Synthetic BIOLOGICS

# Company Overview

March 2019

Updated 3.4.2019

# Forward-Looking Statements

*This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, on Synthetic Biologics' current expectations and projections about future events. In some cases forward-looking statements can be identified by terminology such as "may," "should," "potential," "continue," "expects," "anticipates," "intends," "plans," "believes," "estimates," "indicates," and similar expressions. These statements are based upon management's current beliefs, expectations and assumptions and are subject to a number of risks and uncertainties, many of which are difficult to predict and include statements regarding our timeline for our SYN-004 (ribaxamase), SYN-010 and SYN-020 clinical trials and reporting of data, the size of the market, benefits to be derived from use of SYN-004 (ribaxamase), SYN-010 and SYN-020, our anticipated patent portfolio, and our execution of our growth strategy. The forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those set forth or implied by any forward-looking statements. Important factors that could cause actual results to differ materially from those reflected in Synthetic Biologics' forward-looking statements include, among others, our product candidates demonstrating safety and effectiveness, as well as results that are consistent with prior results, our ability to initiate clinical trials and if initiated, our ability to complete them on time and achieve the desired results and benefits, our clinical trials continuing enrollment as expected, our ability to obtain regulatory approval for our commercialization of product candidates or to comply with ongoing regulatory requirements, regulatory limitations relating to our ability to promote or commercialize our product candidates for the specific indications, acceptance of our product candidates in the marketplace and the successful development, marketing or sale of our products, developments by competitors that render our products obsolete or non-competitive, our ability to maintain our license agreements, the continued maintenance and growth of our patent estate, our ability to become or remain profitable, our ability to establish and maintain collaborations, our ability to obtain or maintain the capital or grants necessary to fund our research and development activities, a loss of any of our key scientists or management personnel, and other factors described in Synthetic Biologics' annual report on Form 10-K for the year ended December 31, 2018, subsequent quarterly reports on Form 10-Qs and any other filings we make with the SEC. The information in this presentation is provided only as of the date presented, and Synthetic Biologics undertakes no obligation to update any forward-looking statements contained in this presentation on account of new information, future events, or otherwise, except as required by law.*

# Financial Snapshot

| Current SYN Snapshot | |
|---|---|
| Exchange | NYSE American |
| Ticker | SYN |
| Cash (as of 12/31/2018) | ~$28.9 million |
| Average Daily Volume (3M ADV) | 386,000 |
| Headquarters | Rockville, MD |

| Synthetic Biologics, Inc. Capitalization Table December 31, 2018 | |
|---|---|
| Common Shares Outstanding | 15,484,411 |
| Series A Preferred Shares[2] | 120,000 |
| Series A Common Equivalents | 634,921 |
| Series B Preferred Shares | 9,161 |
| Series B Common Equivalents | 7,966,087 |
| Stock Options Issued (2007 & 2010 Plans)[3] | 938,982 |
| Total Outstanding Warrants[4] | 18,915,850 |

[1]Based on Annual Report on Form 10-K filed with the SEC 2/27/2019
[2]Series A Preferred Shares accrue a 2% dividend; conversion is $18.90
[3]As of 12/31/2018 weighted average exercise price is $15.18
[4]As of 12/31/2018 weighted average exercise price is $3.85

# About Synthetic Biologics

- Diversified microbiome-focused company pioneering proprietary early & late-stage product candidates designed to protect and preserve the gut microbiome:
  - **SYN-010**, for the treatment of an underlying cause of irritable bowel syndrome with constipation (IBS-C);
  - **SYN-004** (ribaxamase), for the prevention of acute graft-vs-host disease (aGVHD), VRE colonization/ bacteremia and primary *C. difficile* infection (CDI); and,
  - **SYN-020**, potential to treat multiple diseases that stem from GI inflammation, colitis and "leaky gut"
- Targeting large unmet medical needs and significant market opportunities in hematologic cancer therapy, opportunistic infections, antimicrobial resistance (AMR) and the treatment of GI disorders by harnessing the potential of the gut microbiome
- Developing robust pipeline of product candidates leveraging proprietary formulations
- Expanding intellectual property estate protecting platform product candidates
- Sufficient capital to fund lead programs through Q1 2020

# Our Leadership Team

**Steven Shallcross, CEO & CFO**
*Vanda Pharmaceuticals, Inc., Empire Petroleum Partners, LLC, Innocoll AG (formerly privately held Innocoll Holdings, Inc.)*

**Raymond Stapleton, PhD, SVP, Manufacturing**
*Merck & Co., Inc.*

**Michael Kaleko, MD, PhD, SVP R&D**
*Genetic Therapy, Inc. (Novartis), Advanced Vision Therapies (currently known as Wellstat Ophthalmics)*

**Deb Mathews, PharmD, VP Medical Affairs**
*Bayer Healthcare Pharmaceuticals, Novartis*

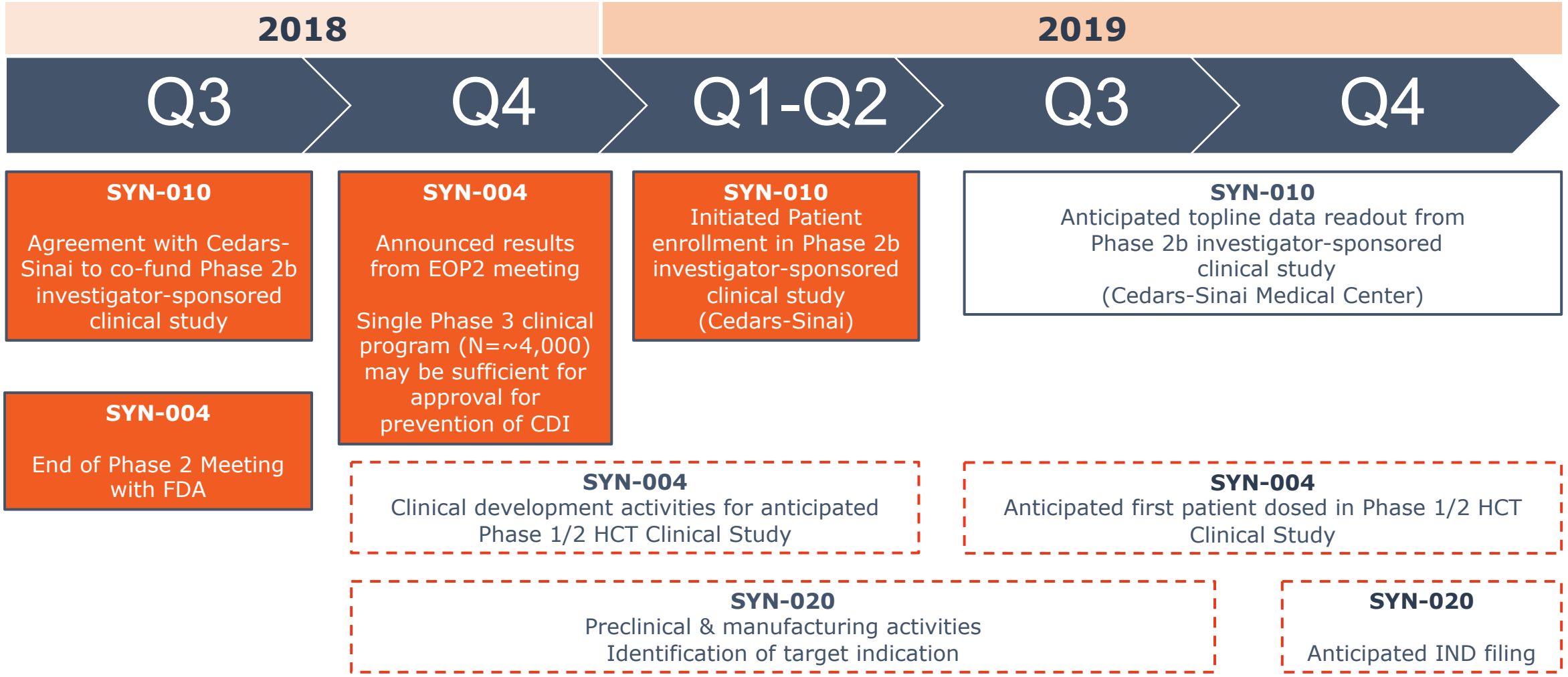
**Vince Wacher, PhD, Product Development & Partnering**
*Verva Pharmaceuticals Ltd., Eastman Chemical Company*

# SYN Portfolio

| Product Candidate | Indication (expansion) | Target | Preclinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|---|
| **Gastroenterology** | | | | | | |
| **SYN-010** | **IBS-C** (CIC) | Gut Methanogens | → | → | → | Cedars Sinai 2b |
| **Cancer Treatment Complications** | | | | | | |
| **SYN-004 (ribaxamase)** | **aGVHD in HCT** (VRE) | IV cephalosporins<br>IV penicillins | → | → | → | Est. Phase 1/2 H2 2019 |
| **SYN-020 (IAP)** | **Radiation Enteropathy** (CPI) | Multiple | → | Est. filing IND Q4 2019 | | |
| **SYN-006 (carbapenemase)** | **aGVHD in HCT** (CRE) | IV carbapenems | → | | | |
| **Infectious Disease** | | | | | | |
| **SYN-004 (ribaxamase)** | **CDI** (AMR) | IV cephalosporins<br>IV penicillins | → | → | → | FDA Phase 3<br>N≈4,000 |
| **SYN-007 (ribaxamase) DR** | **AAD** (AMR) | PO cephalosporins<br>PO penicillins | → | Potential pediatric opportunity | | |

**AAD** antibiotic associated diarrhea; **aGVHD** acute graft-vs-host disease; **AMR** antimicrobial resistance; **CDI** *Clostridium difficile* infection; **CIC** chronic idiopathic constipation; **CPI** checkpoint inhibitor autoimmune enteropathy; **CRE** carbapenem resistant enterococci; **DR** delayed release; **Est.** estimated; **HCT** hematopoietic cell transplant patients; **IAP** intestinal alkaline phosphatase; **IBS-C** irritable bowel syndrome with constipation; **VRE** vancomycin resistant enterococci.

# Milestones & Potential Value Drivers




*Based on management's current beliefs & expectations



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# SYN-010

## Novel Treatment for IBS-C

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# Constipation is an Enormous Problem

Up to **14%** of US adults (**6%** Chinese adults) have chronic constipation

$3,508 average additional healthcare cost in US per patient per year

Up to **5%** of US adults (**1%** Chinese adults) suffers from **IBS-C**

$3,856 average additional healthcare cost per patient per year

Only **8%** of IBS patients and **14%** of chronic constipation patients are completely satisfied with current therapies

Variable efficacy, unwanted side-effects, **unpredictable diarrhea**

Suares NC (2011) *Am J Gastroenterol* **106**:1582-92. Zhao Y-F (2011) *Aliment Pharmacol Ther* **34:** 1020–1029. Cai Q (2014) *J Med Economics* **17:**148-58. Doshi JA (2014) *J Manag Care Spec Pharm* **20:**382-90. Long Y (2017) *Neurogastroenterol Motil* **29:** e12897. International Foundation for Functional Gastrointestinal Disorders https://iffgd.org/images/pdfs/IBSpatients.pdf. Quigley EMM (2018) *Adv Ther* **35:**967-80.



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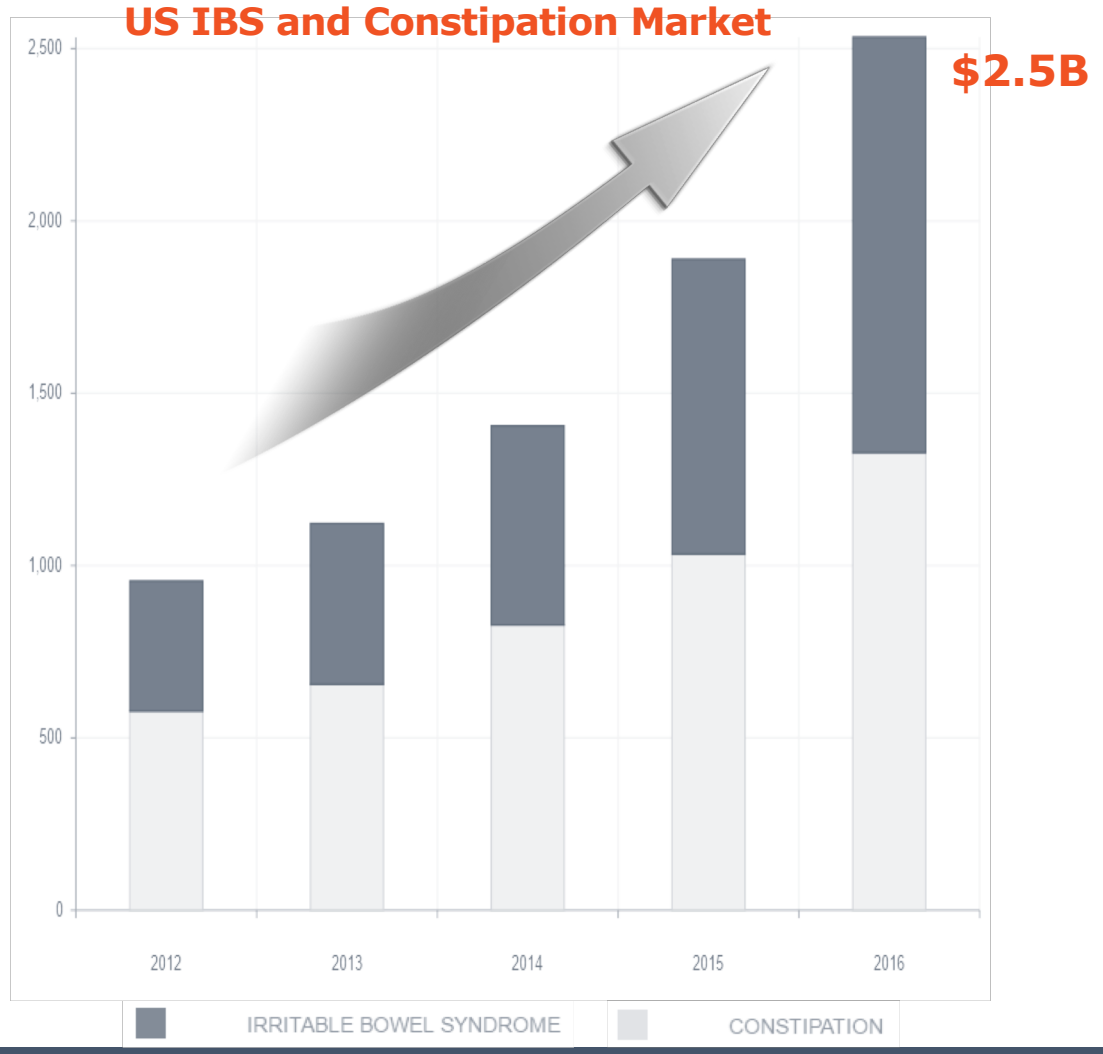
# IBS and Constipation Markets are Growing

More than 2x growth in 4 years

## Market Growth Drivers

- Digital and DTC campaigns are enhancing awareness of both IBS and gut health
- New entrants are growing the market, not cannibalizing it
- Opportunity for treatments with a novel mode-of-action and improved side-effect profile




IMS Health Analytics Link custom report (last accessed, August 2017)



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# SYN-010 is a Unique Approach to Treating IBS-C

Directly targeting a microbial cause of IBS-C symptoms

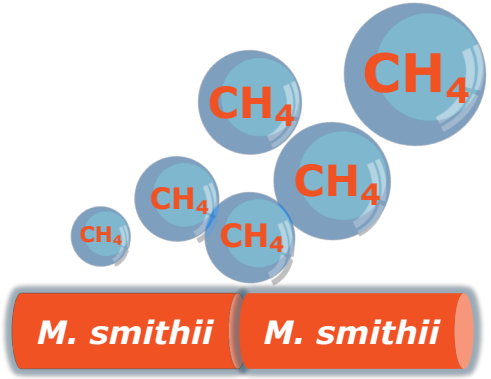
**Linaclotide**
**Lubiprostone**
**Plecanatide**
**Tenapanor**
**PEG**
**Senna**

**⇧Hydration⇧**

**Bisacodyl**
**Erythromycin**
**Prucalopride**
**Senna**

**⇧Motility⇧**

**SYN-010**




**⇩Methane⇩**

➔ **Constipation**
➔ **Pain**
➔ **Bloating**

Intestinal methane production alters gut motility and slows intestinal transit: Triantafyllou K (2014) *J Neurogastroenterol Motil* **20:**31-40. Chang B (2016) *Am J Gastroenterol* **112**:186-7. Pimentel M (2006) *Am J Physiol Gastrointest Liver Physiol* **290:**G1089-95. [6]Park YM (2017) *Neurogastroenterol Motil* Sep;29(9). doi: 10.1111/nmo.13077. Suri J (2018) *Medicine (Baltimore)* **97:**e10554.



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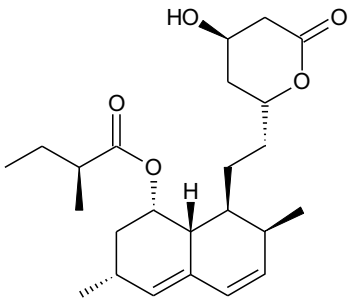
# SYN-010 Modified Release Lovastatin Lactone

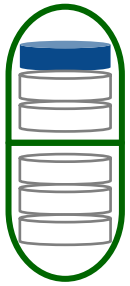
Preserve lovastatin in the lactone form; target methanogens in the lower GI tract

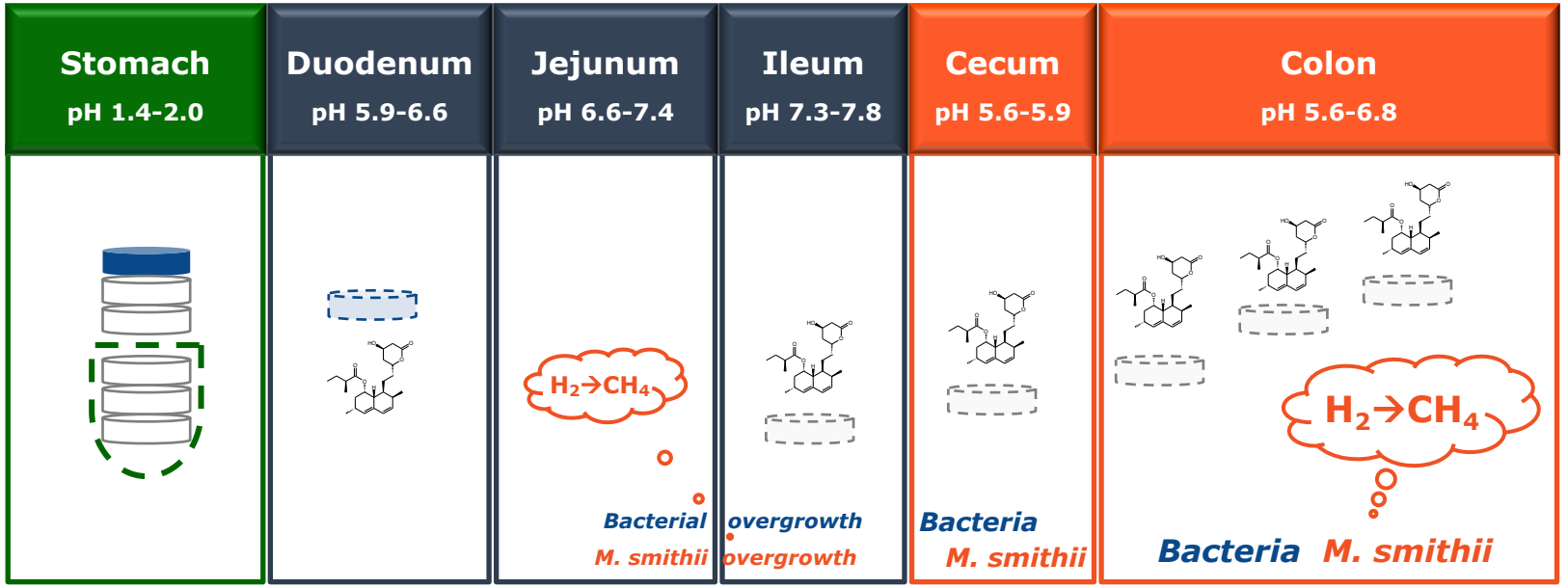
**Lovastatin lactone**




- Inhibits $CH_4$ production
- No effect on cholesterol
- Intestinal site-of-action
- Only $CH_4$-inhibiting statin

**SYN-010**






**Enteric protection limits lactone → β-hydroxyacid**

**Phase 1 data indicates delivery of lactone throughout the colon**

Hubert S (2017) *J Pharm Sci* **107:**662-71. Marsh E (2015) *Am J Gastroenterol* **110 (Suppl 1)**:S753.



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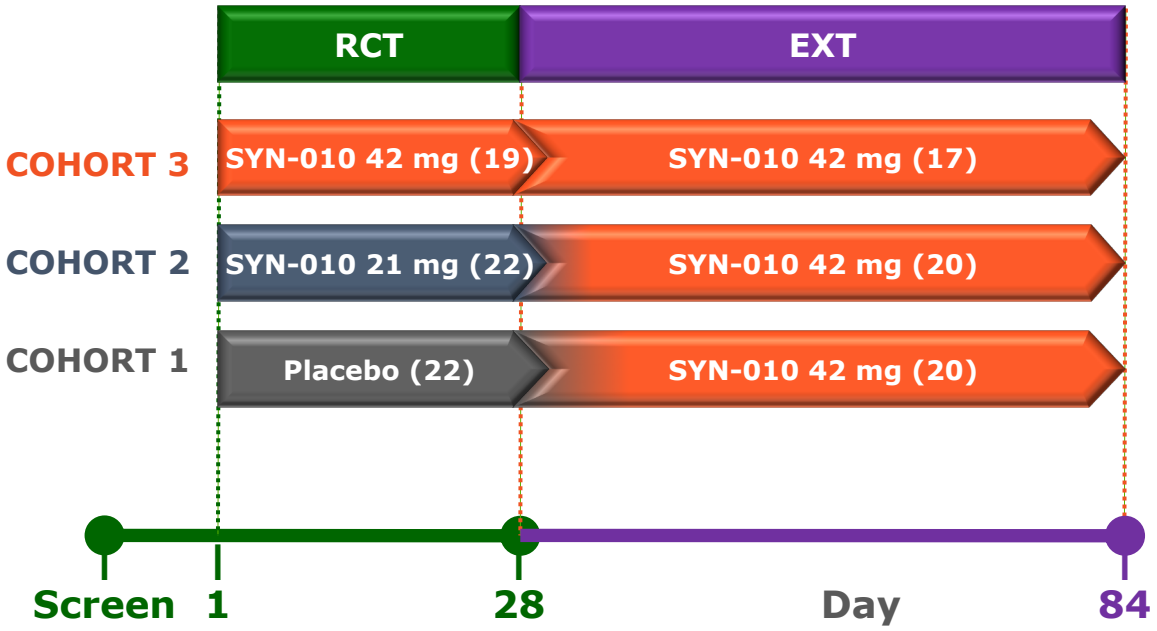
# SYN-010 Clinical Proof-of-Concept

## Phase 2a exploratory study in patients with IBS-C

Randomized, placebo-controlled 4-week study (**RCT**) followed by 8-week open-label extension (**EXT**)[1]




- Patients meeting Rome III criteria for IBS-C enrolled at 12 sites in the USA
  - Breath methane >10 ppm at screening
- Single, daily oral doses of SYN-010
  - IBS-C symptoms reported daily using ePRO devices
- Symptom responses observed over 12-weeks
  - Increased BM frequency, decreased breath methane
  - Improvement in abdominal pain
  - Reduction in bloating (>70% response rate)
  - No drug-related diarrhea[2]
- Absence of 12-week placebo-controlled data means results **compelling** but not conclusive

[1]All patients who completed the RCT were eligible to enter the EXT, no new patients were enrolled in EXT. [2]One case of diarrhea reported after the study was completed but determined to be unrelated to study drug by investigator. **BM** bowel movement.



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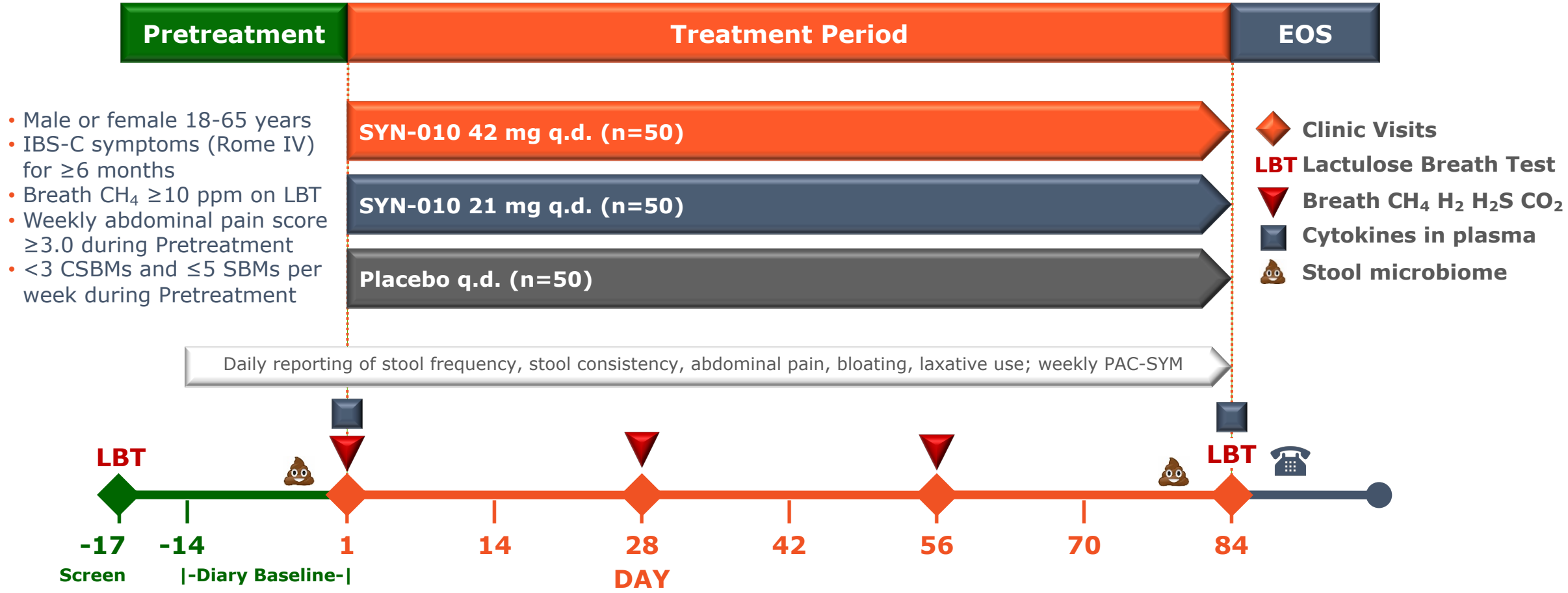
# SYN-010 Phase 2b Clinical Trial

## SYN-010 effects on IBS-C symptoms, breath gases and microbiome parameters




Single-center study conducted by the Cedars-Sinai Medical Center (Los Angeles, CA) Medically Associated Science and Technology (**MAST**) Program
Complete spontaneous bowel movements (**CSBMs**), worst abdominal pain score (0-10), worst abdominal bloating score (0-4), stool consistency (Bristol Stool Form Scale) and laxative use are recorded by patients each day via a web portal (REDCap). Primary endpoint = change from Baseline in the weekly average number of CSBMs during the 12-week Treatment Period for SYN-010 relative to placebo



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# SYN-010 Potential Differentiating Benefits

- Targets a microbial cause of IBS-C symptoms
  - Anticipate more **predictable** efficacy, potential patient selection with biomarker
- Chronic daily therapy for the lifetime of the disease
  - May **normalize** bowel habits, avoid cycling through symptom relief and recurrence
- Potential safety and efficacy benefits
  - High **bloating** response rate in Phase 2a studies[1]
  - No drug-related **diarrhea** or **nausea**[2]
- May enable payer- and consumer-friendly pricing

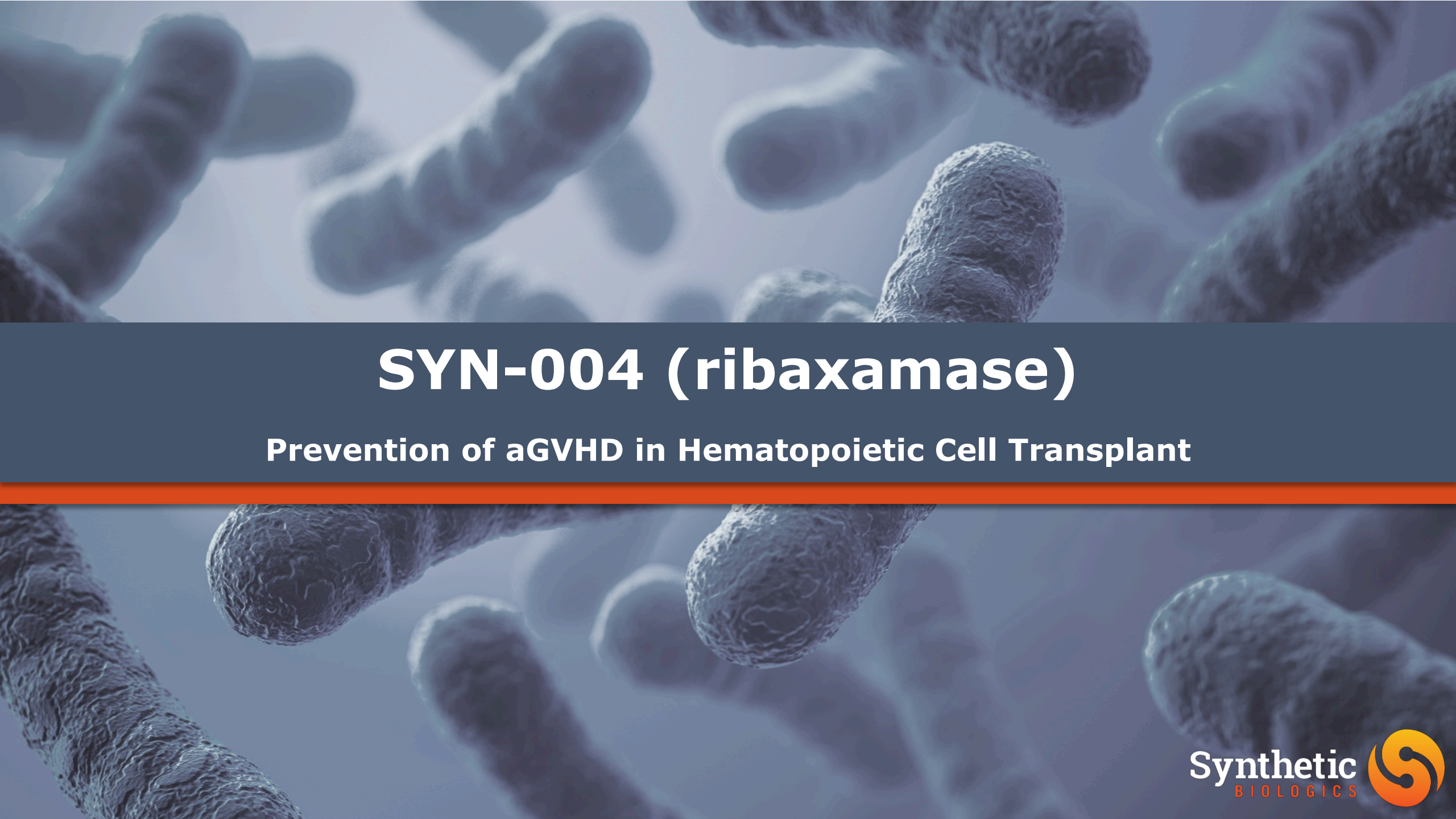
[1]IBS-C patients have reported bloating as the most bothersome symptom affecting their QoL: Neri L (2016) *Neurogastroenterol Motil* **28:**581–91. Kanazawa M (2016) *BioPsychoSoc Med* **10:**19. [2]Prucalopride (2 mg q.d.) showed high rates of nausea (14%), diarrhea (13%) and headaches (19%) compared to placebo (7%, 5%, 9%) in Phase 3 trials of CIC; MOTEGRITY™ (prucalopride) tablets, for oral use. Prescribing information 2018.

# SYN-010 Strategy

Use Phase 2b data to re-engage FDA and potential partners

- EOP2 meeting held with FDA after Phase 2a clinical trial (July 2016)
  - Agreed on Phase 3 program to address dose-response, evaluate potential food effects, and establish long-term safety (~$80M)
- Potential to simplify Phase 3 program based on Phase 2b data
  - Ideally, propose a single SYN-010 dose, significantly reducing development cost and time and increasing flexibility of study design
- Plan to leverage Phase 2b data and reduced-cost Phase 3 program (if agreed) to obtain a development and commercialization partnership
  - Topline data readout expected in 2H 2019
  - Prior interest expressed in SYN-010; however, development cost and risk was not supported by Phase 2a results

FDA expressed interest in new modes-of-action to treat IBS-C and acknowledged in end-of-phase 2 (**EOP2**) meeting minutes that Mevacor® safety data would be supportive for potential SYN-010 505(b)2 registration pathway.



# SYN-004 (ribaxamase)

## Prevention of aGVHD in Hematopoietic Cell Transplant

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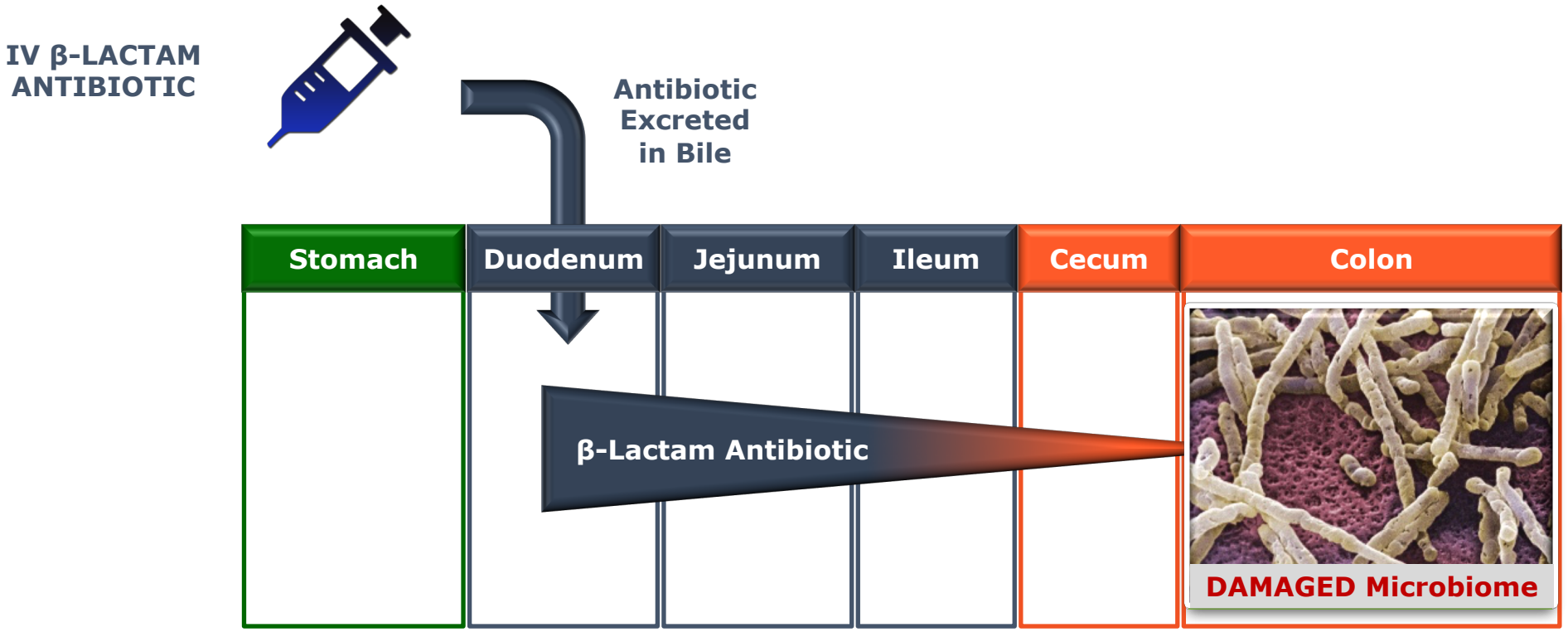
# The Gut Microbiome and Disease Prevention

- The gut microbiome is a **complex** community of ~39 trillion microbes in our gastrointestinal tract[1]
  - Predominantly reside in the colon
- The microbiome is **integral** to our health[2]
  - Cancer, CNS, GI, immune system, infection, metabolism
- **Antibiotic** damage to the microbiome can cause disease
  - Emergence of pathogens and MDROs
  - Detrimental changes to microbial metabolome
  - Impaired gut barrier function and inflammation

[1]Sender (2016) *Cell* **164:**337-40. [2]Knight R (2017) *Annu Rev Genomics Hum Genet* **18:**65-86. **MDRO** multidrug resistant organism

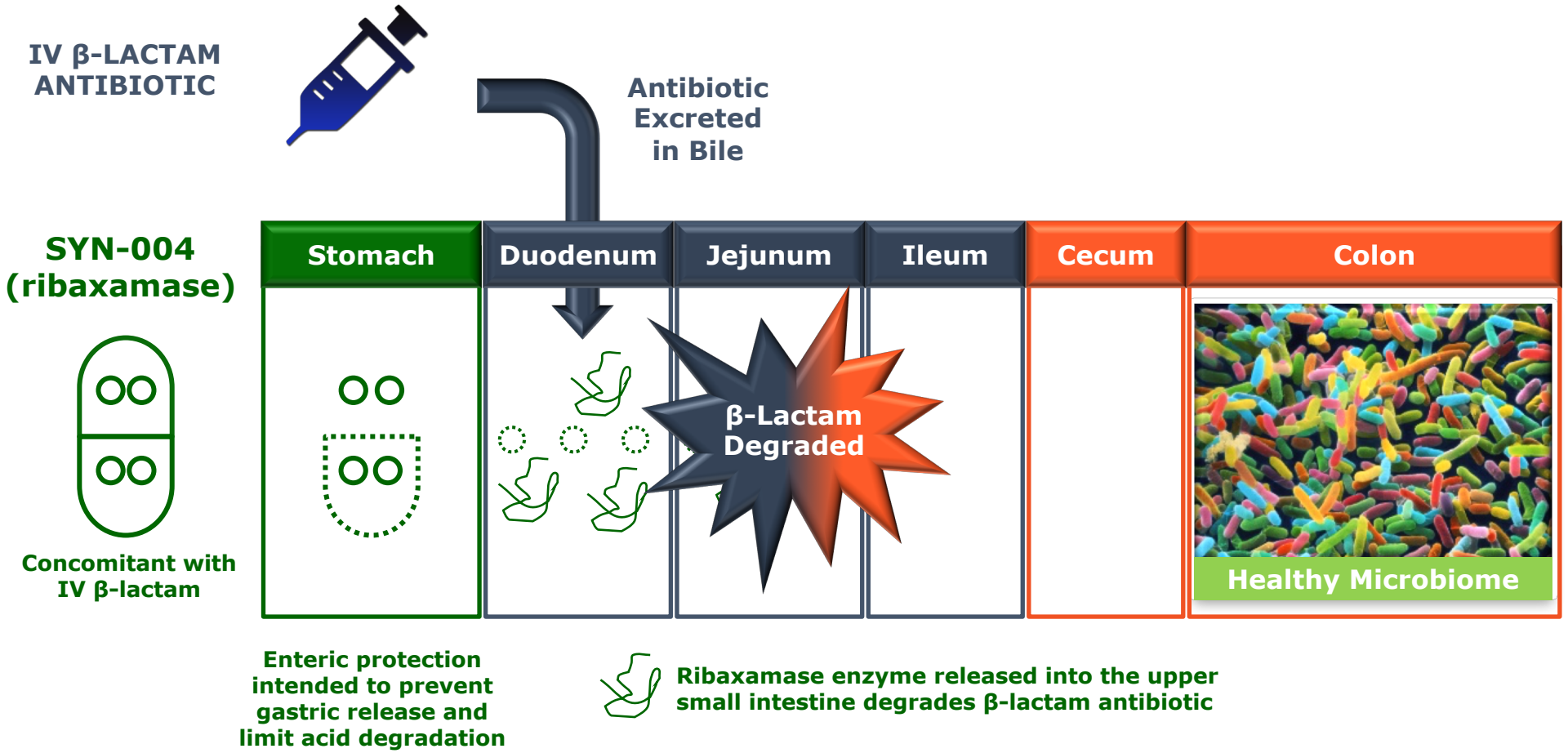
# SYN-004 (ribaxamase) to Protect the Gut Microbiome

β-lactam antibiotic excreted into the GI tract damages the microbiome



# SYN-004 (ribaxamase) to Protect the Gut Microbiome

## Degrading β-lactam antibiotic excreted into the GI tract




SYN-004 (ribaxamase) is an enteric-protected formulation of a proprietary class A β-lactamase enzyme that degrades penicillins and cephalosporins



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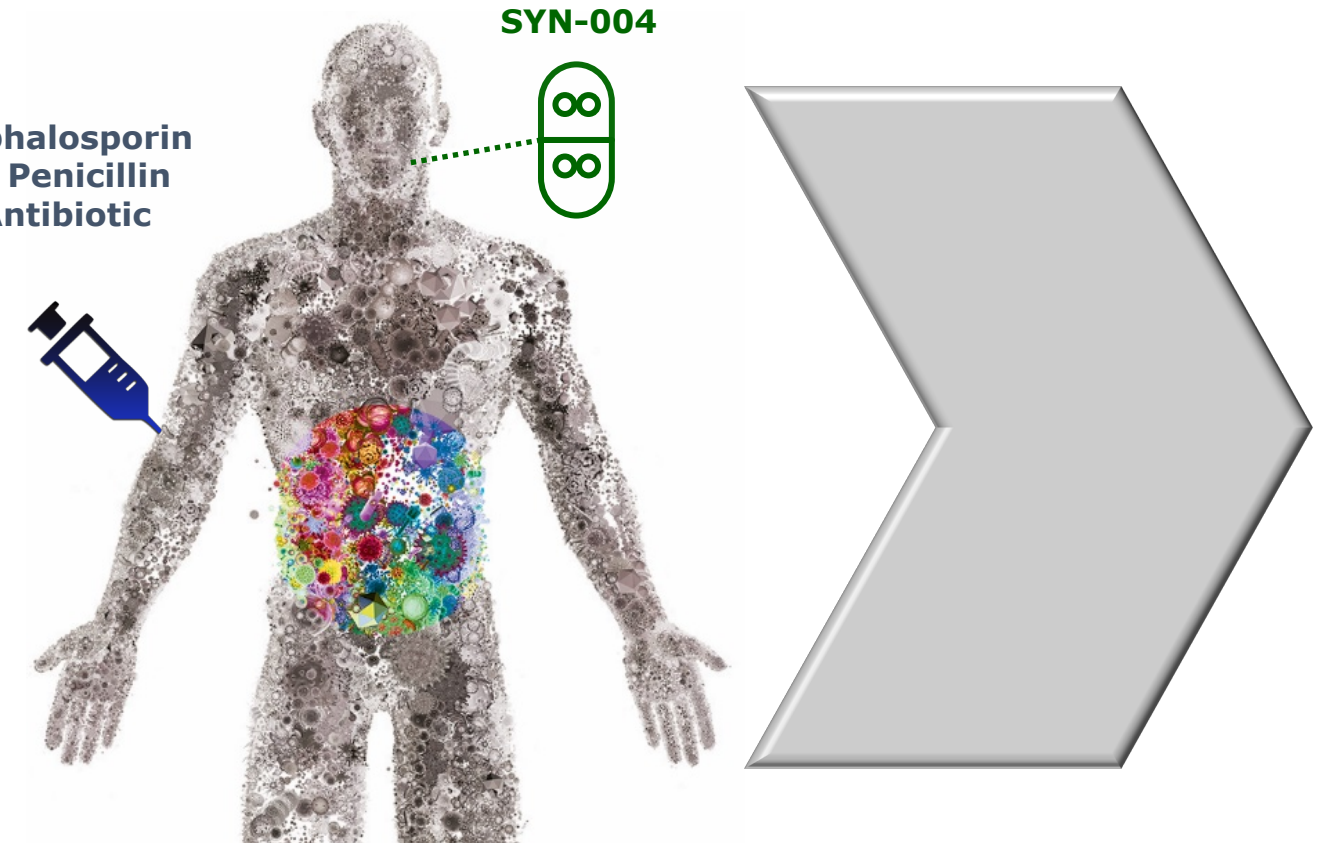
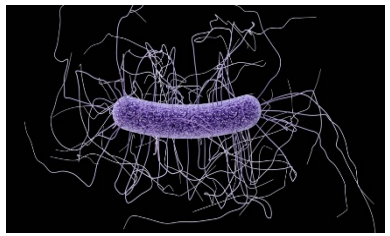
# SYN-004: Multiple Disease Prevention Opportunities



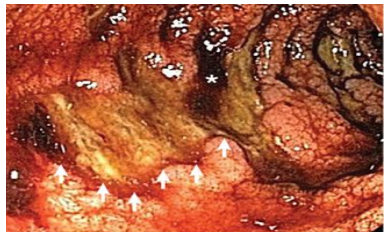



**CDI**

*Clostridium difficile* Infection


**AMR**

Antimicrobial Resistance



**aGVHD**

acute Graft-vs-Host Disease

**AMR** infographic: https://www.antimicrobialsworkinggroup.org/antimicrobial-resistance/
**aGVHD** image: Naymagon S (2017) *Nature Rev Gastroenterol Hepatol* **14**: 711–26



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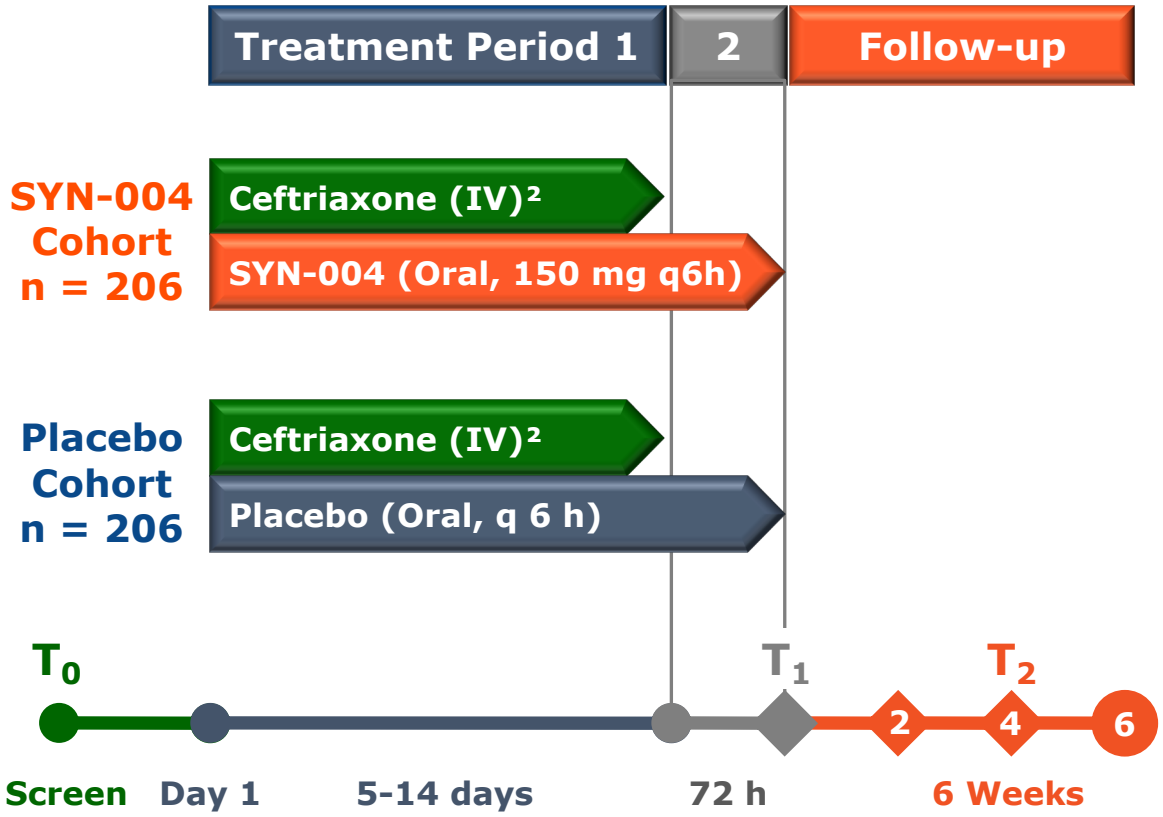
# SYN-004 (ribaxamase) Clinical Proof-of-Concept

Protected the microbiome and prevented CDI and AMR




- Patients admitted for treatment of LRTI at 54 sites (Europe, North America)
- **Achieved primary endpoint**
  - **Reduced CDI** incidence by 71.4% vs Placebo (1.0% vs 3.4% P=0.045)
- **Preserved the microbiome**
  - **Reduced** ceftriaxone-mediated loss of microbial diversity vs Placebo
- **Suppressed AMR**
  - **Reduced VRE** colonization by 43.9% vs Placebo (P=0.0002)
  - **Reduced** expression of multiple AMR genes

Kokai-Kun JF (2017) *Gastroenterology* **152 (Suppl 1):**S1309. P-values are based on one-sided z-test (Chi-square) for the comparison of SYN-004 to Placebo.
**LRTI** clinical diagnosis of moderate to severe lower respiratory tract infection. **VRE** vancomycin resistant enterococci



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# Allogeneic Hematopoietic Cell Transplantation (HCT)

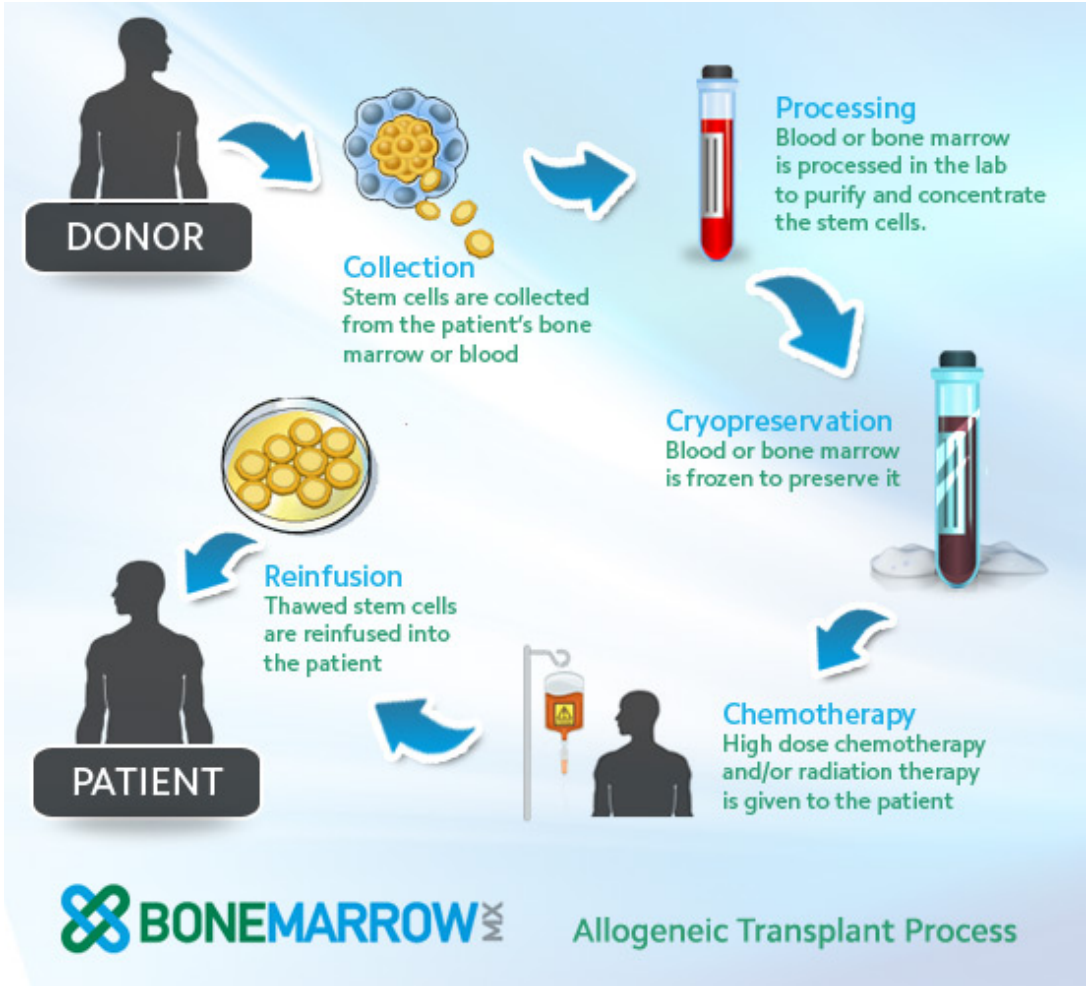


**Image credit:** http://www.bonemarrowmx.com/allogeneic-bone-marrow-transplant/

- Approximately **8,539** allogeneic HCT procedures conducted in the USA (~4,500 in China) in 2016[1,2]
- **IV β-lactam** antibiotics are used to treat febrile neutropenia in 80-90% of allogeneic HCT recipients[3]
- **Microbiome damage** by IV β-lactam antibiotics is strongly associated with aGVHD, VRE bacteremia and CDI[4-7]
- **aGVHD** occurs in 40-60% of allogeneic HCT recipients and is a leading cause of graft failure and mortality[8-9]

[1]D'Souza A, Fretham C. Current use and outcome of hematopoietic stem cell transplantation: CIMBTR summary and slides, 2017. http://www.cimbtr.org. [2]Xu L-P (2017) *Bone Marrow Transplant* **52:**1512-8. [3]Kimura S (2014) *J Infect* **69:**13-25. [4]Shono Y (2016) *Sci Transl Med* **8:**339ra71. [5]Taur Y (2012) *Clin Infect Dis* **55:** 905-14. [6]Dubberke ER et al. (2010) *Clin Transplant* **24:** 192-8. [7]Satlin MJ (2016) *Transpl Infect Dis* **19:**e12762. [8]Sung AD (2013) *Stem Cell Transplant Med* **2:**25-32. [9]Johnson BH (2019) *Biol Blood Marrow Transplant* 2019 Jan 6. pii: S1083-8791



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# SYN-004 (ribaxamase) to Prevent aGVHD in HCT

Potential to save lives and reduce costs

- In-patient costs for allogeneic HCT in the USA range from **$180,000 to >$300,000** depending on the disease severity[1-3]
  - All-cause costs for allogeneic HCT in the USA in 2014 were >$600,000 per patient (up to 12 months post transplant)[3]
- Allogeneic HCT recipients who develop aGVHD have a **3-fold increase in mortality** (16.2% vs 5.3%) and almost 2-fold increase in hospital costs[1]
  - Increased costs attributed to increase length of stay in hospital
- **Prevention** of aGVHD is an absolute necessity in allogeneic HCT
  - 1° aGVHD treatments (steroids) fail in ≥50% patients resulting in poor survival[4,5]
- Even a 20% reduction in aGVHD by SYN-004 (ribaxamase) could significantly **improve outcomes** and reduce costs
  - e.g. Save at least 4 lives and ~$1.4M in-hospital costs per 100 allogeneic HCT recipients[5]

[1]Yu J (2018) *Curr Med Res Opin* **21:**1-12. [2]Broder MS (2017) *Am Health Drug Benefits* **10:**366-74. [3]Bonafede M (2017) *J Med Econ* **20:**1244-51. [4]Xhaard A (2012) *Biol Blood Marrow Transplant* **18:**406-13. [5]Bader P (2018) *Bone Marrow Transplant* **53:**852-62. [5]Calculation assumes 40% rate of aGVHD, $180,000 per patient added costs for aGVHD; 16.2% in-hospital mortality with aGVHD; and 50% steroid refractory aGVHD with 20% 2-year survival.



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# SYN-004 (ribaxamase) Strategy

## Planning to initiate investigator initiated study 2H 2019

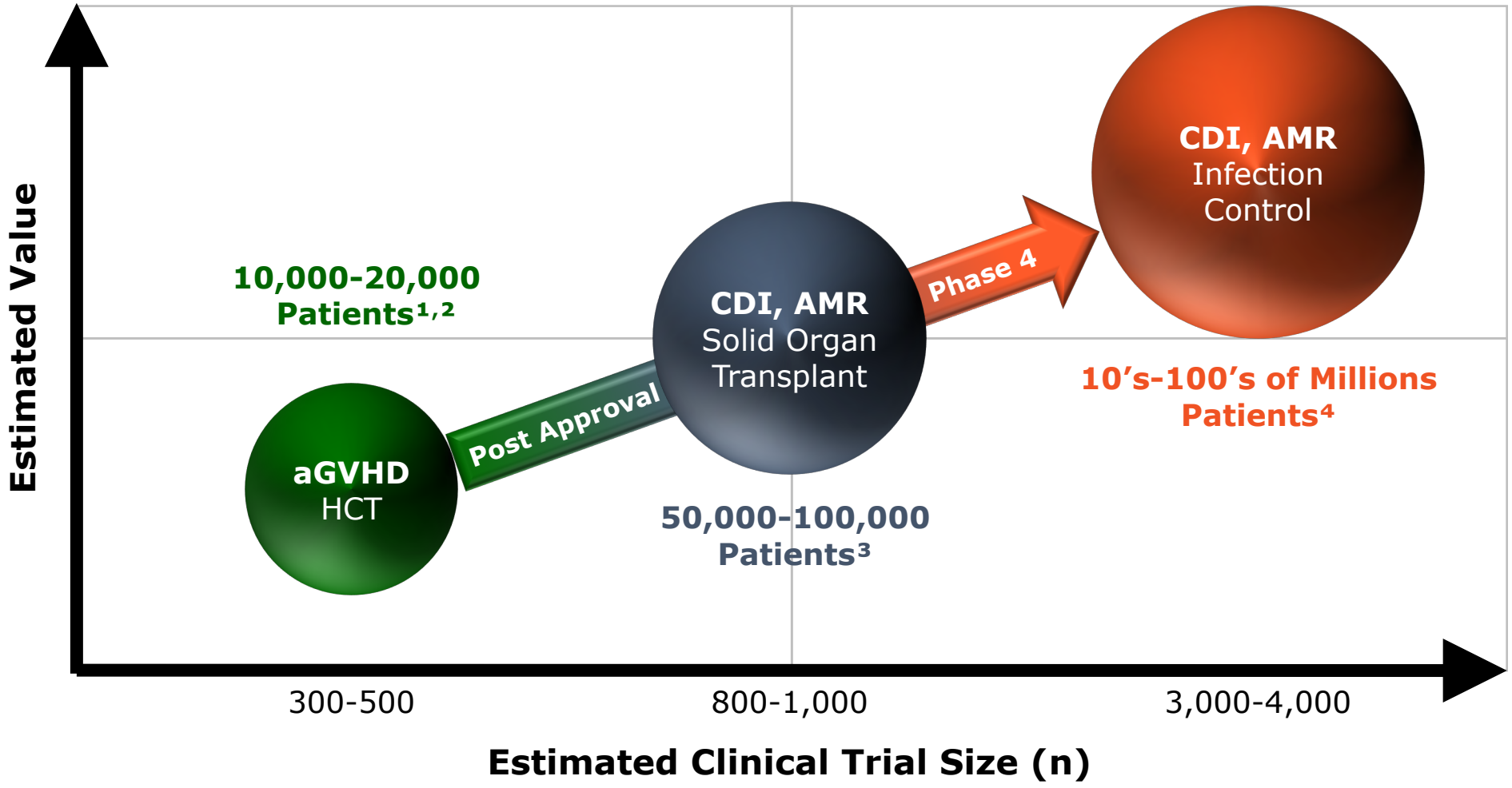
- Phase 1/2 clinical trial to evaluate SYN-004 safety[1]
  - Allogeneic HCT recipients (n≈40) receiving IV β-lactam antibiotics to treat neutropenic fever
  - Critical to demonstrate that SYN-004 does not alter antibiotic PK or efficacy
  - Key investigators identified, clinical protocols and pre-IND package in development
  - Intend to apply for Orphan Drug designation

- Potential Phase 3 clinical development program[2]
  - Allogeneic HCT recipients (n≈300-500) receiving IV β-lactam antibiotics to treat neutropenic fever
  - 1° endpoint likely aGVHD-free survival
  - 2° endpoints may include aGVHD incidence and severity, overall survival, non-relapse mortality
  - Evaluation of VRE colonization/bacteremia, CDI support post-market development in broader indications

- Specialized patient population provides opportunity for SYN to market without a partner
  - Significant potential benefit may permit SYN-004 pricing flexibility, potential access to NTAP

[1]Clinical trial programs have not yet been discussed with regulatory agencies. [2]Estimated Phase 3 study size and potential endpoints based on clinical trial designs reported on Clinicaltrials.gov. **NTAP** Medicare New Technology Add-on Payment.

# SYN-004 (ribaxamase) Long-Term Value Strategy




Estimated patient numbers are worldwide per annum. [1]D'Souza A, Fretham C. Current use and outcome of hematopoietic stem cell transplantation: CIMBTR summary and slides, 2017. Available at http://www.cimbtr.org. [2]Xu L-P (2017) *Bone Marrow Transplant* **52:**1512-8.
[3]https://www.who.int/transplantation/gkt/statistics/en/
[4]Estimated from IV penicillin and cephalosporin use data extracted from IMS Health 2017.

# SYN-020

## Treatment of Specific Colitis Conditions

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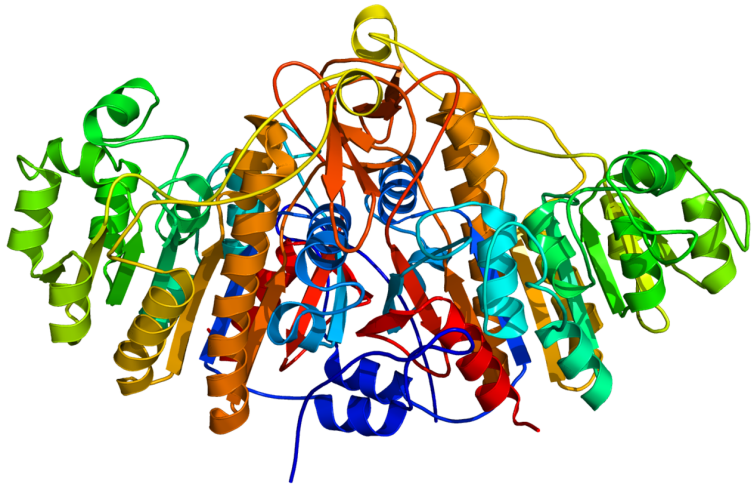
# Intestinal Alkaline Phosphatase

A naturally-occurring protein with the unique capacity to treat many diseases

- IAP is a naturally-occurring enzyme produced in the small intestine
  - 150 kD homodimer coordinating $Mg^{2+}$ and $Zn^{2+}$



- Maintains gastrointestinal homeostasis[1,2]
- Detoxifies inflammatory mediators[3]
  - Endotoxin, bacterial DNA, flagellin, nucleotides
- Tightens the gut barrier[4,5]
  - Prevents "leaky gut"
  - Diminishes endotoxemia
- Promotes the growth of commensal intestinal flora[6]

[1]Bilski J (2017) *Mediators Inflamm* **2017:**9074601. [2]Estaki M (2014) *World J Gastroenterol* **20:**15650-6. [3]Chen KT (2010) *Am J Physiol Gastrointest Liver Physiol* **299:**G467-75. [4]Liu W (2016) *J Am Coll Surg* **222:**1009-17. [5]Martinez-Moya P (2012) *Pharmacol Res* **66:**144-53. [6] Malo MS (2010) *Gut* **59:**1476-84.



Synthetic BIOLOGICS

# IAP has Demonstrated Efficacy in Animals and Humans

| Model | Outcome |
|---|---|
| **Humans** | |
| Ulcerative Colitis | Clinical improvement in refractory UC at 21 days following one week of cIAP infusion via nasoduodenal tube[1] |
| Type 2 Diabetes | High IAP levels are associated with protection from diabetes even in obese individuals[2] |
| **Mice** | |
| Leaky Gut | Diminished endotoxemia in high-fat diet (HFD) fed mice[3]<br>Increased expression of zonulin/occludin[4] |
| Antibiotic-mediated dysbiosis | Accelerated recovery of microbial diversity after antibiotic damage to microbiome[5]<br>Protected from overgrowth by *C. difficile* and *S. typhimurium*[6] |
| Colitis | Improved intestinal tissue histology and inflammatory cytokine profiles in multiple rodent models[7] |
| Metabolic Syndrome | Prevented and reversed multiple symptoms in high-fat diet (HFD) fed mice[3]<br>Ameliorated symptoms arising from azithromycin treatment in HFD fed mice[8] |

[1]Lukas M (2010) *Inflamm Bowel Dis* **16:**1180-6. [2]Malo MS (2015) *EBioMedicine* **2:**2016. [3]Kaliannan K (2013) PNAS **110:**7003-8.
[4]Hamarneh SR (2014) *Ann Surg* **260:**706-14. [5]Malo MS (2010) *Gut* **59:**1476-84. [6]Alam SN (2014) *Ann Surg* **259:**715-22.
[7]Tuin A (2009) *Gut* **58:**379-87. [8]Economopoulos KP (2016) *Diabetes Obes Metab* **18:**519-27.



Synthetic BIOLOGICS

# Overcoming Key IAP Development Challenges

## Synthetic Biologics expertise in protein manufacture and oral delivery

- Manufacturing has limited the clinical progress of oral IAP
  - cIAP is extracted from calf intestine and requires extensive purification, costing up to $10,000/g[1]
  - IAP yields are very low (**10-500 mg/L**) in many manufacturing platforms[2-5]

- Synthetic Biologics has developed a stable cell line expressing high levels of IAP (**>3 g/L**)
  - Synthetic Biologics IAP has equivalent activity to cIAP and is stable in chyme
  - COGS estimated to be a few dollars per day at commercialization

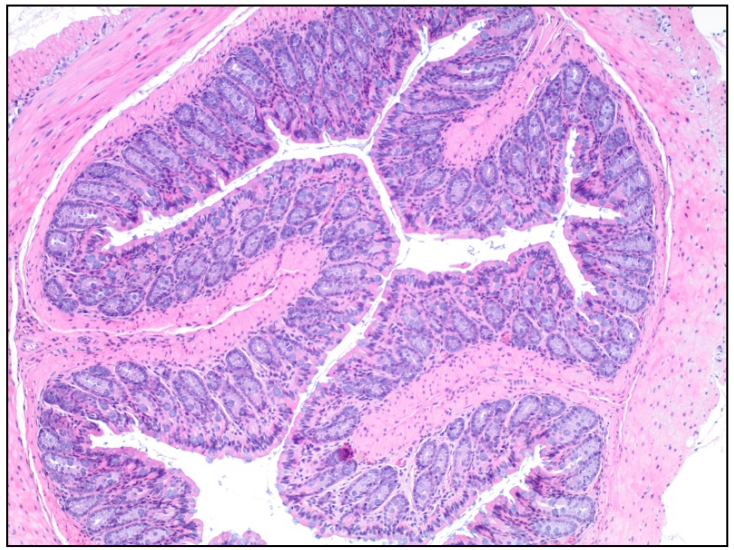
- Synthetic Biologics has developed novel tablet formulations with different release profiles
  - Enteric coatings applied to prevent degradation in the stomach and enable release in different regions of the GI tract
  - Patent applications filed around formulations and release profiles

[1]https://www.sigmaaldrich.com/catalog/product/sigma/p0114?lang=en&region=US. [2]Nam JH (2007) *Biotechnol Prog* **23:**652-60 [3]Chen YH (2004) *Protein Expr Purif* **36:**90-9. [4]Aldag I (2011) *BMC Biotechnology* **11:**11. [5]Yeatts AB (2012) *Biotechnol Bioeng* **109:**2381-91.

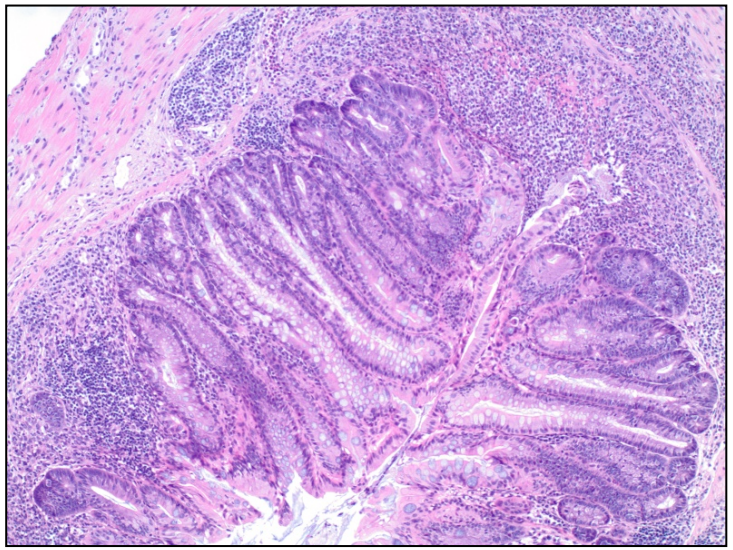
# SYN-020 (IAP) Protects the Intestinal Mucosa

## Reduced submucosal inflammation in DSS-colitis model

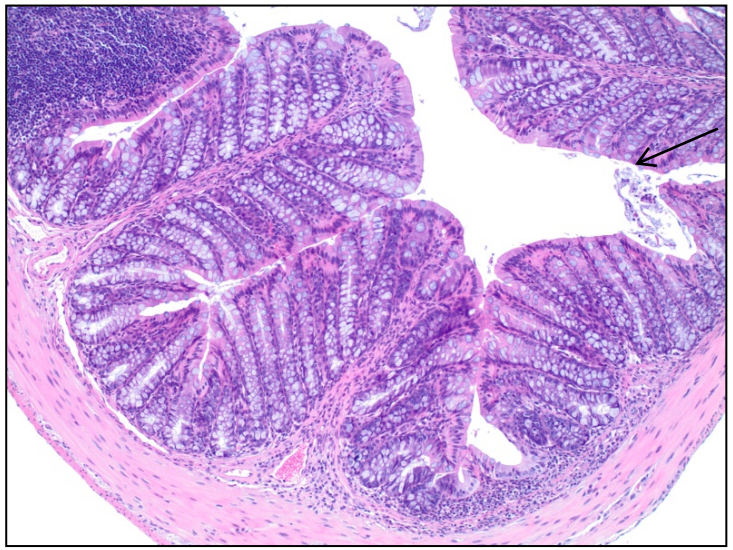
**Control**



**Vehicle**



**SYN bIAP II, 500 U/day**



Male C57BL/6 mice were treated with Dextran Sulfate Sodium Salt (**DSS**; 3%) each day for 5 days. SYN bIAP II (100 and 500 U q.d.) was administered by gavage from days 5-17. Mice were sacrificed on day 17 and tissues collected for histological analysis[1,2].

[1]Bol-Schoenmakers M (2010) *Eur J Pharmacol.* **633:**71-7
[2]Efficacy equivalent to literature reports was seen at a SYN bIAP II dose of 100 U/day

# SYN-020 (IAP) Status

## Planning IND filing in Q4 2019

- Treatment/prevention of radiation enteropathy secondary to cancer therapy
  - Pelvic and abdominal irradiation is used >300,000 times annually in US[1]
  - 60-80% of radiation-treated cancer patients suffer acute bowel toxicity
  - Significant unmet need for both inflammatory acute and fibrosing chronic syndromes
  - SYN animal efficacy data support the use of IAP to treat the acute toxicity

- Phase 1 clinical trial to evaluate SYN-020 safety
  - Cancer patients (n≈18) requiring pelvic radiation ± chemotherapy
  - 1° endpoints are safety and SYN-020 PK (plasma, feces)
  - 2° endpoints include diarrhea, intestinal mucosa protection
  - Key investigators identified, clinical protocols and pre-IND package in development

- Phase 1 data may support expanded evaluation in other partnerable indications
  - Autoimmune enteropathy secondary to cancer therapy with checkpoint inhibitors[2]

[1]Radiation is used in 50% of cancer patients and has a role in 25% of cures. [2]Recent published data suggests similar enteropathy occurs with CAR-T therapies; Hauer-Jensen M (2014) *Nat Rev Gastroenterol Hepatol* **11:**470-9



Synthetic BIOLOGICS 32

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# Appendix

March 2019

# SYN-010

## Novel Treatment for IBS-C

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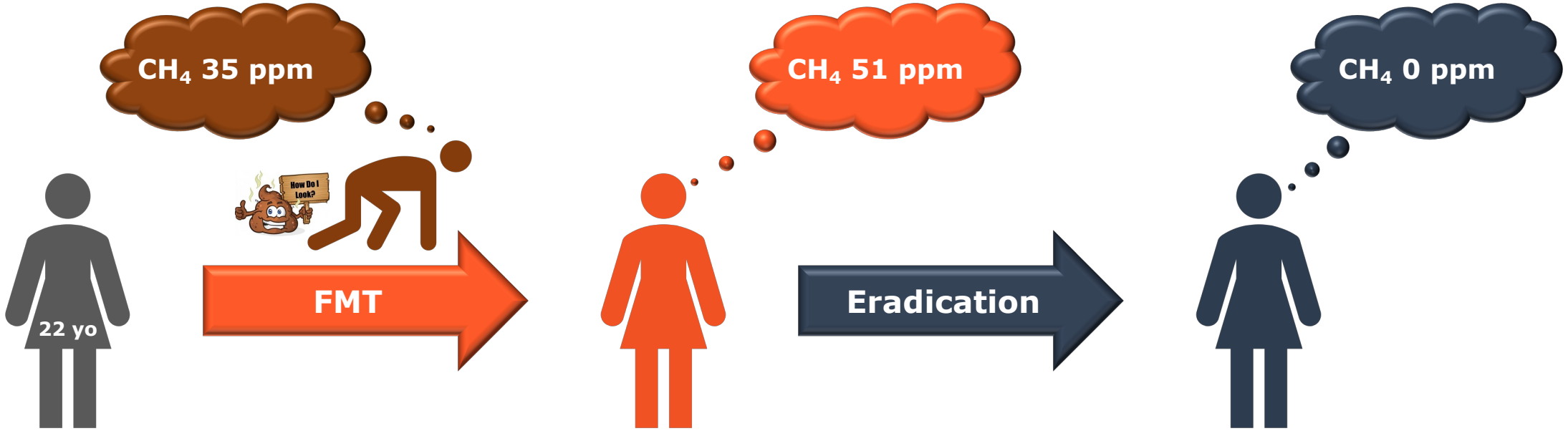
# $CH_4$ Causality: IBS-C Symptoms Transmitted by FMT




**CDI**

**No other GI symptoms**

**No CDI**

**Severe constipation**
**bloating, distension!!**

**No CDI**

**No other GI symptoms**

Chang B (2016) *Am J Gastroenterol* **112**: 186-7. **CDI** = Clostridium difficile infection unresolved by vancomycin and metronidazole.
**Eradication** = 14 days of rifaximin 550 mg t.i.d. plus neomycin 500 mg b.i.d.



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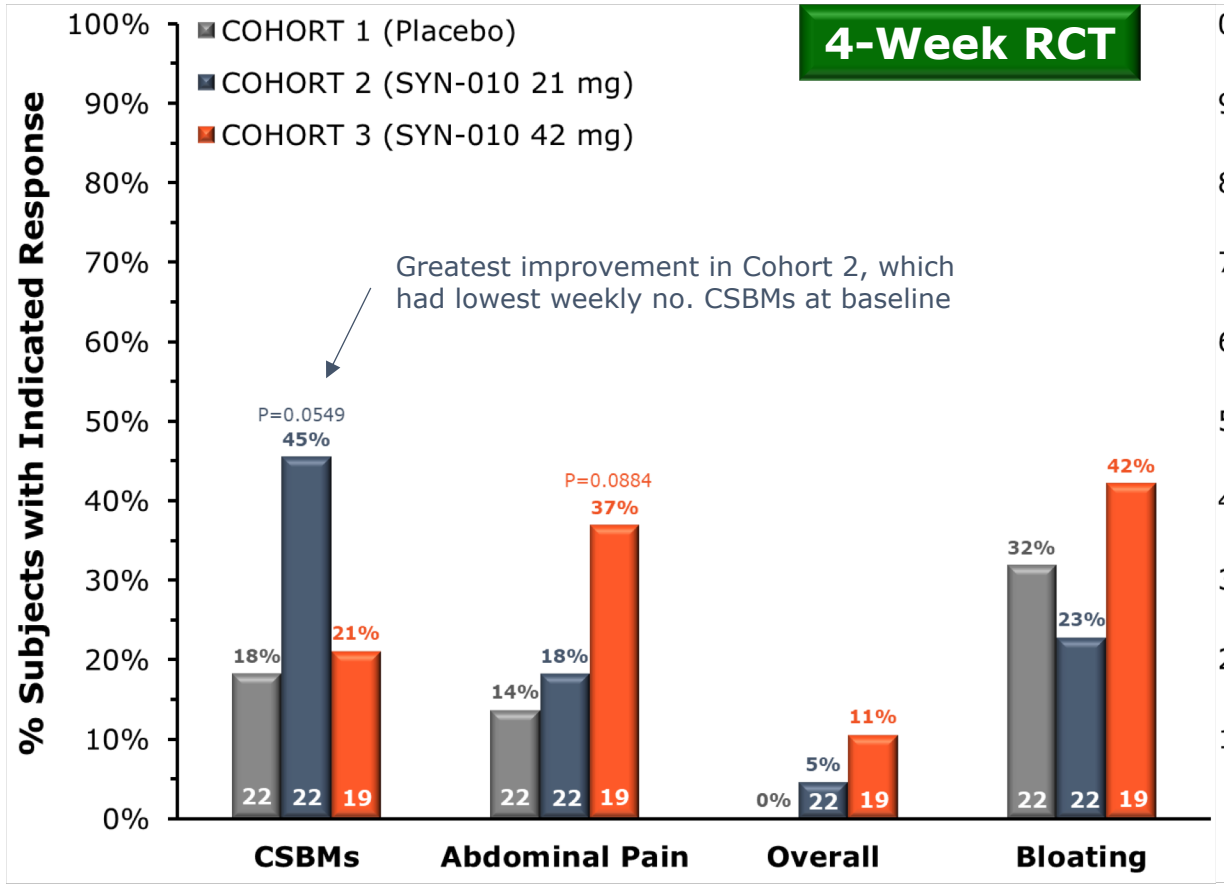
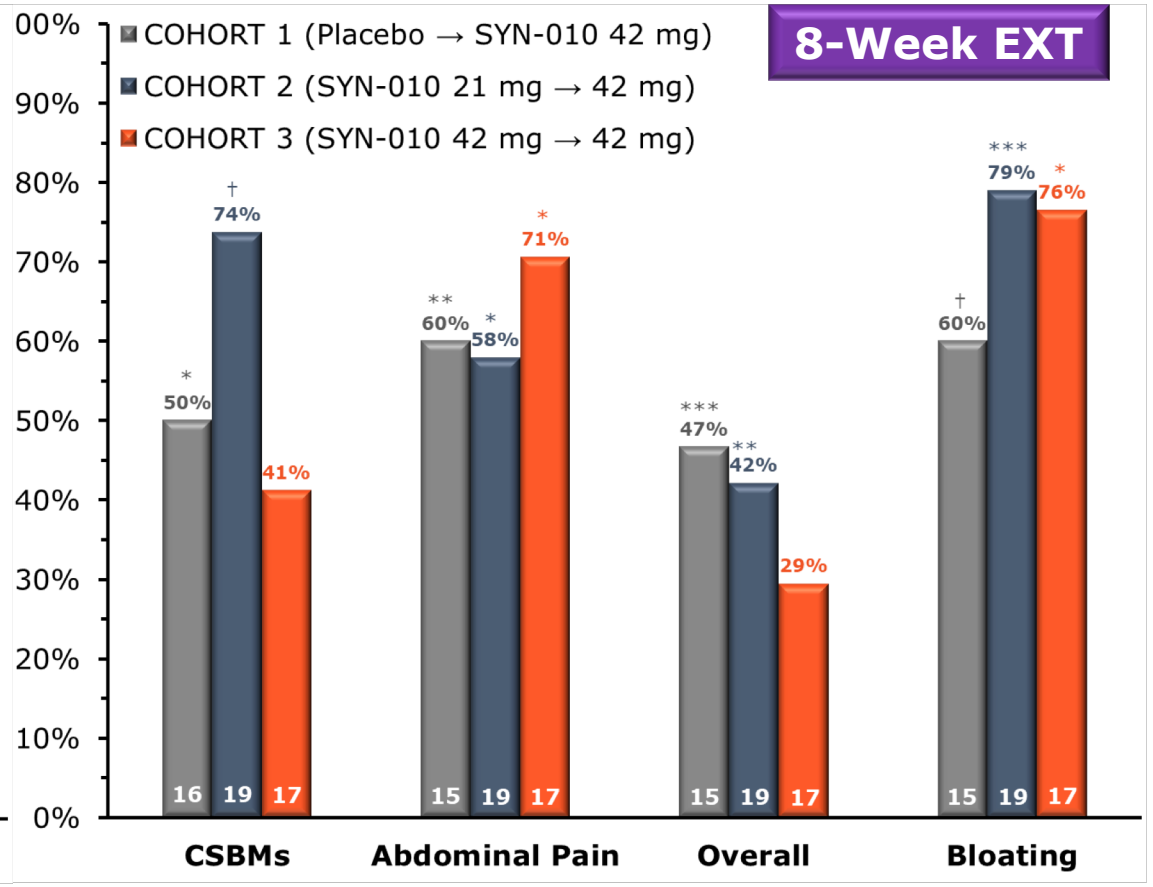
# IBS-C Symptom Responses in Phase 2a Clinical Trials




Nominal P-values (Chi-square) are for SYN-010 vs Placebo. Numerical increase from baseline in weekly CSBMs for Cohort 2 was statistically different to Placebo (P<0.05)

Nominal P-values (Chi-square) are for within group comparison of EXT to RCT
*P<0.05, **P<0.005, ***P<0.0005, †P<0.1.

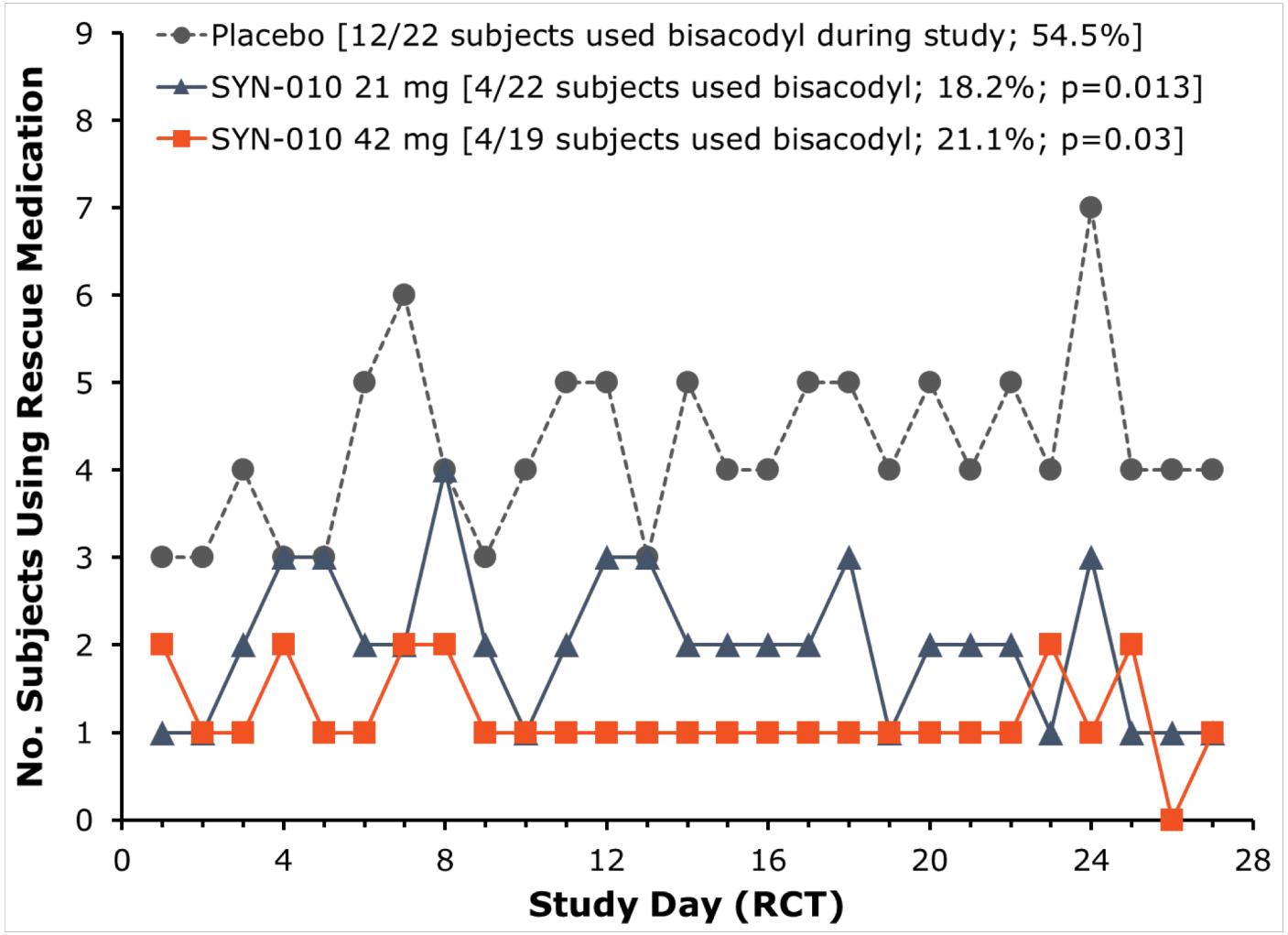
**CSBM Response:** An increase from day 1 baseline of ≥1 Complete Spontaneous Bowel Movement per week in ≥50% of the weeks.
**Abdominal Pain (or Bloating) Response:** A ≥30% decrease from baseline in weekly average worst abdominal pain (or bloating) score in ≥50% of weeks.
**Overall Response:** A CSBM Response and an Abdominal Pain Response in the same week in ≥50% of the weeks in the treatment period (FDA, EMA).

# SYN-010 Very Well-Tolerated in Phase 2a Studies

| Parameter | Cohort 1 | | Cohort 2 | | Cohort 3 | |
|---|---|---|---|---|---|---|
| **Study** | **RCT** | **EXT** | **RCT** | **EXT** | **RCT** | **EXT** |
| SYN-010 Dose | Placebo | 42 mg | 21 mg | 42 mg | 42 mg | 42 mg |
| Enrolled, n | 22 | 17 | 22 | 20 | 19 | 17 |
| Withdrew, n | 2 | 2 | 2 | 2 | 2 | 1 |
| Reported SAE, n | 0 | 0 | 0 | 0 | 0 | 0 |
| Reported TEAE, n | 1 | 2 | 2 | 2 | 2 | 2 |
| **Treatment Emergent Adverse Event (TEAE; Relationship to Treatment)[1]** | | | | | | |
| RCT, weeks 1-4s | 01 Gastroenteritis (unlikely) | | 04 Headache (probable)<br>05 Intermittent rectal bleeding (unrelated) | | 07 Elevated GGT (probable)<br>08 Elevated AST creatine kinase (possible) | |
| EXT, weeks 5-12 | **02 Diarrhea (unrelated)[2]**<br>03 Elevated ALT AST ALP LDH GGT (unlikely)[3] | | 05 Proctitis (unrelated)<br>06 First degree AV block (unrelated)<br>Leg cramp (possible)<br>Headache (possible) | | 09 Elevated creatine kinase (unrelated)<br>10 Elevated creatine kinase (unrelated) | |

[1]Numbers are masked Subject ID; TEAEs were all of mild or moderate intensity.
[2]Commenced after last dose of study drug. [3]Resulted in withdrawal from the study.

# SYN-010 Groups Used Less Rescue Mediation




**Decreased rescue laxative use consistent with increased SBMs**

[1]Rescue medication use was reported by subjects each day in an electronic diary. [2]Nominal P values for Fisher's exact test vs Placebo.



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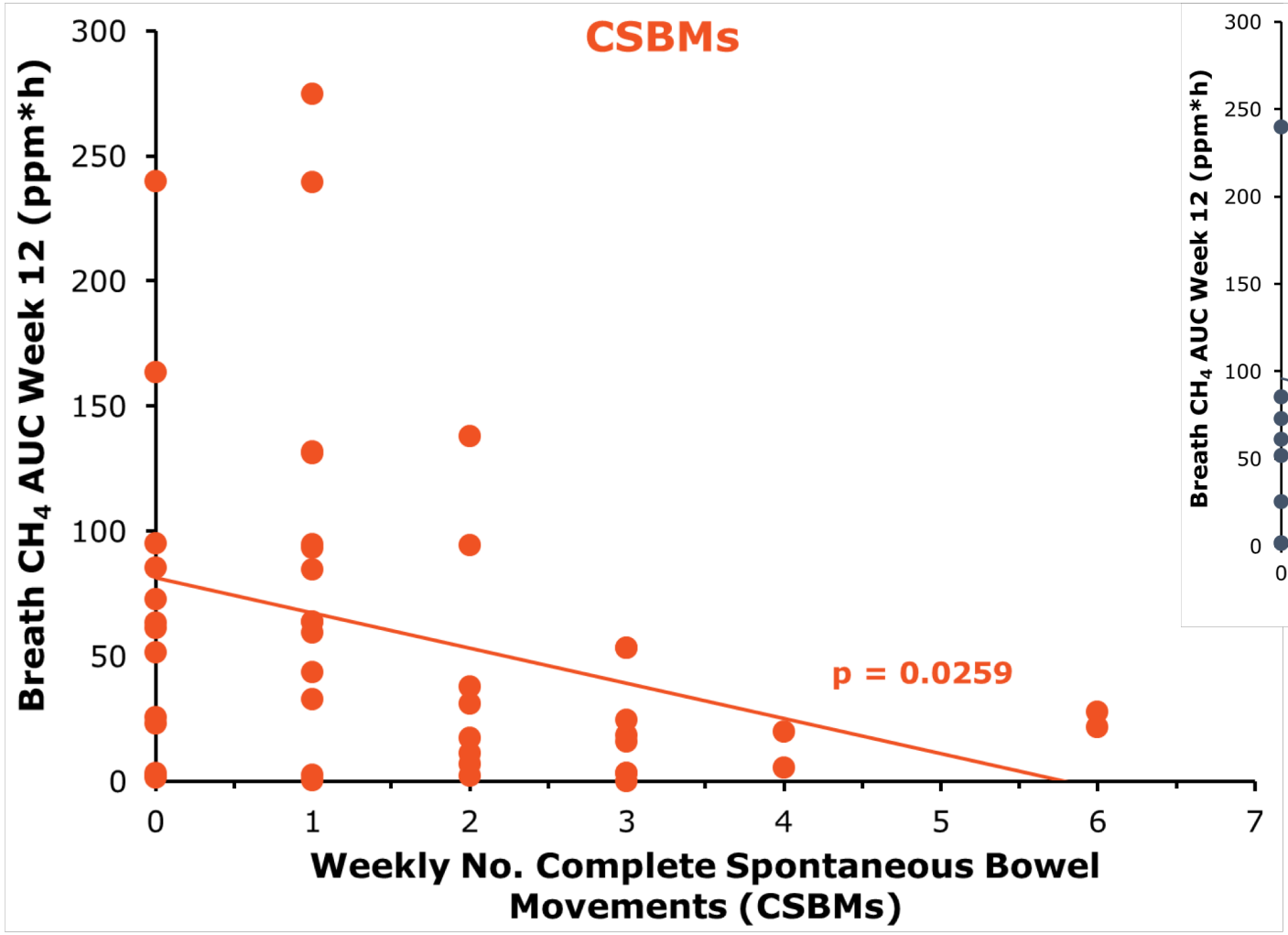
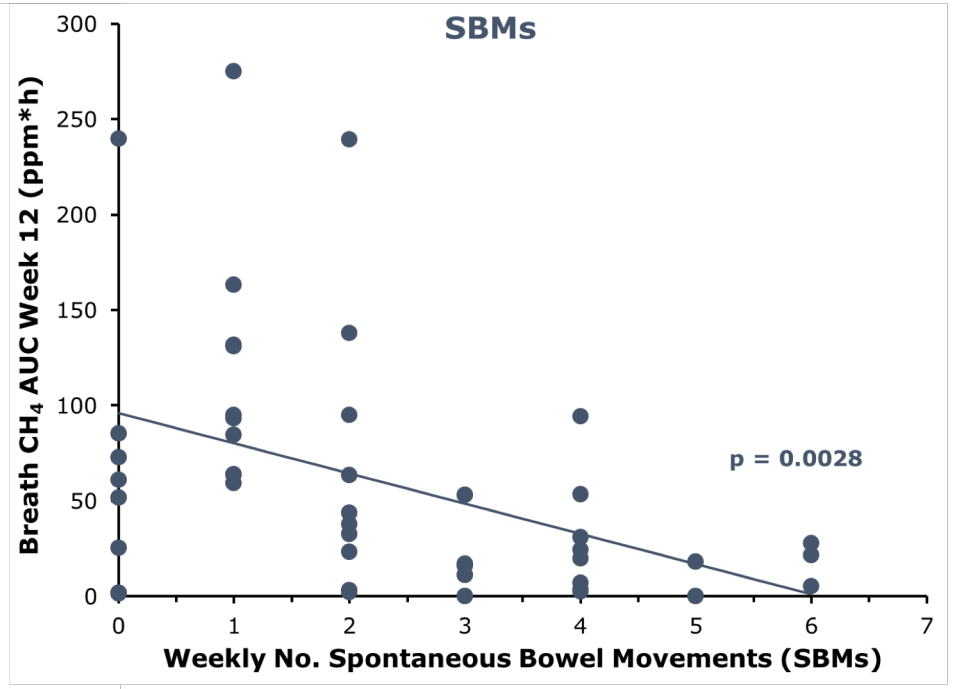
# Lower Methane Correlated with Increased BMs



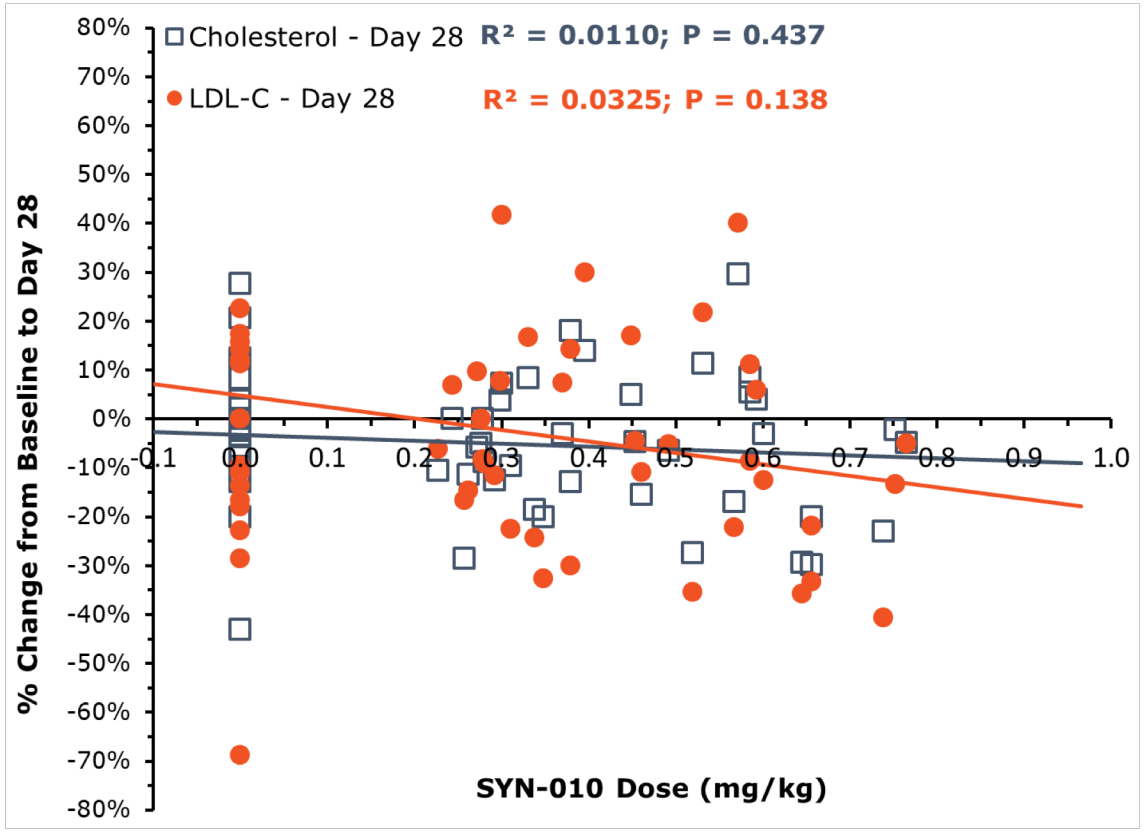

**SBMs and CSBMs increased when methane is reduced**

[1]Correlation line represents least-squares linear regression modeling.
[2]Weekly no. CSBMs at Week 12 (mean±SD) for all subjects completing the EXT (n=48): 1.54±1.52

# SYN-010 No Meaningful or Persistent Systemic Effects

## Consistent with reduced systemic exposure to lovastatin β-hydroxyacid

- Plasma trough levels of lovastatin species measured during the RCT were low and variable[1]
  - ≥50% of patients had undetectable plasma trough levels of each analyte on days 7, 28
- No significant changes were observed in mean ALT or creatine kinase over the 12-week period
  - Liver and muscle markers known to be modulated by lovastatin formulations used to lower cholesterol
- Small, transient reductions in lipid parameters observed at week 1
  - Not different to Placebo at week 4 and not different to baseline at week 12




[1]Wacher V (2016) *Am J Gastroenterol* **111 (Suppl 1)**:S256. Changes in cholesterol, LDL-C, and triglycerides did not correlate with SYN-010 dose, or with changes in body weight, changes in breath methane, or plasma trough levels of either lovastatin lactone or lovastatin β-hydroxyacid.

# SYN-010 Prior Regulatory Interactions

## EOP2 meeting with FDA after Phase 2a Study (July 2016)

- FDA recommended a first **Phase 2/3 adaptive** clinical trial (~$25M)
  - Single daily doses of Placebo, SYN-010 21 mg or SYN-010 42 mg for 12 weeks
  - Both low- and high-breath methane patients to be included

- FDA required **additional** studies (~$45M)
  - Second 12-week phase 3 study with 4-week randomized withdrawal (per guidance)
  - Food effects study measuring plasma and stool levels in IBS-C patients
  - Pediatric study (to be agreed)
  - Pharmacokinetic study vs reference listed drug  for 505(b)(2) pathway
  - 52 week safety study per ICH E1 guidelines

- New FDA meeting to be requested after completion of Phase 2b clinical trial
  - Ideally propose a single dose to **simplify Phase 3** program, reduce development cost and time

IBS-C is the predominant IBS subtype diagnosed in children, with few current treatment options.
FDA acknowledged in EOP2 meeting minutes that Mevacor® safety data would be supportive for potential SYN-010 505(b)2 registration pathway.



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# SYN-010 Comparison to Other IBS-C Products

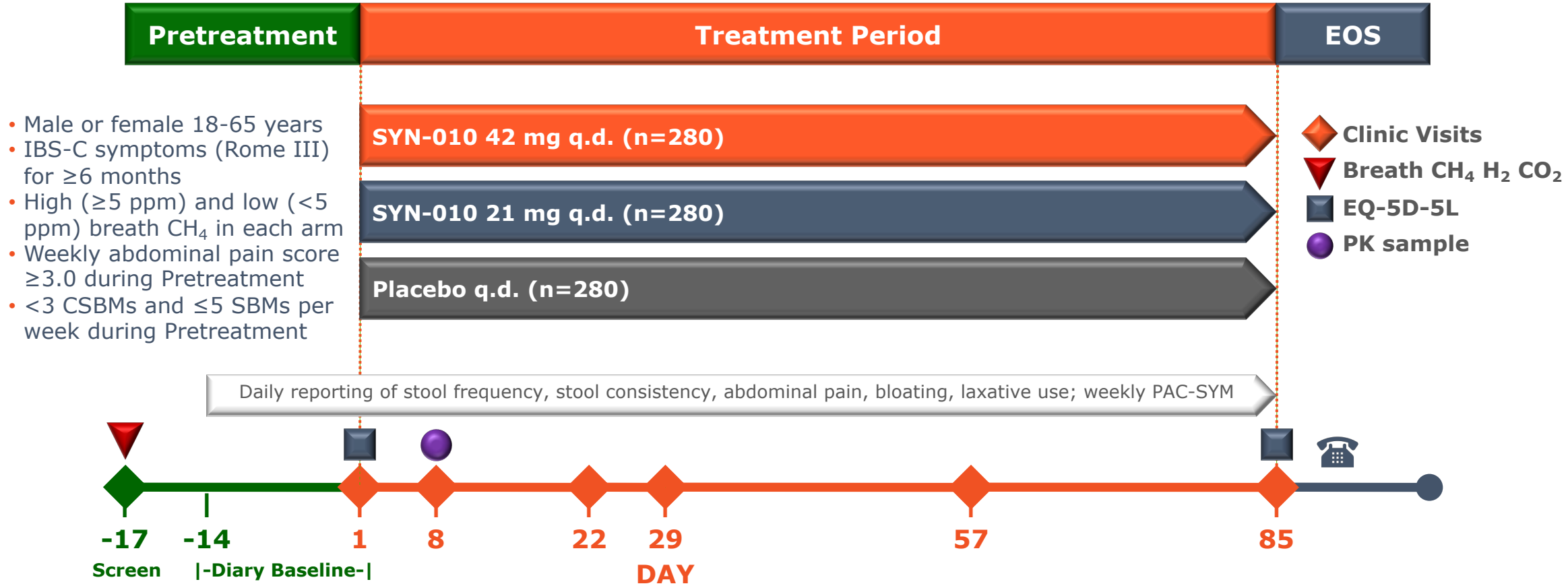
| Parameter | SYN-010 | Linaclotide | Lubiprostone | Plecanatide | Tenapanor |
|---|---|---|---|---|---|
| **Company** | **Synthetic Biologics** | **Allergan / Ironwood** | **Takeda / Sucampo** | **Synergy** | **Ardelyx** |
| Brand | -- | Linzess® | Amitiza® | Trulance™ | -- |
| Current Status | Phase 2b | Market | Market | Market | Phase 3 |
| **Clinical Trial (No. Weeks)** | **Phase 2a Open Label EXT (8)[1]** | **Phase 3 (12)[2]** | **Phase 3 (12)[3]** | **Phase 3 (12)[4]** | **Phase 2b (12)[5]** |
| Dose | 42 mg q.d. | 290 µg q.d. | 8 µg b.i.d. | 3 mg q.d. | 50 mg b.i.d. |
| Subjects on Drug (Placebo) | 54 (--) | 806 (798) | 325 (180) | 728 (733) | 84 (89) |
| **Response Drug (Placebo), % Subjects** | | | | | |
| CSBM Response | 55.8 (--) | 48.2 (26.1) | -- | 40.9 (31.4) | 60.7 (33.7) |
| Abdominal Pain Response | 62.7 (--) | 49.5 (36.0) | 36.7 (25.2) | 36.8 (27.3) | 65.5 (48.3) |
| Overall Response | 39.2 (--) | 33.6 (17.4) | 26.3 (15.3) | 25.7 (15.9) | 50.0 (23.6) |
| Bloating Response | **72.5** (--) | 43.2 (26.8) | 32.0 (25.1) | *Improved* | 59.5 (41.6) |
| Diarrhea Incidence | **1.9** (--)[6] | 19.3 (2.8) | 4.9 (3.3) | 4.3 (1.0) | 11.2 (0.0) |
| Nausea Incidence | **0.0** (--)[7] | *No data* | 9.3 (5.5) | *No data* | 3.4 (1.1) |

**CSBM Response:** increase of ≥1 CSBM per week vs baseline in ≥50% of weeks
**Abdominal Pain Response:** a ≥30% decrease vs baseline in weekly average worst abdominal pain score in ≥50% of weeks
**Bloating Response:** a ≥30% decrease vs baseline in weekly average bloating score in ≥50% of weeks
**Overall Response:** a CSBM Response and an Abdominal Pain Response in the same week in ≥50% of weeks

[1]Study not prospectively powered for formal statistical evaluation of clinical endpoints. [2]Chey W (2012) *Am J Gastroenterol* **107:**1072-12 and Rao (2012) *Am J Gastroenterol* **107:**1714-24. [3]Chang W (2016) *Aliment Pharmacol Ther* **44:**1114-22; calculations used SBMs as CSBMs not reported. [4]Brenner D (2018) *Am J Gastroenterol* **113:**735-45. [5]Chey W (2017) *Am J Gastroenterol* **112:**763-74. [6]**One case of diarrhea, not drug related.** [7]Prucalopride (2 mg q.d.) showed high rates of nausea (14%), diarrhea (13%) and headaches (19%) compared to placebo (7%, 5%, 9%) in Phase 3 trials of CIC; MOTEGRITY prescribing

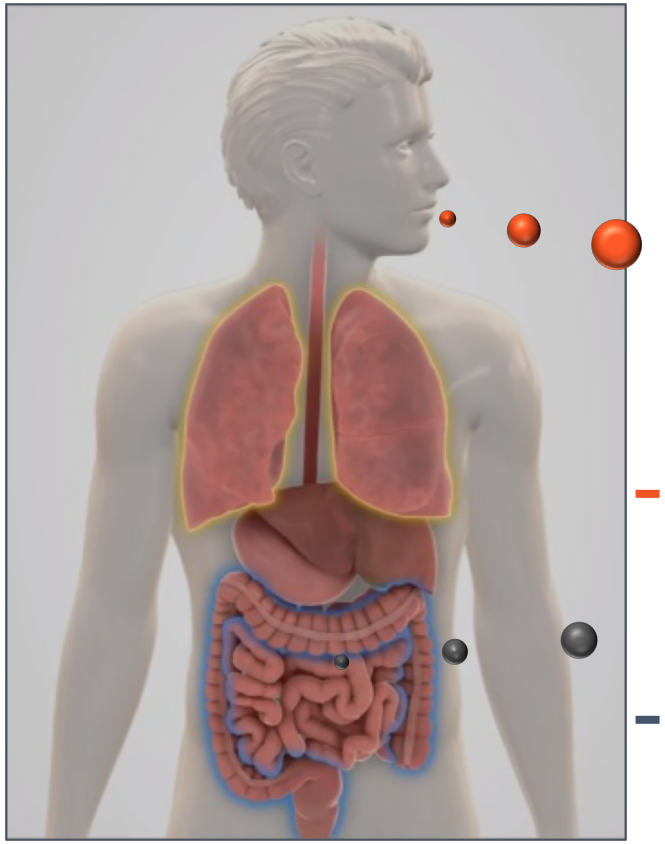
# SYN-010 Phase 2b/3 Adaptive Clinical Trial (FDA)

## SYN-010 effects on IBS-C symptoms in high- and low-breath methane producers




Multicenter study (up to 150 sites) with an optional interim futility analysis to be conducted when 50% the patients have completed 12 weeks of the study
Complete spontaneous bowel movements (**CSBMs**), worst abdominal pain score (0-10), worst abdominal bloating score (0-4), stool consistency (Bristol Stool Form Scale) and laxative use are recorded by patients each day using an e-PRO device.
Primary endpoint = Proportion of Overall Responders during the 12-week Treatment Period

# Why Include Low Breath Methane Patients?



**Breath $CH_4$ Detectable (≥3 ppm)**

**Elevated Gut $CH_4$**

***M. smithii*** **(copies/g wet stool)[1]**

**~$10^6$**

**~$10^4$**

**Constipated**

**Healthy**

IBS-C patients with low breath $CH_4$ but high gut $CH_4$ should also benefit from SYN-010[1]

[1]Kim G (2012) *Dig Dis Sci* **57:** 3213-8; the population prevalence of IBS-C patients with low breath $CH_4$ but constipating gut $CH_4$ has not been established.

# SYN-010 Patent Position

Extensive patent portfolio, multiple protection strategies

**~60 Granted Patents and ~25 Pending Applications (US & International)**

**Patented Methods of Treatment**

**Broadest Indication**

**Expires 2023**

**Patented and Pending Methods of Treatment**

**Treat Constipation with SYN-010 in Screened Patients**

**Expires 2034**

**Pending Patent Applications**

- **Formulations**
- **Methods of Use in Specific Patient Populations**
- **Clinical Dosing**

**Expires 2035**

Principal intellectual property licensed from Cedars-Sinai Medical Center (Los Angeles, CA)



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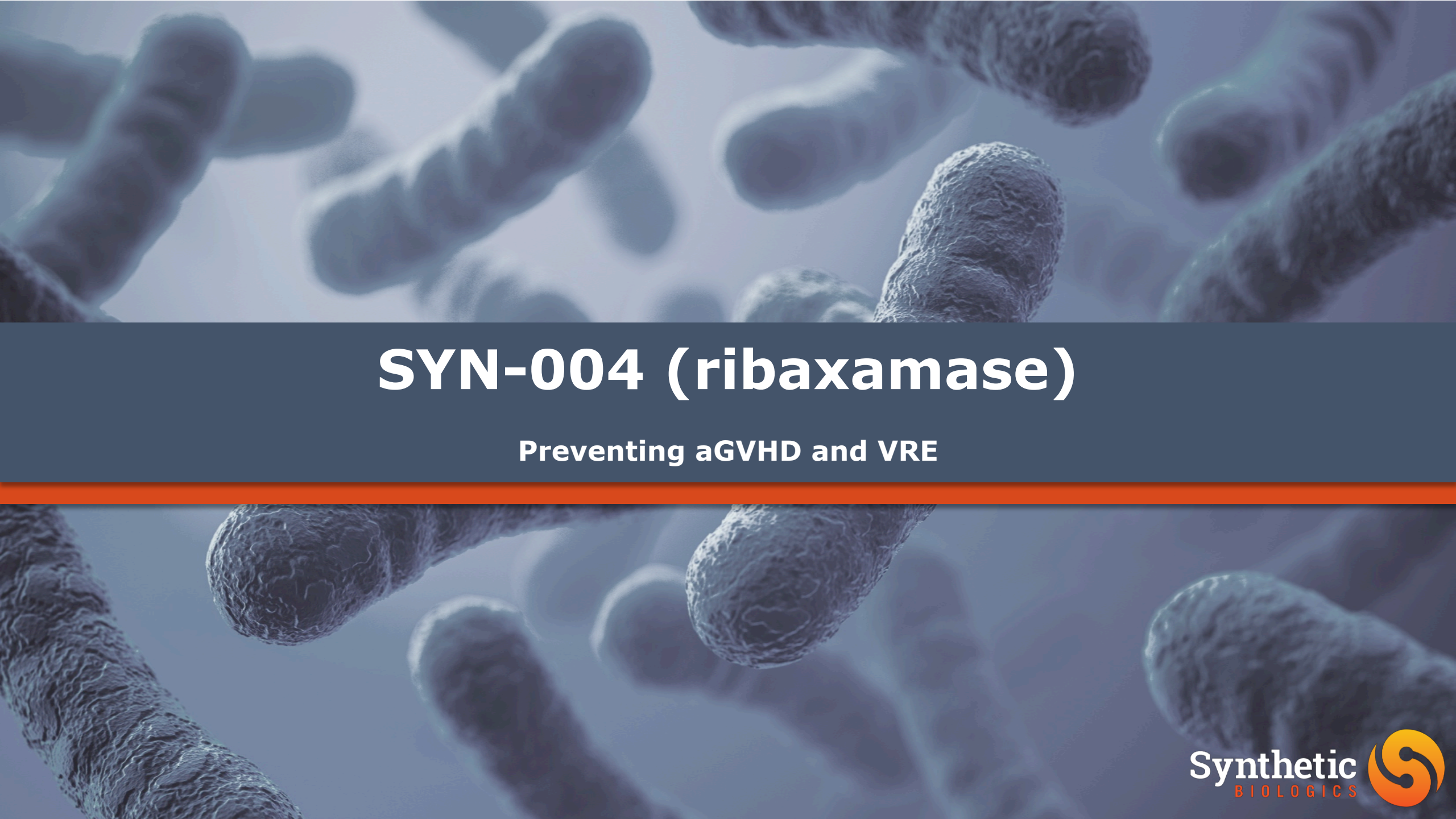

# SYN-004 (ribaxamase)

## Preventing aGVHD and VRE

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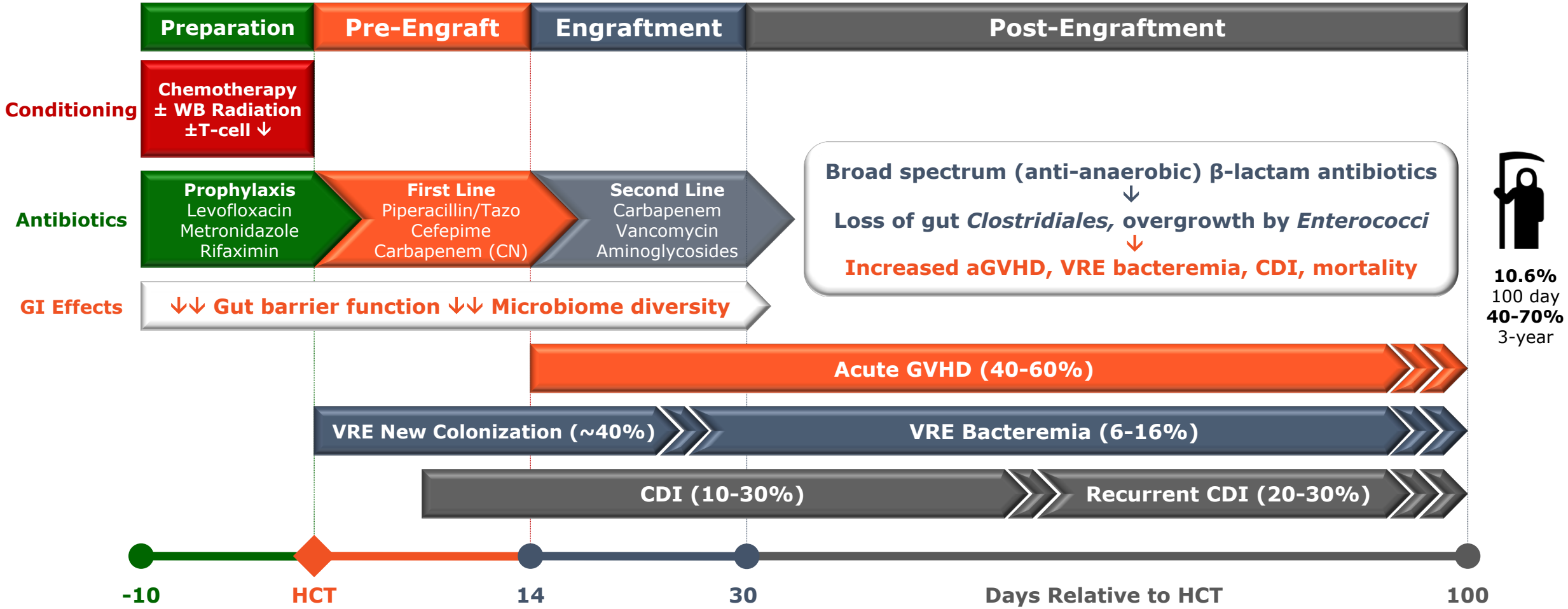
# Allogeneic HCT, Antibiotics and Adverse Outcomes




Shono Y (2016) *Sci Transl Med* **8:** 339ra71. Taur Y (2012) *Clin Infect Dis* **55:** 905-14. Tavadze M (2014) *Bone Marrow Transplant* **49:** 1310-16. Dubberke ER (2010) *Clin Transplant* **24:** 192-8. Dubberke ER (2017) *Transplant Dir* **3:**e145. D'Souza A (2017) *Biol Blood Marrow Transplant* **23:**1417-21.



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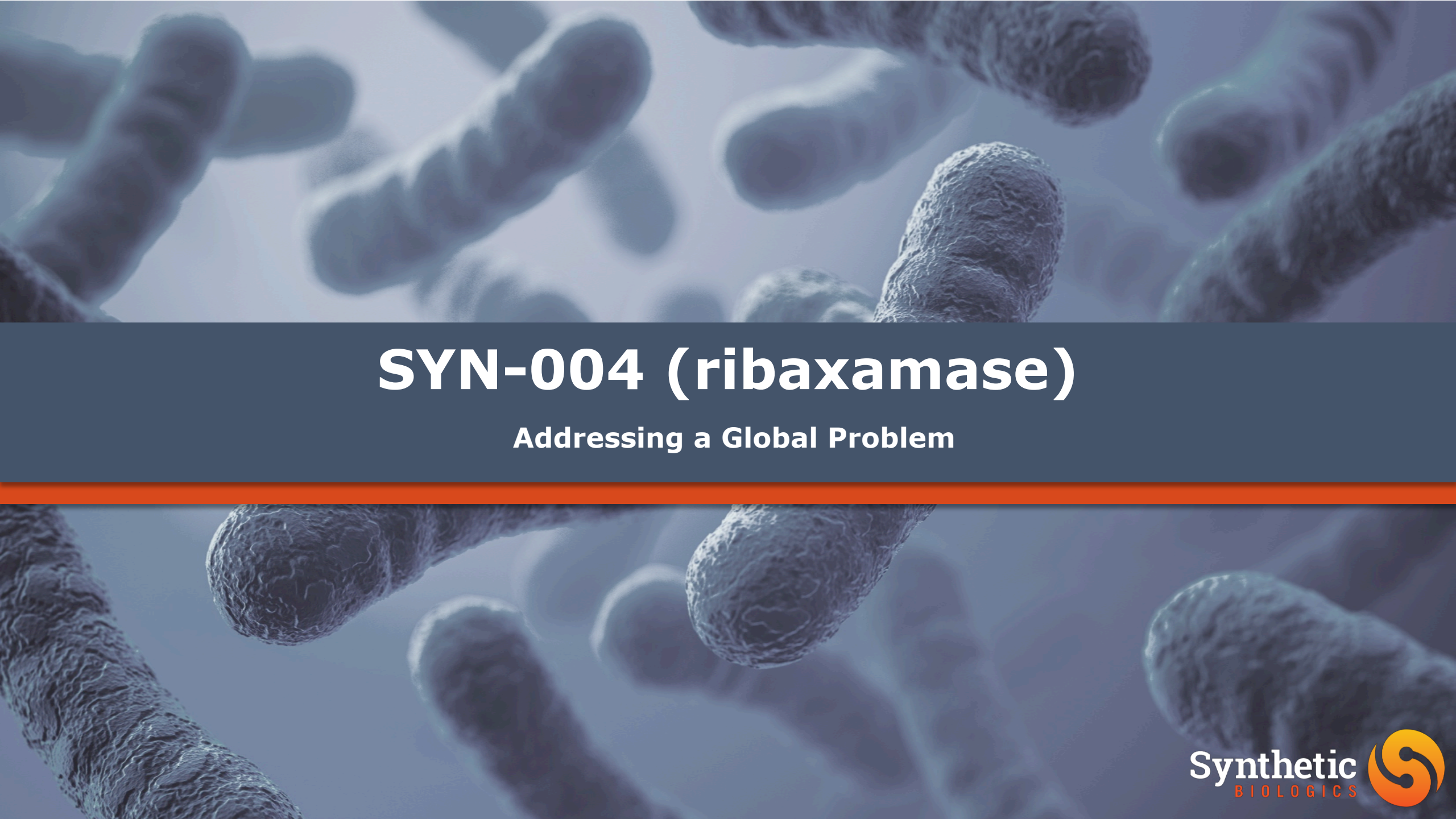

# SYN-004 (ribaxamase)

## Addressing a Global Problem

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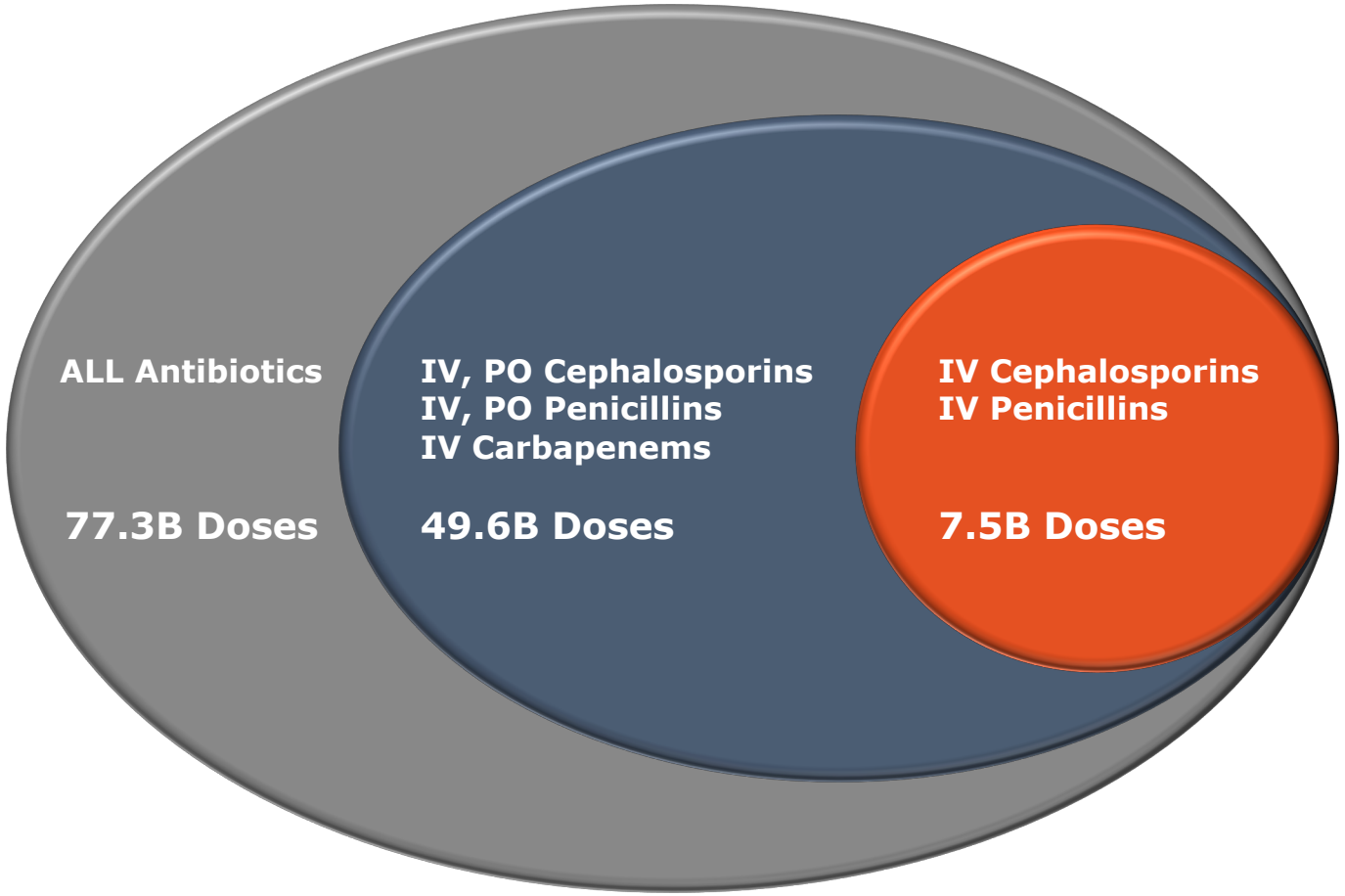
# Antibiotics can Damage the Microbiome

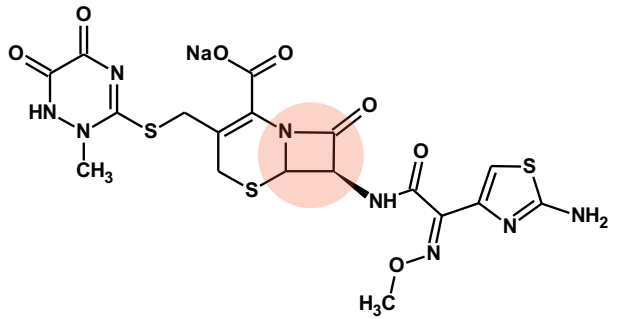
## Antibiotic use worldwide




## β-Lactam Antibiotics

**Some of the worst intestinal microbiome damaging agents**

~64% of the World's antibiotics
~57% of US antibiotics
100's of millions of patients



Data extracted from IMS Health 2017; doses in standard units. Macrolides, fluoroquinolones and tetracyclines make up the majority of the remaining non-β-lactam antibiotics



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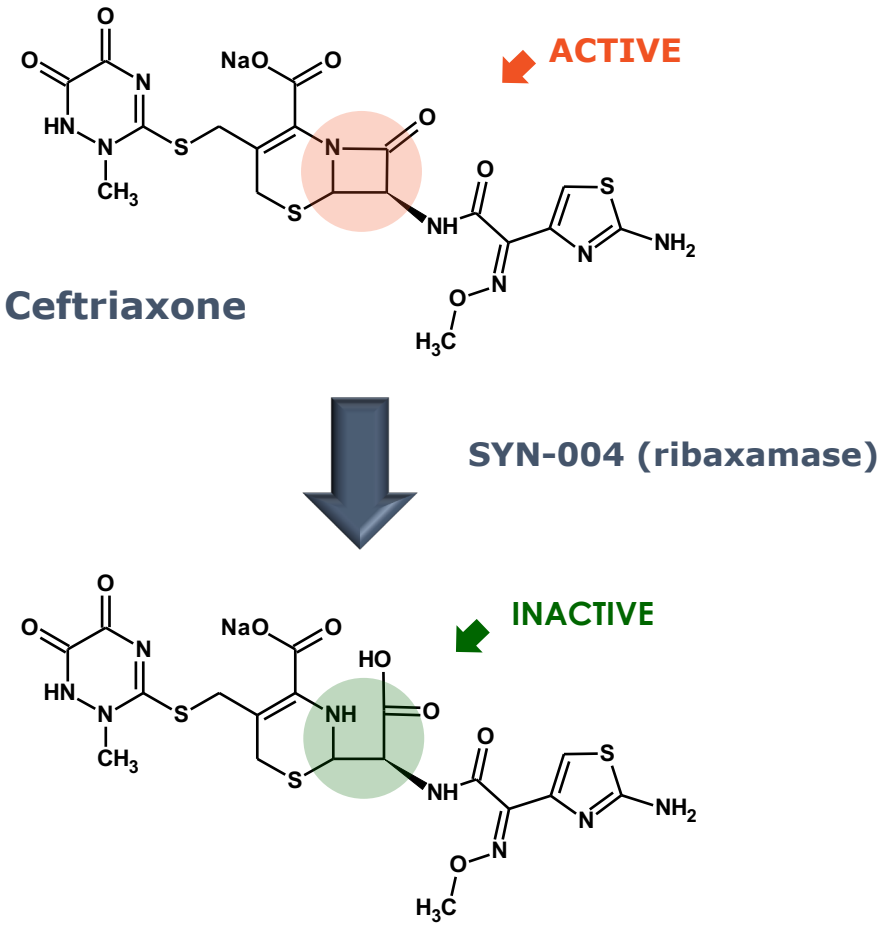
# SYN-004 (ribaxamase)

Proprietary oral formulation of an antibiotic-degrading enzyme

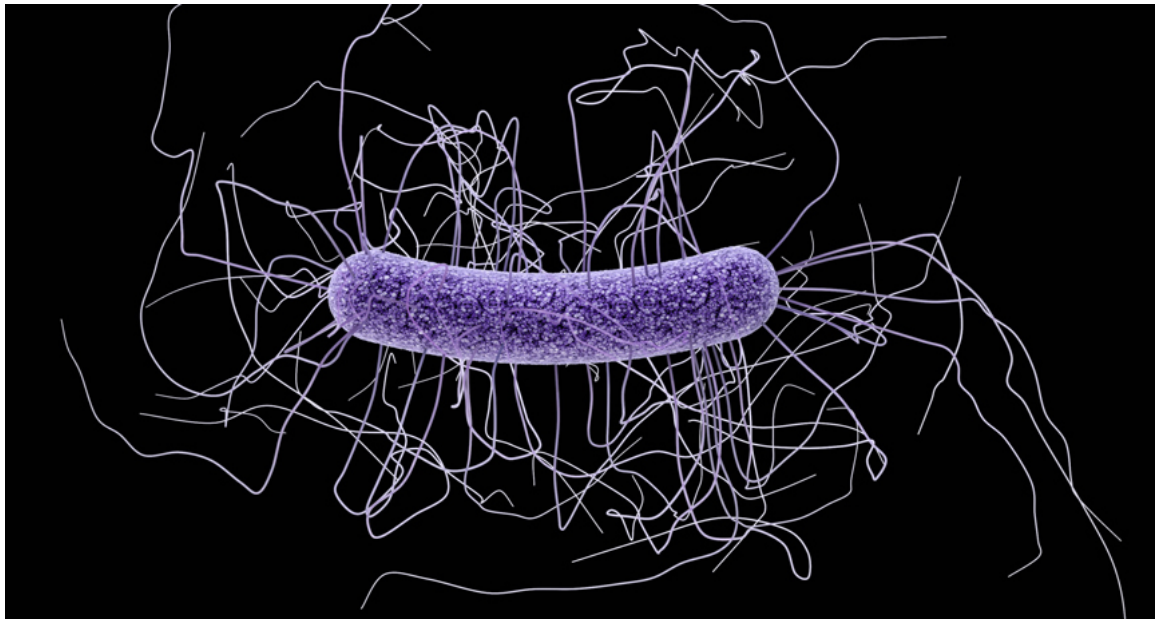
- Enteric-protected, oral formulation of a proprietary class A, β-lactamase (P3A)
  - First generation enzyme (P1A) was successfully evaluated in over 250 subjects in European Phase 1 and Phase 2 clinical trials with ampicillin and piperacillin/tazobactam
  - Limited activity against cephalosporins
- P3A was modified from the first generation enzyme (P1A) to expand activity to include cephalosporins



# *Clostridium difficile*

Gram positive, spore-forming bacterium

- Exists as toxigenic and non-toxigenic species in the colon
  - Up to 15% of healthy adults have asymptomatic *C. difficile* colonization[1,2]
  - Readily transmitted by contact with spores
- Symptomatic *C. difficile* infection (**CDI**) is due to secretion of an enterotoxin (toxin A; TcdA) and a cytotoxin (toxin B; TcdB)
  - Toxins can cause diarrhea and inflammation
  - Serious complications of CDI include pseudomembranous colitis, toxic megacolon, colon perforation, sepsis and death



**A major cause of CDI is disruption to the gut microbiome by antibiotics**

[1]Furuya-Kanamori L et al. (2015) *BMC Infect Dis* **15**:516. [2]Donskey CJ et al. (2015) *Infect Dis Clin N Am* **29:** 13–28

# *Clostridium difficile* Infection is Costly

Epidemiological and economic burden of CDI in the USA from a modeling approach[1]

**606,058**

CDI patients in the USA in 2014

**>1 in 5**

experience at least one CDI recurrence

**~7**

extra days spent in the hospital by CDI patients[2]

**$5.4B**

added cost to healthcare and community in 2014

**44,500**

CDI-attributable deaths (7%)

[1]Desai K (2016) *BMC Infect Dis* (2016) **16:**303. Overnight stays in the hospital contributed 78% of the total direct and indirect costs of CDI cases in healthcare facilities and 52% of costs for CDI cases originating in the community. [2]van Kleef E (2014) *J Hosp Infect* **88**:213-7



Synthetic BIOLOGICS

# Antimicrobial Resistance (AMR)

- AMR is a serious global threat - world leaders are taking action
- Governments recognize the need to expedite drug review timelines
- Leaders in industry and academia are developing action plans
- Worldwide concern over potential **Antibiotic Armageddon**[1]
  - Failure to address AMR may result in 10 million deaths worldwide by 2050, costing $100 trillion in economic output[2]
- Synthetic Biologics is pioneering therapeutics to **prevent** the emergence of AMR
  - Awarded CDC contract to evaluate the ability of ribaxamase to prevent AMR[3]

FDA HHS

CDC Centers for Disease Control and Prevention

World Health Organization

**Declaration on Combatting Antibiotic Resistance – 2016**

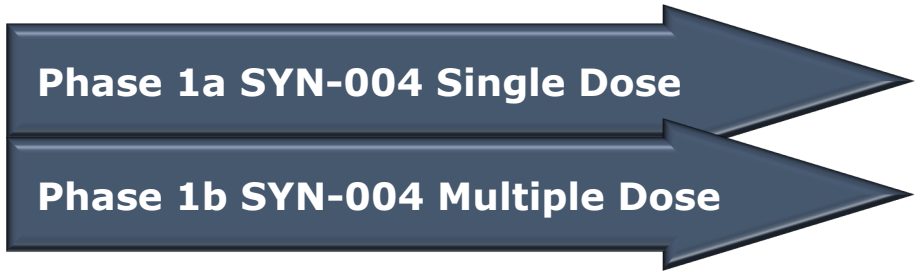
[1]European Society of Clinical Microbiology and Infectious Diseases https://www.escmid.org/
[2]https://www.antimicrobialsworkinggroup.org/antimicrobial-resistance/
[3]CDC Advanced and Innovative Solutions to Improve Public Health Broad Agency Announcement (BAA) 2016-N-17812.



Synthetic BIOLOGICS

# SYN-004 (ribaxamase) Development


- Safe and well tolerated in dogs (*NOAEL 57 mg/kg/day*)[1]
- Degraded ceftriaxone in the chyme (*no effect on plasma levels*)
- Protected the pig gut microbiome from β-lactam antibiotics
- Prevented emergence of antimicrobial resistance genes[2,3]




- Healthy subjects (*up to 300 mg q6h x 7 days*)[4]
- Oral doses well tolerated with few AEs
- Negligible systemic bioavailability
- Was not immunogenic


- Healthy subjects with functioning ileostomies[5]
- Degraded ceftriaxone in the chyme
- Did not alter ceftriaxone plasma levels
- Degradation of ceftriaxone was unaltered by PPI

[1]Kokai-Kun JF et al. (2016) *Int J Toxicol* **35:** 309-16. [2]Kaleko M et al. (2016) *Anaerobe* **41:** 58-67. [3]Connelly S et al. (2017) *J Appl Microbiol* ePub Feb 28.
[4]Roberts T et al. (2016) *Clin Drug Investig* **36:** 725-34. [5]Kokai-Kun JF et al. (2017) *Antimicrob Agents Chemother* **61:** e02197-16



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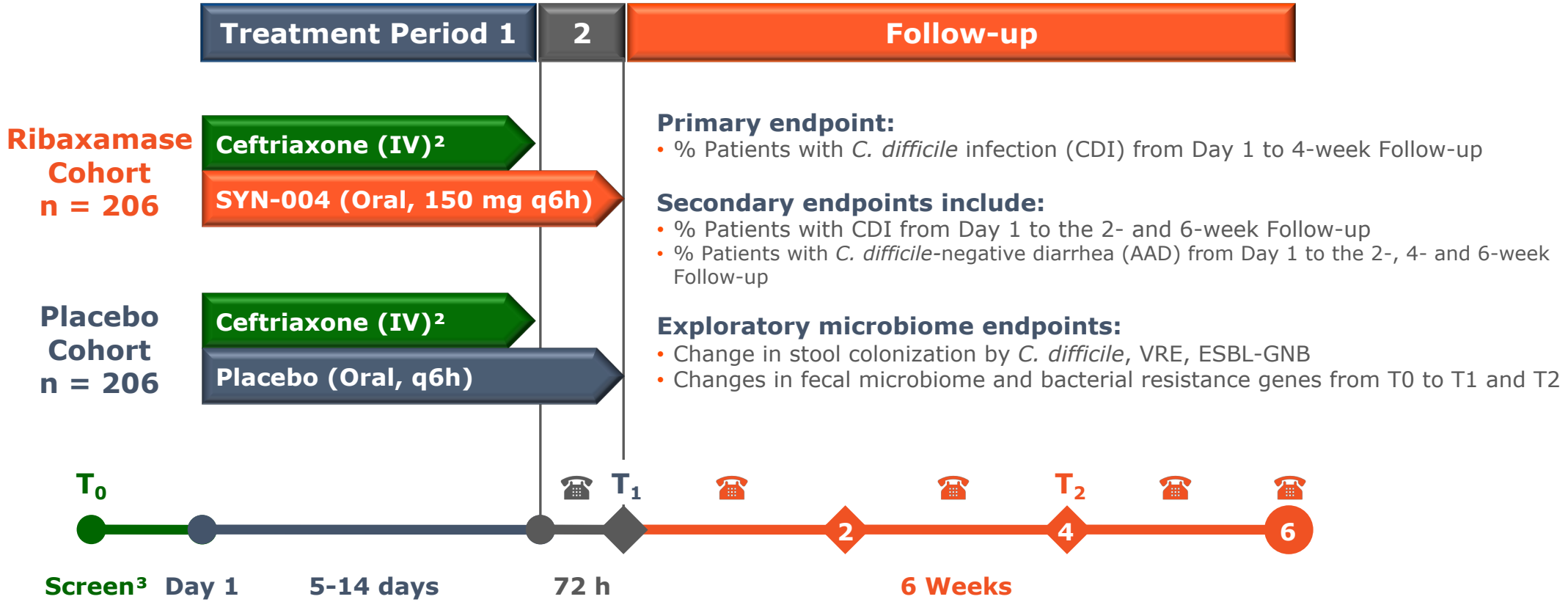
# SYN-004 (ribaxamase) Phase 2b Clinical Trial

## Prevention of CDI in patients receiving IV ceftriaxone to treat a LRTI




**Primary endpoint:**
- % Patients with *C. difficile* infection (CDI) from Day 1 to 4-week Follow-up

**Secondary endpoints include:**
- % Patients with CDI from Day 1 to the 2- and 6-week Follow-up
- % Patients with *C. difficile*-negative diarrhea (AAD) from Day 1 to the 2-, 4- and 6-week Follow-up

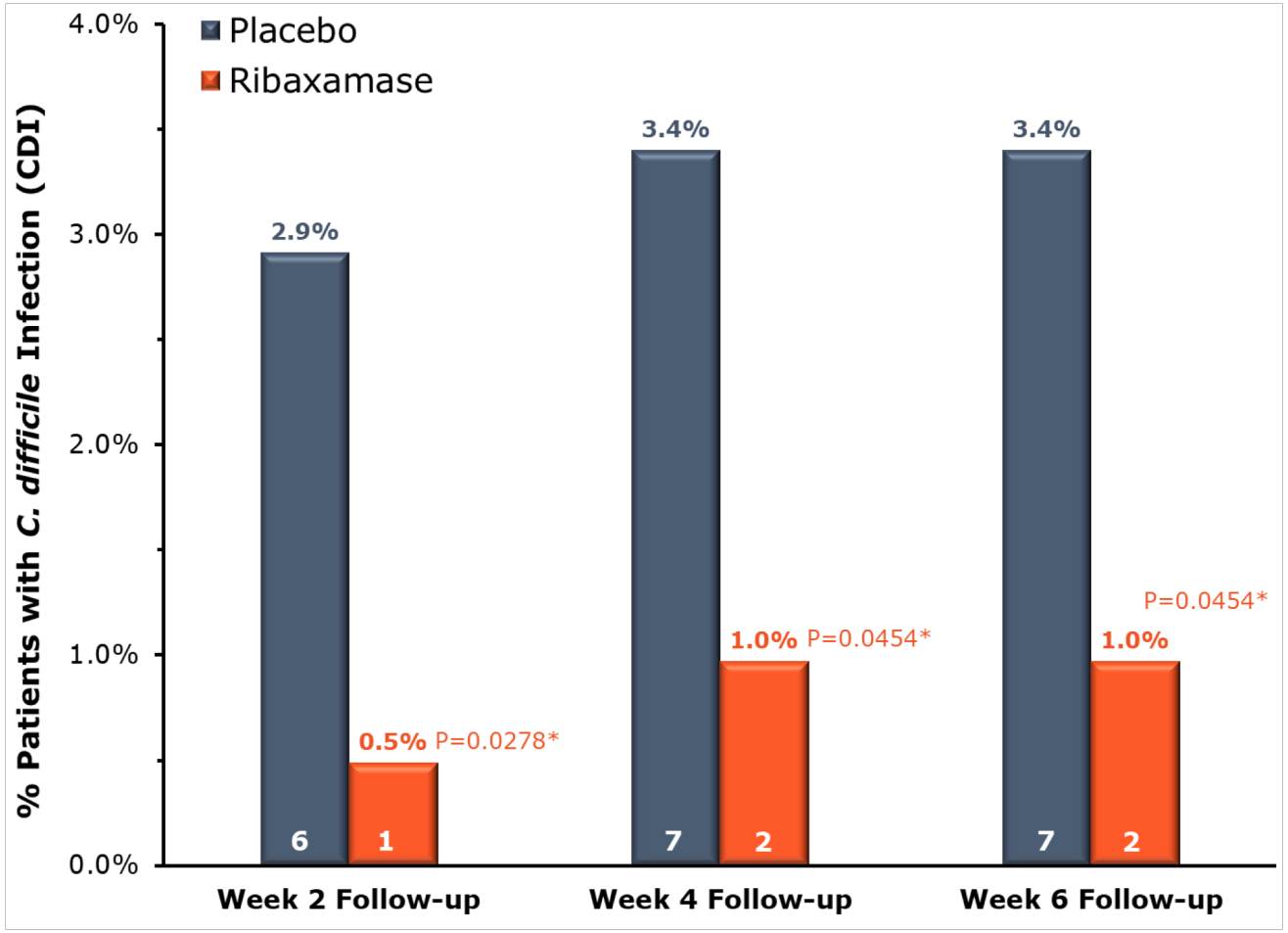
**Exploratory microbiome endpoints:**
- Change in stool colonization by *C. difficile*, VRE, ESBL-GNB
- Changes in fecal microbiome and bacterial resistance genes from T0 to T1 and T2

◆ **Clinic visit. $T_0$ $T_1$ $T_2$ = rectal swabs for colonization and fecal samples for microbiome analysis**

[1]**LRTI** clinical diagnosis of moderate to severe lower respiratory tract infection.
[2]Ceftriaxone in-patient IV dosing regimen and length of dosing were determined by local standard-of-care
[3]84 sites were opened; however, only 54 sites enrolled patients: 5 sites in North America and 49 sites in Europe
[4]**VRE** vancomyin-resistant enterococci; **ESBL-GNB** extended spectrum β-lactamase Gram negative bacteria

# SYN-004 (ribaxamase) Phase 2b Trial Results

## Ribaxamase caused a 71.4% reduction in CDI (achieved primary endpoint)




[1]Patients are determined to have **CDI** (also called *C. difficile* associated diarrhea or CDAD) if they have diarrhea and the stool sample is positive for *C. difficile* toxin A and/or B (or their respective genes, tcdA and/or tcdB) using the local site laboratory results (approved ELISA or NAAT assay)
[2]Confirmatory analyses at a central lab identified CDI in 8 Placebo and 2 ribaxamase treated subjects at week 4 (P=0.0268*)
*P-values are based on one-sided z-test (Chi-square) for the comparison of ribaxamase to Placebo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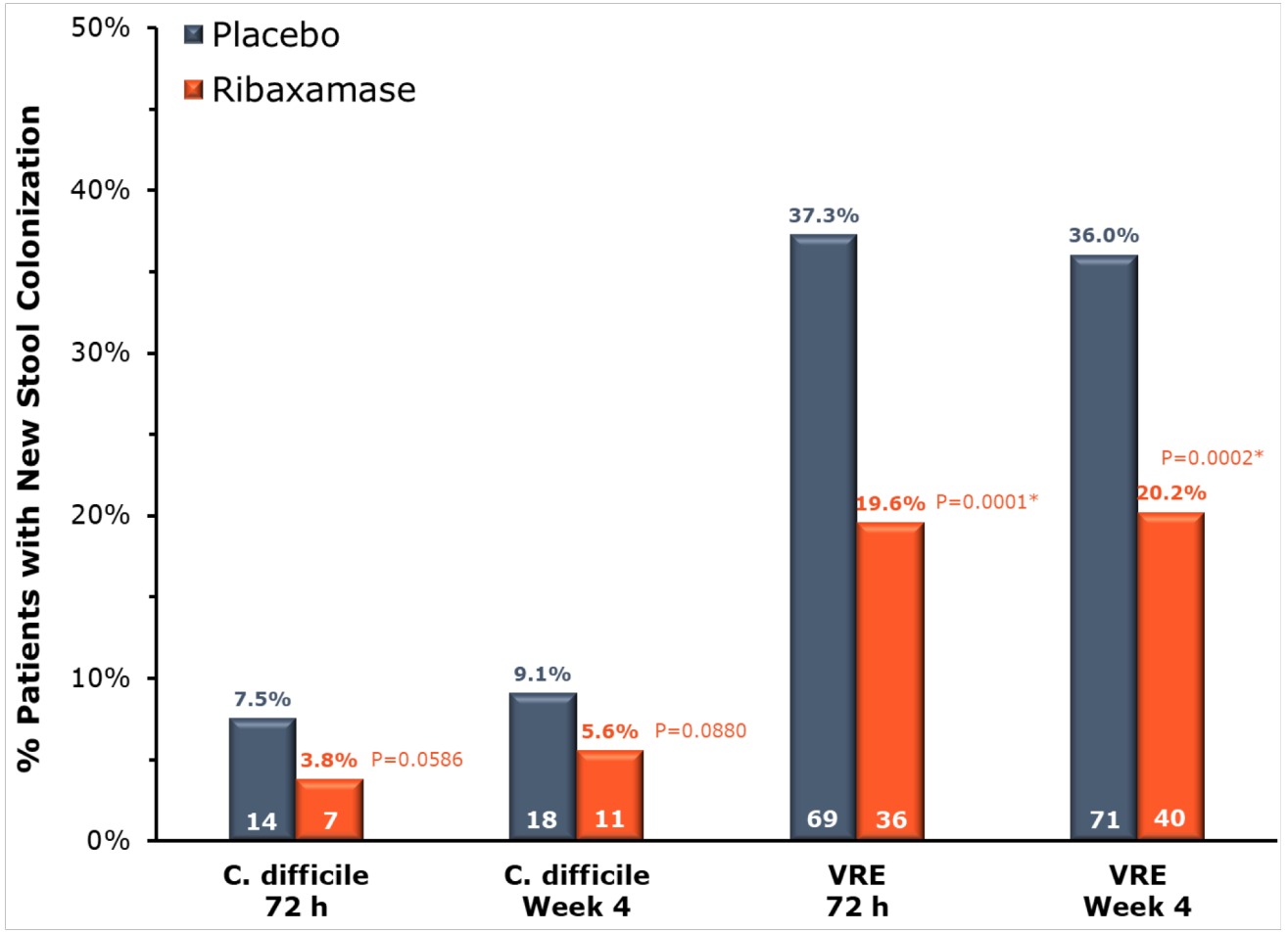
# SYN-004 (ribaxamase) Phase 2b Trial Results

## Ribaxamase caused a 43.9% reduction in new colonization by VRE




[1]**VRE** = Vancomyin-resistant enterococci; new colonization means patient samples were negative at screening ($T_0$) but positive at either $T_1$ (72h) or $T_2$ (Week 4) so $T_2$ (Week 4) data are cumulative and include $T_1$. [2]New *C. difficile* colonization is not the same as CDI and may be asymptomatic; none of the subjects who developed CDI in this study were colonized with *C. difficile* at baseline or had CDI prior to ribaxamase therapy. [3]P-values are based on one-sided z-test (Chi-square) for the comparison of ribaxamase to Placebo



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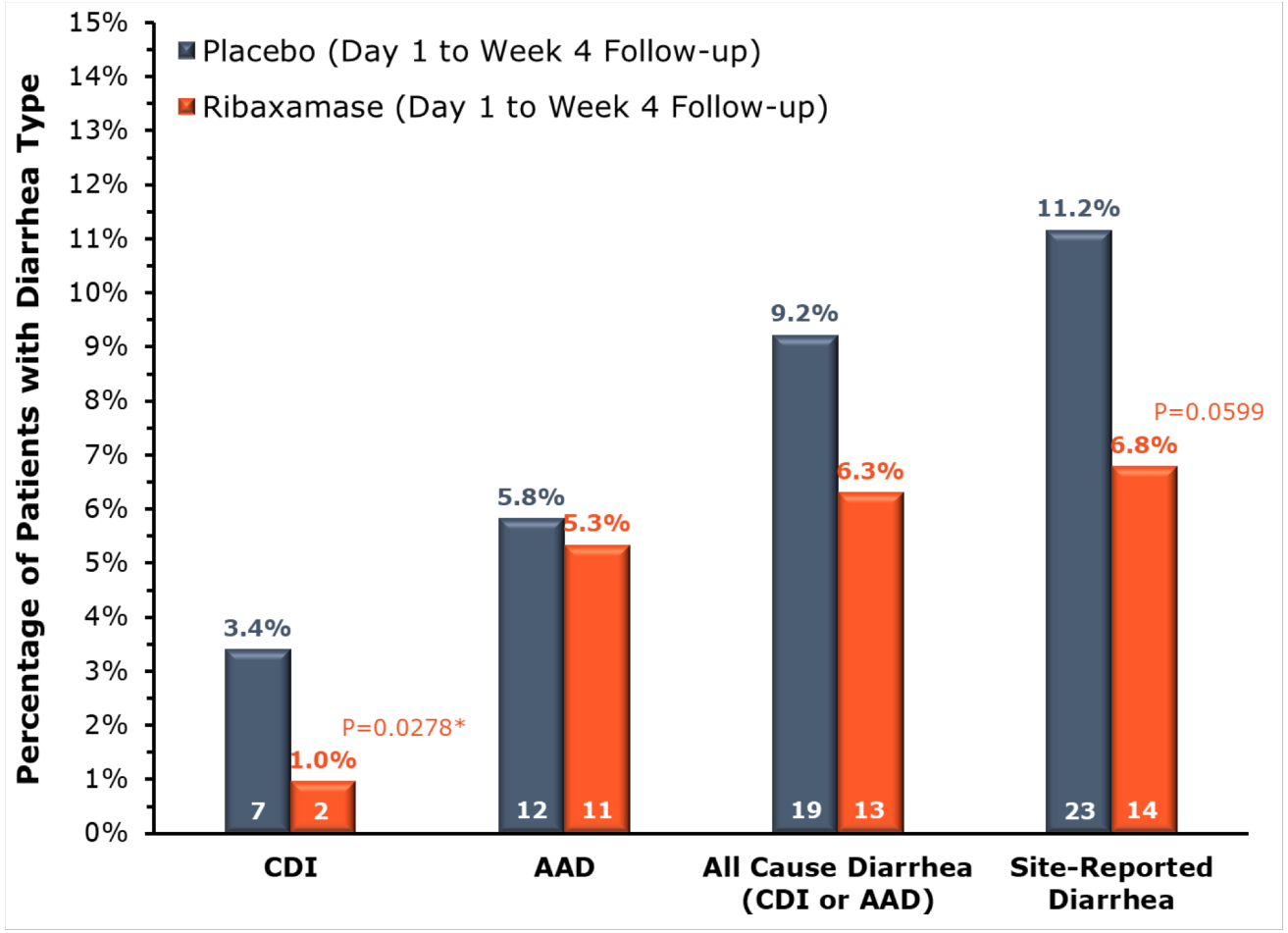
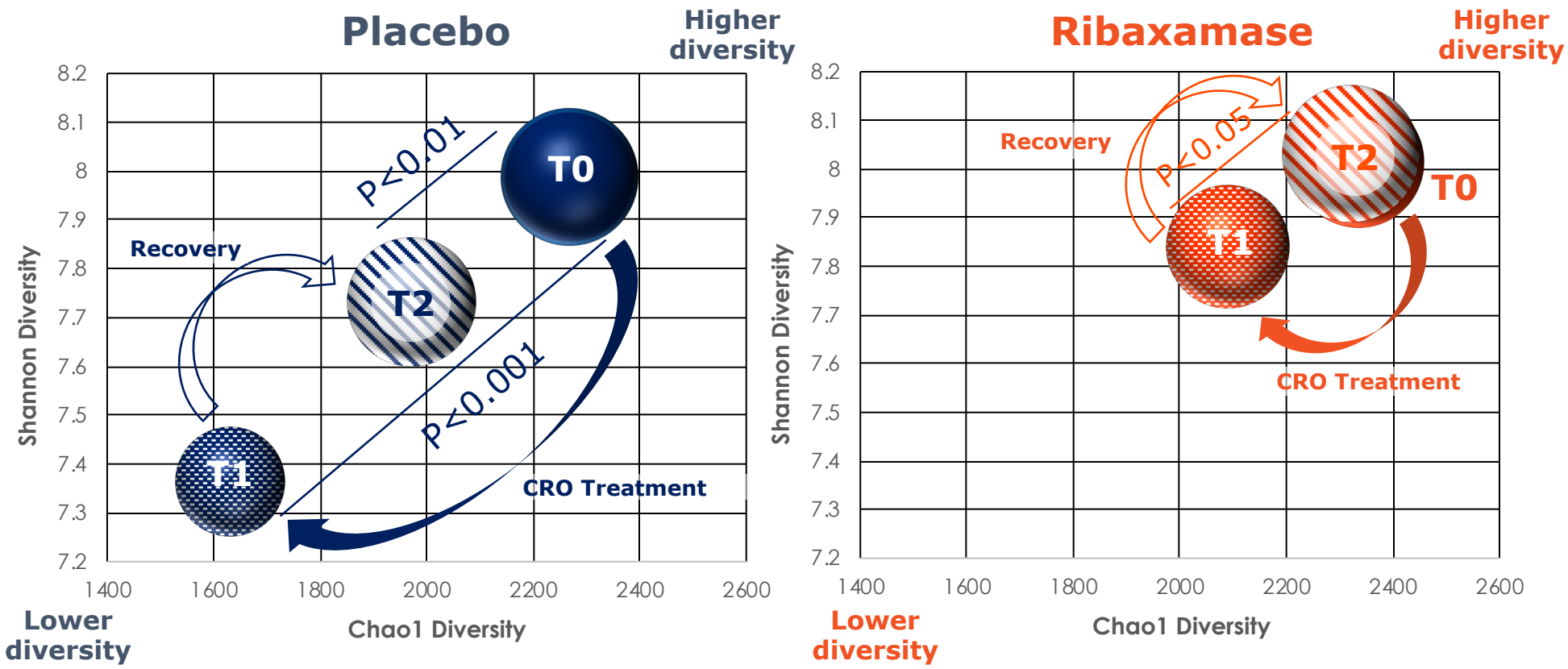
# SYN-004 (ribaxamase) Phase 2b Trial Results

## Trend to decreased diarrhea overall in ribaxamase treatment groups




[1]**CDI** (also called *C. difficile* associated diarrhea or CDAD) means the diarrhea stool sample is positive for *C. difficile* toxin A and/or B (or their respective genes, tcdA and/or tcdB); if negative, the diarrhea is categorized as **AAD** (antibiotic associated diarrhea)
[2]Sites reported diarrhea if the patients had 3 or more unformed stools (6 or 7 on the Bristol Stool Form Scale) per 24 hour period
[2]P-values are based on one-sided z-test (Chi-square) for the comparison of SYN-004 to Placebo

# SYN-004 (ribaxamase) Protected the Gut Microbiome




Compared to T0, patients receiving ribaxamase demonstrated **significantly better maintenance and recovery** of microbial diversity at T1 and T2 versus Placebo

[1]Shannon Index and Chao1 represent α-diversity, a measure of the microbial community composition within a sample
[2]Size of each ball is relative to the standard error of the sample group

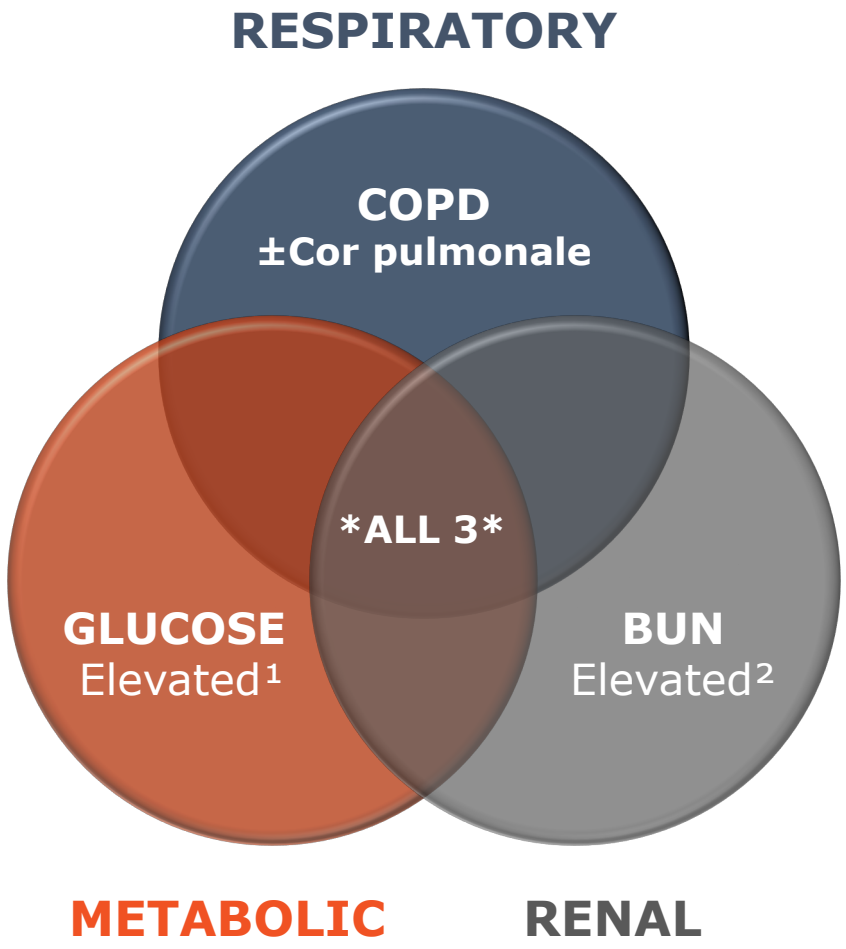
# SYN-004 (ribaxamase) Phase 2b Safety

| Parameter | Placebo | Ribaxamase |
|---|---|---|
| **Dose** | | |
| Ceftriaxone IV infusion, days | 8.4±2.9 | 8.5±3.1 |
| Ceftriaxone, total g received | 17.7±6.9 | 18.9±9.1 |
| Study drug exposure, days | 11.0±3.3 | 11.0±3.5 |
| **Demographics** | | |
| Subjects, n (% Female) | 206 (38.8%) | 206 (35.4%) |
| White/Caucasian, n (%) | 205 (99.5%) | 206 (100%) |
| Age, years | 69.7±9.4 | 68.8±9.4 |
| BMI, kg/m² | 26.9±5.4 | 26.5±5.3 |
| **Treatment Emergent Adverse Events (TEAEs)** | | |
| Subjects with at least 1 TEAE, n (%) | 91 (44.2%) | 84 (40.8%) |
| Drug-related TEAE, n (%) | 1 (0.5%) | 5 (2.4%) |
| Subjects with at least 1 SAE, n (%) | 21 (10.2%) | 33 (16.0%) |
| **Drug-related SAE, n (%)** | **0 (0%)** | **0 (0%)** |
| Subjects with Fatal TEAE, n (%) | 5 (2.4%) | 11 (5.3%) |
| Cancer COD | 2 (1.0%) | 2 (1.0%) |
| Respiratory COD | 2 (1.0%) | 3 (1.5%) |
| **Cardiac COD** | **1 (0.5%)** | **6 (2.9%)[1,2]** |

**Difference in cardiac fatal AEs is attributable to a disparity in underlying health and comorbidities**

All subjects were hospitalized for treatment of moderate to severe lower respiratory tract infection (**LRTI**); data are mean±SD unless indicated.
**SAE** Serious Adverse Even. **COD** cause-of-death. [1]One subject died on Study day 1. [2]Non-fatal cardiovascular TEAEs were not different for SYN-004 (3) and Placebo (4).

# Fatal AEs Associated with Key Cardiac Risk Factors




- Patients with one or more of these 3 factors accounted for:
  - 79% of patients in the Placebo group
    - 100% of Fatal AEs in the Placebo group (5/5)
  - 78% of patients in the SYN-004 group
    - 82% of Fatal AEs in SYN-004 group (9/11)
    - 5 of 6 Cardiac Fatal AEs in the SYN-004 group
- Percentage of patients with ALL 3 risk factors was **2.3-times higher** in the SYN-004 (ribaxamase) treatment group compared to Placebo
  - Accounted for 4 of 6 cardiac fatal AEs in the SYN-004 group

[1]Plasma glucose >7.8 mmol/L at Screening. [2]Blood urea nitrogen (**BUN**) >8.2 mmol/L at Screening. **COPD**=chronic obstructive pulmonary disease reported in patient history.



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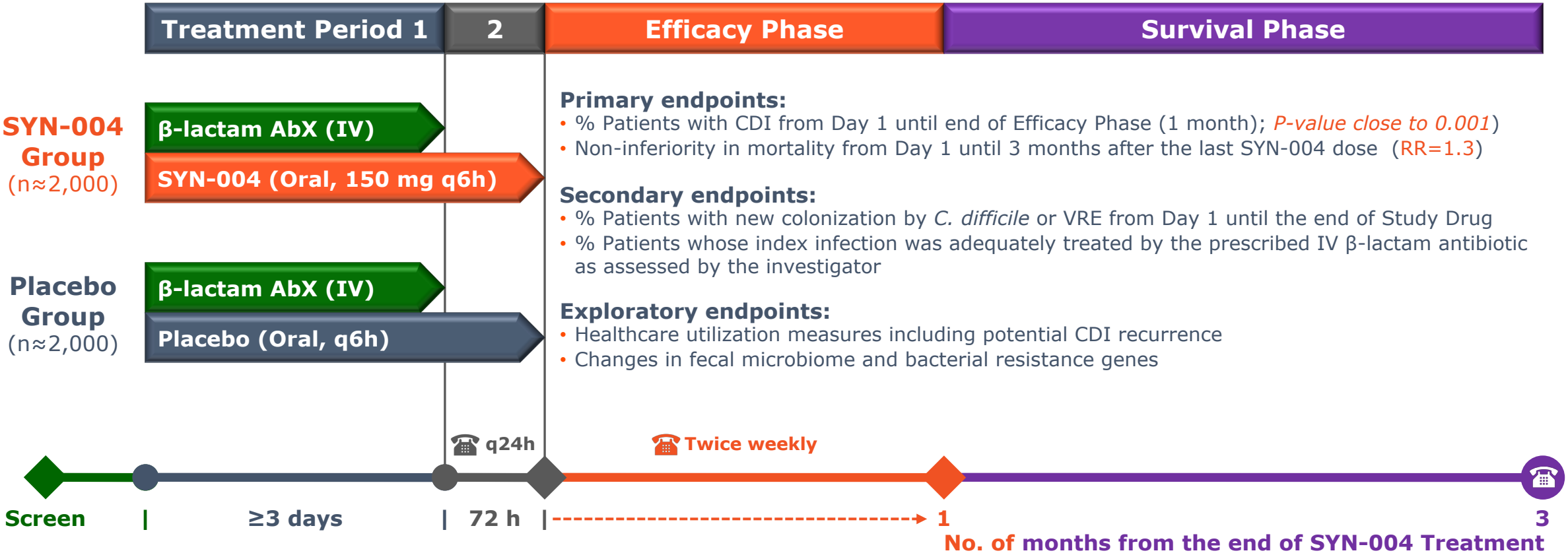
# SYN-004 (ribaxamase) Phase 2b Safety Summary

- The increased number of cardiac fatal AEs in the SYN-004 treatment group was attributable to a **random disparate distribution of cardiac risk factors** that predisposed patients in the SYN-004 group to worse clinical outcomes
  - *"No support for a reasonable possibility of a causal relationship between the exposure to SYN-004 and the occurrence of the reported fatal AE was identified in any of the cases reviewed in this subset."*
    - United BioSource Corporation (UBC)[1]
- There is **no mechanistic rationale** for why a non-absorbed enzyme, confined to the intestinal tract, would adversely impact cardiovascular parameters
  - No SAEs or cardiovascular signals were observed in Phase 1 or Phase 2a clinical trials
- Synthetic Biologics takes patient safety very seriously and will continue to prioritize and expand safety monitoring in Phase 3 clinical trials[2]

[1]United BioSource Corporation. "Safety Evaluation of the Findings from the SYN-004 Phase 2b Study (Protocol SB-2-004-005)". 30 May 2017
[2]Delaying antibiotic treatment to enable stratification and randomization of patients by risk factor prior to study drug administration is infeasible (if not unethical) as the patients present with an acute infection and need to be treated with antibiotic immediately.

# SYN-004 (ribaxamase) Phase 3 Clinical Trial (FDA)

## Prevention of CDI in patients receiving IV β-lactam antibiotics




**Clinic visit:** fecal swabs (colonization) and fecal samples (microbiome analysis)

**β-lactam AbX** = penicillins (piperacillin/tazobactam, ampicillin/sulbactam) and cephalosporins (ceftriaxone, cefepime, cefoperazone); IV dosing regimen and hospital length of stay determined by local standard-of-care and some patients may continue IV AbX off-site after hospital discharge. **Index infection** = infection with suspected anatomical site, incl. lower respiratory tract, complicated urinary tract, surgical site, and intraabdominal infections. **CDI** *Clostridium difficile* infection. **VRE** vancomycin resistant enterococci.



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# SYN-004 (ribaxamase) Patent Position

Extensive patent portfolio, multiple protection strategies

**~60 Granted Patents and ~55 Pending Applications (US & International)**

**Patented ribaxamase Composition of Matter**

**Expires 2031**

**Patented other β-Lactamase Composition of Matter & Uses**

**Expires 2035**

**Pending Patent Applications**

- Methods of Manufacture
- Clinical Dosing, Formulation
- Methods of Treatment

**Expires 2035/6**

# SYN-007 (ribaxamase) DR

## Protecting the microbiome from ORAL β-lactam antibiotics

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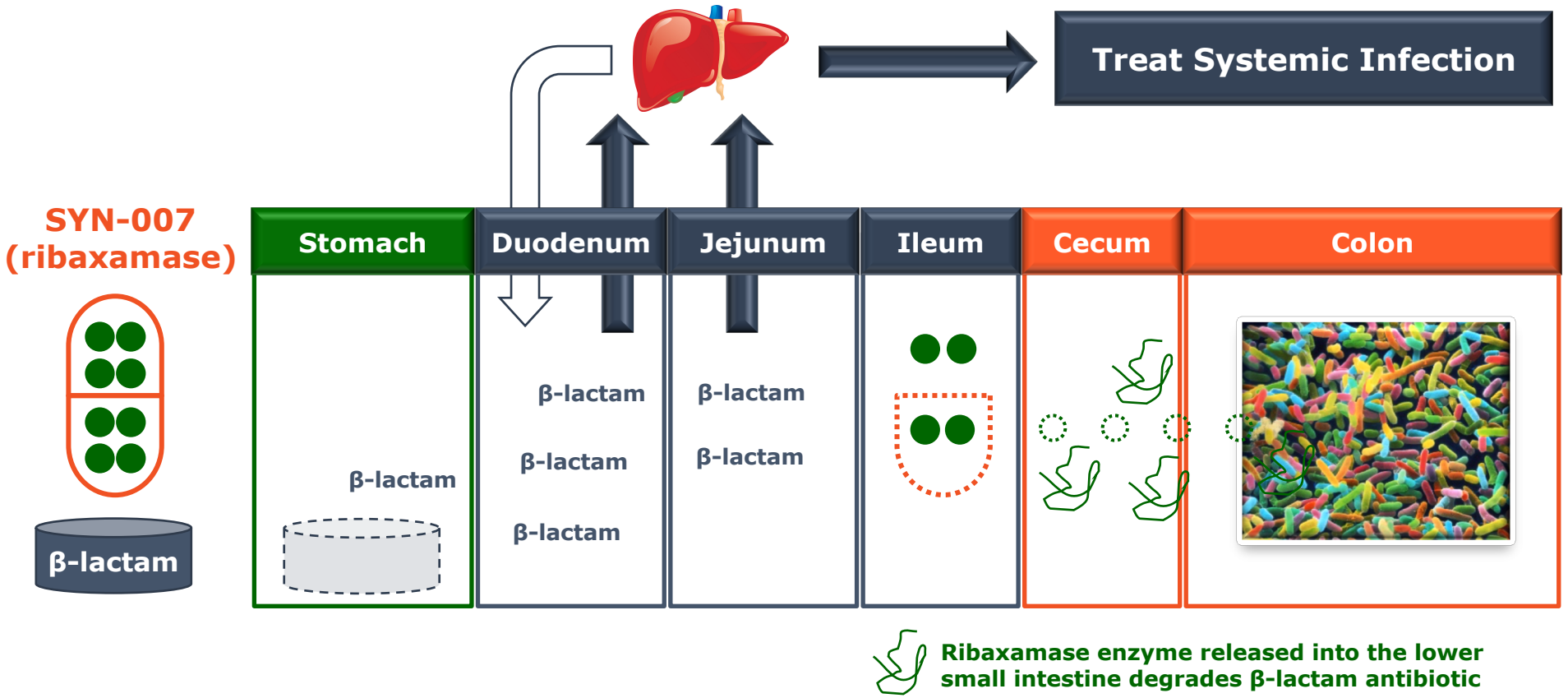
# SYN-007 (ribaxamase) DR for Oral β-Lactams

Designed to prevent oral β-lactam antibiotics from reaching the colon



# SYN-007 (ribaxamase) DR Potential Indication

Prevention of antibiotic associated diarrhea (**AAD**) in children


**2-18%**

**Diarrhea**

**20-70%**

**Diarrhea**


**Amoxicillin**

**SYN-007**

**Amoxicillin + Clavulanate**

Kuehn (2015) *J Pediatr Pharmacol Ther* **20:** 90–104. Tähtinen PA (2011) *N Engl J Med.* **364:**116-26. Ferreira JB (2006) *Braz J Otorhinolaryngol.* **72:**104-11



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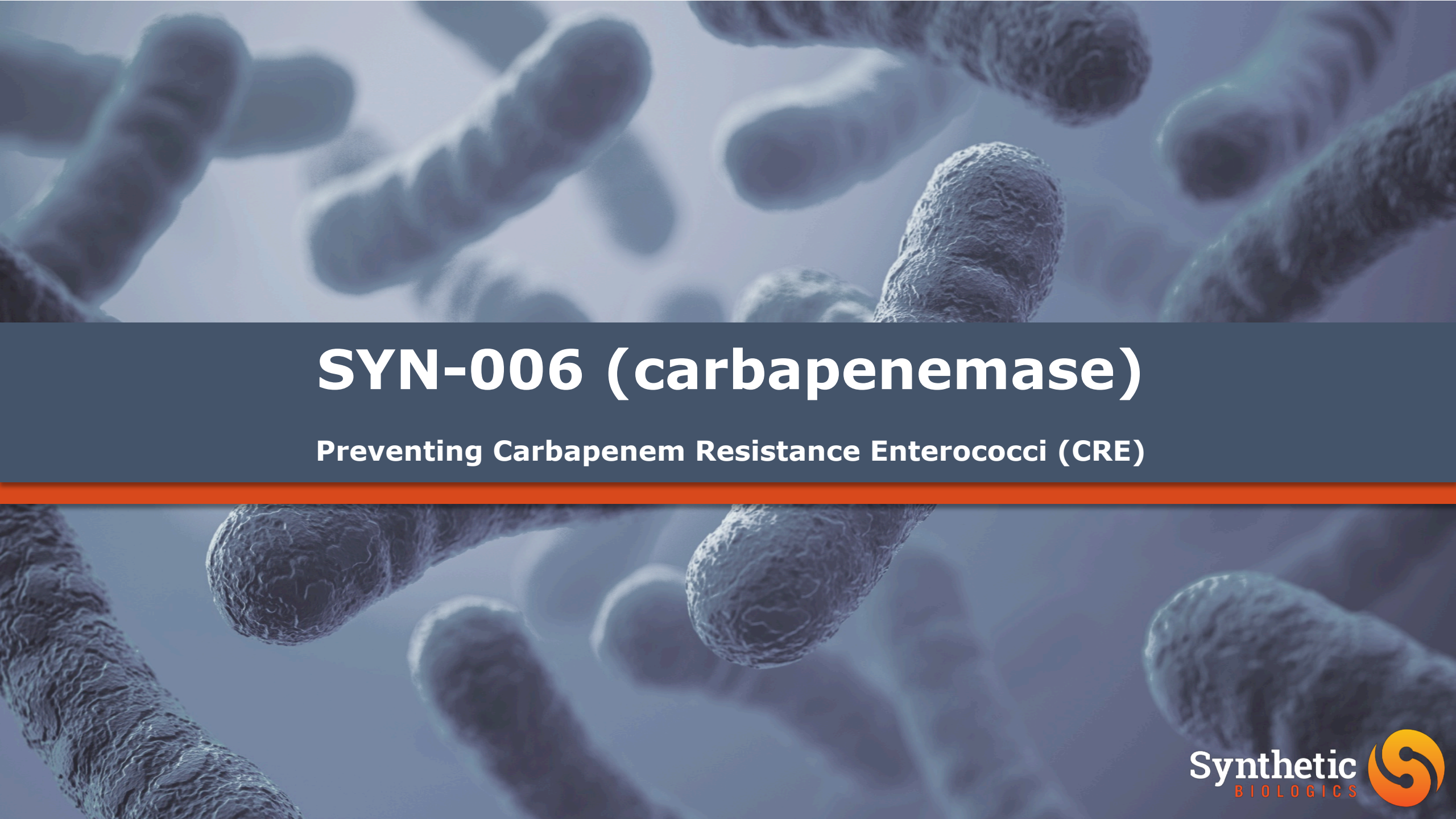
# SYN-007 (ribaxamase) DR Status

## Opportunity for innovation, manufacturing and rapid advance to the clinic

- Preclinical proof-of-concept achieved in dog models
  - Patent applications filed
  - Potential to expand preclinical evaluation to oral cephalosporins (cefuroxime, cefaclor)
  - Same enzyme as phase 3 product SYN-004; anticipate limited requirement for preclinical toxicology
- Potential to rapidly advance to Phase 1 clinical trials to evaluate SYN-007 dose
  - Confirm absence of effects on amoxicillin pharmacokinetics
  - Measure effects on microbiome in stool samples
- Undertake age de-escalating Phase 2/3 clinical trial in children with infections
  - Primary endpoint reduction in AAD (use PRO diaries to ensure rigorous reporting)
  - Ensure no adverse impact on amoxicillin cure rates
- Development work required
  - Finalize formulation and pediatric delivery
  - CMC process development and GMP manufacture

**AAD** antibiotic associated diarrhea



# SYN-006 (carbapenemase)

## Preventing Carbapenem Resistance Enterococci (CRE)

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# SYN-006 (carbapenemase)

Next-generation antibiotic degrading enzyme with broader spectrum of activity

- Carbapenems are potent β-lactam antibiotics
  - Carbapenems are typically second-line therapy for febrile neutropenia (**FN**) in the USA but are **first-line** therapy for FN in China
  - Carbapenems and clindamycin were associated with more CDI than other antibiotics in randomized clinical trials and carbapenem resistance is a growing global concern
- **SYN-006** is an enteric-protected oral formulation of a class B metallo-β-lactamase enzyme (**P2A**)
  - Degrades carbapenems (ertapenem, imipenem, meropenem) **in addition to** cephalosporins and penicillins
- Advancing SYN-006 has potential therapeutic and strategic benefit
  - Broader spectrum β-lactamase activity expands use
  - Significant interest in China due to increasing rates of fatal **CRE bacteremia**

Freifeld AG (2011) *Clin Infect Dis* **52:**e56-e93. Han L (2018) *Front Immunol* **9:**669. Vardakas KZ (2016) *Int J Antimicrob Agents* **48:** 1-10. Meletis G (2016) *Ther Adv Infect Dis.* **3:**15-21. **CRE:** carbapenem resistant enterococci.

# SYN-006 (carbapenemase) Strategy

Opportunity for innovation, manufacturing and rapid advance to the clinic

- Preclinical proof-of-concept achieved in dog and pig models
  - Protected the gut microbiome without altering systemic ertapenem and meropenem PK[1,2]
  - Patent applications filed
- Potential to rapidly advance to Phase 1 clinical trials
  - Confirm absence of effects on IV carbapenem pharmacokinetics
  - Measure effects on microbiome in stool samples
- Phase 2/3 studies directed to prevention of aGVHD, CRE colonization/bacteremia
  - CRE bacteremia rates are increasing worldwide
- Development work required
  - Finalize formulation and dosing regimen
  - CMC process development and GMP manufacture

Kaleko M (2017) IDWeek 2017, San Diego, CA. Connelly (2016) ASM Microbe 2016, Boston, MA. Potter RF (2016) *Drug Resist Updat* **29:**30–46.
**CRE** carbapenem resistant enterococci

# SYN-006 (carbapenemase) China Clinical Strategy

## Prevention of CRE in cancer chemotherapy patients

- Potential clinical indication recommended by China KOL
  - Hematologist and Vice Chair of a National Committee evaluating infectious complications in cancer
- Carbapenems are first-line treatment for febrile neutropenia (FN) in hematologic cancer patients in China (PIP/TAZO 2°)
  - Clinical site performs ~600 HCTs p.a. (30-40% allogeneic); complicated post-transplant care structure[1]
  - Clinical site administers chemotherapy to 1,000-2,000 patients p.a. who have hematologic malignancies but don't get HCT (60-70% get FN)[2]
- Infection by CRE is a recognized and increasing health threat in China
  - KOL estimated CRE infection rate is 10-20% in non-HCT chemotherapy patients
  - Very poor prognosis/high mortality in patients with CRE bacteremia
- CRE is a specific area of interest for China CDC
  - Strong potential China-first/China specific rationale for development funding
  - Prevention of CRE in China could be a parallel path to prevention of aGVHD indication in USA
- Further detailed diligence on CRE colonization vs bacteremia and potential SYN-006 benefit is underway

[1]HCT patients spend 20 days in hematology ward then sent to a separate hospital for post-HCT care and follow-up
[2]Non-HCT chemotherapy patients who get a fever but don't have neutropenia will be treated with a cephalosporin instead of a carbapenem