ALN-GO1
Investigational RNAi Therapeutic for the Treatment of Primary Hyperoxaluria Type 1
Tuesday, September 27, 2016
Agenda

Welcome
• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
• David-Alexandre Gros, M.D., Senior Vice President, Chief Business Officer

Overview of Primary Hyperoxaluria Type 1
• Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children's Hospital NHS Trust

Caregiver Perspective
• Jennifer Lawrence, M.D., Mother of a PH1 patient

ALN-GO1 Program
• David Erbe, Ph.D., Director, Research

Q&A Session
Reminders

Event will run for approximately 60 minutes

Q&A Session at end of presentation
• Submit questions at bottom of webcast screen
• Questions may be submitted at any time

Replay, slides and audio available at www.alnylam.com
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; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; 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; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors 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. 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

- Harness natural pathway
- Catalytic mechanism
- Silence any gene in genome
- Upstream of today’s medicines
- Clinically proven approach
Alnylam Strategic Therapeutic Areas (STArts)

Investigational pipeline focused in 3 STArts

- **Genetic Medicines**: RNAi therapeutics for rare diseases
- **Cardio-Metabolic Diseases**: RNAi therapeutics for dyslipidemia, NASH, type 2 diabetes, hypertension, and other major diseases
- **Hepatic Infectious Diseases**: RNAi therapeutics for major liver infections beginning with hepatitis B & D
# Alnylam Development Pipeline

## Genetic Medicines

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<thead>
<tr>
<th>Category</th>
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<th>Development</th>
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## Hepatic Infectious Diseases

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# Alnylam Development Pipeline

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*Updated September 25, 2016*
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Q&A Session
Primary Hyperoxaluria

Sally-Anne Hulton

Birmingham Children's Hospital UK
Clinical presentation & diagnosis

asymptomatic \(\rightarrow\) stones single or recurrent \(\rightarrow\) nephrocalcinosis \(\rightarrow\) renal impairment

Stone in urine

Stone to laboratory for analysis

Calcium Oxalate present

Specific blood and urine tests
Oxalate Synthesis

** Peroxisome **

- Serine → Hydroxypyruvate
  - AGT
- Pyruvate + Alanine

** Cytosol **

- Hydroxypyruvate → D-glycerate
  - GRHPR
  - NADPH → NADP+

- Glycine → Glyoxylate
  - GO
- Glycollate + H₂O₂ → Oxidative Stress
  - LDH
  - NAD⁺ → NADH

** Mitochondrion **

- Hydroxyproline → 4-OH-oxoglutarate
  - HOGA
  - Pyruvate + Glyoxylate
  - X

- Oxalate Synthesis
  - LDH
  - NAD⁺ → NADH
Urinary metabolites to aid preliminary PH diagnosis: glycerate, glycolate and HOG

Urine analysis

Hewitt & Rumsby, UCLH 2013
PH mutations & diagnosis

• PH1 AGXT gene chr 2

  PH1 incidence 6 to 7 per million population

• PH2 GRHPR gene chr 9

• PH3 HOGA1 gene chr 10

  PH1 $\rightarrow$ plasma oxalate + glycollate

  $\rightarrow$ urine oxalate

  PH2 $\rightarrow$ urine L-glyceric acid

    (may be absent)

  PH3 $\rightarrow$ urine oxalate + glycollate

    $\rightarrow$ urine Ca + uric acid

Database of pathological mutations + polymorphic variants
http://www.uclh.nhs.uk/phmd
Age of onset: comparative UK data
PH1, 2 and 3

% PH Patients

Age of onset in years

<1y 1-4.9 5-9.9 10-14.9 15-19.9 20-39.9 40-80

PH1
PH2
PH3
Consequences of PH1

• Phenotypic variability

• Systemic deposition of Ox in all organs
  – bones
  – myocardium, vasculature, AV block
  – cutaneous
  – bone marrow: EPO resistant anaemia
  – eyes: retina
  – neurological

• Progressive renal impairment
Factors impacting on renal survival

- Degree of hyperoxaluria
- Nephrocalcinosis
- Specific mutation

Mandrile G et al, Kid Int. 2014: 86(6):1197-204
Consequences of PH1

Female aged 9 years with calcification of kidneys, marked osteopoenia. Pin in femoral neck following fracture.

Oxalate crystals on fundoscopy and in retina on post mortem
Consequences of PH1

Endomyocardial biopsy right ventricle

Giant cell with crystals

Gangrene of fingers with osteolysis in secondary oxalosis

Index and middle finger

Courtesy of S Arampatzis, D Fuster
University Hospital of Bern, Switzerland
Infantile Systemic Oxalosis

• Poorer prognosis for PH1 in neonates
• Early death is common
  – 50% have ESRD at diagnosis and 80% develop ESRD by 3 years\(^1\)
• Difficult to diagnose and treat
  – Normal ranges of urinary/plasma oxalate not clearly defined for neonates
  – Acute renal failure common problem in infancy; hampers urinary excretion of oxalate, so that oxalate levels may appear to be normal
• Only effective treatment option early hepato-renal transplantation

\(^1\) Millan et al. Transplantation. 2003; 76:1458-63
PH1 Patient Population

OxalEurope data

• Approx 690 – 740 PH1 patients to date

• 51 of 132 PH1 patients: systemic oxalosis\textsuperscript{1}

\textsuperscript{1}Garrelfs S et al. IPNA 2016
PH1: age at diagnosis n=297

- Age 0 – 1
- Age 1 – 10 years
- Age 10 – 20 years
- Age 20 – 40 years
- Age > 40 years

Percent
Diagnosis often missed or delayed
  – Lack of availability of adequate diagnostic tools
  – Highly variable age of onset, presentation and progression

Indications of significant number of undiagnosed patients in Asia and Middle East:
  – Oxalate in urine of 24-40% of Pakistani children with stones\(^1\)

150 Pakistani patients with PH1 studied\(^2\)

Estimates suggest high disease burden: incidence of **1 in 14 500** (based on UK data\(^3\)) with gene frequency ranges from 1 in 4000 to 200 000 (cf 1 in 200 000 in Europeans)

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\(^1\)Rizvi SA et al. Ind J Urol 2007: 23(4) 420-7
\(^3\)Hutchesson AC et al. J Med Gen 1998;35(5) 366-70
PH1 patient Kaplan-Meier survival curve

n=410 with full AGXT genotype
Death in 13%

Mandrile G et al. Kid Int. 2014; 86(6):1197-204
Patient survival PH1: importance of ESRD

Graph showing patient survival over age (years) with lines indicating survival with and without ESRD.
Early therapy

• affects long term outcome
• 20/27 PH1 children stable GFR over 20yrs
• document genetic data
• allows time to reflect on phenotypic variability

Fargue S et al KI 2009; 76: 767-73
Conservative treatment

1. Minimize absorption of oxalate
   - Avoid Vit C / high oxalate foods
   - Oxalobacter formigines

2. Reduce oxalate synthesis
   - Vit B6 pyridoxine
   - Gly170Arg or Phe1 52Ile mutation

3. Minimize oxalate deposition in kidney
   - ↑ Fluid intake 2.5 l/m²/day minimum
   - ↓ Salt Na⁺ intake
   - Potassium citrate to reduce urine acidity
On-going management

Annual GFR ml/min/1.73m$^2$

- If $> 60$ → stable
- If 40-60 → consider isolated liver Tx
  - review genotype $\text{Gly170Arg}$
- If $< 40$ → combined liver/ kidney Tx
Dialysis in PH

• Unable to reduce oxalate load

• Weekly clearance = 6-9 mmol/wk/SA equivalent to 2 days of endogenous oxalate production

• Haemo clearance better at 120ml/min than PD at 7ml/min

Perit Dial Int 1994; 14; 81-84
NDT 2001; 16: 2407-11
KI 2006; 70: 1642-8
Isolated liver transplant

- ? Timing + genotype Gly170Arg
- Drugs compromise renal function
- Possible subsequent renal Tx

Patient survival in pre-emptive Liver Tx

82% at 10 yrs of age
72% at 20 yrs of age
5 out of 24 (21%) patients died

Perera T et al NDT 2010; 26(1)354-9
Ped Transpl 2000; 4: 177-81
Hepato-renal transplantation

• Combined
  – Total hepatectomy required
  – 80% patient 5yr survival with GFR of 40-60
  – Risk factors:
    age < 5 yrs
    dialysis > 2 yrs
    poor renal graft function

• Sequential
  – liver 1st then kidney
    • advantage of early liver replacement of AGT
    • can delay renal Tx
  – cadaveric or LRD or combination

Ellis et al NDT 2001; 16: 348-54

Harambat J et al KI 2010; 77: 383-5
Brinkert F et al Transplant 2009; 15: 1415-21
Patient survival after combined hepato-renal transplant

82% at 5 yrs
74% at 10 yrs
66% at 20 yrs

24 out of 113 (21%) patients died
Current problems

• Management of recurrent stones
• Oxalate deposition systemically and in the transplanted kidney – sometimes immediate graft loss
• Management of recurrent bone fractures
• Coordinated care for multisystem disease
Current Research

• Gene therapy
  – In vivo (gene delivered by vector)
  – Ex vivo on induced pluripotent stem cells (iPSC) together with hepatocellular Tx

• Systems development
  – Mouse knockout – single or multiple:
    AGT / GRHRP / HOGA1 / GO

• RNAi therapeutics
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Q&A Session
The Story of George
And his family: Josie (age 14) George (age 12)
Told by his mom.
I am a full time working mom and adult endocrinologist
January 2013, George passed his first kidney stone

- Stone passed was one of six
- Probably had passed a couple prior but we mistook them for a bout of gastroenteritis or a muscle ache after playing tennis
- Removal of the remaining 5 would require a series of painful surgeries and procedures
George maintained his caring spirit

- Recovery was difficult
- In spite of pain, he kept an optimistic attitude
- First remark after awakening from initial surgery: “I am glad this happened to me and not Josie”
George doing homework before surgery
Diagnosis of Hyperoxaluria

• Receiving the diagnosis – surreal
• Paucity of treatment options and possibility of kidney – liver transplantation made diagnosis frightening
• After receiving diagnosis, we found the Oxalosis and Hyperoxaluria Foundation (OHF)
• Within 24 hours, we had contacted the Mayo Clinic Hyperoxaluria Center and Dr. Dawn Milliner and started treatment
• Received genetic testing results as we were landing in Rochester a month later
WELCOME TO THE OHF

The Only Foundation in The World Dedicated to improving the care and treatment and finding a cure for Oxalosis, Primary Hyperoxaluria and other hyperoxaluria related stone diseases.
George has been an inspiration to us through this experience with his optimism and courage

- Optimism and courage
- Progressed to drinking three liters within a couple of weeks
- Drinking continuously is not easy
- Diagnosis made just weeks before his annual trip to camp
  - Drinking more
  - Medications away from home
George at camp a few weeks after the diagnosis
Everyone plays an important role

- Josie – reminds and encourages George to drink when he gets frustrated

- Parents help George reinvent plans of how to accomplish water and medications while at school

- We take turns awakening him at night to empty bladder and drink

- Grandparents take turns helping him
Slings are helpful... always carry a water bottle for drinking
Camelbak
Reading to Christ Church Preschool with a bottle in sling
We have a variety of water bottles and slings and camelbaks
Daily prevention medications ... liquid potassium citrate 2 teaspoons three times daily and B6
Tennis – start drinking early and continuously
Cross country – can not drink too close to run
Kidney function is the key to George’s future

![Graph showing kidney function over time]

- 61 mL/min/BSA on 01/15/2016 at 10:05 AM
- 70 mL/min/BSA on 01/19/2015 at 1:13 PM
As parents we want to do everything possible to maintain George's kidney function

• We have committed to support the OHF

• Thrilled with possibilities in treatment options companies such as Alnylam are investigating
Thank you
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Q&A Session
Primary Hyperoxaluria Type 1 (PH1)

• Rare, autosomal recessive disease
• Prevalence of 1-3:1,000,000
• Deficiency of hepatic alanine-glyoxylate aminotransferase (AGT) leads to excessive hepatic oxalate production
• Systemic oxalosis occurs as renal function declines
• Minority of patients respond to Vitamin B6, a co-factor of AGT
• Conservative therapy with hyperhydration and crystallization inhibitors
• Metabolic correction requires liver transplantation, typically performed in combination with renal transplant
Investigational Therapeutic Approach: RNAi

• Harness a natural pathway of gene silencing to regulate protein production

• Sequence-dependent degradation of target mRNA confers exquisite specificity

• Conjugation to the sugar GalNAc allows efficient delivery to hepatocytes and subcutaneous administration

• General approach clinically validated with human proof-of-concept in multiple clinical development programs
PH1 Pathophysiology

Healthy Pathway

![Healthy Pathway Diagram]

PH1 Pathway

![PH1 Pathway Diagram]
ALN-GO1 Therapeutic Hypothesis
Knockdown of Liver GO Enzyme to Reduce Oxalate

ALN-GO1 Effect in healthy volunteers

ALN-GO1 Effect in PH1 patients
### Part A: Single-Ascending Dose (SAD) | Randomized 6:2, Single-blind, Placebo-controlled

- 0.3 mg/kg x 1 SC, N=8
- 1.0 mg/kg x 1 SC, N=8
- 3.0 mg/kg x 1 SC, N=8
- 6.0 mg/kg x 1 SC, N=8

Healthy adult volunteers
Outcome evaluations: Safety and Pharmacodynamics

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

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

PH1 patients, ages 6-64 years
GFR>45 ml/min/1.73m²
Outcome evaluations: Safety and Pharmacodynamics

Clinicaltrials.gov identifier: NCT02706886
### Demographic

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<td>Number enrolled</td>
<td>N=32 (ALN-GO1:Placebo = 24:8)</td>
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<tr>
<td>Median Age (range)</td>
<td>29 years (22 - 42)</td>
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<tr>
<td>Gender</td>
<td>16 females, 16 males</td>
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<td>Race (n)</td>
<td>White / Caucasian 25 Asian 2 African 2 Other 3</td>
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*Data as of: 17 August 2016
Milliner et al., IPNA, September 2016
ALN-GO1 Phase 1/2 Interim Study Results*
Safety: Part A (Healthy Volunteers)

ALN-GO1 was generally well-tolerated in healthy volunteers

No drug-related SAEs or discontinuations due to AEs

Total of 61 AEs reported in 5 placebo and 21 ALN-GO1 treated healthy volunteers

- AEs occurring in greater than 10% of ALN-GO1 treated subjects included nasopharyngitis (N=6), headache (N=5), and transient injection site pain (N=4).
  - All AEs were mild to moderate with the exception of one healthy volunteer in the lowest dose cohort who had transient, asymptomatic CPK elevation which was unrelated to study drug.

No clinically significant changes in vital signs or EKG

*Data as of: 17 August 2016
Milliner et al., IPNA, September 2016
ALN-GO1: Plasma Pharmacokinetics
Part A (Healthy Volunteers)

- ALN-GO1 was rapidly absorbed after subcutaneous injection with mean plasma $t_{\text{max}}$ of approximately 3 to 6 hours
- Plasma exposures increased proportionally with dose
- Plasma concentrations declined rapidly after $t_{\text{max}}$ with a short elimination $t_{1/2}$ (~ 3.5 to 7 hours), consistent with rapid uptake by the liver

*Data as of: 2 September 2016
Milliner et al., IPNA, September 2016
ALN-GO1 Phase 1/2 Interim Study Results*
Plasma Glycolate: Part A (Healthy Volunteers)

• A dose-dependent increase in plasma glycolate levels is observed, with earliest onset of activity at higher doses evident by Day 29 post dose and sustained until Day 85

• The lowest dose with appreciable glycolate increase is 1 mg/kg
ALN-GO1 Phase 1/2 Interim Study Results*
Urine Glycolate: Part A (Healthy Volunteers)

- A dose-dependent increase in urine glycolate activity is observed, with onset of activity evident by Day 29 post dose

SEM; Standard error of the mean; Cr: Creatinine
*Data as of: 2 September 2016
Milliner et al., IPNA, September 2016
ALN-GO1 Phase 1/2 Interim Study Results
Summary: Part A (Healthy Volunteers)

• ALN GO1 is a novel, subcutaneously administered investigational RNAi therapeutic designed to reduce the hepatic production of oxalate in PH1 patients

• Preliminary data in healthy adult volunteers suggest that single doses of ALN-GO1 are generally well tolerated

• ALN-GO1 demonstrates dose-dependent and sustained pharmacodynamic activity, with the expected effect of increasing plasma and urine glycolate levels in healthy volunteers

• A starting regimen for the investigation of PH1 patients will be 1.0 mg/kg q28 days, where the increased glycolate levels observed in healthy volunteers is expected to translate into a reduction in urinary oxalate excretion in patients
Agenda

Welcome
• Josh Brodsky, Associate Director, Investor Relations & Corporate Communications

Introduction
• David-Alexandre Gros, M.D., Senior Vice President, Chief Business Officer

Overview of Primary Hyperoxaluria Type 1
• Sally-Anne Hulton, M.D., FRCPCH, MRCP, FCP, MBBCh, Consultant Paediatric Nephrologist and Clinical Lead, Birmingham Children's Hospital NHS Trust

Caregiver Perspective
• Jennifer Lawrence, M.D., Mother of a PH1 patient

ALN-GO1 Program
• David Erbe, Ph.D., Director, Research

Q&A Session
Upcoming RNAi Roundtable

ALN-HBV for the treatment of Hepatitis B Virus (HBV) Infection

*Tuesday, October 11, 9:00 a.m. – 10:00 a.m. ET*

• Barry Greene, President
• Laura Sepp-Lorenzino, Ph.D., Vice President, Entrepreneur-in-Residence
• Guest Speaker: Heiner Wedemeyer, M.D., Managing Senior Physician and Assistant Professor in the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School

For more information, please visit [www.alnylam.com/roundtables](http://www.alnylam.com/roundtables)
Thank you

www.alnylam.com