Delivering on the therapeutic potential of CRISPR/Cas9: Development of an LNP-mediated genome editing therapeutic for the treatment of ATTR

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Disclosure: Employee of Intellia Therapeutics, Inc.
This press release contains “forward-looking statements” of Intellia Therapeutics, Inc. (“Intellia”) within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia’s ability to advance and expand the CRISPR/Cas9 technology to develop into human therapeutic products, as well as our CRISPR/Cas9 intellectual property portfolio; our ability to achieve stable or effective genome editing; our ability to administer multiple doses of our CRISPR/Cas9 product candidates; the potential timing and advancement of our preclinical studies, including continuing non-human primate studies for our Transthyretin Amyloidosis (“ATTR”) program and other programs (such as alpha-1 antitrypsin deficiency (AATD)), and clinical trials; the timing and potential achievement of milestones to advance our pipeline; our ability to replicate results achieved in our preclinical studies, including those in our ATTR, AATD and Wilms’ Tumor 1 (WT1) programs, in any future studies, including human clinical trials; the potential development of other in vivo or ex vivo cell therapeutics of all types, and those targeting WT1 in particular, using CRISPR/Cas9 technology; our ability to continue to conduct successful Investigational New Drug (“IND”) enabling studies of a lead ATTR development candidate and subsequently submitting an IND application by the end of 2019 that will be accepted by the regulatory agencies; our intent to present additional data for organs beyond the liver, additional insertion/repair data, and preclinical data in support of our first ex vivo programs on immuno-oncology and autoimmune/inflammation indications during 2018; the expansion of our fully automated bioinformatics platform; our ability to advance a development candidate for a second indication by late 2018; our potential ability to conduct a pre-IND meeting with the U.S. Food and Drug Administration (“FDA”) for ATTR; the intellectual property position and strategy of Intellia’s licensors or other parties from which it derives rights; actions by government agencies; the impact of our collaborations on our development programs; the potential timing of regulatory filings regarding our development programs; the potential commercialization opportunities, including value and market, for product candidates; our expectations regarding our uses of capital, expenses, future accumulated deficit and other 2018 financial results; and our ability to fund operations through mid-2020.

Any forward-looking statements in this presentation are based on management’s current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: risks related to Intellia’s ability to protect and maintain our intellectual property position; risks related to the ability of our licensors to protect and maintain their intellectual property position; uncertainties related to the initiation and conduct of studies and other development requirements for our product candidates; the risk that any one or more of Intellia’s product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies will not be predictive of future results in connection with future studies; and the risk that Intellia’s collaborations with Novartis or Regeneron or its other ex vivo collaborations will not continue or will not be successful. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause Intellia’s actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in Intellia’s most recent annual report on Form 10-K and quarterly reports on Form 10-Q filed with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties, and other important factors in Intellia’s other filings with the Securities and Exchange Commission. All information in this presentation is as of the date of the release, and Intellia Therapeutics undertakes no duty to update this information unless required by law.
Hereditary Transthyretin Amyloidosis (hATTR) Is a Rare Disease Typically Fatal if Untreated

**Amyloidogenic TTR Cascade**

- Liver
  - Suppression of amyloidogenic TTR
- TTR Tetramer
  - TTR stabilization
- TTR Monomer
- Misfolded State
- Amyloid Fibril
  - Fibril degradation

**About ATTR**

- Autosomal dominant disease
- Caused by misfolded transthyretin (transports thyroxine and retinol-binding protein), which affects nerves, heart, kidneys and eyes
- >100 known mutations with V30M and V122I among the most common associated with the diseases
- Estimated 50,000 hATTR patients worldwide
- Typically fatal within 2-15 years from onset of symptoms

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Intellia’s Modular Lipid Nanoparticle (LNP) System Delivers CRISPR/Cas9 to Make an In Vivo Edit

Lipid nanoparticles

Degradable ionizable lipid

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<th>Component</th>
<th>Function</th>
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<tr>
<td>Degradable ionizable lipid</td>
<td>Encapsulation; Endosomal escape</td>
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<tr>
<td>Cholesterol</td>
<td>Stabilization</td>
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<tr>
<td>Structural lipid/Neutral lipid</td>
<td>Stabilization; Better processing</td>
</tr>
<tr>
<td>PEG lipid/Shielding lipid</td>
<td>Prevent aggregation; Control particle PK</td>
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Component functions include encapsulation, endosomal escape, stabilization, and better processing.
Intellia’s Modular Lipid Nanoparticle (LNP) System Delivers CRISPR/Cas9 to Make an *In Vivo* Edit

Intellia’s LNP delivery system includes a single guide RNA, mRNA encoding *S. pyr.* Cas9 and a lipid formulation encapsulating these:

**Cas9 mRNA (4500 nts)**

**sgRNA (100 nts)**

Editing *in vivo* requires cargo release, mRNA translation, RNP assembly and Cas9 import into the cell’s nucleus.
Durable Liver Editing and Knockdown of TTR Persists 12 Months in Mice with No Histological Findings

Single administration given at Day 1

Hepatocytes | Non-Hepatocytes
---|---
Hepatocytes | Endothelial cells, Kupffer cells, Lymphocytes, Biliary cells, Stellate cells
~50 to 70% | ~30 to 50%

No transformation or neoplastic changes observed across >100 mice over time up to 12 months post-edit
Liver Editing Efficiency Is Not Affected by Pre-Dosing with LNP-mRNA Cas9

Repeat dose shown to be feasible in mice; potential generation and subsequent neutralizing effect of Ab against LNP-CRISPR/Cas9 not seen
Mouse Multi-Dose Study: Repeat Low Dose of LNPs with CRISPR/Cas9 Is Comparable to Single High Dose

Multiple weekly or monthly doses of 0.5 mg/kg are comparable to one 2 mg/kg dose
Editing Strategy Relies on Knockout Caused by Error-Prone Non-Homologous End Joining (NHEJ) of a Double-Strand Break in Liver Cells

Chromosome 18: 31591726 to 31599011

signal peptide

alt start
V30M

Exon 2

KO via frameshift and nonsense-mediated decay

CRISPR Double-Stranded Break

NHEJ Repair with INDELS
Lead Human TTR CRISPR/Cas9 LNPs Demonstrate On-Target Editing, and Reduction of mRNA and TTR Protein in Primary Human Hepatocytes *In Vitro*

**Exon 2**

- **Edit/KO**
- **mRNA**
- **TTR protein**
Top Human Guides Exhibit Robust, Dose-Responsive Liver Editing and Reduction of TTR in huTTR Mice

![Diagram showing liver editing and reduction of TTR in huTTR mice.]

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Findings from huTTR V30M Mouse Model Study Recapitulate TTR Deposition Phenotype in Tissues and the Nervous System

Homozygous for the human mutant V30M TTR transgene in a mouse Ttr-null background transgenic mice contain approximately ~47 copies of huTTR V30M

Mouse model from Santos et al. 2003; In collaboration with U. of Porto
Decreasing Serum TTR by Editing the huTTR V30M Mouse Model Via CRISPR/Cas9
LNP Dramatically Decreases Amyloid Deposition in Tissues

Mouse model from Santos et al. 2003; In collaboration with U. of Porto
Therapeutically Relevant Reduction of Serum TTR Protein Achieved in Initial Non-Human Primate (NHP) Studies After a Single Dose of LNPs with CRISPR/Cas9

Liver Editing

- mRNA improvement
- LNP formulation
- Cargo ratio
- Guide chemistry

% TTR Protein Knockdown

In an ongoing study, durability of editing and reduction of circulating TTR has been demonstrated >6 months
LNPs and Cargo Exhibit 18-24 Hour T1/2 and Are Cleared from Circulation and Liver Within 5 days in NHP
High Correlation Achieved Between Liver Edit and Reduction of TTR; >35-40% Liver Edit Needed to Achieve Therapeutically Meaningful Reduction of TTR

- Liver biopsy taken from right lobe
- Fragments taken from 4 lobes of liver

Range of doses; single- and repeat-dose portrayed from lead candidate
Summary

- LNPs encapsulating CRISPR/Cas9 components targeting human *TTR* enable significant editing of the *TTR* gene across multiple species, including mice and NHPs.

- Following a single dose of LNP-delivered CRISPR/Cas9 in mice:
  - Editing levels achieved that resulted in >97% reduction in circulating serum TTR protein.
  - Reduction of circulating levels of TTR sustained for at least 12 months.
  - No significant histopathology findings noted.

- Humanized mouse model of hATTR that expresses the V30M mutant form of the human TTR protein demonstrated rescue of amyloid deposition in multiple tissues after a single dose of LNPs containing the CRISPR/Cas9 components.

- In NHPs, achieved a therapeutically meaningful level of TTR protein reduction that correlated with robust and significant editing in the liver.

- *S. py.* Cas9 mRNA, sgRNA and ionizable lipid are quickly cleared from circulation, with the lipid having plasma and liver half-lives of 20 hours and 17 hours, respectively, in NHPs.

- Demonstrated the potential of LNP delivered *in vivo* CRISPR/Cas9 gene editing; suggests that future therapies based on this platform may enable next-generation, curative treatment paradigms for chronic genetic diseases such as ATTR.
## Acknowledgements

### Intellia team

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### Regeneron team

- Augustine Choy
- Meghan Drummond-Samuelson
- Jeff Haines
- William Poueymirou

### University of Porto team

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- Maria João Saraiva
- Anabela Teixeira