Dyne Therapeutics Announces Positive Initial Clinical Data from ACHIEVE Trial in DM1 Patients and DELIVER Trial in DMD Patients Demonstrating Promise of the FORCE™ Platform in Developing Therapeutics for Rare Muscle Diseases

January 3, 2024

- In Phase 1/2 ACHIEVE Trial, DYNE-101 Demonstrated Dose-Dependent Splicing Correction, Muscle Delivery and DMPK Knockdown -

- All Evaluable Patients in the 3.4 mg/kg Cohort Treated with DYNE-101 Q4W Demonstrated Consistent Splicing Correction with a 19% Mean Improvement Across 22-Gene Panel at 3 Months -

- Improvement in Myotonia (vHOT) as well as Fatigue (MDHI) Observed in Lowest Dose ACHIEVE Cohort at 6 Months -

- In Phase 1/2 DELIVER Trial, DYNE-251 Showed 0.88% Mean Dystrophin Expression at 6 Months in 5 mg/kg Cohort Administered Monthly; Greater Than 2.5 Times Higher Dystrophin Than Reported for Weekly Administered Current Standard of Care[1] -

- Favorable Safety Profile for DYNE-101 and DYNE-251 Has Supported Dose Escalation; Enrollment Complete in 5.4 mg/kg Cohort of ACHIEVE Trial and 20 mg/kg Cohort of DELIVER Trial -

- Virtual Webcast Event Today, Wednesday, January 3 at 8:00 a.m. ET -

WALTHAM, Mass., Jan. 03, 2024 (GLOBE NEWSWIRE) -- Dyne Therapeutics, Inc. (Nasdaq: DYN), a clinical-stage muscle disease company focused on advancing innovative life-transforming therapeutics for people living with genetically driven diseases, today announced positive initial clinical data from its ACHIEVE trial of DYNE-101 in patients with myotonic dystrophy type 1 (DM1) and its DELIVER trial of DYNE-251 in patients with Duchenne muscular dystrophy (DMD) who are amenable to exon 51 skipping.

“We are excited that Dyne’s first clinical data in two programs have demonstrated proof-of-concept and validated the promise of the FORCE™ platform in developing targeted therapeutics for rare muscle diseases. In addition to the opportunity with our co-lead programs, this clinical validation reinforces the potential of FORCE to deliver for patients in other areas, including building a global DMD franchise, addressing FSHD and exploring diseases involving the CNS,” said Joshua Brumm, Dyne’s president and chief executive officer. “The safety profiles for both DYNE-101 and DYNE-251 have supported dose escalation to a combined 10 cohorts and the administration of nearly 600 doses across both the ACHIEVE and DELIVER trials. This positions us to optimize dose and dose regimen in both trials with the goal of initiating registrational cohorts as we end 2024. We anticipate reporting data for multiple, higher dose cohorts from both trials in the second half of 2024, while continuing to pursue expedited regulatory pathways and working to help address the urgent need for therapeutics for people living with DM1 and Duchenne.”

“These compelling initial data from our ACHIEVE and DELIVER trials highlight the exciting opportunity we have to advance our investigational therapeutics for devastating diseases with no or limited treatment options. DYNE-101 demonstrated early dose-dependent results, including in correction of splicing, the key biomarker for DM1, as well as meaningful improvement in myotonia at the lowest dose. Treatment with DYNE-251 surpassed the level of dystrophin production reported for the standard of care for DMD exon 51 with a fraction of the dose. Underpinning these results are favorable safety profiles, which are critical in the development of therapies for chronic diseases,” said Wildon Farwell, M.D., MPH, Dyne’s chief medical officer. “We are grateful to the participants, clinicians and the community for their ongoing partnership as we collectively strive to transform the treatment of rare muscle diseases.”

Phase 1/2 ACHIEVE Trial of DYNE-101 in DM1

The initial efficacy assessment of the DYNE-101 ACHIEVE trial is based on data from 32 adult DM1 patients enrolled in the randomized, placebo-controlled multiple ascending dose (MAD) portion of the trial, including 6-month data from the 1.8 mg/kg (approximate ASO dose) cohort (n=16) and 3-month data from the 3.4 mg/kg Q4W cohort (n=16). In each of these cohorts, participants were randomized to receive either DYNE-101 (n=6) or placebo (n=4) once every four weeks or participants in the recovery arm (n=6) received two doses of DYNE-101 followed by placebo for the remainder of the MAD portion of the trial.

In the ACHIEVE trial, DYNE-101 demonstrated a dose-dependent splicing correction and increase in muscle delivery and *DMPK* knockdown while also showing functional improvement in myotonia. Key initial findings from ACHIEVE include:

- **Muscle Delivery:** Administration of 3.4 mg/kg of DYNE-101 Q4W demonstrated a mean ASO muscle concentration of 21.5 ng/g at 3 months, while administration of 1.8 mg/kg Q4W showed a mean ASO muscle concentration of 10.0 ng/g at 3 months.
- ***DMPK* Knockdown:** Evaluable patients in the 3.4 mg/kg Q4W group had a 40% mean *DMPK* knockdown from baseline compared to 25% in patients in the 1.8 mg/kg Q4W group at 3 months.
- **Splicing:** Evaluable patients treated with 3.4 mg/kg Q4W of DYNE-101 had a 19% mean splicing correction from baseline across a broad, 22-gene panel at 3 months, with all evaluable participants experiencing an improvement. Patients in the 1.8 mg/kg Q4W group at 3 months had a 13% mean splicing correction.
- **Function:** Patients treated with 1.8 mg/kg of DYNE-101 Q4W had a mean 3.8 second benefit in myotonia at 6 months as measured by video hand opening time (vHOT). Myotonia, which is difficulty in relaxing muscles, is a common symptom of DM1 patients.

- **Patient Reported Outcome (PRO):** Patients in the DYNE-101 1.8 mg/kg Q4W group experienced an overall improvement at 6 months in the Myotonic Dystrophy Health Index (MDHI), including the fatigue subscale, suggesting potential benefit of DYNE-101 in the CNS.

Safety and tolerability data in this initial assessment of the ACHIEVE trial are based on 45 patients enrolled through the 5.4 mg/kg Q8W cohort of the MAD portion. As of the data cutoff date[2], DYNE-101 has demonstrated a favorable safety profile. The majority of treatment-emergent adverse events were mild or moderate and no related serious treatment-emergent adverse events have been identified. In addition, no participants demonstrated treatment-emergent anemia, and no clinically meaningful changes were observed in kidney or liver parameters. All participants who have completed the MAD portion of ACHIEVE have enrolled in the 24-week open-label extension (OLE).

Enrollment is complete through the 5.4 mg/kg Q8W cohort of the ACHIEVE trial (48 total patients enrolled), and approximately 300 doses have been administered to date, supporting dose escalation up to 6.8 mg/kg. Dyne anticipates providing its next clinical data update from the ACHIEVE trial in the second half of 2024.

Phase 1/2 DELIVER Trial of DYNE-251 in DMD

The initial efficacy assessment of the DYNE-251 DELIVER trial is based on 6-month data from 6 male patients with DMD amenable to exon 51 skipping enrolled in the 5 mg/kg (approximate PMO dose) cohort of the randomized, placebo-controlled MAD portion of the trial. Patients were randomized to receive either DYNE-251 (n=4) or placebo (n=2) once every four weeks. Once every 4-week administration of DYNE-251 reached levels of dystrophin expression, exon skipping and percent dystrophin positive fibers that exceeded levels reported in a clinical trial for the current weekly standard of care for DMD exon 51, eteplirsen, at 6 months[1] with a 24-fold lower total PMO dose. Key initial findings from DELIVER include:

- **Muscle delivery:** DYNE-251 showed a mean 657 ng/g PMO muscle drug concentration at 6 months.
- **Exon 51 skipping:** DYNE-251 demonstrated a mean absolute exon skipping level of 0.90% and a 0.80% change from baseline at 6 months. The current standard of care, eteplirsen, which is administered weekly, showed a 0.59% mean absolute exon skipping level and a 0.40% change from baseline at 6 months. [1]
- **Dystrophin expression measured by Western blot:** Patients treated with DYNE-251 had a mean absolute dystrophin level of 0.88% of normal and a 0.28% change from baseline at 6 months. Eteplirsen reached a mean absolute dystrophin level of 0.30% of normal and a 0.06% change from baseline at 6 months.[1]
- **Percent dystrophin positive fibers:** DYNE-251 demonstrated 22.2% mean level of dystrophin positive fibers (PDPF) and a 19.8% change from baseline at 6 months. Eteplirsen showed a 19.6% mean level of PDPF and a 10.7% change from baseline at 6 months.[1]

Safety and tolerability data in the DELIVER trial are based on 37 patients enrolled through the 20 mg/kg cohort of the MAD portion. As of the data cutoff date[2], DYNE-251 has demonstrated a favorable safety profile. The majority of treatment-emergent adverse events were mild or moderate and no related serious adverse events have been identified. In addition, no participants demonstrated treatment-emergent anemia, and no clinically meaningful changes were observed in kidney parameters or electrolytes, including magnesium. All participants who have completed the MAD portion of DELIVER have enrolled in the 24-week OLE.

Enrollment is complete through the 20 mg/kg cohort of the DELIVER trial (40 total patients enrolled) and approximately 275 doses have been administered to date, supporting dose escalation up to 40 mg/kg. Dyne anticipates providing its next clinical data update from the DELIVER trial in the second half of 2024.

Virtual Event

Dyne will host a live video webcast event, “Achieving the Promise of FORCE to Deliver for Patients,” to discuss these ACHIEVE and DELIVER data today, January 3, 2024, at 8:00 a.m. ET. Dyne’s leadership team will be joined by two leading neuromuscular disease experts: Valeria A. Sansone, M.D., Ph.D., and Perry Shieh, M.D., Ph.D. Dr. Sansone is Clinical and Scientific Director at the Clinical Center NeMO in Milan, Professor of Neurology, University of Milan, and a principal investigator for the ACHIEVE trial. Dr. Shieh is Professor of Neurology and Pediatrics at the David Geffen School of Medicine at UCLA, a Neurologist at the Ronald Reagan UCLA Medical Center in Los Angeles, and a principal investigator for the DELIVER trial.

The live webcast will be available in the Events & Presentations page of the Investors & Media section of Dyne’s website and a replay will be accessible for 90 days following the presentation. An accompanying slide presentation will also be available. To access the presentation, register for the live webcast and replay, please visit https://investors.dyne-tx.com/news-and-events/events-and-presentations.

About ACHIEVE

ACHIEVE is a Phase 1/2 global clinical trial evaluating DYNE-101, consisting of a 24-week multiple ascending dose (MAD) randomized placebo-controlled period, a 24-week open-label extension and a 96-week long-term extension. The trial, which is designed to be registrational, is enrolling adult patients with myotonic dystrophy type 1 (DM1) who are 18 to 49 years of age. The primary endpoints are safety and tolerability, with secondary endpoints of pharmacokinetics and pharmacodynamics, including change from baseline in splicing, as well as measures of muscle strength and function. For more information on the ACHIEVE trial, visit https://www.clinicaltrials.gov/ (NCT05481879).

About DYNE-101

DYNE-101 is an investigational therapeutic being evaluated in the Phase 1/2 global ACHIEVE clinical trial for people living with DM1. DYNE-101 consists of an antisense oligonucleotide (ASO) conjugated to a fragment antibody (Fab) that binds to the transferrin receptor 1 (TfR1) which is highly expressed on muscle. It is designed to enable targeted muscle tissue delivery with the goal of reducing toxic *DMPK* RNA in the nucleus, releasing splicing proteins, allowing normal mRNA processing and translation of normal proteins, and potentially stopping or reversing the disease progression. DYNE-101 has been granted orphan drug designation by the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of DM1.

About Myotonic Dystrophy Type 1 (DM1)

DM1 is a rare, progressive, genetic disease that affects skeletal, cardiac and smooth muscle. It is a monogenic, autosomal dominant disease caused by an abnormal trinucleotide expansion in a region of the *DMPK* gene. This expansion of CTG repeats causes toxic RNA to cluster in the nucleus, forming nuclear foci and altering the splicing of multiple proteins essential for normal cellular function. This altered splicing, or spliceopathy, results in a wide range of symptoms. People living with DM1 typically experience myotonia and progressive weakness of major muscle groups, which can affect mobility, breathing, heart function, speech, digestion and vision as well as cognition. DM1 is estimated to affect more than 40,000 people in the United States and over 74,000 people in Europe, but there are currently no approved disease-modifying therapies.

About the DELIVER Trial

DELIVER is a Phase 1/2 global clinical trial evaluating DYNE-251, consisting of a 24-week multiple ascending dose (MAD) randomized placebo-controlled period, a 24-week open-label extension and a 96-week long-term extension. The trial, which is designed to be registrational, is enrolling ambulant and non-ambulant males with Duchenne muscular dystrophy who are ages 4 to 16 and have mutations amenable to exon 51 skipping. The primary endpoints are safety, tolerability and change from baseline in dystrophin levels as measured by Western blot. Secondary endpoints include measures of muscle function, exon skipping and pharmacokinetics. For more information on the DELIVER trial, visit https://www.clinicaltrials.gov/ (NCT05524883).

About DYNE-251

DYNE-251 is an investigational therapeutic being evaluated in the Phase 1/2 global DELIVER clinical trial for people living with DMD who are amenable to exon 51 skipping. DYNE-251 consists of a phosphorodiamidate morpholino oligomer (PMO) conjugated to a fragment antibody (Fab) that binds to the transferrin receptor 1 (TfR1) which is highly expressed on muscle. It is designed to enable targeted muscle tissue delivery and promote exon skipping in the nucleus, allowing muscle cells to create a truncated, functional dystrophin protein, with the goal of stopping or reversing disease progression. DYNE-251 has been granted fast track, orphan drug and rare pediatric disease designations by the U.S. Food and Drug Administration for the treatment of DMD mutations amenable to exon 51 skipping.

In addition to DYNE-251, Dyne is building a global DMD franchise and has preclinical programs targeting other exons, including 53, 45 and 44.

About Duchenne Muscular Dystrophy (DMD)

DMD is a rare disease caused by mutations in the gene that encodes for dystrophin, a protein critical for the normal function of muscle cells. These mutations, the majority of which are deletions, result in the lack of dystrophin protein and progressive loss of muscle function. DMD occurs primarily in males and affects an estimated 12,000 to 15,000 individuals in the U.S. and 25,000 in Europe. Loss of strength and function typically first appears in pre-school age boys and worsens as they age. As the disease progresses, the severity of damage to skeletal and cardiac muscle often results in patients experiencing total loss of ambulation by their early teenage years and includes worsening cardiac and respiratory symptoms and loss of upper body function by the later teens. There is no cure for DMD and currently approved therapies provide limited benefit.

About Dyne Therapeutics

Dyne Therapeutics is a clinical-stage muscle disease company focused on advancing innovative life-transforming therapeutics for people living with genetically driven diseases. With its proprietary FORCE™ platform, Dyne is developing modern oligonucleotide therapeutics that are designed to overcome limitations in delivery to muscle tissue. Dyne has a broad pipeline for serious muscle diseases, including clinical programs for myotonic dystrophy type 1 (DM1) and Duchenne muscular dystrophy (DMD) and a preclinical program for facioscapulohumeral muscular dystrophy (FSHD). For more information, please visit https://www.dyne-tx.com, and follow us on X, LinkedIn and Facebook.

Forward-Looking Statements

This press release contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this press release, including statements regarding Dyne's strategy, future operations, prospects and plans, objectives of management, the potential of the FORCE platform, the anticipated timelines for reporting data from the DYNE-101 and DYNE-251 clinical trials, and plans to optimize dose and dose regimen for DYNE-101 and DYNE-251, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "predict," "project," "potential," "should," or "would," or the negative of these terms, or other comparable terminology are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Dyne may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; the timing of and Dyne's ability to initiate and enroll patients in clinical trials; whether results from preclinical studies and initial data from early clinical trials will be predictive of the final results of the clinical trials or future trials; whether Dyne's cash resources will be sufficient to fund the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; as well as the risks and uncertainties identified in Dyne's filings with the Securities and Exchange Commission (SEC), including the Company's most recent Form 10-Q and in subsequent filings Dyne may make with the SEC. In addition, the forward-looking statements included in this press release represent Dyne's views as of the date of this press release. Dyne anticipates that subsequent events and developments will cause its views to change. However, while Dyne may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Dyne's views as of any date subsequent to the date of this press release.

1. No head-to-head trials have been conducted comparing DYNE-251 to eteplirsen. Eteplirsen data may not be directly comparable due to differences in trial protocols, dosing regimens and patient populations. Accordingly, these cross-trial comparisons may not be reliable. Eteplirsen data from *J Neuromuscul Dis*. 2021; 8(6): 989–1001

2. Safety data as of December 6, 2023

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