TG Therapeutics Announces FDA Approval of BRIUMVI™ (ublituximab-xiiy)

December 28, 2022

BRIUMVI is the first and only anti-CD20 monoclonal antibody approved for patients with relapsing forms of multiple sclerosis that can be administered in a one-hour infusion twice-a-year following the starting dose

U.S. Commercial launch expected Q1 2023

Company to host conference call on Thursday, December 29, 2022 at 8:30 AM ET

A Media Snippet accompanying this announcement is available by clicking on the image or link below:

NEW YORK, Dec. 28, 2022 (GLOBE NEWSWIRE) -- TG Therapeutics, Inc. (NASDAQ: TGTX) today announced the U.S. Food and Drug Administration (FDA) has approved BRIUMVI™ (ublituximab-xiiy), for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Approval was granted for this indication based on data from the ULTIMATE I & II Phase 3 trials, which demonstrated superiority over teriflunomide in significantly reducing the annualized relapse rate (ARR, the primary endpoint), the number of T1 Gd-enhancing lesions and the number of new or enlarging T2 lesions. Results from the ULTIMATE I & II trials were recently published in August 2022 in *The New England Journal of Medicine*.

BRIUMVI is the first and only anti-CD20 monoclonal antibody approved for patients with RMS that can be administered in a one-hour infusion following the starting dose. The administration schedule of BRIUMVI consists of a day one infusion of 150mg administered in four hours, a day 15 infusion of 450mg administered in one hour, followed by 450mg infusions every 24 weeks administered in one hour.

Michael S. Weiss, the Company's Chairman and Chief Executive Officer, stated, "Today's FDA approval marks an exciting day for everyone touched by MS and everyone that has worked on the development of BRIUMVI. We believe in the importance of treatment alternatives for patients and believe the profile of BRIUMVI offers unique attributes to patients and physicians alike. We have built a strong commercial team with deep knowledge of the MS landscape and look forward to launching in Q1 2023." Mr. Weiss continued, "We want to thank the patients and their families, the clinical investigators and their teams, and our advisors for their support and participation in our trials, and for helping us get to this point. We remain committed to the patients we serve and providing seamless access to BRIUMVI once launched."

Lawrence Steinman, MD, Zimmermann Professor of Neurology & Neurological Sciences, and Pediatrics at Stanford University, stated, "Over the past several years we have seen a dramatic shift in the MS treatment landscape towards the use of B-cell therapy, which has shown to be highly effective in reducing relapses in patients. The outcome of the ULTIMATE I & II trials evaluating ublituximab, a novel targeted anti-CD20 agent designed for efficient B-cell depletion that supported this approval, represents an important milestone in the history of MS research as the first Phase 3 study of an anti-CD20 monoclonal antibody in patients with relapsing MS to produce an annualized relapse rate of less than 0.10, which translates to less than 1 relapse in 10 years. This approval is great news for patients living with MS and provides an appealing treatment alternative that can be administered in a one-hour infusion twice-a-year following the starting dose, which I believe is an added benefit to patients."

"We are pleased to have a new treatment approved for people with relapsing forms of Multiple Sclerosis. MS is an unpredictable disease of the central nervous system that affects each person differently. Since we know that early treatment can minimize disease progression, it is incredibly important for people with MS to have a choice of treatment options to find the one that works best for them," said Bari Talente, Executive Vice President, Advocacy & Healthcare Access at the National MS Society.

June Halper, MSN, APN-C, MSCN, FAAN, Chief Executive Officer of the Consortium of Multiple Sclerosis Centers has stated, "The approval of BRIUMVI is wonderful news. MS is most frequently diagnosed during the prime of a person's life when they are just starting a career or beginning a family. The availability of anti-CD20s has launched a new era of high efficacy therapies for multiple sclerosis. The addition of BRIUMVI has added to the hope chest of patients, families, and the MS professional community. As a multi-disciplinary organization centered on the needs of those with MS, we appreciate the increasing array of treatment choices. Congratulations to TG Therapeutics from the CMSC and our leadership."

ABOUT THE ULTIMATE I & II PHASE 3 TRIALS
ULTIMATE I & II are two randomized, double-blind, double-dummy, parallel group, active comparator-controlled clinical trials of identical design, in patients with RMS treated for 96 weeks. Patients were randomized to receive either BRIUMVI, given as an IV infusion of 150 mg administered in four hours, 450 mg two weeks after the first infusion administered in one hour, and 450 mg every 24 weeks administered in one hour, with oral placebo administered daily; or teriflunomide, the active comparator, given orally as a 14 mg daily dose with IV placebo administered on the same schedule as BRIUMVI. Both studies enrolled patients who had experienced at least one relapse in the previous year, two relapses in the previous two years, or had the presence of a T1 gadolinium (Gd)-enhancing lesion in the previous year. Patients were also required to have an Expanded Disability Status Scale (EDSS) score from 0 to 5.5 at baseline. The ULTIMATE I & II trials enrolled a total of 1,094 patients with RMS across 10 countries. These trials were led by Lawrence Steinman, MD, Zimmermann Professor of Neurology & Neurological Sciences, and Pediatrics at Stanford University. Additional information on these clinical trials can be found at www.clinicaltrials.gov (NCT03277261; NCT03277248).

EFFICACY & SAFETY DATA IN RELAPSING FORMS OF MULTIPLE SCLEROSIS
The efficacy and safety of BRIUMVI was evaluated in the ULTIMATE I & II Phase 3 trials.

The following table summarizes the key clinical and MRI endpoints in RMS patients from the ULTIMATE I & II Phase 3 trials:

	ULTIMATE I		ULTIMATE II	
Endpoints	**BRIUMVI**	**Teriflunomide**	**BRIUMVI**	**Teriflunomide**
Clinical Endpoints[1]				
Annualized Relapse Rate (Primary Endpoint)	0.076	0.188	0.091	0.178
Relative Reduction	59% (p<0.001)		49% (p = 0.002)	
Proportion of Patients with 12-week Confirmed Disability Progression[2,3]	5.2% BRIUMVI vs. 5.9% teriflunomide			
Risk Reduction (Pooled Analysis)[4]	16% (p = 0.510)			
MRI Endpoints[5]				
Mean number of T1 Gd-enhancing lesions per MRI[6]	0.016	0.491	0.009	0.250
Relative Reduction	97% (p<0.001)		97% (p<0.001)	
Mean number of new or enlarging T2 hyperintense lesions per MRI[6]	0.213	2.789	0.282	2.831
Relative Reduction	92% (p<0.001)		90% (p<0.001)	

[1]Based on Modified Intent-to-Treat (mITT) Population, defined as all randomized patients who received at least one infusion of study medication and had one baseline and post-baseline efficacy assessment. ULTIMATE I: BRIUMVI (N=271), teriflunomide (N=274). ULTIMATE II: BRIUMVI (N=272), teriflunomide (N=272).

[2] Data prospectively pooled from ULTIMATE I and ULTIMATE II: BRIUMVI (N=543), teriflunomide (N=546).

[3]Defined as an increase of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or 0.5 point or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.

[4]Based on Hazard Ratio.

[5]Based on MRI-mITT population (mITT patients who have baseline and post-baseline MRI). ULTIMATE I: BRIUMVI (N=265), teriflunomide (N=270). ULTIMATE II: BRIUMVI (N=272), teriflunomide (N=267).

[6]At Week 96.

The below table summarizes adverse reactions occurring in RMS patients with an incidence of at least 5% for BRIUMVI and higher than teriflunomide from ULTIMATE I & II. The most common cause of discontinuation in patients treated with BRIUMVI was infection (1.3%).

Adverse Reactions	**BRIUMVI (N=545) %**	**Teriflunomide (N=548) %**
Infusion reactions	48	12
Upper respiratory tract infections[a]	45	41
Lower respiratory tract infections[b]	9	7
Herpes virus-associated infections[c]	6	5
Pain in extremity	6	4
Insomnia	6	3
Fatigue	5	4

[a]Includes the following: nasopharyngitis, upper respiratory tract infection, respiratory tract infection, respiratory tract infection viral, pharyngitis, rhinitis, sinusitis, acute sinusitis, tonsillitis, laryngitis, chronic sinusitis, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection, chronic tonsillitis, pharyngitis streptococcal, sinusitis bacterial, and tonsillitis bacterial.

[b]Includes the following: Bronchitis, pneumonia, tracheitis, tracheobronchitis, COVID-19 pneumonia, bronchitis bacterial, and pneumonia viral

[c]Includes several related Preferred Terms.

ABOUT BRIUMVI™ (ublituximab-xiiy)

BRIUMVI is a novel monoclonal antibody that targets a unique epitope on CD20-expressing B-cells. Targeting CD20 using monoclonal antibodies has proven to be an important therapeutic approach for the management of autoimmune disorders, such as RMS. BRIUMVI is uniquely designed to lack certain sugar molecules normally expressed on the antibody. Removal of these sugar molecules, a process called glycoengineering, allows for efficient B-cell depletion at low doses.

BRIUMVI is indicated for the treatment of adults with relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

IMPORTANT SAFETY INFORMATION

Contraindications: BRIUMVI is contraindicated in patients with:

- Active HBV infection

- A history of life-threatening infusion reaction to BRIUMVI

WARNINGS AND PRECAUTIONS

Infusion Reactions: BRIUMVI can cause infusion reactions, which can include pyrexia, chills, headache, influenza-like illness, tachycardia, nausea, throat irritation, erythema, and an anaphylactic reaction. In MS clinical trials, the incidence of infusion reactions in BRIUMVI-treated patients who received infusion reaction-limiting premedication prior to each infusion was 48%, with the highest incidence within 24 hours of the first infusion. 0.6% of BRIUMVI-treated patients experienced infusion reactions that were serious, some requiring hospitalization.

Observe treated patients for infusion reactions during the infusion and for at least one hour after the completion of the first two infusions unless infusion reaction and/or hypersensitivity has been observed in association with the current or any prior infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion. Administer the recommended pre-medication to reduce the frequency and severity of infusion reactions. If life-threatening, stop the infusion immediately, permanently discontinue BRIUMVI, and administer appropriate supportive treatment. Less severe infusion reactions may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

Infections: Serious, life-threatening or fatal, bacterial and viral infections have been reported in BRIUMVI-treated patients. In MS clinical trials, the overall rate of infections in BRIUMVI-treated patients was 56% compared to 54% in teriflunomide-treated patients. The rate of serious infections was 5% compared to 3% respectively. There were 3 infection-related deaths in BRIUMVI-treated patients. The most common infections in BRIUMVI-treated patients included upper respiratory tract infection (45%) and urinary tract infection (10%). Delay BRIUMVI administration in patients with an active infection until the infection is resolved.

Consider the potential for increased immunosuppressive effects when initiating BRIUMVI after immunosuppressive therapy or initiating an immunosuppressive therapy after BRIUMVI.

Hepatitis B Virus (HBV) Reactivation: HBV reactivation occurred in an MS patient treated with BRIUMVI in clinical trials. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with BRIUMVI. Do not start treatment with BRIUMVI in patients with active HBV confirmed by positive results for HBsAg and anti-HB tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult a liver disease expert before starting and during treatment.

Progressive Multifocal Leukoencephalopathy (PML): Although no cases of PML have occurred in BRIUMVI-treated MS patients, JCV infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies.

If PML is suspected, withhold BRIUMVI and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

MRI findings may be apparent before clinical signs or symptoms; monitoring for signs consistent with PML may be useful. Further investigate suspicious findings to allow for an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis.

If PML is confirmed, treatment with BRIUMVI should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to initiation of BRIUMVI for non-live vaccines. BRIUMVI may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines during or following administration of BRIUMVI has not been studied. Vaccination with live virus vaccines is not recommended during treatment and until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with BRIUMVI During Pregnancy: In infants of mothers exposed to BRIUMVI during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines as measured by $CD19^+$ B-cells. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines. Inactivated or non-live vaccines may be administered prior to B-cell recovery. Assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted.

Fetal Risk: Based on data from animal studies, BRIUMVI may cause fetal harm when administered to a pregnant woman. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. A pregnancy test is recommended in females of reproductive potential prior to each infusion. Advise females of reproductive potential to use effective contraception during BRIUMVI treatment and for 6 months after the last dose.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Decrease in immunoglobulin M (IgM) was reported in 0.6% of BRIUMVI-treated patients compared to none of the patients treated with teriflunomide in RMS clinical trials. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing BRIUMVI therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Most Common Adverse Reactions: The most common adverse reactions in RMS trials (incidence ≥ 10% and >teriflunomide) were upper respiratory tract infections (40%) and infusion reactions (34%). Please visit https://www.tgtherapeutics.com/label-prescribing-info/uspi-briumvi.pdf for full Prescribing Information and Medication Guide.

Physicians, pharmacists, or other healthcare professionals with questions about BRIUMVI should visit www.briumvi.com.

ABOUT BRIUMVI PATIENT SUPPORT

BRIUMVI Patient Support is a flexible program designed by TG Therapeutics to support patients through their treatment journey in a way that works best for them. More information about the BRIUMVI Patient Support program can be accessed at www.briumvipatientsupport.com.

ABOUT MULTIPLE SCLEROSIS
Relapsing multiple sclerosis (RMS) is a chronic demyelinating disease of the central nervous system (CNS) and includes people with relapsing-remitting multiple sclerosis (RRMS) and people with secondary progressive multiple sclerosis (SPMS) who continue to experience relapses. RRMS is the most common form of multiple sclerosis (MS) and is characterized by episodes of new or worsening signs or symptoms (relapses) followed by periods of recovery. It is estimated that nearly 1 million people are living with MS in the United States and approximately 85% are initially diagnosed with RRMS.[1,2] The majority of people who are diagnosed with RRMS will eventually transition to SPMS, in which they experience steadily worsening disability over time. Worldwide, more than 2.3 million people have a diagnosis of MS.[1]

CONFERENCE CALL INFORMATION
The Company will host a conference call Thursday, December 29, 2022, at 8:30 AM ET, to discuss the FDA approval of BRIUMVI.

In order to participate in the event by phone (audio only), please call 1-877-407-8029 (U.S.), 1-201-689-8029 (outside the U.S.), Conference Title: TG Therapeutics. A live webcast of this call, inclusive of slides, will also be available on the Events page, located within the Investors & Media section, of the Company's website at http://ir.tgtherapeutics.com/events. A recording of this event will also be available for replay at www.tgtherapeutics.com, for a period of 30 days after the call.

ABOUT TG THERAPEUTICS
TG Therapeutics is a biopharmaceutical company focused on the acquisition, development and commercialization of novel treatments for B-cell diseases. In addition to a research pipeline including several investigational medicines, TG has received approval from the U.S. FDA for BRIUMVI™ (ublituximab-xiiy), for the treatment of adult patients with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. For more information, visit www.tgtherapeutics.com, and follow us on Twitter @TGTherapeutics and on LinkedIn.

Cautionary Statement
This press release contains forward-looking statements that involve a number of risks and uncertainties. For those statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release. In addition to the risk factors identified from time to time in our reports filed with the U.S. Securities and Exchange Commission (SEC), factors that could cause our actual results to differ materially include the below.

Such forward looking statements include but are not limited to statements regarding expectations for the timing and success of our commercial launch and availability of BRIUMVI™ (ublituximab-xiiy) for relapsing forms of multiple sclerosis (RMS); anticipated healthcare professional and patient acceptance and use of BRIUMVI for the FDA-approved indications, and statements regarding the results of the ULTIMATE I & II Phase 3 studies and BRIUMVI as a potential treatment for RMS.

Additional factors that could cause our actual results to differ materially include the following: the Company's ability to establish and maintain a commercial infrastructure for BRIUMVI, and to successfully or in the timeframe projected, launch, market and sell BRIUMVI; the failure to obtain and maintain requisite regulatory approvals, including the risk that the Company fails to satisfy post-approval regulatory requirements, the potential for variation from the Company's projections and estimates about the potential market for BRIUMVI due to a number of factors, including, further limitations that regulators may impose on the required labeling for BRIUMVI (such as modifications, resulting from safety signals that arise in the post-marketing setting or in the long-term extension study from the ULTIMATE I and II clinical trials); the Company's ability to meet post-approval compliance obligations (on topics including but not limited to product quality, product distribution and supply chain, pharmacovigilance, and sales and marketing); the Company's reliance on third parties for manufacturing, distribution and supply, and other support functions for our clinical and commercial products, including BRIUMVI, and the ability of the Company and its manufacturers and suppliers to produce and deliver BRIUMVI to meet the market demand for BRIUMVI; potential regulatory challenges to the Company's plans to seek marketing approval for the product in jurisdictions outside of the U.S.; the uncertainties inherent in research and development; and general political, economic and business conditions, including the risk that the ongoing COVID-19 pandemic could have on the safety profile of BRIUMVI and any of our other drug candidates as well as any government control measures associated with COVID-19 that could have an adverse impact on our research and development plans or commercialization efforts. Further discussion about these and other risks and uncertainties can be found in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021 and in our other filings with the U.S. Securities and Exchange Commission.

Any forward-looking statements set forth in this press release speak only as of the date of this press release. We do not undertake to update any of these forward-looking statements to reflect events or circumstances that occur after the date hereof. This press release and prior releases are available at www.tgtherapeutics.com. The information found on our website is not incorporated by reference into this press release and is included for reference purposes only.

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PDF attachments accompanying this release are available at:

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http://ml.globenewswire.com/Resource/Download/648f04c7-93bb-4da2-8c5b-09eb737fd014

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1. MS Prevalence. National Multiple Sclerosis Society website. https://www.nationalmssociety.org/About-the-Society/MS-Prevalence. Accessed October 26, 2020. **2.** Multiple Sclerosis International Federation, 2013 via Datamonitor p. 236.