Archamps (France), May 2, 2019 at 07:00 am CET

Genkyotex Reports Clinical Evidence of Anti-fibrotic Activity by GKT831 in Liver Fibrosis Patients

Top Line Efficacy Results from Phase 2 Primary Biliary Cholangitis (PBC) Trial

- ***22% reduction in liver stiffness in PBC patients with liver fibrosis compared to a 4% increase for placebo (p=0.038), supports anti-fibrotic mechanism***
- ***Statistically significant reduction in alkaline phosphatase (ALP) for overall treatment effect (p=0.002)***
- ***Reduction of 19% in gamma glutamyl transpeptidase (GGT) maintained over 24 weeks but not statistically significant at week 24***
- ***Genkyotex to hold a conference call and webcast today at 1 pm CEST (in French) and at 2pm CEST (in English)***

Genkyotex (Euronext Paris & Brussels: FR0013399474 – GKTX) announced today top-line efficacy data for its NOX1/4 inhibitor GKT831 Phase 2 trial in primary biliary cholangitis (PBC). In a pre-defined patient population with an estimated liver fibrosis stage of F3 or higher, GKT831 achieved a 22% reduction in liver stiffness compared to a 4% increase for placebo (p=0.038). The top-line data provide a clinical proof of concept for GKT831 and highlight its potential as an anti-fibrotic therapy in the liver and other organs. Further analyses are ongoing and the full results will be submitted for presentation at an upcoming international liver conference.

Elias Papatheodorou, Chief Executive Officer of Genkyotex, said: *"The trial results provide evidence for a potential breakthrough treatment in complex and difficult to treat fibrotic disorders. We thank participating patients, their families, and the medical teams involved in this landmark clinical trial. We are looking forward to advancing GKT831 into late stage clinical trials in PBC and other fibrotic liver diseases, like NASH and PSC. In addition, we anticipate the launch of the NIH funded Phase 2 trial of GKT831 to treat lung fibrosis in the coming months."*

The 24-week double-blind, placebo-controlled Phase 2 PBC study enrolled 111 patients in 9 countries, making it one of the largest and longest Phase 2 trials ever conducted in this indication. The primary endpoint was defined as the percent GGT reduction at week 24 and secondary endpoints included ALP changes, Fibroscan® elastography and quality of life (QoL). Statistical significance for all endpoints at week 24 was set at p<0.023, according to the Hochberg adjustment method for multiple analyses.

At week 24, GGT reductions were -9% for placebo, -5% for 400mg OD, and -19% for 400mg BID. These changes did not achieve statistical significance at week 24, although statistical significance was achieved at the 6-week interim analysis. In patients with higher baseline GGT (≥ 2.5 XULN, n=86), GGT reductions were -6% for placebo, -14% for 400mg OD, and -21% for 400mg BID (p<0.039). A statistically significant reduction in overall treatment effect was observed for alkaline phosphatase (ALP) levels (p=0.002) over the course of the treatment period. At week 24, GKT831 400mg BID achieved meaningful reductions in

alkaline phosphatase (ALP). Changes were -3% for placebo, -10% for 400mg OD, and -13% for 400mg BID ($p<0.049$ vs placebo). No changes were observed for total bilirubin (+11% for placebo, +5% for 400mg OD, and +15% for 400mg BID). On the composite endpoint of serum ALP <1.67xULN, an ALP decrease >15%, and total bilirubin (TB) <ULN, the response rates were 5% for placebo, 18% for 400mg OD, and 25% for 400mg BID.

Liver stiffness was measured by Fibroscan® transient elastography. Liver stiffness is an indicator of liver inflammation (edema), cholestasis and fibrosis. In multiple liver diseases, including PBC, NASH and PSC, liver stiffness correlates with liver fibrosis stage (F0 to F4). In PSC, increases in liver stiffness are associated with adverse disease outcomes, including liver transplant, hepatic complication and death[1][2][3].

In PBC, a value greater than 9.6 kPa measured with Fibroscan® indicates fibrosis stage of F3 or higher. In the GKT831 Phase 2 PBC trial liver stiffness was determined in the intention to treat (ITT) population and in the predefined population of patients with a baseline value of 9.6 kPa or higher. Valid liver stiffness measurements (LSM) were obtained at baseline and at week 24 in 91 patients.

At baseline median LSM was 10.7 kPa for placebo, 12.5 kPa for 400mg OD, and 8.3 kPa in the 400mg BID group. Median absolute changes at week 24 were +0.4 kPa for placebo, +0.1 for 400mg OD, and -0.4 kPa for 400mg BID. In the 45 patients with baseline LSM > 9.6 kPa (the predefined value for advanced disease), median baseline LSM was 12.3 kPa for placebo, 14.1 kPa for 400mg OD, and 12.1 kPa in the 400mg BID group. Mean percent changes at week 24 were +4% for placebo, -4% for 400mg OD, and -22% for 400mg BID ($p<0.038$).

Quality of life was evaluated with the PBC-40 questionnaire, which evaluates several important quality of life domains, which are presented in the table below. GKT831 improved parameters important for the quality of life of patients, such as fatigue, emotional and social domains.

Favorable trends on additional secondary endpoints related to liver inflammation and fibrosis were observed but did not reach statistical significance. GKT831 exhibited a favorable safety profile throughout the 24-week treatment period. No drop outs or treatment interruptions due to pruritus or fatigue were reported. Only two serious adverse events were reported, a grade 1 urinary infection and multiple bone fractures related to a traffic accident. Both cases were deemed unrelated to study drug by the investigators.

Philippe Wiesel, Chief Medical Officer of Genkyotex, said: *"These results indicate that GKT831 has the potential to address the major unmet medical need in fibrotic liver diseases, which is to delay disease progression, obviating the need for transplant and death in multiple fibrotic disorders. In addition, in PBC, improvement in quality of life is key for patients and we are excited to see positive trends in multiple QoL domains important to PBC patients. Finally, the excellent safety profile of GKT831 has exhibited over*

[1] Corpechot C et al. Baseline Values and Changes in Liver Stiffness Measured by Transient Elastography Are Associated With Severity of Fibrosis and Outcomes of Patients With Primary Sclerosing Cholangitis. Gastroenterology 2014;146:970–979.

[2] Corpechot C et al. Assessment of Biliary Fibrosis by Transient Elastography in Patients With PBC and PSC.

[3] Park CC et al. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients with Biopsy-proven Nonalcoholic Fatty Liver Disease. Gastroenterology. 2017 February ; 152(3): 598–607.e2. doi:10.1053/j.gastro.2016.10.026.

the course of the treatment period clearly indicates that GKT831 may also be developed in combination with other complementary mechanisms of action, like generically available fibrates or UDCA."

About the PBC phase 2 trial of GKT831 in PBC

The 24-week randomized, double-blind, placebo-controlled study was conducted in 62 centers in the USA, Canada, Belgium, Germany, Greece, Italy, Spain, UK and Israel. The trial enrolled PBC patients with inadequate response to ursodeoxycholic acid (UDCA). This is a difficult to treat patient population likely to progress to cirrhosis, liver transplant or death. To be eligible for the trial, patients were required to have elevated alkaline phosphatase (ALP; >1.5XULN) and elevated gamma glutamyl transpeptidase (GGT; >1.5 XULN).

The primary efficacy endpoint was percent change in GGT at week 24. Key secondary endpoints include additional markers of liver and bile duct injury, markers of inflammation, non-invasive markers of liver fibrosis. In addition, indicators of quality of life including pruritus and fatigue were assessed. Markers of bile acid metabolism and immune activation were also investigated.

A total of 111 patients have been allocated according to a 1:1:1 randomization ratio to three groups: UDCA plus placebo, UDCA plus GKT831 400mg once a day (OD) and UDCA plus 400mg twice a day (BID). This trial is one of the largest Phase 2 PBC trials conducted to date. Additional information about the trial design and eligibility criteria, can be found at ClinicalTrial.gov: NCT03226067.

Change in Quality of Life score

Percent changes in QoL domain scores	Placebo	GKT831 400mg OD	GKT831 400mg BID
Symptoms	1.1	1.1	-3.7
Itch (Pruritus)	-6.8	-11.4	-9.5
Emotional	8.7	4.9	-16.9
Fatigue	2.4	0.3	-9.9
Social	9.3	8.1	-7.7
Cognitive	5.2	16	-1.9

Conference call details

Genkyotex will hold a conference call today at **1 pm CEST (in French)** and **at 2 pm CEST (in English)**. The call will be hosted by Elias Papatheodorou, CEO of Genkyotex; Philippe Wiesel, Chief Medical Officer of Genkyotex and Alexandre Grassin, VP Finance & Administration.

French language Call at 1 pm Paris time:

Participants numbers for the call :

FR : +33 (0) 1 7037 7166
UK : +44 (0) 20 3003 2666
US : +1 212 999 6659

Webcast link : https://channel.royalcast.com/webcast/genkyotexfr/20190502_1/

English language Call at 2 pm Paris time:
Participants numbers for the call :

FR : +33 (0) 1 7037 7166
UK : +44 (0) 20 3003 2666
US : +1 212 999 6659

Webcast link : https://channel.royalcast.com/webcast/genkyotexen/20190502_1/

To ensure that the conference call starts on time, please dial in 5-10 minutes before the scheduled start time.

About Genkyotex

Genkyotex is the leading biopharmaceutical company in NOX therapies, listed on the Euronext Paris and Euronext Brussels markets. A leader in NOX therapies, its unique therapeutic approach is based on a selective inhibition of NOX enzymes that amplify multiple disease processes such as fibrosis, inflammation, pain processing, cancer development, and neurodegeneration.

Genkyotex's platform enables the identification of orally available small-molecules that selectively inhibit specific NOX enzymes. Genkyotex is developing a pipeline of first-in-class product candidates targeting one or multiple NOX enzymes. The lead product candidate, GKT831, a NOX1 and NOX4 inhibitor is evaluated in a phase II clinical trial in primary biliary cholangitis (PBC, a fibrotic orphan disease) and in an investigator-initiated Phase II clinical trial in Type 1 Diabetes and Kidney Disease (DKD). A grant from the United States National Institutes of Health (NIH) of $8.9 million was awarded to Professor Victor Thannickal at the University of Alabama at Birmingham (UAB) to fund a multi-year research program evaluating the role of NOX enzymes in idiopathic pulmonary fibrosis (IPF), a chronic lung disease that results in fibrosis of the lungs, the core component of the program will be to conduct a Phase 2 trial with the GKT831 in patients with IPF. This product candidate may also be active in other fibrotic indications. Its second product candidate, GKT771, is a NOX1 inhibitor targeting multiple pathways in angiogenesis, pain processing, and inflammation, currently undergoing preclinical testing.

Genkyotex also has a versatile platform well-suited to the development of various immunotherapies (Vaxiclase). A partnership covering the use of Vaxiclase as an antigen per se (GTL003) has been established with Serum Institute of India Private Ltd (Serum Institute), the world's largest producer of vaccine doses, for the development by Serum Institute of cellular multivalent combination vaccines against a variety of infectious diseases.

***For further information, please go to** www.genkyotex.com.*

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French Markets Authority (the AMF) on 26 April 2019 under number R.19-014, and those linked to changes in economic conditions, the financial markets, or the markets on which Genkyotex is present. Genkyotex products are currently used for clinical trials only and are not otherwise available for distribution or sale.

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