Terns Reports Positive Top-line Results from Phase 1 Proof of Concept Clinical Trial of THR-β agonist TERN-501

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Terns plans to initiate first FXR/THR-β agonist combination trial in NASH in 1H 2022

FOSTER CITY, Calif., Nov. 09, 2021 (GLOBE NEWSWIRE) -- Terns Pharmaceuticals, Inc. (“Terns” or the “Company”) (Nasdaq: TERN), a clinical-stage biopharmaceutical company developing a portfolio of small-molecule single-agent and combination therapy candidates for the treatment of non-alcoholic steatohepatitis (NASH) and other chronic liver diseases, today reported positive top-line results from a Phase 1 clinical trial of TERN-501, a thyroid hormone receptor beta (THR-β) agonist in development for the treatment of patients with NASH.

The Phase 1 clinical trial includes single ascending dose (SAD), multiple ascending dose (MAD) and drug-drug interaction (DDI) cohorts evaluating the safety, tolerability, pharmacodynamics (PDs) and pharmacokinetics (PKs) of TERN-501. Healthy volunteers with mildly elevated low-density lipoprotein (LDL) cholesterol were randomized to placebo (n=2) or TERN-501 (n=6) in each cohort. Volunteers randomized to TERN-501 received single doses of 3, 10, 30 or 60 mg of TERN-501 in the SAD portion of the study or multiple doses of 3, 6 or 10 mg of TERN-501 once daily for 14 days in the MAD portion of the study. In the DDI portion of the study, volunteers received open label TERN-501 co-administered with TERN-101, the Company’s liver-distributed farnesoid X receptor (FXR) agonist also in development for the treatment of NASH.

TERN-501 was generally safe and well-tolerated in the SAD and MAD cohorts with a similar incidence of adverse events (AEs) across all TERN-501 treatment groups and placebo. All AEs were mild to moderate with no apparent dose relationship. There were no treatment-emergent serious AEs (SAEs) and no volunteer discontinued TERN-501 or the study due to any AE. There were no cardiac safety signals, no incidence of diarrhea and no differences between TERN-501 dose groups and placebo in change from baseline in heart rate, blood pressure or other vital signs. Thyroid function test results were consistent with other THR-β agonists currently in clinical development, and there were no findings of clinical hyper- or hypo-thyroidism. There were no clinically meaningful differences between placebo and any TERN-501 dose group in liver function abnormalities or mean change from baseline in liver transaminases at Day 15 in the MAD cohorts.

In the SAD and MAD cohorts, TERN-501 demonstrated a predictable PK profile with low variability. Study drug plasma exposures were linear and approximately dose-proportional with no overlap between dose strengths. There was no significant accumulation of drug over 14 days of dosing. TERN-501 plasma half-life was greater than 13 hours in all single and repeat dose cohorts, supporting once-daily dosing. The overall PK profile indicates TERN-501 is well-suited for co-formulation with other small molecule NASH agents as an oral, once-daily fixed dose combination.

Significant effects on sex hormone binding globulin (SHBG), a key PD marker of THR-β engagement linked to NASH histologic efficacy, were observed following treatment with TERN-501. As further described in the table below, SHBG increases observed with 14 days of TERN-501 treatment were significant, dose dependent, and have been associated with robust reductions in MRI proton density fat fraction (MRI-PDFF) and NAFLD Activity Score in a precedent late-stage clinical NASH trial.

In addition, significant reductions were observed in atherogenic lipids including LDL cholesterol and apolipoprotein B (Apo-B), comparable to or greater than those observed in Phase 1 studies of other THR-β agonists being studied in late-stage clinical trials. All TERN-501 dose groups demonstrated significant decreases in LDL cholesterol compared to placebo during the dosing period. The maximum mean LDL cholesterol decreases over the treatment period were -22%, -28% and -27% for 3, 6 and 10 mg doses, respectively, compared to placebo (-8%).

The PD results from these MAD cohorts are summarized below:

	TERN-501 MAD (QD) Mean % Change from Baseline to Day 15			
	Placebo (N=6)	3 mg (N=6)	6 mg (N=6)	10 mg (N=6)
Sex Hormone Binding Globulin (%)	-12%	55%	134%*	166%*
Low Density Lipoprotein - cholesterol (%)	-4%	-17%	-19%	-21%*
Triglycerides (%)	-16%	-22%	-21%	-36%

Apolipoprotein-B (%)	-6%	-18%*	-23%*	-28%*

Note: Day 15 represents 24 hours following the last dose of TERN-501
* p-value vs. placebo: <0.05

In the SAD cohorts, single doses of TERN-501 up to 60 mg resulted in significant and dose-dependent reductions in Apo-B and LDL cholesterol and significant increases in SHBG relative to placebo. Additional data from the SAD cohorts will be presented at AASLD The Liver Meeting® Digital Experience in November 2021.

In the DDI cohort, the combination of TERN-101 and TERN-501 was well tolerated. Preliminary PK results support the co-administration of TERN-101 and TERN-501 in NASH patients, with no apparent need for dose adjustment.

"The TERN-501 proof of concept data are highly encouraging and indicate potent liver target engagement and the potential for broad benefits in NASH patients. We are particularly pleased to see high TERN-501 exposures at lower doses than initially projected accompanied by marked dose-dependent increases in SHBG and decreases in LDL cholesterol. These results, along with the predicted non-variable PK of TERN-501 as well as its low potential for drug-drug interactions, may offer an advantage within the THR-β agonist class," said Erin Quirk, M.D., president, chief medical officer and head of R&D at Terns. "Taken together with its significant changes in PD markers and positive Phase 1 safety profile observed in the trial, we believe TERN-501 is strongly positioned to be a promising therapeutic candidate for NASH and is well suited for co-formulation and combination therapy development. We are excited to move forward with our plan to initiate the first NASH trial of TERN-101, our FXR agonist, in combination with TERN-501, our THR-β agonist, in the first half of 2022."

About TERN-501
TERN-501 is a thyroid hormone receptor beta (THR-β) agonist with high metabolic stability, enhanced liver distribution and greater selectivity for THR-β compared to other THR-β agonists in development. Agonism of THR-β increases fatty acid metabolism via mitochondrial oxidation and affects cholesterol synthesis and metabolism. As a result, THR-β stimulation has the ability to reduce hepatic steatosis and improve serum lipid parameters including LDL cholesterol and triglycerides. In vivo NASH studies in a rodent model have demonstrated that low-doses of TERN-501 achieved complete resolution of steatosis and reductions in serum lipids, hepatic inflammation and fibrosis. TERN-501 has high liver distribution and is 23-fold more selective for THR-β than for THR-α activation in a cell free assay, thereby minimizing the risk of cardiotoxicity and other off-target effects associated with non-selective THR stimulation. Finally, TERN-501 has been designed to be metabolically stable and is therefore expected to have little pharmacokinetic variability and a low clinical dose, making it an attractive candidate for use in fixed-dose combinations for NASH treatment. Terns received Fast Track designation from the U.S. Food and Drug Administration (FDA) for TERN-501 for the treatment of NASH in June 2021.

About Terns Pharmaceuticals
Terns Pharmaceuticals, Inc. is a clinical-stage biopharmaceutical company developing a portfolio of small-molecule single-agent and combination therapy candidates for the treatment of non-alcoholic steatohepatitis, or NASH, and other chronic liver diseases. Terns' pipeline includes three clinical stage development programs including an FXR agonist, a VAP-1 inhibitor and a THR-β agonist, and a preclinical GLP-1 receptor agonist program. Terns is focused on developing combination therapies based on clinically validated and complementary mechanisms of action to address the multiple hepatic disease processes of NASH in order to drive meaningful clinical benefits for patients. For more information, please visit: www.ternspharma.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements about Terns Pharmaceuticals, Inc. (the "Company," "we," "us," or "our") within the meaning of the federal securities laws, including those related to the Company's expectations of timing and potential results of the Company's clinical trials and other development activities, including in relation to the therapeutic potential of TERN-501; the potential for thyroid hormone receptor beta (THR-β) to be a therapeutic target for NASH; the potential utility and progress of the Company's product candidates in NASH, including the clinical utility of the data from and the endpoints used in the Phase 1 trial; the Company's clinical development plans and activities, including the development plans for TERN-501 in combination with TERN-101 and potentially other product candidates; the Company's expectations regarding the profile of its product candidates, including tolerability, safety, metabolic stability and pharmacokinetic profile; and the Company's ability to continue to execute on its clinical strategy and plans. All statements other than statements of historical facts contained in this press release, including statements regarding the Company's strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "positioned," "potential," "predict," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. The Company has based these forward-looking statements largely on its current expectations, estimates, forecasts and projections about future events and financial trends that it believes may affect its financial condition, results of operations, business strategy and financial needs. In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. These statements are subject to risks and uncertainties that could cause the actual results and the implementation of the Company's plans to vary materially, including the risks associated with the initiation, cost, timing, progress and results of the Company's current and future research and development activities and preclinical studies and clinical trials. In particular, the impact of the COVID-19 pandemic on the Company's ability to progress with its research, development, manufacturing and regulatory efforts, including the Company's clinical trials for its product candidates, will depend on future developments that are highly uncertain and cannot be

predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the United States and in other countries, and the effectiveness of actions taken globally to contain and treat the disease. These risks are not exhaustive. For a detailed discussion of the risk factors that could affect the Company's actual results, please refer to the risk factors identified in the Company's SEC reports, including but not limited to its Annual Report on Form 10-K for the year ended December 31, 2020 and its Quarterly Reports on Form 10-Q for the periods ended March 31, 2021 and June 30, 2021. Except as required by law, the Company undertakes no obligation to update publicly any forward-looking statements for any reason.

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