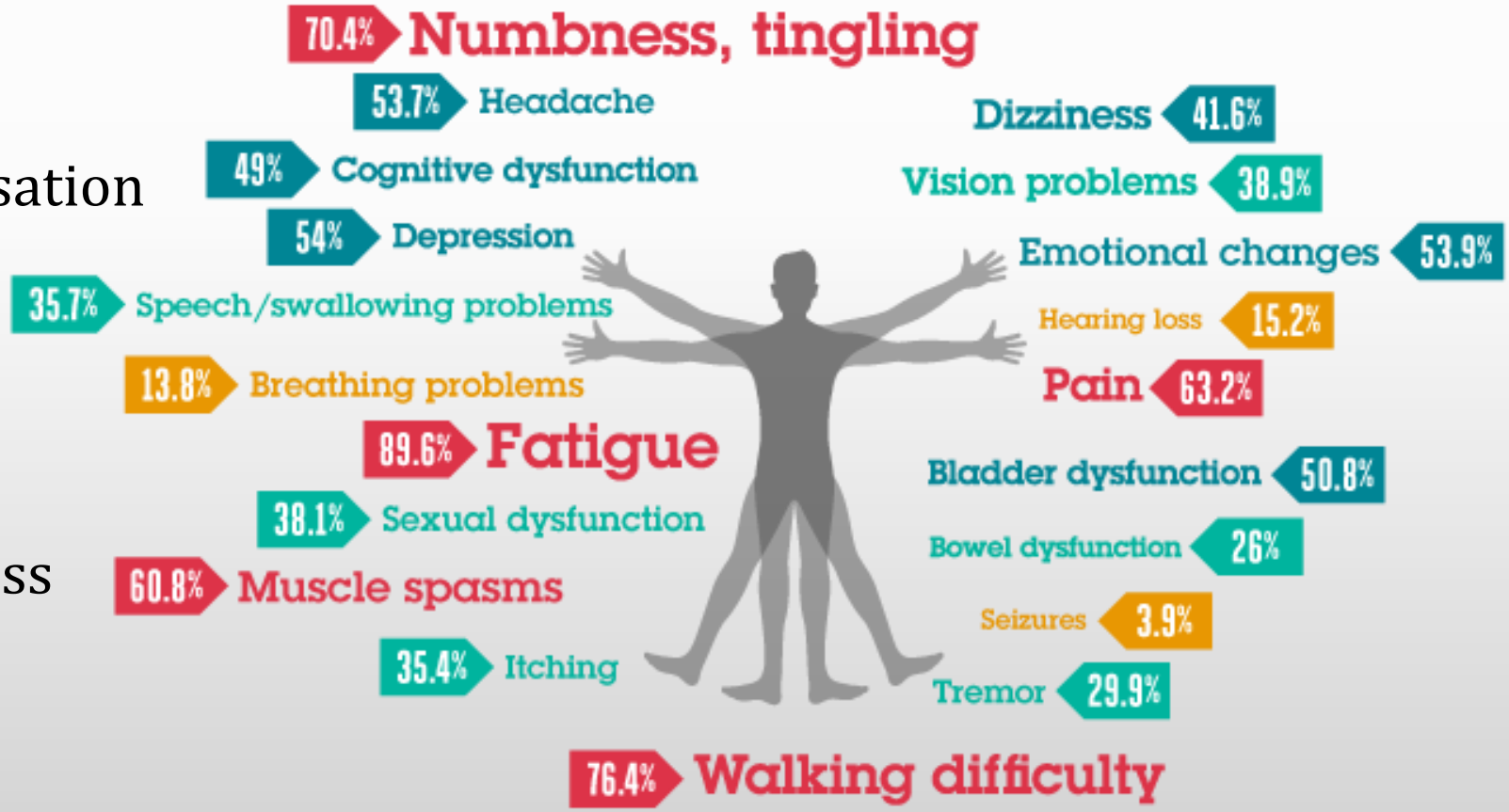
**Nerve signals are damaged, causing symptoms**

# PATHOPHYSIOLOGY



# CLINICAL PRESENTATION

- Symptoms of MS may develop over time and can range from mild to severe. Examples of symptoms include:
  - Fatigue
  - Numbness, tingling sensation
  - Chronic pain
  - Difficulty walking
  - Muscles stiffness
  - Difficulty coordinating
  - Vision impairment or loss
  - Clinical depression
  - Speech difficulty
  - Tremor



# DIAGNOSIS

- Diagnosis of MS is not based solely off of symptoms, as a physician must find evidence of damage (lesions) in the brain, spinal cord, or optic nerve using MRI and rule out any other potential causes
- The McDonald Criteria is a tool used often in conjunction with other various tests to help with the diagnostic process

| Number of Clinical Attacks/ Exacerbations | Number of Lesions With Objective Clinical Evidence | Additional Data needed for a Diagnosis of MS |
|---|---|---|
| ≥ 2 clinical attacks | ≥ 2 | None* |
| | 1 | None* |
| | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI |
| 1 clinical attack | ≥ 2 | Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands |
| | 1 | All of the above |

*No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered.

# TYPES OF MS

**Clinically Isolated Syndrome (CIS)**

- An episode of symptoms, caused by inflammation and demyelination of the CNS, that lasts for at least 24 hours
- May or may not lead to a future diagnosis of MS depending on the formation of lesions

**Relapsing-Remitting MS (RRMS)**

- Most common form of MS, 85% of patients
- Patient has chronic attacks, followed by periods of remission and worsening symptoms over time

**Secondary Progressive MS (SPMS)**

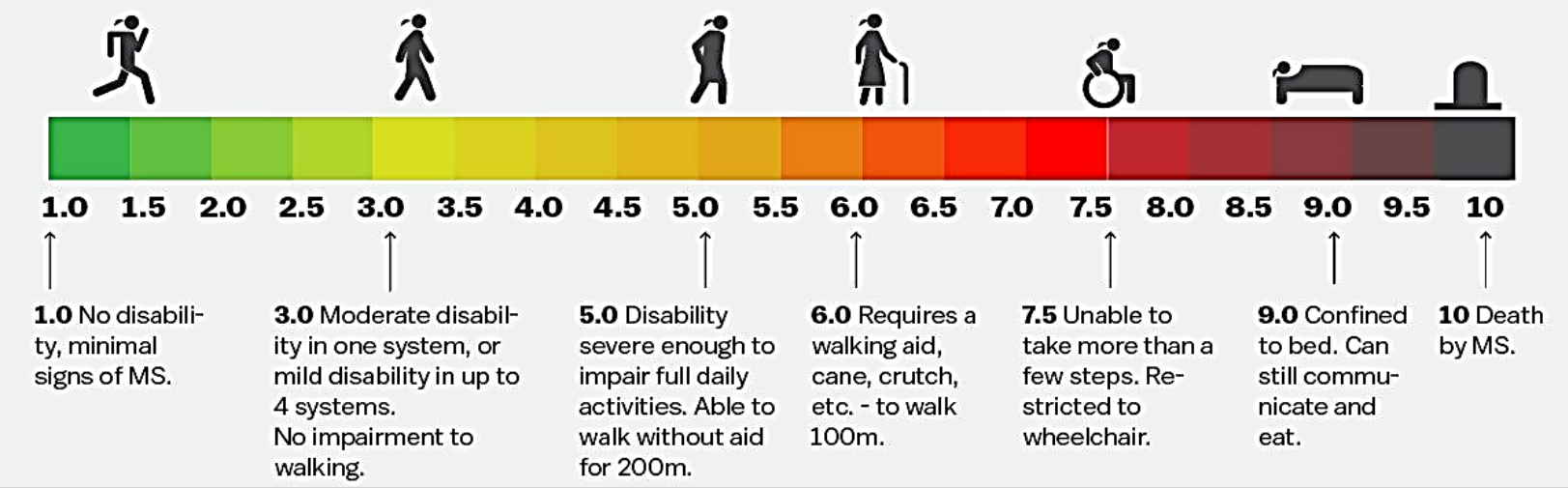
- Initially begins as RRMS, however, over time a progressive worsening of symptoms and neurologic function occur

**Primary Progressive MS (PPMS)**

- From the onset of symptoms, patient become progressively worse and has a continuous decline of neurologic function

# SCORING

- The two most common scoring assessments used are:
  - **<u>Functional Systems Scores (FSS):</u>**
    - Provides score in certain functional areas
      - Pyramidal functions
      - Cerebellar functions
      - Brainstem functions
      - Sensory function
      - Bowel and bladder function
      - Visual function
      - Cerebral functions
  - **<u>Expanded Disability Status Scale (EDSS)</u>**
    - Provides the patient's ambulation/ level of disability score
- Both the FSS and EDSS are scored based off of physician examination and judgement



# TREATMENT OF MS

**Preventative Treatment for MS Attacks**

- Corticosteroids
- Plasmapheresis

**Treatment for Primary-Progressive MS (prevent or reduce progression)**

- Ocrelizumab (Ocrevus®)

**Treatment for Relapsing-Remitting MS (prevent or reduce progression)**

- Beta interferons*
- Glatiramer acetate (Copaxone®)
- Dimethyl fumarate (Tecfidera®)*
- Fingolimod (Gilenya®)*
- Teriflunomide (Aubagio®)*
- Natalizumab (Tysabri®)
- Alemtuzumab (Lemtrada®)
- Ocrelizumab (Ocrevus®)
- Mitoxantrone
- Azathioprine (Azasan®)* → off-label
- Ofatumumab (Arzerra®)→off-label

*First-line treatment

Non-Pharm Therapy:

- Physical Therapy
- Stress management

Additional Symptomatic Treatment Medications:

- Muscle relaxants
- Bladder control meds
- Erectile dysfunction meds
- Antidepressants

# TREATMENT OF MS

## Guideline: 2018 American Academy of Neurology- Disease Modifying Therapies for Adults With Multiple Sclerosis

**Clinical question 1: In people with RRMS, are DMTs superior to placebo or other DMTs as measured by ARRs?**

The efficacy of DMTs for preventing relapses was assessed in most trials by measuring the proportion of people with MS with relapses compared with placebo over 2 years. Annualized relapse rates were derived from this information. Results are reported by medication (medications alphabetized).

*Alemtuzumab*

One Class I study[e33] and 1 Class II study[e34] (Class II owing to unclear allocation concealment) evaluated the proportion of people with RRMS with at least 1 relapse at 2 years with alemtuzumab treatment compared with interferon beta-1a subcutaneously 3 times per week. Meta-analysis of data from 914 participants revealed a risk ratio (RR) of 0.43 (95% CI, 0.29–0.61), favoring alemtuzumab. Meta-analysis of data from the same 2 studies revealed a raw mean difference (RMD) in the ARR of 0.26 (95% CI, 0.22–0.29), favoring alemtuzumab.

*Conclusions*

For individuals with RRMS, alemtuzumab is more effective than interferon beta-1a subcutaneously 3 times per week in reducing the risk of relapse at 2 years (high confidence in the evidence, 1 Class 1 study, 1 Class II study; confidence upgraded owing to magnitude of effect). For individuals with RRMS, alemtuzumab is more effective than interferon beta-1a subcutaneously 3 times per week in reducing the ARR (high confidence in the evidence, 1 Class I study, 1 Class II study; confidence upgraded owing to magnitude of effect).

Clinical question (i.e. Is DMT superior to placebo or other DMT as measured by ARR?)

Evidence-based data for specific drug

Guideline recommendation for the specific drug

# TREATMENT OF MS

Pharmacological Treatment Recommendations

| Disease Modifying Therapy (DMT) for Patients with RRMS | Evidence |
|---|---|
| Alemtuzumab | • More effective than interferon beta-1a in reducing risk of relapse and reducing the annualized relapse rate (ARR)<br>• Possibly more effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the volume of T2 lesions from baseline to 2 years (moderate evidence)<br>• More effective in reducing the risk of disability progression over 2 years |
| Cladribine | • For individuals with RRMS, cladribine is more effective than placebo in reducing the ARR |
| Daclizumab High-yield Process | • Daclizumab HYP is more effective than placebo in decreasing the risk of at least 1 relapse at 1 year<br>• More effective than placebo in preventing new or newly enlarging T2 lesions at 1 year<br>• More effective than placebo in decreasing the risk of disability progression at 1 year |

# TREATMENT OF MS

| Disease Modifying Therapy (DMT) for Patients with RRMS | Evidence |
|---|---|
| Dimethyl Fumarate | • More effective than placebo in decreasing the risk of at least 1 relapse at 2 years<br>• More effective than placebo in decreasing the number of new or enlarging T2 lesions at 2 years<br>• More effective than placebo in decreasing the risk of disability progression over 2 years |
| Fingolimod | • More effective than placebo in reducing the risk of relapse over 2 years<br>• More effective than placebo in reducing the risk of new or enlarging T2 lesions at 2 years<br>• More effective than placebo in reducing the risk of disability progression over 2 years |
| Glatiramer Acetate | • More effective than placebo in reducing the ARR<br>• More effective than placebo in decreasing the number of new or enlarging T2 lesions at 2 years |
| Interferon Beta-1a IM Weekly/ Interferon Beta-1b Subcutaneous Alternate Day | • More effective than placebo in reducing the risk of relapse over 24 months |

# TREATMENT OF MS

| Disease Modifying Therapy (DMT) for Patients with RRMS | Evidence |
|---|---|
| Mitoxantrone | • More effective than placebo in decreasing the risk of relapse at 2 years<br>• More effective than placebo in decreasing the number of new lesions on T2 at 2 years<br>• More effective than placebo in decreasing the risk of disability progression at 2 years |
| Natalizumab | • More effective than placebo in reducing the risk of relapse at 2 years and reducing the ARR<br>• More effective than placebo in reducing the risk of at least 1 new or enlarging T2 lesion at 1 year and in reducing the MRI T2 lesion load at 2 years<br>• More effective than placebo in decreasing the risk of disability progression at 2 years |

# TREATMENT OF MS

| Disease Modifying Therapy (DMT) for Patients with RRMS | Evidence |
|---|---|
| Ocrelizumab | • More effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in reducing the ARR<br>• More effective than interferon beta-1a 44 micrograms subcutaneous 3 times per week in decreasing the proportion of individuals with new or newly enlarged lesions on T2 MRI<br>• Also more effective in decreasing the risk of in-study disease progression over 2 years |
| Pegylated Interferon | • Is more effective than placebo in reducing the risk of relapse and the ARR at 1 year<br>• More effective than placebo in reducing the number of new or newly enlarging T2 lesions at 1 year<br>• More effective decreasing the risk of disability progression at 1 year |

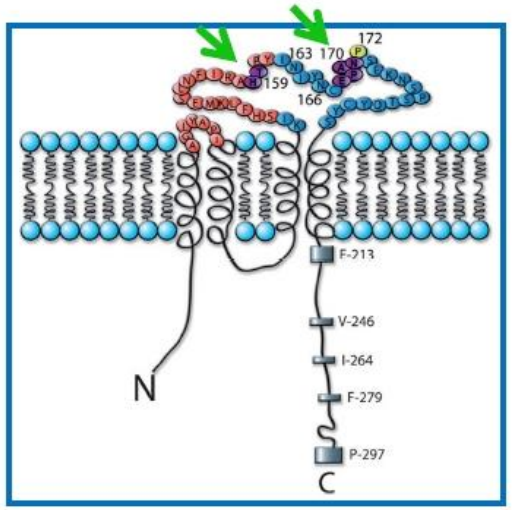
# UBLITUXIMAB

## TG Therapeutics pipeline product (TG-1101)

- Anti-CD20 monoclonal antibody
- Developed for:
  - Non-Hodgkin's lymphoma, chronic lymphocytic lymphoma (currently in phase 3 development)
  - Multiple sclerosis (phase 3 development)

### Ublituximab: A Novel Glycoengineered Anti-CD20 mAb

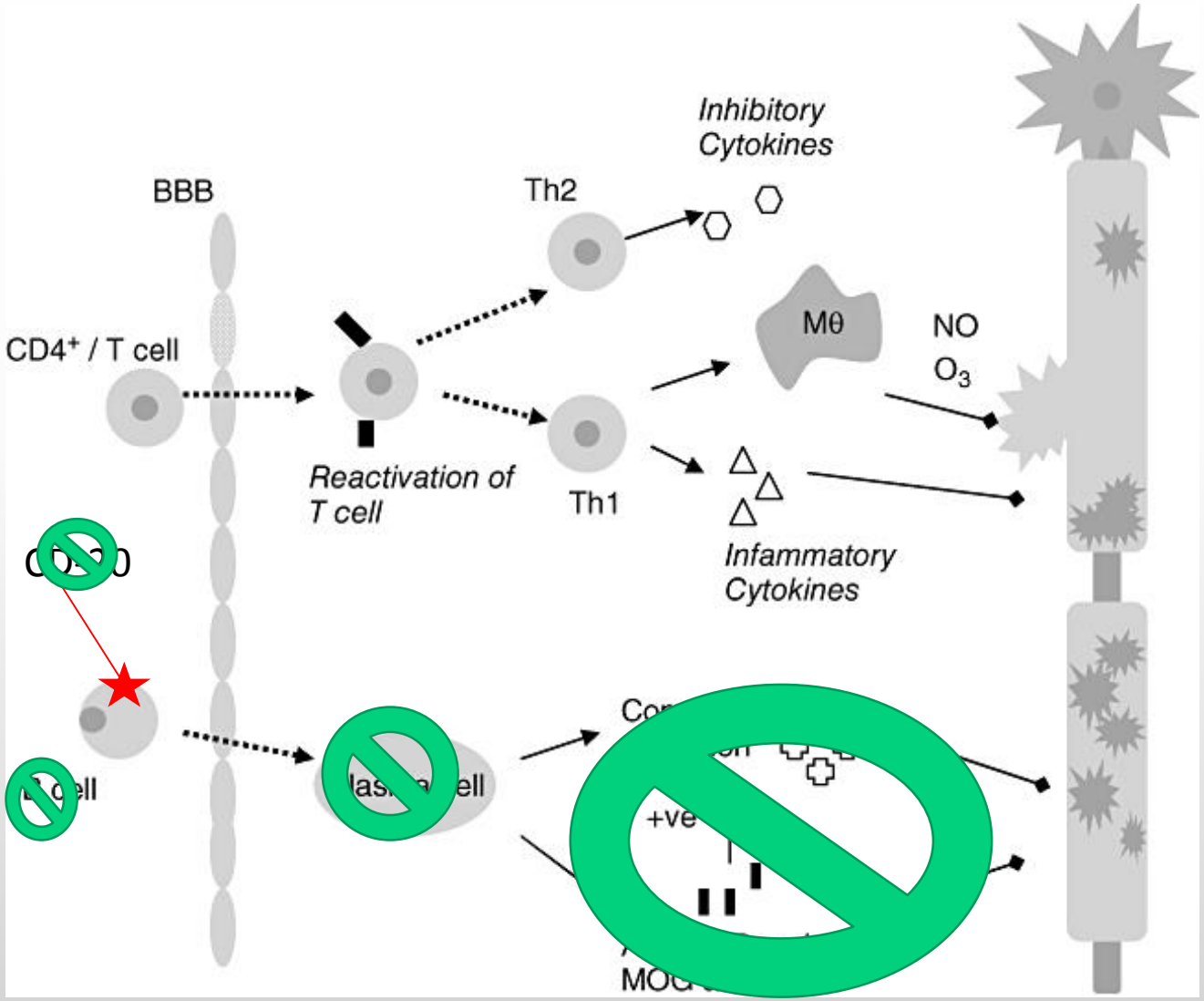
- Unique protein sequence
- Type 1 Chimeric IgG1 mAb
- Potential advantages over current standard of care:
  - Glycoengineered for significantly enhanced ADCC
  - Activity in "low" CD20 expressing cell lines, a characteristic of rituximab resistance
  - Binds to a novel epitope on CD20




TG Therapeutics

# UBLITUXIMAB

- Potential MOA in MS:
  - CD-20 is a protein expressed on all B-cells and increases in concentration as the B-cell matures
  - By targeting cells with the CD-20 protein, ublituximab could potentially eliminate B-cells, resulting in decreased CNS inflammation



# Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions

**Poster session presented at: 70th Annual Conference of the American Academy of Neurology, on April 24th, 2018 in Los Angeles, CA**

Inglese M, Petracca M, Cocozza S, Wray S, Racke M, Shubin R, Twyman C, Eubanks JL, Mok K, Weiss M, Fox E, Neurology and Radiology Icahn School of Medicine at Mt. Sinai Medical Center, Hope Neurology, The Ohio State University Medical Center, Wexner Medical Center, 4SC3 Research Group, Associates in Neurology, TG Therapeutics, Inc., Central Texas Neurology Consultants

# PHASE 2 STUDY

## Trial Design

- 52 week, phase 2, randomized, placebo-controlled, multi-centered study
- 48 patients randomized in 3:1 ratio to ublituximab or placebo
- Patients enrolled into Cohorts 1-6
- Patients un-blinded on study day 28
- NCT number: NCT02738775
- Current status: active, not recruiting
- Estimated study completion date: February 2019

## Treatment group

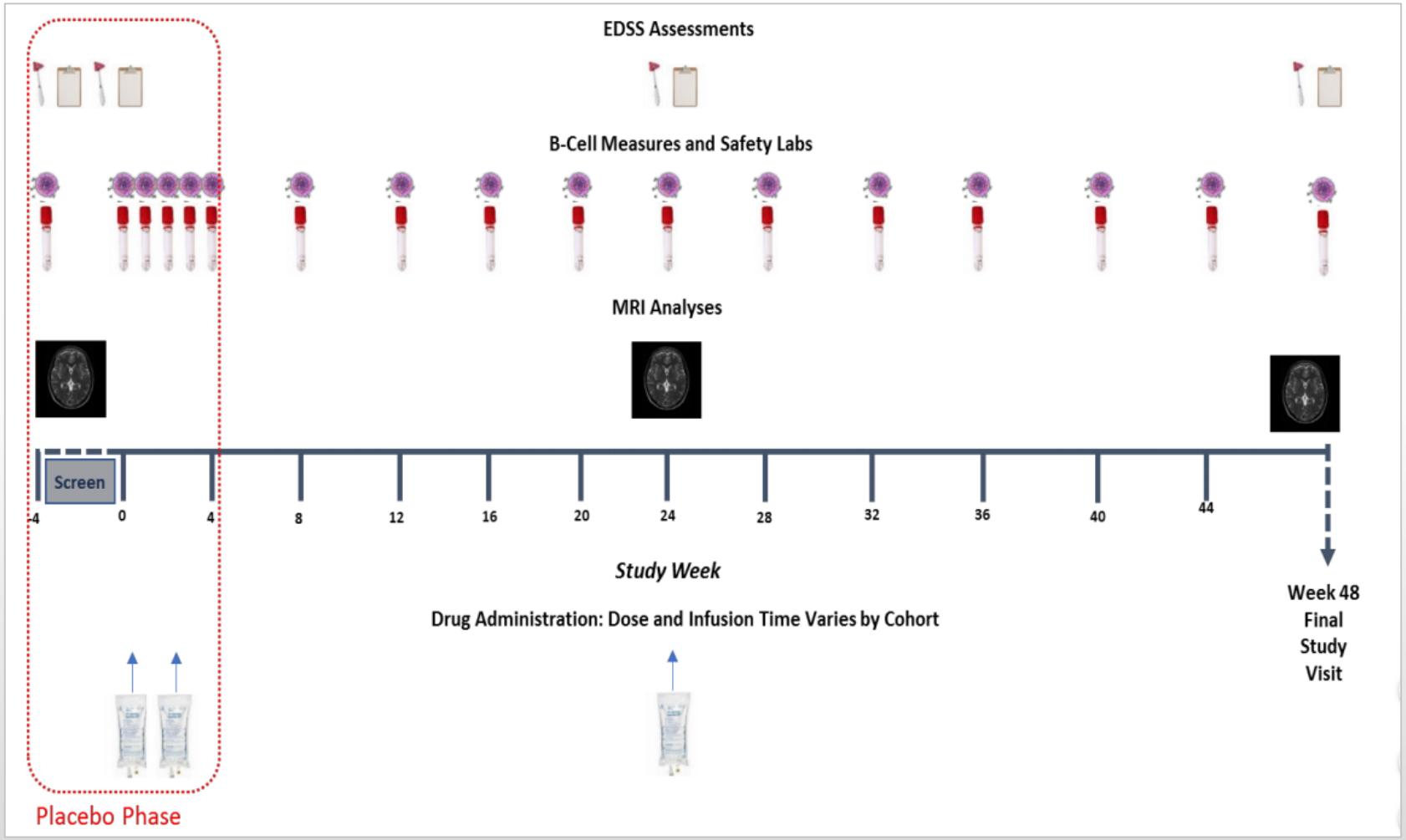
- IV ublituximab (dose and infusion rates changed for each cohort at day 15 and week 24)

## Control group

- IV placebo (infusion rates changed for each cohort at day 15 and week 24)

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY




Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY

| | 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 |

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY

## Inclusion criteria:

- Diagnosis of relapsing-remitting MS (as per 2010 McDonald Criteria)
- One of the following:
  - One confirmed MS relapse in the past year
  - 2 relapses in the past two years
  - At least one active Gd-enhancing T1 lesion at the screening MRI

## Endpoints

- Primary endpoint: Responder's 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
- Safety and efficacy at week 24 of the 48 week study reported in all cohorts

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY

## 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±6.4 |
| **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% | 6.8±7.7 |
| | UTX (n=6) | 39±12 | 50% | 0.20±0.10 |
| **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% | 8.0±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**

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY

## Baseline Characteristics

| Baseline T1 Gd –Enhancing Lesions | |
|---|---|
| **Number of Gd enhancing lesions** | Number of Subjects N=48 (%) |
| **0** | 30 (63%) |
| **1** | 1 (2%) |
| **2** | 1 (2%) |
| **3** | 4 (8%) |
| **≥4** | 12 (25%) |

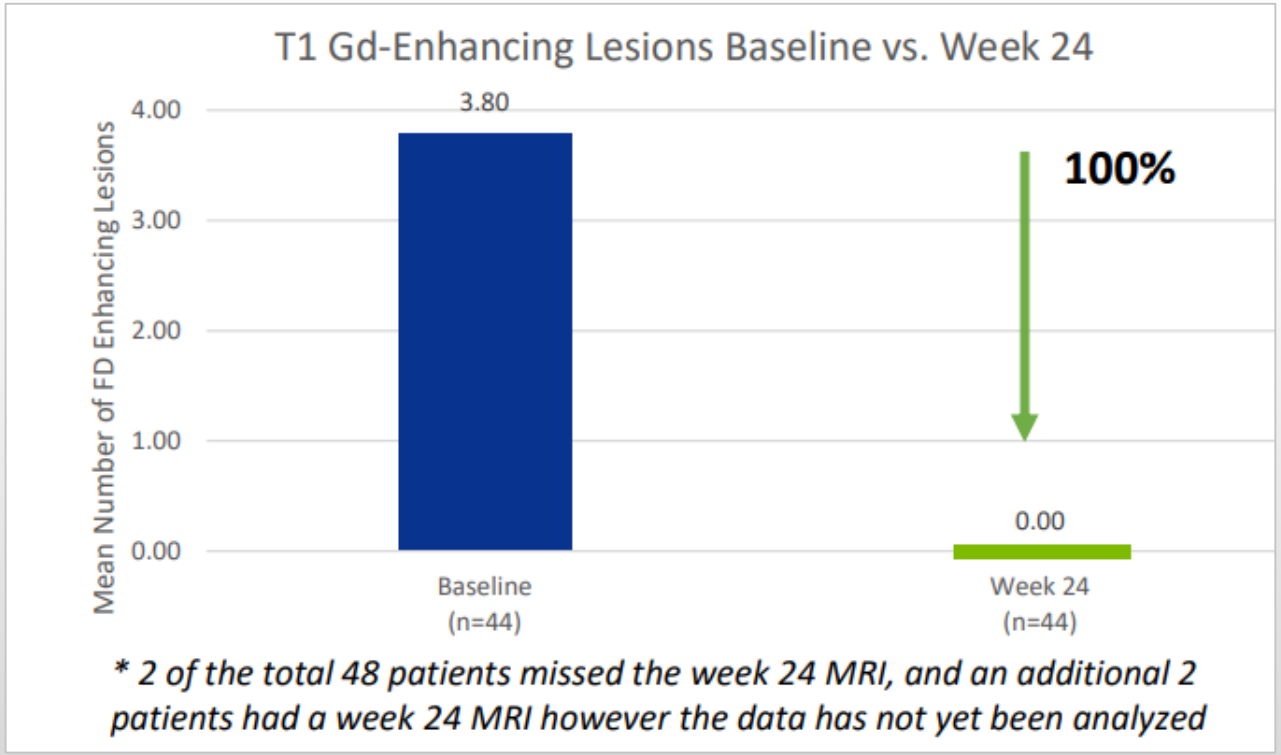
- 17 subjects (35%) presented with ≥2 Gd-enhancing lesions at baseline
- Mean number of T1-Gd lesions at baseline was 3.48 ± 7.66 (N=48)
- Mean T2 lesion volume at baseline was 14.87 ± 20.45 $cm^3$

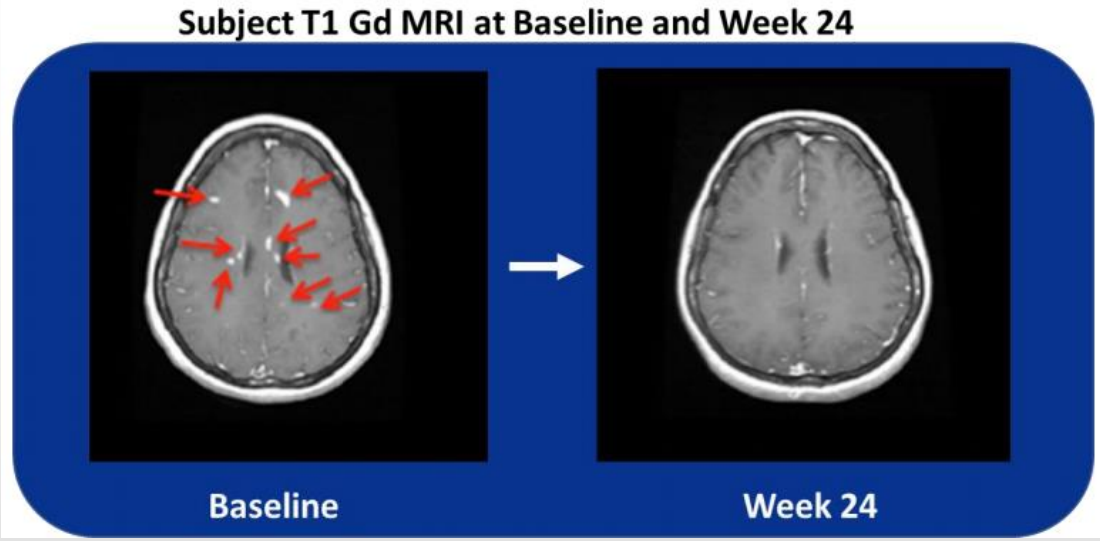
Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY RESULTS

## T1 Gd-Enhancing Lesions

- No T1 Gd-enhancing lesions detected in any subjects at week 24 (p=0.003)



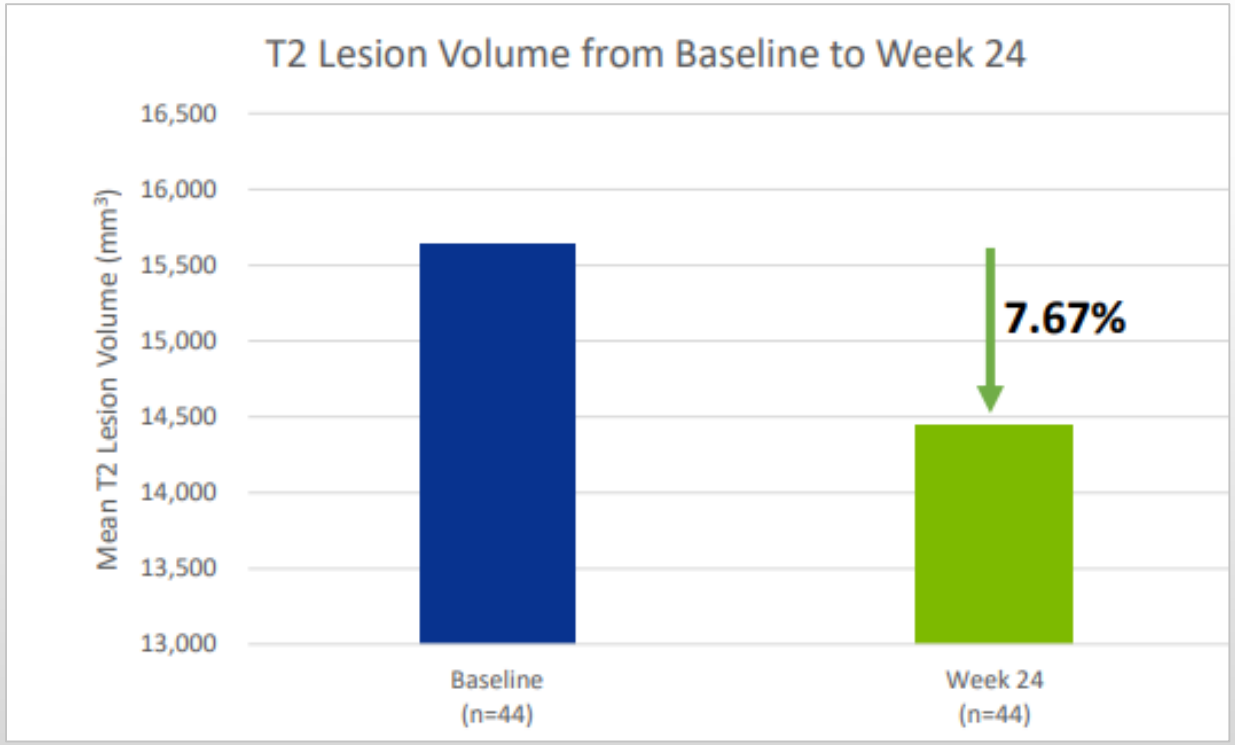




Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY RESULTS

## T2 Lesion Volume

- There was a decrease of 7.67% (p=0.004) in T2 lesion volume at week 24 compared to baseline

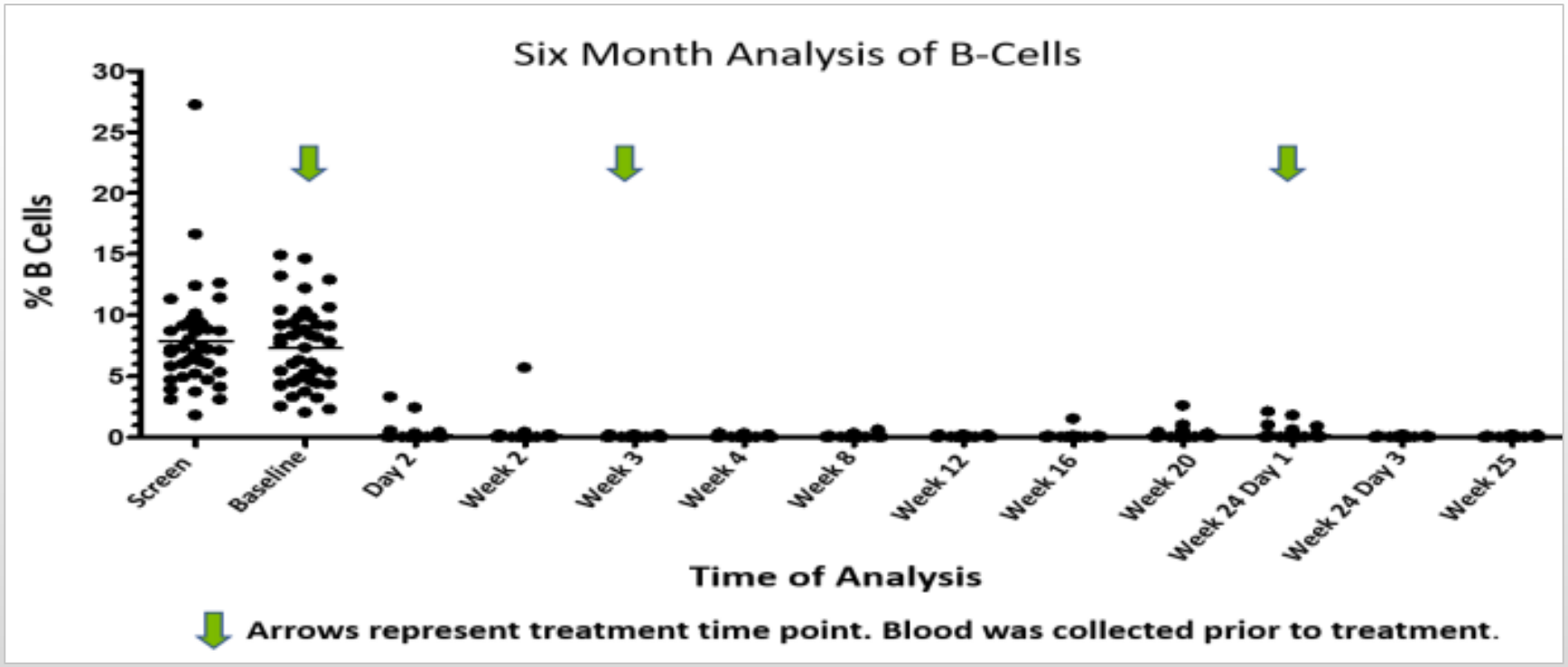



Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY RESULTS

## B-Cell Depletion

- At week 4, median 99% B-cell depletion was observed and maintained at week 24 (n=44)

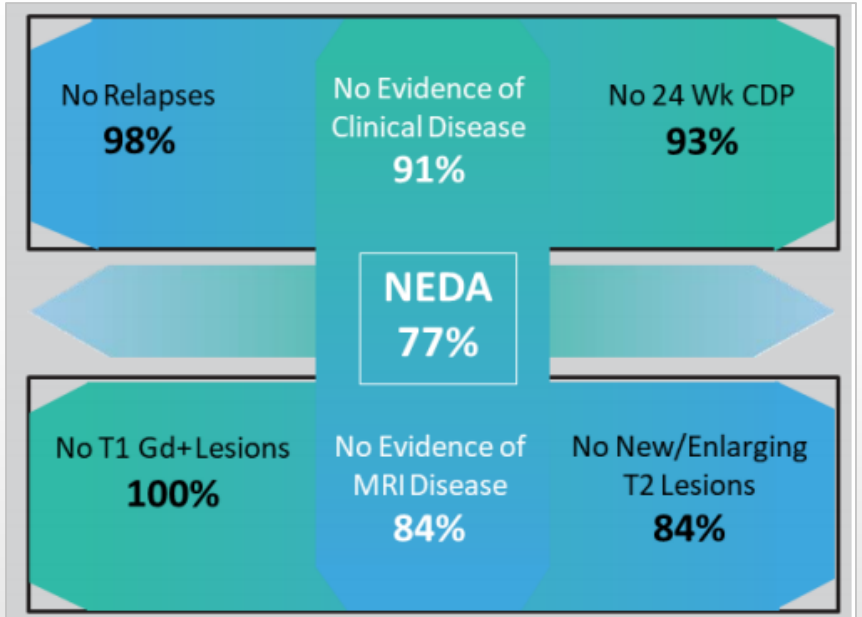



Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY RESULTS

## Annualized Relapse Rate (ARR)

- ARR: 0.5 (n=48) observed at week 24
- At Week 24, 43 of 48 subjects were evaluated for no evidence of disease activity (NEDA):
  - 98% of subjects were relapse free
  - 93% of subjects did not experience 24 week confirmed disability progression
  - 100% of subjects did not have any Gd-enhancing lesions
  - 84% of subjects did not have any new/enlarging T2 lesions
  - 76% of subjects achieved clinical and MRI outcomes consistent with NEDA



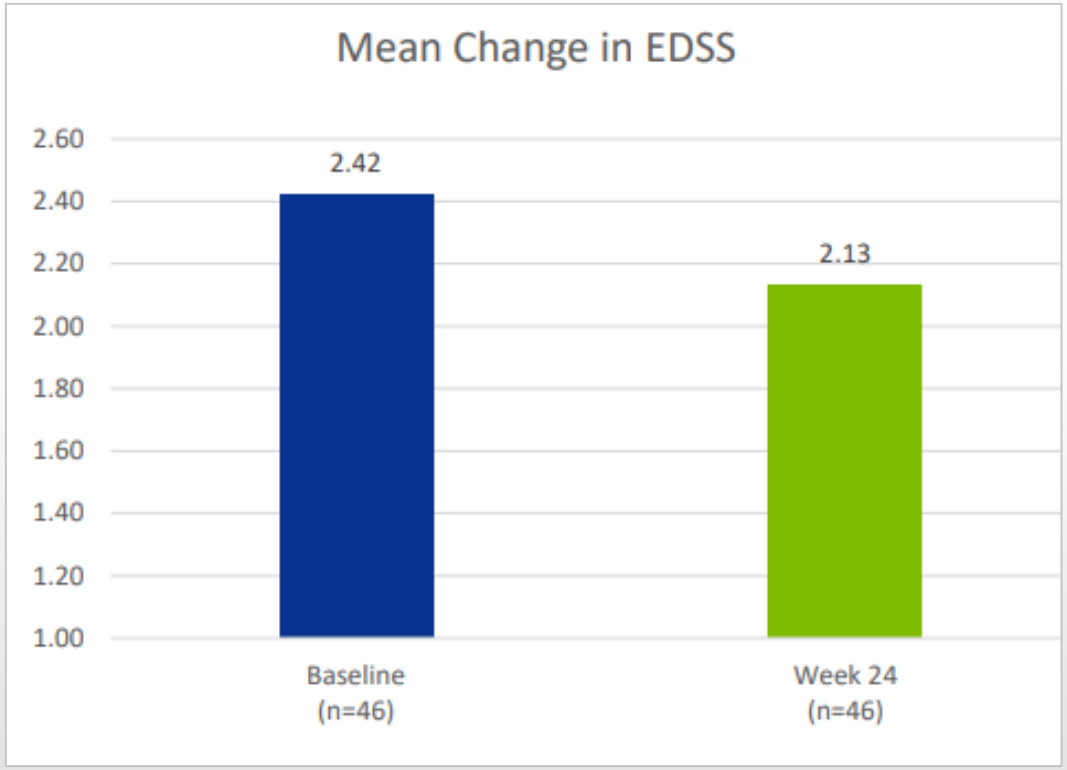

*CDP = Confirmed Disability Progression based on Week 24 EDSS Assessment vs baseline*

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY RESULTS

## Expanded Disability Status Scale (EDSS)

- 83% of subjects showed improved or stable EDSS
- Mean EDSS at baseline was 2.42 ± 1.39; Median=2.5
- At Week 24, the mean EDSS was 2.13. Mean change from baseline was 0.29 ± 0.93 points




Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY SAFETY

## Safety and Tolerability

- Ublituximab was well-tolerated, there were no discontinuations due to drug
- 41 infusion reactions (grade 1 or 2) occurred in 20 patients

| Event, n (%) | (N=48) | |
|---|---|---|
| **Any adverse event[1]** | 40 (83%) | |
| **Most frequently reported adverse events[2]** | All Grades | Grade 3/4 |
| Infusion-related reaction | 20 (42%) | - (-) |
| Headache | 10 (21%) | - (-) |
| Fatigue | 9 (19%) | 3 (6%) |
| Dizziness | 7 (15%) | - (-) |
| Numbness | 6 (13%) | - (-) |
| Nausea/Vomiting | 5 (10%) | - (-) |
| Common Cold | 5 (10%) | - (-) |

[1] Reflects total number of patients that experienced one or more adverse event.
[2] These events were reported by at least 10% of patients and are listed by decreasing incidence.

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 2 STUDY CONCLUSIONS

The results presented in this study, provide support for further clinical trials, including the upcoming Phase 3 ULTIMATE trial

- The data from the study also provided support for a rapid infusion time for the phase 3 trials (450 mg/ 1hr)

Ublituximab showed a statistically significant decrease in T1 lesions and T2 lesion volume, in addition to a reduction in B-cells in all patients at week 24

Ublituximab was well-tolerated, with infusion reactions (grade 1 or 2) being the most common AE

Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.

# PHASE 3 TRIALS

## ULTIMATE 1 and ULTIMATE 2 Trials

**Study Design**

- Phase 3, randomized (1:1 ratio), multi-centered, double-blinded, active-controlled study
- NCT numbers: ULTIMATE 1- NCT03277261, ULTIMATE 2- NCT03277248
- Current status: recruiting
- Estimated study completion date: 09/30/2021

**Treatment Group**

- IV ublituximab + oral placebo

**Active Comparator Group**

- Oral teriflunomide + IV placebo

**Primary Endpoint**

- Annualized relapse rate (ARR) (96 weeks of therapy)

**Secondary Endpoint**

- Number of patients with treatment-related adverse events

# PHASE 3 TRIALS

## Inclusion Criteria

- 18-55 age
- Diagnosis of RRMS (McDonald criteria 2010)
- Active disease
- Expanded disability status scale (EDSS) 0-5.5 (inclusive) at screening

## Exclusion Criteria

- Treatment with prior Anti-CD20 or other B cell directed treatment
- Treatment with the following therapies at any time prior to randomization: alemtuzumab, natalizumab, teriflunomide, leflunomide and stem cell transplantation
- Diagnosed with Primary Progressive MS (PPMS)
- Pregnant or nursing

# COMPETITOR PRODUCTS

## Alemtuzumab (Lemtrada®)

- **Sanofi Genzyme**, FDA approval: Sep 19, 2007
- **MOA**: monoclonal antibody that binds to CD-52 on B and T-cells, monocytes, macrophages, and NK cells causing lysis and depletion of cells

## Natalizumab (Tysabri®)

- **Biogen**, FDA approval: Nov 23, 2004
- **MOA**: monoclonal antibody that prevents migration of leukocytes into parenchymal tissue by inhibiting the action of alpha-4 integrin antibodies

## Ocrelizumab (Ocrevus®)

- **Roche-Genentech**, FDA approval: Mar 29, 2017
- **MOA**: monocloncal antibody that binds to CD-20, leading to complement-mediated lysis and antibody-dependent cellular cytolysis of B-cells

## Ofatumumab (Arzerra®)

- **Novartis**, FDA approval: Oct 26, 2009
- **MOA**: monocloncal antibody that binds to CD-20, causing B-cell lysis

# PLACE IN THERAPY

- Ublituximab may have the potential to improve MS patient outcomes
- However…
  - This phase 2 study should complete and report its final findings at week 48
  - The phase 3 studies should be completed and report its results
  - In addition, further studies should be conducted comparing it's efficacy in comparison to other current treatment to options determine it's clinical value
  - Long-term studies should also be conducted to determine any long term safety concerns in MS patients
- The results reported thus far for the phase 2 study may have been misleading because it did not present the results comparing the placebo cohorts vs the treatment cohorts, which may lead to inflated numbers

# REFERENCES


- A Phase 3, Randomized, Multi-center, Double-blinded, Active-controlled Study to Assess the Efficacy and Safety/Tolerability of Ublituximab (TG-1101; UTX) as Compared to Teriflunomide in Subjects With Relapsing Multiple Sclerosis (RMS) [Internet]. Full Text View - ClinicalTrials.gov. [cited 2018Sep]. Available from: https://clinicaltrials.gov/ct2/show/NCT03277261?term=ultimate&cond=multiple sclerosis&rank=1
- A Phase 3, Randomized, Multi-center, Double-blinded, Active-controlled Study to Assess the Efficacy and Safety/Tolerability of Ublituximab (TG-1101; UTX) as Compares to Teriflunomide in Subjects With Relapsing Multiple Sclerosis (RMS) (ULTIMATE 2) [Internet]. Full Text View - ClinicalTrials.gov. [cited 2018Sep12]. Available from: https://clinicaltrials.gov/ct2/show/NCT03277248?term=ultimate&cond=multiple sclerosis&rank=2
- Functional Systems Scores (FSS) and Expanded Disability Status Scale (EDSS) [Internet]. National Multiple Sclerosis Society. [cited 2018Sep]. Available from: https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-Disab
- Gajofatto A, Benedetti MD. Treatment strategies for multiple sclerosis: When to start, when to change, when to stop? World J Clin Cases. 2015 Jul 16; 3(7): 545–555.
- Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. Handb Clin Neurol. 2014;122:231-66.
- Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.
- Hardy, Richard (2008). "Chapter 7: B Lymphocyte Development and Biology". In Paul, William. Fundamental Immunology (Book) (6th ed.). Philadelphia: Lippincott Williams & Wilkins. pp. 237–269. ISBN 0-7817-6519-6.

# REFERENCES


- Inglese M, et al. Final MRI Results At 6 Months From A Phase 2 Multicenter Study Of Ublituximab, A Novel Glycoengineered Anti-CD20 Monoclonal Antibody(mAb), In Patients With Relapsing Forms Of Multiple Sclerosis (RMS), Demonstrates Complete Elimination Of Gd-Enhancing Lesions. Poster session presented at: American Academy of Neurology Annual Conference. 70th Annual Conference of the American Academy of Neurology; 2018 Apr 24; Los Angeles, CA.
- Ingram G, Hakobyan S, Robertson NP, Morgan BP. Complement in multiple sclerosis: its role in disease and potential as a biomarker. Clin Exp Immunol. 2009 Feb;155(2):128-39.
- Kamm CP, Uitdehaag BM, Polman CH. Multiple sclerosis: current knowledge and future outlook. Eur Neurol. 2014;72(3-4):132-41.
- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.
- Lexicomp Online [Internet]. Hudson, Ohio: Lexi-Comp Inc., 2018. Alemtuzumab; updated 2018 Jul 31; cited 2018 Sep]. Available from: http://online.lexi.com
- Lexicomp Online [Internet]. Hudson, Ohio: Lexi-Comp Inc., 2018. Natalizumab; updated 2018 Sep 10; cited 2018 Sep]. Available from: http://online.lexi.com
- Lexicomp Online [Internet]. Hudson, Ohio: Lexi-Comp Inc., 2018. Ocrelizumab; updated 2018 Jun 26; cited 2018 Sep]. Available from: http://online.lexi.com
- Lexicomp Online [Internet]. Hudson, Ohio: Lexi-Comp Inc., 2018. Ofatumumab; updated 2018 Aug 24; cited 2018 Sep]. Available from: http://online.lexi.com

# REFERENCES


- Multiple sclerosis [Internet]. Mayo Clinic. Mayo Foundation for Medical Education and Research; 2017 [cited 2018Sep]. Available from: https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/diagnosis-treatment/drc-20350274
- MS Symptoms [Internet]. National Multiple Sclerosis Society. [cited 2018Sep]. Available from: https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms
- Rae-Grant A, Day GS, Marrie RA, et al; for the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90:789–800.
- Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis; Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology . Neurology 2018;1-228.
- Rahmanzadeh R, Weber MS, Brück W, Navardi S, Sahraian MA. B cells in multiple sclerosis therapy-A comprehensive review. Acta Neurol Scand. 2018 Jun;137(6):544-556.
- Thompson AJ, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-173.
- Types of MS [Internet]. National Multiple Sclerosis Society. [cited 2018Sep11]. Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS
- What Causes MS? [Internet]. National Multiple Sclerosis Society. [cited 2018Sep]. Available from: https://www.nationalmssociety.org/What-is-MS/What-Causes-MS
- What Is MS? [Internet]. National Multiple Sclerosis Society. [cited 2018Sep]. Available from: https://www.nationalmssociety.org/What-is-MS

# QUESTIONS?

zkakar@mail.usciences.edu