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Transforming Medicine Through Synthetic Biology

Proof of Concept for SYNB8802 for Enteric Hyperoxaluria

Top-Line Results from Phase 1b Study

December 15, 2022

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Speakers

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Opening Remarks

Dr. Aoife Brennan
President & CEO

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Enteric Hyperoxaluria & the Burden of Recurrent Kidney Stones

POC Achieved with Urinary Oxalate Lowering from Phase 1b Study

SYNB8802: Potential for First Approved Treatment for Enteric Hyperoxaluria

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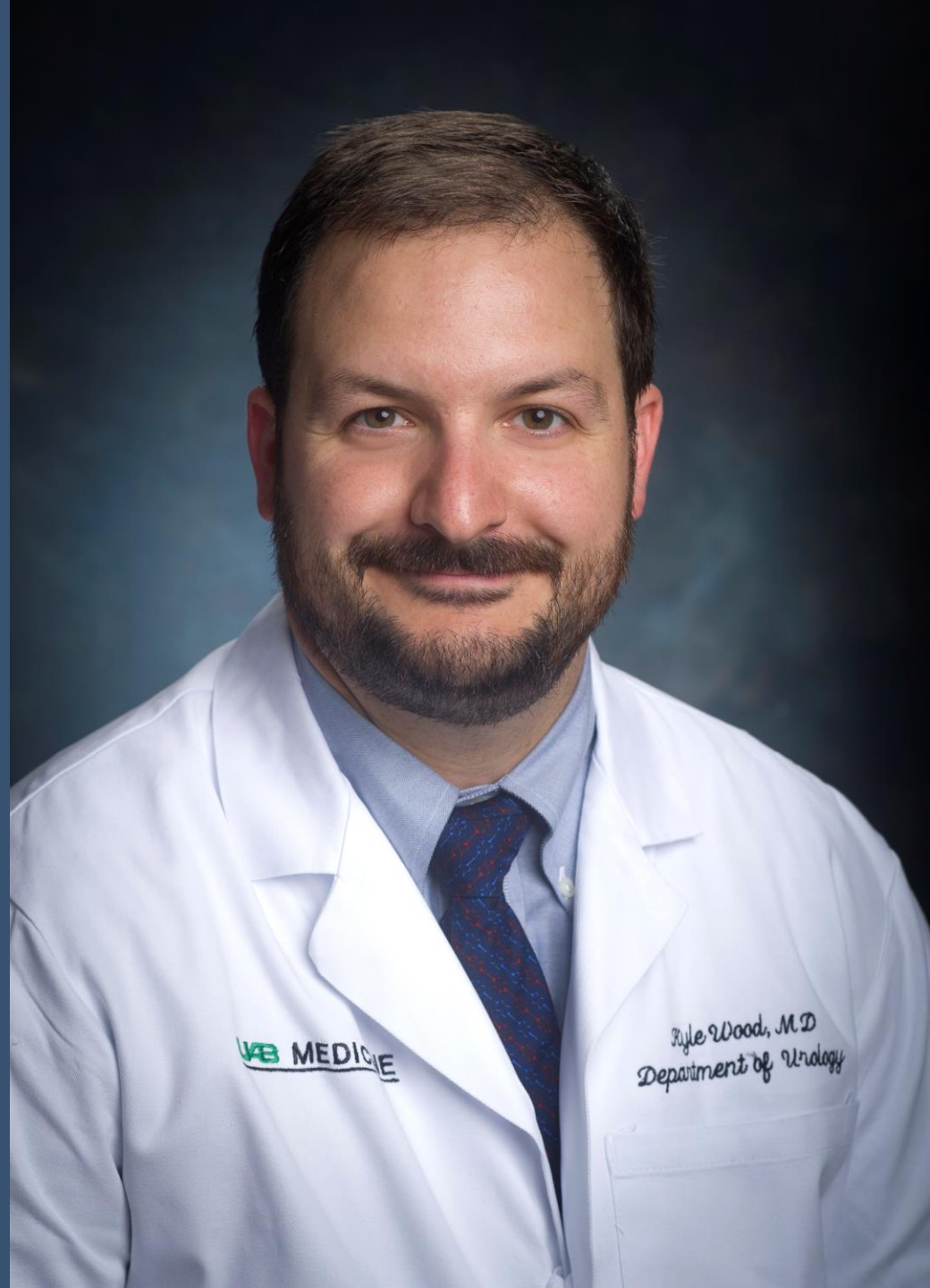
Enteric Hyperoxaluria & Recurrent Kidney Stones: An Overview

Dr. Kyle Wood
Associate Professor, Urology
University of Alabama at Birmingham



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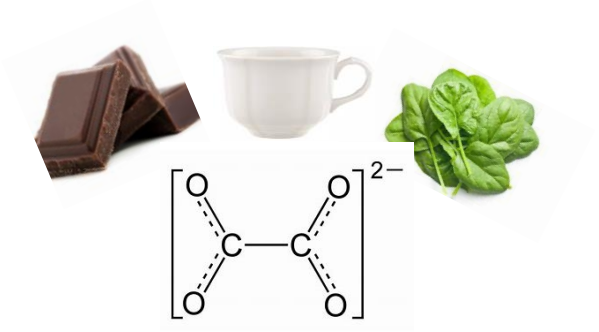
Enteric Hyperoxaluria (EH) & Recurrent Kidney Stones



Dietary Oxalate*: plant-derived; in excess, **absorbed from GI tract** into circulation

Circulating **oxalate results in crystal formation** and chronic, recurrent kidney stones

Excruciating Pain

- Oxalate **crystals damage kidneys**, impair renal function
- Can lead to CKD, ESRD, nephrocalcinosis, systemic oxalosis

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GI = gastrointestinal, CKD = chronic kidney disease, ESRD = end stage renal disease. 1. D'Costa, et al. Nephrol Dial Transplant (2020)

Urinary Oxalate Levels: Recognized Predictor of Recurrent Stones

Higher urinary oxalate (UOx) levels predict stone events in EH patients, with **~20% decrease in UOx** associated with **~25%** reduction in annual stone event risk[1]

Nephrol Dial Transplant (2020) 1–8
doi: 10.1093/ndt/gfaa281

Subsequent urinary stone events are predicted by the mag of urinary oxalate excretion in enteric hyperoxaluria

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ABSTRACT

Data directly demonstrating the relationship between urinary oxalate (UOx) excretion and stone events in those with enteric hyperoxaluria (EH) are limited. Therefore, we assessed the relationship between UOx excretion and risk of kidney stone events in a retrospective population-based EH cohort. In all, 297 patients from Olmsted County, Minnesota were identified with EH based upon having a 24-h UOx ≥40 mg/24 h preceded by a diagnosis or procedure associated with malabsorption. Diagnostic codes and urologic procedures consistent with kidney stones during follow-up after baseline UOx were considered a new stone event. Logistic regression and accelerated failure time modeling were performed as a function of UOx excretion to predict the probability of new stone event and the annual rate of stone events, respectively, with adjustment for urine calcium and citrate. Mean ± standard deviation age was 51.4 ± 11.4 years and 68% were female. Median (interquartile range) UOx was 55.4 (46.6–73.0) mg/24 h and 81 patients had one or more stone event during a median follow-up time of 4.9 (2.8–7.8) years. Higher UOx was associated with a higher probability of developing a stone event ($P < 0.01$) and predicted an increased annual risk of kidney stones ($P = 0.001$). Estimates derived from these analyses suggest that a 20% decrease in UOx is associated with 25% reduction in the annual odds of a future stone event. Thus, these data demonstrate an association between baseline UOx and stone events in EH patients and highlight the potential benefit of strategies to reduce UOx in this patient group.

Background. Data directly demonstrating the relationship between urinary oxalate (UOx) excretion and stone events in those with enteric hyperoxaluria (EH) are limited.

Methods. We assessed the relationship between UOx excretion and risk of kidney stone events in a retrospective population-based EH cohort. In all, 297 patients from Olmsted County, Minnesota were identified with EH based upon having a 24-h UOx ≥40 mg/24 h preceded by a diagnosis or procedure associated with malabsorption. Diagnostic codes and urologic procedures consistent with kidney stones during f baseline UOx were considered a new stone even gression and accelerated failure time modeling w as a function of UOx excretion to predict the prob stone event and the annual rate of stone events with adjustment for urine calcium and citrate.

Results. Mean ± SD age was 51.4 ± 11.4 years an male. Median (interquartile range) UOx was 55 mg/24 h and 81 patients had ≥1 stone event du follow-up time of 4.9 (2.8–7.8) years. Higher UO ated with a higher probability of developing ($P < 0.01$) and predicted an increased annual stones ($P = 0.001$). Estimates derived from these gest that a 20% decrease in UOx is associated wit tion in the annual odds of a future stone event.

Conclusions. These data demonstrate an association betwee baseline UOx and stone events in EH patients and highlight th potential benefit of strategies to reduce UOx in this patie group.

Keywords: enteric hyperoxaluria, hyperoxaluria, kidne stones, nephrolithiasis, urine oxalate

INTRODUCTION

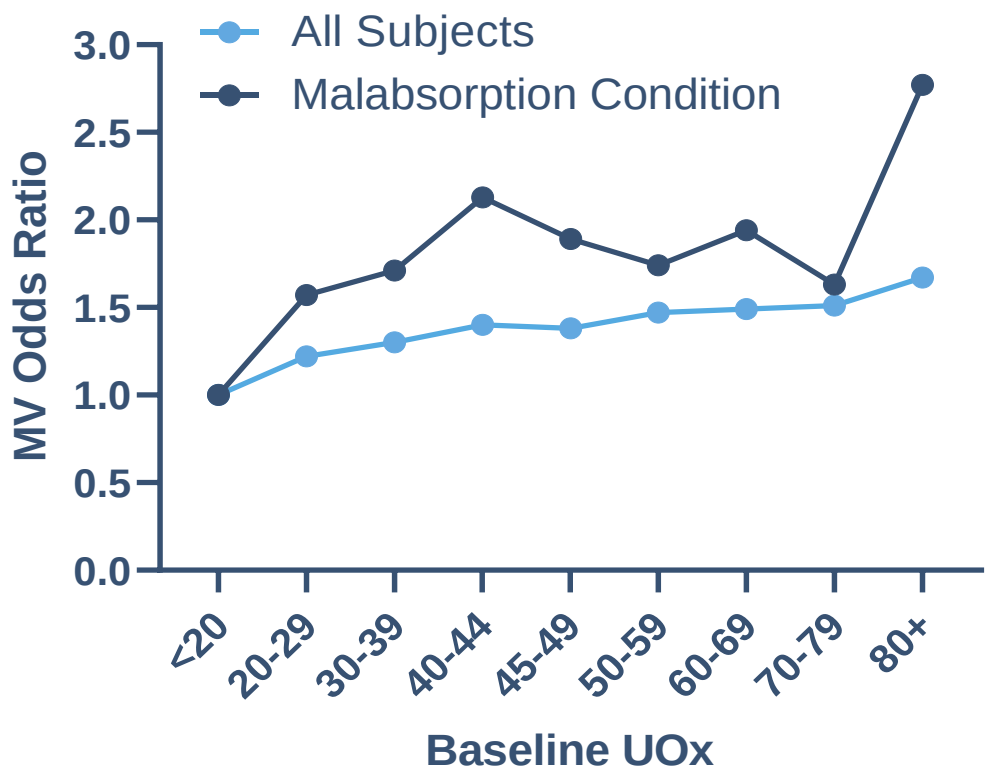
Enteric hyperoxaluria (EH) can be caused by any gastrointest nal condition that is associated with fat malabsorption. The cu rent assumption is that increased delivery of fat to the larg intestine results in greater complexation of calcium with fatt acids, leading to less calcium available to form an insolubl complex with oxalate, resulting in an increase in free oxala that can then be absorbed [1]. Increased delivery of bile acids t the colon in those patients with diseases of the distal ileum ma also increase intestinal permeability and contribute to increase oxalate absorption. EH causes include malabsorptive bariatr surgical procedures [2–8], inflammatory bowel disease (espe cially including those after ileocecal resection) [9], exocrin

FIGURE 3: Annual event rate of stone development as a function of baseline UOx.

1. D'Costa, et al. Nephrol Dial Transplant (2020)

Urinary Oxalate Levels – and GI Malabsorption - Also Increase Risk for CKD

Incident CKD Risk vs. Baseline Urinary Oxalate & GI Malabsorption



Methodology

- Largest population-based study on the relationship of urinary oxalate levels and incident CKD to date
  - Dataset includes 426,896 patients without CKD at baseline and includes 12,522 with GI malabsorption

Findings

- Among patients without a history of CKD, higher urine oxalate is associated with higher risk of developing incident CKD
  - Prevalence of CKD was twice as high in patients with UOx $\geq$ 80 mg/d compared with $<$ 20 mg/d
  - Risk is substantially higher among those with an underlying malabsorptive condition

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Hyperoxaluria May Have Genetic or Enteric Etiology

	Primary Hyperoxaluria (PH)	Enteric Hyperoxaluria (EH)
Pathology	Rare genetic condition	Dietary oxalate hyperabsorption
Onset	Pediatric	Adult
Etiology	Genetic liver enzyme deficiency	Underlying insult to bowel: including IBD, bariatric surgery, other chronic GI conditions
UOx. Levels	90 – 500 mg / 24 hrs (~10x normal)	45 – 130 mg / 24 hrs (~3x normal)

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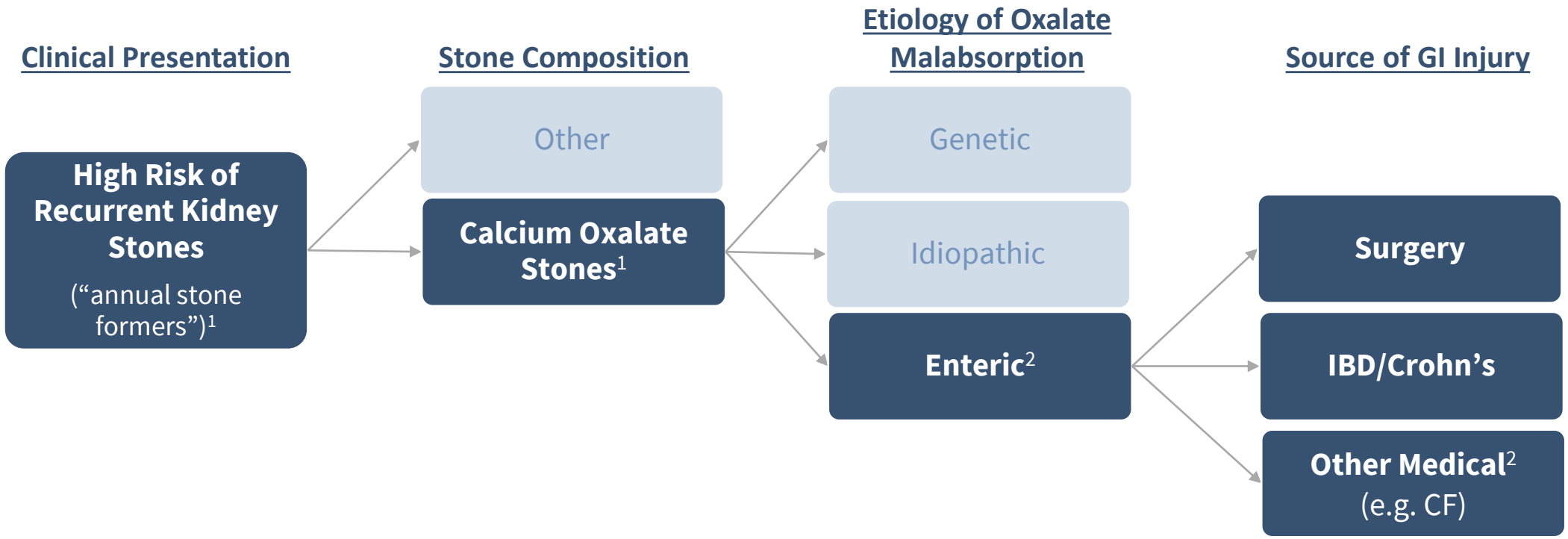
Clinical Path: Differential Diagnosis to Enteric Hyperoxaluria



Estimated U.S. Population:[1,2]

(>3mm)	**x**	**(~75%)**	**x**	**(~10%)**	**=**	**~200,000-300,000**

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1. Ziemba 2017 2. Synlogic 2022 Qualitative Market Research & Real World Evidence analyses by Trinity Partners

Today, Treatment for EH is Limited to Dietary Restrictions

Stone Etiology	***Current Management Strategy***
Low Volume	Increase fluid intake
Hypocitraturia	Citrate supplements
Hyperoxaluria	Low oxalate diet, calcium supplements, change IBD Tx (if applicable)
Hypercalciuria	May include low sodium diet or thiazide diuretics
High Uric Acid	Increase fluid intake

- Modest efficacy
- Avoids healthy foods (e.g. green vegetables)
- Calcium supplements can exacerbate hypercalciuria
- **Treatment is even less effective for *enteric* hyperoxaluria**

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Source: Synlogic 2022 Qualitative Market Research, In-depth interviews with U.S. stone clinic physicians treating patients with recurrent stones

Proof of Concept Data for SYNB8802

Caroline Kurtz, PhD.
Chief Development Officer

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SYNB8802: Consuming Oxalate in the GI Tract to Prevent Absorption

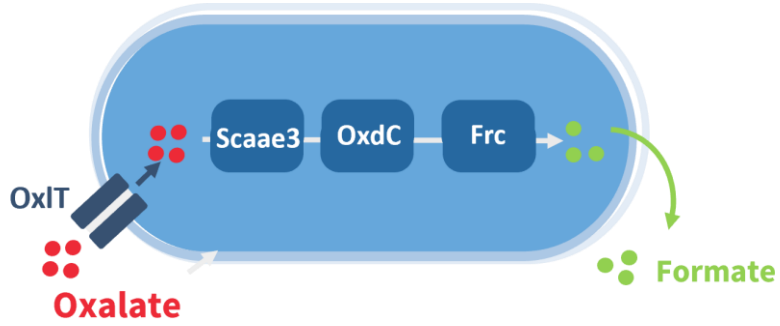
Our Approach

Oral therapy

Consume oxalate in the GI tract

Reduce oxalate in the urine

Precision Engineering of Probiotic



Consumes Oxalate Throughout GI Tract

GI = gastrointestinal

SYNB8802 Differentiation: Targeting Oxalate Throughout the GI Tract

Oxalate Absorption

Dietary Oxalate	ABSORPTION: Healthy State	ABSORPTION: Disease State	SITES OF ACTION: Allena Pharmaceuticals	SITES OF ACTION: Novome Biotechnologies	SITES OF ACTION: synlogic
Stomach	☑	☑	☑		☑
Small Intestine	☑	☑			☑
Colon		☑		☑	☑

- SYNB8802 consumes oxalate throughout the GI tract
- **Extends duration of action, increasing oxalate-lowering** efficacy potential

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GI=gastrointestinal

SYNB8802-CP-002 Phase 1b Study Design

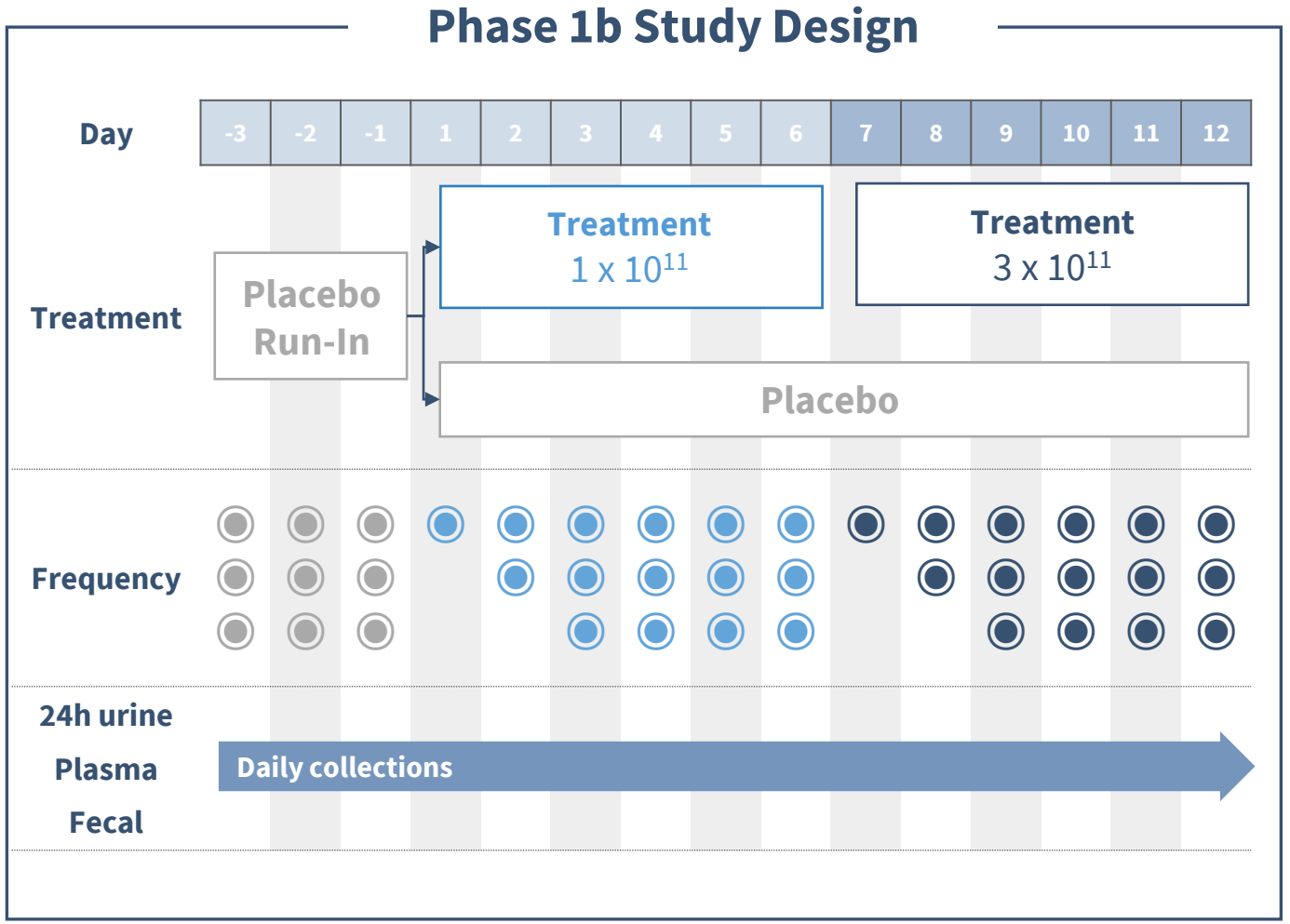
Randomized, placebo-controlled parallel arm, in-patient study

Primary endpoint: safety and tolerability

Controlled diet: Standardized dietary oxalate intake[1]

Patient population: prior Roux-en-Y gastric bypass, with abnormal GI physiology typical of EH

Disposition: 11 patients, 7 received SYNB8802 and 4 received placebo, 1 patient discontinued during placebo treatment



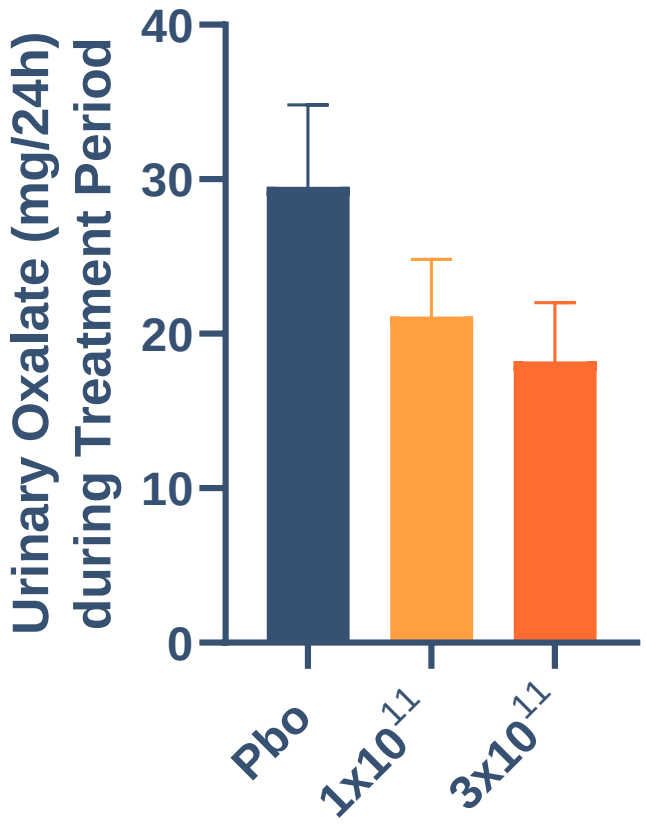
[1] Meals contained an average level of oxalate and low calcium, divided over 3 meals a day during in patient stay

*Pbo contains bicarbonate

Urinary Oxalate Levels Show Dose-Related Change with SYNB8802

Urinary Oxalate Values During Dosing Period*

Phase 1b SYNB8802-CP-002 Study



- Urinary oxalate levels at screening were consistent with diet and patient population (at ~30), and generally remained consistent with baseline values during the treatment period for placebo patients
- For both treatment periods, at both dose levels, dose-related reduction in urinary oxalate levels in response to SYNB8802 were observed

* Per pharmacometrics analysis including data from 7 patients receiving SYNB8802 at both the $1x10^{11}$ and $3x10^{11}$ dose levels and 4 patients receiving placebo

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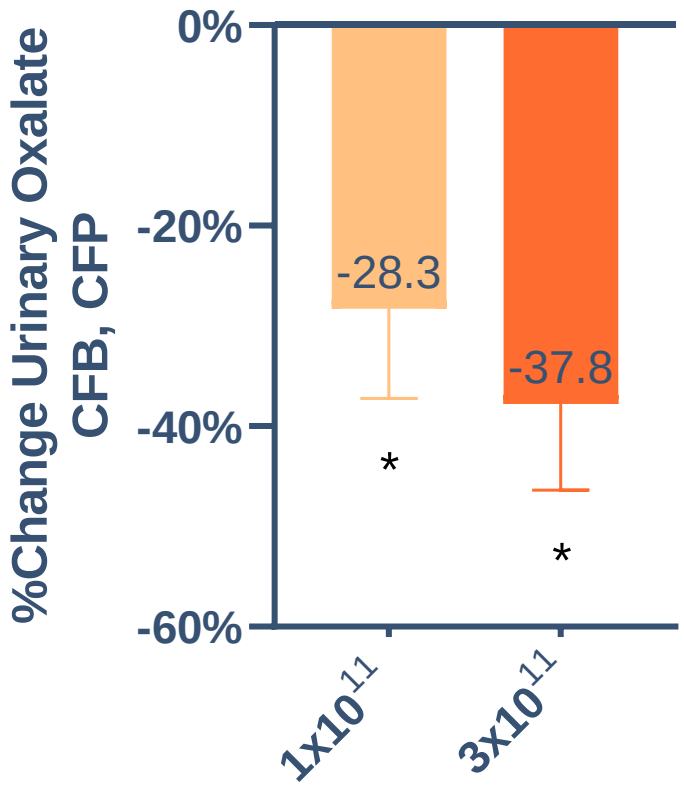
POC Achieved by Lowering of Urinary Oxalate

SYNB8802 Urinary Oxalate Lowering vs. Baseline Compared to Placebo*

Phase 1b SYNB8802-CP-002 Study



- Findings demonstrate that by consuming oxalate in the GI tract to prevent its absorption, SYNB8802 resulted in changes in urinary oxalate in gastric bypass patients
- Data analyzed using a pharmacometric model that enabled use of data from all patients on all study days

* Per pharmacometrics analysis including data from 7 patients receiving SYNB8802 at both the $1x10^{11}$ and $3x10^{11}$ dose levels and 4 patients receiving placebo
CFB=change from baseline, CFP=change from placebo

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Safety and Tolerability Findings

SYNB8802 – Proof of Concept from 002 Study Top-Line Results

- SYNB8802 was well tolerated, with **no serious adverse events**
- The most common adverse events were **GI-related, mild, and transient**
- The GI-related AEs occurred at a **similar frequency in active and placebo** groups
- One patient in the placebo group discontinued during dosing due to the need for antibiotics

SYNB8802: Proof of Concept Achieved, Focused Path Forward

- **EH: Well-recognized burden** of recurrent stones, with no FDA approved specific medical treatment options

- **SYNB8802:** POC data shows potential for a **powerfully differentiated** treatment
  - Dose related lowering of UOx established in patients with gastric bypass
  - Validated mechanism of metabolizing oxalate in GI tract to prevent its absorption
  - Both $1x10^{11}$ and $3x10^{11}$ doses exceeded -20% threshold for clinically meaningful reduction in recurrent stone risk, with urinary oxalate lowering of -38% vs. placebo at the $3x10^{11}$ dose TID

- **Enriched, concentrated target patient population: EH with highly recurrent stones**
  - Profoundly affected by pain, interventions of recurrent stones
  - Connected to specialists (e.g. stone clinics)

- **Path forward: plan to advance towards registrational trial, likely clinical endpoint of stone disease progression**

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Cross-Platform Implications

Dave Hava, PhD
Chief Scientific Officer

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SYNB8802 POC: A Milestone for Synthetic Biotic Platform

- ✓ **3rd positive data readout in 4Q 2022,** following proof of concept in PKU, and proof of mechanism in HCU
- ✓ **2nd disease state with POC achieved**
- ✓ **Platform experience accelerates learnings,** for dosing, tolerability

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Concluding Remarks

Dr. Aoife Brennan
President & CEO

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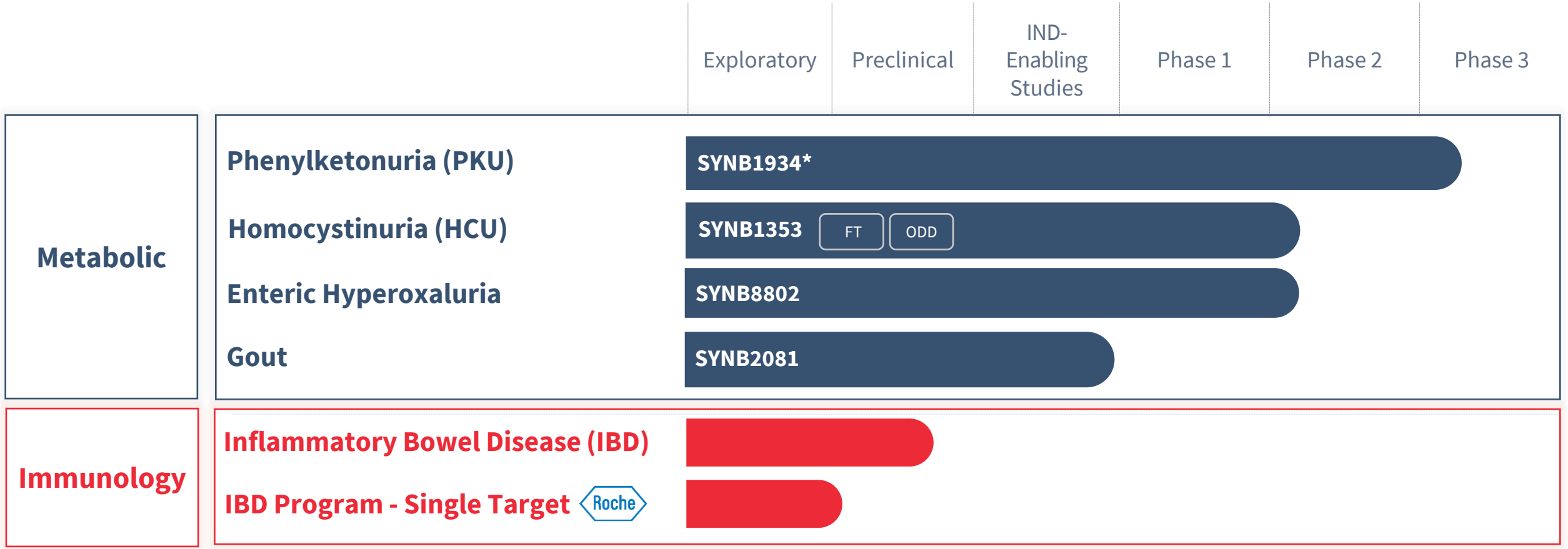
Advancing a New Class of Biotherapeutics



FT = Fast Track granted by FDA

ODD = Orphan Drug Designation granted by FDA

*First generation SYNB1618 for PKU received both ODD and FT designations by the FDA and orphan medicinal product designation by the EMA.

Available For Questions

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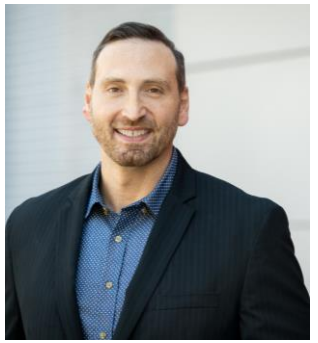
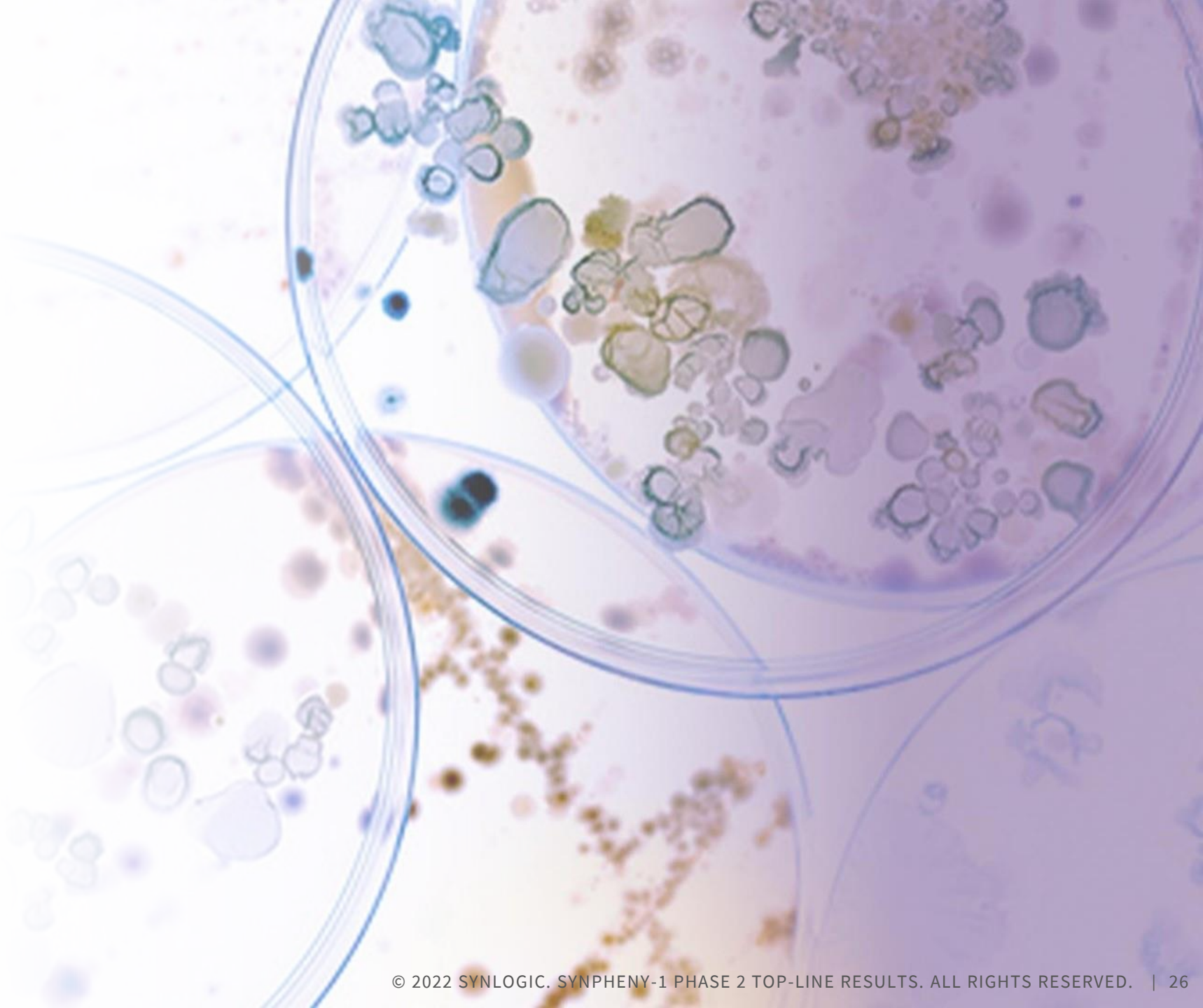


Antoine Awad
Chief Operating Officer

Thank You



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