Wave Life Sciences Reports First Quarter 2022 Financial Results and Provides Business Update

May 12, 2022

Delivered first clinical data demonstrating target engagement and translation of PN chemistry's impact in clinic; Adapting ongoing Phase 1b/2a FOCUS-C9 clinical trial to optimize dose level and frequency, with additional single and multidose data expected throughout 2022

Clinical data also expected in 2022 from Huntington's disease (WVE-003) and Duchenne muscular dystrophy (WVE-N531) trials

Robust preclinical datasets for first-in-class AATD program demonstrate restoration of levels of AAT relevant for potential lung protection and reduction of liver-damaging aggregates with GalNAc AIMers; IND enabling toxicology studies for lead AATD candidate on-track to initiate in 3Q 2022

Wave to host investor conference call and webcast at 8:30 a.m. ET today

CAMBRIDGE, Mass., May 12, 2022 (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 financial results for the first quarter ended March 31, 2022 and provided a business update.

"Thus far in 2022, Wave has achieved several important milestones, with the highlight being our first clinical data demonstrating successful target engagement with WVE-004 in the ongoing FOCUS-C9 clinical trial for C9-ALS and C9-FTD. We observed potent and durable reductions of the poly(GP) biomarker with low single doses of WVE-004, demonstrating that our preclinical data for PN-containing oligonucleotides are beginning to translate in the clinic," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "These initial results are compelling and reinforce the potential of our unique oligonucleotide platform and our expectation to see the advantages of PN chemistry manifest in our other pipeline programs. We also continue to rapidly advance our WVE-003 program for HD and WVE-N531 program for DMD towards initial data updates later this year. We are also pleased with the recognition we are receiving with our endogenous RNA editing modality, which is being highlighted through scientific presentations and our recent Nature Biotechnology publication. Alpha-1 antitrypsin deficiency (AATD) is uniquely suited for an RNA editing therapeutic, and our AATD program is rapidly advancing towards clinical development with IND enabling studies on track to initiate in the third quarter of this year."

Recent Pipeline and Business Highlights

Announced first clinical data from ongoing FOCUS-C9 trial of WVE-004 for C9-ALS and C9-FTD demonstrating potent and durable target engagement with low, single doses

- In April 2022, Wave announced a positive update to its ongoing FOCUS-C9 trial of WVE-004 (stereopure, PN-modified silencing oligonucleotide) for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD). The update was driven by the observation of potent and durable reductions of poly(GP) dipeptide repeat proteins in cerebrospinal fluid (CSF), a C9-ALS/C9-FTD disease biomarker that, when reduced in CSF, indicates WVE-004's engagement of target in the brain and spinal cord. Based on the poly(GP) reduction data, the observation period for single dose cohorts is being extended and additional patients are being enrolled into the trial to further characterize depth of knockdown, durability and longer-term safety profile. Wave plans to share this recently announced clinical data in an oral presentation at the upcoming European Network to Cure ALS (ENCALS) Meeting in Edinburgh, Scotland, which is taking place June 1 – 3, 2022.
- FOCUS-C9 (NCT04931862) is an adaptive trial that was designed to rapidly optimize dose level and frequency based on early indicators of target engagement. WVE-004 is designed to selectively target transcript variants containing a hexanucleotide repeat expansion (G_4C_2) associated with the C9orf72 gene for the treatment of C9-ALS and C9-FTD, thereby reducing pathological mRNA products and toxic DPR proteins, including poly(GP). Planning is underway to initiate an open-label extension (OLE) clinical trial in mid-2022.

Continued to advance clinical trials evaluating WVE-003 targeting SNP3 for Huntington's disease (HD) and WVE-N531 for Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping

- WVE-003 for HD (PN-modified silencing oligonucleotide) is being evaluated in the ongoing, adaptive, double-blind Phase 1b/2a SELECT-HD (NCT05032196) clinical trial. WVE-003 is designed to selectively target the mutant allele of the huntingtin (mHTT) gene, while leaving the wild-type (healthy) HTT (wtHTT) protein relatively intact.
- WVE-N531 for DMD (PN-modified splicing oligonucleotide) is being evaluated in an open-label, intra-patient dose escalation (NCT04906460) clinical trial. Dose escalation is ongoing and being guided by tolerability and plasma PK, with possible cohort expansion informed by an assessment of drug distribution in muscle and biomarkers, including dystrophin, following multiple doses of WVE-N531.

Presented preclinical AIMer data for AATD program supporting the potential for a novel, first-in-class, subcutaneous therapeutic to address

both lung and liver manifestations of disease

- In March 2022, preclinical data for Wave's Alpha-1 antitrypsin deficiency (AATD) AIMer program demonstrating restoration of functional AAT protein and reduction of liver aggregates in a transgenic mouse model was shared in a Featured Session at the 7th Annual Oligonucleotide & Precision Therapeutics (OPT) Congress. At 19 weeks, GalNAc-conjugated SERPINA1 AIMers resulted in approximately 60% RNA editing of SERPINA1 transcript and circulating serum AAT levels (18.5 uM) in AIMer administered mice that were approximately 5-fold greater than PBS-administered controls.
- Today, May 12, 2022, at the TIDES USA: Oligonucleotide & Peptide Therapeutics Conference, Wave is presenting additional preclinical data that confirmed restored AAT protein in serum was functional at week 19, as measured by a 3-fold increase in neutrophil elastase inhibition over placebo control. A histological analysis indicated reduction of liver aggregates in a transgenic mouse model at 19 weeks with AIMers. Wave will also share these data in an oral presentation at the American Society of Gene and Cell Therapy (ASGCT) 25th Annual Meeting taking place May 16 – 19, 2022 in Washington, D.C.

Scientific publications highlight breadth and potential of Wave's therapeutic oligonucleotide platform, including novel PN-chemistry and RNA editing modality

- In March 2022, preclinical proof-of-concept data for Wave's novel ADAR-mediated RNA base editing modality was published in the journal *Nature Biotechnology* – the first scientific publication to report that RNA base editing in NHPs can be achieved with a simplified oligonucleotide approach. Data reported include an *in vivo* study where Wave's GalNAc-conjugated A-to-I(G) RNA base editing oligonucleotides ("AIMers") yielded up to 50% editing of ACTB (Beta-actin) transcript in the liver of non-human primates (NHPs), with editing levels persisting as high as 40% for more than one month.
- In February 2022, two papers were published in the journal *Nucleic Acids Research* (NAR) that reported a multitude of preclinical *in vitro* and *in vivo* studies demonstrating the incorporation of PN backbone chemistry modifications (PN chemistry) in stereopure silencing oligonucleotides (publication link) and stereopure splicing oligonucleotides (publication link) significantly improves potency, distribution, and durability of effect.
- Wave has published a total of eight peer-reviewed papers thus far in 2022.

Key Anticipated 2022 Milestones

WVE-004 for C9-ALS and C9-FTD:

- Additional single and multidose clinical data for WVE-004 expected throughout 2022. Wave expects to use these data to optimize WVE-004 dose level and frequency, as well as to enable discussions with regulatory authorities regarding the next phase of development later in 2022.
- Planning underway to initiate an open-label extension (OLE) clinical trial in mid-2022.

WVE-003 for HD:

- Clinical data expected in 2022 for WVE-003 to provide further insight into the clinical effects of PN chemistry and enable decision-making for this program.

WVE-N531 for DMD:

- Clinical data, including muscle biopsies, expected in 2022 for WVE-N531 to provide further insight into the clinical effects of PN chemistry and enable decision-making for this program.

AIMer GalNAc-conjugated program for AATD:

- Wave expects to select an AATD AIMer development candidate and initiate IND-enabling toxicology studies in the third quarter of 2022.

First Quarter 2022 Financial Results and Financial Guidance

Wave reported a net loss of $37.8 million in the first quarter of 2022, as compared to $42.5 million in the same period in 2021.

Wave recorded revenue of $1.8 million for the first quarter of 2022, primarily under the Takeda Collaboration. Wave did not record any revenue under the Takeda Collaboration in the first quarter of 2021.

Research and development expenses were $27.5 million in the first quarter of 2022 as compared to $33.4 million in the same period in 2021. The decrease in research and development expenses in the first quarter was primarily due to decreased external expenses related to our previously disclosed discontinued PRECISION-HD programs, partially offset by increased internal and external expenses related to PRISM, including ADAR editing, and other ongoing programs.

General and administrative expenses were $12.4 million in the first quarter of 2022 as compared to $10.1 million in the same period in 2021. The increase in general and administrative expenses in the first quarter of 2022 was primarily due to increases in compensation-related expenses, as well as increases in professional services expenses and other general and administrative operating expenses.

As of March 31, 2022, Wave had $111.7 million in cash, cash equivalents and short-term investments. As of December 31, 2021, Wave had $150.6 million in cash and cash equivalents. This decrease was mainly due to Wave's year-to-date net loss of $37.8 million.

Wave expects that its existing cash, cash equivalents and short-term investments will enable the company to fund its operating and capital expenditure requirements into the second quarter of 2023.

Investor Conference Call and Webcast
Wave management will host an investor conference call today at 8:30 a.m. ET to discuss the company's first quarter 2022 financial results and provide a business update. The conference call may be accessed by dialing (866) 220-8068 (domestic) or (470) 495-9153 (international) and entering conference ID: 092347. The live webcast may be accessed from the Investor Relations section of the Wave Life Sciences corporate website at ir.wavelifesciences.com. Following the webcast, a replay will be available on the website.

About the FOCUS-C9 Clinical Trial
The FOCUS-C9 trial is an ongoing, global, multicenter, randomized, double-blind, placebo-controlled Phase 1b/2a clinical trial to assess the safety and tolerability of single- and multiple-ascending intrathecal doses of WVE-004 for people with C9-ALS and/or C9-FTD. Additional objectives include measurement of poly(GP) DPR proteins in the cerebrospinal fluid (CSF), plasma and CSF pharmacokinetics (PK), and exploratory biomarkers and clinical outcomes. The FOCUS-C9 trial is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee.

In an initial data analysis, reductions in poly(GP) were observed across all active treatment groups (10 mg, n=2 patients; 30 mg, n=4 patients; 60 mg, n=3 patients), reaching statistical significance versus placebo (n=3 patients) after single 30 mg doses, with a 34% reduction in poly(GP) at day 85 (p=0.011). At the time of analysis, none of the patients dosed with 60 mg had reached day 85. As the poly(GP) reduction in the 30 mg single dose cohort does not appear to have plateaued, Wave will extend the observation period from approximately three months (85 days) to approximately six months to identify the maximum reduction of poly(GP) and duration of effect of low single doses. Based on the durability and potency observed in the 30 mg cohort, FOCUS-C9 has been adapted to include additional patients receiving 20 mg and 30 mg single doses of WVE-004. Adverse events (AEs) were balanced across treatment groups, including placebo, and were mostly mild to moderate in intensity. Four patients (including one on placebo) experienced severe and/or serious adverse events; three were reported by the investigators to be related to ALS or administration, and one was reported by the investigator to be related to study drug. There were no treatment-associated elevations in CSF white blood cell counts or protein and no other notable laboratory abnormalities were observed.

Support for FOCUS-C9 is provided by the Alzheimer's Drug Discovery Foundation.

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.

A hexanucleotide repeat expansion (G4C2) is the most common known genetic cause of the sporadic and inherited forms of ALS and FTD. The expansion leads to production of modified sense and antisense transcripts that can form nuclear RNA foci and encode dipeptide protein repeats (DPRs), which are believed to drive disease pathology. Additionally, the G4C2 expansion can decrease expression of C9orf72 protein, affecting regulation of neuronal function and the immune system.

In the United States, mutations of the C9orf72 gene are present in approximately 40% of familial ALS cases and ~8-10% of sporadic ALS cases. In FTD, the mutations appear in 38% of familial cases and 6% of sporadic cases.

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 mHTT 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 developing the disease. There are currently no approved disease-modifying therapies available.

About Duchenne Muscular Dystrophy
Duchenne muscular dystrophy (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. Approximately 8%-10% of DMD patients have mutations amenable to treatment with an exon 53 skipping therapy. Exon skipping aims to address the underlying cause of DMD by promoting the production of dystrophin protein to stabilize or slow disease progression.

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 initiation, site activation, patient recruitment, patient enrollment, dosing, generation of data and completion of our adaptive 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 preclinical data to predict the behavior of our compounds in humans; our identification and expected timing of future product candidates and their therapeutic potential; the anticipated therapeutic benefits of our potential therapies compared to others; our ability to design compounds using multiple modalities and the anticipated benefits of that model; the potential benefits of PRISM, including our novel PN backbone chemistry modifications, and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the potential benefits of our novel ADAR-mediated RNA editing platform capabilities, including our AIMers, compared to others; anticipated benefits of our proprietary manufacturing processes and our internal manufacturing capabilities; the benefit of nucleic acid therapeutics generally; the strength of our intellectual property; our assumptions based on our balance sheet and the anticipated duration of our cash runway; our intended uses of capital; and our expectations regarding the impact of the COVID-19 pandemic on our business. 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 and the timing thereof, which may not support further development of product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, including their receptiveness to our adaptive trial designs; our effectiveness in managing future clinical trials and regulatory interactions; the effectiveness of PRISM, including our novel PN backbone chemistry modifications; the effectiveness of our novel ADAR-mediated RNA editing platform capability and our AIMers; 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; our ability to manufacture or contract with third parties to manufacture drug material to support our programs and growth; our ability to obtain, maintain and protect our intellectual property; our ability to enforce our patents against infringers and defend our patent portfolio against challenges from third parties; competition from others developing therapies for similar indications; our ability to maintain the company infrastructure and personnel needed to achieve our goals; the severity and duration of the COVID-19 pandemic and variants thereof, and its negative impact on the conduct of, and the timing of enrollment, completion and reporting with respect to our clinical trials; and any other impacts on our business as a result of or related to the COVID-19 pandemic, 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.

WAVE LIFE SCIENCES LTD.
UNAUDITED CONSOLIDATED BALANCE SHEETS

(In thousands, except share amounts)

	March 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 61,713	$ 150,564
Short-term investments	50,000	—
Prepaid expenses	6,940	6,584
Other current assets	5,730	5,416
Total current assets	124,383	162,564
Long-term assets:		
Property and equipment, net	21,046	22,266
Operating lease right-of-use assets	17,594	18,378
Restricted cash	3,651	3,651
Other assets	685	148
Total long-term assets	42,976	44,443
Total assets	$ 167,359	$ 207,007
Liabilities, Series A preferred shares and shareholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 9,853	$ 7,281
Accrued expenses and other current liabilities	7,087	14,861
Current portion of deferred revenue	36,426	37,098
Current portion of operating lease liability	5,120	4,961
Total current liabilities	58,486	64,201
Long-term liabilities:		
Deferred revenue, net of current portion	76,567	77,479

Operating lease liability, net of current portion	23,617	24,955
Other liabilities	868	—
Total long-term liabilities	$ 101,052	$ 102,434
Total liabilities	$ 159,538	$ 166,635
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at March 31, 2022 and December 31, 2021	$ 7,874	$ 7,874
Shareholders' equity (deficit):		
Ordinary shares, no par value; 60,859,968 and 59,841,116 shares issued and outstanding at March 31, 2022 and December 31, 2021, respectively	$ 751,229	$ 749,851
Additional paid-in capital	91,951	87,980
Accumulated other comprehensive income	95	181
Accumulated deficit	(843,328)	(805,514)
Total shareholders' equity (deficit)	$ (53)	$ 32,498
Total liabilities, Series A preferred shares and shareholders' equity (deficit)	$ 167,359	$ 207,007

WAVE LIFE SCIENCES LTD.
UNAUDITED CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2022	**2021**
Revenue	$ 1,750	$ —
Operating expenses:		
Research and development	27,470	33,393
General and administrative	12,374	10,078
Total operating expenses	39,844	43,471
Loss from operations	(38,094)	(43,471)
Other income, net:		
Dividend income and interest income, net	26	11
Other income, net	254	996
Total other income, net	280	1,007
Loss before income taxes	(37,814)	(42,464)
Income tax provision	—	—
Net loss	$ (37,814)	$ (42,464)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (0.62)	$ (0.86)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	60,516,616	49,101,606
Other comprehensive loss:		
Net loss	$ (37,814)	$ (42,464)
Foreign currency translation	(86)	(120)
Comprehensive loss	$ (37,900)	$ (42,584)

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.