Wave Life Sciences Announces Nucleic Acids Research Publication Highlighting Potential Best-in-Class siRNAs Designed with Wave Platform Chemistry

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Published preclinical data demonstrate unprecedented Ago2 loading following administration of single subcutaneous siRNA dose, leading to improved potency and durability in vivo versus comparator siRNA formats

RNAi is one of multiple Wave modalities being advanced in strategic research collaboration with GSK

CAMBRIDGE, Mass., April 20, 2023 (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 the publication of preclinical data for the company's small interfering RNA (siRNA) designs in the journal *Nucleic Acids Research*. Data reported include an *in vivo* study where a Wave subcutaneously administered, GalNAc-conjugated siRNA maintained approximately 80% silencing of *HSD17B13* transcripts for three months in the liver of transgenic mice, while a comparator siRNA format lost silencing activity at the same timepoint. The paper, titled "Impact of stereopure chimeric backbone chemistries on the potency and durability of gene silencing by RNA interference," is available here.

"Wave's experience with RNA-directed pharmacology, GalNAc conjugation and advancements in our proprietary chemistry have enabled the addition of RNA interference (RNAi) to our tools for discovery and drug development. This publication demonstrates that by applying our best-in-class oligonucleotide chemistry, including judiciously placed PN backbone chemistry modifications, we can dramatically improve potency and durability for GalNAc-conjugated siRNAs versus comparator siRNA formats. These silencing benefits appear to be driven, at least in part, by an approximate 10-fold increase in Ago2 loading resulting from our novel PN linkages," said Chandra Vargeese, PhD, Chief Technology Officer and Head of Platform Discovery Sciences at Wave Life Sciences. "Moreover, we observed impressive silencing across multiple hepatic targets – mouse *Ttr* and human *HSD17B13* – reinforcing the therapeutic potential of our approach to RNAi."

"Wave has built the most versatile RNA medicines platform in the industry, with multiple modalities to optimally address disease biology. We continue to lead the field in RNA editing with our alpha-1 antitrypsin deficiency program and are also advancing a differentiated exon skipping portfolio in DMD, led by WVE-N531 for those amenable to exon 53 skipping. With RNAi, we have opened up a whole new capability set. The data in this publication, coupled with our recent unconjugated siRNA data showing 70-90% mRNA silencing and broad tissue exposure across six brain regions in mice,[1] demonstrate our potential for achieving best-in-class silencing," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "We expect our work in RNAi to deliver near-term value through collaborations, including our active research collaboration with GSK."

Wave's siRNA designs leverage the company's novel, clinically validated and RNA-focused discovery and development platform. In this publication, Wave's siRNAs are compared to reference molecules based on siRNAs from a commercial company with a clinically proven track record in RNAi. Highlights from the publication include:

- Application of one of Wave's most effective siRNA designs ("HSD-1930") led to 80% silencing of human *HSD17B13* mRNA in transgenic mice, which persisted for three months after administration of a single 3 mg/kg subcutaneous dose.
    - In this same study, a comparator molecule ("HSD-1933") achieved 60% silencing of human *HSD17B13* mRNA at week 7, with the effect returning nearly to baseline (5% silencing) by week 14, or approximately three months.
    - Differences in Argonaute-2 (Ago2) loading between HSD-1930 and HSD-1933 were substantial, with significantly more HSD-1930 than HSD-1933 found in complex with Ago2 at two weeks and seven weeks post-dose. By the final three-month time point, about 10-fold more HSD-1930 was loaded onto Ago2 than HSD-1933.
    - Wave also investigated a lower 1.5 mg/kg dose of HSD-1930 and observed similar results (75% mRNA silencing after three months), suggesting this lower dose is sufficient to maximize silencing.
- Several guiding principles for the design of Wave's siRNAs were defined through analysis of the relationship between chemical modifications and silencing activity of mouse *Ttr* and human *HSD17B13*. These design principles were applicable across both targets.
    - In particular, the use of PN backbone chemistry modifications (phosphoryl guanidine) in certain positions decreased thermal stability of the siRNA duplex, translating to the 10-fold increase observed in Ago2 loading and enhanced silencing activity.
    - Importantly, the improved Ago2 loading observed with PN-containing siRNAs did not disrupt endogenous RNAi pathways, as off-target gene expression changes in the presence of these siRNAs were minimal in hepatocytes. This suggests there may be ample untapped capacity in endogenous RNAi pathways to further improve siRNA-mediated silencing.
    - PN backbone chemistry modifications in the tested *Ttr* siRNAs also enhanced Ago2 loading without elevating serum biomarkers for liver dysfunction.

1. Wave Life Sciences Fourth Quarter and Full Year 2022 Business Update available here

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 within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, our belief that our experience with RNA-directed pharmacology, GalNAc conjugation and advancements in our proprietary chemistry may translate to best-in-class medicines; our belief that our siRNA designs demonstrate greater potential silencing benefits than comparator formats; our belief that judiciously placed PN backbone chemistry modifications result in improved potency and durability *in vivo* relative to comparator siRNA formats; and our understanding of what our published preclinical data portend for our work in other hepatic targets and its best-in-class therapeutic potential in humans. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release and actual results may differ materially from those indicated by these forward-looking statements as a result of these risks, uncertainties and important factors, including, without limitation, the risks and uncertainties described in the section entitled “Risk Factors” in Wave’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as amended, and in other filings Wave makes with the SEC from time to time. Wave undertakes no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

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