# Intellia Therapeutics 43rd Annual J.P. Morgan Healthcare Conference

John Leonard, M.D.

President and Chief Executive Office

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SHANNA Living with hereditary angioedema type 1



#### Intellia Therapeutics' Legal Disclaimer

This presentation contains "forward-looking statements" of Intellia Therapeutics, Inc. ("Intellia", "we" or "our") 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 about Intellia's beliefs and expectations regarding: our ability to successfully develop and commercialize nexiguran ziclumeran ("nex-z"), formerly known as NTLA-2001, for the treatment of transthyretin ("ATTR") amyloidosis and NTLA-2002 for the treatment of hereditary angioedema ("HAE") to address the significant unmet needs of patients and prescribers in HAE and ATTR amyloidosis; our ability to achieve near-term clinical milestones, including dosing the first patient in the Phase 3 HAELO trial for NTLA-2002 in the first guarter of 2025, completing enrollment in the Phase 3 HAELO trial in the second half of 2025, dosing the first patient in the Phase 3 MAGNITUDE-2 trial for hereditary ATTR amyloidosis with polyneuropathy ("ATTRv-PN") in the first guarter of 2025 and completing enrollment in 2026, enrolling at least 550 patients across the Phase 3 MAGNITUDE trial for ATTR amyloidosis with cardiomyopathy ("ATTR-CM") in 2025, substantially completing enrollment of the MAGNITUDE trial for ATTR-CM in 2026, and completing enrollment of the MAGNITUDE trial for ATTR-CM in 2027; the expected timing of data releases from our clinical trials of nex-z and NTLA-2002, including presenting longer-term data from the Phase 1/2 study of NTLA-2002, longer-term data from the Phase 1 study of nex-z in 2025, results from the HAELO trial for NTLA-2002 in 2026, and results from the MAGNITUDE-2 trial for ATTRv-PN in 2027; our ability to prepare for commercial launch, including having all commercial capabilities in place by end of 2026; our interactions with regulatory authorities, including the potential submission of a biologics license application for NTLA-2002 for the treatment of HAE in 2026; our ability to launch NTLA-2002 as our first commercial product in 2027; our ability to optimize the impact of our collaborations on our development programs, including our collaboration with Regeneron Pharmaceuticals, Inc. and their codevelopment program for ATTR amyloidosis, and to advance additional development candidates; our expectations regarding our uses of capital, expenses, and ability to fund operations through first commercial launch in the first half of 2027; and the potential commercial opportunities, including the value and market potential for our product candidates, including the potential of nex-z and NTLA-2002 to be single-dose treatments, the potential of nex-z to halt and reverse disease, result in lifelong, stable TTR reduction, be best TTR-directed drug, and represent a meaningful revenue opportunity starting in 2029, and the potential of NTLA-2002 to be a functional cure, eliminate significant treatment burden, eliminate HAE attacks and chronic prophylaxis, and represent a meaningful revenue opportunity starting in 2027.

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 its intellectual property position; risks related to Intellia's relationship with third parties, including our contract manufacturers, licensors and licensees; risks related to the ability of our licensors to protect and maintain their intellectual property position; uncertainties related to the authorization, initiation and conduct of preclinical and clinical studies and other development requirements for our product candidates successfully; risks related to the results of preclinical studies or clinical studies not being predictive of future results in connection with future studies; the risk that clinical study results will not be positive; risks related to the development and advancement of novel platform capabilities, such as DNA writing technology and gene editing in tissues outside the liver; risks related to Intellia's future function and our ability to fund our operations; risks related to Intellia's and other key personnel to execute its strategic plans, including completing pivotal clinical trials and commercial lauch of its product candidates, such as nex-z and NTLA-2002. For a discussion of these and other risks factors" in Intelleia's most recent Quarterly Report on Form 10-Q as well as discussions of potential risks, uncertainties, and other important factors, any of which could cause Intellia's other filings with the Securities and ther important factors in Intellia's most recent Quarterly Report on Form 10-Q as well as discussions of potential risks, uncertainties, and other important factors in Intellia's other filings with the Securities and Exchange Commi



## Leveraging Gene Editing Technology to Develop Differentiated Medicines for Superior Patient Outcomes



Treat patients at the root cause of their disease



Reduce burden to the patient and healthcare system



Single dose treatment with potential lifelong benefit



Best-in-class outcomes for patients



Bringing Innovative Solutions to Patients

3

actively enrolling Phase 3 studies







Deep Clinical Experience

Nearly 200

patient-years of experience

# **100+ patients**

significant clinical experience and data presented to date

4+

years of follow-up in earliest dosed patients

Regulatory and Scientific Expertise

12+

health authority approvals for clinical studies

Multiple

regulatory designations



New England Journal of Medicine publications



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#### Two Late-stage Assets with Breakthrough Profiles and Blockbuster Potentials

#### THREE COMMERCIAL LAUNCHES EXPECTED STARTING IN 2027

	NTLA-2002	Nex-z*
Target Indication	Hereditary Angioedema (HAE)	Transthyretin amyloidosis (ATTR)
Unique Proposition	Potentially first to offer <b>lifelong freedom</b> from attacks and prophylaxis after a <b>single dose</b>	Potential to be the first to <b>stabilize or reverse</b> disease progression with a <b>single dose</b>
Program Status	Phase 3 initiated <b>RMAT, ODD, PRIME</b> BLA submission planned in 2026	Phase 3 enrolling <b>RMAT &amp; ODD designation</b> <b>PN BLA submission planned in 2028</b> <b>CM enrollment completion by early 2027</b>
Total Market	WW Prevalence <b>~150,000</b> <sup>1</sup> Projected to reach global sales of \$ <b>5B</b> <sup>2</sup> by 2028	WW Prevalence <b>250,000 to 500,000</b> <sup>3-6</sup> Projected to reach global sales of <b>\$12B</b> <sup>2</sup> by 2028

Data for 108 patients presented across programs; robust treatment effect continues at longest follow up through 2 years

\* Nex-z (nexiguran ziclumeran), formerly referred to as NTLA-2001.

1. Zuraw et al 2008; 2. Evaluate Pharma Consensus Analyst forecasts October-December 2024; 3. Hawkins et al, 2015; 4. Maurer et al, 2019; 5. Nativi-Nicolau et al, 2021; 6. Gillmore et al, 2022

Abbreviations: **RMAT** – Regenerative Medicine Advanced Therapy; **ODD** - Orphan Drug Designation; **PRIME** – Priority Medicine; **BLA** – Biologics License Application; **WW** – worldwide; PN – Polyneuropathy; **CM** - Cardiomyopathy



#### **Treatment is Designed for Patient and Provider-Friendly Experience\***







## **Building on Recent Accomplishments**

# 2024 Key Achievements

Clinical data suggest nex-z may halt and potentially reverse disease progression for ATTR amyloidosis

Phase 1/2 data indicate NTLA-2002 may be a functional HAE cure for most patients

Nex-z RMAT designation for ATTR PN

Initiated 3 pivotal Phase 3 studies

## 2025 Operational Excellence



### 2026 Readying for Commercialization

Phase 3 HAELO results and first planned BLA submission in 2026

Complete enrollment for MAGNITUDE-2 in ATTR-PN

Substantially complete enrollment for MAGNITUDE in ATTR-CM

Continue to build for commercial success





### **Accelerating Clinical Development**

2024 Key Achievements

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## **Preparing the Market for Launch**

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# Maturing as a Fully-integrated, Commercial-stage Company

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Abbreviations: **RMAT** – Regenerative Medicine Advanced Therapy; **ATTR** – Transthyretin amyloidosis; **HAE** – Hereditary Angioedema; **PN** – Polyneuropathy; **CM** – Cardiomyopathy; **YE** – yearend; **BLA** – Biologics License Application

Focused on Completing Clinical Programs and Capitalizing on Multi-billion Dollar Commercial Opportunities



## **Delivering on 3 Phase 3 Studies by 2027**



# NTLA-2002

Hereditary Angioedema: Currently a Life-long Genetic Condition with Significant Burden



#### Rare, genetic and life-threatening disease

- Patients have unpredictable, recurrent, painful and potentially life-threatening swelling attacks.<sup>1,2</sup>
- Symptoms often begin in the **first decade of life** and typically worsen in puberty.<sup>3,4</sup>
- Attacks can be triggered by stress, trauma, infection, fatigue, and hormones.<sup>2</sup>
- Approximately 6K patients in the US.<sup>5</sup>

#### **Despite available treatments, significant unmet need persists**

- Many patients only achieve partial clinical control.<sup>6,7,8</sup>
- Patients make lifestyle modifications to manage fear and anxiety.<sup>9</sup>
- Treatment burden negatively affects patients, especially those taking injectable medications.<sup>10</sup>
- Insurance delays and denials associated with maintaining access have significant impacts on individuals with HAE.<sup>11</sup>

<sup>1</sup> Zuraw, NEJM (2008), <sup>2</sup> Busse and Christiansen, NEJM (2020), <sup>3</sup> Norris et al., Allergy Asthma Proc. (2022),
 <sup>4</sup> Pancholy et al., Curr Opin. Pediatr. (2019), <sup>5</sup> Busse et al., JACI In Practice (2021), <sup>6</sup> Banerji et al., JAMA (2018)
 <sup>7</sup> Zuraw et al., Allergy Clin. Immunol. (2021), <sup>8</sup> Longhurst et al., NEJM (2017), <sup>9</sup> Bork et al., Allergy Asthma Clin. Immunol. (2021), <sup>10</sup> Radojicic et al., Allergy Asthma Proc. (2021), <sup>11</sup> Arora et al., JACI In Practice (2023)



#### Intellia is Committed to Ending the Disease and Treatment Burden of HAE

HAE TREATMENT EVOLUTION							
Goal:	SURVIVAL	>>>	PREVENTION	<b>&gt;&gt;&gt;</b>	CURE		
Disease Burden:	Attacks Treated with On-Demand Treatment		Attack Frequency Reduced with Chronic Prophylaxis		Life-long Freedom from Attacks		
Treatment Burden:	Dozens of Injections Annually		Multiple Injections / Hundreds of Pills Annually		Life-long Freedom from Chronic Therapy		

#### Patients report significant disease and treatment burden with available therapies<sup>1</sup>

"I would love to not have to ever take another injection or another pill. It would be amazing"

"I am hesitant to switch jobs because I know these are expensive treatments and I may not always have access"

"Treatment has improved but I am still **experiencing a high number of attacks**"



## NTLA-2002 Has the Potential to Be a Functional Cure for Patients With HAE

#### PHASE 1 & 2 RESULTS NTLA-2002

- Phase 2 data show the potential of a single 50mg dose to eliminate attacks and chronic prophylaxis<sup>1, 2</sup>
  - All 11 patients had a reduction in attacks
  - All but 1 patient remained free from chronic prophylaxis
  - Most patients achieved complete elimination of attacks
  - Safety profile continued to be highly encouraging\*
- Demonstrated durability through 2 years in phase 1<sup>3</sup>

# 100%

of patients had **reduction in attacks** 

73%

of patients **attack free and off chronic prophylaxis** 

2 Cohn et al., ACAAI (2024) https://www.intelliatx.com/wp-content/uploads/Intellia\_NTLA-2002-Phase-2-Data-Investor-Presentation\_10.24.24\_vF.pdf

3 Longhurst, EAACI (2024) https://www.intelliatx.com/wp-content/uploads/EAACI-NTLA-2002-Phase-1-Update\_2June24.pdf

#### **CROSS TRIAL COMPARISON\***

PRODUCT	Study Phase	% of Patients Attack-Free*	% of Patients Attack-Free w/o chronic prophylaxis		DOSING REGIMEN
NTLA-2002 (investigational)	Phase 2 <sup>1</sup>	<b>73%</b> at 16 wks	<b>73%</b> at 16 wks	1x infusion / lifetime	
<b>Donidalorsen</b> (investigational)	Phase 3 <sup>2</sup>	<b>35-43%</b> at 24 wks	0%	<b>6–12</b> injections / year	$\begin{array}{c} \mathbf{T} & \mathbf{T} \\ \hline \mathbf{I} & \mathbf{I} \\ \mathbf{I} & \mathbf{I} \\ \end{array}$
<b>Garadacimab</b> (investigational)	Phase 3 <sup>3</sup>	<b>62%</b> at 26 wks	0%	<b>12</b> injections / year	
TAKHZYRO (lanadelumab-flyo) injection	Phase 3 <sup>4</sup>	<b>31-44%</b> at 26 wks	0%	<b>13–26</b> injections / year	I       I
<b>orladeyo</b> <sup>®</sup> (berotralstat) capsules 150 mg	Phase 3 <sup>5,6</sup>	No statistical difference	0%	Daily oral tablets	
C1 Esterase Inhibitor Subcutaneous (Human)	Phase 3 <sup>7</sup>	Not measured	0%	<b>104</b> injections / year	

For illustrative purposes only.

\*This graphic includes data from the blinded time periods of distinct clinical trials with their own enrollment criteria and methodologies. Cross-trial comparisons have inherent limitations and should be interpreted with caution.". **Sources**: 1. Cohn et al., NEJM (2024), 2. Riedl et al, N. Engl. J. Med (2024), 3. Craig et al, Lancet (2023), 4. Banjeri, et al, JAMA (2018), 5. Zuraw et al, J. All. Clin. Imm. (2021), 6. Wolfe Research (2024), 7. Longhurst et al, N. Engl. J Med (2017), 8. CINRYZE FDA Package Insert; **Abbreviations**: **HAE** – Hereditary Angioedema; **TEAEs** – Treatment Emergent Adverse Events; **Wks** – Weeks



# A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of NTLA-2002 in Patients with HAE



#### NTLA-2002 Upcoming 2025 Milestones

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O Dose first patient in pivotal Phase 3 HAELO trial for HAE in 1Q25

- Complete enrollment in the HAELO study
- Present longer-term data from the Phase 1/2 study

Clinicaltrials.gov ID: NCT06634420

\* Patients on long-term prophylaxis are required to wash out of therapy prior to the run-in period of screening.

<sup>1</sup> week 28 data expected to support BLA filing in 2026. Optional Blinded Crossover @ week 28. Patients will be observed in extended follow-up.



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#### **Uniquely Positioned for Product Leadership in a Growing HAE Market**

NTLA-2002 demonstrated unprecedented efficacy with a single dose

#### HAE MARKET OPPORTUNITY

# Global market projected to reach ~5B dollars by 2028<sup>1</sup>

4.9 3.5 3.0 2024 2026 2028 Physicians seeking **simpler**, **more effective solutions** and **easier access to therapy** for patients<sup>2</sup>

"I have to **go through the paperwork every year** with these patients and every time they change insurances...We actually have a whole section in our clinic with **staff dedicated to getting these medicines approved**. That's how much of a burden it is."

**U.S. HAE HCP** 

"If you're telling me that there's a medicine that doesn't require repeat dosing, that's like nothing else we have available." U.S. HAE HCP *"What it's offering very simply is the potential for having a onetime therapy that over time, if all goes well, allows patients to not require any more treatment and potentially not even any more disease management..."* 

**U.S. HAE HCP** 

HCPs willing to offer NTLA-2002 to **all patients regardless of severity** in the first **3 years**<sup>3</sup>

75%

#### NTLA-2002 represents a meaningful revenue opportunity starting in 2027



# Nex-z

Nex-z (nexiguran ziclumeran) formerly referred to as NTLA-2001

# Transthyretin Amyloidosis (ATTR):

Large and Growing Market with Significant Unmet Need



#### Severe, fatal, progressive disease with a shortened life expectancy

- CM patients have debilitating shortness of breath, arrythmias, reduced mobility and quality of life, as well as a high rate of hospitalization
- Wild-type disease, the most common form, occurs with aging, and manifests as heart failure; inherited TTR mutations lead to rapidly progressive heart failure and/or polyneuropathy
- 20K incident US CM patients; increasing rates due to an aging population and improved disease awareness
- PN presents as motor and sensory dysfunction, muscle wasting, weight loss, as well as autonomic neuropathy with severe GI symptoms

#### Despite available treatments, significant unmet need persists

- Inconsistent and slow TTR lowering response observed with silencers<sup>1</sup>
- In phase 3 studies of silencer or stabilizer therapies for CM, the annual rate of CV events or death is high at ~15% of enrolled patients in the first year<sup>1,2</sup>
- Even on existing therapies, CM patients have a marked decline in quality of life, and functional capacity as measured by 6MWT<sup>1,2</sup>
- **Treatment adherence** due to frequent administration/polypharmacy remains an issue



#### Intellia is Committed to Developing the Best Treatment for ATTR Amyloidosis

ATTR TREA	TMENT EVOLUTION						
Goal:	PALLIATION	DISEASE SLOWING	<b>&gt;&gt;&gt;</b>	DISEASE STASIS OR REVERSAL			
Disease Burden:	Progressive Disease Treated with Palliative Therapy	d Therapies Slow but Do Not Stop or Reverse Progression		Life-long Reduction in Disease Burden			
Treatment Burden:	Ineffective	Multiple Injections / Hundreds of Pills Annually with Inconsistent Response		Life-long Freedom from Chronic Therapy			
What US HCPs and Patients have to say about current therapies in ATTR <sup>1</sup>							
"Even with tafamidis." "Traveling for regular infusions is <b>time away</b> "Every year, there is a fight							

#### "Even with tafamidis, progression is a question of when, not if."

– US Amyloidosis KOL

Traveling for regular infusions is time away from my family, but I just couldn't bring myself to do injections at home."

- ATTR Patient

"Every year, there is a fight because insurance tries to deny my lifesaving medication."

- ATTR Patient



# Nex-z Phase 1 Results for ATTR-CM Show Potential to be Best TTR-Directed Drug

#### PHASE 1 RESULTS NEX-Z<sup>1</sup>



- **Deep, rapid, consistent and durable** reductions in serum TTR
- Stability or improvement of disease markers in a population with advanced disease which is expected to progress rapidly
- 66% of patients had no worsening
   in any marker (NT-proBNP,Troponin,
   6MWT) at 12 months
- Encouraging safety and tolerability<sup>1</sup>
- Updated Dec. 2024: Low rate of hospitalization for cardiac disease, (genotype-weighted) 0.11 events/pt/yr, is favorable based on reference studies<sup>3</sup> with higher rates

#### Change in NYHA Class at 12 months

100%		8% Worsened	
90%	_		
80%	_	-	
70%	_	44% No Change	
60%	_		
50%	_		
40%			
30%			
20%		47% Improved	
10%			
0%			

#### Phase 3 MAGNITUDE (CM) and MAGNITUDE 2 (PN) global studies are actively recruiting patients

\*This graphic includes data from distinct clinical trials with their own enrollment criteria and methodologies. Cross-trial comparisons have inherent limitations and should be interpreted with caution **Sources**: 1. Fontana et al, N. Engl. J. Med (2024), 2. Fontana et al, N. Engl. J. Med (2024), 3. Gillmore et al, N. Engl. J. Med (2024) **Abbreviations**: **6MWT** - 6-minute walk test; **NT-proBNP –** N-terminal pro-B-type natriuretic peptide; **NYHA** - New York Heart Association



# Phase 3 Studies in Patients with ATTR-CM and ATTR-PN

MAGNITUDE PROGRAM	N	R	Nex-z (Single 55	mg IV infusion) + SOC* cebo + SOC*	
MAGNITUDE CLINICAL TRIAL ATTR-CM	765	2:1	<ul> <li>Primary Endpoint</li> <li>CV-related mortality and CV-related events</li> </ul>	<b>Key Secondary Endpoints</b> <ul> <li>TTR and KCCQ-OS score</li> </ul>	
MAGNITUDE-2 CLINICAL TRIAL ATTRV-PN	50	1:1	<ul><li>Primary Endpoints</li><li>mNIS+7 and serum TTR</li></ul>	<ul> <li>Key Secondary Endpoints</li> <li>Norfolk QOL-DN, mBMI and TTR</li> </ul>	

Nex-z Upcoming 2025 Milestones

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O Dose first patient in pivotal Phase 3 MAGNITUDE-2 trial for PN in 1Q25

O Enroll >550 CM patients cumulatively in MAGNITUDE trial

O Present longer-term data from the Phase 1 study in CM and PN

#### ATTR MARKET OPPORTUNITY

# Global market projected to reach ~12B dollars by 2028<sup>1</sup>



Patients want a **highly effective** therapy **and freedom** from chronic treatment<sup>2</sup>



High willingness of cardiologists to prescribe nex-z **across US and other major developed markets**<sup>3</sup>



#### Nex-z represents significant revenue opportunities starting by 2029



**Sources**: 1. Evaluate Pharma Consensus Analyst forecasts as of December 2024. 2. Intellia commissioned ATTR patient and caregiver interviews (n=46); 3. Intellia commissioned Physician quantitative survey (n=232) based on nex-z target product profile



#### **Pipeline**

PROGRAM	APPROACH	Research and Preclinical	Early-Stage Clinical	Late-Stage Clinical	PARTNERS	
In Vivo: CRISPR is the therapy						
NTLA-2002: Hereditary Angioedema	Knockout					
Nex-z*: Transthyretin Amyloidosis	Knockout				LEAD Intelia REGENERON	
Hemophilia A / B***	Insertion					
Research Programs for Extra-hepatic Targets	Various				THERAPEUTICS ** REGENERON SPARING VISION	
Ex Vivo: CRISPR creates the therapy						

**Research Programs** 

Allogeneic and other

her

Intelia\*\* HERAPEUTICS

Lead refers to lead development and commercial party.

\* Nex-z (nexiguran ziclumeran), formerly referred to as NTLA-2001

\*\* Intellia is advancing both wholly owned and partnered programs.

26 \*\*\* Hemophilia A program is in the research stage; Hemophilia B is being advanced by Regeneron – Intellia is eligible for milestones and royalties.



# Upcoming 2025 Key Milestones for NTLA-2002 and Nex-z



Sufficient Cash to Fund Operations through First Commercial Launch (1H 2027)



#### Intellia is Well-positioned for Near-term Value Creation

#### COMPANY OUTLOOK



#### Phase 3 programs actively recruiting

Management team's **prior track record** in development and commercialization of **best-in-class** medicines, including one-time therapies

#### Potential blockbusters: NTLA-2002 and nex-z

Feedback from market research confirms **strong receptivity and willingness to prescribe/use** NTLA-2002 and nex-z emerging product profiles

# Focus to successfully launch NTLA-2002 in 2027

Commercial and medical affairs teams' prior track record of launching **multiple blockbusters**, including in **HAE and heart failure** 

#### Planning to have all commercial capabilities in place by end of 2026





Developing Best in Class Therapies by Realizing the Promise of Gene Editing

At Intellia, we innovate every day to make CRISPR-based medicines a reality for patients.

This is just the beginning of a revolution.



# THERAPEUTICS