TG Therapeutics Announces Extension of U.S. FDA BLA/sNDA PDUFA Date for Ublituximab Plus UKONIQ® (U2) to Treat Patients with CLL and SLL

March 3, 2022

FDA sets updated PDUFA goal date of June 25, 2022

NEW YORK, March 03, 2022 (GLOBE NEWSWIRE) -- TG Therapeutics, Inc. (NASDAQ: TGTX), today announced the U.S. Food and Drug Administration (FDA) has extended the Prescription Drug User Fee Act (PDUFA) goal date to June 25, 2022 for the Biologics License Application (BLA) and supplemental New Drug Application (sNDA) for ublituximab in combination with UKONIQ® (umbralisib) as a treatment for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

The FDA notified the Company that the updated overall survival analyses which were submitted to the FDA in February 2022, constituted a major amendment to the applications, and therefore the FDA is extending the PDUFA date to provide time for a full review of the submissions.

Michael S. Weiss, Chairman and Chief Executive Officer of TG Therapeutics stated, “As mentioned on our earnings call earlier this week, we believed an extension of the PDUFA date was a likely scenario especially given the proposed timing of the upcoming ODAC meeting. We hope this extension provides the time needed to give proper attention and review to the U2 BLA/sNDA.” Mr. Weiss continued, “We continue to believe in the potential of U2 to provide a meaningful treatment option to patients with CLL and SLL.”

ABOUT THE ODAC MEETING
In general, the Oncologic Drugs Advisory Committee (ODAC) reviews and evaluates data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer and makes appropriate recommendations to the Commissioner of Food and Drugs. Although the FDA will consider the recommendation of the ODAC Committee, the final decision regarding the approval of a product is made solely by the FDA.

The FDA has notified the Company that potential questions and discussion topics for the ODAC include: the benefit-risk of the U2 combination in the treatment of CLL or SLL, and the benefit-risk of UKONIQ in relapsed/refractory marginal zone lymphoma (MZL) or follicular lymphoma (FL). In addition, as part of the benefit-risk analysis, the overall safety profile of the U2 regimen, including adverse events (serious and Grade 3-4), discontinuations due to adverse events, and dose modifications, is expected to be reviewed. The FDA’s concern giving rise to the ODAC meeting appears to stem from an early analysis of overall survival from the UNITY-CLL trial.

Overall survival was designated as a secondary efficacy outcome 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 Special Protocol Assessment (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 overall survival from the UNITY-CLL trial. As of September 2021, the cut-off date for the overall survival analysis requested by the FDA during their review, there was an imbalance in favor of the control arm (HR: 1.23) though this result was not statistically significant. However, when excluding deaths related to COVID-19, the two arms were approximately balanced (HR: 1.04) with again no statistically significant difference between the treatment groups with regard to overall survival. In February 2022, the Company submitted updated overall survival data with the same September 2021 cut-off date. The Company will continue to evaluate this endpoint over time as more events are available and will continue to analyze how COVID-19 may be impacting the analysis.

The date of the ODAC meeting has not yet been determined, although the FDA has stated that it is targeting holding the ODAC in March or April 2022.

ABOUT UNITY-CLL PHASE 3 TRIAL AND THE BLA/sNDA SUBMISSION
UNITY-CLL is a global, Phase 3, randomized, controlled clinical trial comparing the combination of ublituximab plus UKONIQ (umbralisib), or U2, 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 randomized patients into four treatment arms: ublituximab single agent, UKONIQ single agent, ublituximab plus UKONIQ, and an active control arm of obinutuzumab plus chlorambucil. A prespecified interim analysis was conducted to assess the contribution of ublituximab and UKONIQ in the U2 combination arm and allowed for the termination of the single agent arms. Accordingly, the UNITY-CLL Phase 3 trial continued enrollment in a 1:1 ratio into the two combination arms: the investigational arm of U2 and the control arm of obinutuzumab plus chlorambucil. Approximately 420 subjects enrolled to the two combination arms and approximately 60% of patients were treatment-naïve and 40% were relapsed or refractory. The primary endpoint for this study was superior progression-free survival (PFS) for the U2 combination compared to the control arm. The trial met its primary endpoint, with U2 significantly prolonging independent review committee (IRC) assessed PFS vs. control (median 31.9 months vs 17.9 months; hazard ratio 0.546 ($p<0.0001$)) at a median follow-up of 36.7 months, and results were presented at the American Society of Hematology (ASH) Annual Meeting in December 2020. The UNITY-CLL Phase 3 trial is being conducted under a Special Protocol Assessment (SPA) agreement with the U.S. Food and Drug Administration (FDA).

The BLA/sNDA submissions of U2 to treat CLL were based on the results of the UNITY-CLL trial. The FDA previously granted Fast Track designation to the U2 combination for the treatment of adult patients with CLL and orphan drug designation for ublituximab in combination with UKONIQ for the treatment of CLL.

ABOUT CHRONIC LYMPHOCYTIC LEUKEMIA
Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia. It is estimated there will be more than 20,000 new cases of CLL diagnosed in the United States in 2020 and approximately 45,000 new cases globally in 2020.[1,2] Although signs and symptoms of CLL may disappear

for a period of time after initial treatment, the disease is considered incurable and many people will require additional treatment due to the return of malignant cells.

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 malignancies and autoimmune diseases. In addition to an active research pipeline including five investigational medicines across these therapeutic areas, TG has received accelerated approval from the U.S. FDA for UKONIQ® (umbralisib), for the treatment of adult patients with relapsed/refractory marginal zone lymphoma who have received at least one prior anti-CD20-based regimen and relapsed/refractory follicular lymphoma who have received at least three prior lines of systemic therapies. Currently, the Company has three programs in Phase 3 development for the treatment of patients with relapsing forms of multiple sclerosis (RMS) and patients with chronic lymphocytic leukemia (CLL) and several investigational medicines in Phase 1 clinical development. 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.

[1] Cancer Stat Facts: Leukemia — Chronic Lymphocytic Leukemia (CLL). National Cancer Institute Surveillance, Epidemiology, and End Results Program website. https://seer.cancer.gov/statfacts/html/clyl.html. Accessed October 26, 2020.

[2] EpiCast Report: Chronic Lymphocytic Leukemia – Epidemiology Forecast to 2025. Available at: https://store.globaldata.com/report/gdhcer164-17–epicast-report-chronic-lymphocytic-leukemia-epidemiology-forecast-to-2025/.

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 the BLA/sNDA submission of ublituximab in combination with UKONIQ® (umbralisib), the FDA's planned ODAC meeting to review the benefit-risk of UKONIQ monotherapy and in combination with ublituximab, the FDA review and potential approval of the BLA/sNDA and the timing thereof, the potential benefits, safety and efficacy of ublituximab in combination with UKONIQ in CLL, the clinical development of our product candidates, and anticipated milestones. 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 will not approve the BLA/sNDA submissions; the risk that FDA will withdraw approval of UKONIQ for the treatment of relapsed or refractory MZL or FL; the risk that safety issues or trends observed in the UNITY-CLL study, including rates of serious adverse events and Grade 3 or greater adverse events, discontinuation rates due to adverse events, and dose modifications due to adverse events will prevent approval of ublituximab in combination with UKONIQ or, if approved, will lead to a REMS or other actions for risk management; the risk the Company will voluntarily withdraw the BLA/sNDA for ublituximab in combination with UKONIQ after further analysis of data from the UNITY-CLL study; the risk that the outcome of the ODAC meeting is not favorable or, even if favorable, the FDA does not approve the U2 combination or does so in a narrowly defined population or imposes certain restrictions or warnings that negatively impact the commercial potential of U2 in CLL, the currently approved indications of UKONIQ, or any future indications for UKONIQ or ublituximab; the risk that the FDA does not take action on the BLA/sNDA by the PDUFA target goal date of June 25, 2022; the risk that the U2 regimen, or any other product candidates, will not be commercially successful if approved; the risk that the differentiated tolerability profile for UKONIQ previously observed in clinical trials will not be reproduced in the UNITY-CLL trial or any other on-going studies or the FDA will disagree with our interpretation of the safety of UKONIQ, ublituximab or any of our drug candidates; the uncertainties inherent in research and development; and the risk that the ongoing COVID-19 pandemic and associated government control measures 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, 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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