HighTide Therapeutics, Inc.
君圣泰医药
(Incorporated in the Cayman Islands with limited liability)
(Stock Code: 2511)

HIGHTIDE THERAPEUTICS ANNOUNCES BERBERINE URSODEOXYCHOLATE (HTD1801) MEETS THE PRIMARY ENDPOINTS IN TWO PHASE 3 CLINICAL TRIALS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

This announcement is made by HighTide Therapeutics, Inc. (the "**Company**", together with its subsidiaries, the "**Group**") on a voluntary basis to inform the shareholders and potential investors of the Company about the latest business development of the Group.

The board of directors (the "**Board**") of the Company announces that two Phase 3 trials (SYMPHONY 1 and SYMPHONY 2) of berberine ursodeoxycholate (HTD1801) in Chinese patients with type 2 diabetes mellitus (T2DM) met their primary endpoints and gated secondary endpoints. HTD1801 is the Company's lead compound, an in-house developed, first-in-class, gut-liver anti-inflammatory metabolic modulator.

The results of these two Phase 3 clinical trials provide robust evidence that HTD1801 delivers comprehensive benefits for patients with T2DM. Based on these highly positive read-outs, HighTide plans to submit a new drug application (NDA) for HTD1801 as a treatment for T2DM to the Center for Drug Evaluation (CDE) of China's National Medical Products Administration (NMPA) later this year.

SYMPHONY 1 (NCT06350890) and SYMPHONY 2 (NCT06353347) are multicenter, randomized, double-blind, placebo-controlled, Phase 3 clinical trials designed to evaluate the efficacy and safety of HTD1801 in adults with T2DM with inadequate glycemic control despite dietary and exercise interventions (SYMPHONY 1; N=407) or inadequately controlled with metformin (SYMPHONY 2; N=549). The primary endpoint in both studies was the change in HbA1c from baseline with HTD1801 compared to placebo after 24 weeks of treatment. Gated secondary endpoints included the percentage of subjects achieving HbA1c <7.0%, change in fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), glutamyl transpeptidase (GGT) and high-sensitivity C-reactive protein (hs-CRP).

The primary endpoint was achieved in both trials, showing a clinically meaningful, consistent glucose-lowering effect of HTD1801

SYMPHONY 1 (HTD1801 as monotherapy): At week 24, the reduction from baseline in HbA1c with HTD1801 (-1.3%) was superior to placebo. Further, those with more severe disease had a greater decrease with HTD1801: reduction in HbA1c was -1.5% for those with a baseline HbA1c ≥8.5%.

SYMPHONY 2 (HTD1801 as an add-on therapy to Metformin): At week 24, the reduction from baseline in HbA1c with HTD1801 (-1.2%) was superior to placebo. Further, those with more severe disease had a more significant decrease with HTD1801: reduction in HbA1c was -1.6% for those with a baseline HbA1c ≥8.5%.

In both Phase 3 trials, the efficacy on HbA1c reduction in patients treated with HTD1801 was sustained through week 24, indicating HTD1801 potential for sustained efficacy on HbA1c reduction.

In both trials, gated secondary endpoints were achieved, suggesting multiple advantages of HTD1801 beyond glucose-lowering including improvement in cardiometabolic risk indicators

At week 24, in both studies, the proportion of patients who achieved HbA1c <7.0% was significantly higher in the HTD1801 treatment groups compared to placebo. Improvements in HbA1c with HTD1801 were paralleled with significant improvements in postprandial and fasting plasma glucose compared with placebo. In addition, HTD1801 demonstrated lipid-lowering effects, including significant reductions in low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C). Moreover, HTD1801 treatment led to reductions in key inflammatory biomarkers – glutamyl transpeptidase (GGT) and high-sensitivity C-reactive protein (hs-CRP) – both of which are associated with cardiovascular risk in patients with T2DM.

Favorable safety and tolerability profile

Overall, safety and tolerability were favorable and consistent with previous clinical trials of HTD1801. The most commonly reported adverse events were gastrointestinal. In both studies <2% of patients discontinued early due to an adverse event. The incidence of hypoglycemia was low, with no severe hypoglycemia events reported.

ABOUT BERBERINE URSODEOXYCHOLATE (HTD1801)

Berberine ursodeoxycholate (HTD1801) is an orally delivered, gut-liver anti-inflammatory metabolic modulator being developed for the treatment of metabolic and digestive diseases. HTD1801, an ionic salt of berberine and ursodeoxycholate, is a new molecular entity with a unique dual mechanism of action: AMP kinase activation and NLRP3 inflammasome inhibition. These two key mechanistic pathways have been associated with improvements in insulin resistance, glucose metabolism, lipid metabolism, and hepatic inflammation, potentially providing a comprehensive treatment platform for the multifaceted nature of complex metabolic diseases.

HTD1801 is being developed for multiple indications. In addition to T2DM, its efficacy in treating metabolic dysfunction-associated steatohepatitis (MASH) has been demonstrated in a Phase 2a clinical trial and a global multicenter Phase 2b trial assessing the histologic benefit of HTD1801 is currently ongoing, with topline results expected in 2025.

ABOUT HIGHTIDE THERAPEUTICS, INC.

HighTide Therapeutics, Inc. (Stock Code: 2511.HK) is a globally integrated biopharmaceutical company focusing on the discovery and development of first-in-class multifunctional multi-targeted therapies with poly-indication potential across chronic liver and metabolic diseases with significant unmet medical needs. HighTide is currently developing several clinical assets and associated global intellectual property rights, and advancing multiple mid-to-late-stage clinical trials including therapies for metabolic dysfunction-associated steatohepatitis (MASH), type 2 diabetes mellitus (T2DM), severe hypertriglyceridemia (SHTG) and primary sclerosing cholangitis (PSC). Berberine ursodeoxycholate (HTD1801), HighTide's lead drug candidate, received Fast Track designation from the United States Food and Drug Administration for both MASH and PSC and Orphan Drug designation for PSC. HTD1801 has been included in the National Major New Drug Innovation Program under the 13th Five-Year Plan for Major Technology Project in China.

Cautionary statement required by Rule 18A.05 of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited: The Company cannot guarantee that HTD1801 will ultimately be successfully marketed. Shareholders and potential investors of the Company are advised to exercise caution when dealing in the shares of the Company.

By order of the Board
HighTide Therapeutics, Inc.
Dr. LIU Liping
Executive Director and Chief Executive Officer

Hong Kong, April 15, 2025

As at the date of this announcement, the Board comprises Dr. LIU Liping and Ms. YU Meng as executive Directors; Dr. ZHU Xun, Mr. MA Lixiong and Mr. JIANG Feng as non-executive Directors; and Mr. TAN Bo, Dr. LI Jin and Mr. HUNG Tak Wai as independent non-executive Directors.