Wave Life Sciences Highlights Pipeline Progress and Expansion Leveraging New PN Backbone Chemistry Modifications

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Three clinical trials to begin in 2021 with compounds containing Wave's novel PN backbone chemistry modifications

Data from ongoing PRECISION-HD and OLE clinical trials for Huntington's disease expected by end of 1Q 2021

Potential best-in-class ADAR editing platform capability continues to advance, with validation of proprietary in vivo modeling system and delivery of in vivo alpha-1 antitrypsin deficiency data expected 1H 2021

CAMBRIDGE, Mass., Jan. 11, 2021 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced key upcoming milestones for 2021, including the initiation of new clinical trials, expected data readouts, and continued advancement of Wave's proprietary discovery and drug development platform, PRISM™.

"2020 was a year of focused and formative progress for Wave, which culminated with submissions of clinical trial applications for two new programs. We continued to deliver on our ambitious goals despite the pandemic and are now on a course to unlock significant value from our pipeline and platform starting in 2021. Our research and clinical teams have made impressive headway across our portfolio of investigational stereopure oligonucleotides, and today we are advancing more than a dozen silencing, splicing and editing programs across various stages of development," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "This year, we plan to initiate clinical trials for three compounds containing PN backbone chemistry modifications, which have been shown preclinically to increase potency, exposure and durability across various modalities. With our three new trials, we'll be able to more fully assess the potential of this novel chemistry advancement for the field of genetic medicine. They also offer the opportunity to deepen our impact in Huntington's disease and extend our research to others struggling with amyotrophic lateral sclerosis, frontotemporal dementia, and neuromuscular diseases."

"We also plan to deliver comprehensive data results from the ongoing PRECISION-HD trials late in the first quarter to enable a decision regarding potential Phase 3 development for WVE-120101 and WVE-120102, our first-generation Huntington's disease candidates. Lastly, we continue to invest in PRISM and look forward to contributing new findings in oligonucleotide design and delivery. Taken together, these advancements across our pipeline and platform are setting us up to become a leading genetic medicines company focused on delivering a new era of RNA therapeutics."

Advancing three clinical programs utilizing compounds containing Wave's novel PN backbone chemistry modifications to first-in-human studies: Wave expects to initiate dosing in three proof-of-concept studies in 2021, which will assess target engagement, impact on key disease biomarkers, and initial safety for WVE-003 in Huntington's disease (HD), WVE-004 in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), and WVE-N531 in Duchenne muscular dystrophy (DMD). All three compounds have novel designs incorporating PN backbone chemistry modifications, an advancement from Wave's PRISM platform.

WVE-003 for HD: WVE-003 is Wave's first HD candidate to use PN backbone chemistry modifications and is designed to selectively target the mRNA transcript produced by the mutant allele of the *huntingtin* (mHTT) gene, while leaving the wild-type (wtHTT) protein relatively intact. While the primary driver of HD is believed to be a dominant gain of function in mHTT protein, the concurrent loss of function of wtHTT protein may also be an important component of the pathophysiology of HD. A growing body of scientific evidence suggests that preserving as much of the essential wtHTT protein as possible is important for favorable health outcomes over a lifetime with the disease.

- In December 2020, Wave submitted a clinical trial application (CTA) for WVE-003. Wave expects to initiate dosing in HD patients with SNP3 in 2021.
- The WVE-003 program is leveraging learnings and clinical expertise gained through the ongoing Phase 1b/2a PRECISION-HD studies, as well as learnings in oligonucleotide design gained through the PRISM platform.

WVE-004 for ALS and FTD: WVE-004 is an investigational variant-selective silencing candidate designed to selectively target the transcript variants containing a hexanucleotide repeat expansion (G4C2) in the *C9orf72* gene, while sparing the healthy C9orf72 protein. G4C2 expansions are one of the most common genetic causes of the sporadic and inherited forms of ALS and FTD.

- In December 2020, Wave submitted a CTA for WVE-004. Wave expects to initiate dosing in ALS and FTD patients with G4C2 expansions in 2021.

WVE-N531 for DMD: Based on compelling preclinical data, Wave is advancing WVE-N531 to explore exon skipping in dystrophic muscle. WVE-N531 was developed as an investigational treatment for DMD in boys amenable to exon 53 skipping and will be Wave's first splicing candidate incorporating PN backbone chemistry modifications to be assessed in the clinic.

- Wave expects to submit a CTA for WVE-N531 by the end of the first quarter in 2021.

PRECISION-HD clinical trials in HD: The PRECISION-HD1 and PRECISION-HD2 Phase 1b/2a and open label extension (OLE) trials evaluating WVE-120101 and WVE-120102 (respectively) in HD are ongoing. WVE-120101 and WVE-120102 are investigational stereopure oligonucleotides designed to selectively target the mHTT mRNA transcript, thereby leaving the wtHTT protein relatively intact.

- The 32 mg cohorts added to both PRECISION-HD trials in 2020 are fully enrolled and dosing is underway in the multidose portions.
- At the end of the first quarter, Wave expects to report data from both PRECISION-HD trials as well as available data from both ongoing OLE trials. These data are expected to enable a decision regarding potential Phase 3 development.

- º The analysis of PRECISION-HD2 will be comprised of biomarker and safety data from all cohorts, including all patients from the 32 mg cohort.
- º The analysis of PRECISION-HD1 will be comprised of biomarker and safety data from all completed cohorts, including all patients from the 16 mg cohort. Due to clinical site restrictions related to the COVID-19 pandemic, the last two patients in the PRECISION-HD1 32 mg cohort are currently scheduled to complete dosing in March 2021.

- The OLE trials have been enrolling patients from PRECISION-HD2 since October 2019 and PRECISION-HD1 since February 2020. The vast majority of eligible patients from the PRECISION-HD trials have enrolled in the OLEs.
  - º Patients in the PRECISION-HD OLEs have begun transitioning to the 32 mg doses.
  - º PRECISION-HD2 patients have received up to 16 monthly doses of 8 or 16 mg of WVE-120102 in the OLE.
  - º PRECISION-HD1 patients have received up to 9 monthly doses of 8 or 16 mg of WVE-120101 in the OLE.

ADAR-mediated RNA editing (ADAR editing) platform capability: Wave's novel RNA editing modality also incorporates PN backbone chemistry modifications and uses endogenous ADAR (adenosine deaminases acting on RNA) enzymes via free uptake (non-viral, no nanoparticles) of A-to-I (G) RNA editing oligonucleotides. ADAR editing has the potential to unlock many new therapeutic applications, including restoration, modification or upregulation of proteins.

To support the advancement of best-in-class RNA editing candidates, Wave is developing a proprietary *in vivo* modeling system which crosses humanized ADAR mice with transgenic disease models. Wave expects to validate this modeling system in the first half of 2021.

SERPINA1 program for alpha-1 antitrypsin deficiency (AATD) with ADAR editing: In November 2020, Wave announced that its first ADAR editing program would be for AATD, which will target the G-to-A disease-causing mutation in mRNA coded by the *SERPINA1* Z allele. By correcting the single RNA base mutation, ADAR editing may provide an ideal approach for increasing circulating levels of wild-type AAT protein and reducing aggregation in the liver, thus simultaneously addressing both the lung and liver manifestations of the disease.

In a primary hepatocyte *SERPINA1* Z cell model, Wave demonstrated that editing the Z transcript back to wild-type restored native protein folding and secretion from hepatocytes. Wave expects to deliver *in vivo* data supporting the continued development of its AATD program in the first half of 2021.

Central nervous system (CNS) programs in collaboration with Takeda: Wave is leveraging learnings from PRISM to design additional stereopure oligonucleotides with optimized profiles for CNS indications, including in Alzheimer's disease, Parkinson's disease and others, as part of its ongoing collaboration with Takeda. Wave is utilizing PN backbone chemistry modifications to produce compelling *in vivo* data and progress multiple preclinical programs.

About Huntington's disease
Huntington's disease (HD) is a debilitating and ultimately fatal autosomal dominant neurological disorder, characterized by cognitive decline, psychiatric illness and chorea. HD causes nerve cells in the brain to deteriorate over time, affecting thinking ability, emotions and movement. HD is caused by an expanded cytosine-adenine-guanine (CAG) triplet repeat in the huntingtin (HTT) gene that results in production of mutant HTT (mHTT) protein. Accumulation of mutant HTT causes progressive loss of neurons in the brain. Wild-type, or healthy, HTT (wtHTT) protein is critical for neuronal function and suppression may have detrimental long-term consequences. Approximately 30,000 people in the United States have symptomatic HD and more than 200,000 others are at risk for inheriting the disease. There are currently no approved disease-modifying therapies available. Between Wave's three investigational molecules, the company has the potential to provide allele-selective therapeutic options for up to 80% of people with HD.

About amyotrophic lateral sclerosis and frontotemporal dementia
Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disease in which the progressive degeneration of motor neurons in the brain and spinal cord leads to the inability to initiate or control muscle movement. People with ALS may lose the ability to speak, eat, move and breathe. ALS affects as many as 20,000 people in the United States.

Frontotemporal dementia (FTD) is a fatal, neurodegenerative disease in which progressive nerve cell loss in the brain's frontal lobes and temporal lobes leads to personality and behavioral changes, as well as the gradual impairment of language skills. It is the second most common form of early-onset dementia after Alzheimer's disease in people under the age of 65. FTD affects as many as 70,000 people in the United States.

ALS and FTD can be caused by mutations in the *C9orf72* gene, which provides instructions for making protein found in various tissues, including nerve cells in the cerebral cortex and motor neurons. In the U.S., mutations of the *C9orf72* gene are present in approximately 40% of familial ALS cases and 8% to 10% of sporadic ALS cases. In FTD, the mutations appear in 38% of familial cases and 6% of sporadic cases.

About Duchenne muscular dystrophy (DMD)
DMD is a fatal X-linked genetic neuromuscular disorder caused predominantly by out-of-frame deletions in the dystrophin gene, resulting in absent or defective dystrophin protein. Dystrophin protein is needed for normal muscle maintenance and operation. Because of the genetic mutations in DMD, the body cannot produce functional dystrophin, which results in progressive and irreversible loss of muscle function, including the heart and lungs. Worldwide, DMD affects approximately one in 5,000 newborn boys.

About PRISM™
PRISM is Wave Life Sciences' proprietary discovery and drug development platform that enables genetically defined diseases to be targeted with stereopure oligonucleotides across multiple therapeutic modalities, including silencing, splicing and editing. PRISM combines the company's unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, the company continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles.

About Wave Life Sciences
Wave Life Sciences (Nasdaq: WVE) is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines across multiple therapeutic modalities using PRISM, the company's proprietary discovery and drug development platform that enables the precise design, optimization and production of stereopure oligonucleotides. Driven by a resolute sense of urgency, the Wave team is targeting a broad range of genetically defined diseases so that patients and families may realize a brighter future. To find out more, please visit www.wavelifesciences.com and follow Wave on Twitter @WaveLifeSci.

Forward-Looking Statements
This press release contains forward-looking statements concerning our goals, beliefs, expectations, strategies, objectives and plans, and other statements that are not necessarily based on historical facts, including statements regarding the following, among others: the anticipated commencement, patient enrollment, data readouts and completion of our clinical trials, and the announcement of such events; the protocol, design and endpoints of our ongoing and planned clinical trials; the future performance and results of our programs in clinical trials; future preclinical activities

and programs; regulatory submissions; the progress and potential benefits of our collaborations with partners; the potential of our *in vitro* and *in vivo* preclinical data to predict the behavior of our compounds in humans; our identification of future candidates and their therapeutic potential; the anticipated therapeutic benefits of our potential therapies, including our compounds containing PN chemistry, compared to others; our ability to design compounds using multiple modalities and the anticipated benefits of that model; the potential benefits of PRISM and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the potential benefits of our novel ADAR-mediated RNA editing platform capabilities compared to others; and the benefit of nucleic acid therapeutics generally. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including the following: our ability to finance our drug discovery and development efforts and to raise additional capital when needed; the ability of our preclinical programs to produce data sufficient to support our clinical trial applications and the timing thereof; the clinical results of our programs, which may not support further development of product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; our effectiveness in managing future clinical trials and regulatory interactions; the effectiveness of PRISM, including PN backbone chemistry modifications and ADAR editing; the effectiveness of our novel ADAR-mediated RNA editing platform capability; the continued development and acceptance of oligonucleotides as a class of medicines; our ability to demonstrate the therapeutic benefits of our candidates in clinical trials, including our ability to develop candidates across multiple therapeutic modalities; our dependence on third parties, including contract research organizations, contract manufacturing organizations, collaborators and partners; and competition from others developing therapies for similar indications, as well as the information under the caption “Risk Factors” contained in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in other filings we make with the SEC from time to time. We undertake no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances**.**

Investor Contact:
Kate Rausch
617-949-4827
krausch@wavelifesci.com

Media Contact:
Alicia Suter
617-949-4817
asuter@wavelifesci.com

Source: Wave Life Sciences USA, Inc.