# Pharmacokinetics and Pharmacodynamics of Lumasiran: Analysis of Four Clinical Studies

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# Disclosures



- **J M Gansner, G Robbie:** employees of Alnylam Pharmaceuticals and hold shares in Alnylam Pharmaceuticals.
- **B Habtemariam:** former employee of Alnylam Pharmaceuticals.

# Primary Hyperoxaluria Type 1 and Lumasiran

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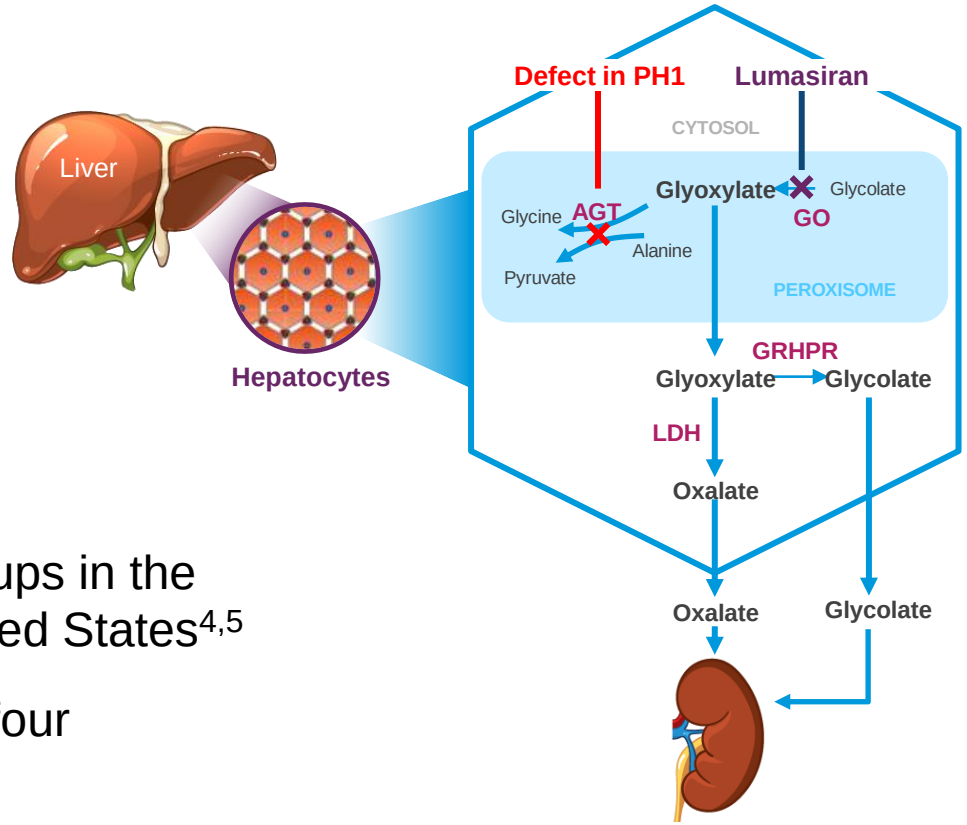
- PH1 is characterized by hepatic oxalate overproduction due to a deficiency in the hepatic peroxisomal enzyme AGT[1,2]
- Excess oxalate results in recurrent kidney stones, nephrocalcinosis, progressive kidney disease, and multi-organ damage[1,2]
- Lumasiran is a liver-targeted N-acetylgalactosamine–conjugated RNAi therapeutic designed to reduce hepatic oxalate production by inhibiting GO[3]
- Lumasiran is approved for the treatment of PH1 in all age groups in the European Union and in pediatric and adult patients in the United States[4,5]
- We describe lumasiran PK and PD in patients with PH1 from four clinical studies




AGT, alanine-glyoxylate aminotransferase; GO, glycolate oxidase; PD, pharmacodynamics; PH1, primary hyperoxaluria type 1; PK, pharmacokinetics; RNAi, ribonucleic acid interference.

1. Cochat P, Rumsby G. *N Engl J Med*. 2013;369:649-58. 2. Danpure CJ. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: The McGraw-Hill Companies, Inc.; 2019.
3. Liebow A, et al. *J Am Soc Nephrol*. 2017;28:494-503. 4. Oxlumo [summary of product characteristics]. Amsterdam, Netherlands: Alnylam Netherlands; 2020. 5. Oxlumo [package insert]. Cambridge, MA: Alnylam Pharmaceuticals; 2020.

# Lumasiran Weight-Based Dosing

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- The dosing regimen was selected to achieve similar liver concentrations and target suppression in all weight groups
- Based on allometric principles regarding growth rate, relative liver size, and drug clearance rate[1]:
  - Children who weigh <20 kg require a higher dose to achieve liver concentration and target suppression similar to children who weigh ≥20 kg
  - Children who weigh <10 kg require more frequent ongoing dosing (monthly) to keep up with the rapid pace of growth

| Lumasiran Weight-Based Dosing | | |
|---|---|---|
| **Patient Weight** | **Loading Dose** | **Maintenance Dose** |
| <10 kg | 6 mg/kg once monthly for 3 doses | 3 mg/kg once monthly, beginning 1 month after the last loading dose |
| 10 to <20 kg | 6 mg/kg once monthly for 3 doses | 6 mg/kg once every 3 months (quarterly), beginning 1 month after the last loading dose |
| ≥20 kg | 3 mg/kg once monthly for 3 doses | 3 mg/kg once every 3 months (quarterly), beginning 1 month after the last loading dose |

1. Anderson BJ, Holford NHG. *Annu Rev Pharmacol Toxicol*. 2008;48:303-332.

# Pooled PK and PD Data Analysis

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| Pooled Studies | | | |
|---|---|---|---|
| | Phase 3 | | |
| Phase 1/2 | ILLUMINATE-A | ILLUMINATE-B | ILLUMINATE-C |
| Part A:<br>• Healthy volunteers<br>• Age 18–64 years<br><br>Part B:<br>• Genetically confirmed PH1<br>• Age 6–64 years<br>• eGFR >45 mL/min/1.73m$^2$ | • Genetically confirmed PH1<br>• Age ≥6 years<br>• eGFR ≥30 mL/min/1.73m$^2$ | • Genetically confirmed PH1<br>• Age <6 years<br>• eGFR >45 mL/min/1.73m$^2$ if ≥12 months old or normal serum creatinine for age if <12 months old | • Genetically confirmed PH1<br>• All ages<br>• eGFR ≤45 mL/min/1.73m$^2$ if ≥12 months old or elevated serum creatinine for age if <12 months old<br>• Cohort A: no hemodialysis<br>• Cohort B: hemodialysis |

eGFR, estimated glomerular filtration rate.

# Baseline Demographic and Clinical Characteristics



| | No Hemodialysis (N=75) | Hemodialysis (N=15) | All Patients (N=90) |
|---|---|---|---|
| | Median (Range) | | |
| Age (years) | 11 (2–60) | 14 (2–59) | 11 (2–60) |
| Weight (kg) | 38 (5–121) | 20 (7–85) | 34 (5–121) |
| eGFR (mL/min/1.73m$^2$) | 85 (9–174)[a] | – | 85 (9–174)[a] |

[a]N=72.

# Comparable Lumasiran PK Across Dosing Categories

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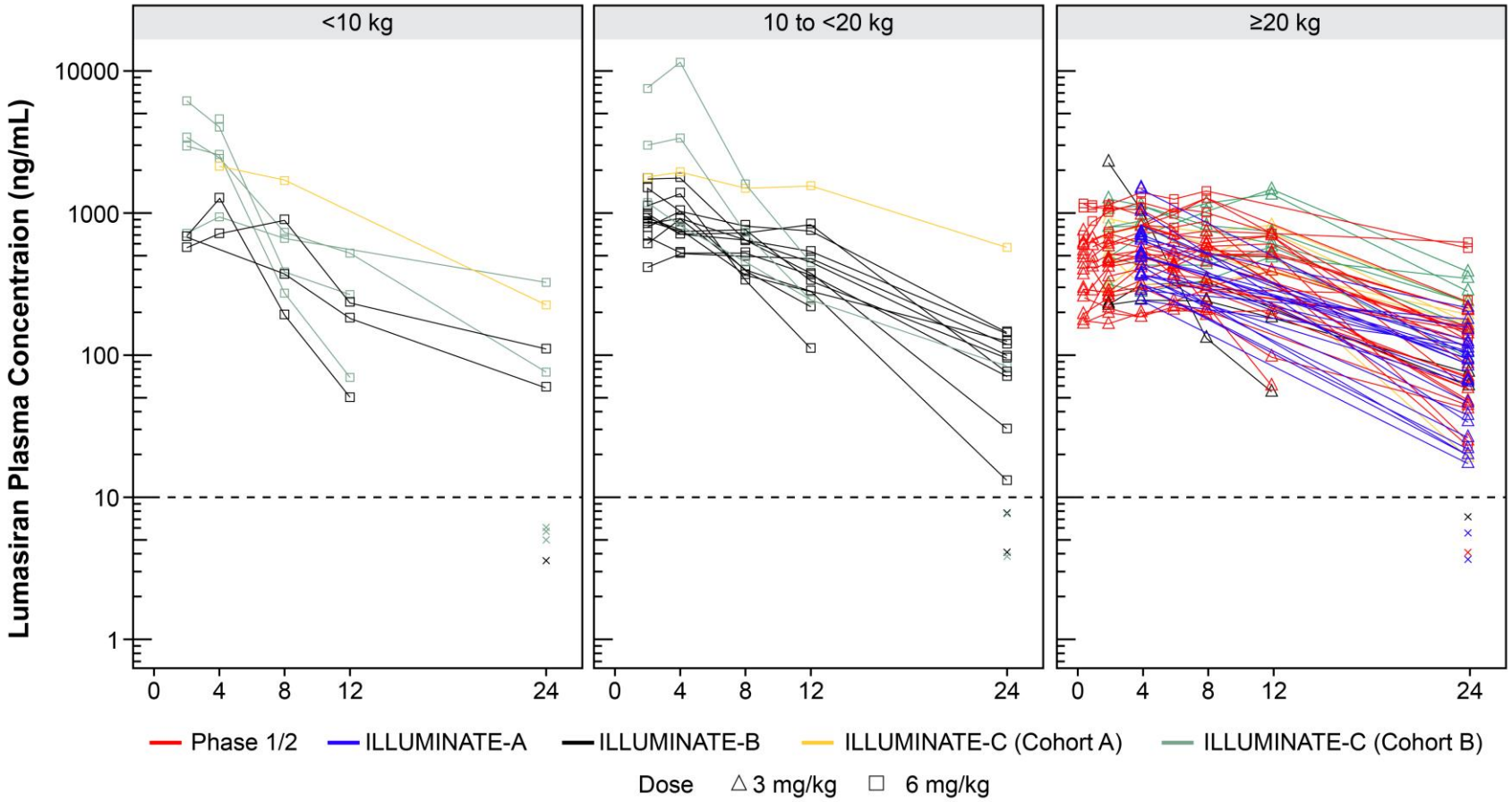
- The recommended dose regimen for lumasiran led to comparable plasma concentration and exposure across weight categories
- Patients weighing <20 kg exhibited faster plasma clearance, consistent with allometric principles
- Lumasiran plasma concentrations reached lower limit of quantitation within 24 to 48 hours, indicating rapid liver uptake, regardless of kidney function




Dashed lines represent the lower limit of quantitation for lumasiran (10 ng/mL). Crosses indicate post-dose samples reported as below the lower limit of quantitation.

# Comparable Lumasiran PK Across Weight Categories

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- Lumasiran showed comparable $C_{max}$ and AUC across a range of body weights
- Transiently higher plasma concentrations in patients with severe kidney impairment and end-stage kidney disease consistent with low renal excretion of lumasiran
- Median (range) $T_{max}$ was 4.0 (0.5–12) hours and mean (%CV) half-life was 5.2 (47%) hours

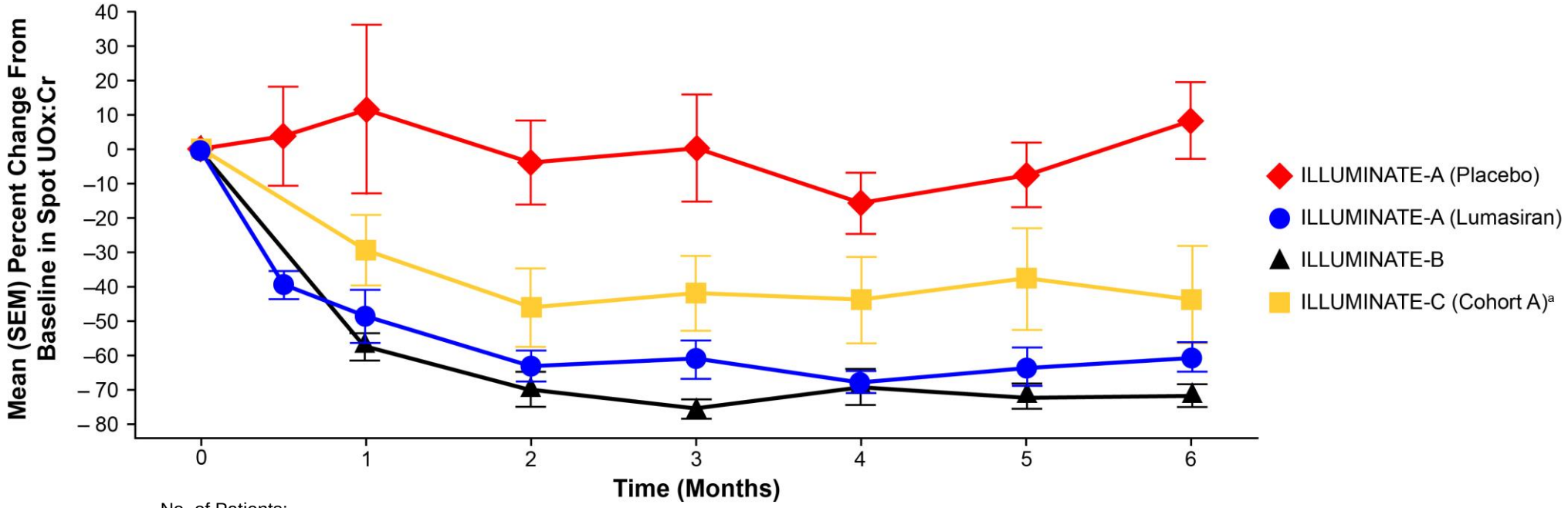
| PK Parameter | Weight Category | Phase 1/2, ILLUMINATE-A, ILLUMINATE-B | ILLUMINATE-C |
|---|---|---|---|
| | | Median (Range) | |
| $C_{max}$ (ng/mL) | <10 kg | N=3<br>890 (678–1,280) | N=6<br>3,190 (938–6,150) |
| | 10 to <20 kg | N=11<br>912 (523–1,760) | N=4<br>2,670 (1,180–11,500) |
| | ≥20 kg | N=48<br>446 (389–2,280) | N=11<br>811 (494–1,470) |
| $AUC_{0\text{-last}}$ (h*ng/mL) | <10 kg | N=3<br>6,270 (5,920–8,510) | N=6<br>16,200 (9,430–24,300) |
| | 10 to <20 kg | N=11<br>8,110 (7,050–13,300) | N=4<br>24,800 (6,290–50,900) |
| | ≥20 kg | N=12<br>6,210 (2,890–10,700) | N=11<br>10,100 (6,850–17,500) |

$AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time of administration (0) to the last measurable time point (last); $C_{max}$, maximum plasma concentration; CV, coefficient of variation; $T_{max}$, time to reach maximum plasma concentration.

# Comparable Spot UOx:Cr Reduction Across Studies



- At Month 6, mean percent reduction in spot UOx:Cr ranged from 44.1% to 71.7% across studies




No. of Patients:

| | | | | | | |
|---|---|---|---|---|---|---|
| N= | 13 | 13 | 12 | 13 | 13 | 13 |
| N= | 25 | 25 | 26 | 25 | 25 | 25 |
| N= | 18 | 18 | 18 | 18 | 18 | 18 |
| N= | 6 | 6 | 6 | 6 | 6 | 6 |

[a]Lower spot UOx:Cr reduction is likely due to small sample size.
UOx:Cr, urinary oxalate:creatinine ratio.

# Consistent Plasma Oxalate Reduction Across Studies

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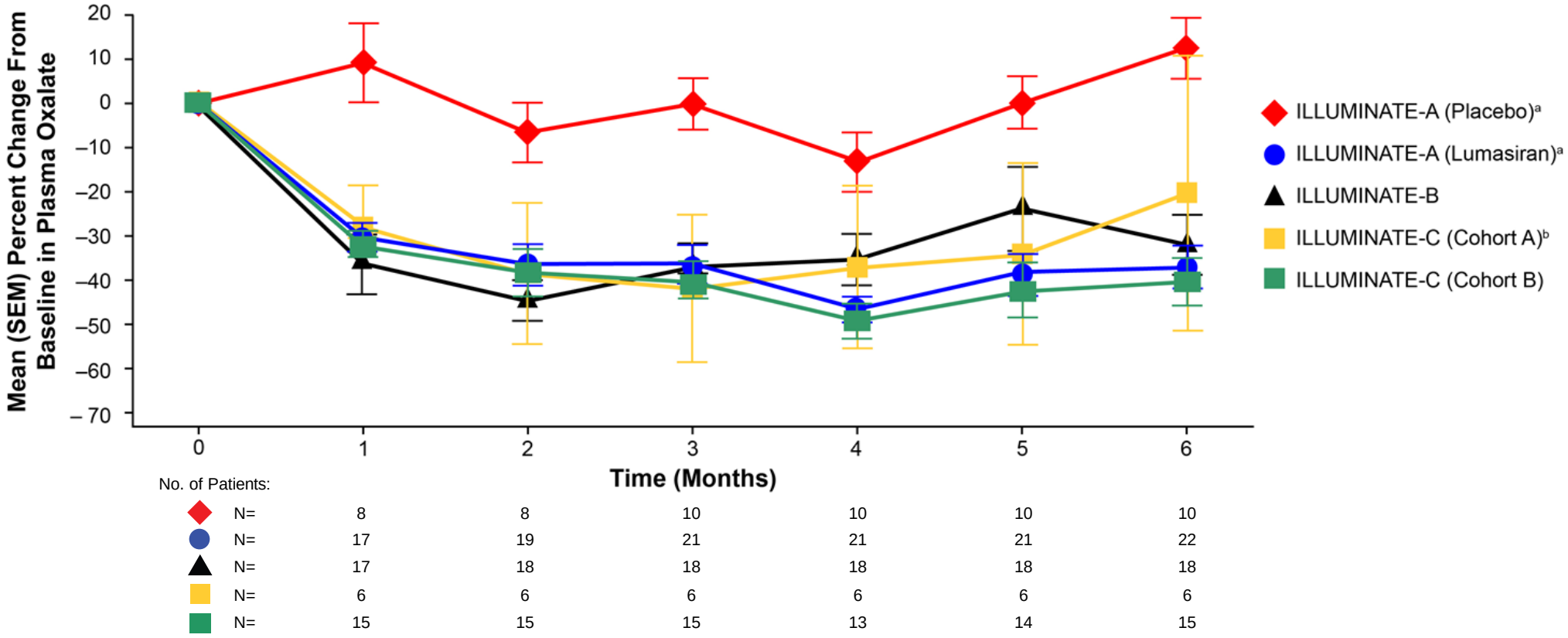
- At Month 6, mean percent reduction in plasma oxalate ranged from 20.3% to 40.3% across studies




No. of Patients:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ◆ | N= | 8 | 8 | 10 | 10 | 10 | 10 |
| ● | N= | 17 | 19 | 21 | 21 | 21 | 22 |
| ▲ | N= | 17 | 18 | 18 | 18 | 18 | 18 |
| ■ | N= | 6 | 6 | 6 | 6 | 6 | 6 |
| ■ | N= | 15 | 15 | 15 | 13 | 14 | 15 |

[a]POx analysis set (patients who received any amount of study drug and had baseline POx level ≥1.5×LLOQ; LLOQ=5.55 µmol/L). [b]Variable POx reduction is likely due to small sample size. LLOQ, lower limit of quantitation; POx, plasma oxalate.

# Comparable Liver Exposure and Target Engagement Across Studies

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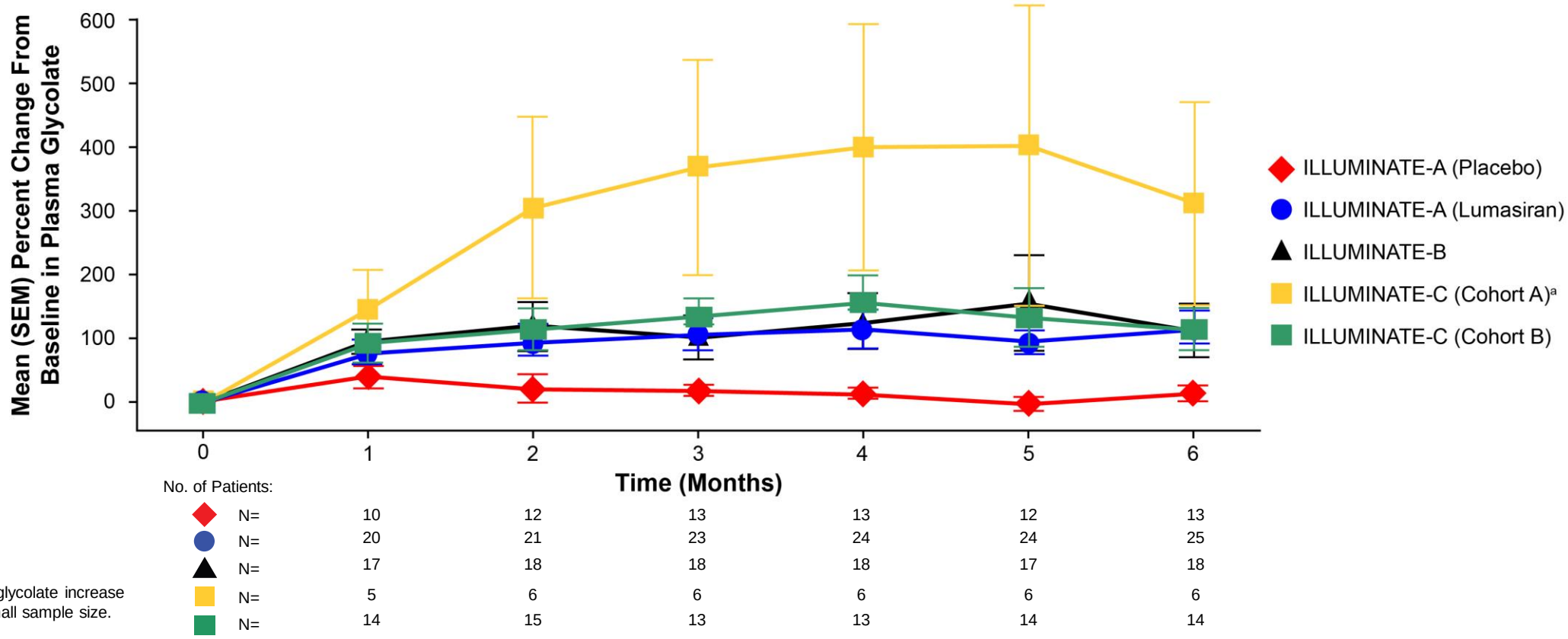
- At Month 6, plasma glycolate levels showed an approximately 2-fold elevation and plateau, consistent with the mechanism of action of lumasiran
- These data suggest comparable liver exposure and target engagement across studies




[a]Greater plasma glycolate increase is likely due to small sample size.

# Conclusions

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- The recommended weight-based dosing regimens of lumasiran achieved comparable PK, target engagement, and efficacy for patients with PH1 of all ages and degrees of kidney function, including patients on hemodialysis
- In the ILLUMINATE-A, ILLUMINATE-B, and ILLUMINATE-C studies, the most common adverse event related to lumasiran was injection-site reaction


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