Lumasiran, for the Treatment of Primary Hyperoxaluria Type 1

August 19, 2021
 Agenda

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

 Introduction
 • Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

 Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
 • Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

 Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
 • John Gansner, MD, PhD – Director, Clinical Research

 Lumasiran Commercial Progress PH1
 • Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, 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
Alnylam Forward Looking Statements

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, including expectations regarding our aspiration to become a leading biotech company, and the planned achievement of our “Alnylam P=25” strategy, plans for additional global regulatory filings and the continuing product launches of our approved products and the approved product of our partner, plans for continued development, regulatory review and expected regulatory filings for vutrisiran and, by our partner, for fitusiran, the timeline for continued development and results from ongoing and planned clinical studies of lumasiran and plans for potential supplemental regulatory filings, the potential of OXLUMO (lumasiran) as a treatment option for patients with PH1, estimates of the PH1 patient population, plans for additional global regulatory filings and the continuing launch of OXLUMO in additional territories to drive growth, and the potential of global, multi-channel initiatives underway to improve PH1 disease awareness. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including lumasiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products, including OXLUMO, globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO (and potentially vutrisiran) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. 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 and Commercially Established Approach with Transformational Potential

- Nobel Prize-winning science
- Silence any gene in genome with siRNAs
- Potent and durable mechanism of action
- Product engine for sustainable innovation
- Multiple products impacting patients globally
Patients: Over 0.5 million on Alnylam RNAi therapeutics globally
Products: 6+ marketed products in rare and prevalent diseases
Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year
Performance: ≥40% revenue CAGR through YE 2025
Profitability: Achieve sustainable non-GAAP profitability within period
## Additional Alnylam and Partner Launches Planned Over Next 12-24 Months

**Compelling Commercial Profile of Existing and Emerging Medicines**

<table>
<thead>
<tr>
<th>Year</th>
<th>ONPATTRO (patisiran)</th>
<th>GIVLAARI (givosiran)</th>
<th>OXLUMO (lumasiran)</th>
<th>Leqvio® (inclisiran)</th>
<th>Vutrisiran</th>
<th>Fitusiran*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>ONPATTRO is indicated in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.1</td>
<td>GIVLAARI is indicated in the U.S. for the treatment of adults with acute hepatic porphyria.2</td>
<td>OXLUMO is indicated in the U.S. for the treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients.3</td>
<td>Leqvio is approved in the EU for the treatment of adults with hypercholesterolemia or mixed dyslipidemia.4</td>
<td>Vutrisiran</td>
<td>Fitusiran*</td>
</tr>
<tr>
<td>2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td></td>
<td></td>
<td>Leqvio® (inclisiran)</td>
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<td></td>
</tr>
<tr>
<td>2022-2023</td>
<td>Vutrisiran</td>
<td>Fitusiran*</td>
<td></td>
<td>Vutrisiran</td>
<td>Fitusiran*</td>
<td></td>
</tr>
</tbody>
</table>

Leqvio® (inclisiran)

- NDA resubmitted
- PDUFA date January 1, 2022
- PDUFA date April 14, 2022

### Additional Information

1. ONPATTRO is approved in U.S. and Canada for the PN of hATTR amyloidosis in adults, and in EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. For additional information on ONPATTRO, see Full Prescribing Information.

2. GIVLAARI is approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older. For additional information on GIVLAARI, see Full Prescribing Information.

3. OXLUMO is approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups. For additional information on OXLUMO, see Full Prescribing Information.

4. Novartis has obtained global rights to develop, manufacture and commercialize inclisiran under a license and collaboration agreement with Alnylam Pharmaceuticals, a leader in RNAi therapeutics.

* Sanofi Genzyme is leading and funding development of fitusiran and will commercialize fitusiran, if successful.

Anticipated dates of launch based on current development timelines for investigational therapeutics and assuming positive pivotal study data and regulatory approval.

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Robust pipeline fuels sustainable product launches **beyond 2021,** leveraging global commercial infrastructure.

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## Alnylam Clinical Development Pipeline

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

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

<table>
<thead>
<tr>
<th>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</th>
<th>LATE STAGE (Phase 2-Phase 3)</th>
<th>REGISTRATION/COMMERCIAL(^1) (OLE/Phase 4/IIS/registries)</th>
<th>COMMERCIAL RIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>hATTR Amyloidosis-PN(^2)</strong></td>
<td>Global</td>
<td>Milestones &amp; up to 20% Royalties(^5)</td>
<td>Global</td>
</tr>
<tr>
<td>Acute Hepatic Porphyria(^6)</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Hyperoxaluria Type 1(^4)</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leqvio(^\circledast) (inclisiran) Hypercholesterolemia</td>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vutrisiran(^*)</td>
<td>hATTR Amyloidosis-PN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patisiran</td>
<td>ATTR Amyloidosis</td>
<td></td>
<td></td>
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<tr>
<td>Vutrisiran(^*)</td>
<td>ATTR Amyloidosis</td>
<td></td>
<td></td>
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<tr>
<td>Fitusiran(^*)</td>
<td>Hemophilia</td>
<td>15-30% Royalties</td>
<td></td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Severe PH1 Recurrent Kidney Stones</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>Cemdisiran(^*)</td>
<td>Complement-Mediated Diseases</td>
<td>50-50</td>
<td></td>
</tr>
<tr>
<td>Cemdisiran/Pozelimab Combo(^6)</td>
<td>Complement-Mediated Diseases</td>
<td>Milestone/Royalty</td>
<td></td>
</tr>
<tr>
<td>Belcesiran(^7)</td>
<td>Alpha-1 Liver Disease</td>
<td>Ex-U.S. option post-Phase 3</td>
<td></td>
</tr>
<tr>
<td>ALN-HBV02 (VIR-2218)(^8)</td>
<td>Hepatitis B Virus Infection</td>
<td>50-50 option post-Phase 2</td>
<td></td>
</tr>
<tr>
<td>Zilebesiran (ALN-AGT)*</td>
<td>Hypertension</td>
<td>Global</td>
<td></td>
</tr>
<tr>
<td>ALN-HSD*</td>
<td>NASH</td>
<td>50-50</td>
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As of August 2021
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Q&A Session
Primary Hyperoxaluria Type 1
Context and Overview

Jeffrey M. Saland, M.D.
Chief, Pediatric Nephrology & Hypertension
Mount Sinai Kravis Children’s Hospital, NYC
This program is sponsored by Alnylam Pharmaceuticals
I am presenting on behalf of the company
I have received honoraria for my participation, and participated as an investigator in clinical trials studying lumasiran, and I have also received compensation for consulting services provided to Alnylam.
This is not a CME presentation
There will be a moderated Q&A at the end of this presentation. Questions will be reviewed by Alnylam
Goals: Context and Overview

Context:

• Introduction to kidney stone disease
• Discuss typical metabolic workup & hyperoxaluria

Overview:

• Discuss genetic testing
• Discuss Primary Hyperoxaluria Type 1
Kidney Stone Disease:
Lifetime Stone Prevalence (United States)

It’s common:
~ 1 in 15 women &
~ 1 in 10 men
suffer a stone

Risk varies by
• Sex
• Age (not shown)
• self-reported race
  (NHANES survey data)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>History of kidney stones, males</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted, % (95% CI)</td>
<td>Adjusted, % (95% CI)</td>
<td></td>
</tr>
<tr>
<td>All groups</td>
<td>10.6 (9.4–11.9)</td>
<td>10.3 (9.2–11.3)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, white</td>
<td>12.8 (11.3–14.3)</td>
<td>11.8 (10.4–13.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.1 (5.7–8.4)</td>
<td>8.8 (7.4–10.2)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, black</td>
<td>4.5 (3.4–5.6)</td>
<td>4.8 (3.7–5.9)</td>
<td></td>
</tr>
<tr>
<td>Other race/multiracial</td>
<td>5.6 (2.5–8.8)</td>
<td>5.3 (2.2–8.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>History of kidney stones, females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted, % (95% CI)</td>
<td>Adjusted, % (95% CI)</td>
<td></td>
</tr>
<tr>
<td>All groups</td>
<td>7.1 (6.4–7.8)</td>
<td>6.7 (6.1–7.4)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, white</td>
<td>7.9 (7.0–8.8)</td>
<td>7.5 (6.7–8.4)</td>
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</tr>
<tr>
<td>Hispanic</td>
<td>5.7 (4.6–6.9)</td>
<td>6.1 (4.9–7.3)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, black</td>
<td>4.2 (2.7–5.7)</td>
<td>4.2 (2.8–5.6)</td>
<td></td>
</tr>
<tr>
<td>Other race/multiracial</td>
<td>6.1 (2.7–9.6)</td>
<td>5.6 (2.4–8.8)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.

Kidney Stone Recurrence

Median ~15 per 100 person years (~ every 7 years)

But the rates are skewed:
• After a first stone: 6 per 100 person-year (1 every 17 years)
• After > 1 stone: 16 per 100 person-year (1 every 6 years)

Upshot:
• one stone maybe bad luck
• 2 stones or more, probably not bad luck

Doesn’t apply to kids, all should be considered abnormal
.... the stones also ;)

Kidney Stone Evaluation
Guidelines

- **First stone:**
  - review medical, dietary, & family history
  - Basic labs, analyze the stone (if caught)

- **2 or more stones, risk factors*, children:**
  - full diagnostic evaluation

*Risk factors: family history, multiple stones at presentation, uncommon stone type, gastrointestinal disease, dietary risk, osteoporosis, nephrocalcinosis, reduced renal function

PH1: Stone Analysis
Nearly All Patients Have a Stone

Pure Calcium Oxalate (monohydrate) stones especially with a clear color instead of the usual dark color suggest primary Hyperoxaluria, and should prompt definitive diagnostic testing.

But… Ca-Oxalate Stones are Common

Stone composition and morphology is complex and occurs on a spectrum.

Such analysis alone is not reliable enough to rule-out a diagnosis and there are many clinical scenarios that can cause frequent Ca-oxalate stones.

<table>
<thead>
<tr>
<th>Morphological subtype</th>
<th>Stone morphology</th>
<th>Common etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main component</td>
<td>Surface</td>
<td>Section</td>
</tr>
<tr>
<td>Whewellite</td>
<td></td>
<td>Dietary hyperoxaluria, low diuresis (high oxalate concentration) Randall’s plaque</td>
</tr>
<tr>
<td>Type Ia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whewellite</td>
<td></td>
<td>Stasis, low diuresis Total crystallization conversion from weddelite to whewellite</td>
</tr>
<tr>
<td>Type Ib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whewellite</td>
<td>Primary hyperoxalurias (mainly type I by AGXT mutation)</td>
<td></td>
</tr>
<tr>
<td>Type Ic</td>
<td></td>
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<tr>
<td>Whewellite</td>
<td>Malformational arthropathy, stasis and confined multiple stones</td>
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</tr>
<tr>
<td>Type Id</td>
<td></td>
<td></td>
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<tr>
<td>Whewellite</td>
<td>Enteric hyperoxaluria Inflammatory bowel diseases (Crohn disease) Fluid resections Chronic pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>

Timed Urine Collection
AKA your waste tells a story!

18th century – New England Erik Svetoft

Robert Short/CBC

20th century – United States Erik Svetoft

J ROMEO Pop Science PUBLISHED APR 03, 2020 (drawings)
Timed Urine Collection
(Not A Popular Activity)
(And Needs Good Instruction)
(Usually 24 hours)
Timed Urine Collection (Metabolic Evaluation)

Stone Risk Factors / Cystine Screening:

<table>
<thead>
<tr>
<th>DATE</th>
<th>SAMPLE ID</th>
<th>Vol 24</th>
<th>SS CaOx</th>
<th>Ca 24</th>
<th>Ox 24</th>
<th>Cit 24</th>
<th>SS CaP</th>
<th>pH</th>
<th>SS UA</th>
<th>UA 24</th>
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<td>305</td>
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<td>32</td>
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<td>5.729</td>
<td>1.75</td>
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<td>11.90</td>
<td>205</td>
<td>41</td>
<td>308</td>
<td>1.24</td>
<td>5.874</td>
<td>1.57</td>
<td>0.828</td>
</tr>
</tbody>
</table>

REFERENCE RANGE
- Vol: 0.5 - 4L
- SS CaOx: 6 - 30
- Ca: male <250, female <200
- Ox: 20 - 40
- Cit: male <450, female <550
- SS CaP: 0.5 - 2
- pH: 5.8 - 6.2
- SS UA: 0 - 1
- UA: male <0.800, female <0.750

Dietary Factors

<table>
<thead>
<tr>
<th>DATE</th>
<th>SAMPLE ID</th>
<th>Na 24</th>
<th>K 24</th>
<th>Mg 24</th>
<th>P 24</th>
<th>Nh4 24</th>
<th>Cl 24</th>
<th>Sul 24</th>
<th>UUN 24</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/07/15</td>
<td>S16694029</td>
<td>299</td>
<td>73</td>
<td>70</td>
<td>1.109</td>
<td>29</td>
<td>287</td>
<td>40</td>
<td>13.08</td>
<td>1.3</td>
</tr>
<tr>
<td>08/15/15</td>
<td>S14276676</td>
<td>128</td>
<td>58</td>
<td>60</td>
<td>1.021</td>
<td>44</td>
<td>122</td>
<td>45</td>
<td>11.51</td>
<td>1.1</td>
</tr>
<tr>
<td>08/14/15</td>
<td>S16694027</td>
<td>138</td>
<td>52</td>
<td>69</td>
<td>0.923</td>
<td>36</td>
<td>133</td>
<td>40</td>
<td>10.59</td>
<td>1.1</td>
</tr>
</tbody>
</table>

REFERENCE RANGE
- Na: 50 - 150
- K: 20 - 100
- Mg: 30 - 120
- P: 0.6 - 1.2
- Nh4: 15 - 60
- Cl: 70 - 250
- Sul: 20 - 80
- UUN: 6 - 14
- PCR: 0.8 - 1.4

High Urine Oxalate = Hyperoxaluria :/

<table>
<thead>
<tr>
<th>Stone Risk Factors / Cystine Screening:</th>
<th>Not Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Sample ID</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>08/14/15</td>
<td>S16694027</td>
</tr>
</tbody>
</table>

| Reference Range | 0.5 - 4L | 6 - 3L | male < 250 | female < 200 | male > 450 | female > 550 | 0.5 - 2 | 5.8 - 6.2 | 0 - 1 | male < 0.8 | female < 0.75 |

<table>
<thead>
<tr>
<th>Dietary Factors</th>
<th>Na 24</th>
<th>K 24</th>
<th>Mg 24</th>
<th>P 24</th>
<th>Nh4 24</th>
<th>Cl 24</th>
<th>Sul 24</th>
<th>UUN 24</th>
<th>PCR</th>
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<td>11/07/15</td>
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</tr>
</tbody>
</table>

| Reference Range | 50 - 150 | 20 - 100 | 30 - 120 | 0.6 - 1.2 | 15 - 60 | 70 - 250 | 20 - 80 | 6 - 14 | 0.8 - 1.4 |

40 mg oxalate = 0.44 mMol
80 mg/day suggests PH

Oxalate – Oxalic Acid

Combines well with Calcium and forms a highly insoluble molecule / crystal nidus (0.12 millimole/liter pure water at 37°C)*

0.44 mmol needs 3.7L of water to dissolve (urine has better solubility with stone inhibitors like citrate and Na, K, Mg, acids also– thank goodness for urine!)

*Ibas, F Et al. Crystals 2020, 10
Goals: Context and Overview

Context:
- Introduction to kidney stone disease
- Discuss typical metabolic workup & hyperoxaluria

Overview:
- Discuss genetic testing
- Discuss Primary Hyperoxaluria Type 1
Hyperoxaluria
Primary or Secondary (Enteric)

- History and physical
- Family history
- Dietary history
- Low Ca intake
- Intestinal diseases
- Fat malabsorption

Genetic testing for PH
Per Rare Kidney Stone Consortium (RKSC) data:
- Identifies about 90% of cases

Primary Hyperoxaluria Type 1 (PH1)

Genetic testing for PH
RKSC data:
• Identifies about 90%
• About 70% are PH1

Prevalence
• Historical 1-10 per million, higher regionally
• Likely underdiagnosed (clinical variability)
• Median diagnosis age in childhood
• Diagnosis possible at any age

Genetic prevalence estimates:
• 1 in 150,000

Primary Hyperoxaluria Type 1
An Autosomal Recessive Disease

Glycolate is a normal product of metabolism.

Normally it’s metabolized to glyoxylate then reacts with alanine to form pyruvate and glycine.

In PH1, glyoxylate builds up and some gets metabolized to oxalate and some back to glycolate.

Alanine:glyoxylate aminotransferase (product of AGXT gene); GR = glyoxylate reductase; GO = glycolate oxidase; LDH = lactate dehydrogenase; DAO = D-amino acid oxidase.

Danpure C, J: Nephron Exp Nephrol 2004
Primary Hyperoxaluria Type 1
Signs, Symptoms, Manifestations

- Infantile: severe (poor growth, kidney failure)
- Nephrocalcinosis (widespread calcium oxalate deposition throughout the kidneys)
- Kidney stones
- Progressive CKD (chronic kidney disease) or failure

With lower (< about 30-45 ml/min/1.73m²) kidney function, Systemic oxalosis occurs
- Bone / bone marrow
- Heart
- Skin
- Eye
- Thyroid, joints, muscle, others
Primary Hyperoxaluria Type 1
Signs, Symptoms, Manifestations

From RKSC data on 247 PH1 patients:

Progression to end-stage kidney disease (ESKD) can occur at different rates, but most patients eventually progress to kidney failure

- By age 35, about 50% of patients with PH1 have progressed to ESKD
- By age 60, about 90% of patients with PH1 will have progressed to ESKD
- Declines in kidney function can occur suddenly, even in patients with previously stable kidney function.

Hopp et al. JASN 2015;26:2559-2570
Primary Hyperoxaluria (all types)
Rate of Progression to Kidney Failure Depends on Uox

Renal survival was examined by quartile of urine oxalate excretion at diagnosis.

Among patients with PH who did not have ESRD at diagnosis, renal survival estimates at 10, 20, and 30 years were worst for those with Uox excretion ≥ 2.4 mmol/1.73m² per 24 hours
- (2.4 mmol = 211 mg)
- (1.6 mmol = 140 mg)
- PH1 patients’ median ~ 2 mmol = 180 mg

HR, 3.4 for quartile Q4 vs quartiles Q1–Q3; 95% CI, 1.4 to 7.9

Primary Hyperoxaluria Type 1
Signs, Symptoms, Manifestations

• Diagnosis delays of years after symptom onset is common
• Up to 50% of adults diagnosed already have significant kidney disease
• 10% diagnosed after kidney failure sometimes after recurrence in a transplant!

Primary Hyperoxaluria Type 1
Therapeutic Approaches to Prevent Complications

Hydration (Hyperhydration)
- Drinking large volumes of fluid at regular intervals over the entire day and night
- Dissolves calcium oxalate (prevents supersaturation)
- Small children may require a gastronomy or nasogastric tube to enable this
- 2-3 L/m² per 24 hours

Alkali citrate or pyrophosphate-containing solutions
- Inhibit calcium oxalate crystallization

Pyridoxine (Vitamin B6)
- About 30-50% of PH1 patients have significant (up to 30% Uox reduction) benefit
- p.Gly170Arg is associated with best B6 response

Dietary changes: of limited benefit

Primary Hyperoxaluria Type 1
Other Treatments

Stones
• Urological procedures
• Routine approaches to stone-related infections

Chronic kidney disease (CKD)
• Routine approaches to anemia, metabolic, cardiovascular complications

Kidney Failure
• Dialysis—not routine: need frequent, prolonged and still often inadequate
• Isolated kidney transplant (mobilization of oxalate and recurrence)
• Liver-kidney transplant (mobilization of oxalate, liver tx complications)
Graft results very poor for kidney only, patient survival better for combined
dialysis.

Dialysis results would be worse
Summary

- PH1 usually presents as a kidney stone disease
- Index of suspicion is needed, PH1 is rare, but also under-diagnosed
- Metabolic and genetic evaluation is readily available to diagnose PH1

- PH1 can result in significant morbidity from stones and their complications
- PH1 usually leads to kidney failure, especially when untreated
- Renal outcomes of PH are related to degree of urinary oxalate excretion
- Renal failure is a devastating outcome with systemic oxalosis risk

- Traditional treatments include “hyperhydration”, Vitamin B6, and crystal inhibitors
- Historical outcomes after kidney failure and transplant are challenging
- Historically observed outcomes highlight unmet needs for PH1 patients
Agenda

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

Introduction
  • Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
  • Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
  • John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
  • Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session
Lumasiran
Marketed RNA interference Therapeutic for Primary Hyperoxaluria Type 1 (PH1)

Lumasiran:
• SC-administered small interfering RNA (siRNA)
  – Harnesses natural RNA interference (RNAi) mechanism
• Targets the mRNA for HAO1 which encodes glycolate oxidase (GO) in the liver
• Decreased production of GO reduces hepatic oxalate production

Lumasiran Therapeutic Hypothesis:

HAO1, hydroxyacid oxidase 1
ILLUMINATE Phase 3 Program is Largest Clinical Development Program in PH1 to Evaluate Lumasiran Across all Ages and Full PH1 Disease Spectrum

**ILLUMINATE·A**

Double-blind, placebo-controlled trial in PH1 patients ≥6 years old with eGFR ≥30 mL/min/1.73m²

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**ILLUMINATE·B**

Single arm, open-label study in PH1 patients <6 years old with eGFR >45 mL/min/1.73m²

- Primary endpoint results presented October 2020 ASN; Publication expected 2021

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**ILLUMINATE·C**

Single arm, open-label study in PH1 patients with severe renal impairment (eGFR<45) including those on hemodialysis

- Topline results released July 2021; topline results for systemic oxalosis expected 2023

---

Phase 2 study in recurrent calcium oxalate kidney stone formers expected to initiate in 2021

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1
**ILLUMINATE•A Phase 3 Study Design**

Randomized, Double-Blind Study in Primary Hyperoxaluria Type 1 Patients

**PATIENT POPULATION (N=39)**

- Adults and children ≥6 years
- Urinary oxalate excretion ≥0.7 mmol/24hr/1.73m²
- Confirmed AGXT mutations
- eGFR ≥30 mL/min/1.73m²

**6-MONTH DOUBLE-BLIND TREATMENT PERIOD**

- **Lumasiran**
  - qM × 3 loading dose, then q3M<sup>a</sup>
  - 3.0 mg/kg subcutaneously

- **Placebo**
  - qM × 3 loading dose, then q3M subcutaneously

**54-MONTH EXTENSION PERIOD**

- **Lumasiran**
  - q3M
  - 3.0 mg/kg subcutaneously<sup>b</sup>

---

NCT03681184; EudraCT Number: 2018-001981-40

<sup>a</sup>Maintenance dose of 3.0 mg/kg (q3M) started 1 month after last loading dose.  
<sup>b</sup>Patients randomized to placebo received loading doses of 3.0 mg/kg lumasiran at Months 6, 7, and 8; patients randomized to lumasiran received a maintenance dose of 3.0 mg/kg lumasiran at Month 6, and placebo at Months 7 and 8.  
1 mmol/24hr/1.73m² = 90 mg/24hr/1.73m²
**Percent Change in 24hr Urinary Oxalate**

**Double-blind Period**
Mean Baseline UOx in Both Groups: 1.8 mmol/24hr/1.73m²

**Extension Period**
- Lumasiran/Lumasiran (N=26)
- Placebo/Lumasiran (N=13)

Primary Endpoint<sup>a</sup>: -53.5% Versus placebo; p=1.7x10⁻¹⁴

-57.3%<sup>b</sup> Versus baseline

-64.1% Versus baseline

<table>
<thead>
<tr>
<th>Study visit</th>
<th>BL</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
<th>M7</th>
<th>M8</th>
<th>M9</th>
<th>M12</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients:</td>
<td>N=</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup>ULN=0.514 mmol/24hr/1.73m² for 24-hour UOx corrected for BSA; eligibility criteria required UOx ≥0.7 mmol/24hr/1.73m²

<sup>b</sup>LS mean difference from baseline to Month 6 (average of Month 3 through Month 6). Baseline is the median of all valid 24-hr urine assessments at Month 6 (or, if the patient does not have two valid assessments at Month 6, then the baseline is calculated using the latest three valid 24-hour urine collections)

Data in graph are mean ± SEM of observed values

BSA, body surface area; LS, least-squares; SEM, standard error of mean; UOx, urinary oxalate

**ILLUMINATE•A** Extension Period: Proportion of Patients with 24hr Urinary Oxalate Level ≤1.5×ULN

Comparable Proportion of Patients in the Placebo/Lumasiran Crossover Group Achieved Near Normalization or Normalization (≤1.5×ULN) of 24hr UOx After 6 Months of Treatment

- **84%** of patients receiving lumasiran achieved near normalization or normalization (≤1.5×ULN) of 24hr UOx excretion at Month 6, compared with 0% of placebo-treated patients.

- **77%** of crossover patients achieved near normalization or normalization of 24hr UOx after 6 months of treatment*

---

Proportion of patients who achieved near normalization or normalization of 24-hour urinary oxalate was sustained through Month 12

*ULN=0.514 mmol/24hr/1.73m² for 24-hour UOx corrected for BSA
BSA, body surface area; ULN, upper limit of normal; UOx, urinary oxalate

*Adapted from McGregor T et al. OxalEurope Meeting 2020. Presentation.*
ILLUMINATE•A Safety Results with Ongoing Dosing

Safety Profile Remained Consistent at Month 12

- Overall mean exposure: 9.9 months (range 2.8–15.1 months) with 233 doses given
  - 35 patients treated for ≥6 months and 10 patients for ≥12 months
- Majority of AEs were mild in severity
- Most common related AEs (≥10%) were injection-site reactions, which were mild and transient
  - Erythema, pain, pruritus, or swelling at the injection site most common symptoms
- 1 patient with serious AE of urosepsis (severe), considered not related to study drug
- No treatment interruptions or discontinuations related to lumasiran; no deaths
- No clinically relevant changes in laboratory measures (including LFTs), vital signs, and electrocardiograms were observed

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo/ Lumasiran (N=13)</th>
<th>Lumasiran/ Lumasiran (N=26)</th>
<th>All Lumasiran (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>9 (69)</td>
<td>24 (92)</td>
<td>33 (85)</td>
</tr>
<tr>
<td>Serious AE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Severe AE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>AE leading to discontinuation of study treatment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>AEs occurring in ≥10% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reactions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (39)</td>
<td>11 (42)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (8)</td>
<td>6 (23)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>4 (15)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (15)</td>
<td>2 (8)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1 (8)</td>
<td>3 (12)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Urosepsis, considered not related to study drug by the Investigator. <sup>b</sup>Fatigue and disturbance in attention, considered not related to study drug by the Investigator. <sup>c</sup>Includes adverse events of injection-site reaction, injection-site pain, injection-site erythema, and injection-site discomfort

AE, adverse event; LFT, liver function test; PH1, primary hyperoxaluria type 1


Safety data from first dose of lumasiran to data cut-off date: 1 May 2020.
**ILLUMINATE•B Phase 3 Study Design**

Open-Label, Multicenter, Single-Arm Study in Young Patients with PH1

**PATIENT POPULATION (N=18)**

- Infants and children <6 years
- Elevated urinary oxalate:creatinine ratio
- Confirmed AGXT mutations
- eGFR >45 mL/min/1.73m² if ≥12 months old; normal serum creatinine if <12 months old

**6-MONTH PRIMARY ANALYSIS PERIOD**

Lumasiran
qM × 3 loading dose, then qM or q3M maintenance dosing dependent on weight

**54-MONTH EXTENSION PERIOD**

Lumasiran
qM or q3M maintenance dosing dependent on weight

---

NCT03905694; EudraCT Number: 2018-004014-17

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

AGXT, alanine-glyoxylate aminotransferase gene; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; qM, monthly; qM × 3, once monthly for 3 consecutive months; qM, quarterly
**ILLUMINATE•B** Primary Endpoint: Percent Change in Urinary Oxalate Excretion from Baseline to Month 6

Rapid and Sustained Reduction in Spot Urinary Oxalate:Creatinine Ratio Across All Weight Groups

-72.0%a Versus baseline

*aLS mean reduction from baseline to Month 6 (average of Month 3 through Month 6)
Data in graph are presented as mean ± SEM of observed values
BL, baseline; LS, least-squares; M, month; SEM, standard error of the mean; ULN, upper limit of normal
Adapted from Deschenes et al. American Society of Nephrology 2020. Presentation PO1624.
ILLUMINATE•B Safety Results

- No deaths, discontinuations or withdrawals, or severe AEs
- One serious AE occurred which was considered not related to lumasiran
- Most common drug-related AE was injection-site reactions in 3 (17%) patients; all were mild and transient
- No clinically relevant changes in laboratory measures, vital signs, or electrocardiograms related to lumasiran were observed
- No hepatic events were reported

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>&lt;10 kg (N=3)</th>
<th>10 to &lt;20 kg (N=12)</th>
<th>≥20 kg (N=3)</th>
<th>All Treated (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 AE</td>
<td>3 (100)</td>
<td>12 (100)</td>
<td>3 (100)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>At least 1 drug-related AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>0</td>
<td>0</td>
<td>2 (17)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>2 (17)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1 (33)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>At least 1 serious AE</td>
<td>0</td>
<td>0</td>
<td>1 (33)*</td>
<td>1 (6)*</td>
</tr>
<tr>
<td>At least 1 severe AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Discontinuations/withdrawal</td>
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<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Safety data from first dose of lumasiran to data cut-off date: 30 June 2020.

*aViral infection, considered not related to the study drug by the Investigator
AE, adverse event; SAE, serious adverse event
**ILLUMINATE•C Lumasiran Phase 3 Study**

Open-Label, Multicenter, Single-Arm Study in Patients with Advanced PH1

**PATIENT POPULATION (N=21)**

- All ages
- Plasma oxalate ≥20 µmol/L
- Confirmed AGXT mutations
- eGFR <45 mL/min/1.73m² if ≥12 months old; elevated serum creatinine if <12 months old

**6-MONTH PRIMARY ANALYSIS PERIOD**

- **Lumasiran†**
  - Cohort A – No hemodialysis

- **Lumasiran†**
  - Cohort B – Hemodialysis

**54-MONTH EXTENSION PERIOD**

- **Lumasiran†**
  - Cohort A – No hemodialysis

- **Lumasiran†**
  - Cohort B – Hemodialysis

---

**Topline results released July 2021; full results are expected to be presented at a medical meeting later this year**

NCT04152200; EudraCT Number: 2019-001346-17

†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
• Lumasiran achieved substantial reductions in plasma oxalate relative to baseline
  – In both dialysis-independent and -dependent patients

• Lumasiran demonstrated an encouraging safety and tolerability profile
  – No deaths or drug related SAEs
  – Most common AEs were ISRs in 5 patients (23.8%), all of which were mild
  – Two discontinuations due to AEs, both occurring during extension period and neither related to study drug

• Supplemental regulatory filings expected to be submitted to FDA and EMA in late 2021
eGFR from Baseline to Month 12 in ILLUMINATE-A and Baseline to Month 6 in ILLUMINATE-B

eGFR remained stable through the treatment period in both studies

Change in eGFR from baseline was a secondary endpoint in both ILLUMINATE-A and ILLUMINATE-B.
Data in graph are presented as mean ± SEM of observed values.

Exploratory Analysis of Kidney Stone Event Rates

ILLUMINATE-A\textsuperscript{a}

**Lumasiran/Lumasiran**

- Prior 12 Months: 3.19
- Month 6: 1.09
- Month 12: 0.85

**Placebo/Lumasiran**

- Prior 12 Months: 0.54
- Month 6: 0.66
- Month 12: 0.17

Error bars represent 95% CI.

\textsuperscript{a}Randomization was not stratified by kidney stone events at baseline.

\textsuperscript{b}Patient reported history of kidney stone events.

\textsuperscript{c}Annualized rate was not calculated for patients <6 months old.

---

**ILLUMINATE•A Exploratory Analysis of Nephrocalcinosis**

Nephrocalcinosis grade mostly stable or improved

<table>
<thead>
<tr>
<th></th>
<th>6 Months of Placebo*</th>
<th>6 Months of Lumasiranb</th>
<th>12 Months of Lumasiranc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=13)</td>
<td>(N=36)</td>
<td>(N=24)</td>
</tr>
<tr>
<td>Percent of Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>8%</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Stable</td>
<td>85%</td>
<td>81%</td>
<td>46%</td>
</tr>
<tr>
<td>Improved</td>
<td>0%</td>
<td>11%</td>
<td>25%</td>
</tr>
<tr>
<td>Data N/A</td>
<td>8%</td>
<td>6%</td>
<td>Data not available (N/A)</td>
</tr>
</tbody>
</table>

*Includes 6 months of placebo treatment for patients originally randomized to placebo. Data N/A for one patient who had kidney ultrasound at Month 6, but the images were not adequate for grading nephrocalcinosis. **Includes first 6 months of treatment for patients originally randomized to lumasiran and the first 6 months of lumasiran treatment for patients originally randomized to placebo. Data N/A for 2 patients who did not have kidney ultrasound after 6 months of lumasiran treatment. ***Includes 12 months of treatment for patients originally randomized to lumasiran. Data N/A for 4 patients who did not have kidney ultrasound after 12 months of lumasiran treatment, for 1 patient who discontinued treatment, and for 1 patient who withdrew from the study. Two patients in the lumasiran group did not have valid kidney ultrasounds at baseline and were excluded from the current analysis. One placebo crossover patient did not have kidney ultrasound before the first dose of lumasiran and was also excluded from the current analysis.

ILLUMINATE•B  Exploratory Analysis of Nephrocalcinosis
Nephrocalcinosis grade stable or improved

6 Months of Lumasiran (N=18)

<table>
<thead>
<tr>
<th>Condition</th>
<th>N/A</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>100%</th>
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</thead>
<tbody>
<tr>
<td>Worsened</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56%</td>
</tr>
<tr>
<td>Improved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Data N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Largest clinical development program in PH1 across all patient types
- Significant and sustained lowering of UOx in infants, children and adults with preserved renal function in ILLUMINATE-A and B
- Substantial reduction of POx in patients with severe renal impairment including those on hemodialysis in ILLUMINATE-C
- Encouraging signs of improved clinical outcomes and measures in an otherwise progressive disease with stable eGFR, reduction in kidney stones and improvement in nephrocalcinosis grade
- Encouraging safety and tolerability profile
- ILLUMINATE-C topline results on systemic oxalosis endpoints expected 2023
### Alnylam Clinical Development Pipeline

#### Focused in 4 Strategic Therapeutic Areas (STArs):
- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

#### EARLY/MID-STAGE (IND/CTA Filed-Phase 2)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Disease Area</th>
<th>STAr</th>
<th>COMMERCIAL RIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>hATTR Amyloidosis-PN²</td>
<td>Genetic Medicines</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Acute Hepatic Porphyria³</td>
<td>Cardio-Metabolic Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Primary Hyperoxaluria Type 1⁴</td>
<td>Cardio-Metabolic Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Leqvio® (inclisiran)</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Milestones &amp; up to 20% Royalties⁵</td>
</tr>
<tr>
<td>Vutrisiran*</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Patisiran</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Vutrisiran*</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Fitusiran*</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>15-30% Royalties</td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>Cemdisiran*</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>50-50</td>
</tr>
<tr>
<td>Cemdisiran/Pozelimab Combo⁶</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Milestone/Royalty</td>
</tr>
<tr>
<td>Belcesiran⁷</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Ex-U.S. option post-Phase 3</td>
</tr>
<tr>
<td>ALN-HBV02 (VIR-2218)⁸</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>50-50 option post-Phase 2</td>
</tr>
<tr>
<td>Zilebesiran (ALN-AGT)*</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>Global</td>
</tr>
<tr>
<td>ALN-HSD*</td>
<td>Infectious Diseases</td>
<td>EARLY/MID-STAGE (IND/CTA Filed-Phase 2)</td>
<td>50-50</td>
</tr>
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</table>

#### LATE STAGE (Phase 2-Phase 3)

<table>
<thead>
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<th>Therapy</th>
<th>Disease Area</th>
<th>STAr</th>
<th>COMMERCIAL RIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vutrisiran</td>
<td>Genetic Medicines</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>Global</td>
</tr>
<tr>
<td>Patisiran</td>
<td>Genetic Medicines</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>Global</td>
</tr>
<tr>
<td>Vutrisiran*</td>
<td>Genetic Medicines</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>Global</td>
</tr>
<tr>
<td>Leqvio® (inclisiran)</td>
<td>Infectious Diseases</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>Global</td>
</tr>
<tr>
<td>Vutrisiran*</td>
<td>Infectious Diseases</td>
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<td>Global</td>
</tr>
<tr>
<td>Lumasiran</td>
<td>Infectious Diseases</td>
<td>LATE STAGE (Phase 2-Phase 3)</td>
<td>Global</td>
</tr>
<tr>
<td>Cemdisiran*</td>
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</tr>
</tbody>
</table>

#### REGISTRATION/COMMERCIAL (OLE/Phase 4/IIS/registries)

<table>
<thead>
<tr>
<th>Therapy</th>
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</tr>
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</tr>
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</tr>
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<td>REGISTRATION/COMMERCIAL (OLE/Phase 4/IIS/registries)</td>
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<td>Global</td>
</tr>
</tbody>
</table>

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² Includes marketing application submissions; ³ Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; ⁴ Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; ⁵ Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; ⁶ Regeneron has obtained global rights to develop, manufacture and commercialize inclisiran; ⁷ 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; ⁸ Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; ⁹ Dicemsa is leading and funding development of Belcesiran; ¹⁰ Vir is leading and funding development of ALN-HBV02; ¹¹ Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of August 2021
Recurrent Calcium Oxalate Kidney Stone Disease

Prevention of stone recurrence offers an opportunity to avoid painful stone episodes and invasive procedures\(^1\)

- Recurrent kidney stone disease is associated with significant clinical burden including pain, infection/sepsis, hospitalizations, and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease\(^2\)-\(^4\)

- There are limited effective treatment options and despite best standard of care (dietary/lifestyle changes, citrate supplementation, thiazide diuretics, etc.) recurrent stones still occur\(^5,6\)

- Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals with up to 2.5 million Americans having recurrent calcium oxalate stone disease with elevated urinary oxalate\(^7-9\)


CKD, chronic kidney disease; M, million; UOx, urinary oxalate
Lumasiran Life-cycle Management: Proof-of-concept Phase 2 in Recurrent Stone Former Population

• Rationale:
  – Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals\(^1\)-\(^2\)
  – Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine\(^3\)-\(^4\)
  – Liver production of oxalate is expected to be a significant driver of high urinary oxalate based on a healthy volunteer study\(^4\)
  – Lumasiran is designed to reduce hepatic production of oxalate through inhibition of GO\(^5\)

• Population: Recurrent calcium oxalate kidney stone disease and elevated 24-hour urinary oxalate levels
  – Excludes patients with secondary causes of elevated urinary oxalate/recurrent kidney stones

• Primary Endpoint: Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)

• Expected to initiate in 2021


GO, glycolate oxidase
Agenda

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

Introduction
  • Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Primary Hyperoxaluria Type 1 Burden of Disease and Diagnosis
  • Jeffrey M. Saland, MD, MSCR – Professor, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Recent Highlights, Lumasiran Program: Primary Hyperoxaluria Type 1 & Recurrent Stone Formers
  • John Gansner, MD, PhD – Director, Clinical Research

Lumasiran Commercial Progress PH1
  • Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session
OXLUMO® (lumasiran) Market Opportunity
First-in-Class Product Profile in Ultra-Rare Orphan Disease

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th>DIAGNOSIS</th>
<th>DISEASE BURDEN</th>
<th>COST BURDEN</th>
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</thead>
<tbody>
<tr>
<td>~3,000</td>
<td>~50%</td>
<td>30–65%</td>
<td>$1M+</td>
</tr>
<tr>
<td>potentially symptomatic patients in U.S./EU</td>
<td>currently diagnosed(^1); mean time to diagnosis ~6 years(^2)</td>
<td>reach end-stage renal disease before diagnosis(^2)</td>
<td>average cost (transplant &amp; lifelong immunosuppression)</td>
</tr>
</tbody>
</table>

**OXLUMO | PRIMARY HYPEROXALURIA TYPE 1**

>$500M potential market opportunity

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OXLUMO Global Commercialization
Ensuring Availability Around the World

• Now approved in US, EU and Brazil
• Launched in USA and Germany
• Named patient sales in France and other markets
• Additional EU launches underway in Netherlands and Luxembourg in 2021 and Italy, Spain and Belgium expected in 2022.
• Partnerships in Israel and Turkey to provide access to OXLUMO in 2021 and 2022
• Continued global regulatory filings and launches planned across regions
OXLUMO® Launch Update: Q2 2021
Strong Second Quarter Performance with Broad Utilization across Age Groups and eGFR Categories

$16M
OXLUMO Global Q2 2021 Net Product Revenues

~100
Patients Worldwide on Commercial OXLUMO at end of Q2 2021

Q1 2021

~50

Q2 2021

~100

Q2 U.S. Highlights

7 Value-Based Agreements (VBAs) finalized

>80% covered U.S. lives with confirmed access to OXLUMO, if prescribed

Bringing RNAi Therapeutics to Patients Worldwide
Robust Medical Affairs and Commercial Platform Leverageable for Continued Success

Support and Retention

Access

Diagnosis

Education

Engagement and Advocacy

Strong Product Profile & First to market

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1

Business Excellence

Alnylam

Harvard Pilgrim Health Care

Humana

GeneAct

AlnylamAct

aboutph1.com

takeonph1.com

Oxalosis & Hyperoxaluria Foundation

RARE Kidney Stone Consortium

American Urological Association

Medscape

PeerVoice

medthority
Planned Next Steps for Lumasiran

- **Approval:** Brazil *June 2021*

- **Label Expansion:** sNDA/T2V Filing POx

- **Potential Approval:** Switzerland *Late 2021*

- **Label Expansion:** sNDA/T2V Filing Systemic Oxalosis

**Topline ILLUMINATE-C**  
POx 29 July 2021

**Detailed ILLUMINATE-B**  
Results ASN 2020

**Recurrent Stone Formers (RSF)**  
Phase 2 starts enrollment *Late 2021*

**Detailed ILLUMINATE-C**  
results planned Q4

**Topline RSF Results**  
Expected Mid 2023

**ILLUMINATE-C**  
Systemic Oxalosis  
M24 topline results in 2023

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sNDA = supplemental new drug application ; T2V = Type 2 Variation ; POx = Plasma Oxalate ; NC = nephrocalcinosis
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Lumasiran Commercial Progress PH1
• Jerome Valkenburg, MS, MScBA – Sr. Director & Program Lead, Lumasiran

Q&A Session
Upcoming RNAi Roundtables

Liver-Directed RNAi Pipeline Programs
• Monday, September 20, 11:00 am ET

CNS & Extrahepatic RNAi Pipeline Programs
• Friday, October 1, 1:30 pm ET

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company’s website, [www.alnylam.com/capella](http://www.alnylam.com/capella)
To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED