Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1
Agenda

Welcome
• Joshua Brodsky – Director, Investor Relations & Corporate Communications

Introduction
• Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Primary Hyperoxaluria Type 1 & Physician Perspective
• Elaine M. Worcester, M.D. – Nephrologist & Professor of Medicine, University of Chicago Medicine

Patient & Caregiver Perspective
• Andrew – Patient Diagnosed with Primary Hyperoxaluria Type 1
• Nicole – Andrew’s Wife and Caregiver

Early Stage Clinical Data & ILLUMINATE Studies
• Kenji Fujita, M.D. – Vice President, Clinical Development

Lumasiran Program Opportunity in PH1 & Disease Education/Diagnosis Initiatives
• Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Q&A Session
Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation
- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface.

Replay, slides and transcript available at www.alnylam.com/capella
This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including lumasiran; pre-clinical and clinical results for our product candidates, including lumasiran; actions or advice of regulatory agencies, including with respect to lumasiran; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; the timing of regulatory submissions for our product candidates, including lumasiran, and our ability to obtain and maintain regulatory approval, pricing and reimbursement for such products, including lumasiran; our progress in establishing a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including lumasiran if approved by regulatory agencies; competition from others using similar technology and developing products for similar uses; as well as those risks more fully discussed in our most recent report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors or risks materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. The safety and efficacy of lumasiran are being evaluated in the ILLUMINATE Phase 3 program and have not yet been reviewed by the FDA, EMA or any other regulatory agency. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.
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Q&A Session
RNAi Therapeutics: New Class of Innovative Medicines
Clinically Proven Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome
- Potent and durable mechanism of action
- Product engine for sustainable pipeline
- Now commercial
# Alnylam Clinical Development Pipeline

**Focused in 4 Strategic Therapeutic Areas (STAs):**

<table>
<thead>
<tr>
<th>Cytogenetic Medicines</th>
<th>Cardio-Metabolic Diseases</th>
<th>Human POC(^1)</th>
<th>Breakthrough Designation</th>
<th>Early Stage</th>
<th>Late Stage</th>
<th>Registration/Commercial(^3)</th>
<th>Commercial Rights</th>
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<tr>
<td>Genomic Medicine</td>
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### Early Stage

**hATTR Amyloidosis\(^2\)**  
- POC, proof of concept as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies  
- **Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy**

<table>
<thead>
<tr>
<th><strong>Cemdisiran</strong></th>
<th><strong>Pozelimab</strong></th>
<th><strong>Combo</strong>(^4)</th>
<th><strong>Complement-Mediated Diseases</strong></th>
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<tbody>
<tr>
<td><strong>Inclisiran</strong></td>
<td>Acute Hepatic Porphyria</td>
<td><strong>Hemophilia</strong> and Rare Bleeding Disorders</td>
<td>Hypercholesterolemia</td>
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<td><strong>Lumisiran</strong></td>
<td>Primary Hyperoxaluria Type 1</td>
<td><strong>Primary Hyperoxaluria Type 1</strong></td>
<td>Hyperlipidemia</td>
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<tr>
<td><strong>Vutrisiran</strong></td>
<td>ATTR Amyloidosis</td>
<td><strong>ATTR Amyloidosis</strong></td>
<td>Hypercholesterolemia</td>
</tr>
</tbody>
</table>

**Cemdisiran/Pozelimab Combo\(^4\)**  
- Includes marketing application submissions

**ALN-AAT02**  
- **Alpha-1 Liver Disease**

**ALN-HBV02 (VIR-2218)**  
- **Hepatitis B Virus Infection**

**ALN-AGT**  
- **Hypertension**

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1. POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
2. Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy
3. Includes marketing application submissions
4. Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

As of October 2019
# Alnylam Clinical Development Pipeline

**Focused in 4 Strategic Therapeutic Areas (STArs):**

<table>
<thead>
<tr>
<th>HUMAN POC</th>
<th>BREAKTHROUGH DESIGNATION</th>
<th>EARLY STAGE (IND or CTA Filed Phase 2)</th>
<th>LATE STAGE (Phase 2-Phase 4)</th>
<th>REGISTRATION/COMMERCIAL</th>
<th>COMMERCIAL RIGHTS</th>
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As of October 2019
Primary Hyperoxaluria Type 1
Rare Genetic Disorder of Increased Endogenous Oxalate Synthesis

Primary Hyperoxaluria Type 1 (PH1):
- Due to defect in liver peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)
- Phenotype varies significantly in patients and may present at any age, typically in childhood
- Prevalence of PH1: 1-3/1,000,000 in Europe\(^1\) and ~32/1,000,000 in Middle East\(^2\)

Pathophysiology\(^1\):
- Overproduction of oxalate results in insoluble calcium oxalate crystals leading to urolithiasis, nephrocalcinosis, and kidney failure
- Disease course ultimately leads to multi-organ damage from systemic oxalosis

No therapies are approved for treatment of PH1

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Q&A Session
Primary Hyperoxaluria
Inherited diseases that lead to increased production of Oxalate by the liver. Oxalate is toxic and cannot be degraded in the human body. The kidney must excrete oxalate. Oxalate is poorly soluble and calcium oxalate crystals form in the kidneys leading to stones and kidney failure.

Genetic defects in glyoxylate metabolism resulting in the three types of primary hyperoxaluria (PH)

PH1 (80% of cases)
Absence or decreased activity of AGT

PH2 (10% of cases)
Absence or decreased activity of GRHPR

PH3 (5% of cases)
Absence of HOGA

AGT: Alanine:glyoxylate aminotransferase
GRHPR: Glyoxalate reductase/hydroxypyruvate reductase
HOGA: 4-hydroxy-2-oxoglutarate aldolase

Prevalence data from Rare Kidney Stone Consortium
Prevalence of PH1

PH1 prevalence estimated at 1-3 cases/million people in Europe.

Prevalence is increased in countries with high rates of consanguineous marriages, such as the Middle East, Pakistan and North Africa.

PH1 causes about 1-2% of pediatric ESRD in Europe, but 17% in Tunisia.

OxalEurope data, thanks to SF Garrelfs
Stages of disease in PH1

Cochat and Rumsby, NEJM 369:649, 2013
Patterns of presentation of PH:
1. Infantile oxalosis (26%) with nephrocalcinosis, failure to thrive, UTI. ESRD mean age 3 yr.
2. Childhood (30%) with frequent kidney stones, chronic kidney disease
3. Stone formation in adulthood (30%)
4. Recurrence after transplant for ESRD of unknown cause (10%)
5. Diagnosis after family screening (13%)

Variation in presentation may be due to the type of gene mutation. There may also be effects of environment or disease-modifying genes.
Range of oxalate excretion in PH1

One subject each of PH2 and PH3 included

Mobley et al Urolithiasis 44: 333, 2016
Urine oxalate:creatinine ratios from patients ≥ 5 years old
(Normal < 50 at age 5, < 25 by age 20)

Figure 3. Box and whisker plot of oxalate:creatinine ratios from patients aged five years or over, stratified according to diagnosis (PH1, PH2, PH3, all PH and ‘Others’). The circle represents the mean, the horizontal line the median, the box the interquartile range, the whiskers the 2.5th and 97.5th percentiles and the diamonds the 24 patients from the ‘others’ group with grossly elevated results.
Median age at symptom onset 4-5 years

Early diagnosis facilitates treatment to decrease stones and nephrocalcinosis and delay ESRD.

ESRD at diagnosis

< 18 yr – 34%
> 18 yr – 74%
25 yr old man presented with severe acute kidney failure after strenuous exercise
Normal kidney function 3 months earlier, no clinical history of stones

Kidney biopsy

ESRD in Primary Hyperoxaluria

N= 409 patients (73% with PH1)
112 patients presented with ESRD:
  PH1 35%
  PH2 10%
  PH3 0

Renal survival in 297 patients
without ESRD at diagnosis

Zhao et al. CJASN 11:119, 2016, Rare Kidney Stone Consortium
Prognosis for renal survival among patients with Primary Hyperoxaluria

In PH patients who did not have ESRD at the time of diagnosis, prognosis was related to oxalate excretion.

Mortality is much higher in patients with ESRD

Zhao et al CJASN 2016
Outcome of PH1 correlates with AGXT mutation type

Patient survival in the OxalEurope Cohort (n=526)

Age at ESRD was higher for those with at least one mutated G170R allele.

Mandrile et al. KI 86:1197, 2014
Organ involvement by oxalosis in PH1 with kidney failure

Oxalosis occurs when oxalate excretion by the kidney cannot keep up with production.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>Kidney</td>
<td>Stones, nephrocalcinosis</td>
</tr>
<tr>
<td>Frequent</td>
<td>Bone</td>
<td>Fractures, bone pain, poor growth</td>
</tr>
<tr>
<td></td>
<td>Eyes</td>
<td>Vision loss</td>
</tr>
<tr>
<td>Often</td>
<td>Arteries</td>
<td>Calcification</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Heart failure, abnormal rhythm, enlargement</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Occasional</td>
<td>Skin, nerves, muscle, bowel, joints</td>
<td></td>
</tr>
</tbody>
</table>
Native kidney from patient with PH1 and ESRD, removed at time of transplant

CT scan of kidney from 56 yr old man with PH1 on dialysis for 2 months

First stone – age 37
PH1 diagnosis – age 47
ESRD – age 56
History of > 20 stones

34 y/o F with PH1- CT progression 3 yrs
Oxalosis in Primary Hyperoxaluria

Femur of 3 year old child with followup three days later showing pathologic fracture

Calcification in the heart

Calcifications in blood vessels

Rootman et al Clinical Imaging 2018
Relationship between eGFR and plasma oxalate

- No stones
- Idiopathic stones
- Enteric hyperoxaluria
- Primary hyperoxaluria

Effect of dialysis on serum oxalate

Perinpam et al, Clin Biochem 2017
Hoppe et al KI 1999
Current treatment

- Hydration – goal to achieve fluid intake of 4 liters/day in adults, 2-3 liters in children, 1-1.5 in infants (may require placement of gastrostomy tube)
- Prompt treatment for vomiting or diarrhea, avoid salt depletion
- Crystallization inhibitors:
  - Citrate – 30-60 meq/day in adults
  - Orthophosphate
- Pyridoxine in patients with responsive mutations
- Use of endoscopic techniques for stone removal
- Renal replacement therapy and transplant
  - Combined liver and kidney, or sequential liver then kidney
  
  Patient survival after LKT 74% at 10 years
Current problems

- Improve awareness of Primary Hyperoxaluria to allow earlier detection and treatment
- Aggressive management to decrease recurrent stones, which may also decrease crystal deposition in tissue that leads to renal failure
- Better treatments to prevent renal failure
- Better treatments to avoid systemic oxalosis
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Q&A Session
Delay in diagnosis
Life on Dialysis
April 2018-August 2019
Destination: Liver/Kidney Transplant
Aug. 9th 2019
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Q&A Session
Lumasiran
Investigational RNA interference Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

Lumasiran (ALN-GO1):
• SC-administered small interfering RNA (siRNA)
  – Harnesses natural RNA interference (RNAi) mechanism

Therapeutic Hypothesis:
• Lumasiran targets the mRNA for HAO1 which encodes glycolate oxidase (GO) in the liver; the decreased production of GO reduces hepatic oxalate production

Lumasiran Therapeutic Hypothesis:

The safety and efficacy of lumasiran have not been evaluated by the U.S. Food and Drug Administration (FDA) or any other health agencies.
Lumasiran Phase 1/2 Study†

Study Design & Demographics: Part B (Patients with PH1)

Multiple-Ascending Dose (MAD) | Randomized 3:1, Single-blind, Placebo-controlled

1.0 mg/kg, q28d x 3 SC, N=4
3.0 mg/kg, q28d x 3 SC, N=4
3.0 mg/kg, q84d x 2 SC, N=4

Expansion Cohorts | Open-label

1.0 mg/kg, q28d x 3 SC, N=4
3.0 mg/kg, q28d x 3 SC, N=4

Inclusion Criteria:
• Patients with PH1
• Ages 6-64 years
• eGFR > 45 ml/min/1.73m²
• Urinary oxalate excretion > 0.70 mmol/24h/1.73m²

Key Endpoints:
• Safety and tolerability
• Urinary oxalate excretion
• Urinary oxalate to creatinine ratio

After median follow up of 9.8 months (range: 5.6 – 15.2), all patients enrolled in an open-label extension (OLE) study# for long-term dosing

†NCT02706886; #NCT03350451

eGFR, estimated glomerular filtration rate
# Lumasiran Phase 1/2 Study

## Patient Demographics: Part B (Patients with PH1)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Result (N=20)</th>
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<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>14.9 (6–43)</td>
</tr>
<tr>
<td>Age &lt;18 years</td>
<td>80%</td>
</tr>
<tr>
<td>Gender, females</td>
<td>65%</td>
</tr>
<tr>
<td>Mean weight, kg (range)</td>
<td>50.0 (21.3–112.5)</td>
</tr>
<tr>
<td>Mean eGFR, mL/min/1.73m² (range)</td>
<td>77.3 (42.5–130.7)</td>
</tr>
<tr>
<td>Mean Urine Oxalate Content, mmol/24hr/1.73m² (range)</td>
<td>1.69 (0.83–2.97)</td>
</tr>
<tr>
<td>Mean 24-hour Urine Oxalate:Creatinine Ratio (range)</td>
<td>0.17 (0.07–0.30)</td>
</tr>
</tbody>
</table>

**eGFR**, estimated glomerular filtration rate
Lumasiran Phase 1/2 Study Results

Safety: Part B (Patients with PH1)

Multiple doses of lumasiran well tolerated in patients with PH1

- No discontinuations from study treatment
- SAEs reported in 1 (33%) patient during placebo dosing and 4 (20%) patients after lumasiran dosing; none considered related to study drug by investigator
  - Placebo: 1 patient with SAEs of acute pyelonephritis and kidney stones
  - Lumasiran: 1 patient with kidney stones; 1 patient with vomiting; 1 patient with gastroenteritis; and 1 patient with abdominal pain, fever and vomiting
- AEs reported in 2 (66.7%) patients during placebo dosing and 20 (100%) patients after lumasiran dosing
  - Majority of AEs were mild or moderate in severity and considered unrelated to study drug by investigator
  - Severe AEs reported: 1 (33%) patient during placebo dosing (acute pyelonephritis) and 1 (5%) patients after lumasiran dosing (kidney stone); none considered related to study drug by investigator
  - AEs reported in >3 patients receiving lumasiran: pyrexia (N=6); vomiting, cough, abdominal pain, headache (N=5 each); and rhinitis and nephrolithiasis (N=4 each)
  - Self-limiting injection site reactions (ISRs) reported in 3 (15%) patients receiving lumasiran; all mild or moderate and none affected dosing
- No clinically significant laboratory changes
Lumasiran Phase 1/2 Study Results

Pharmacodynamics: Urinary Oxalate Content in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate of 75% (range: 43-92%) relative to baseline after lumasiran dosing in all cohorts† (N=20)

• The mean reduction relative to baseline 28 days post last dose of lumasiran was 66%
• 100% of patients achieved a urinary oxalate level ≤1.5x ULN and 70% of patients achieved a urinary oxalate level within the normal range‡
  - Among patients receiving 3.0 mg/kg monthly or quarterly doses of lumasiran, 11/12 (92%) achieved urinary oxalate levels within the normal range

Pharmacodynamics: Urinary Oxalate Content in Part B (Patients with PH1)


Only data points with at least 3 contributing patients are represented.

†Patients who had a valid 24-hour urinary oxalate assessment; placebo data not shown due to limited valid collections
‡1.5x ULN is defined as 0.69 mmol/24hr/1.73m²; normal range is defined as ≤0.46 mmol/24hr/1.73m²


Only data points with at least 3 contributing patients are represented.

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Lumasiran Phase 1/2 Study Results

Pharmacodynamics: Urinary Oxalate:Creatinine Ratio in Part B (Patients with PH1)

Mean maximal reduction in urinary oxalate:creatinine ratio of 77% (range: 50-95%) after lumasiran dosing in all cohorts (N=20)


*Patients randomized to placebo received subsequent dosing of lumasiran and are included in the lumasiran dosing cohort in which they were randomized with Day 1 relative to first dose of lumasiran; patient randomized to placebo in 3 mg/kg quarterly dosing only received a single dose of lumasiran on Day 1
Lumasiran Phase 1/2 and Phase 2 OLE

Study Design

- Patients previously dosed in Phase 1/2† study eligible to enroll into Phase 2^ open-label extension (OLE) study
  - All patients completed follow-up in Phase 1/2 have enrolled in OLE (N=20)
    - Data presented here represent 18 patients dosed in Phase 2 OLE, as of 8 Feb 2019
    - Preliminary efficacy data of urinary oxalate and urinary oxalate/creatinine ratio includes 9 and 10 patients, respectively, who have reached Day 85
- Patients have been on study for a median of 4 months (range: 0.03–8.36; N=18)

### Phase 1/2 Part B – Patients with PH1 (N=20)

- 1.0 mg/kg, q28d x 3 SC, N=8
- 3.0 mg/kg, q28d x 3 SC, N=8
- 3.0 mg/kg, q84d x 2 SC, N=4

### Phase 2 OLE (N=18)

- 1.0 mg/kg, q28d SC, N=3
- 3.0 mg/kg, q28d SC, N=6
- 3.0 mg/kg, q84d SC, N=9

Inclusion Criteria:
- Patients with PH1
- Ages 6-64 years
- eGFR > 45 ml/min/1.73m²
- Urinary oxalate excretion ≥ 0.70 mmol/24h/1.73m²

- Doses listed are the initial dose patients received in the Phase 2 OLE
- Patients were started at their original dose from the Phase 1/2 study unless different dose approved prior to dosing
Lumasiran Phase 2 OLE Study

Summary of Initial Results*

As of February 2019, patients have been on OLE for a median of 4 months (range: 0.03–8.36; N=18)

- Multiple doses of lumasiran demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study treatment or drug-related SAEs
- Mean maximal reduction in urinary oxalate of 72% (range: 41-90%) relative to Phase 1/2 baseline after lumasiran dosing in all cohorts (N=9)†

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*Data cut-off: 8 Feb 2019; †Patients who had a valid 24-hour urinary oxalate at or after Day 85; ‡Patients with a urinary oxalate assessment performed in the Phase 1/2 study collected within 30 days before Day 1 were not required to repeat the assessment

In the Phase 1/2 Study, lumasiran lowered UOx below 1.1 mmol/24hr/1.73m² in all patients with baseline excretion ≥ 1.6 mmol/24hr/1.73m².

- Renal survival was examined by quartile of urine oxalate (UOx) excretion (mmol/24hr/1.73m²) at diagnosis in patients with any form of PH. Among patients with PH who did not have ESRD at diagnosis, renal survival estimates were lower in those with highest level of urinary oxalate excretion.
Lumasiran Phase 1/2 Study Results

Summary and Next Steps

- Lumasiran (ALN-GO1) is a subcutaneously administered investigational RNAi therapeutic specifically designed to reduce hepatic production of oxalate in patients with PH1.

- Adult and pediatric patients receiving lumasiran experienced clinically significant and sustained reductions in urinary oxalate to normal or near normal levels.

- Multiple doses of lumasiran have demonstrated an acceptable safety profile in patients with PH1 with no discontinuations from study or drug related SAEs.

- Data support the therapeutic hypothesis and the continued development of lumasiran across a spectrum of patients with PH1 in the Phase 3 ILLUMINATE trials.
Lumasiran ILLUMINATE•A Phase 3 Study
Randomized, Double-Blind Study in Primary Hyperoxaluria Type 1 Patients

**ENROLLMENT COMPLETED**
Patient Population

- Adults & children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m²
- Confirmed alanine glyoxalate aminotransferase (AGXT) mutations
- eGFR >30 mL/min/1.73m²

2:1 RANDOMIZATION

Lumasiran
3xqM loading dose, then q3M
3.0 mg/kg SC

or

Placebo
3xqM loading dose, then q3M SC

Primary Endpoint

- Percent change in urinary oxalate excretion from baseline (average percent change from baseline across months 3 through 6)

Topline ILLUMINATE-A results expected in **late 2019**
NDA submission planned in **early 2020** (assuming positive results)

*FDA Breakthrough and EMA PRIME Designations

NCT03681184; EudraCT Number: 2018-001981-40

† 3.0 mg/kg once monthly for 3 consecutive months (loading dose phase) followed by 3.0 mg/kg once every 3 months (maintenance phase) starting 1 month after last loading dose
Lumasiran **ILLUMINATE•B** Phase 3 Study

Open-Label Study in Pediatric Primary Hyperoxaluria Type 1 Patients

**NOW ENROLLING**

**Patient Population (N=8)**
- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed alanine glyoxylate aminotransferase (AGXT) mutation
- eGFR >45 mL/min/1.73 m² if ≥12 months old; non-elevated serum creatinine if <12 months old

**Primary Endpoint**
- Percent change in urinary oxalate excretion at 6 months (average percent change from baseline across months 3 through 6)

**Open-Label Extension ‡**

**ILLUMINATE-C** expected to initiate in **late 2019**

**Topline ILLUMINATE-B results expected in **mid-2020**

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† Patients <10 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 3.0 mg/kg. Patients ≥10 kg to <20 kg: Three monthly loading doses at 6.0 mg/kg then maintenance dose of 6.0 mg/kg. Patients ≥20 kg: Three monthly loading doses at 3.0 mg/kg then maintenance dose of 3.0 mg/kg

‡ Continued weight-based dosing using weight obtained 7 days prior to dosing

**FDA Breakthrough and EMA PRIME Designations**
Lumasiran Registralional Program
Robust Registrational Program to Evaluate Lumasiran Across all Ages and Full PH1 Disease Spectrum

ILLUMINATE-A
Double-blind, placebo-controlled trial in PH1 patients at least 6 years old with preserved renal function

ILLUMINATE-B
Single arm, open-label study in PH1 patients less than 6 years old with preserved renal function

ILLUMINATE-C
Single arm, open-label study in PH1 patients with impaired renal function

- Expanded Access Protocol (EAP) for PH1 patients at least 6 years old with preserved renal function recently approved in U.S.
Agenda

Welcome
• Joshua Brodsky – Director, Investor Relations & Corporate Communications

Introduction
• Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Primary Hyperoxaluria Type 1 & Physician Perspective
• Elaine M. Worcester, M.D. – Nephrologist & Professor of Medicine, University of Chicago Medicine

Patient & Caregiver Perspective
• Andrew – Patient Diagnosed with Primary Hyperoxaluria Type 1
• Nicole – Andrew’s Wife and Caregiver

Early Stage Clinical Data & ILLUMINATE Studies
• Kenji Fujita, M.D. – Vice President, Clinical Development

Lumasiran Program Opportunity in PH1 & Disease Education/Diagnosis Initiatives
• Pritesh Gandhi, PharmD. – Vice President, General Manager, Lumasiran

Q&A Session
## Lumasiran Market Opportunity

Ultra-Rare Orphan Disease with Potential First-in-Class/Best-in-Class Medicine

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th>DIAGNOSIS</th>
<th>DISEASE BURDEN</th>
<th>COST BURDEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>~3–5K patients in U.S./EU&lt;sup&gt;1&lt;/sup&gt;</td>
<td>~50% currently diagnosed&lt;sup&gt;2&lt;/sup&gt;; mean time to diagnosis ~6 years&lt;sup&gt;3&lt;/sup&gt;</td>
<td>30–65% reach end-stage renal disease before diagnosis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>$1M+ average cost (transplant &amp; lifelong immunosuppression)</td>
</tr>
</tbody>
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### LUMASIRAN | PRIMARY HYPEROXALURIA TYPE 1

>$500M potential market opportunity

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Launch of Children’s Animation Video Series for PH1

- First-of-its-kind animated video series for kids about kids living with PH1; fills a significant gap in educational content for young patients
- 4-part video series and additional content in development; 1st video debuted in early Sept; remaining videos by EOY
- Enthusiastic reception from PH1 community
- Developed in partnership with the Oxalosis & Hyperoxaluria Foundation (OHF)

"The emotions children experience when diagnosed with PH1 can be overwhelming. Many parents are left searching for ways to explain what’s going on to not only their small children, but also the people who make up their support system. I’m so excited to see PH1 of a Kind come to life – it will be an incredibly valuable resource that this community so very much needs and deserves."

- Kim Hollander – Executive Director, OHF

Learn more at ph1ofakind.com
Increasing PH1 Awareness

Education Initiatives Developed for Physicians

A kidney stone may be a sign of a metabolic stone disease, such as primary hyperoxaluria type 1 (PH1), that can result in progressive renal impairment. So, any unusual presentation among stone formers merits further investigation.

**HUMBLED TO BE A LITIGATION**
- Have a stone?
- Family history of stones?
- Stones may be larger on average, such as nephrolithiasis.
- Family history of stones?
- Biochemical complication, eg, hypercalciuria or nephrolithiasis.
- Stones are larger on average, such as nephrolithiasis.

In the workup of such patients, a specialist may identify a mutation or biochemical component as the underlying cause of kidney stone formation. If one is suspected, diagnosing PH1 disease is straightforward. Prompt management may help to mitigate damage that may result in the need for burdensome supportive care, such as dialysis for some patients.

Refer your patients for a full metabolic workup when you suspect a metabolic stone disease and visit AboutPH1.com

A kidney stone may be a sign of a metabolic stone disease, such as primary hyperoxaluria type 1 (PH1), that can result in progressive renal impairment. So, any unusual presentation among stone formers merits further investigation. There are additional clinical red flags that, when also present, indicate a likely systemic condition:

- Abnormal urinary chemistry
- High serum calcium
- High calcium intake high oxalate intake
- High oxalate intake high calcium intake
- Impaired kidney function/end-stage renal disease (ESRD)
- Nephrolithiasis
- Failure to thrive (infants)

Once suspected, confirming PH1 with genetic testing may reduce an often lengthy daily diagnostic, which may include the overall outcome. Unfortunately, PH1 patients are often already suffering from irreparable kidney damage when diagnosed, with up to 70% of diagnoses in adults occurring after progression to ESRD.

Consider genetic testing for your patients when you suspect a metabolic stone disease and visit AboutPH1.com.
Alnylam Act® – Primary Hyperoxaluria Type 1
No-Charge, Third-Party Genetic Testing and Counseling Program

Reduce barriers to genetic testing and counseling to help people make more informed decisions about their health

Tests and services are performed by independent third parties

Available in U.S. and Canada (genetic counseling service available in U.S.)

Healthcare professionals who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use or support any Alnylam product*

More information regarding this program available at: www.alnylamact.com

*At no time does Alnylam receive patient-identifiable information. Alnylam receives contact information for healthcare professionals who use this program.
Potential Timeline for Initial Approval

U.S. and E.U.
2020

ROW
2022+
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Q&A Session
SAVE THE DATE

Alnylam R&D Day

Friday, November 22, 2019
Westin Times Square
New York City
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED