

Ionis Pharmaceuticals Announces Publication in Nature Biotechnology of a Novel Mechanism of Action for Antisense Drugs That Significantly Expands Therapeutic Opportunities

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-Innovative New Mechanism Allows Antisense Drugs to Increase the Production of Specific Proteins By Up to 150%-

CARLSBAD, Calif., July 12, 2016 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced the publication of new research findings in *Nature Biotechnology* describing a new mechanism of action for antisense technology, which further expands the potential reach of antisense technology. The paper entitled "Translation efficiency of mRNAs is increased by antisense oligonucleotides targeting upstream open reading frames" (Liang et al., *Nature Biotechnology*, [Advanced Online Publication, July 2016](#)), documents the validation of a new mechanism of action in antisense drug technology that increases the expression and production of specific therapeutic target proteins. Because many diseases can be positively impacted by increasing the levels of a specific protein, antisense drugs designed to act via this new mechanism have the potential to expand the application of this drug class to treat new diseases and therapeutic areas.



"Recent progress has shown that many mRNAs down-regulate their own translation, thus limiting the amount of the specific protein encoded by the mRNA that is translated. We can now use antisense technology to alter this mechanism and increase the production of specific proteins," said Stanley T. Crooke, M.D., Ph.D., chief executive officer and chairman at Ionis and principal author on the paper. "Therefore, antisense technology, which has been used primarily to decrease the production of proteins, can now be used to treat diseases associated with inadequate protein production. This substantially broadens the therapeutic potential of the antisense platform."

The findings published in *Nature Biotechnology* report data from a series of studies designed to increase the production of therapeutic target proteins *in vivo* and *in vitro* by increasing the translational efficiency of specific messenger RNAs (mRNA) with antisense oligonucleotides (ASO). Using their expertise in RNA technology, Ionis scientists evaluated five ASOs that bind to mRNA sequences in upstream open reading frames (uORF) within the 5' untranslated region to specifically increase the amount of protein translated from a downstream primary open reading frame (ORF). In both human and murine cells, the ASOs acting through this new mechanism of action were able to increase the amount of proteins expressed from 30% to 150% in a dose-dependent manner. In addition, the ASO-mediated increases in protein expression were sequence specific and occurred at the level of translation. These findings support the utility of these modified ASOs as a significantly useful class of therapeutic agents with broad utility.

ABOUT IONIS PHARMACEUTICALS, INC.

Ionis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Ionis has created a large pipeline of first-in-class or best-in-class drugs, with over a dozen drugs in mid- to late-stage development. Drugs currently in Phase 3 development include volanesorsen, a drug Ionis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with either familial chylomicronemia syndrome or familial partial lipodystrophy; IONIS-TTR_{Rx}, a drug Ionis is developing with GSK to treat patients with all forms of TTR amyloidosis; and nusinersen, a drug Ionis is developing with Biogen to treat infants and children with spinal muscular atrophy. Ionis' patents provide strong and extensive protection for its drugs and technology. Additional information about Ionis is available at www.ionispharma.com.

IONIS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding the therapeutic and commercial potential of Ionis' technologies and products in development, including nusinersen, IONIS-TTR_{Rx} and volanesorsen. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2015, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this release, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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