



Ionis and Metagenomi Gene Editing Collaboration

November 14, 2022

Nasdaq: IONS



On Today's Webcast



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Forward-Looking Statements

This presentation includes forward-looking statements regarding our collaboration and license agreement with Metagenomi, Inc., the therapeutic and commercial potential of genetic targets using gene editing technologies, Ionis' technologies, and Ionis' other products in development. 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, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. 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, 2021, and our most recent Form 10-Q quarterly filing, which are on file with the Securities and Exchange Commission. Copies of this and other documents are available at www.ionispharma.com.

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

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Introduction



Brett Monia, Ph.D.
Chief Executive Officer

Expanding the Reach of our Technology with Gene Editing Capabilities

Expands technology capabilities to address more diseases and more patients with unmet medical needs

Accelerates potential to deliver gene edited medicines

Focuses initially on validated liver targets while in parallel, exploring novel extra-hepatic targets

Moves us closer to becoming a leader in precision genetic medicines

Expanding the Reach of our Technology with Gene Editing



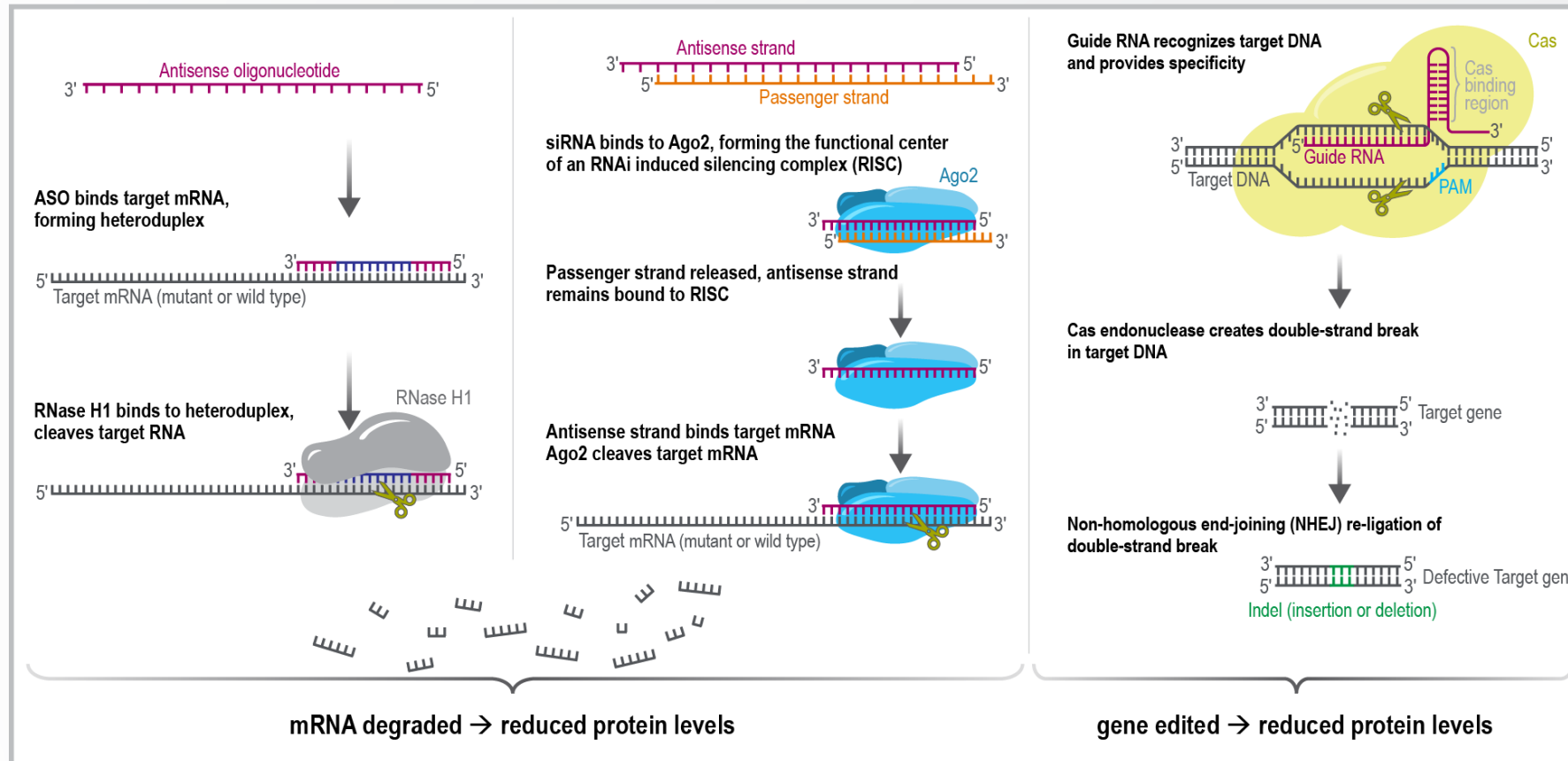
C. Frank Bennett, Ph.D.
Executive Vice President, Chief Scientific
Officer

Gene Editing is a Natural Extension of RNA-targeted Therapeutics

A. Antisense oligonucleotide (ASO)

B. Small interfering RNA (siRNA)

C. CRISPR-Cas gene editing



Platforms share nucleic acid hybridization principles

Gene editing uses specific RNA-guided nucleases to precisely modify DNA

Metagenomi has a broad, differentiated gene editing platform

Adapted from *J Peripher Nerv Syst.* 2022 Nov 8. doi: 10.1111/jns.12519

Ionis + Metagenomi Advancing Gene Editing



Eric Swayze, Ph.D.
Executive Vice President, Research

Multiple Near- and Longer-Term Opportunities to Deliver Value and Broaden our Reach to More Patients

Near-Term Opportunities

- Validated liver targets currently in our pipeline and de novo targets
- Includes follow-on programs for certain near-term commercial opportunities

Longer-Term Opportunities

- Explore delivery to extra-hepatic tissues in parallel
- Exploit expertise in targeted delivery and alternative routes of delivery
- Utilize Ionis' medicinal chemistry capabilities to further optimize CRISPR-CAS enzymology
- Explore additional mechanisms beyond DNA cutting

Conclusion



Brett Monia, Ph.D.
Chief Executive Officer

Well Positioned for Accelerated Growth

Building the Ionis
**Commercial
Pipeline**

Expanding and
Diversifying our
Technology

Delivering an
Abundance of
New Medicines to
the **Market**

Q&A



Brett Monia, Ph.D.
Chief Executive Officer

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A Force for Life

