Transforming care for people with recurring kidney stones

by treating enteric hyperoxaluria

Oxidien™ Pharmaceuticals

Oxidien: state-of-the-art enteric hyperoxaluria therapy

Enteric hyperoxaluria – unmet medical need (1)

Hyperoxaluria (high oxalate in urine) is associated with recurrent kidney stones, inflammation, progression of CKD, and ESKD. It cause ***significant morbidity***, costly monitoring and interventions, and is a burden to patients and the healthcare system.

OX1 – A new molecular entity (2)

OX-1 is a proprietary, state-of-the-art, enzyme to degrade oxalate in the gut. Proof-of-mechanism data show promise for higher efficacy in patients. Demonstrated good safety profile consistent with other oral enzymes. Encouraging FDA feedback ahead of phase 2 program. Anticipating ***expedited development path and accelerated approval pathway to market***.

Substantial market opportunity (3)

There are currently ***no approved therapies*** adequately treating enteric hyperoxaluria – markets estimated at ***$2B+ US*** and ***$5B+ worldwide***. Potential opportunity to be ***first-in-class*** in an untapped market.

Team (4)

Committed founders/management have ***deep technology expertise across oxalate-degrading platforms and modalities***. and are supported by a ***world-class Scientific/Medical Advisory Board*** and Strategic Advisory Board.

Seeking licensing partner to expedite development of lead drug candidate

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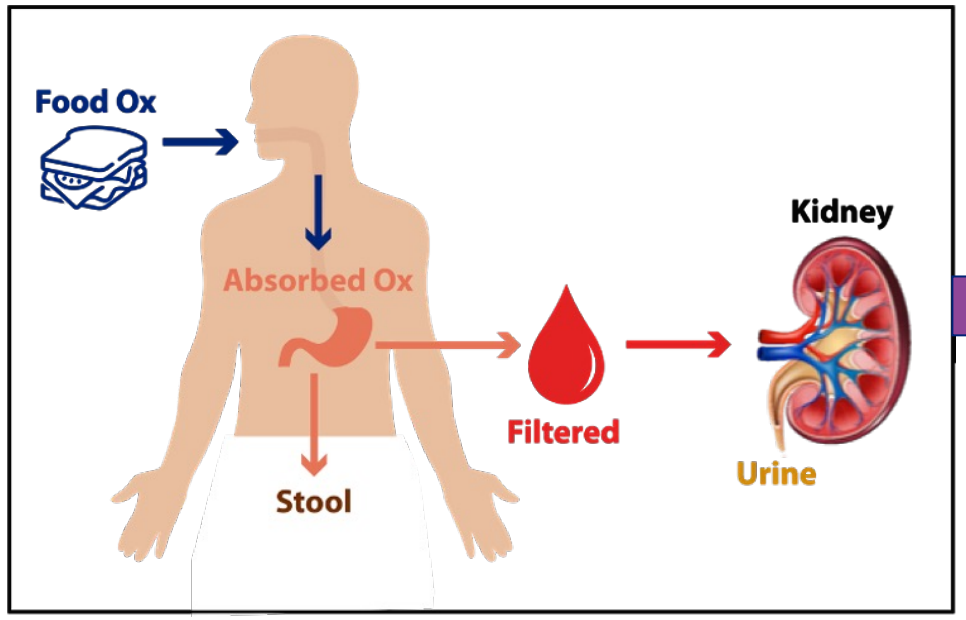
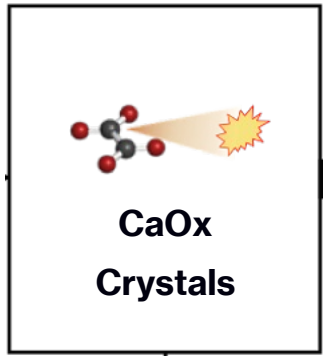
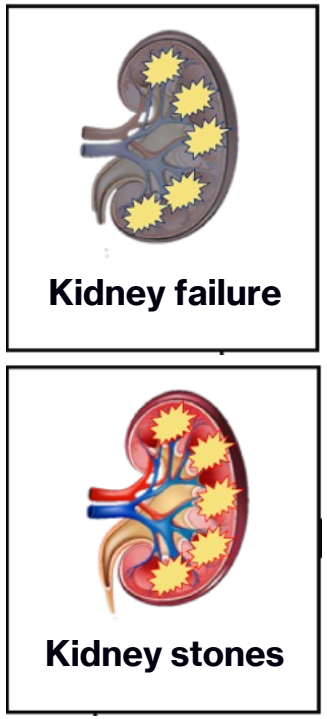
Disease Overview
Development Landscape

Enteric hyperoxaluria – disease with significant morbidity







Dietary oxalate:

- ✓ Highly prevalent in healthy diet
- ✓ Patients hyper absorb oxalate
- ✓ Close to complete excretion via kidneys

Crystals form:

- ✓ Inflammatory responses
- ✓ Tissue damage
- ✓ Impaired renal function

Morbidity:

- ✓ Severe pain
- ✓ Progression of CKD
- ✓ Chronic stone formation
- ✓ ESKD, systemic oxalosis

Healthcare impact:

- ✓ ER visits, hospitalizations
- ✓ Procedures for management of KSD

CKD = Chronic Kidney Disease
ESRD = End-stage Kidney Disease
KSD = kidney stones disease

1. Bhasin, B., Urekli, H.M., Atta, G. M. *World J Nephrol.* 2015; 4(2): 235-244
2. Waikar, S.S., *JAMA Intern Med*. 2019; 179(4):542-551
3. Jaeger, P., Robertson, W.G., Nephron Physiol (2004) 98:64-71

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Treatment strategies are suboptimal

Treatment strategies in Enteric Hyperoxaluria

Dietary intervention:

- ✓ high fluid intake,
- ✓ ***oxalate restriction***,
- ✓ decreased sodium and fat intake

Targeted therapies:

- ✓ thiazide diuretics
- ✓ potassium citrate
- ✓ calcium supplementation

Enteric hyperoxaluria patients experience recurrent kidney stones and loss of kidney function.

Standard of care does not adequately prevent later stage costly interventions.

Shockwave lithotripsy, ureteroscopy, percutaneous nephrolithotomy

Dialysis, transplantation

There are currently no FDA approved treatments for enteric hyperoxaluria

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EH patient populations in the U.S. and worldwide

U.S. patient population: 250,000* of which 150,000 have CKD and 100,000 have stones

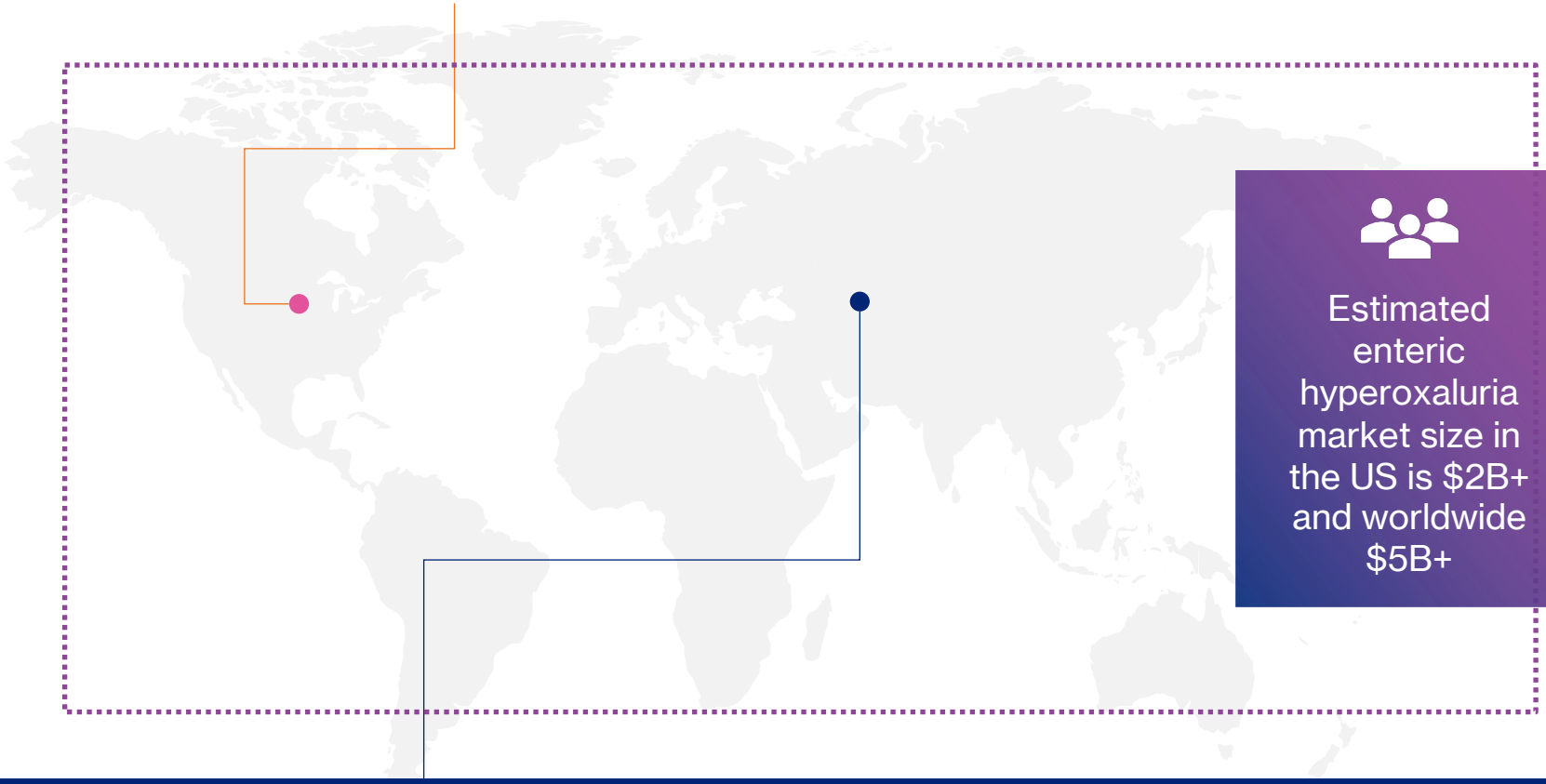
5,000*
Short Bowel Syndrome

15,000*
Chronic Pancreatitis

30,000*
Celiac Disease

50,000*
Intestinal Bowel Disease, Crohn's Disease and Ulcerative colitis

150,000*
Roux-en-Y Gastric Bypass



Estimated enteric hyperoxaluria market size in the US is $2B+ and worldwide $5B+

Worldwide EH population estimated to be one million patients^

* Poster presented at Kidney week 2019: SA-PO-276. The 52nd Annual Meeting of the ASN. Nov. 2019.
^ DR-037 Global Prevalence of Secondary Hyperoxaluria report on file.
# 1,000,000 EH globally x (100,000/250,000) = 400,000 stone formers globally (100,000 in the U.S. and 300,000 in the rest of the world)

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Opportunity to learn from pioneers

Need improved molecules:

Hard to change underlying molecule's capacity and constraints even with complex, costly, formulations or other encapsulation.

Need convenient dosing:

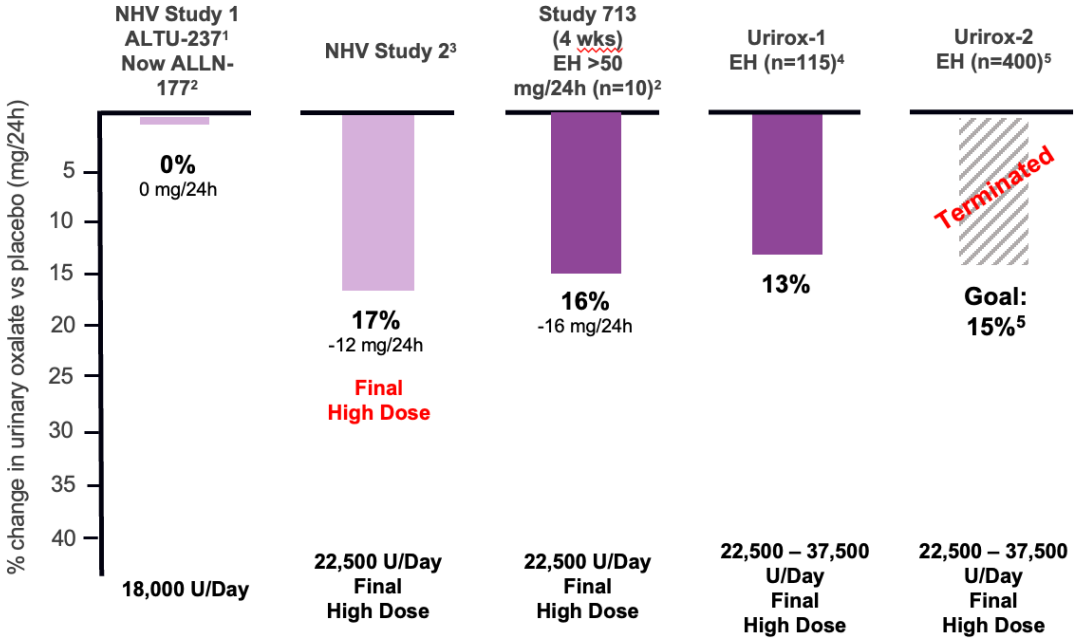
Product format (*e.g.* sachet vs capsule), number of capsules per dose, and doses per day impact patient compliance and potentially variability in outcomes.

Need tolerable effective dose:

Gut-restricted and specific oral enzymes have demonstrated a good safety profile even at higher doses, important for chronic drug.

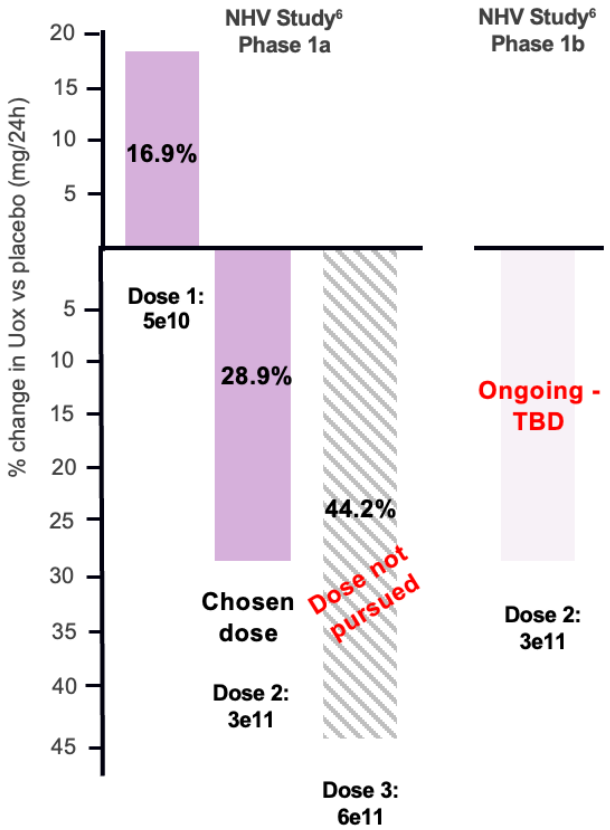
Parameter	Oxidien (S. elongates)	Allena (B. subtilis)	Synlogic (E. coli)
Where it works	Stomach/small intestine	Stomach/small intestine	Stomach/small intestine/large intestine
Dosing	Single pill 3/day	Two pills up to 5/day	Undisclosed
Fast-acting	✓	✓	X
Defined regulatory path	✓	✓	X
No oxalate "threshold" needed	✓	X	X
Uox reduction well into normal range	✓	X	X
% subjects who show clinically meaningful response	60%	30%	Not disclosed

What have we learned?



Graph (left): Allena Pharma's NHV studies, and placebo-controlled studies evaluating Reloxaliase in EH patients. **First NHV study not successful. Second NHV study successful on high dose. Phase 3 study terminated due to a lack of sufficient power at the number of patients defined by the protocol.**

Graph (right): Synlogic's dose-finding study evaluating three doses (5e10, 3e11, 6e11) of the SYNB8802 live biotherapeutic in NVH on a controlled diet. **Mid dose (3e11 organisms per dose) was chosen for Phase 1b.**



We believe there is significant room for upside with a novel oral enzyme composition

1. Atti, K.M., and Grujic, D. Anion Transporters and Oxalate Homeostatis: From Genes to Diseases December 8-9, 2008.
2. Allena Pharmaceuticals S-1. Describes the license of ALTU-237 "now called ALLN-177". (21.31mg – 4.85mg)/103 mg per 24h = 16%
3. Langman, C.B., et al. *Am J Nephrol* 2016; 44:150-158
4. Allena Pharmaceuticals Corp. Presentation July 2021 (22.6 – 9.7 = 12.9% red.)
5. Allena Pharmaceuticals 8-K Filed March 18, 2022.
6. Synlogic (SYBX) Corporate Presentation March 2022.

GI = Gastrointestinal
Uox = Urinary Oxalate
Pbo = Placebo
NHV = Normal Healthy Volunteers

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Lead Candidate: OX-1

For Enteric Hyperoxaluria

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OX-1 – the future lies beyond old molecules

New molecular entity

OX-1 is a ***new and proprietary*** type of oxalate decarboxylase (OxdC) enzyme, designed to effectively degrade oxalate to natural byproducts in the upper GI-tract.

Advantages

High-potency with unique level of pH stability in the upper GI-tract that appers to have ***improved kinetics (Km)***.

Clinical data with positive effect and ***good safety profile.***

Product Profile

A ***single capsule*** of OX-1 is taken by mouth, with meals, up to three times per day to remove oxalate in the upper GI-tract.

Manufacturing Process and Stability

OX-1 is manufactured by recombinant expression in *e.coli*. Initial product candidate is ***stored at room-temperature***.

Next-generation enzyme for meaningful reduction in oxalate

Novel compositions protected in a total of fourteen patents

United States

Europe

Other Major Markets

Patent Family 1 (2010):
Earlier patent family filed expected LOE 2030 - presents barrier to entry and prior art.

- Barriers to entry

Patent Family 2 (2015):
Patents approved or pending for OX-1 in the United States, European Union, Canada, China, Australia, Korea and India. LOE in 2035.

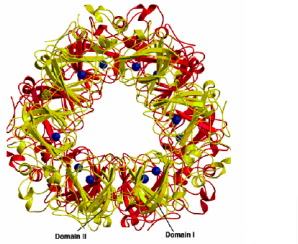
- Protecting the lead

Primed for expansion

OX-1 advantages

Improved kinetics (Km) and pH profile

OxdC from *B. subtilis*[1] (enzyme which Allena used)



Peak Rate: 40 umole/min/mg
(1 umole=90ug oxalate)

At 0.3mM oxalate, rate is estimated at ***0.8 umole/min/mg***

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Peak Rate: 120 umole/min/mg
(1 micromole=90ug oxalate)

At 0.3mM oxalate, rate is estimated at ***60umole/min/mg***

synlogic

Peak Rate: 1.5 umole/h/ 1e9 cells[3]
(1 micromole=90ug oxalate)

Selective and localized activity

synlogic

Oxalobacter^ enzymes in *E. coli Nissle chassis*

- Potential for activity in all gut segments[2].
- Non-selective organism, other carbon sources:
  - Glucose
  - Lactose
  - Sorbitol
  - Xylose
  - Arabinose
  - Mannose
  - Rhamnose

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Novel OxDC# enzyme

- ✓ Local activity in upper GI tract.
- ✓ Selective for oxalate, other known substrates (data on file):
  - None

Broader pH-activity profile, improved kinetics and selective activity

^ Used by OxThera and Allena Pharmaceuticals, no longer in development.
# Different from OxThera's and Allena's enzymes – new IP

1. Tanner, A. et al. J. Biol. Chem. 2001; 276:43627-43634
2. SYBX Corp. presentation March 2021 p. 25.
3. Lubkowicz, D. et al. Mol. Sys. Biol. 2022; 18:e10539

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GI = Gastrointestinal.
Ox = Oxalate
Conc. = Concentration
Est. = Estimated

What does Km mean?

Simplified Example Based On Km Reported in Literature^:

Per Tanner[1] *et al*:

- ***At 0.5mM of oxalate OxdC from B. subtilis would degrade 45 mg oxalate in ~7 hours***
- ***At 0.5mM of oxalate, OX-1 would degrade 45 mg oxalate in <9 minutes***

Concentration of oxalate *in vivo* is estimated to be between 0.3 – 1 mM.

1 mg of enzyme from *S. elongates* (**OX-1**)

Oxalate degraded in

< 9 minutes

1 mg of enzyme from *B. subtilis* (**Reloxaliase**)

Oxalate degraded in

~ 7 hours

^ The oxalate amount (mg) is referring to available oxalate (soluble); hence, this is a simplified example assuming maximum activity for each enzyme. This example is not considering pH since the two enzymes cannot be compared at the same pH (the enzyme from *B. subtilis* is inactive < pH 3).

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1. Tanner, A. et al. *J. Biol. Chem.* 2001; 276:43627-43634

OX-1 – favorable safety profile in healthy volunteers

Event Description	OX-1 (active)	Placebo
Musculoskeletal stiffness	0	2
Abdominal pain	1	0
Diarrhoea	1	0
Dyspepsia	0	1
Nausea	1	0
Vomiting	1	0
Headache	1	0
Dysmenorrhea	1	1
Overall	**6 (4 NHV)^**	**4 (3 NHV)**

^ One NHV reported 3 AEs, all occurring in conjunction with constipation

- ✓ No Serious Adverse Events
- ✓ No product-related Adverse Events (AE)
- ✓ All AEs were mild to moderate
- ✓ Safety profile in healthy volunteers resembling gut-restricted oral enzymes

Safety profile consistent with other oral enzymes studied in late-stage trials

NHV = Normal Healthy Volunteer
AE = Adverse Event

[1] Quintero E. *et al. KIDNEY360* (2020); 1:1284-1290.

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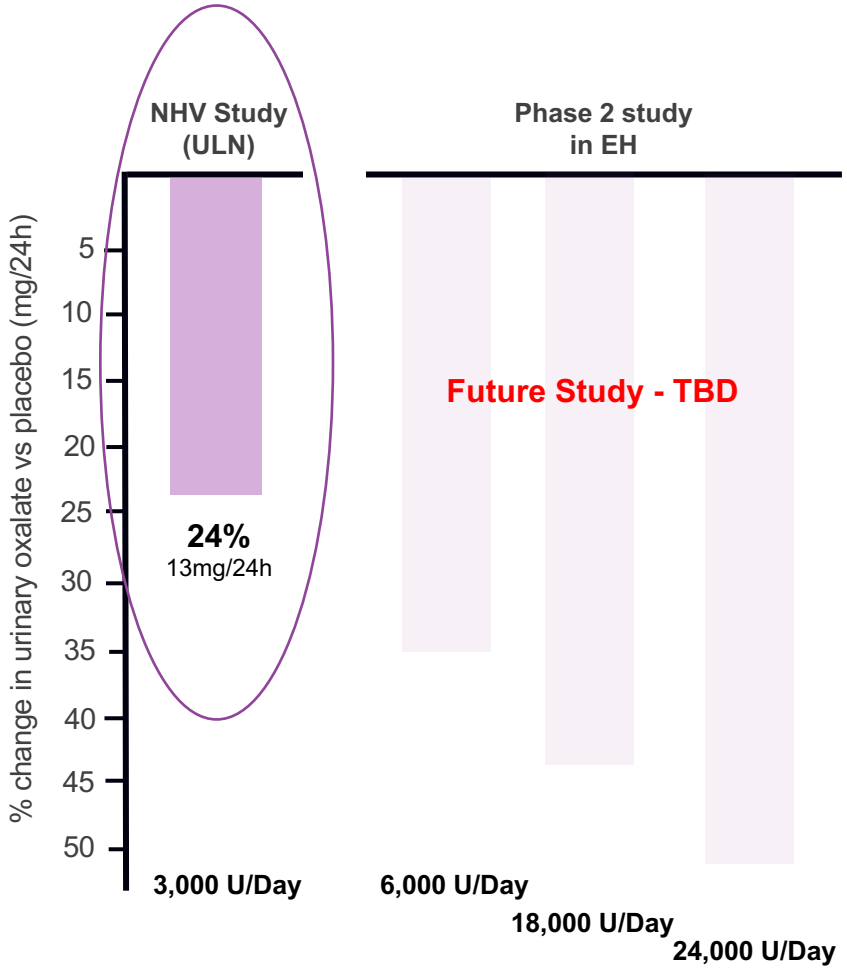
OX-1 – opportunity to achieve even higher reduction



- ✓ In NHV study, OX-1 demonstrated compelling proof-of-mechanism with ***significant Uox reduction vs placebo at low dose***.[1,2]
- ✓ Safety data to date provide support for evaluation of higher doses.
- ✓ Oxidien has yet to perform a dose-finding study; hence, still has an opportunity to achieve even higher reduction vs pbo.

Learnings to date indicate that there is room for upside with a tolerable oral composition

1. Quintero E. *et al. KIDNEY360* (2020); 1:1284-1290.
2. Allena high dose up to 37,500 U/day. OX-1 studied in NHV was 3000 U/day.

Uox = Urinary Oxalate
ULN = Upper Limit of Norma
Pbo = Placebo
NHV = Normal Healthy Volunteers

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OX-1 overall development and regulatory profile to date

Strain development, cell banks, assays, toxicology data

- Recombinant strain development successfully completed and cell banks successfully released for initial use.
- Activity assay validated. Purity assay developed (underdoing validation).
- Toxicology studies show NOAEL (no-observed-adverse-effect-level) at 50-fold safety margin as compared to highest dose to be evaluated in the clinic. All tox work required for Phase 2 completed with no tox end-points met.

Manufacturing/ CMC

- Drug substance process successfully transferred to cGMP manufacturer and successfully scaled.
- Sachet product form (used in first-in-man study) ready to be re-formulated into oral dosage form.
- Have R&D stability of spray-dried dispersion (SDD) at room temperature.
- One technical run and two cGMP runs successfully produced at scale, tested, and released.

Clinical data

- First-in-man study completed with sachet form of OX-1. Met all pre-determined end-points in healthy volunteers fed a controlled diet.
- Clinical data prove biological activity in the stomach: a 56% removal of oral bio-load/dietary oxalate resulted in a clinically meaningful 29% reduction ($p<0.0001$) in urinary oxalate from baseline at a daily dose of 3000U.

Regulatory communication

- Receipt of written responses from PIND Type B meeting request.
- The encouraging responses provide additional clarity on the development program and regulatory pathway.
- Agency expressed consideration for “substantial changes in urinary oxalate” as conditional end-point for registrational trial.

CMC, clinical data and regulatory feedback to date provides an encouraging, risk mitigating development path heading into Phase 2

OX-1 for Enteric Hyperoxaluria

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OX-1: Target product profile

Target Patient Population	Initial: adults with enteric hyperoxaluria and recurrent kidney stones with underlying GI disorders and preserved renal function.
Safety	Tolerability consistent with oral enzyme: **mild to moderate GI disturbances anticipated also at higher doses**.
Efficacy	Conditional endpoint (**acc. approval**) **: reduction in urinary oxalate.** Long-term endpoint: reduced kidney stone disease progression (reduced stone formation).
Dosage	**Single oral solid dosage form up to 3x per day.**

Phase 2 program overall development plan

Pre-clinical

- Determine PK parameters through a single-dose non-GLP study in 36 rats (male and female).
- Determine safety pharmacology through a single-dose GLP study in 12 dogs during which we will monitor cardiac and respiratory markers up to 24h post dose and include ophthalmology parameters.
- Time schedule: not a critical path item, completed alongside DP development.

DP Development

- Transition from sachet format to oral solid dosage (OSD) with already identified contract manufacturer. Conduct stability studies and complete comparability program.
- Time schedule: critical path item – preparations and assumptions organized to complete in 12 mos. following new capital raise.

Manufacturing

- Transfer drug substance process to a new, pre-determined, manufacturer using our current cell banks. Manufacture new cGMP master and working cell bank.
- Manufacture new drug product (DP) lots and clinical trial materials.
- All manufacturers have been chosen; hence, programs are ready to start.

Clinical

- Goal of Phase 2 study: (1) determine dose for a registrational trial, (2) establish sufficient safety database for longer Phase 3 trials, (3) increase understanding for the safety and efficacy in the different sub-populations of EH.
- Planned Phase 2 study design is presented on the next slide.

PK = pharmacokinetic

Development plan phase 2

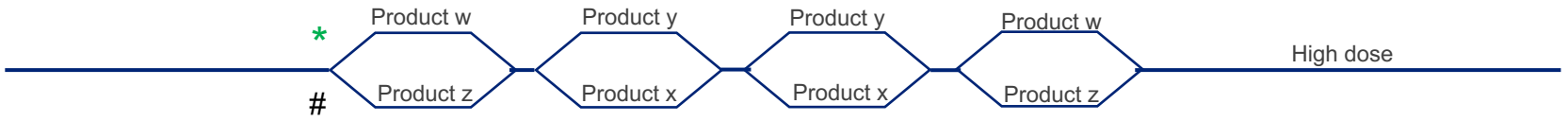
Placebo-controlled, double-blind, dose-finding cross-over study in enteric hyperoxaluria

Screening 2-3 weeks	Dose-finding study 4 weeks	Extension (high dose) 2 weeks	Follow-up 1 week

Eligibility criteria:

- Uox > 50mg/24h
- eGFR > 30mL/min/1.73m2

n = 28 - 32



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Primary End-points	• Percent change in Uox excretion compared to baseline • Safety end-points
Secondary End-points	• Percent change in Uox excretion compared to placebo • Mean change in Uox excretion as compared to placebo, and as compared to baseline • Proportion of subjects with a >30% reduction from baseline in 24-hour Uox excretion • Proportion of subjects with a >25% reduction from baseline in 24-hour Uox excretion

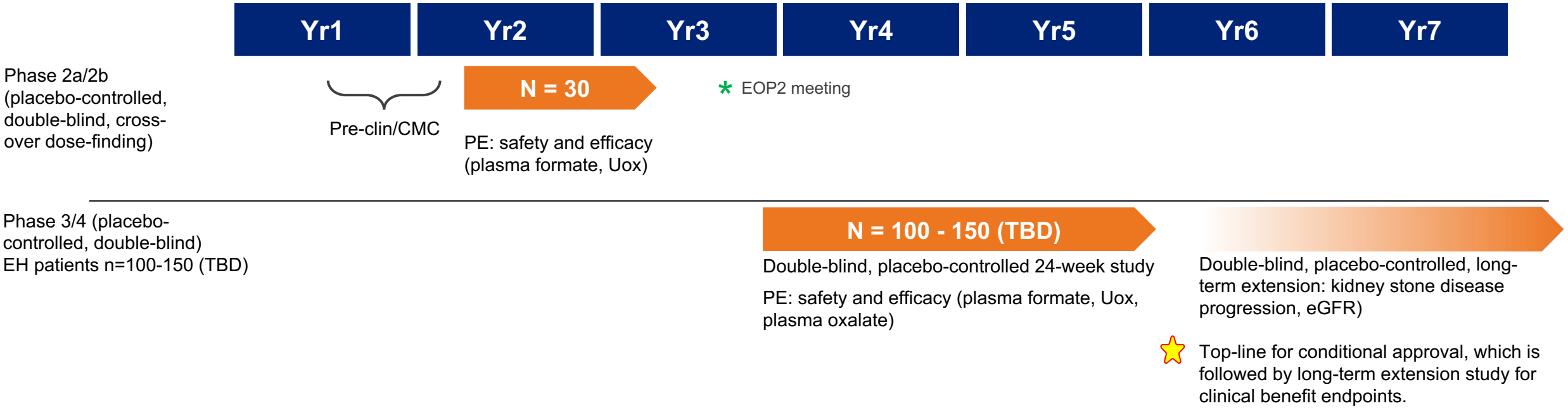
* - Randomization
# - Graphic is simplified (cross-over has 4 different start doses)

^ - 24-h urine collection
b - blood potassium, formate, plasma oxalate

EH = Enteric hyperoxaluria
Uox = Urinary oxalate (mg/24h)
eGRF = Estimated Glomerular Filtration Rate

GOAL: Successful completion is anticipated to provide appropriate data for phase 3 design and create meaningful value for strategic corporate options

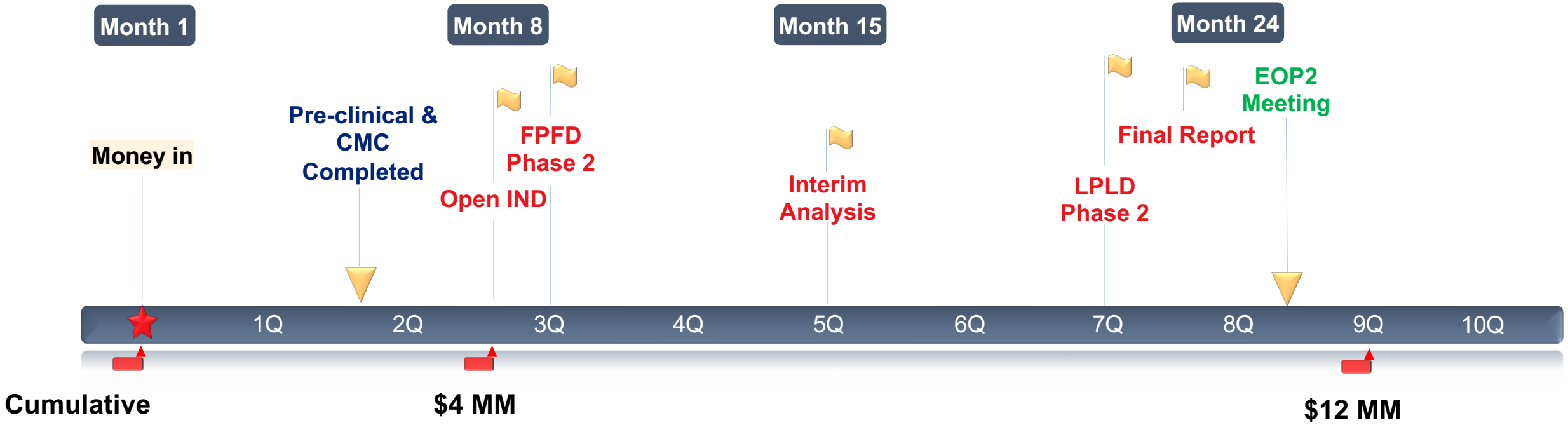
Forward development plan



Opportunity for an expedited development path and accelerated approval to market

EH = Enteric Hyperoxaluria
CMC = Chemistry Manufacturing and Controls
PE = Primary Endpoint
EOP = end of phase 2

Estimated Capital Requirements and Timeline



CMC = Chemistry Manufacturing and Controls
FPFD = First Patient First Dose
LPLD = Last Patient Last Dose
EOP = End of Phase 2

Opportunity for significant value inflection within 24 months

Thank you

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