Inotersen and Beyond
A Comprehensive Antisense Therapeutic Strategy for all Forms of ATTR

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Disclosures

- Dual appointment at University of California San Diego and Ionis Pharmaceuticals
**Inotersen**

An Antisense Approach to Treat TTR-related Amyloid Diseases

- Binds to *TTR* messenger RNA (mRNA)
  - Binds to wild-type (normal) *TTR* mRNA and all known mutations
  - Results in degradation of *TTR* mRNA and lowering of TTR protein production
- TEGSEDI reduces production of both mutant and wild-type TTR protein by the liver
- Self-administered as a once-weekly, at-home SC injection with no pretreatment requirements

![A Generation 2.0+ Antisense Oligonucleotide (ASO)](image)
# Inotersen

## Overview of Development Path

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<td>Good Safety/Tolerability Robust TTR Reductions</td>
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**Inotersen**

**Pivotal Phase 3 and OLE Study In Adults with hATTR-PN**

NEURO-TTR

- **International, randomized, double-blind, placebo-controlled Phase 3 study**

  - **Screen**: Stratified for stage of disease, TTR mutation, and previous treatment (tafamidis or diflunisal)
  - **Randomization (2:1)**: n = 112
  - **Inotersen**: n = 87
  - **Placebo**: n = 52
  - **15 months of treatment**
    - Inotersen-inotersen: Ongoing: n = 58 (68%), Discontinued: n = 27 (32%) Week 104: n = 40 (47%)
    - Placebo-inotersen: Ongoing: n = 35 (70%), Discontinued: n = 15 (30%) Week 104: n = 19 (38%)

**Open-Label Extension**

- Inotersen-inotersen: Ongoing: n = 58 (68%), Discontinued: n = 27 (32%) Week 104: n = 40 (47%)
- Placebo-inotersen: Ongoing: n = 35 (70%), Discontinued: n = 15 (30%) Week 104: n = 19 (38%)

>139 patients (80.3%) completed the NEURO-TTR study, and >95% of patients who completed dosing participated in the OLE

**Coprimary end points**: modified Neuropathy Impairment Score +7 composite score (mNIS+7) and Norfolk Quality of Life-Diabetic Neuropathy total score (QoL-DN) measured at week 66

- The n values for NEURO-TTR represent the number of patients randomized and treated.
- Discontinuations in the inotersen-inotersen group were due to adverse event or serious adverse event (n = 15), voluntary withdrawal (n = 6), investigator judgment (n = 3), stopped per stopping rules (n = 1), and other (n = 2). Discontinuations in the placebo-inotersen group were due to voluntary withdrawal (n = 5), investigator judgment (n = 4), adverse event or serious adverse event (n = 3), liver transplantation (n = 1), disease progression (n = 1), and other (n = 1).
- Not all patients had completed 2 years in the OLE as of May 31, 2018.
- Discontinuations in the placebo-inotersen group were due to voluntary withdrawal (n = 5), investigator judgment (n = 4), adverse event or serious adverse event (n = 3), liver transplantation (n = 1), disease progression (n = 1), and other (n = 1).

**Inotersen**

**Rapid reduction in serum TTR levels**

Median serum TTR reductions in the placebo-inotersen group reached a nadir of 78% below OLE baseline from week 13 to 104.

Median serum TTR reductions in the inotersen group in NEURO-TTR reached a nadir of 79% below baseline from week 13 to 65\(^1\)

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Inotersen

hATTR PN progression slowed with greater stabilization in patients who initiated treatment with Inotersen earlier

mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy questionnaire total score; PN, peripheral neuropathy; QoL, quality of life; SE, standard error. The minimum clinically meaningful score-change for the mNIS+7 is two-points.
Inotersen
Summary of Clinical Study Results

• NEURO-TTR
  • Inotersen demonstrated significant, sustained improvements in measures of both neuropathy and quality of life in the pivotal randomized, double-blind, placebo-controlled phase 3 trial
  • Serious side effects, included thrombocytopenia and glomerulonephritis

• NEURO-TTR OLE
  • Data from the long-term extension study showed benefits of early therapy with inotersen based on measures of objective neuropathic progression and neuropathy-related quality of life
  • No new safety signals identified
  • No new cases of grade 4 platelet count decrease or acute glomerulonephritis
Inotersen
Conclusions

Both primary endpoints, mNIS+7 and Norfolk QoL–DN, favoured inotersen vs placebo

SC injections were successfully administered at home outside pre-specified clinical visits

Enhanced safety monitoring enabled early detection and management of thrombocytopenia and glomerulonephritis

Inotersen modified the course of neuropathy and improved the QoL of patients with hATTR

Inotersen is a novel, convenient and effective treatment for hATTR*

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*Inotersen is authorised for the treatment of stage 1 or stage 2 PN in adult patients with hATTR. DN, diabetic neuropathy; hATTR, hereditary transthyretin amyloidosis; mNIS+7, modified neuropathy impairment score +7; QoL, quality of life; SC, subcutaneous.
AKCEA-TTR-L_{Rx}

Patients with Hereditary and Wildtype ATTR
AKCEA-TTR-L\textsubscript{Rx}  
In Development to Treat Patients with All Forms of TTR Amyloidosis

- Utilizes our most advanced LICA chemistry, providing high potency with potential for improved convenience and tolerability
- In partnership with Akcea Therapeutics, a rapid and comprehensive development strategy is underway to treat all forms of TTR amyloidosis

*Co-developing with Akcea*
LICA (Ligand Conjugated Antisense)
Game Changing Advance in Potency

ASGR mediates productive uptake of GalNAc₃-Conjugated ASOs by hepatocytes

- Enhanced tissue-specific potency
- Low dose volume
- Monthly dosing regimen

Increased Potency Observed with GalNAc$_3$-Conjugated PS 2’MOE ASOs across Phase 1 Healthy Volunteer Studies

GalNAc$_3$-conjugated ASOs have demonstrated a 20 to 30-fold increase in potency and an improved safety and tolerability profile compared to parent ASOs in human clinical trials.

AKCEA-TTR-L\textsubscript{Rx}  
Anticipated Profile

• High Potency  
  • ≥ 90% reduction in TTR levels at low doses
• Convenience  
  • Once monthly low volume self-administered SC injection
• Improved safety & tolerability profile  
  • No unusual monitoring (including platelets/renal)
• Combination with stabilizers not contraindicated
AKCEA-TTR-L$_{Rx}$
Phase 1/2 Study Objectives

• Primary Objective:
  ▪ Evaluate the safety and tolerability of single and multiple subcutaneous doses of AKCEA-TTR-L$_{Rx}$ in healthy volunteers and patients with ATTR

• Secondary and Exploratory Objectives:
  ▪ Evaluate the pharmacokinetics and pharmacodynamics following single and multiple subcutaneous doses of AKCEA-TTR-L$_{Rx}$ in healthy volunteers and patients with ATTR
AKCEA-TTR-L<sub>Rx</sub>
Phase 1 Study Design in Healthy Volunteers

A randomized, blinded, placebo-controlled, dose-escalation study

**Screening**
- 4 weeks

**Dosing**
- Day 1: 29
- Day 29: 57
- Day 57: 85

**Post-Treatment Evaluation Period**
- 13 weeks

Day 203
End Study

Subcutaneous Injections
- monthly multiple dose cohorts
- single dose cohort

<table>
<thead>
<tr>
<th>Healthy Volunteers</th>
<th>Cohorts</th>
<th># Doses</th>
<th>AKCEA-TTR-L&lt;sub&gt;Rx&lt;/sub&gt; (n)</th>
<th>PBO (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>90 mg</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>120 mg</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
AKCEA-TTR-L$_{Rx}$
Dose-dependent Reductions in TTR Levels in Healthy Volunteers
AKCEA-TTR-L\textsubscript{Rx} Summary Phase 1 Results in Healthy Volunteers

Robust PD Profile

- TTR reductions maintained between monthly doses as predicted by PK properties of these drugs
- Maximum mean reductions of 86% and 94%, from baseline two weeks after the 4\textsuperscript{th} dose of 45 and 90 mg, respectively

No Safety Issue Identified

- No SAEs
- No treatment-related safety signals
  - No effect on platelets
  - No hepatic or renal safety signals
  - No dose discontinuations
AKCEA-TTR-L$_\text{Rx}$
Development Path
# Inotersen

## Investigator Initiated Phase 2 ATTR-CM Studies

<table>
<thead>
<tr>
<th>Phase/Study</th>
<th>Phase II Investigator Study (M. Benson, MD)</th>
<th>Phase II Investigator Study* (R. Falk, MD)</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>ATTR-CM (n=33)</td>
<td>ATTR-CM (n~50)</td>
</tr>
<tr>
<td>Design</td>
<td>Open-Label up to 5 years</td>
<td>Open-Label up to 3 years</td>
</tr>
<tr>
<td>Key Endpoints</td>
<td>Safety/Tolerability Efficacy vs Natural History Data</td>
<td>Safety/Tolerability Efficacy vs Patient Hx &amp; Disease Nat Hx</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Outcome</td>
<td>Long-Term Safety demonstrated w/ Evidence of Efficacy</td>
<td>Just initiated</td>
</tr>
</tbody>
</table>

* See abstract, this meeting
**Phase 2 Open-Label Investigator Initiated Study**  
Benson & Dasgupta, Indiana University School of Medicine

<table>
<thead>
<tr>
<th>Single center, investigator trial in patients with TTR cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Wild-type and hereditary ATTR-CM</td>
</tr>
<tr>
<td>• Open-label design</td>
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<tr>
<td>• Up to 5 years of treatment</td>
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</table>

Objective is to evaluate long-term safety and clinical efficacy of inotersen in patients with ATTR cardiomyopathy (vs natural history data)

**Main inclusion criteria:**

- Biopsy-proven ATTR cardiomyopathy with clinical CHF symptoms (hereditary or wild type)
- LVW thickness $\geq$ 1.3 cm on transthoracic echocardiography

Inotersen 300 mg SC weekly
### Patient Disposition and Baseline Characteristics

#### Enrollment

<table>
<thead>
<tr>
<th>N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary n=10</td>
</tr>
<tr>
<td>Wild-type n=23</td>
</tr>
</tbody>
</table>

#### Study Withdrawals

- October 2018: 5 Withdrawals
- 1 year: 2 Withdrawal
- 2 years: 2 Withdrawals
- 3 years: 2 Withdrawals

#### Baseline

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Wild-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>63.4</td>
</tr>
</tbody>
</table>

#### Mutations

<table>
<thead>
<tr>
<th></th>
<th>Hereditary</th>
<th>Wild-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>T60A</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>V30M</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>P24S</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

#### Other

<table>
<thead>
<tr>
<th></th>
<th>Hereditary</th>
<th>Wild-Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacemaker</td>
<td>1 (10%)</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>2 (20%)</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>CAD</td>
<td>0</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>HTN</td>
<td>2 (20%)</td>
<td>9/23 (39%)</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; HTN, hypertension

9 Study Withdrawals: 6 Voluntary; 2 Non-compliance; 1 Death, Non-related.

Dasgupta, et al. (2019, manuscript submitted). Inotersen Therapy of Transthyretin Amyloid Cardiomyopathy
Phase 2 ATTR-CM: Case Presentation
63-year-old Caucasian male with threonine-60-alanine mutation

- LVEF remained in the normal range
- LV longitudinal strain remained stable
- BNP decreased from 161 to 22 pg/ml without the use of diuretics
- 6MWD increased 97.2 meters

Phase 2 Investigator Study of Inotersen Demonstrates Stabilization or Improvements of TTR Cardiomyopathy

Patients treated for more than 3 years

Inotersen
Demonstrates Stabilization and Improvements in TTR Cardiomyopathy Investigator Study

• **No severe** thrombocytopenia or drug-related renal adverse events

• Mild injection site reactions in 25% patients, with a few patients experiencing mild flu-like symptoms

• One non-drug related death after surgery due to cardiac arrest

• **Strong evidence** of efficacy at 2 and 3 years of therapy compared to natural history
  • Improved 6 minute walk distance
  • Reduced left ventricular mass
  • Decrease in mean BNP compared to baseline
AKCEA-TTR-L_{Rx} 
ATTR-CM Phase 3 Study Schema and Key Information

A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AKCEA-TTR-L_{Rx} in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)

- Sample size: ~750
- Primary composite endpoint:
  CV death and CV clinical events
- Secondary endpoints:
  6MWT, KCCQ, CV clinical events
- Exploratory endpoints:
  Echo, biomarkers, PROs, (potential CMRI sub-study)
Adults with hATTR-PN meeting all 3 of the following criteria:

- **Stage 1 or Stage 2**
- **Documented TTR genetic mutation**
- **Symptoms and signs consistent with polyneuropathy** (NIS ≥ 10 and ≤ 130)
A Comprehensive Therapeutic Franchise to Treat All Forms of Transthyretin Amyloidosis

Inotersen demonstrated substantial benefit with manageable safety in Phase 3 NEURO-TTR study

- First-approved RNA-targeted therapeutic for hATTR-PN
- Published in *New England Journal of Medicine* (Benson, M.D. et al. 2018; 379: 22-31)
- Approved in the US, Canada and European Union for the treatment of polyneuropathy in adult patients with hATTR

**NEURO-TTR OLE** demonstrating long-term benefit with no new safety concerns with long-term treatment

- Patients previously on placebo experiencing disease stabilization
- Disease improvement achieved in many patients
- Earlier treatment results in better outcomes

Long-term safety with strong evidence of clinical efficacy in patients with wild type and hereditary TTR cardiomyopathy *(Benson & Dasgupta, Open-label Phase 2 Investigator Initiated Study)*

Development of LICA follow-on medicine (AKCEA-TTR-L<sub>Rx</sub>) for all forms of ATTR underway

- Phase I study in healthy volunteer nearly complete
- Phase III pivotal studies in hATTR-PN & ATTR-CM to initiate in 2H 2019