

**Open Label Extension (OLE) of 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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# Disclosures

## **Research Support:**

- TG Therapeutics
- Acorda
- Biogen
- Celgene
- Chugai
- EMD Serono
- MedDay
- Novartis
- Roche-Genentech
- Sanofi Genzyme
- Teva Neuroscience

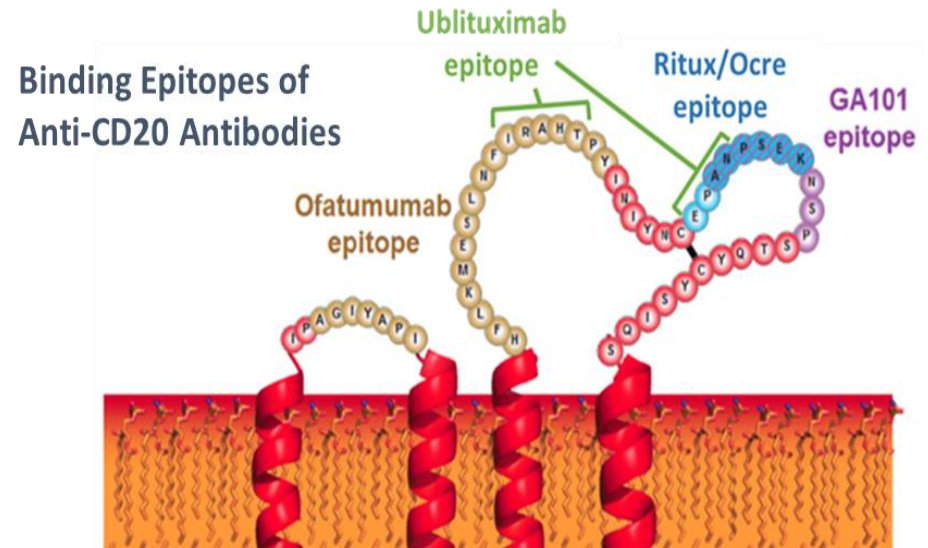
## **Consultancy/Advisory/Speaker:**

- TG Therapeutics
- Acorda
- Bayer
- Biogen
- EMD Serono
- Genentech
- Novartis
- Roche-Genentech
- Sanofi Genzyme
- Teva Neuroscience

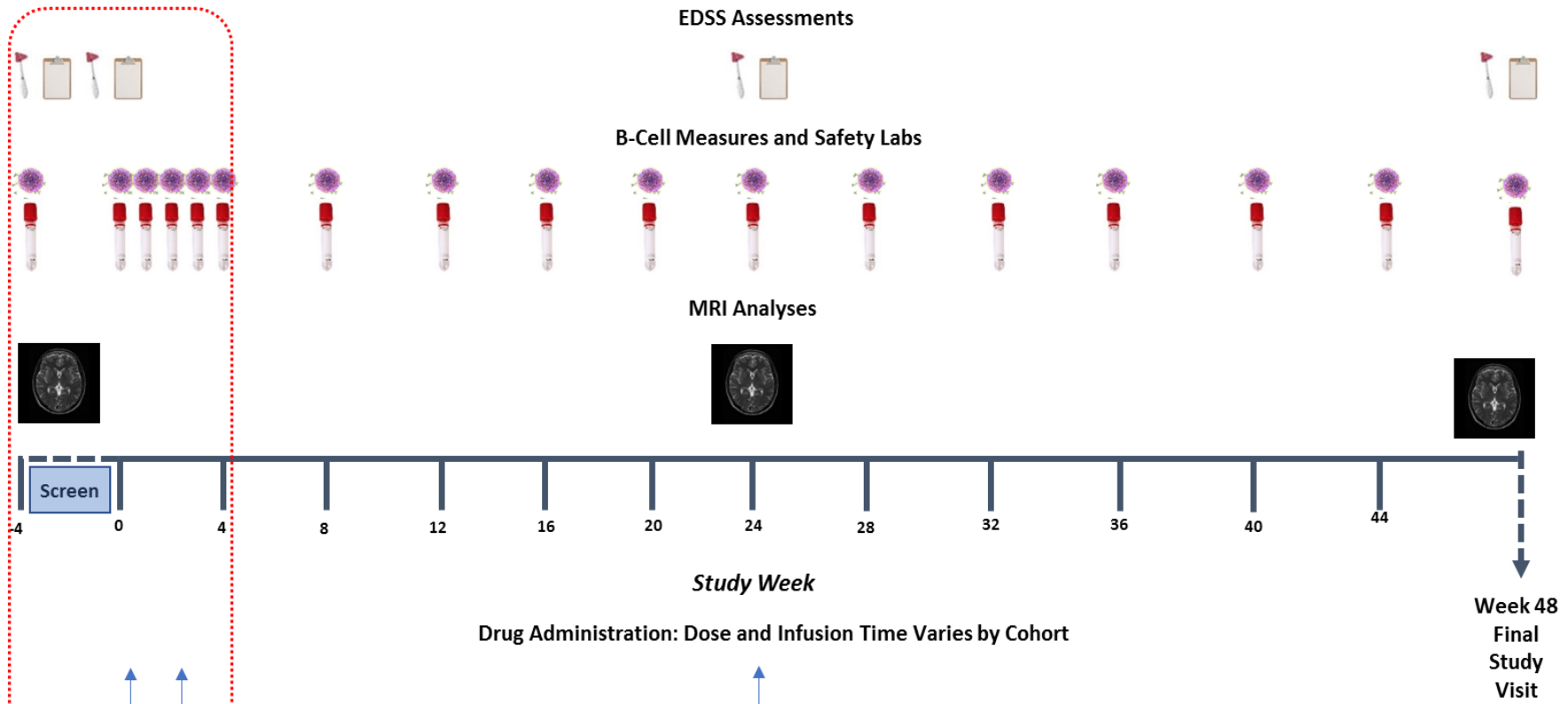
*Presented analyses included data that were not source document verified.*

# Ublituximab (TG-1101)

- 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
  - Infusion times as low as one hour



# Ublituximab Phase 2 RMS: Design



Placebo Phase

Primary Efficacy Endpoint: Responders Rate

Responders Rate = Subjects who have  $\geq 95\%$  B-cell depletion at Week 4

	Clinical Assessment
	B cell & Labs
	MRI
	Infusion

# Ublituximab Phase 2 RMS: Key Inclusion and Exclusion Criteria

## Key Inclusion Criteria:

- 18-55 age
- Diagnosis of RMS (McDonald criteria 2010)
- $\geq 2$  relapses in prior 2 years or 1 relapse in the year prior to screening and/or  $\geq 1$  Gd enhancing lesion
- Active disease
- EDSS 0-5.5 (inclusive)

## Key Exclusion Criteria:

- Treatment with Anti-CD20 within last 12 months
- Treatment with alemtuzumab within last 12 months
- Prior DMT exposure within days of screening
  - 90 days with fingolimod and natalizumab
  - 30 days with glatiramer acetate, interferons, dimethyl fumarate, or glucocorticoids

# Ublituximab Phase 2 RMS: Treatment Regimen

Cohort	Randomization	Treatment Period		
	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

# Ublituximab Phase 2 RMS & OLE: Baseline Characteristics & Patient Disposition

## PATIENT DEMOGRAPHICS

### Baseline Demographics

Cohort	Subjects and treatment	Age (Years) <sup>1</sup>	Gender (% Female)	Disease Duration (Years) <sup>1,2</sup>
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
<b>Total</b>	<b>N=48</b>	<b>40±10</b>	<b>65%</b>	<b>7.7±8.1</b>

<sup>1</sup> Mean ± Standard Deviation

<sup>2</sup> 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

## PATIENT DISPOSITION

### 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

# Ublituximab Phase 2 RMS & OLE: Safety & Tolerability

## Adverse Event Summary\*

	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%)	23 (51%)	2 (4%)
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%)

\*Excludes Infusion Related Reactions (IRRs)

- Ublituximab was well tolerated with a median duration of follow-up of 97.5 weeks
- No drug related discontinuations occurred during the Phase 2 or on the OLE
  - One subject withdrew from the study due to pregnancy but continued to be followed with safety lab monitoring and immunological analyses
- One Grade 3/4 event of fatigue was deemed possibly related to ublituximab
- No deaths reported on study



# Ublituximab Phase 2 RMS & OLE: Safety & Tolerability

## All AEs Deemed at Least Possibly Related to UTX\*

Event, n (%)	Phase 2 (N=48)		OLE (N=45)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Most frequently reported Adverse Events (AEs)				
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%)	- (-)

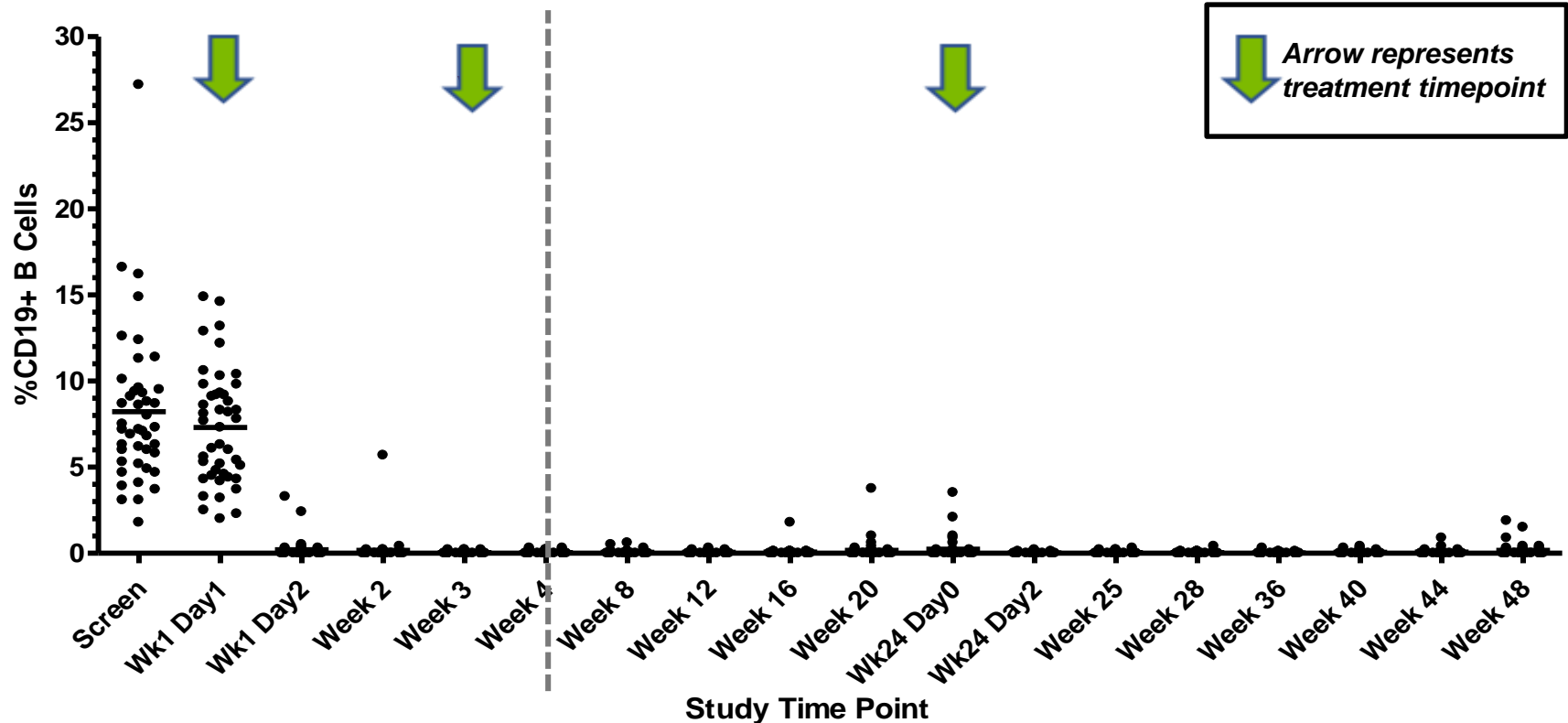
\*Excludes Infusion Related Reactions (IRRs)

# Ublituximab Phase 2 RMS: Infusion Related Reaction (IRR)

## INFUSION RELATED REACTIONS (IRRs)

- 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 4 patients (9%), 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).
- Of the 168 infusions administered during the Phase 2 and the OLE, at the Phase 3 dose/infusion time, there were 20 IRR events in 13 patients, representing 12% of the infusions, all Grade 1 or 2.

# Ublituximab Phase 2 Results: Primary Endpoint – B cell Depletion



- 100% Responders Rate
  - (48/48) subjects met the primary end point 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

# Ublituximab Phase 2 RMS: MRI T1 Gd Enhancing Lesions

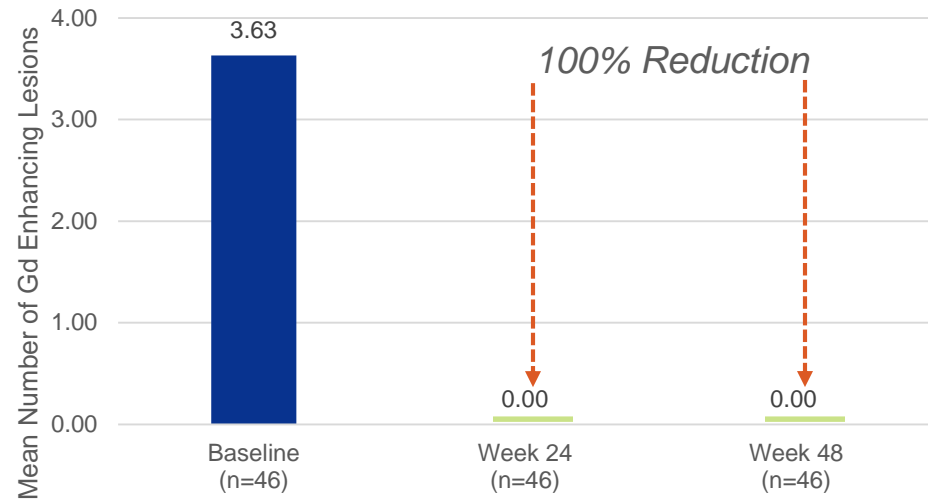
## Baseline (n=46):

- Mean =  $3.63 \pm 7.80$  T1 Gd lesions
- 39% had  $\geq 1$  T1 Gd lesions
- 26% had  $\geq 4$  T1 Gd lesions

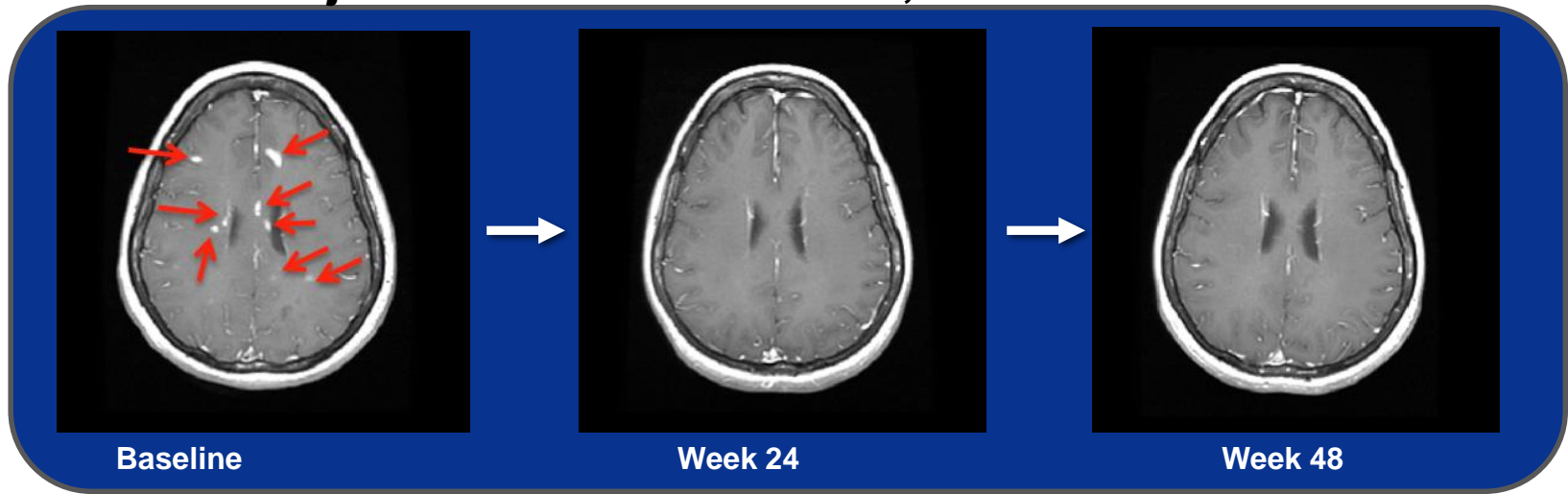
## Week 24 & Week 48 (n=46):

- No T1 Gd lesions found in any scans
- 100% reduction from baseline ( $p=0.003$ )

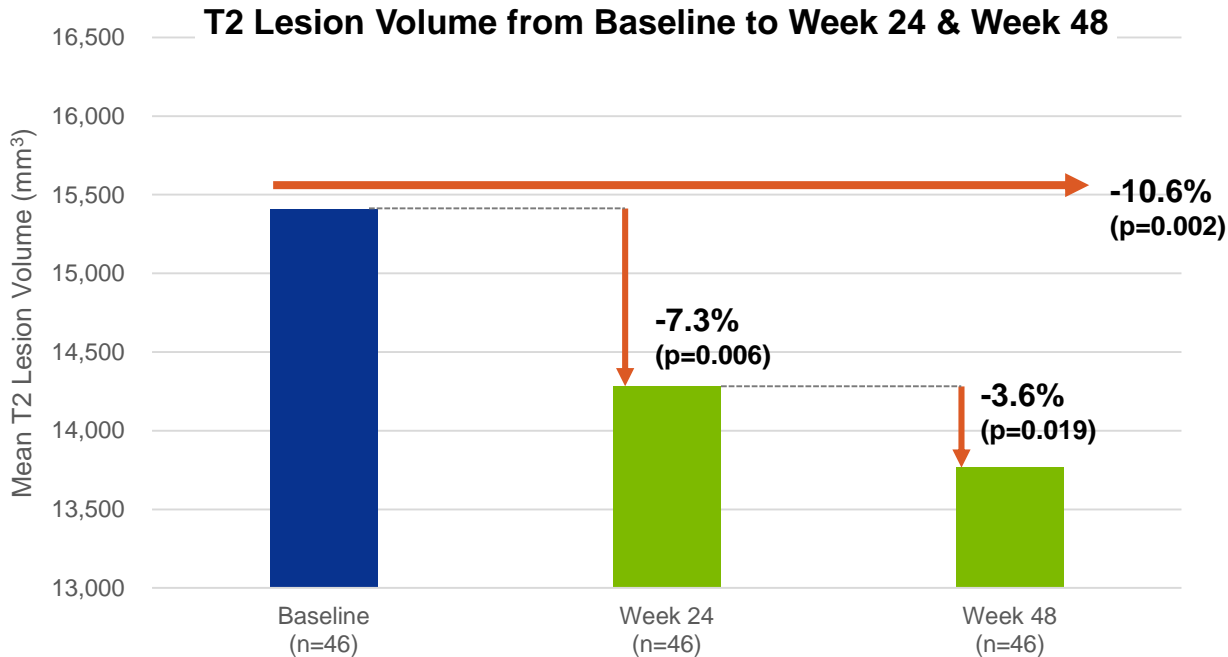
T1 Gd Enhancing Lesions Baseline vs.  
Week 24 & Week 48



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



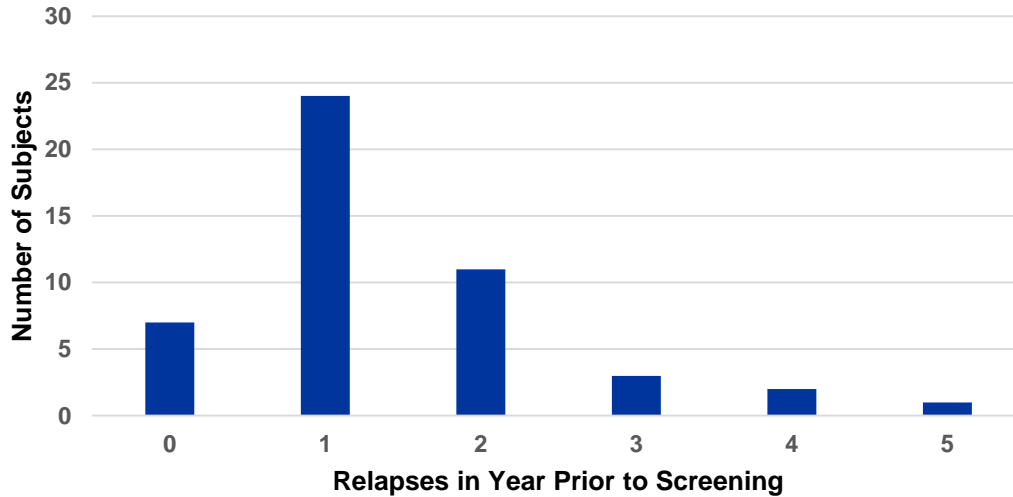
# Ublituximab Phase 2 RMS Results: MRI T2 Lesion Volume



- Decrease of 7.3% in T2 lesion volume at Week 24 compared to baseline and a further decrease of 3.63% from Week 24 to Week 48
- The mean number of new/enlarging (NEL) T2 lesions from baseline to Week 24 was  $0.20 \pm 0.43$  NEL/subject
- The mean number of new/enlarging (NEL) T2 lesions from Week 24 to Week 48 was  $0.04 \pm 0.29$  NEL/subject

# Ublituximab Phase 2 RMS Results: Annualized Relapse Rate (ARR)

Relapse History at Study Entry



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

## At Week 48:

- Annualized Relapse Rate (ARR) of 0.07
  - ARR calculated based on 48 subjects with a mean follow up of approximately 47 weeks (20 min – 48 max weeks)
- 93% of subjects were relapse free

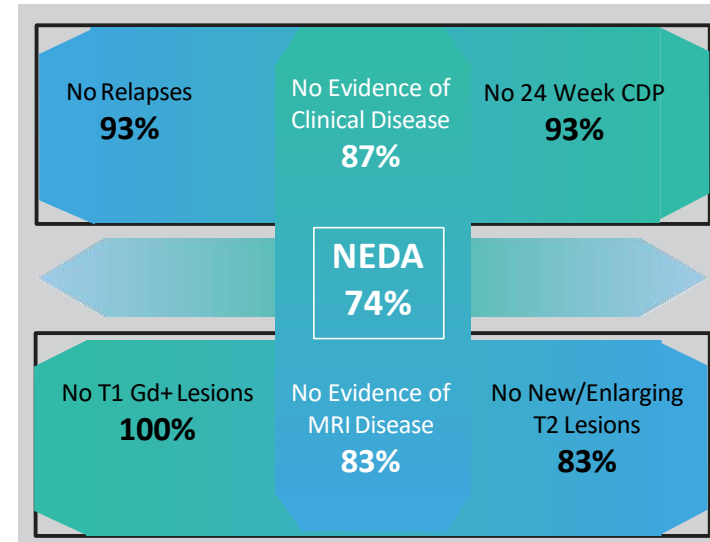
# Ublituximab Phase 2 RMS Results: Disability

- Mean EDSS at baseline was  $2.44 \pm 1.36$ ; Median=2.5 (n=48)
- Disability at Week 48:
  - 7% of subjects met criteria for 24 Week Confirmed Disability Progression (CDP) \*
  - 17% of subjects met criteria for 24 Week Confirmed Disability Improvement (CDI) \*

*\*24 Week Confirmed Disability Progression (CDP) is defined as an increase of  $\geq 1.0$  point from the baseline EDSS score (that is not attributable to another etiology e.g. fever, concurrent illness, concomitant medication) when the baseline score is 5.5 or less, and  $\geq 0.5$  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  $\geq 1.0$  EDSS points from baseline.*

# Ublituximab Phase 2 RMS Results: NEDA at Week 48

- At Week 48, 46\* subjects received all assessments to be evaluated for NEDA:
  - 93% of subjects were relapse free
  - 93% of subjects did not experience 24 week confirmed disability progression (CDP)
  - 100% of subjects did not have any Gd enhancing lesions
  - 83% of subjects did not have any new/enlarging T2 lesions on any scan (either Week 24 or Week 48)
  - 74% of subjects achieved clinical and MRI outcomes consistent with NEDA



\* 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

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

24 Week Confirmed Disability Progression (CDP) is defined as an increase of  $\geq 1.0$  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  $\geq 0.5$  when the baseline score is above 5.5, that is confirmed in a subsequent EDSS assessment 24 weeks later



# Ublituximab Phase 2 RMS & OLE: Long Term Safety Conclusions

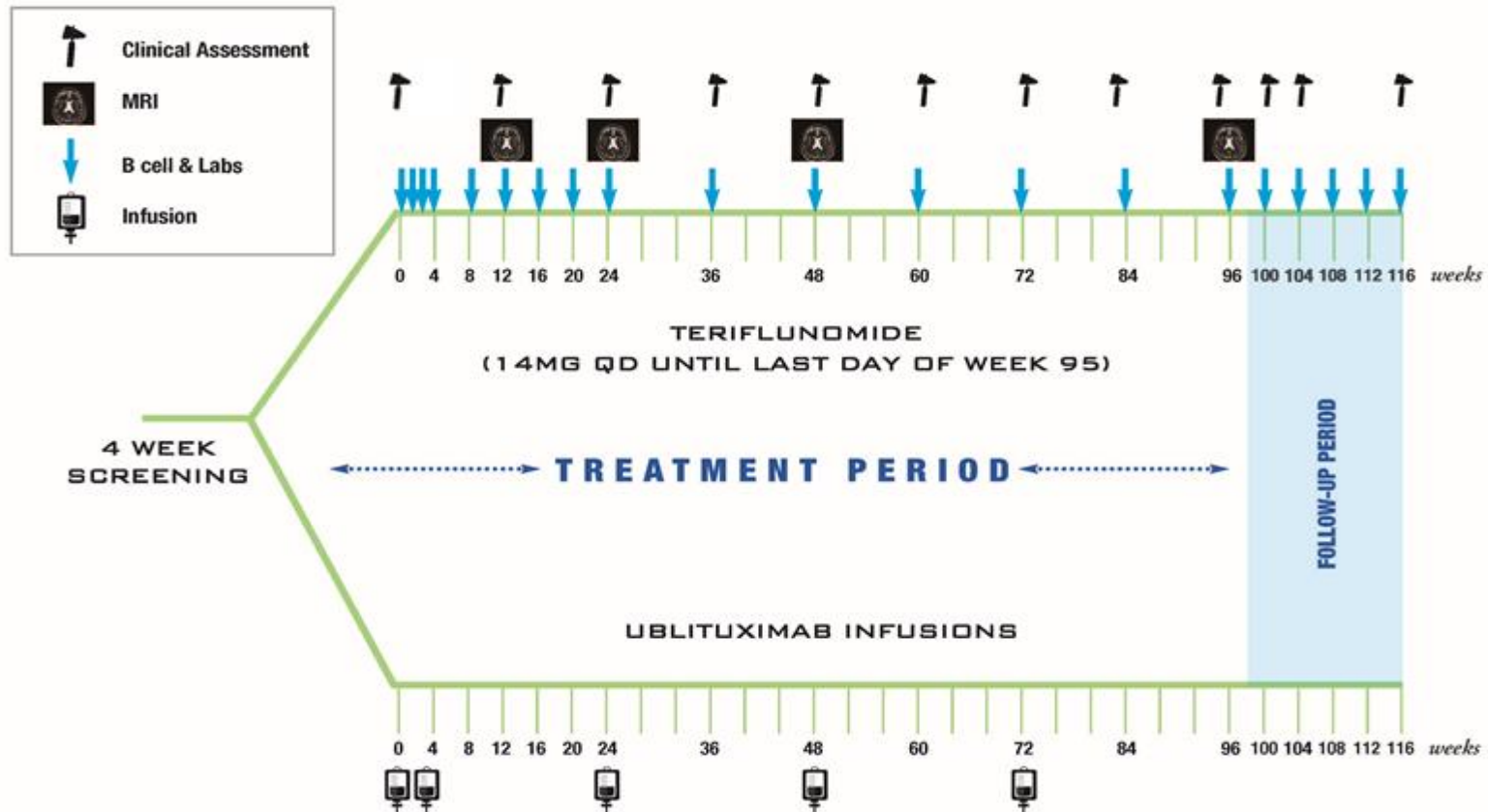
- Ublituximab continues to be well tolerated, with a median duration of follow-up of 97.5 weeks
- AEs deemed at least possibly related to UTX were infrequent during the OLE with all doses of 450mg administered in a one hour infusion (Phase 3 dose)
- Infusion Related Reactions (IRRs) were rare during the OLE, occurring in only 4 patients (9%), all Grade 1 or 2. No subjects discontinued due to an AE related to ublituximab on the Phase 2 or during the OLE.
- [No study discontinuations related to ublituximab]

# Ublituximab Phase 2 RMS: Efficacy Conclusions

- B cells are efficiently depleted in most patients within 24 hours of receiving the first dose of ublituximab
  - Median 99% B cell depletion was observed at Week 4, and maintained at Week 24 and Week 48
- 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.
- No T1 Gd-enhancing lesions were detected in any subjects at Week 24 or Week 48 (100% reduction;  $p=0.003$ )

**Long term safety data, and Phase 2 efficacy 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).**

# ULTIMATE I and II Study Design



- **Primary Endpoint:** Annualized Relapse Rate (ARR) at 96 weeks in RMS subjects treated with ublituximab
- **Enrollment complete in the ULTIMATE Phase 3 Program**

# Thank You to Our Study Sites and Their Patients

- Hope Neurology, Knoxville, TN: Sibyl Wray, MD
  - Coordinator: Brenda Whitehead, CCRP
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- Ohio State University, Columbus, OH: Richard Kissel, MD
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  - Coordinator: Laura Sanders, CCRC
- Central Texas Neurology, Round Rock, TX: Edward Fox, MD, PhD
  - Coordinator: Lori Mayer, RN, DNP
- University of Colorado, Aurora, CO: Timothy Vollmer, MD
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- Neurology Center of San Antonio, TX: Ann Bass, MD
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