89bio's Phase 2b ENLIVEN Trial of Pegozafermin in Nonalcoholic Steatohepatitis (NASH) Achieved High Statistical Significance on Both Primary Histology Endpoints with Weekly (QW) and Every-Two-Week (Q2W) Dosing at 24 Weeks

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- 44mg Q2W dose had a placebo-adjusted effect size of 20% on at least one-stage fibrosis improvement without worsening of NASH (p=0.008) and 24% on NASH resolution without worsening of fibrosis (p=0.0005) -

- 30mg QW dose had a placebo-adjusted effect size of 19% on at least one-stage fibrosis improvement without worsening of NASH (p=0.008) and 21% on NASH resolution without worsening of fibrosis (p=0.0009) -

- 44mg Q2W and 30mg QW doses had at least one-stage fibrosis improvement without worsening of NASH at 3.5 times placebo rate and NASH resolution without worsening of fibrosis at 12 to 14 times placebo rate -

- Every-two-week dose data reinforces pegozafermin's potential to be a differentiated treatment ideally suited for a chronic, asymptomatic disease like NASH -

– Positive data from this rigorous trial supports advancement to Phase 3 –

– Conference call and webcast today at 5:00 a.m. PDT/8:00 a.m. EDT –

SAN FRANCISCO, March 22, 2023 (GLOBE NEWSWIRE) -- 89bio, Inc. (Nasdaq: ETNB), a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of liver and cardiometabolic diseases, today announced positive topline data from the Phase 2b ENLIVEN trial evaluating treatment with pegozafermin in patients with nonalcoholic steatohepatitis (NASH). In the study, both the 44mg every-two-week (Q2W) and 30mg weekly (QW) doses met, with high statistical significance, both the primary histology endpoints per the U.S. Food and Drug Administration (FDA) guidance on endpoints and statistical analysis.

The 44mg Q2W and the 30mg QW dose groups both demonstrated at least one-stage fibrosis improvement without worsening of NASH (27% and 26%, respectively) at 3.5 times the placebo rate (7%) and NASH resolution without worsening of fibrosis (26% and 23%, respectively), between 12 to 14 times the placebo rate (2%). The ENLIVEN study biopsies were scored independently by three expert blinded pathologists to minimize individual reader bias and inter-reader variability.

"I was pleased to see the impressive results on the critical histology endpoints and non-invasive tests in the ENLIVEN trial. I was especially encouraged by the significant improvement in fibrosis relative to placebo, as fibrosis is a key driver of NASH disease progression which can lead to cirrhosis and other negative clinical outcomes," said Arun J. Sanyal, MBBS, M.D., Professor, Departments of Medicine, Physiology, and Molecular Pathology, Virginia Commonwealth University. "These data are all the more significant given the rigor of the study methodology, including how the biopsies were read to reduce the impact of reader bias and variability. The ENLIVEN study followed a stringent analytical plan consistent with FDA guidance, and the low placebo response rate provides high confidence that this trial showed the true potential treatment effect of pegozafermin."

Table 1. Histological Outcome Measures* at Week 24

	Placebo (n=61)	15mg QW (n=14)	30mg QW (n=66)	44mg Q2W (n=51)
At least one-stage fibrosis improvement without worsening of NASH[1]	7%	22%	26%	27%
p-value		p=0.1	p=0.008	p=0.008
NASH resolution without worsening of fibrosis[2]	2%	37%	23%	26%
p-value		p<0.0001	p=0.0009	p=0.0005

* Multiple imputation analysis via Cochran-Mantel-Haenszel (CMH) test stratified by Type 2 Diabetes Mellitus status (yes vs. no) and fibrosis stage (F2 vs. F3)

[1] Improvement in liver fibrosis by ≥1 stage and no worsening of steatohepatitis defined as no increase in NAFLD Activity Score (NAS) for ballooning, inflammation, or steatosis (FDA draft guidance).

[2] Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning and any value for steatosis (FDA draft guidance).

Results were consistent and achieved statistical significance for the 44mg Q2W and 30mg QW dose groups using multiple imputation analysis (as shown in Table 1), completers analysis (patients who had baseline and end of treatment biopsies at week 24), and intention-to-treat (ITT) analysis (Phase 3 analysis plan). Using the completers analysis methodology on the fibrosis endpoint, the placebo-adjusted effect size for the 44mg Q2W and 30mg QW dose groups was 20% and 19%, respectively (p=0.008 and p=0.009, respectively), and on the NASH resolution endpoint, the placebo-adjusted effect size for the 44mg Q2W and 30mg QW dose groups was 24% and 21%, respectively (p=0.0004 and p=0.0009, respectively). Results were also statistically significant for both doses on both primary histology endpoints using an ITT analysis that imputes patients with missing biopsies as non-responders.

“The treatment effect and highly statistically significant results observed across the two FDA approvable histology endpoints is very encouraging and clearly support advancement into Phase 3 development,” said Rohit Loomba, M.D., MHSc, Director, NAFLD Research Center, University of California San Diego, and lead investigator of ENLIVEN. “These data are amongst one of the most consistent data sets for drugs in clinical development for NASH with a parallel improvement in both MRI-PDFF and ALT, and bodes well for the likelihood of success in the upcoming Phase 3 program. Given NASH is a chronic and often asymptomatic disease, I am excited to see the strong efficacy and tolerability results observed with every-two-week dosing as this would provide clinicians and patients multiple advantages.”

Meaningful changes were observed compared to baseline in liver fat and other key non-invasive tests (“NITs”) of liver inflammation and fibrosis. Improvements were also observed in HbA1c and across important lipid markers that are important factors for an effective treatment for NASH.

Table 2. Liver Non-Invasive Tests (NITs) Results [marker of]

	Placebo (n= 61)	**30mg QW (n= 66)**	**44 mg Q2W (n= 51)**
Mean Change from Baseline[1]			
MRI-PDFF [liver fat content][2]	-14%	-52%***	-54%***
ALT [liver damage]	-5%	-42%***	-32%***
VCTE kPA [liver stiffness]	0.7	-3.0**	-2.4**
Pro-C3 [collagen deposition]	6%	-18%***	-17%***
Responder Analysis[1]			
cT1 Responders[3] [liver inflammation/fibrosis]	14%	61%***	38%*

***p<0.001, **p<0.01, *p<0.05 versus placebo.

[1] Results for the 15mg QW dose on the NITs in table are (all are shown as changes from baseline except cT1 which is responder analysis): MRI-PDFF -33%; ALT -38%; VCTE kPA -1.6; Pro-C3 -5%; cT1 40%

[2] MRI-PDFF Analysis set in subjects with >10% liver fat (n=125)

[3] A patient is designated a cT1 responder with ≥80 msec reduction in hepatic fibro-inflammation as compared to baseline. cT1 analysis was performed at sites where available.

The ENLIVEN study also included 14 biopsy-confirmed NASH patients with compensated cirrhosis (F4 patients) who were not part of the primary analysis but continued in the study, 12 of which underwent a follow-up biopsy at week 24. In descriptive analysis of these data, five out of 11 pegozafermin-treated patients experienced at least one-stage improvement in liver fibrosis with no worsening of NASH by week 24 compared with zero out of one patient on placebo. An additional four pegozafermin-treated patients experienced at least one-stage improvement in liver fibrosis.

Pegozafermin continued to demonstrate a favorable safety and tolerability profile consistent with prior studies. Across dose groups, the most frequently reported treatment-related adverse events (AEs) were Grade 1 or 2 gastrointestinal events (diarrhea, nausea and increased appetite) most of which were mild to moderate in nature. Rates of treatment-related AEs observed were less frequent with the Q2W dosing regimen. A total of five patients treated with pegozafermin were discontinued due to treatment-related AEs all of which were Grade 2 compared with none for placebo. A single drug-related serious adverse event of uncomplicated pancreatitis was experienced by a patient in the 44mg Q2W dose group after a single dose of pegozafermin which resolved in a short time period.

“Our vision has been to develop a therapy that addresses the liver and cardiometabolic manifestations of this complex liver disease and do so in a well-tolerated and convenient way for seamless integration into patient lives,” said Hank Mansbach, Chief Medical Officer of 89bio. “These data demonstrate that we are on our way to making this vision a reality and highlight pegozafermin’s potentially differentiated profile based on its efficacy and tolerability results to date and convenient dosing interval. We are pleased to see that every-two-week dosing produced remarkably similar results to weekly dosing, which is expected to provide us optionality as we work with the FDA to advance pegozafermin into Phase 3 development.”

Today’s Conference Call Information
89bio will host a conference call and webcast at 5:00 a.m. PDT / 8:00 a.m. EDT today, March 22, 2023. Analysts and investors can participate in the conference call by dialing +1 (877) 407-0784 for domestic callers and +1 (1-201-689-8560) for international callers, using the conference ID 13737204. The webcast can be accessed live here and on the Events & Presentations page in the Investors section of the 89bio website, www.89bio.com. The webcast will be archived on 89bio’s website for at least 30 days after the conference call.

About ENLIVEN
ENLIVEN is a multicenter, randomized, double-blind, placebo-controlled Phase 2b trial designed to evaluate the safety and efficacy of weekly or every-two-week dosing of pegozafermin for the treatment of patients with fibrosis stage F2 - F3 NASH and NAS ≥ 4 for 48 weeks. In the study, 219 patients were randomized and dosed with pegozafermin 44mg Q2W, 30mg QW, 15mg QW, or placebo; 27 patients were prospectively excluded from the primary analysis population based on fibrosis stage or NAS score resulting in 192 patients in the full analysis set.

Primary outcomes measured were proportion of participants with resolution of NASH without worsening of fibrosis and proportion of participants with ≥1 stage decrease in fibrosis stage with no worsening of NASH at 24 weeks. Secondary measures included change from baseline in liver fat, liver enzymes, noninvasive markers of liver fibrosis, glycemic control, lipoproteins, and body weight as well as safety and tolerability measures. Study patients are being treated in a blinded extension phase for 24 weeks for a total treatment period of 48 weeks, with some placebo patients re-randomized to receive pegozafermin in the extension phase.

In the ENLIVEN study, biopsies were scored independently by three pathologists on the NAS components and fibrosis using the NASH-CRN criteria. Pathologists were blinded to the clinical trial participant, treatment, and study timepoint. There was protocol-specific training before and during the study to improve concordance between readers. The scores from each reader were then compared by an algorithm. If all three agreed on the score, that was recorded as the final score. If there was disagreement, the mode was selected and if that was not available the median or consensus call score was recorded. On average, full agreement or mode determined the final score for more than 95% of the biopsies.

About pegozafermin
Pegozafermin is a specifically engineered glycoPEGylated analog of fibroblast growth factor 21 (FGF21) being developed for the treatment of non-alcoholic steatohepatitis (NASH) and severe hypertriglyceridemia (SHTG). FGF21 is an endogenous hormone that modulates important drivers of lipid metabolism and NASH including triglyceride reduction, glycemic control, steatosis, inflammation and fibrosis. Pegozafermin was specifically engineered using a unique glycoPEGylated technology to extend the half-life while maintaining potency.

About 89bio
89bio is a clinical-stage biopharmaceutical company dedicated to the development and commercialization of innovative therapies for the treatment of liver and cardiometabolic diseases. The company's lead product candidate, pegozafermin, is currently being developed for the treatment of NASH and SHTG. The company is headquartered in San Francisco. For more information, visit www.89bio.com or follow the company on LinkedIn.

Forward-looking Statements
Certain statements in this press release may constitute "forward-looking statements" within the meaning of the federal securities laws, including, but not limited to, statements regarding the therapeutic potential, efficacy and clinical benefits of pegozafermin, the safety and tolerability profile of pegozafermin, pegozafermin as a potentially differentiated treatment for NASH, 89bio's clinical development plans for pegozafermin, including commencement of a Phase 3 trial based on results from the Phase 2b ENLIVEN trial, the potential dosing regimen of pegozafermin, if approved, and the relationship between the results from the positive data from Phase 2b ENLIVEN trial and results of future clinical studies. Words such as "may," "might," "will," "objective," "intend," "should," "could," "can," "would," "expect," "believe," "design," "estimate," "predict," "potential," "anticipate," "goal," "opportunity," "develop," "plan" or the negative of these terms, and similar expressions, or statements regarding intent, belief, or current expectations, are forward looking statements. While 89bio believes these forward-looking statements are reasonable, undue reliance should not be placed on any such forward-looking statements, which are based on information available to us on the date of this release. These forward-looking statements are based upon current estimates and assumptions and are subject to various risks and uncertainties (including, without limitation, those set forth in 89bio's filings with the SEC), many of which are beyond 89bio's control and subject to change. Actual results could be materially different. Risks and uncertainties include: expectations regarding the clinical benefit and safety of pegozafermin; expectations regarding the initiation of the first Phase 3 trial in NASH; 89bio's ability to execute on its strategy; positive results from a clinical study may not necessarily be predictive of the results of future or ongoing clinical studies; 89bio's substantial dependence on the success of it lead product candidate; competition from competing products; expectations regarding FDA approval and feedback; the effect of the COVID-19 pandemic on 89bio's clinical trials and business operations, and the impact of general economic, health, industrial or political conditions in the United States or internationally; the sufficiency of 89bio's capital resources and its ability to raise additional capital; and other risks and uncertainties identified in 89bio's Annual Report on Form 10-K for the year ended December 31, 2022 and other subsequent disclosure documents filed with the SEC. 89bio claims the protection of the Safe Harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. 89bio expressly disclaims any obligation to update or alter any statements whether as a result of new information, future events or otherwise, except as required by law.

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