Pipeline Overview & Updates from ATTR and ALN-PCSsc

Akshay Vaishnaw, M.D., Ph.D.
Executive VP of R&D and Chief Medical Officer
## Development Pipeline

### Genetic Medicines

<table>
<thead>
<tr>
<th>Category</th>
<th>Discovery</th>
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### Cardio-Metabolic Diseases

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### Hepatic Infectious Diseases

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- 7 clinical programs
- 6 with human POC

Updated December 6, 2015
# Development Pipeline

## Genetic Medicines

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Transthyretin-Mediated Amyloidosis (ATTR) Program
Unmet Need and Product Opportunity

**Progressive, debilitating monogenic disease**
- ATTR is significant orphan disease
  - ~50,000 Patients worldwide
- Clinical pathology
  - Onset ~40 to >60 yr; fatal within 2-15 years
  - Two predominant forms
    - Familial amyloidotic polyneuropathy (FAP)
    - Familial amyloidotic cardiomyopathy (FAC)
- Halting disease progression remains unmet need
  - Liver transplantation required early
  - TTR stabilizers provide modest benefit

**Mutant transthyretin (TTR) is genetic cause**
- Autosomal dominant with >100 defined mutations
- Misfolds and forms amyloid deposits in nerves, heart, other tissues

**RNAi opportunity as potentially transformative therapy**
- Knockdown disease-causing protein
- Aim to halt progression, possibly achieve regression
- Value proposition supported by pharmacoeconomics and cost of disease burden
- Concentrated provider base and active patient community
## Patisiran, Revusiran & ALN-TTRsc02 for ATTR

### Alnylam Reproducible and Modular Platform

<table>
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<tr>
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<th>Genetically validated, liver-expressed target gene</th>
<th>Mutant <strong>Transthyretin (TTR)</strong> is disease-causing protein in Transthyretin-Mediated Amyloidosis (ATTR)</th>
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<td>1</td>
<td><strong>Biomarker for POC in Phase 1</strong></td>
<td>Blood-based biomarker <strong>TTR</strong> causes amyloid deposits in nerves (FAP) and heart (FAC)</td>
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<td><strong>Definable path to approval and market</strong></td>
<td>Streamlined clinical development plans</td>
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<td>Established Endpoints:</td>
<td>• <strong>Neurological Impairment Score (FAP)</strong></td>
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<td>• <strong>6 Minute Walk Distance (FAC)</strong></td>
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TTR Knockdown and Clinical Outcomes
Rationale for Expected Benefit

TTR knockdown is validated approach

- ~50% Knockdown in other systemic amyloidoses
  - Disease improvement or stabilization
- Elimination of mutant TTR following liver transplantation
  - Disease improvement or stabilization
- V30M transgenic mouse model data
  - Complete amyloid regression with TTR knockdown

Gillmore et al., Lancet; 358:24-9 (2001)

~50% Lowering in AL Amyloidosis

~50% Lowering in AA Amyloidosis
RNAi Therapeutics for ATTR Amyloidosis
Patisiran and Revusiran

Patisiran for Familial Amyloidotic Polyneuropathy (FAP)
- Intravenous administration
- Positive Phase 2 results in FAP patients
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Clinical endpoints every 6 months
  - Positive 18-month data reported at EC-ATTR, November 2015
  - 24-month data expected in 2016
- APOLLO Phase 3 trial ongoing
  - Over 40 sites in over 15 countries
  - Expect to complete enrollment in next 2-3 months
  - If positive, APOLLO to enable NDA submission in 2017
  - APOLLO-OLE ongoing

Revusiran for Familial Amyloidotic Cardiomyopathy (FAC)
- Subcutaneous administration
  - STC “first generation” chemistry
- Positive Phase 2 study results
  - TTR cardiac amyloidosis patients
- Phase 2 Open-Label Extension (OLE) study ongoing
  - Clinical endpoints every 6 months
  - Positive 6-month data reported at EC-ATTR, November 2015
  - 12-month data expected in 2016
- DISCOVERY study ongoing
  - Prevalence of TTR mutations in suspected cardiac amyloidosis
  - Multi-center study; up to 1,000 patients
- ENDEAVOUR Phase 3 trial ongoing
- Also advancing ALN-TTRsc02
  - ESC “second generation” chemistry
  - IND expected in early 2016
  - Phase 3 start planned for 2017
Patisiran Phase 2 OLE Preliminary Study Results*
Change in mNIS+7 at 18 Months

Evidence that neuropathy progression potentially halted at 18 months
• Mean mNIS+7 increase of 1.7 points observed
  ◦ Similar result in patients with/without concurrent TTR stabilizer therapy
• Compares favorably with 22 to 26 point mNIS+7 increase estimated from historical data sets
• Sustained TTR knockdown through 21 months (mean max KD of 91%; max KD up to 96.2%)
• Generally well tolerated out to 23 months
  ◦ No drug-related SAEs
  ◦ Mild flushing (25.9%) and infusion-related reactions (18.5%) most common adverse events
  ◦ No significant lab findings, no drug-related discontinuations

Potent knockdown of disease-causing non-native TTR (NNTTR) species of approximately 90%^*

*Phase 2 OLE results based on data in database as of September 22, 2015; Adams, EC-ATTR, November 2015
^Collaboration with Kelly Lab at Scripps and Misfolding Diagnostics, Inc.
Adams, AAN Apr. 2015
Suhr, ANA, Sept. 2015
Patisiran Phase 2 OLE Preliminary Study Results* 
Improvement in Nerve Fiber Density

First-ever evidence suggesting TTR knockdown can lead to nerve regeneration
- Mean 4.9 m/mm³ increase from baseline in sweat gland nerve fiber density from distal thigh skin biopsy (p<0.001)
  - Read histologically by central lab in masked manner
- Recent paper^ shows lower sweat gland nerve fiber density associated with greater walking disability and shorter time to loss of ambulation

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Phase 2 OLE results based on data in database as of September 22, 2015; Adams, EC-ATTR, November 2015
^Chao C et al., Ann Neurol. 78:272-83 (2015)
**APOLLO Phase 3 Study Design**

**Enrollment Nearing Completion**

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**Patient Population**
- FAP: any TTR mutation, Stages 1 and 2
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

**Endpoints**
- mNIS+7 at 18 months
- Norfolk QOL-DN
- NIS-weakness
- mBMI
- 10-meter walk test
- COMPASS-31
- EQ-5D QOL
- NIS+7
- Serum TTR levels
- Cardiac assessments
- Grip strength
- Rausch-built Overall Disability Scale

**Statistical Considerations**
- Placebo-estimated mNIS+7 progression rate of 17.8 points/yr derived from natural history study of 283 FAP patients
- Study with 90% power to detect as little as 37.5% difference in ΔmNIS+7 between treatment groups with 2-sided alpha=0.05
- Potential interim analysis for efficacy under consideration; regulatory discussions pending

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All completers eligible for patisiran treatment on Phase 3 OLE study (APOLLO-OLE)

**Expect to complete enrollment in next 2-3 months, in support of 2017 NDA if positive**

Clinicaltrials.gov # NCT01960348
Revusiran Phase 2 OLE Preliminary Study Results*

Open label, multi-dose study in TTR cardiac amyloidosis patients

- 6 Month study results, includes patients with FAC and senile systemic amyloidosis (SSA)
- Weekly SC doses of 500 mg
- Up to 97.5% TTR knockdown with similar effects toward WT and mutant protein
- Stable 6-MWD in majority of evaluable patients (N=15)
  - Mean decline of 20-24 meters in FAC and SSA patients
- Generally well tolerated in majority of patients
  - SAEs in 8 patients (32%), including one death due to infiltrative cardiomyopathy; all SAEs deemed not related to drug
  - Majority of AEs mild or moderate; ISRs reported in 11 patients (44%)
  - As previously reported, 3 discontinuations due to ISRs or diffuse rash; no further discontinuations due to ISRs

*Results as of October 13, 2015; Gilmore, EC-ATTR, November 2015
Phase 3 Study Design

**Patient Population**
- Documented TTR mutation, including V122I or other
- Amyloid deposits on biopsy (cardiac or non-cardiac)
- History of heart failure
- Evidence of cardiac amyloid involvement by echocardiogram

**Endpoints**
- Change in 6-MWD at 18 months compared to baseline
- Percent reduction in serum TTR over 18 months
- Composite CV mortality and CV hospitalization
- Change in NYHA class
- Change in Kansas City Cardiomyopathy Questionnaire (KCCQ)

**Statistical Considerations**
- Placebo-estimated decline in 6-MWD of ~140 meters over 18 months in natural history study of 137 FAC patients (N=39 for 6-MWD data)
- 90% Power to detect as little as 39% difference in 18 mo change from baseline 6-MWD between treatment groups with significance level of p <0.05
- Un-blinded interim analysis for futility when ~50% of patients reach 18 mos

All completers eligible for revusiran treatment on Phase 3 OLE study
TTR Knockdown Selected Studies of Patisiran, Revusiran, and ISIS-TTR\textsubscript{Rx}

Mean [±/ SEM] Serum TTR Knockdown Over Time by Different RNA Therapeutics*

Different RNA Therapeutics
- ISIS-TTR\textsubscript{Rx}, Regraphed data
- Patisiran OLE (N=27)
- Revusiran OLE (N=25)

Sustained TTR Reductions Observed Over 1 Year of Treatment

*The above graphs do not represent data from head-to-head studies and direct comparisons can not be made. All trials were performed independently. Inset: Benson et. al., EC-ATTR 2015 (abstract # PM14)
Superior TTR Knockdown with ALN-TTRsc02
ALN-TTRsc02 Compared to Revusiran in NHP**

**Data on graph does not represent a side by side study. The two NHP studies were performed independently.
# ATTR Target Product Profiles

**Patisiran, Revusiran & ALN-TTRsc02**

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<tr>
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<th>Patisiran</th>
<th>Revusiran</th>
<th>ALN-TTRsc02</th>
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<tr>
<td><strong>Indication</strong></td>
<td>• TTR-mediated familial amyloidotic polyneuropathy (FAP)</td>
<td>• TTR-mediated familial amyloidotic cardiomyopathy (FAC)</td>
<td>• All patients with ATTR amyloidosis</td>
</tr>
<tr>
<td><strong>Dose and Regimen</strong></td>
<td>• 0.3 mg/kg once every 3 weeks</td>
<td>• 500 mg daily x 5 days, followed by 500 mg weekly maintenance</td>
<td>• 50-100 mg quarterly (qQ)</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>• IV infusion with premedication</td>
<td>• Subcutaneous via auto-injector</td>
<td>• &lt;1mL, subcutaneous via auto-injector</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Primary: Prevent progression of neuropathy</td>
<td>• Primary: Maintain 6-minute walk distance</td>
<td>• Primary: &gt; 90% suppression of circulating TTR</td>
</tr>
<tr>
<td></td>
<td>• Secondary: Maintain QoL and nutritional status</td>
<td>• Secondary: Reduction in risk of disease progression and death</td>
<td>• Secondary: Disease stabilization or better</td>
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<tr>
<td><strong>Safety</strong></td>
<td>• Low incidence of mild-moderate infusion reactions</td>
<td>• Mild-moderate ISRs</td>
<td>• Very low incidence of mild-moderate ISRs</td>
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<td>• No significant impact on liver or kidney function</td>
<td>• Low incidence of mild, reversible LFT changes</td>
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Target product profiles for investigational RNAi therapeutics reflect current thinking on desired product characteristics and are subject to change.
## Development Pipeline

### GENETIC MEDICINES
- **TTR-Mediated Amyloidosis**
  - **Discovery**: Patisiran
  - **Development**: Revisiran
- **Hemophilia and Rare Bleeding Disorders**
  - **Discovery**: Fitusiran
- **Complement-Mediated Diseases**
  - **Discovery**: ALN-CC5
- **Hepatic Porphyrias**
  - **Discovery**: ALN-AS1
- **Alpha-1 Antitrypsin Deficiency**
  - **Discovery**: ALN-AAT
- **Primary Hyperoxaluria Type 1**
  - **Discovery**: ALN-GO1
- **TTR-Mediated Amyloidosis**
  - **Discovery**: ALN-TTRsc02
- **Beta-Thalassemia/Iron-Overload Disorders**
  - **Discovery**: ALN-TMP
- **Additional Genetic Medicine Programs**

### CARDIO-METABOLIC DISEASES
- **Hypercholesterolemia**
  - **Discovery**: ALN-PCSsc
- **Hypertriglyceridemia**
  - **Discovery**: ALN-AC3
- **Mixed Hyperlipidemia/Hypertriglyceridemia**
  - **Discovery**: ALN-ANG
- **Hypertension/Preeclampsia**
  - **Discovery**: ALN-AGT
- **Additional Cardio-Metabolic Programs**

### HEPATIC INFECTIOUS DISEASES
- **Hepatitis B Virus Infection**
  - **Discovery**: ALN-HBV
- **Hepatitis D Virus Infection**
  - **Discovery**: ALN-HDV
- **Chronic Liver Infection**
  - **Discovery**: ALN-PDL
- **Additional Hepatic ID Programs**

*Updated December 8, 2015*
# Development Pipeline

## Genetic Medicines
- **TTR-Mediated Amyloidosis**
- **Hemophilia and Rare Bleeding Disorders**
- **Complement-Mediated Diseases**
- **Hepatic Porphyrias**
- **Alpha-1 Antitrypsin Deficiency**
- **Primary Hyperoxaluria Type 1**
- **TTR-Mediated Amyloidosis**
- **Beta-Thalassemia/Iron-Overload Disorders**
- **Additional Genetic Medicine Programs**

### Phase 1
- **Patisiran**
- **Fitusiran**
- **ALN-CC5**
- **ALN-AS1**
- **ALN-AAT**
- **ALN-G01**
- **ALN-TTRsc02**

### Phase 2
- **ALN-TMP**

### Phase 3
- **Revisiran**

## Cardio-Metabolic Diseases
- **Hypercholesterolemia**
- **Hypertriglyceridemia**
- **Mixed Hyperlipidemia/Hypertriglyceridemia**
- **Hypertension/Preeclampsia**
- **Additional Cardio-Metabolic Programs**

### Phase 1
- **ALN-AC3**
- **ALN-ANG**
- **ALN-AGT**

### Phase 3
- **ALN-PCSsc**

## Hepatic Infectious Diseases
- **Hepatitis B Virus Infection**
- **Hepatitis D Virus Infection**
- **Chronic Liver Infection**
- **Additional Hepatic ID Programs**

### Phase 1
- **ALN-HBV**

### Phase 2
- **ALN-HDV**

### Phase 3
- **ALN-PDL**
Unmet need in hypercholesterolemia

- Elevated LDL-C validated risk factor for coronary heart disease (CHD)
- 34 million Americans have hypercholesterolemia (> 240 mg/dL)
- Recent clinical studies
  - Many patients on statins do not meet LDL-C goal
  - Lower LDL-C is better (IMPROVE-IT)
- Multiple genetically defined patient subgroups

PCSK9 is genetically validated target

- GOF mutations associated with hypercholesterolemia and premature CHD
- LOF mutations associated with hypocholesterolemia and decreased CHD risk

Blazing e al Am. Heart J; 168:205 (2014)
**ALN-PCSsc for Hypercholesterolemia**
Alnylam Reproducible and Modular Platform

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<td><strong>PCSK9</strong> protein decreases LDL-C receptor levels, resulting in elevated cholesterol in blood.</td>
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<td>Loss-of-function mutations in PCSK9 associated with lower LDL-C and decreased CV risk</td>
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<td>Blood-based biomarkers for regulation of cholesterol levels:</td>
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<td></td>
<td>• <strong>PCSK9</strong></td>
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<td>• <strong>LDL-C</strong></td>
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<td>Pivotal trial in broad population of ACVD patients; focused FH studies</td>
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<td>Established Endpoint: <strong>LDL-C</strong></td>
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ALN-PCSsc Phase 1 Study
Healthy Subjects with LDL-C >100mg/dl, On or Off Statins

**Primary objectives**
- Safety, tolerability

**Secondary objectives**
- PK, PCSK9 and LDL-C reduction

**Part A: Single Dose (SAD)**
Randomized 3:1, Single blind, Placebo controlled
- 25 mg x 1 SC
- 100 mg x 1 SC
- 300 mg x 1 SC
- 500 mg x 1 SC
- 800 mg x 1 SC

**Part B: Multi-Dose (MD)**
Randomized 6:2, Single blind, Placebo controlled, On or off statins
- 125mg qW x 4 SC
- 250mg q2W x 2 SC
- 300mg qM x 2 SC
- 500 mg qM x2 SC
+/- Statin

= dose
Initial ALN-PCSsc Phase 1 Study Results
SAD PCSK9 Knockdown Relative to Baseline

Max PCSK9 knockdown of 88.7% with mean max of 82.3 ± 2.0%

Fitzgerald et al., AHA, Nov. 2015
Initial ALN-PCSsc Phase 1 Study Results
MD PCSK9 Knockdown Relative to Baseline

Max PCSK9 knockdown of 94.4% with mean max of 88.5 ± 1.6%

Fitzgerald et al., AHA, Nov. 2015
Initial ALN-PCSsc Phase 1 Study Results
SAD LDL-C Lowering Relative to Baseline

Max LDL-C reduction of 78.1% with mean max of 59.3 ± 5.0%

Fitzgerald et al., AHA, Nov. 2015
Initial ALN-PCSsc Phase 1 Study Results
MD LDL-C Lowering Relative to Baseline

Mean (+/− SEM) LDL-C Reduction Relative to Baseline

Treatment

- Placebo
- 300 mg S ^ qMx2
- 125 mg qWX4
- 500 mg qMx2
- 250 mg q2WX2
- 500 mg S ^ qMx2
- 300 mg qMx2

S ^ =On a stable dose of statins
Two MD subjects excluded:
One placebo subject elected to discontinue;
One subject in 300 mg statin group was incarcerated on Day 14

Max LDL-C reduction of 83.0% with mean max of 64.4 ± 5.4%
# ALN-PCSsc Target Product Profile

<table>
<thead>
<tr>
<th>ALN-PCSsc</th>
<th>Target Product Profile</th>
</tr>
</thead>
</table>
| **Indication** | • Treatment of elevated LDL-cholesterol in patients on diet and maximally tolerated statin therapy  
• Atherosclerotic cardiovascular disease (ASCVD)  
• ASCVD Risk Equivalents (e.g., diabetes)  
• HeFH  
• HoFH |
| **Dose and Regimen** | • Quarterly (qQ) or bi-annually (q2Q) |
| **Route of Administration** | • Low volume, subcutaneous injection |
| **Efficacy** |  
**Primary**  
• LDL-C reduction of ≥50% in combination with statins  
**Secondary**  
• >80% patients reaching goal of <70mg/dl LDL-C  
• Prevention of cardiovascular events |
| **Safety** | • Comparable or better than MAbs |

Target product profiles for investigational RNAi therapeutics reflect current thinking on desired product characteristics and are subject to change.
ORION-1 Phase 2 Clinical Study

480 ASCVD subjects with elevated LDL-C on maximal lipid lowering therapy

**Primary objectives**
- LDL-C levels at day 180

**Secondary objectives**
- Safety and tolerability, PCSK9 and LDL-C reduction and duration of effect qQ vs Bi-annual, proportion of patients reaching global lipid guidelines, changes in other lipoprotein levels

**Randomized 3:1, Double blind, Placebo controlled**

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
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<tbody>
<tr>
<td>Placebo x 1 SC</td>
<td>60</td>
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<tr>
<td>200 mg x 1 SC</td>
<td>60</td>
</tr>
<tr>
<td>300 mg x 1 SC</td>
<td>60</td>
</tr>
<tr>
<td>500 mg x 1 SC</td>
<td>60</td>
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</table>

Open label extension

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
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<tbody>
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<tr>
<td>100 mg qQ x 2 SC</td>
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<td>200 mg qQ x 2 SC</td>
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<tr>
<td>300 mg qQ x 2 SC</td>
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## Development Pipeline

### Genetic Medicines

<table>
<thead>
<tr>
<th>Condition</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td>TTR-Mediated Amyloidosis</td>
<td>ALN-GO1</td>
<td>ALN-TTRsc02</td>
<td>Patisiran</td>
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<tr>
<td>Hemophilia and Rare Bleeding Disorders</td>
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<td>ALN-CC5</td>
<td>Fitusiran</td>
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<tr>
<td>Complement-Mediated Diseases</td>
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<td>Revusiran</td>
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<td>Hepatic Porphyrias</td>
<td>ALN-AS1</td>
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<td>Alpha-1 Antitrypsin Deficiency</td>
<td>ALN-AAT</td>
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<td>Primary Hyperoxaluria Type 1</td>
<td>ALN-TMP</td>
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<td>Beta-Thalassemia/Iron-Overload Disorders</td>
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<td>Additional Genetic Medicine Programs</td>
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### Cardio-Metabolic Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Hypercholesterolemia</td>
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<td>ALN-PCSsc</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>ALN-AC3</td>
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<td>Mixed Hyperlipidemia/Hypertriglyceridemia</td>
<td>ALN-ANG</td>
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<tr>
<td>Hypertension/Preeclampsia</td>
<td>ALN-AGT</td>
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<td>Additional Cardio-Metabolic Programs</td>
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### Hepatic Infectious Diseases

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<th>Condition</th>
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<th>Phase 3</th>
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<tbody>
<tr>
<td>Hepatitis B Virus Infection</td>
<td>ALN-HBV</td>
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<td>Hepatitis D Virus Infection</td>
<td>ALN-HDV</td>
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<td>Chronic Liver Infection</td>
<td>ALN-PDL</td>
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<td>Additional Hepatic ID Programs</td>
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7 clinical programs 6 with human POC