TG Therapeutics Announces Voluntary Withdrawal of the BLA/sNDA for U2 to Treat Patients with CLL and SLL

April 15, 2022

Company voluntarily withdraws UKONIQ® from sale for approved indications of relapsed/refractory MZL and FL
Company to host conference call, Monday, April 18, 2022 at 8:30 AM ET

NEW YORK, April 15, 2022 (GLOBE NEWSWIRE) -- TG Therapeutics, Inc. (NASDAQ: TGTX), today announced that the Company has voluntarily withdrawn the pending Biologics License Application (BLA)/supplemental New Drug Application (sNDA) for the combination of ublituximab and UKONIQ® (umbralisib) (combination referred to as U2) for the treatment of adult patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The decision to withdraw was based on recently updated overall survival (OS) data from the UNITY-CLL Phase 3 trial that showed an increasing imbalance in OS. Additional details are included below in the section entitled “ABOUT UNITY-CLL PHASE 3 TRIAL AND THE WITHDRAWAL OF THE BLA/sNDA SUBMISSION.”

In addition, the Company announced that it has voluntarily withdrawn UKONIQ from sale for the approved indications of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen and for the treatment of adult patients with follicular lymphoma (FL) who have received at least three prior systemic therapies. UKONIQ was granted accelerated approval in these indications in February 2021. The Company’s decision to withdraw UKONIQ from sale was primarily based on the withdrawal of the BLA and sNDA for U2 in CLL.

Michael S. Weiss, Chairman and Chief Executive Officer of TG Therapeutics stated, “We were very disappointed to see that the recently updated overall survival data showed an increasing survival imbalance in favor of the control arm. Accordingly, we and our advisors determined that we should withdraw the BLA/sNDA for U2 in CLL. Additionally, we made the difficult decision to withdraw UKONIQ from sale for the approved indications in MZL/FL. We want to thank the patients, families and practitioners who worked with us in our search for novel treatment options for patients with B-cell malignancies.”

Mr. Weiss continued, “While we had hoped to bring U2 to patients with CLL, this will now permit us to focus our attention, passion and energy to building out our multiple sclerosis and autoimmune platform. With our ublituximab BLA pending for patients with relapsing forms of multiple sclerosis and a PDUFA goal date of September 28, 2022, we are excited about the possibility of bringing ublituximab to patients with RMS. If approved, we believe the differentiated profile of ublituximab with its one-hour infusion will be welcomed by the MS community.”

ABOUT UNITY-CLL PHASE 3 TRIAL AND THE WITHDRAWAL OF THE BLA/sNDA SUBMISSION
UNITY-CLL, a global, Phase 3, randomized, controlled clinical trial, compared the U2 combination, to an active control arm of obinutuzumab plus chlorambucil in patients with both treatment-naïve and relapsed or refractory chronic lymphocytic leukemia (CLL). The trial met its primary endpoint, with U2 significantly prolonging independent review committee (IRC) assessed progression-free survival (PFS) vs. the control arm. The UNITY-CLL Phase 3 trial was conducted under a Special Protocol Assessment (SPA) agreement with the U.S. Food and Drug Administration (FDA). Based on the results of the UNITY-CLL trial, a BLA and sNDA were submitted to the FDA for U2 to treat patients with CLL/SLL.

In November 2021, the FDA notified the Company that it planned to host an Oncologic Drug Advisory Committee (ODAC) meeting in connection with its review of the pending BLA/sNDA and to discuss the benefit risk of UKONIQ in its approved indications. While the FDA identified a number of concerns, the FDA’s desire to host an ODAC appeared to stem from an early ad hoc analysis of overall survival (OS) from the UNITY-CLL trial.

OS was designated as a secondary efficacy endpoint in the UNITY-CLL protocol but was not part of the primary analysis in accordance with the study’s statistical analysis plan agreed upon via a SPA, and therefore, was not analyzed or included in the BLA/sNDA. Additionally, the study was not powered for overall survival. As part of the ongoing review of the BLA/sNDA, the FDA requested an early analysis of OS from the UNITY-CLL trial. In a first analysis of OS using a cut-off date of September 2021, there was an imbalance in favor of the control arm (HR: 1.23). However, based on the ad hoc nature of the analysis, approximately 15% of patients had missing or outdated survival data. Further, when excluding deaths related to COVID-19, the two arms were approximately balanced (HR: 1.04). In February 2022, the Company submitted updated OS data with the same September 2021 cut-off date, but with reduced missing data and additional OS events, which showed an improvement from the previously reported OS data. Neither the original preliminary OS results nor the updated preliminary OS results were statistically significant.

Pursuant to a recent information request made by the FDA, updated OS data were collected that showed an increasing imbalance in favor of the control arm, differing from the improved results provided to the FDA in February 2022. Based on these new data, the Company decided to withdraw the pending BLA/sNDA for U2 to treat CLL/SLL and accordingly the April 22, 2022, ODAC meeting will be canceled.

In addition, based on the Company’s decision to withdraw UKONIQ from sale, we anticipate that the FDA will withdraw the accelerated approval for the product.

The FDA also has scheduled an ODAC meeting for April 21, 2022, in which it plans to discuss the appropriate approach for phosphatidylinositol-3-kinase inhibitors under development for treatment of hematologic malignancies. UKONIQ is within this class of drugs and may be discussed during this
meeting.

CONFERENCE CALL INFORMATION
The Company will host a conference call Monday, April 18, 2022, at 8:30 AM ET, to discuss the regulatory updates.

To participate in the conference call, please call 1-877-407-8029 (U.S.), 1-201-689-8029 (outside the U.S.), Conference Title: TG Therapeutics Update Call. A live audio webcast will be available on the Events page, located within the Investors & Media section, of the Company's website at http://ir.tgtherapeutics.com/events. An audio recording of the conference call will also be available 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 completed a Phase 3 program for ublituximab, an investigational glycoengineered monoclonal antibody that targets a unique epitope on CD20-expressing B-cells, to treat patients with relapsing forms of multiple sclerosis (RMS). For more information, visit www.tgtherapeutics.com, and follow us on Twitter @TGTherapeutics and Linkedin.

UKONIQ® is a registered trademark of TG Therapeutics, Inc.

ABOUT UKONIQ® (umbralisib)
UKONIQ is the first and only oral inhibitor of phosphoinositide 3 kinase (PI3K) delta and casein kinase 1 (CK1) epsilon. PI3K-delta is known to play an important role in supporting cell proliferation and survival, cell differentiation, intercellular trafficking and immunity and is expressed in both normal and malignant B-cells. CK1-epsilon is a regulator of oncoprotein translation and has been implicated in the pathogenesis of cancer cells, including lymphoid malignancies.

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen and for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

These indications are approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION
Infections: Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

Neutropenia: Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 10^9/L (Grade 3-4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia.

Diarrhea or Non-Infectious Colitis: Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis.

Hepatotoxicity: Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

Severe Cutaneous Reactions: Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade. Provide supportive care as appropriate.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5: UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons, frequently in patients who also have aspirin hypersensitivity.

Embryo-fetal Toxicity: Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose.

Serious adverse reactions occurred in 18% of 221 patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were

diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

The most common adverse reactions (>15%), including laboratory abnormalities, in 221 patients who received UKONIQ were increased creatinine (79%), diarrhea-colitis (58%, 2%), fatigue (41%), nausea (38%), neutropenia (33%), ALT increase (33%), AST increase (32%), musculoskeletal pain (27%), anemia (27%), thrombocytopenia (26%), upper respiratory tract infection (21%), vomiting (21%), abdominal pain (19%), decreased appetite (19%), and rash (18%).

Lactation: Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose.

Please visit www.tgtherapeutics.com/prescribing-information/uspi-ukon for full Prescribing Information and Medication Guide.

Cautionary Statement

This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, including statements relating to overall survival information from the UNITY-CLL study, a potential path forward for U2 in the future, the withdrawal of sale of UKONIQ in its approved indications and the potential FDA approval of ublituximab in RMS. In addition to the risk factors identified from time to time in our reports filed with the U.S. Securities and Exchange Commission, factors that could cause our actual results to differ materially are the following: the risk that the FDA does not approve the pending BLA for ublituximab in RMS; the risk that we are unable to successfully launch, market and sell ublituximab in RMS, if approved by the FDA; the risk that we decide not to continue to treat and/or follow patients in the UNITY-CLL study or that the FDA issues a full clinical hold for the UNITY-CLL study preventing us from continuing to treat patients, the risk that we are unable or choose not to find a path forward for bringing to market UKONIQ and/or ublituximab in CLL or any other hematologic indication; the risk that the Company no longer develops investigational products in oncology indications, including the development of any combinations of our proprietary investigational products or third-party products with UKONIQ and/or ublituximab for oncology indications; our ability to advance drug candidates into and successfully initiate, progress or complete clinical trials; the uncertainties inherent in research and development; and our ability to attract and maintain key management and other personnel necessary to continue development and commercialization activities.

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, as updated by our subsequent Quarterly Reports on Form 10-Q, 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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