TG Therapeutics Announces European Commission Approval for BRIUMVI® (ublituximab-xiiy) for the Treatment of Relapsing Forms of Multiple Sclerosis in Adults

June 1, 2023

NEW YORK, June 01, 2023 (GLOBE NEWSWIRE) -- TG Therapeutics, Inc. (NASDAQ: TGTX), today announced that the European Commission (EC) has granted approval of BRIUMVI® (ublituximab-xiiy) for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

BRIUMVI was granted approval by the U.S. Food and Drug Administration on December 28, 2022, for the treatment of RMS in adults. BRIUMVI is the first and only anti-CD20 monoclonal antibody approved in the U.S. and now the European Union (EU) for adult patients with RMS that can be administered in a one-hour infusion following the starting dose.

Michael S. Weiss, the Company's Chairman and Chief Executive Officer, stated, "We are very pleased that the European Commission has approved BRIUMVI for the treatment of adult patients with multiple sclerosis. This brings us one step closer to our goal of providing MS patients in Europe with an alternative treatment option that can be delivered in a one-hour infusion every 6 months following the starting dose and we are targeting commercial availability later this year."

The EC approval is 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 published in August 2022 in *The New England Journal of Medicine.*

With this approval, the centralised marketing authorisation is now valid in all European Union (EU) Member States, Iceland, Norway and Liechtenstein.

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).

ABOUT BRIUMVI™ (ublituximab-xiiy) 150 mg/6 mL Injection for IV
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.

A list of authorized specialty distributors can be found at www.briumvi.com.

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 of at least 10%) were infusion reactions and upper respiratory tract infections.

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]

ABOUT TG THERAPEUTICS
TG Therapeutics is a fully integrated, commercial stage, 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 the results of the ULTIMATE I & II Phase 3 studies and BRIUMVI as a treatment for relapsing forms of Multiple Sclerosis (RMS). Additional factors that could cause our actual results to differ materially include the following: the risk that the data from the ULTIMATE I & II trials that we announce or publish may change, or the product profile of BRIUMVI may be impacted, as more data or additional endpoints are analyzed; the risk that data may emerge from future clinical studies or from adverse event reporting that may affect the safety and tolerability profile and commercial potential of BRIUMVI; the risk that any individual patient's clinical experience in the post-marketing setting, or the aggregate patient experience in the post-marketing setting, may differ from that demonstrated in controlled clinical trials such as ULTIMATE I and II; the risk that BRIUMVI will not be commercially successful in the US or ex US; our ability to expand our commercial infrastructure, and successfully market and sell BRIUMVI in RMS, specifically in the EU where the Company currently does not have a commercial presence and where a commercialization partner has not yet been identified; the Company's reliance on third parties for manufacturing, distribution and supply, and a range of other support functions for our commercial and clinical 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; the failure to obtain and maintain requisite regulatory approvals, including in the EU, and including the risk that the Company fails to satisfy post-approval regulatory requirements; 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, 2022 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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[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.